

Seasonality in epidemic models: a literature review

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Abstract We provide a review of some key literature results on the influence of seasonality and other time heterogeneities of contact rates, and other parameters, such as vaccination rates, on the spread of infectious diseases. This is a classical topic where highly theoretical methodologies have provided new insight on the seemingly random behavior observed in epidemic time-series. We follow the line of providing a highly personal non-systematic review of this topic, mainly based on the history of mathematical epidemiology and on the impact of reviewed articles. Our aim is to stress some issues of increasing interest, such as the public health implications of the biomathematical literature and the impact of seasonality on epidemic extinction or elimination.

Keywords Infectious diseases · Seasonality · Vaccine · Behavior · Public health

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1 Introduction

The introduction of the one-year periodic contact rate (also known as ‘transmission rate’ [38]) in various deterministic epidemic models allowed significant scientific discoveries. In particular, this allowed demonstrating that the rich variety of oscillatory phenomena observed in several epidemiological time series can stem from deterministic phenomena such as the seasonality of weather and the school calendar, and not by the chance alone. Soper [102] was the first author to suggest this in 1928.

Although there is an ongoing debate on this point, it is appropriate to quote an interesting observation by Keeling, Rohani and Grenfell: *‘The observed epidemics cannot be solely the product of noise, either internally generated or external, as very similar large amplitude epidemics are observed for all population sizes, despite the fact that the relative amount of noise experienced will be very different’* [72].

A large number of scientific papers have investigated the rich nonlinear effects caused by periodically varying contact rates in epidemic models, and some excellent reviews exist [2, 57].

Widely speaking, these reviews have mainly focused on how time heterogeneous in contact rates induces various forms of time heterogeneity in the endemic state. Less interest has elicited the other side of the coin: how the stability of disease-free equilibrium depends on the seasonality, a topic that is far less trivial than one could believe.

In order to provide a useful review to our readership, and not *‘yet another review paper on periodic parameters in epidemic models’*, we follow a few points of interest: (i) we maintain, especially in the first subsection, a historical perspective; (ii) we try to link the advances in the field of mathematical epidemiology to those of nonlinear physics and analysis; (iii) we point out the relevance for public health; (iv) we stress the relevance of seasonality in determining the properties of the disease-free equilibrium; (v) we focus on the role of seasonality on vector-borne diseases; and last but not least (vi) we provide a strictly personal way of choosing topics and papers: an objective and complete treatise would be impossible in a narrow bunch of pages.

Finally, we stress that our review will not cover the whole area of non-autonomous deterministic epidemic models. This subject is wide and also includes classes of diseases non reviewed here, such as the so-called men-environment-men diseases (e.g. those diseases with oro-faecal contagion mechanisms based on environment pollution) for which temporal heterogeneity can be important [20].

2 The golden age

In the late seventies, research in mathematical epidemiology started paying attention to the mechanistic explanation of some well-known characteristics of time-series of some infectious diseases, and especially of childhood infectious diseases (CID). Indeed, classical susceptible-infectious-recovered (SIR) and susceptible-exposed-infectious-recovered (SEIR) models with vital dynamics predict constant endemic steady states.

Of course, taking into account unavoidable randomness—both intrinsic (due to low predicted prevalence) and extrinsic (random immigrations and other factors that were not taken into account in the above mentioned models)—one could expect that theoretical endemic equilibria of deterministic systems in the real world correspond to fluctuating time-series of various amplitudes.

On the contrary, some observed time-series were of a totally different nature. CID showed, in particular, a series of recurrent epidemics whose peaks sometime revealed a rough periodicity as, for example, alternation of large and small epidemics in a biennial periodic fashion [14, 69, 90, 102, 105]. In his 1918 pioneering paper [15], Brownlee performed a Fourier analysis of the time-series of measles-related deaths in London between 1838 and 1913, which showed a multi-peak spectrum. However, a strong peak centered at 1.865 years (97 weeks), thus very close to 2 years, was observed plus other important peaks at 0.5, 1, 2.1 and 2.2 years, whose amplitude was the half of the above-mentioned peak at 1.865 years. In the same paper, the periodogram corresponding to the interval 1703–1828 reveal a far more complex scenario, but again the maximum peak is around 2 years. This phenomenon was a first evidence of some underlying deterministic mechanism driving these ‘periodic’ epidemics, although stochastic birth-death epidemic models were used by Bartlett [10] to explain periodicity in certain measles time-series. In other cases, the amplitude of epidemic was widely distributed, so that a genuine stochastic mechanism could have been the driving ‘force’ behind this behavior.

These observations were contemporary to the early diffusion of computers in the academic world (the UNIX operating systems as well as the related C programming language were developed in 1969 [73, 74]) amidst the first real wave of large use of computers for simulations.

Moreover, theoretical investigations in nonlinear mechanics had shown that a nonlinear dynamical system periodically forced with a period T could exhibit solutions with periods that are integer multiples of T . London and Yorke [83] were the first to show that the biennial fashion of CID epidemics could be simply explained by the periodic fluctuation of the contact rate. In their famous paper they considered the time series data of CIDs in New York City and Baltimore. The data were fitted by a periodically forced model with delay and showed that the resulting contact rate is essentially periodic, apart from a minor stochastic component.

London and Yorke pointed out two synergetic factors contributing to the one-year periodicity of the contact rate: (i) weather seasonality: climatic factors that might enhance the transmission of infectious diseases, such as cold weather, decreased indoor relative humidity, etc.; (ii) seasonality of ‘social behavior’ of children due to school terms. This was mirrored by ‘the sharp rise and fall in ...the mean monthly contacts for all three diseases’ investigated in [83].

It is of interest to note that the time-series analyzed in [83] were characterized by alternating large and small epidemics with a wide distribution of both the large and the small peaks. In other words the time-series qualitatively seemed to be chaotic.¹ On the contrary, the simulations obtained by the periodically filtered contact rate (see

¹ Incidentally, the term ‘chaos’ was first introduced in the literature by Yorke himself 2 years later [81].

Figure 3 of [83]) are two-year periodic for measles and one-year periodic for mumps and chickenpox. In other words, although the authors failed to link seasonality of the contact rate with chaotic time-series of CIDs (since they mainly focused on explaining the biennial alternation of large and low CID epidemics), they were nonetheless the first to obtain a seasonally varying contact rate from such data.

Stirzaker [103] was the first to employ the theory of parametric nonlinear resonance to explain the role of parametric oscillations in the induction of biennial recurrent epidemics.

However, both the models adopted by London and Yorke and by Stirzaker were peculiar in that, in absence of oscillations of contact rates, they predicted endemic prevalence for any value of the contact rate. In other words, in these models the classical disease-extinction threshold did not occur. This was pointed out by Dietz [28], who was the first to investigate the effects of one-year periodic contact rate in the classical SIR and SEIR model. He considered a periodically varying contact rate given by (we will refer to this as *Dietz's model*)

$$\beta(t) = \beta_m(1 + A \cos(\omega t)).$$

Note that the parameter A measures the degree of seasonality of the contact rate [87]. Dietz showed that a one year periodic contact rate can induce solutions with period bigger than one year. In his paper, Dietz also considered the important case of vaccination of a fraction p of newborns.

Grossman [60] applied approximated analytical methods of nonlinear oscillation theory to study the onset of subharmonic resonance in Dietz's SIR model. He obtained a threshold effect depending on the amplitude, A , of the sinusoidal perturbation of the contact rate.

Pluriannual and other patterns caused by one-year oscillations of the contact rate in Dietz's SIR and SEIR models were investigated in depth by Smith, Schwartz and Aron in 1983–1985, who first introduced the modern terminology and methods of the theory of period-doubling bifurcations.

Smith [100] employed rigorous nonlinear analysis methods developed by Hale [27,62,63] to show that at the above mentioned threshold value of A a period-two solution stems from a period-one solution via bifurcation, and that this period-two bifurcation is stable.

Quite interestingly, Smith showed in [100] the possibility of multi-stability: the coexistence of multiple locally stable periodic solutions of various integer periods, again adopting methodologies introduced by Hale et al. [24,64].

This fascinating kind of multi-stability is much more complex than the coexistence of multiple stable equilibrium points. However for Dietz's SEIR model, Smith and Schwartz [99] showed an even more complex scenario: the possible coexistence of infinite stable multi-year solutions! This allowed them to formulate the hypothesis that the irregularity of CID time series can be explained as noise-induced jumps between basins of attraction of coexisting locally attractive dynamic periodic orbits, thus resulting in a marked aperiodicity of the observations. We remind the reader that the SEIR model with constant contact rate is monostable. The analysis of the attraction basins for a case of bi-stability of Dietz's SEIR model is investigated in [98], where it is

shown that the basin of attraction of the stable solutions were strongly mixed amongst each other.

Quite interestingly, Aron [4] showed that in some cases the presence of coexistent multiple stable periodic solutions of disparate periods in Dietz's SEIR model can be triggered by the presence of vaccination of newborns.

Aron and Schwartz [5] numerically investigated Dietz's SEIR model to show the existence of pluriannual solutions. In particular, they also showed that increasing the amplitude, A , of the sinusoidal component of the contact rate, the system undergoes a series of period doubling bifurcations. Thus, they predicted that for such model a transition to chaotic solutions via a Feigenbaum cascade of such bifurcations [50, 51] was very likely. We stress here that this has been the first time that a purely deterministic mechanism was heuristically used to explain apparently stochastic behavior of CID time series.

Note that in 1984 the onset of chaotic behavior via a Feigenbaum cascade of period doubling bifurcation had been shown for the periodically forced Lotka–Volterra–Gause model by Inoue and Kamifukumoto [68].

In the same period, the early 1980s, there was an unparalleled *impetum* in the study on how to find/characterize the chaotic behavior in time series, especially with the publication of fundamental papers, such as: *Characterization of Strange Attractors* by Grassberger and Procaccia [56] (see also [11]); *Detecting strange attractors in turbulence* by Takens [106]; *The dimension of chaotic attractors* by Farmer, Ott and the pioneer of seasonality effects in epidemiology, Yorke [49]; *Determining Lyapunov exponents from a time series* by Wolf et al. [114].

These new exciting methodologies were applied by Shaffer and Kot [76, 96] to the time-series for measles in New York and Baltimore. We recall that these time-series were among those investigated by London and Yorke [83]. They obtained strong evidence of the chaoticity of these time-series. In particular, they showed the presence of a pseudo-bidimensional strange attractor, and that the Poincaré section of the attractor generated a one dimensional map flow (scalar discrete system):

$$X_{n+1} = F(X_n),$$

where $F(x) = Cxe^{-bx}$. Moreover, the resulting Liapunov exponents were positive, for both the New York city and Baltimore data sets.

Schaffer and Kot also examined data for mumps and chickenpox, heuristically showing simple dynamics affected mainly by the interplay between noise and deterministic one-year fluctuations. In a follow-up paper, they obtained similar and deeper results concerning time series of six types of CID for the city of Copenhagen [88].

At the end of the 1980s, the state of the art of the analysis of the irregular and regular fluctuations observed for CID time-series was very well summarized by Olsen and Shaffer in the abstract of their landmark 1990 paper *Chaos versus noisy periodicity: alternative hypotheses for childhood epidemics* [87]. They wrote:

Whereas case rates for some childhood diseases (chickenpox) often vary according to an almost regular annual cycle, the incidence of more efficiently transmitted infections such as measles is more variable. Three hypotheses have

been proposed to account for such fluctuations: (i) Irregular dynamics result from random shocks to systems with stable equilibria; (ii) The intrinsic dynamics correspond to biennial cycles that are subject to stochastic forcing; (iii) Aperiodic fluctuations are intrinsic to the epidemiology.

In that work they ‘read’ the CID time series by means of Dietz’s SEIR model to show that the prevalence data are inherently chaotic. Namely, they show that using epidemic parameters ‘appropriate for measles’ one can observe that: (i) the first period doubling bifurcation is observed at a threshold value close to $A = 0.2$; (ii) further increase of the degree of seasonality leads to a Feigenbaum cascade of period doubling bifurcations [50,51]; (iii) at around $A = 0.28$ the solutions are chaotic. On the contrary, adopting epidemic parameters coherent with chickenpox one gets—if the population is large enough—annual epidemics for the range $A \in (0, 0.3)$. Therefore Dietz’s SEIR model generates artificial time series closely resembling those observed in some American and European locations. The result does not sensibly change after adding stochastic perturbations to the model. Finally, they stressed that in all cases, the presence of a non-zero degree of seasonality is important to understand the studied time-series.

In the above-illustrated papers, one-parameter bifurcations of Dietz’s SEIR model were investigated, except for a non-systematic study concerning a narrow parametric subset in [5]. However, it is well-known that multidimensional bifurcation analysis is able to explain in greater detail the asymptotic behavior of a dynamical system [61].

The first work where a systematic two-dimensional bifurcation analysis of Dietz’s SEIR model was performed is [77]. They also were the first to investigate the two-parameters bifurcation scenario for Dietz’s SIR model, which exhibits strange attractors. Thus, at the best of our knowledge [77] was the first work to show that a latency period between the infection and infectivity is not necessary for an epidemic model to exhibit chaotic behavior. Moreover, by the authors showed that the bifurcation portrait is more complex corresponding to low values of the latency length of the SEIR model.

The degree of seasonality needed to trigger chaos in Dietz’s SEIR model is around 30%, which is often judged excessively large [46]. Lloyd [82] pointed out that in more realistic epidemic models, where infectious and latent times are not exponentially distributed, the level of seasonality needed to induce chaos could be different. Namely, under the assumption that epidemic parameters follow an Erlang distribution, the threshold to chaos is reduced compared to the classical Dietz’s SEIR model. Moreover, another factor that can trigger, at low levels of seasonality, chaotic behavior is the presence of extrinsic noise, as showed by Billings and Schwartz in [12].

A somewhat inverse approach, compared to all the above-summarized bifurcation studies, has been adopted in [58], where mean value and seasonality degree of the contact rate are fixed and the bifurcation parameter is the period of the sinusoidal oscillations. The CID time-series used by many authors concerned a relatively limited time range of some decades of the 20th Century. Much longer historical time series for CID and smallpox were analyzed by Duncan, Duncan and Scott in a series of interesting works that we could define as ‘historical epidemiology’ [40–45]. In these works Dietz’s SIR and SEIR models were fit to long time-series and important epidemiological inferences were proposed.

Note that the first rigorous proof of the existence of chaos in an epidemic model, obtained by applying Melnikov method [61, 113], was proposed by Glendinning and Perry [55] for a SIR model with a nonlinear force of infection of the type $F = \beta(t)I^2$. To the best of our knowledge, a formal proof showing the existence of chaos for Dietz's classical SIR and SEIR models is still missing. Moreover, in the analysis of [55], the authors set a very sharp constraint, i.e. that 'the timescales for infection, recovery and reproduction are all of the same order of magnitude'.

3 The decline of the 'sinusoidal age'

In 1984, Schenzle [97] studied the comparison of pre-vaccination and post-vaccination eras in measles transmission. He introduced both age and time heterogeneity in the contact rate. The most interesting feature of this work is that the components of the contact rate matrix $\beta(a_1, a_2; t)$ do not evolve sinusoidally as assumed in the previous literature, but in a periodic piecewise constant fashion. This assumption was based on the key idea that the main temporal heterogeneity for CID is induced by the alternation of school terms and school holidays. This led Schenzle to model $\beta(a_1, a_2; t)$ as follows:

$$\beta(a_1, a_2; t) = \beta_0(a_1, a_2) + H(t)\beta_1(a_1, a_2),$$

where $H(t)$ is the indicator function of the school terms, i.e. $H(t) = 1$ when the schools are open, and $H(t) = 0$ during holidays. Thus $\beta(a_1, a_2; t)$ passes from the low value $\beta_0(a_1, a_2)$ during the holidays to a larger value $\beta_0(a_1, a_2) + \beta_1(a_1, a_2)$ during the school terms.

Thus, the problem of modeling the influence of school calendar in a realistic way was set, and some works appeared that took into account the relevance of this topic. For example in 1988, Kot et al. [76] proposed a non-sinusoidal continuous version of the contact rate given by

$$\beta(t) = \beta_0(1 + \beta_1\phi(t)),$$

where the degree of seasonality,

$$\phi(t) = \frac{0.68 + \cos(\omega t)}{1 + (2/3)\cos(\omega t)},$$

was chosen to model 'more accurately...asymmetries in the school year' than sinusoidal functions.

The interest for Schenzle's approach to modeling the periodic fluctuations of the contact rate was revived thanks to the paper [46] where a simple two state Schenzle-like contact rate in a SEIR model was used (in conjunction with data on birth rates) to explain a number of features of interest observed in the time-series of measles in some large cities in the UK and USA. First, from the theoretical point of view, the degree of seasonality necessary to induce chaos was shown to be smaller for the two-state $\beta(t)$ compared to its sinusoidally varying version. Second, the authors showed

that for a relatively small average value of β (denoted by $\langle\beta\rangle$) many periodic solutions coexist, whereas for large average values only few coexisting periodic solution are predicted. Moreover, for small $\langle\beta\rangle$ the basins of attraction of the various coexisting stable solutions are strongly mixed, whereas for large $\langle\beta\rangle$ the basins are quite well distinct. Finally, for even larger values of $\langle\beta\rangle$ there is a unique periodic solution. These findings allowed the authors to explain the transitions observed in the above mentioned time series. For example, in London time series the transition from biennial to seemingly erratic time series is explained as a transition from a phase (in the pre vaccination age) where $\langle\beta\rangle$ was large to a post-vaccination introduction phase with a smaller $\langle\beta\rangle$. This can lead to a much richer and complex dynamics due to noise-induced jumps between the multiple coexisting periodic solutions of disparate periods. Similar analysis was adopted to explain the data from Liverpool. An inverse pattern was observed in New York, and explained by means of the proposed mathematical model. In [72] the simulations of [46] were semi-analytically explained as the result of switching between two nonlinear sinks corresponding to the two values of β , and each one has its own distinct pseudo-period. The effect of possible intrinsic and environmental stochasticity was also investigated. Further analytical inferences, and their applications, were also investigated in [104].

Moreover, adopting the Schenzle-like two state $\beta(t)$ in a meta-population SEIR model, the same group of authors was able to mimic the transition from spatial synchrony to asynchrony in the dynamic of measles in UK cities [93].

It is of interest to stress that for whooping cough, the time series cannot be well fit by deterministic models, whereas a stochastic birth-death model with one-year periodic contact rate obtains much better performances [72,94], again confirming the importance of the non-constancy of the contact rate.

Recently, the onset of chaos in the SIR model forced by the two-values β has been analytically shown in [9]. That work stresses the relevance of the opposition between small mortality/birth rate and the large recovery and transmission rate. Namely, the main results of [9] are obtained by assuming that the mortality/birth rate scales as a small parameter ε and the recovery and transmission rate scales as $1/\varepsilon$.

4 Going beyond both sinusoidal and two-valued contact rates

Both the above mentioned approaches in modeling the contact rate $\beta(t)$ have their pros and cons. Dietz's approach consisting in modeling $\beta(t)$ plus a more or less large sinusoidal perturbation is simple and parsimonious. Indeed, the nonlinear system might work to some extent as a nonlinear filter, which could clear out the harmonic of order greater or equal to two. However, one could argue that its continuous nature does not take into account the sudden decrease/increase of contacts between school pupils, which are linked to the alternation of school terms and holidays. This alternation may seem more adequately modeled by a piecewise continuous $\beta(t)$.

On the other hand however, we stress that modeling the contact rate in the latter way, the long periods during which β is constant do not take into account the influence of the weather and of other continuously varying factors. Moreover, a discontinuity in the contacts is maybe realistic when modeling the changes of the infection risk for a single

pupil or workers, but it far less realistic at population level, so that a continuous model of the contact rate is more appropriate. For example: (i) in many countries such as Italy the school calendar is not uniform but it is region-dependent; (ii) in many countries there are remarkable differences between the school and the work calendars, as in France where pupils and their teachers have frequent 2 weeks holidays; (iii) in modern times in large-income countries the holidays of the workers are totally asynchronous; (iv) in many low- and middle- income countries many workers have no holidays at all (which in the past worldwide occurred), or very short and, again, asynchronous. Note that points ii–iv are of the utmost relevance to model childhood infectious diseases since they also affect adults. To summarize, both kind of modeling of the one year periodic fluctuations of the contact rate are good but not fully satisfactory.

As a consequence, two complementary approaches are important. In the first, one considers generic forms for the contact rate. This approach is particularly important to understand how seasonality can impact the stability of the disease free state of an epidemic model. The second approach, instead, consists in finding which contact rate is able to optimally fit given epidemiological data. The latter approach has until now mainly focused on endemic time heterogeneous states, for which data are most frequently available.

4.1 Role of seasonality in the stability of the disease-free state

The global asymptotic stability (GAS) of the disease-free equilibrium (DFE) of an epidemic model has deep public health implications since it means that a disease that is self-extinct or has been eliminated by means of an appropriate control strategy cannot become endemic, even if it should happen a very large epidemic outbreak. If vaccination campaign has been enacted, this circumstance can also be seen as the best sign of the robustness of the adopted strategy. In case of constant contact rate, it is well known that the GAS of the DFE is ruled by the a function of the system parameter termed basic reproduction number, usually denoted as \mathcal{R}_0 . If $\mathcal{R}_0 \leq 1$, then the DFE is GAS. Otherwise, if $\mathcal{R}_0 > 1$, then the DFE is unstable.

Of course, even in the case of seasonally varying β , the assessment of the stability of DFE remains of utmost relevance, but it is far less trivial. Some theoretical works do not set assumptions at all on the ‘shape’ of $\beta(t)$, apart from its positivity, boundedness and periodicity. The first to adopt this quite general approach has been Herbert Hethcote. In his pioneering work on the susceptible-infectious-susceptible (SIS) model with periodic contact rate [66], he was the first to stress the role of (using contemporary words) the average instantaneous basic reproduction number (AIRBN). Given an epidemic model, the AIRBN is formally equal to the \mathcal{R}_0 of the constant coefficient model computed by using the average contact rate. In [66] it is shown that if AIRBN ≤ 1 then the DFE of the SIS model with periodic contact rate is GAS, whereas if AIRBN > 1 the disease remains endemic and exhibits periodic oscillations.

The AIRBN also determines the global stability of the DFE in the SIR and SIRS model under generic periodically varying contact rates. If this average is smaller than one, then the DFE is GAS, otherwise the disease remains endemic and is uniformly persistent. This is a consequence of a more general theorem by Thieme [108,109]

on the qualitative behavior of the SIRS models with very general time-heterogeneous coefficients. Similar GAS conditions for the DFE of the periodic SIR model hold in case of presence of behavior-dependent contact rates [35], pulse vaccination strategies [31], and behavior-dependent voluntary vaccinations [36–38].

For diseases described by multiple epidemic states and/or multiple population subgroups, the AIRBN no longer determines the GAS of the DFE in the general case. For such models, the scenario is often slightly more complex. For example, Aronsson and Mellander investigated the qualitative behavior of the multi-group SIS model for gonorrhoea of [78] in case of a periodic contact rate [6]. They showed that the GAS of the DFE of that model is ensured provided that the dominant eigenvalue of the Floquet matrix associated with the DFE (FMDFE) is inside the unit circle in the complex plane. If this condition does not hold, then the system is globally attracted by a unique periodic solution, with period equal to that of the contact rate. These two results were used in [34] to investigate the global behavior of certain linear and non-linear contact network-based epidemic models.

The behavior of the FMDFE also determines the GAS of the disease-elimination state of SEIR diseases with periodic contact rates in cases with pulse vaccination strategies [30] or voluntary behavior-dependent vaccinations [18]. Note that for the particular case without vaccination, these results imply the GAS of the DFE of the standard SEIR model.

Recently, in [16] the GAS criterion for the DFE of an SEIR model with behavior-dependent vaccination and a periodic contact rate has been numerically compared with the GAS criterion of a model with a constant contact rate. The result (for both the cases of Dietz and two-values contact rate $\beta(t)$) is that the larger the amplitude of the oscillations, the more likely the GAS condition is fulfilled. This apparently paradoxical phenomenon is explained in [16] as a beneficial effect of the phase when the contact rate is under its average value: the reduction of contact rate (for example during holidays) under its annual average over-compensates for its increase during periods of intense contacts.

It is worth of note that in all the works mentioned in this section, the GAS condition for the DFE coincides with its local asymptotic stability (LAS) condition. Thus it is of interest to stress that the LAS of the DFE of a general family of epidemic models with periodic coefficients has been investigated by Heesterbeek and Roberts in [65]. They showed the role for LAS of the FMDFE, and stressed the importance of generalizing the concept of Basic Reproduction Number to non-autonomous epidemic systems.

The computation of the FMDFE can be rarely conducted analytically, with a remarkable exception stressed in [111]: the two values contact rate. Indeed, in such a case the FMDFE is equal to the product of two exponential matrices. The generalization to more complex patterns of N -values contact rates can also easily handled.

For the SEIR model, it has been shown in [111] that the linearized equation at the DFE is equivalent to a Newton equation with damping and elastic force with a periodic elastic coefficient, which in turn can be transformed into a Hill equation [111]. In other words, the local and global stability of the DFE of the SEIR equilibrium is related to the classical mechanics problem of parametric resonance [79], as first suggested in [30]. The Hill equation can be analytically solved for some common functional forms of $\beta(t)$. For example [111]: if the contact rate is of Dietz type, then the solutions of the

Hill equation are Mathieu functions; and if it is a periodic repetition of linear functions, then the solutions are Airy functions. Finally, note that once one has analytically solved (when possible, of course) the Hill equation, one can also analytically compute the FMDFE.

For monostable epidemic models with constant contact rates, the relationships between LAS and GAS conditions for a disease-free or endemic equilibrium point most often coincide. Of course, formally proving this can be very complicated. Instead, in case of vaccination models that are multistable, for example due to the presence of backward bifurcations, the condition ensuring the GAS of the DFE is obviously different from its LAS condition. Moreover, it is also steeper, since it requires a larger vaccine uptake. If the contact rate is periodic, some examples of this scenario have been investigated in [32–34].

In [8], Bacaër and Guernaoui generalized the definition of \mathcal{R}_0 to study a periodically varying vector population in a vector-host disease model. The periodicity is included in the \mathcal{R}_0 through an integral eigenvalue problem. Later on, Bacaër extended this approach and presented additional numerical methods for computing the \mathcal{R}_0 , including the use of Floquet theory for linear ordinary differential equations with periodic coefficients [7].

The general definition of \mathcal{R}_0 in a periodic environment given in [8] has been employed by Wang and Zhao [112] to establish the \mathcal{R}_0 for a large class of periodic compartmental epidemic models. They showed that it is a threshold parameter for the LAS of the disease-free periodic solution (and even for the global dynamics in certain cases).

The class of seasonally forced epidemiological models considered in [112] has been then studied by Bacaër et al. [92] who found several results about the persistence of the disease. Following [54], they used an approach based on average Lyapunov functions to find conditions which guarantee persistence of infected individuals when $\mathcal{R}_0 > 1$. They also found suitable conditions ensuring that the disease dies out if $\mathcal{R}_0 < 1$.

The investigation of conditions ensuring the *uniform persistence* [92, 109, 116] of a given disease in a periodic environment has been the subject of a number of other studies including different epidemiological aspects as latency time, patchy environment, human behavior changes, etc. (see for example, [16, 86, 115]).

4.2 In search of contact rates coherent with epidemiological data

Here we review results obtained in statistical literature on the fitting of the contact rate of epidemic models to epidemiological data.

Of course there are some works where the authors consider a pre-established parameterized model of $\beta(t)$ that depends on few parameters. For example, in [25] the contact rate was assumed to be in Dietz’s form $\beta(t) = \beta_0(1 + \beta_1 \cos(\omega t - \phi))$, which depends on three parameters; in [48], the authors investigated an SEIR model with the above-described two-parameters contact rate, $\beta(t) = \beta_0(1 + \beta_1 \phi(t))$, introduced in [76]. Thus in practice in this type of analysis, the chosen quantitative [25] or semi-qualitative [48] measures of deviation between model outputs and the (real or simulated) disease

time-series is a function of few parameters. The minimization of this function fully determines the contact rate.

In other articles, along the lines outlined by the theoretical works reviewed in Sect. 4.1, no a priori hypotheses on $\beta(t)$ are made (apart from, of course, positivity and boundedness), see e.g. [26, 71, 83, 107]. It is noteworthy that this was the approach originally adopted by London and Yorke [83]. Thus in theory, it is the whole function $\beta(t)$ that ought to be determined by optimization. Of course, in practice, often one discretizes the function as a piecewise-constant [26, 107] or piecewise-linear [83] function or one adopts a truncated Fourier series [26].

An alternative approach has been followed in [91], where no hypotheses were formulated on the contact rate, but cumulative cases were fit to a parameterized function.

Recently, one of the most active research groups in the statistical inference of the seasonality of the contact rate is that of Grenfell and his colleagues. In [13, 53], the data on measles collected in the pre-vaccine age in England and Wales was fit to a time-series-like discrete epidemic model with a time-varying transmission rate (the TSIR model [13, 53]). They showed that although the fitted transmission rate showed a decrease during the holidays terms and an increase with the starts of the school terms, the behavior of $\beta(t)$ is substantially different from a piecewise constant contact rate. In particular: (i) during the school terms the contact rate is not constant and it is non-monotone; and (ii) the transmission rate begins to grow in the last days of holidays.

In [85], the authors investigated the impact of seasonality on dynamics of six infectious diseases by using data of the ‘pre-vaccinated era’ in the city of Copenhagen. Although the fitted average age of infection with measles was in the range of schooling ages, they obtained substantial discrepancies with respect to the model ‘alternating school terms/holidays’. For example, the fitted contact rate for the three major bacterial childhood infections (pertussis, scarlet fever and diphtheria) exhibits large increases during the summer vacations (see Figure 3, right panel, in [85]). Increases of $\beta(t)$ during the summer were also obtained for measles, mumps and varicella (see Figure 3, left panel, in [85]).

Tanaka and Aihara [107] compared the phase portraits of the SIR model induced by a two values $\beta(t)$ with those generated by Metcalf’s fitting [85]. This procedure was done for values of the mortality rate and infectious period ranging in a realistic set. Interestingly, the obtained bifurcation diagrams were remarkably different.

Complex interplays between weather, non-school-related social phenomena and space were revealed in a nation-wide investigation of seasonality in measles transmission in Nigeria by Ferrari et al. [52], who adopted a TSIR meta-population model. As far as weather is concerned, the analyzed data suggested that the contact rate is consistently in anti-phase to the rainfall patterns across the country, but it is not correlated with the longitudinal gradient that the rainfall patterns show. A positive correlation between the degree of seasonality of population size of the cities was found. These results are in agreement with the local phenomenon of agricultural cycles, which causes internal temporary migrations from urban areas to countryside during rainy seasons.

The influences of rainfalls and temperature on smallpox spread in London between 1708 and 1748 were investigated in [39], where (in the framework of an SEIR model

with disease specific fatalities) the authors assumed a linear relationship between the contact rate $\beta(t)$, the temperature $T(t)$, and rain $\rho(t)$ time series:

$$\beta(t) = \beta_0 + \beta_T T(t) + \beta_\rho \rho(t) + w(t),$$

where $w(t)$ is a white noise. Data fitting was obtained by applying nonlinear stochastic filtering theory [70]. In agreement with biological intuition, the fitted values of β_T was positive whereas the fitted value for β_ρ was negative.

Although the assumption of periodic contact rates may be useful and enlightening, in [39, 52] it was shown that this assumption is a rough idealization. Real phenomena mix one-year periodic ‘social’ component to other components that may be stochastic and/or chaotic.

5 Role of seasonality in vector-borne diseases

Mathematical modeling of vector-borne diseases began in the early 20th Century with Ronald Ross’ autonomous ordinary differential equation model of malaria transmission [95]. A major extension of this model that included immunity dynamics in humans and seasonality in vector population densities was the Garki model [29]. Unlike the models for childhood infectious diseases, this difference equation model allowed for arbitrary patterns of seasonality. The authors fit the seasonal pattern of mosquito densities to empirical data from Nigeria on the number of mosquito bites per person per day, allowing them to capture realistic patterns of transmission. Although the authors did not perform much mathematical analysis of this complicated periodically-forced nonlinear model, they validated it against data and used it to determine the effectiveness of two control interventions (spraying houses with insecticides to kill mosquitoes and mass administration of antimalarial drugs to humans) in reducing prevalence and achieving elimination.

As mentioned in Sect. 4.1, Bacaër et al. [7, 8] conducted a more mathematical treatment of the analysis of the impact of seasonality on thresholds for the stability of the disease-free equilibrium, such as the basic reproductive number. Bacaër and Guernaoui derived a compartmental population-based model of a vector-borne disease with a periodically varying vector population [8]. They fit the model parameters to data on cutaneous leishmaniasis from Morocco and numerically evaluated \mathcal{R}_0 through a discretization to show that the epidemic could be stopped if the vector population was reduced by a factor of four. Bacaër extended this approach and presented additional numerical methods for computing \mathcal{R}_0 , using the 2005–2006 chikungunya epidemic in La Réunion as an example [7].

More recent analysis of vector-borne diseases has also shown (the co-existence of different) multi-year epidemic peaks, as had been earlier shown for measles [46]. Chaves and Pascual fit case data of cutaneous leishmaniasis from Costa Rica to various climate predictors to show the existence of approximately three year cycles that are coherent with temperature and El Niño Southern Oscillation indices cycles [21]. Childs and Boots analyzed a malaria model with acquired immunity and periodically varying

mosquito population (with a period of one year) to show the existence of multi-year cycles, that they were able to match to case data from Kenya [22].

Hoshen and Morse developed a model of malaria transmission that included the effects of climate (temperature and rainfall) on mosquito dynamics [67]. They did not analyze it for periodic dynamics, but forced it with results of climate models to develop a full non-autonomous non-periodic model that captured patterns of malaria transmission across various locations in Africa. Tompkins and Ermert similarly developed a model that included the impact of climate and population density on malaria transmission [110]. In addition to forecasting malaria, this model was used to estimate the impact of climate change on malaria distribution [19].

The effects of seasonality in vector-borne disease has also been investigated in connection with disease control. Several recent studies have focused on determining optimal strategies to control/contrast vector-borne diseases in the presence of seasonality. The main mathematical tool used in these studies is optimal control theory [3,80]. In [17], optimal bed-net usage for a dengue disease model with seasonally varying mosquito densities was investigated. One of the main results is that in the presence of oscillations in vector birth rate, when the amplitude of seasonal force is low or moderate, the insecticide spraying results to be very effective in reducing the disease prevalence, both used alone or in combination with personal protections as bed-nets. However, control effects appear to be negligible in regions where there is a clear distinction between the wetter and drier months. Dengue fever has been also targeted in [75], where a two-patch non-autonomous model has been studied to investigate the effects of human movement and seasonality on preventive control interventions such as mosquito repellents, reduction of the impact of vector breeding grounds, and education campaigns to increase personal protection. The optimal use of mosquito reduction strategies and personal protection has also been studied for the case of West-Nile virus model with seasonality in [1].

Individual-based models have increasingly been developed since 1990, with the increasing availability of computational power. Plaisier et al. [89] developed one of the first individual-based models to simulate the transmission and control of onchocerciasis. Since then, a plethora of individual-based models for vector-borne diseases have been developed, primarily for malaria [23,47,59,101], but also for dengue [84]. These models can incorporate multiple dimensions of seasonality, including vector population densities, mosquito feeding frequencies, deployment of control interventions, and even the seasonal movement of humans (for farming or forest work). Although it is difficult to analyze these models mathematically, simulations of ensembles of models with multiple random seeds and parameter values can provide uncertainty estimates for predictions to help guide policy makers.

6 Conclusions

The periodicity of the contact rate, i.e. its time-heterogeneity due to social and weather-related factors has been and is one of most fruitful fields of mathematical and computational epidemiology. Many systematic reviews exist; therefore, we followed the line of providing a highly personal non-systematic review of this topic,

with the aim of stressing some issues that are less reported in previous reviews, and providing a personal view of other better known issues.

Finally, we stress that although less work has been published on the impact of time-heterogeneity of other parameters, a review dedicated to this topic is needed.

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