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A generalized ODE susceptible-infectious-susceptible compartmental model with potentially periodic behavior

Scott Greenhalgh [a, *], Anna Dumas [a]

[a] Department of Mathematics, Siena College, 515 Loudon Road, Loudonville, NY, 12211, USA

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ABSTRACT

Differential equation compartmental models are crucial tools for forecasting and analyzing disease trajectories. Among these models, those dealing with only susceptible and infectious individuals are particularly useful as they offer closed-form expressions for solutions, namely the logistic equation. However, the logistic equation has limited ability to describe disease trajectories since its solutions must converge monotonically to either the disease-free or endemic equilibrium, depending on the parameters. Unfortunately, many diseases exhibit periodic cycles, and thus, do not converge to equilibria. To address this limitation, we developed a generalized susceptible-infectious-susceptible compartmental model capable of accurately incorporating the duration of infection distribution and describing both periodic and non-periodic disease trajectories. We characterized how our model's parameters influence its behavior and applied the model to predict gonorrhea incidence in the US, using Akaike Information Criteria to inform on its merit relative to the traditional SIS model. The significance of our work lies in providing a novel susceptible-infected-susceptible model whose solutions can have closed-form expressions that may be periodic or non-periodic depending on the parameterization. Our work thus provides disease modelers with a straightforward way to investigate the potential periodic behavior of many diseases and thereby may aid ongoing efforts to prevent recurrent outbreaks.

1. Introduction

A rare few ODE compartmental models have solutions that are closed-form expressions. Most view this list as the class of susceptible-infectious and susceptible-infectious-susceptible (SIS) models, which amount to some form of the logistic growth equation (Martcheva, 2015; Nåsell, 2011). Less well-known are the infectious-recovered (IR) models (A. Lloyd, 2017), which are akin to exponential growth, and thereby also deserve inclusion. Historically, these simple models have proven to be of great utility in the study of disease dynamics. For instance, SIS models are commonly used as a first means to predict the total number of people that an epidemic will infect, through the use of the associated final size equation (Brauer, 2006; Martcheva, 2015). They are also used in the framework to estimate the doubling time of an epidemic (Smirnova et al., 2022) and can be applied to determine the vaccination level required to cause disease burnout (van den Driessche, 2017). While IR models may

* Corresponding author.
E-mail address: sgreenhalgh@siena.edu (S. Greenhalgh).
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have fewer applications, they are infamously quoted in media and literature (Fansher et al., 2022), as “exponential growth” is synonymous with most pandemics. Consequently, lay audiences and novice disease modelers are far more likely to be familiar with the behavior of IR models, at least in comparison to other model types.

Inarguably, SI, SIS, and IR differential equation models and their applications have inspired many current and future disease models. These models have limitations though. For instance, their ability to predict the trajectory of diseases is limited, as all trajectories monotonically converge to an equilibrium. Thus, these models cannot predict any form of recurrent epidemics, such as seasonal influenza, measles, and many sexually transmitted infections, among others. While current extensions of these models can address this issue, they do so at the cost of losing the closed-form expressions that make these elementary models convenient.

Here, we propose a new take on the SIS model. We derive our model starting from the general formulation of SIS models as a system of integral equations (Brauer, 2010; Greenhalgh & Rozins, 2021) under a general assumption placed on the duration of infection distribution. For particular cases of this class of distributions, we show that our generalized susceptible-infected-susceptible model (gSIS) reduces to the traditional SIS model (Kermack & McKendrick, 1991a; 1991b; 1991c) with constant coefficients, and the IR model, respectively. Furthermore, while many other works may have tackled SIS models formulated as logistic growth equations (Benardete et al., 2008; Hale & Kocak, 2012; Lopez et al., 2010; Mir & Dubeau, 2016), we illustrate how to connect the time-varying rates directly from the duration of infection distribution and transmission rate. To achieve this, we propose that the duration of infection distribution belongs to a particular family of generalized exponential distribution (Bakouch et al., 2018), rather than the classical exponential distribution that is commonly inappropriate for describing the duration of infection (Conlan et al., 2010; Krylova & Earn, 2013; A. L. Lloyd, 2001a, 2001b; Nguyen & Rohani, 2008).

As proof of concept, we apply our generalized susceptible-infectious-susceptible (gSIS) model to predict gonorrhea incidence in the US. Gonorrhea is a nationally reportable sexually transmitted disease (Centers for Disease Control and Prevention, 2019; 2022), which is typically caused by the spread of bacteria during sexual contact (Buder et al., 2019), although mother-to-child transmission is possible. While medical treatment is available, gonorrhea infection confers little to no immunity (Russell et al., 2020), with re-infection common after subsequent exposures (Fung et al., 2007). However, despite this dynamic of infection, return to susceptibility, and re-infection, trends in gonorrhea infection can appear oscillatory (Tan et al., 2013), rather than convergent to a disease-free or endemic equilibrium, which casts doubt on the applicability of traditional SIS models for predicting disease trends. So, we apply our gSIS model to capture the oscillatory trajectory of gonorrhea in the US, all the while maintaining the convenient properties expected of traditional SIS models.

2. Methods

In what follows, we illustrate a gSIS model, as formulated by a system of ODEs. We derive the model starting from a system of Volterra integral equations, imposing the assumption that the duration of infection belongs to a class of generalized exponential distributions. We then proceed to reduce the model to a logistic growth equation with time-varying parameters, illustrate the closed-form solutions for all special parameter values (Table 1), and completely characterize the stability properties of the system, including the potential occurrence of periodic cycles.

2.1. Generalized differential equation compartmental models

Classically, one of the most general forms of compartmental models are those formulated as a system of Volterra integral equations (Brauer, 2008, 2010; Hethcote & Tudor, 1980; Kermack & McKendrick, 1991a, 1991b, 1991c). For such compartmental models, the proportion of susceptible individuals is typically denoted as $s(t)$, and the proportion of infected individuals is denoted as $i(t)$, (Brauer, 2008, 2010), where $i_0Q(t)$ characterizes the proportion of infected individuals at the beginning of the epidemic. The relation between compartments is given by

Table 1
Summary of gSIS model stability conditions and properties.

Growth rate condition	Hazard rate condition	Closed-form expression	Asymptotically stable DFE	Asymptotically stable periodic solution
$\beta = 0$	$\alpha = 0$ or $w = 0$	Yes	Yes	No
$\beta = 0$	$\alpha \neq 0$ and $w \neq 0$	Yes	Yes	No
$\beta - \rho < 0$	$\alpha = 0$ or $w = 0$	Yes	Yes	No
$\beta - \rho > 0$	$\alpha = 0$ or $w = 0$	Yes	No	No
$\beta - \rho = 0$	$\alpha = 0$ or $w = 0$	Yes	Yes	No
$\beta - \rho = 0$	$\alpha \neq 0$ and $w \neq 0$	Yes	Yes	No
$\beta - \rho < 0$	$\alpha \neq 0$ and $w \neq 0$	Yes	Yes	No
$\beta - \rho > 0$	$\alpha \neq 0$ and $w \neq 0$	Yes	No	Yes

$$s(t) = 1 - i_0 Q(t) - \int_0^t i_{new}(x) Q(t-x) dx,$$
$$i(t) = i_0 Q(t) + \int_0^t i_{new}(x) Q(t-x) dx. \quad 2.1$$

Here $i_{new}(x)$ is the rate of new incidence at time x, i_0 is the initial proportion of infected individuals, and $Q(t-x)$ is the survival function associated with the infectious period distribution, which describes the proportion of individuals that remain infectious at time t given infection occurred at time x.

From (2.1), one can obtain the traditional differential equation SIS model (with recovery rate γ) by imposing $i_{new}(x) = \beta i(x)s(x)$ and $Q(t-x) = e^{-\gamma(t-x)}$, differentiating (2.1) with respect to t, and then substituting the remaining integral terms with the appropriate multiple of equations from (2.1), respectively. Alternatively, by imposing $Q(t-x) = \sum_{n=0}^{k-1} \frac{(\gamma(t-x))^n}{n!} e^{-\gamma(t-x)}$, i.e. an Erlang distributed duration of infection, one obtains the SI^{k}S model (Krylova & Earn, 2013), where the state of infection has been subdivided into k stages.

To obtain new differential equation compartmental models we propose their derivation from a quantity other than incidence, or respectively the proportion of infected individuals, namely person-days of infection. To elaborate, at each fixed time τ during an epidemic, infected individuals remain infectious according to the survival function associated with the (conditional) duration of infection distribution, $P(t,\tau)$, with a subset being newly infected individuals, who remain infectious according to the survival function of the infectious period distribution $Q(t-\tau)$ (Fig. 1), where $t \geq \tau$. The area of the region enclosed by these survival curves is the quantity, "person-days" of infection.

Initially, for this new compartmental model, the number of person-days of infection is denoted as $D(t)$, where $D_{new}(t)$ characterizes the person-days of infection from newly infected individuals who are initially infectious at time t, and person-days susceptible to infection is denoted as $Z(t)$. Thus, the time evolution can be modeled as

$$Z(t) = M(t) - D_0 Q(t) - \int_0^t D_{new}(x) Q(t-x)\, dx$$
$$D(t) = D_0 Q(t) + \int_0^t D_{new}(x) Q(t-x)\, dx, \quad 2.2$$

where $M(t)$ is the total number of all person-days, D_0 is the initial person-days of infection from infectious individuals at the start of the epidemic, and once again $Q(t-x)$ is the survival function associated with the infectious period distribution.

In classical ODE compartmental models, it is assumed by virtue the law of mass action (Al-arydah et al., 2020) that new infections are based on prior knowledge of the infected and susceptible individuals, namely $i_{new}(x)Q(t-x) = \beta i(x)s(x)P(t,x)$ where $P(t,x)$ is the (conditional) duration of infection distribution for individuals infected at time x, with $t \geq x$ (Brauer, 2010; Greenhalgh & Rozins, 2021; Hethcote & Tudor, 1980).

Denoting N as the total population, we assume that

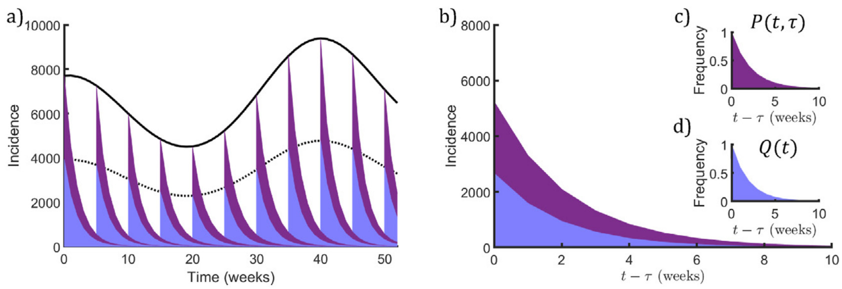

Fig. 1. The survival of infected individuals throughout an outbreak. a) The trajectory of incidence (solid black curve), new incidence (dotted black curve), and the survival of newly infected individuals for remaining infectious at 5-week intervals (blue regions), and the survival of all previously infected individuals for remaining infectious at 5-week intervals (purple plus blue regions) over a total of 50 weeks. b) The survival of newly infected individuals for remaining infectious (blue regions), and the survival of all previously infected individuals for remaining infectious (purple plus blue regions) for a given initial time τ, c) the duration of infection distribution, $P(t,\tau)$, and d) the infectious period distribution $Q(t)$.

$$D_{new}(x)Q(t-x) = \mu N i_{new}(x)Q(t-x) = m(x)N\beta i(x)s(x)P(t,x). \tag{2.3}$$

The main difference from the classical assumption is the inclusion of the average infectious period, μ, and the average duration of infection at time x, $m(x)$, which is referred to as the mean residual waiting-time in the literature (Gupta & Bradley, 2003). It is assumed that new person-days of infection are based on prior knowledge of the infected and susceptible individuals along with their (time-varying) average duration of infection, which is included to reflect that not all currently infected individuals have the same initial moment of infection.

In addition, while many potential forms of $P(t,x)$ exist, we consider it to be defined by (Gupta & Bradley, 2003),

$$P(t,x) = \frac{m(x)}{m(t)}\exp\left(-\int_x^t \frac{1}{m(z)}dz\right), \tag{2.4}$$

along with the associated Equilibrium distribution (Gupta, 2007) of the duration of infection,

$$P_e(t,x) = \frac{m(t)}{m(x)}P(t,x) = \exp\left(-\int_x^t \frac{1}{m(z)}dz\right). \tag{2.5}$$

From equation (2.4), we obtain the person-days of infection at time x, given the number of infected individuals at this time is $I(x)$, as (Bradley & Gupta, 2003)

$$D(x) = \int_x^\infty I(x)P(t,x)dt = I(x)m(x) = Ni(x)m(x).$$

The structure of $D(x)$ in terms of $I(x)m(x)$ implies that we can equivalently represent the area enclosed by the survival curve (Fig. 1a) with a rectangle of width $m(x)$ and height $I(x)$ (Fig. 2).

To convert system (2.2) into one based on the product of incidence and the duration of infection we impose that

$$D(t) = Ni(t)m(t), Z(t) = Ns(t)m(t), \text{and} M(t) = Nm(t). \tag{2.6}$$

From (2.3) and (2.6), it follows that equation (2.2) becomes

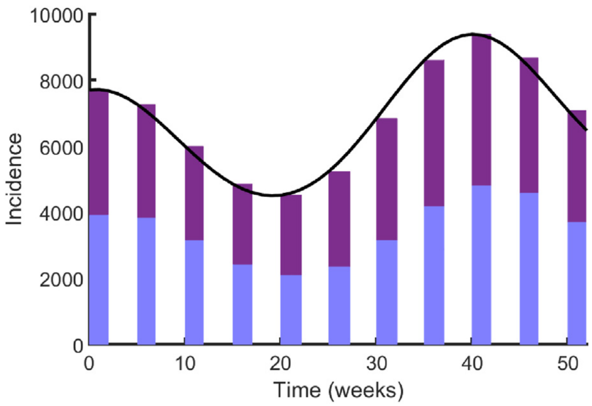

Fig. 2. Person-days of infection throughout an outbreak. Incidence (black curve) and the person-days of infection from newly infected individuals at 5-week intervals (blue regions), and the person-days of infection from previously infected individuals at 5-week intervals (purple plus blue regions).

$$m(t)s(t) = m(t) - i_0 m(0)P(t,0) - \int_0^t \beta i(x)m(x)s(x)P(t,x)\,dx$$
$$m(t)i(t) = i_0 m(0)P(t,0) + \int_0^t \beta i(x)m(x)s(x)P(t,x)dx, \tag{2.7}$$

Multiplying (2.7) through by $P(\tau,t)$, we can predict the survival of person-days of infection from any moment t (ignoring any future transmission) as

$$m(t)i(t)P(\tau,t) = i_0 m(0)P(\tau,0) + \int_0^t \beta i(x)m(x)s(x)P(\tau,x)dx, \tau \geq t \geq x. \tag{2.8}$$

To obtain a generalized differential equation compartmental model (GDECM), we differentiate equation (2.8) with respect to t and divide through by $P(\tau,t)$ to obtain $(i(t)m(t))'$, and then apply the conservation of population to obtain $(s(t)m(t))'$:

$$(s(t)m(t))' = m'(t) - \beta i(t)m(t)s(t) + \left(\frac{m'(t)+1}{m(t)}\right)i(t)m(t),$$
$$(i(t)m(t))' = \beta i(t)m(t)s(t) - \left(\frac{m'(t)+1}{m(t)}\right)i(t)m(t), \tag{2.9}$$

Using the conservation of population $s(t)+i(t)=1$, we can also rewrite system (2.9) as the single ODE,

$$i(t)' = \beta i(t)(1-i(t)) - \left(\frac{2m'(t)+1}{m(t)}\right)i(t). \tag{2.10}$$

Note, that there is a subtle difference between equation (2.10) and the analogous traditional SIS model with time-varying recovery rate. Specifically, the coefficient of the recovery term of (2.10) is $\left(\frac{2m'(t)+1}{m(t)}\right)$ whereas the traditional SIS model would have $\left(\frac{m'(t)+1}{m(t)}\right)$. The seemingly extra $m'(t)$ of the gSIS model accounts for the time variability in the mean residual waiting-time of infected individuals (Greenhalgh & Rozins, 2021).

2.2. The periodic hazard rate and mean residual waiting-time

The hazard rate and mean residual waiting-time functions are constructs often used in survival and reliability analysis to describe the frequency of events and the time remaining in a given state, respectively, after an elapsed period (M. Finkelstein, 2008).

To begin, the hazard rate function, $\eta(t)$, (M. Finkelstein, 2008; Gupta & Bradley, 2003) is connected to the mean residual waiting-time, $m(t)$, through

$$\eta(t) = \frac{m'(t)+1}{m(t)}. \tag{2.11}$$

While many functional forms of hazard rates and mean residual waiting-times exist, most fall into the category of being either non-increasing or non-decreasing (M. S. Finkelstein & Esaulova, 2001). Recent work, however, illustrates the utility of more flexible functional forms. Specifically, hazard rates with a bathtub (M. S. Finkelstein & Esaulova, 2001), upside-down bathtub (Sharma et al., 2014), or roller-coaster (Wong & Lindstrom, n.d.) shape have been applied broadly in various contexts (Gupta & Gupta, 2007).

As the goal of this work is to obtain a potentially periodic closed-formed expression for a gSIS model, we require that the coefficient of the recovery term in (2.10) is periodic. So, we now derive a potentially periodic mean residual waiting-time, depending on model parameterization (Bakouch et al., 2018).

Making the ansatz that $m(t) = p(t)e^{\rho t}$, we have that

$$-\frac{2m'(t)+1}{m(t)} = -\frac{2(p'(t)+\rho p(t))e^{\rho t}+1}{p(t)e^{\rho t}} = -2\rho - 2\frac{p'(t)}{p(t)} - \frac{e^{\rho t}}{p(t)}. \tag{2.12}$$

We also assume that

$$2\frac{p'(t)}{p(t)}+\frac{e^{\rho t}}{p(t)}=\frac{2aw\sin(wt)}{1+a\cos(wt)}, \quad 2.13$$

as the righthand side will eventually yield an integrating factor that is integrable (see Section 2.3) and the first order linear nonhomogeneous ODE,

$$p'(t)-\frac{aw\sin(wt)}{1+a\cos(wt)}p(t)=-\frac{1}{2}e^{\rho t}. \quad 2.14$$

Solving with initial condition $p(0)=p_0$ yields

$$p(t)=\frac{(1+a)}{(1+a\cos(wt))}\left(p_0-\frac{(1+a)\rho^2+4w^2}{\rho(\rho^2+4w^2)(1+a)}\right)+\frac{e^{-\frac{1}{2}\rho t}\left(\rho^2(1+a\cos(wt))+4w^2-2aw\rho\sin(wt)\right)}{(1+a\cos(wt))\rho(\rho^2+4w^2)}.$$

It follows that

$$m(t)=\frac{(1+a)}{(1+a\cos(wt))}\left(p_0-\frac{(1+a)\rho^2+4w^2}{\rho(\rho^2+4w^2)(1+a)}\right)e^{\frac{1}{2}\rho t}+\frac{\left(\rho^2(1+a\cos(wt))+4w^2-2aw\rho\sin(wt)\right)}{(1+a\cos(wt))\rho(\rho^2+4w^2)} \quad 2.15$$

Given this general solution of $m(t)$, several conditions are required for it to be biologically valid. First, $\rho>0$ as when $\rho<0$ the first term goes to zero and the second term oscillates between positive and negative values, which is impossible given durations of infection must be non-negative. Furthermore, given $\rho>0$ then necessarily $p_0=\frac{(1+a)\rho^2+4w^2}{\rho(\rho^2+4w^2)(1+a)}$ as otherwise $m(t)$ would grow exponentially, and eventually exceed any feasible value.

Imposing the suggested condition on p_0 implies

$$m(t)=\frac{\rho^2(1+a\cos(wt))+4w^2-2aw\rho\sin(wt)}{(1+a\cos(wt))\rho(\rho^2+4w^2)}, \quad 2.16$$

where the average infectious period is given by

$$m(0)=\mu=\frac{\rho^2(1+a)+4w^2}{(1+a)\rho(\rho^2+4w^2)}. \quad 2.17$$

2.3. GDECM solutions and properties

Under the assumption that $m(t)$ is time-dependent, equation (2.10) is a Bernoulli equation (Buckley, 1953) of the form

$$\frac{di}{dt}+R(t)i(t)=Q(t)i(t)^n,$$

where $n=2, R(t)=-\beta+\eta(t)+\frac{m'(t)}{m(t)}=-\beta+\frac{2m'(t)+1}{m(t)}, Q(t)=-\beta.$

Thus, the nonlinear ODE can be transformed through $i(t)=1/y(t)$ into the first-order linear non-constant coefficient ODE of the form

$$\frac{dy}{dt}-R(t)y=-Q(t), \quad 2.18$$

which is a first-order linear ODE that can be solved by integrating factors.

Given the definitions of $R(t)$ and $Q(t)$, it follows that the integrating factor of (2.18) is

$$\widehat{\mu}(t)=\exp\left(\int_0^t \beta-\frac{2m'(z)+1}{m(z)}dz\right)=\frac{m(0)^2}{m(t)^2}e^{\beta t-\int_0^t \frac{1}{m(z)}dz}. \quad 2.19$$

and thus, the solution of the transformed ODE is given by

$$y(t) = \frac{1}{\widehat{\mu}(t)} y_0 + \frac{\beta}{\widehat{\mu}(t)} \int_0^t \widehat{\mu}(x) dx. \tag{2.20}$$

Upon reversing the transformation, we have that

$$i(t) = \frac{\widehat{\mu}(t) i_0}{1 + \beta i_0 \int_0^t \widehat{\mu}(x) dx}. \tag{2.21}$$

Turning to the integrating factor $\widehat{\mu}(t)$, the assumed conditions on $m(t) = p(t)e^{\frac{1}{2}\rho t}$ implies

$$\widehat{\mu}(t) = \exp\left((\beta - \rho)t - \int_0^t \frac{2aw\sin(wz)}{1 + a\cos(wz)} dz \right) = \frac{(1 + \alpha\cos(wt))^2}{(1 + \alpha)^2} \exp((\beta - \rho)t). \tag{2.22}$$

It follows because $\widehat{\mu}(t)$ is the product of exponential and positive integer powers of cosine functions that it is also integrable. Thus, for $\beta \neq \rho$, we have that

$$\begin{aligned} \int_0^t \widehat{\mu}(z) dz = & \frac{\exp((\beta - \rho)t)}{(1 + \alpha)^2} \left(\frac{\alpha}{2\left((\beta - \rho)^2 + 4w^2\right)} (\alpha(\beta - \rho)\cos(2wt) + 2\alpha w\sin(2wt) + 4(\beta - \rho)\cos(wt) + 4w\sin(wt)) + \frac{1}{2}\frac{2 + \alpha^2}{\beta - \rho} \right) \\ & - \frac{1}{(1 + \alpha)^2} \left(\frac{\alpha(\beta - \rho)(\alpha + 4)}{2\left((\beta - \rho)^2 + 4w^2\right)} + \frac{1}{2}\frac{2 + \alpha^2}{\beta - \rho} \right), \end{aligned} \tag{2.23}$$

and for $\beta = \rho$ that

$$\int_0^t \widehat{\mu}(z) dz = \frac{1}{2} \frac{\alpha(4 + \alpha\cos(wt))\sin(wt)}{(1 + \alpha)^2 w} + \frac{(2 + \alpha)^2}{2(1 + \alpha)^2} t. \tag{2.24}$$

Naturally, as $m(t), \widehat{\mu}(t),$ and $\int_0^t \widehat{\mu}(z) dz$ have closed-form expressions in terms of elementary functions, the infected proportion $i(t)$ also shares this property.

2.3.1. The case when $\beta = 0$, and $w = 0$ or $\alpha = 0$

In this case, equation (2.10) reduces to an IR model, as described by an exponential decay. The solution of the mean residual waiting-time is given by $m(t) = \frac{1}{\rho}$.

It follows from (2.19) and (2.23) that

$$\widehat{\mu}(t) = \exp\left(\int_0^t -\frac{2m'(z) + 1}{m(z)} dz \right) = \exp\left(-\int_0^t \rho\, dz \right) = \exp(-\rho t) \text{and} \int_0^t \widehat{\mu}(z) dz = \frac{1}{\rho}(1 - \exp(-\rho t)).$$

Thus, by (2.21) the solution is

$$i(t) = i_0 \exp(-\rho t),$$

which decays to the disease-free equilibrium (DFE), namely $\lim_{t\to\infty} i(t) = i_{DFE} = 0$.

2.3.2. The case when $\beta = 0$, and $w \neq 0$ or $\alpha \neq 0$

Similar to Section 2.3.1, this model also reduces to an IR model, but the decay rate is time-dependent. The solution of the mean residual waiting-time is given by (2.16), with the general solution of (2.10) given by

$$i(t) = i_0 \frac{(1+\alpha\cos(wt))^2}{(1+\alpha)^2} \exp((-\rho)t).$$

Naturally, $\lim_{t\to\infty} i(t) = i_{DFE} = 0$.

2.3.3. The case when $\beta - \rho \neq 0$, and $w = 0$ or $\alpha = 0$

For this scenario, the gSIS reduces to the traditional SIS model. The integrating factor and its integral are

$$\widehat{\mu}(t) = \exp((\beta-\rho)t)$$

and

$$\int_0^t \widehat{\mu}(z)dz = \frac{1}{\beta-\rho}(\exp((\beta-\rho)t) - 1).$$

It follows that (2.10) reduces to the logistic curve,

$$i(t) = \frac{i_0 \exp((\beta-\rho)t)}{1 + i_0 \frac{\beta}{\beta-\rho}(\exp((\beta-\rho)t) - 1)}.$$

Thus, two outcomes are possible, first if $\beta - \rho > 0$ then $i(t) \to 1 - \frac{\rho}{\beta}$ as $t \to \infty$, and second when $\beta - \rho < 0$ then $i(t) \to 0$ as $t \to \infty$.

2.3.4. The case when $\beta - \rho = 0$, and $w = 0$ or $\alpha = 0$

Under such conditions, $= 1/\rho$, $\widehat{\mu}(t) = 1$, $\int_0^t \widehat{\mu}(z)dz = t$. It follows that

$$i(t) = \frac{i_0}{1 + \rho i_0 t}.$$

Given that $\rho > 0$, we have that $i(t) \to 0$ as $t \to \infty$.

2.3.5. The case when $\beta - \rho = 0, w \neq 0, \alpha \neq 0$

For this case, we have that $\widehat{\mu}(t) = \frac{(1+\alpha\cos(wt))^2}{(1+\alpha)^2}$ and $\int_0^t \widehat{\mu}(z)dz = \frac{1}{2}\frac{\alpha(4+\alpha\cos(wt))\sin(wt)}{(1+\alpha)^2 w} + \frac{(2+\alpha)^2}{2(1+\alpha)^2} t$. Thus, we have

$$i(t) = \frac{i_0(1+\alpha\cos(wt))^2}{(1+\alpha)^2 + \frac{1}{2}\beta i_0\left(\frac{\alpha}{w}(4+\alpha\cos(wt))\sin(wt) + (2+\alpha)^2 t\right)}.$$

As $\frac{1}{2}\beta i_0(2+\alpha)^2 > 0$, we have that $i(t) \to 0$ as $t \to \infty$.

2.3.6. The case when $\beta - \rho \neq 0, w \neq 0, \alpha \neq 0$

For the final case $m(t), \widehat{\mu}(t)$, and $\int_0^t \widehat{\mu}(z)dz$ are all given by their general forms. Provided $\beta - \rho > 0$, it follows that for sufficiently large t that

$$i(t) = \frac{\widehat{\mu}(t) i_0}{1 + \beta i_0 \int_0^t \widehat{\mu}(x)dx} \approx \frac{\widehat{\mu}(t)}{\beta \int_0^t \widehat{\mu}(x)dx}$$

$$= \frac{(1+\alpha\cos(wt))^2}{\beta\left(\frac{\alpha}{2\left((\beta-\rho)^2+4w^2\right)}(\alpha(\beta-\rho)\cos(2wt)+2\alpha w\sin(2wt)+4(\beta-\rho)\cos(wt)+4w\sin(wt))+\frac{1}{2}\frac{2+\alpha^2}{\beta-\rho}\right)}.$$

Alternatively, if $\beta-\rho<0$ it follows from (2.23) that

$$\lim_{t\to\infty}\beta i_0\int_0^t \widehat{\mu}(z)dz = -\beta i_0\frac{1}{(1+\alpha)^2}\left(\frac{\alpha(\beta-\rho)(\alpha+4)}{2\left((\beta-\rho)^2+4w^2\right)}+\frac{1}{2}\frac{2+\alpha^2}{\beta-\rho}\right)>0,$$

and $\widehat{\mu}(t)\to 0$ as $t\to\infty$. Thus, we have that $i(t)\to 0$ as $t\to\infty$.

3. Application of the methodology to gonorrhea in the United States

To illustrate the utility of our gSIS model, we apply it, and the traditional SIS model to predict gonorrhea incidence in the United States. We estimate parameters by minimizing the least-square error of model predictions with historical data on gonorrhea incidence (Centers for Disease Control and Prevention, 2019; 2022), as well as the literature (Garnett et al., 1999; Hethcote & Yorke, 2014). Specifically, the average duration of infection is based on an average of 1.5 days from gonorrhea exposure to infectiousness (Hethcote & Yorke, 2014), an incubation period of approximately 7.5 days (Centers for Disease Control and Prevention, 2022), and an average of 7.4 days (Centers for Disease Control and Prevention, 2022) from symptom onset to visiting a medical professional for treatment. Altogether, this implies the average duration of infection is $\mu\approx 1.91$weeks.

Using this estimate, we reduce the number of parameters to estimate by imposing that ρ satisfies

$$\mu-\frac{\rho^2(1+a)+4w^2}{(1+a)\rho\left(\rho^2+4w^2\right)}=0,$$

where w and α are determined by minimizing the least-square error between model predictions and gonorrhea incidence data for the gSIS model or set to zero for the traditional SIS model. We also base the total population size on the 15- to 24-year population in the US (Blakeslee, L, Caplan, Z, Meyer, J.A., Rabe, M.A., 2023), who are the primary at-risk group for gonorrhea infection(Centers for Disease Control and Prevention, 2022). Additional details of parameters, including the transmission rate, are available in Table 2.

Given the estimates of model parameters, the (time-varying) average duration of infection varies between 1.83 weeks and 2.17 weeks for the gSIS model and remains constant at 1.91 weeks for the SIS model (Fig. 3). For the models, we have that the DFE is unstable, as $\tilde{\beta}-\tilde{\rho}=0.018>0$, and $\overline{\beta}-\overline{\rho}=0.01>0$ for the gSIS, and SIS models, respectively. Using the estimated parameters (Table 2), the gSIS, and traditional SIS models predict a peak and trough of 4.5–30.1 thousand, and 4.9–93.9 thousand incidences of gonorrhea per week, respectively, over the next 300 weeks (Fig. 4). Furthermore, the period of the epidemic for the gSIS model was estimated as $2\pi/w\approx$ 39.4 weeks, with an amplitude of seasonality of $\alpha\approx$ 0.1571.

To inform on the merit of our predictions, we calculated the Akaike information criteria (AIC) (Lancelot et al., 2002). Briefly, AIC is a mathematical method for comparing how well models fit data, relative to one another, which takes into account model complexity (Symonds & Moussalli, 2011). Assuming model solutions are represented by $i(t;\beta,\alpha,w,i_0,t_0)$, we define the new incidence as

$$\lambda(t;N,\beta,\alpha,w,i_0,t_0)=N\beta\, i(t;\beta,\alpha,w,i_0,t_0)(1-i(t;\beta,\alpha,w,i_0,t_0)),$$

where a subscript of SIS, or gSIS is used to distinguish between cases.

The AIC score (Lancelot et al., 2002) for SIS and gSIS models is then determined from

Table 2
Parameters, base values, and sources.

Parameter	Symbol	SIS value	gSIS value
Population (15–24 yrs) (millions)	N	43	43
Duration of infection (in absence of periodicity)	$1/\rho$	1.91 weeks	1.91 weeks
Transmission rate	β	0.541/week	0.534/week
Period of the epidemic	$2\pi/w$	Undefined	39.4 weeks
Magnitude of seasonality	α	0	0.1571

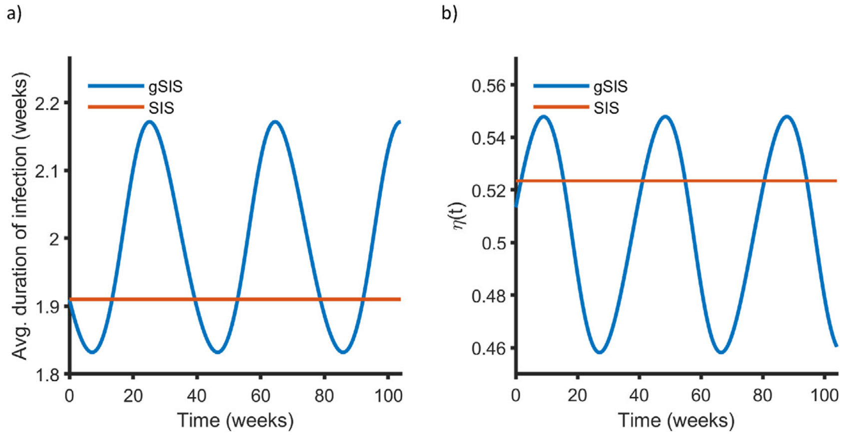

Fig. 3. The mean residual waiting-time and hazard rates of the duration of infection. Estimate of a) the average duration of infection and b) hazard rate of the duration of infection distribution of gonorrhea at time t for the gSIS model with $1/\rho = 1.99$ weeks , $\alpha = 0.1571$, $\frac{2\pi}{w} = 39.4$ weeks (blue dashed curve), and the SIS model with $1/\rho = 1.91$ weeks , $\alpha = w = 0$ (red solid curve).

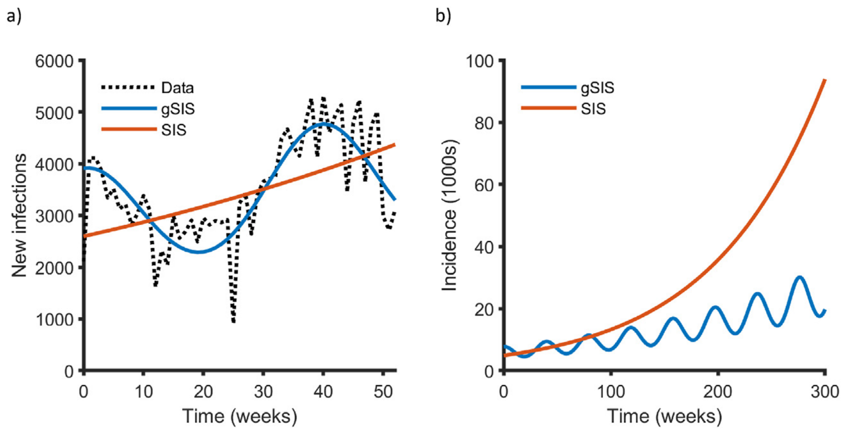

Fig. 4. Model fit and predictions of new gonorrhea infections. The trajectory of new gonorrhea infections based on data (black dotted curve), the gSIS model with $1/\rho = 1.99$ weeks , $\alpha = 0.1571$, $\frac{2\pi}{w} = 39.4$ weeks (blue dashed curve), and the SIS model with $1/\rho = 1.91$ weeks , $\alpha = w = 0$ (red solid curve).

$$AIC = M(\ln(2\pi)+1) + M\ln\left(\frac{1}{M}\sum_{j=0}^{M}(\lambda(j;\beta,\alpha,w,i_0,t_0) - I_{new}(j))^2\right) + 2(k+1)$$

where M is the number of data points, $I_{new}(j)$ is the observed new incidence on the j^{th} week and k is the number of estimated parameters.

4. Discussion

We demonstrated a novel take on SIS models motivated by their extension to compartmental models that track person-days of infection. For our model, we completely characterized its stability behavior, in addition to demonstrating that the SIS and IR families of compartmental models are special cases. Naturally, this guarantees gSIS models will do at least as well as SIS and IR models in application and demonstrates that the family of compartmental models with closed-form solutions is much broader than these classical cases alone. Importantly, this work is also the first to build an SIS compartmental model with time-varying parameters directly from assumptions placed on the duration of infection distribution, while also extending SIS models to potentially feature periodic behavior.

We illustrated a novel SIS model with new solutions that were closed-form expressions beyond the well-known SIS, SI, and IR models. While it remains an open question whether more complex models have such convenient properties, the added flexibility of GDECM should provide a means to obtain additional gSIS models with such features. Furthermore, the GDECM framework may even enable the development of the first SIR models with solutions that have a closed-form expression. If such a SIR model exists, it would imply the existence of an additional conservation law beyond the conservation of population, and therefore could, at least in theory, be tested empirically.

An interesting feature of the gSIS model is that the existence of periodic solutions requires $\beta - \rho > 0$, or equivalently $\frac{\beta}{\rho} > 1$. Typically, for autonomous compartmental models, the existence of periodic solutions (when only one endemic equilibrium exists) requires a specific set of parameter values so that $R_0 \approx 1$, which would be equivalent to $\frac{\beta}{\rho} \approx 1$ for the traditional SIS model, at least according to Hopf-bifurcation theory (Stadtländer, 2010). As such, the condition required for periodic solutions of gSIS models suggests oscillatory dynamics are far more likely, which is corroborated by observed trends of many disease trajectories that feature reproductive numbers greater than one.

The estimated epidemic period of 39.4 weeks provided by the gSIS model closely mirrors the average duration of a school year of approximately 40 weeks (including weekends and holidays). While this similarity could be a coincidence, the high prevalence of gonorrhea among 15-24 year-olds (Centers for Disease Control and Prevention, 2019; 2022), and the known role of the school year in the transmission of other diseases (Keeling et al., 2001; Metcalf et al., 2009), suggest that the length of the school year may play a prominent role in the periodic behavior of gonorrhea.

A further avenue of research is to consider a gSIS multistrain model that features a mixture of distributions with periodic hazard rates. With such a model and distribution, it may be possible to ascertain fundamental frequencies of transmission and infection directly from the model's solution. Subsequently, it may also be possible to determine whether there could be any resonance between strains (Bacaër & Abdurahman, 2008) and how such a thing may contribute to pathogen evolution. Future work could also include the merger of gSIS with techniques for predicting the doubling-time of epidemics. While recent work tackles the question of doubling-time for epidemic models in the context of a modified Richards model (Smirnova et al., 2022) (a generalization of logistic growth), it stands to reason that such analysis could be applied to gSIS models, given their formulations as logistic growth equations with time-dependent parameters. Relatedly, the solutions with closed-form expression of gSIS should also provide a means to estimate a final size function, akin to a final size equation of autonomous SIS models, that could provide details on the number of infected individuals, given only an initial condition and desired time period.

While this work focuses on a modification of differential equation SIS models to include a time-varying average duration of infection, one could also study gSIS models in the context of integral equations. The added flexibility of such a modification to an integral equation description of disease spread may provide a means to tackle open challenges in disease modeling (Lloyd-Smith et al., 2015), such as understanding the endemic equilibrium and defining its stability (Roberts et al., 2015). Similarly, gSIS models could also be generalized to incorporate additional epidemiological states that are pertinent for capturing the dynamics of disease Extending SIS models to the framework of GDECM carries with it many of the limitations of differential equation compartmental models, with a homogeneously mixed population likely being the most prominent drawback. Furthermore, the extension of SIS to gSIS still may not be sufficient to accurately represent the transmission dynamics of gonorrhea, as the inclusion of treatment, asymptomatic infection, and treatment resistance classes, among others, may be required to accurately capture transmission dynamics. Another drawback of gSIS, at least relative to SIS, is that it requires more abundant information on the average duration of infection, namely how it varies in time. While this requirement may not greatly inhibit the theoretical development and application of this new class of models, as extensions of the gSIS model to a SEAIR model are possible (Farrell et al., 2023), it may impede its use in more intensive disease modeling analyses.

In summary, we demonstrated a new type of compartmental model based on extending a simple SIS model to the framework of GDECM. In accomplishing this, we showed how this simple extension adds the potential for rich dynamics, solutions that have closed-form expressions, and its potential to more accurately capture the patterns of disease in a population. Naturally, generalizing compartmental models further will likely only enhance these features and properties, and thereby provide ample avenues for future investigation.

Author's contributions

Anna Dumas: Study design, data collection, writing – original draft preparation.

CRediT authorship contribution statement

Scott Greenhalgh: Conceptualization, Formal analysis, Funding acquisition, Methodology, Software, Supervision, Visualization, Writing – review & editing. **Anna Dumas:** Data curation, Formal analysis, Investigation, Software, Visualization, Writing – original draft.

Declaration of competing interest

The authors declare no conflict of interest.

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