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Genealogy with seasonality, the basic reproduction number, and the influenza pandemic

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Abstract The basic reproduction number R_0 has been used in population biology, especially in epidemiology, for several decades. But a suitable definition in the case of models with periodic coefficients was given only in recent years. The definition involves the spectral radius of an integral operator. As in the study of structured epidemic models in a constant environment, there is a need to emphasize the biological meaning of this spectral radius. In this paper we show that R_0 for periodic models is still an asymptotic per generation growth rate. We also emphasize the difference between this theoretical R_0 for periodic models and the “reproduction number” obtained by fitting an exponential to the beginning of an epidemic curve. This difference has been overlooked in recent studies of the H1N1 influenza pandemic.

Keywords Basic reproduction number · Seasonality · Epidemics · H1N1 influenza

Mathematics Subject Classification (2000) 92D25 · 92D30

1 Introduction

Let us first recall briefly a few things concerning the basic reproduction number R_0 in a constant environment (Diekmann and Heesterbeek 2000). Consider a structured population with m “types” of infected people. Let $J_i(t)$ be the number of *new* infections of type i ($1 \leq i \leq m$) per unit of time at time t, what epidemiologists call

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the incidence (not to confuse with the number of infected people). Let $J(t)$ be the vector $(J_1(t), \dots, J_m(t))$. Many epidemic models lead after linearisation near the disease-free steady state to a system of renewal equations of the form

$$J(t) = \int_0^{t-t_0} K(\tau)\, J(t-\tau)\, d\tau + H(t)\ , \quad (t \geq t_0), \tag{1}$$

where $H(t)$ is a given vector function depending on initial conditions and $K(\tau)$ is a nonnegative square matrix. The basic reproduction number R_0 is then defined as the spectral radius of the next-generation matrix $\mathcal{K} = \int_0^\infty K(\tau)\, d\tau$. It can be interpreted as follows. Set

$$J(t) = \sum_{n \geq 1} J^{(n)}(t), \quad J^{(1)}(t) = H(t), \quad J^{(n+1)}(t) = \int_0^{t-t_0} K(\tau)\, J^{(n)}(t-\tau)\, d\tau,$$

where $t \geq t_0$ and $n \geq 1$. Then $J^{(n)}(t)$ is the vector of incidences belonging to generation n at time t. Let $\|G^{(n)}\|$ be the total size of generation n:

$$G^{(n)} = \int_{t_0}^{\infty} J^{(n)}(t)\, dt, \quad \|G^{(n)}\| = \sum_{i=1}^{m} |G_i^{(n)}| = \sum_{i=1}^{m} G_i^{(n)}. \tag{2}$$

As noticed in Inaba and Nishiura (2008), it follows that

$$G^{(n+1)} = \int_{t_0}^{\infty} \int_0^{t-t_0} K(\tau)\, J^{(n)}(t-\tau)\, d\tau\, dt = \int_0^{\infty} K(\tau) \int_{t_0+\tau}^{\infty} J^{(n)}(t-\tau)\, dt\, d\tau\ .$$

So $G^{(n+1)} = \mathcal{K}\, G^{(n)}$. If the matrix $\mathcal{K}$ is primitive, then it follows from Perron–Frobenius theory that $G^{(n)}/(R_0)^n$ converges to a positive eigenvector of $\mathcal{K}$ as $n \to +\infty$. So R_0 is the asymptotic per generation growth rate:

$$\lim_{n \to +\infty} \sqrt[n]{\|G^{(n)}\|} = R_0.$$

If the population structure is not a discrete set but the continuous set $(0, +\infty)$ as in some age-structured epidemic models, then the theory is very similar: R_0 is the spectral radius of a "next-generation" integral operator with a kernel $\mathcal{K}(x, y)$ and $G^{(n+1)}(x) = \int_0^\infty \mathcal{K}(x, y)\, G^{(n)}(y)\, dy$. The Krein-Rutman theorem shows that $G^{(n)}/(R_0)^n$ converges to a positive eigenfunction of the integral operator. Again R_0 is the asymptotic per generation growth rate.

Finally, if the population structure is discrete but with just one type ($m = 1$), then $G^{(n+1)} = R_0\, G^{(n)}$. In this special case, R_0 is not just the asymptotic per generation growth rate. It is also the average number of secondary cases infected by an index case.

In many applications it is more realistic to assume that the environment is periodic, e.g., because of seasonality. This is the case for most vector-borne diseases, some water-borne diseases, and some air-borne diseases such as influenza. Many periodic epidemic models lead after linearisation near the disease-free state to a system of integral equations of the form (1) but with a matrix kernel $K(t, \tau)$ that depends on t periodically. Let T be the period. In the past, it has been argued that "the concept of R_0 does not make sense in a nonautonomous setting" (Heesterbeek and Roberts 1995), that "concepts such as the basic reproductive number R_0 no longer apply" (in a periodic environment) (Grassly and Fraser 2006), or more recently that "no general method exists for calculating the basic reproduction number, the threshold for disease extinction, in nonautonomous epidemic models" (Wesley and Allen 2009). Bacaër and Guernaoui (2006) suggested nevertheless that R_0 could be defined as the unique real number such that there is a positive T-periodic continuous vector-valued function $U(t)$ satisfying

$$R_0\, U(t) = \int_0^\infty K(t, \tau)\, U(t-\tau)\, d\tau \tag{3}$$

for all t. In other words, R_0 is the spectral radius of the integral operator on the right-hand side of (3) on the space of continuous T-periodic functions. Such a definition of R_0 has been discussed in several articles. Bacaër and Guernaoui (2006) estimated R_0 for an epidemic of leishmaniasis and obtained a closed formula for R_0 in a special case. Bacaër (2007) discussed various methods to compute R_0 numerically, obtained approximate formulas for R_0 when the amplitude of seasonality is small, and estimated R_0 for an epidemic of chikungunya. Bacaër and Ouifki (2007) revisited the case where seasonality is sinusoidal, which leads to a simple characteristic equation for R_0. Wang and Zhao (2008) focused on the special case of systems of ordinary differential equations, thereby extending the method using Floquet theory introduced in Bacaër (2007) and proving rigorously some properties of R_0. Bacaër and Abdurahman (2008) studied cases of resonance, where R_0 is quite different from the value that would be obtained by averaging the model's periodic coefficients. Thieme (2009) studied R_0 for general periodic systems in ordered Banach spaces. Bacaër and Gomes (2009) proved that R_0 is still a threshold for nonlinear epidemic models in a periodic environment. Bacaër (2009) adapted the definition of R_0 to discrete-time periodic models. Nakata and Kuniya (2010) studied the link between R_0 and persistence in a particular epidemic model, following Wang and Zhao (2008).

Despite these works, definition (3) has not yet made its way into the practice of epidemic modelers, as can be seen from the recent "R_0" estimates for the H1N1 influenza pandemic (Boëlle et al. 2009; Fraser et al. 2009; Munayco et al. 2009; Nishiura et al. 2009; Pourbohloul et al. 2009). These estimates are obtained by fitting an exponential to the beginning of the epidemic curve. They do not take into account seasonality. But seasonality is certainly an important factor for influenza epidemics (Lipsitch and Viboud 2009).

In this paper we show that, as in the case of a structured population in a constant environment, R_0 defined by (3) can be interpreted in a periodic environment as an asymptotic per generation growth rate. More precisely, we shall show in Sect. 2 that if $\|G^{(n)}\|$ is again the total expected size of generation n, then

$$\limsup_{n\to+\infty} \sqrt[n]{\|G^{(n)}\|} = R_0. \tag{4}$$

Unfortunately the simple trick which led to the recurrence formula $G^{(n+1)} = \mathcal{K}\, G^{(n)}$ in a constant environment does not work in a periodic environment. So our proof of (4) relies on results for the asymptotic behavior of periodic renewal equations obtained, e.g., in Jagers and Nerman (1985), Michel et al. (2005), Thieme (1984). Whether the "lim sup" in (4) can always be replaced by "lim" is still not clear. Section 3 considers a particular epidemic model with a single type of infected people where the contact rate, the transmission probability and the recovery rate depend on time but not on time since infection: a different proof yields a more precise result with "lim" instead of "lim sup". Section 4 considers the case of discrete-time models. Section 5 emphasizes the problem of estimating R_0 for the ongoing H1N1 influenza pandemic and the fact that R_0 may be a poor predictor of the final epidemic size. Some proofs are included in two appendices.

2 The asymptotic per generation growth rate

Consider a population with m different types of infected people. Let $P_i(t,\tau)$ be the number of people of type i $(1 \le i \le m)$ at time t who have been infected for τ units of time. Assume that $P = (P_1, \ldots, P_m)$ satisfies the partial differential equation

$$\frac{\partial P}{\partial t}(t,\tau) + \frac{\partial P}{\partial \tau}(t,\tau) + B(t,\tau)\, P(t,\tau) = 0, \quad \tau > 0,\ t > t_0, \tag{5}$$

with the initial condition $P(t_0,\tau)$ for $\tau \ge 0$ and the boundary condition

$$P(t,0) = \int_0^\infty A(t,\tau)\, P(t,\tau)\, d\tau, \quad t > t_0. \tag{6}$$

The square matrices $A(t,\tau)$ and $B(t,\tau)$ are assumed to be T-periodic with respect to t and continuous. Moreover we assume that for all $1 \le i, j \le m$,

$$A_{i,j}(t,\tau) \ge 0, \quad B_{i,i}(t,\tau) \ge 0, \quad B_{i,j}(t,\tau) \le 0 \ \text{ if } i \ne j, \quad \sum_i B_{i,j}(t,\tau) \ge 0. \tag{7}$$

In other words, we are considering a multitype continuous-time branching process in a periodic environment. Introduce the matrix function $\Pi(t,t',\tau)$ such that

$$\Pi(t',t',\tau) = I, \quad \frac{\partial \Pi}{\partial t}(t,t',\tau) = -B(t,\tau+t-t')\Pi(t,t',\tau), \quad \forall t > t',$$

where $\tau \geq 0$ and I is the identity matrix of size m. If for example $m = 1$, then $\Pi(t, t', \tau) = \exp(-\int_0^{t-t'} B(t' + s, \tau + s)\, ds)$. Returning to the general case $m \geq 1$, set

$$K(t, \tau) = A(t, \tau)\, \Pi(t, t - \tau, 0), \tag{8}$$

which is T-periodic with respect to t. Assumptions (7) imply that $\Pi(t, t', \tau)$ and $K(t, \tau)$ are nonnegative matrices (Aronsson and Kellogg 1978). If M is a square matrix of size m, set

$$\|M\| = \max_{1 \leq j \leq m} \sum_{i=1}^{m} |M_{i,j}|.$$

This is the usual matrix norm corresponding to the vector norm $\|\cdot\|$ introduced in (2). We assume that there are positive constants α, β, and γ such that

$$\|A(t, \tau)\| \leq \alpha, \quad \|\Pi(t, t', \tau)\| \leq \gamma\, e^{-\beta\,(t-t')} \tag{9}$$

for all $t \geq t'$ and all $\tau \geq 0$. The following lemma recalls the definition of the Malthusian parameter in a periodic environment (Coale 1970, 1972; Jagers and Nerman 1985; Michel et al. 2005; Thieme 1984, 2009; Williams and Dye 1997). For the reader's convenience, we give in Appendix 1 a proof adapted from Jagers and Nerman (1985), Michel et al. (2005), Thieme (1984, 2009).

Lemma 1 *For all $s > -\beta$, consider the bounded linear operator*

$$L_s : V(t) \mapsto \int_0^\infty e^{-s\tau} K(t, \tau)\, V(t - \tau)\, d\tau$$

on the space $\mathcal{P}$ of continuous T-periodic functions from $\mathbb{R}^m$ to $\mathbb{R}^m$ with the norm $\|V\|_\infty = \max\{\|V(t)\|;\ t \in \mathbb{R}\}$. Let $\rho(s)$ be the spectral radius of this operator. Assume that there exists $s_0 > -\beta$ such that $\rho(s_0) > 1$. Then there exists a unique number $r > -\beta$ such that $\rho(r) = 1$. This number r is called the Malthusian parameter.

The following corollary recalls the definition of R_0 from Bacaër and Guernaoui (2006), Bacaër (2007) and its relationship with the Malthusian parameter r (Bacaër and Guernaoui 2006; Bacaër 2007; Thieme 2009).

Corollary 1 *Set $R_0 = \rho(0)$. Then $r > 0$ (resp. $r = 0$, $r < 0$) if and only if $R_0 > 1$ (resp. $R_0 = 1$, $R_0 < 1$).*

Lemma 2 *Set* $J(t) = P(t, 0)$. *Then for all* $t \geq t_0$,

$$J(t) = \int_0^{t-t_0} K(t, \tau)\, J(t - \tau)\, d\tau + J^{(1)}(t) = \sum_{n \geq 1} J^{(n)}(t), \tag{10}$$

$$J^{(1)}(t) = \int_{t-t_0}^{\infty} A(t, \tau)\, \Pi(t, t_0, \tau + t_0 - t)\, P(t_0, \tau + t_0 - t)\, d\tau\ , \tag{11}$$

$$J^{(n+1)}(t) = \int_0^{t-t_0} K(t, \tau)\, J^{(n)}(t - \tau)\, d\tau\ , \quad (n \geq 1), \tag{12}$$

$$\|J^{(n)}(t)\| \leq (\alpha\, \gamma)^n\, e^{-\beta(t-t_0)}\, \frac{(t - t_0)^{n-1}}{(n-1)!} \int_0^{\infty} \|P(t_0, \tau)\|\, d\tau. \tag{13}$$

Proof The renewal equation (10) is obtained by applying the method of characteristics to (5)–(6). Inequality (13) is true for $n = 1$ because of (9) and (11), and follows by induction from (12).

The next lemma recalls the asymptotic behavior of periodic renewal equations discussed in Coale (1970, 1972), Williams and Dye (1997), formally proved in Jagers and Nerman (1985), Michel et al. (2005) when there is a single type ($m = 1$), and formally proved in Thieme (1984, p. 261) when $m \geq 1$ but assuming that the kernel $K(t, \tau)$ given by (8) has a compact support with respect to τ ($K(t, \tau) = 0$ for τ large enough). Because the latter condition is somewhat too restrictive from a mathematical (but not biological) point of view, Appendix 2 sketches an adaptation of the proof given in Michel et al. (2005) to the case $m \geq 1$.

Lemma 3 *Assume that the total reproductive value at* $t = t_0$ *is positive* ($c > 0$ *in Lemma 7, see Appendix* 2). *Then there is a positive periodic function* $w(t)$ *such that* $\|J(t)\| \sim e^{rt}\, w(t)$ *as* $t \to +\infty$.

We arrive at our main theorem.

Theorem 1 *Introduce* $G^{(n)}$ *and* $\|G^{(n)}\|$ *as in* (2). *Then* (4) *holds.*

Proof For all $t \geq t_0$ and $R > 0$, set

$$Z^{(R)}(t) = \sum_{n \geq 1} \frac{J^{(n)}(t)}{R^n}\ .$$

Inequality (13) shows that this is always a converging series. Equation (12) and the monotone convergence theorem (for exchanging a sum and an integral) imply that

$$Z^{(R)}(t) - \frac{J^{(1)}(t)}{R} = \sum_{n \geq 1} \frac{J^{(n+1)}(t)}{R^{n+1}} = \int_0^{t-t_0} \frac{K(t, \tau)}{R}\, Z^{(R)}(t - \tau)\, d\tau.$$

So $Z^{(R)}(t)$ satisfies the periodic renewal equation

$$Z^{(R)}(t) = \int_0^{t-t_0} \frac{K(t,\tau)}{R}\, Z^{(R)}(t-\tau)\, d\tau + \frac{J^{(1)}(t)}{R} \tag{14}$$

and $Z^{(R)}(t)$ can be seen as the incidence in a population where the matrix $A(t,\tau)$ has been divided by R. The basic reproduction number associated with the kernel $K(t,\tau)/R$ is obviously R_0/R.

Assume first that $R > R_0$. Then $R_0/R < 1$. From corollary 1, the Malthusian parameter $r^{(R)}$ associated with (14) is strictly negative. From lemma 3, there exist a positive T-periodic function $w^{(R)}(t)$ such that $\|Z^{(R)}(t)\| \sim w^{(R)}(t)\exp(r^{(R)}t)$ as $t \to +\infty$. So $R > R_0$ implies that

$$\sum_{n\geq 1} \|G^{(n)}\|/R^n = \sum_{n\geq 1}\sum_{i=1}^{m} \int_{t_0}^{\infty} J_i^{(n)}(t)\, dt/R^n = \int_{t_0}^{\infty} \|Z^{(R)}(t)\|\, dt < +\infty.$$

Assume now that $R = R_0$. From corollary 1, the Malthusian parameter associated with (14) is zero. From lemma 3, $\|Z^{(R_0)}(t)\| \sim w^{(R_0)}(t)$ as $t \to +\infty$, where $w^{(R_0)}(t)$ is positive and periodic. So

$$\sum_{n\geq 1} \|G^{(n)}\|/(R_0)^n = \int_{t_0}^{\infty} \|Z^{(R_0)}(t)\|\, dt = +\infty.$$

In summary, we have shown that $1/R_0$ is the radius of convergence of the power series $\sum \|G^{(n)}\|\, z^n$. Theorem 1 then follows from the Cauchy–Hadamard theorem for power series.

Remark
- An element $V \in \mathcal{P}$ can also be seen as an element of the dual space $\mathcal{P}^*$, the "duality product" being $\langle V, W\rangle = \sum_i \int_0^T V_i(t)\, W_i(t)\, dt$. Then

  $$(L_s^* V)(t) = \int_0^{\infty} e^{-s\tau} K'(t+\tau,\tau)\, V(t+\tau)\, d\tau,$$

  where $K'(t,\tau)$ is the transpose matrix of $K(t,\tau)$. The Malthusian parameter can also be introduced by using L_s^*, as in Jagers and Nerman (1985).
- Assumption $\rho(s_0) > 1$ introduced in lemma 1 excludes cases where too many components of the matrix kernel $K(t,\tau)$ are equal to zero. If there exists $s_0 > -\beta$

such that at least one of the following two conditions holds

$$\min_{0\le t\le T}\ \min_{1\le i\le m} \sum_{j=1}^{m} \int_0^\infty e^{-s_0\tau} K_{i,j}(t,\tau)\, d\tau > 1, \tag{15}$$

$$\min_{0\le t\le T}\ \min_{1\le j\le m} \sum_{i=1}^{m} \int_0^\infty e^{-s_0\tau} K_{i,j}(t+\tau,\tau)\, d\tau > 1, \tag{16}$$

then $\rho(s_0) > 1$. Indeed let $\mathbf{1}$ be the function in $\mathcal{P}$ with all its components identically equal to 1. Let c_1 (resp. c_2) be the left-hand side of (15) (resp. (16)). We see that $L_{s_0}\mathbf{1} \ge c_1\,\mathbf{1}$ (resp. $L^*_{s_0}\mathbf{1} \ge c_2\,\mathbf{1}$). It follows that $\rho(s_0) \ge c_1 > 1$ (resp. $\rho(s_0) \ge c_2 > 1$) (Drnovšek 2000). Assumption (15) is a generalization of assumption (5.2) in Michel et al. (2005), which corresponds to $s_0 = 0$ and $m = 1$. Recall that even in Lotka's theory for single-type populations in a constant environment (Feller 1941; Lotka 1939), some condition is needed to ensure that the left-hand side of the Euler–Lotka equation $\int_0^\infty e^{-s\tau} K(\tau)\, d\tau = 1$ takes values bigger than 1 for some s.

- Recall the spectral radius formula $R_0 = \lim_{n\to\infty} \|(L_0)^n\|^{1/n}$. We can extend each $J^{(n)}(t)$ to the real line by setting $J^{(n)}(t) = 0$ for $t < t_0$. Then (12) becomes

$$J^{(n+1)}(t) = \int_0^\infty K(t,\tau)\, J^{(n)}(t-\tau)\, d\tau.$$

Given assumption (9), we can consider the right-hand side of this equation as a linear operator $\widetilde{L}_0$ in the space $L^1(\mathbb{R},\mathbb{R}^m)$ of integrable vector-valued functions with the norm $\|J^{(n)}\|_1 = \int_{-\infty}^{+\infty} \|J^{(n)}(t)\|\, dt = \|G^{(n)}\|$. Then $J^{(n+1)} = \widetilde{L}_0\, J^{(n)} = (\widetilde{L}_0)^n\, J^{(1)}$. Let $\|\cdot\|_1$ be also the norm on the space of bounded linear operators in $L^1(\mathbb{R},\mathbb{R}^m)$. So $\|G^{(n+1)}\| = \|J^{(n+1)}\|_1 \le \|(\widetilde{L}_0)^n\|_1\, \|J^{(1)}\|_1$. Let $\sigma(\widetilde{L}_0) = \lim \|(\widetilde{L}_0)^n\|_1^{1/n}$ be the spectral radius of $\widetilde{L}_0$. Then $\limsup \sqrt[n]{\|G^{(n)}\|} \le \sigma(\widetilde{L}_0)$. So even if we showed that $\sigma(\widetilde{L}_0) = R_0$—which is not obvious as the periodic functions do not belong to $L^1(\mathbb{R},\mathbb{R}^m)$—we would get only "half" of Theorem 1.

3 Special case

In this section, we consider a special case where an elementary proof shows that lim sup in (4) can be replaced by lim. Assume that $m = 1$ and that $A(t,\tau)$ and $B(t,\tau)$ do not depend on the time since infection τ. Write them $A(t)$ and $B(t)$. Assume moreover that the initial condition at $t = t_0$ consists of just one newly infected person: $P(t_0,\tau) = \delta_{\tau=0}$ (Dirac mass). Here we have

$$K(t,\tau) = A(t)\, \exp\left(-\int_{t-\tau}^{t} B(s)\, ds\right). \tag{17}$$

Bacaër and Guernaoui (2006) showed that the spectral radius of L_0 and corresponding eigenfunctions are

$$R_0 = \bar{A}/\bar{B}\ , \quad U(t) = c\, A(t)\, \exp\left[\int_{t_0}^{t} \frac{A(s)}{R_0}\, ds - \int_{t_0}^{t} B(s)\, ds\right], \tag{18}$$

where c is a constant, $\bar{A} = \frac{1}{T}\int_0^T A(t)\, dt$, and $\bar{B} = \frac{1}{T}\int_0^T B(t)\, dt$.

Lemma 4 *For all $n \geq 1$ and $t > t_0$,*

$$J^{(n)}(t) = \frac{A(t)}{(n-1)!}\left[\int_{t_0}^{t} A(s)\, ds\right]^{n-1} \exp\left(-\int_{t_0}^{t} B(s)\, ds\right). \tag{19}$$

Proof We proceed by induction. For $n = 1$, the formula follows from (11) and from our assumption on the initial condition $P(t_0, \tau)$. Assume that the formula is true for n. Then (12), (17) and (19) yield

$$\begin{aligned} J^{(n+1)}(t) &= \frac{A(t)}{(n-1)!}\left[\int_{0}^{t-t_0} A(t-\tau)\left[\int_{t_0}^{t-\tau} A(s)\, ds\right]^{n-1} d\tau\right] \exp\left(-\int_{t_0}^{t} B(s)\, ds\right) \\ &= \frac{A(t)}{n!}\left[\int_{t_0}^{t} A(s)\, ds\right]^{n} \exp\left(-\int_{t_0}^{t} B(s)\, ds\right). \end{aligned}$$

Remark Of course, we have for the total incidence

$$J(t) = \sum_{n=1}^{\infty} J^{(n)}(t) = A(t)\, \exp\left[\int_{t_0}^{t} A(s)\, ds - \int_{t_0}^{t} B(s)\, ds\right].$$

Indeed, recall from Bacaër and Guernaoui (2006) that the model of this section comes from the equation $dI/dt = A(t)\, I(t) - B(t)\, I(t)$ for the total number of infected people $I(t)$. The solution satisfying $I(t_0) = 1$ is $I(t) = \exp\left[\int_{t_0}^{t} A(s)\, ds - \int_{t_0}^{t} B(s)\, ds\right]$. The total incidence is $J(t) = A(t)\, I(t)$.

The next property gives an estimate of the size $G^{(n)}$ of generation n.

Property 1 *For all $n \geq 1$, we have*

$$(R_0)^n\, \frac{e^{-\bar{B}T}(1 - e^{-\bar{B}T})}{\bar{B}T} \leq G^{(n)} \leq (R_0)^n\, \frac{e^{\bar{B}T}(e^{\bar{B}T} - 1)}{\bar{B}T}.$$

Therefore, $\lim \sqrt[n]{G^{(n)}} = R_0$ *as $n \to \infty$.*

Proof First of all, an integration by parts gives

$$G^{(n)}=\int_{t_0}^{\infty} B(t)\,\exp\left(-\int_{t_0}^{t} B(s)\,ds\right)\left[\int_{t_0}^{t} A(s)\,ds\right]^n \frac{dt}{n!}\,.$$

The method of Laplace for the asymptotic estimation of integrals does not seem to be directly applicable here. However, we can write $G^{(n)}=\sum_{k=0}^{+\infty} H_k$, where

$$\begin{aligned}H_k &= \int_{t_0+kT}^{t_0+(k+1)T} B(t)\,\exp\left(-\int_{t_0}^{t} B(s)\,ds\right)\left[\int_{t_0}^{t} A(s)\,ds\right]^n \frac{dt}{n!}\\ &= \int_{0}^{T} B(t_0+\theta)\,\exp\left(-\int_{t_0}^{t_0+kT+\theta} B(s)\,ds\right)\left[\int_{t_0}^{t_0+kT+\theta} A(s)\,ds\right]^n \frac{d\theta}{n!}\\ &= e^{-k\bar{B}T}\int_{0}^{T} B(t_0+\theta)\,\exp\left(-\int_{t_0}^{t_0+\theta} B(s)\,ds\right)\left[k\bar{A}T+\int_{t_0}^{t_0+\theta} A(s)\,ds\right]^n \frac{d\theta}{n!}.\end{aligned}$$

It follows that $e^{-k\bar{B}T}\,F_k \le H_k \le e^{-k\bar{B}T}\,F_{k+1}$, where

$$F_k=\int_{0}^{T} B(t_0+\theta)\,\exp\left(-\int_{t_0}^{t_0+\theta} B(s)\,ds\right)\left[k\bar{A}T\right]^n \frac{d\theta}{n!}=\frac{(k\bar{A}T)^n}{n!}(1-e^{-\bar{B}T}).$$

Since $F_0=0$, we get $\sum_{k=1}^{+\infty} e^{-k\bar{B}T}\,F_k \le G^{(n)} \le e^{\bar{B}T}\sum_{k=1}^{+\infty} e^{-k\bar{B}T}\,F_k$. But

$$e^{-\bar{B}T}\int_{k-1}^{k} e^{-\theta\bar{B}T}\,\theta^n\,d\theta \le e^{-k\bar{B}T}\,k^n \le e^{\bar{B}T}\int_{k}^{k+1} e^{-\theta\bar{B}T}\,\theta^n\,d\theta.$$

Using that $\int_0^\infty e^{-\theta\bar{B}T}\,\theta^n\,d\theta = n!/(\bar{B}T)^{n+1}$, we get

$$e^{-\bar{B}T}\,\frac{n!}{(\bar{B}T)^{n+1}} \le \sum_{k=1}^{+\infty} e^{-k\bar{B}T}\,k^n \le e^{\bar{B}T}\,\frac{n!}{(\bar{B}T)^{n+1}}.$$

Property 1 follows from these estimates.

Remark The special case of this section has another interesting property, which follows immediately from (18) and (19): for all $t > t_0$,

$$Z^{(R)}(t) = \sum_{n\geq 1} \frac{J^{(n)}(t)}{R^n} = \frac{A(t)}{R} \exp\left[\int_{t_0}^{t} \frac{A(s)}{R}\, ds - \int_{t_0}^{t} B(s)\, ds\right]. \qquad (20)$$

In particular, $Z^{(R_0)}(t)$ is one of the eigenfunctions $U(t)$ of (3), corresponding to (18) with $c = 1/R_0$.

4 Discrete-time periodic models

The results and proofs in Sect. 2 can obviously be adapted to periodic discrete-time population models (Bacaër 2009). Let $P(t)$ be a vector of size ω, where the entries can represent different times since infection and different types. Assume that $P(t+1) = M(t)P(t)$ for all $t \geq t_0$, with $M(t) = A(t) + B(t)$, $A(t+T) = A(t)$ and $B(t+T) = B(t)$. Assume that $A_{i,j}(t) \geq 0$, $B_{i,j}(t) \geq 0$, $\sum_i B_{i,j}(t) \leq 1$, and that the spectral radius of the matrix $B(T-1)B(T-2)\ldots B(0)$ is strictly less than 1. Assume (so as to simplify the asymptotic behavior of $P(t)$) that the matrix $M^*(t_0) = M(t_0+T-1)M(t_0+T-2)\ldots M(t_0)$ is primitive and that

$$\begin{pmatrix} 0 & 0 & \cdots & 0 & M(T-1) \\ M(0) & 0 & \cdots & 0 & 0 \\ 0 & M(1) & \ddots & 0 & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & M(T-2) & 0 \end{pmatrix} \qquad (21)$$

is irreducible. In fact, Berman (1979, Theor. 2.2.33) says that if matrix $M^*(t_0)$ is irreducible (in particular if it is primitive) and if (21) has no zero rows or columns, then (21) is irreducible. For $t \geq t_0$, set

$$K(t,1) = A(t), \quad K(t,\tau) = A(t)B(t-1)B(t-2)\cdots B(t-\tau+1), \quad (\tau \geq 2),$$

$$J^{(1)}(t) = K(t, t-t_0+1)P(t_0), \quad J^{(n+1)}(t) = \sum_{\tau=1}^{t-t_0} K(t,\tau)\, J^{(n)}(t-\tau), \quad (n \geq 1),$$

$$G^{(n)} = \sum_{t=t_0}^{\infty} J^{(n)}(t), \quad \|G^{(n)}\| = \sum_i G_i^{(n)}.$$

Following Bacaër (2009), let R_0 be the spectral radius of the matrix

$$\begin{pmatrix} A(0) & 0 & \cdots & 0 \\ 0 & A(1) & \ddots & \vdots \\ \vdots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & A(T-1) \end{pmatrix} \begin{pmatrix} -B(0) & I & 0 & \cdots & 0 \\ 0 & -B(1) & I & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & & \ddots & \ddots & I \\ I & 0 & \cdots & 0 & -B(T-1) \end{pmatrix}^{-1}$$

where I stands for the identity matrix. Assume that $P(t_0) \neq 0$. Then a simple adaptation of the proof in Sect. 2—replacing integrals by sums—shows that R_0 is the asymptotic per generation growth rate: formula (4) still holds.

5 R_0 and the H1N1 influenza pandemic

One of the simplest model for the H1N1 influenza pandemic taking seasonality into account is the SIR model

$$\frac{dS}{dt} = -a(t)\, S(t)\, I(t), \quad \frac{dI}{dt} = a(t)\, S(t)\, I(t) - b\, I(t), \quad \frac{dR}{dt} = b\, I(t), \tag{22}$$

where $a(t)$ has a period $T = 1$ year and where $1/b$ is the mean infectious period (Bacaër and Gomes 2009). $S(t)$ is the fraction of susceptible people, $I(t)$ the fraction of infected people, and $R(t)$ the fraction of people who have recovered and are immune. Hence, $S(t) + I(t) + R(t) = 1$ for all t. Mortality is neglected in this model. Given the introduction of a few infected cases at some time t_0 so that $S(t_0) = 1 - \varepsilon$, $I(t_0) = \varepsilon$, and $R(t_0) = 0$, one of the main goals of epidemic modeling is to try to predict the final size $R(\infty) = \lim_{t\to\infty} R(t)$ of the epidemic.

In a constant environment (with $a(t) = a$ independent of t), Kermack and McKendrick (1927) found a simple relation between $R_0 = a/b$ and $R(\infty)$. The final size $R(\infty)$ is an increasing function of R_0, it is independent of t_0, and it varies very little with ε if ε is small enough. Moreover, R_0 can be estimated by fitting an exponential to the beginning of the epidemic curve. The initial growth rate is equal to $r = a - b$. Knowing the average infectious period $1/b$, one can compute $R_0 = 1 + r/b$. Because of these properties, R_0 has become very popular among epidemic modelers. Of course there are many complicating factors (inhomogeneous population, interventions…) which are responsible for the fact that, in practice, mathematical models have rarely been successful at forecasting the final size of an epidemic.

Returning to system (22) with a periodic $a(t)$, one can still fit an exponential to the beginning of the epidemic curve. This is the method used in Boëlle et al. (2009), Fraser et al. (2009), Munayco et al. (2009), Nishiura et al. (2009), Pourbohloul et al. (2009) for the H1N1 influenza pandemic. This method makes sense because the fitting is done with 1 or 2 months of epidemic data and because the seasonal function $a(t)$ (whose period is one year) varies little on such a time scale. The growth rate is then approximately $a(t_0) - b$ and $a(t_0)/b$ is the so-called "reproduction number" estimated in the references above. Because these references did not consider explicitly the effect of seasonality, some of them used the notation R_0 for $a(t_0)/b$. As an example, Fraser et al. (2009) estimated that $a(t_0)/b$ was in the range 1.4–1.6. For system (22), we have in fact $R_0 = \bar{a}/b$ where $\bar{a}$ is the average of $a(t)$. Indeed, linearizing system (22) near the disease-free steady state ($S = 1, I = 0, R = 0$), we see that $dI/dt = a(t)\,I(t) - b\,I(t)$. This is precisely the case considered in Sect. 3 but with a constant b.

At this point, one may wonder what are the advantages and disadvantages of emphasizing $a(t_0)/b$ instead of $R_0 = \bar{a}/b$, as done in the H1N1 influenza studies already cited. On one side, $a(t_0)$ has the advantage of being easily estimated from epidemic data. In comparison, the estimation of $R_0 = \bar{a}/b$ would require the a priori knowledge of $a(t_0)/\bar{a}$, for which we have in fact very little information. But on the other side, R_0 has precise mathematical properties: Bacaër and Gomes (2009) showed that R_0 serves as a threshold for system (22) and the present paper shows that R_0 is an asymptotic per generation growth rate of the linearized equations near the disease-free steady state.

Both $a(t_0)/b$ and $R_0 = \bar{a}/b$ do not seem to be good predictors of the final epidemic size even for relatively small levels of seasonality. Consider for example the case where $a(t) = \bar{a}(1+e\cos(\omega t))$, $\omega = 2\pi/T$, $T = 1$ year, $b = 100$ per year (so that the infectious period $1/b$ is between 3 and 4 days). Assume that $R_0 = \bar{a}/b = 1.5$, which is supposed to be a typical value for the H1N1 influenza pandemic (Fraser et al. 2009). Assume moreover that $\varepsilon = I(t_0) = 10^{-4}$: one case is introduced in a homogeneously mixing population of 10,000. Notice that the calendar time t has been set so that $a(t)$ reaches its maximum when $t = 0$. So t_0 refers to the time elapsed since then.

Figure 1 shows some level curves of the final epidemic size $R(\infty)$ ($R(\infty) = 0.5, 0.7, 0.9$) when we vary the time t_0 of introduction of the first infected case ($0 \le t_0 \le T$, horizontal axis) and the level e of seasonality ($0 \le e \le 1$, vertical axis). Depending on the choice of (t_0, e), the final size varies from 38 to 94%. Let us emphasize that these different values of $R(\infty)$ correspond to the same value of R_0. On the horizontal axis $e = 0$ (no seasonality), the final size $R(\infty)$ is of course independent of t_0: $R(\infty) = 58\%$. For $e = 5\%$, the final size ranges from 53 to 63% depending on t_0. For $e = 10\%$, it ranges from 48 to 67%. For $e = 15\%$, it ranges from 42 to 70%. So even relatively small levels of seasonality have a significant impact on the final epidemic size.

Figure 2 shows some level curves of $a(t_0)/b$ ($a(t_0)/b = 0.5, 1, 1.5, 2, 2.5$), the so-called "reproduction number" that can be estimated by fitting an exponential to the beginning of an epidemic curve, when we vary the time t_0 of introduction of the first infected case ($0 \le t_0 \le T$, horizontal axis) and the level e of seasonality ($0 \le e \le 1$, vertical axis) as in Fig. 1. It appears that $a(t_0)/b$ can also be a poor predictor of the final epidemic size. The most striking case occurs for $t_0/T = 0.5$ and $e = 1$. In that case, $a(t_0)/b = 0$ (see Fig. 2) but $R(\infty) = 93\%$ (see Fig. 1).

Real life estimates of the amplitude e of seasonality are difficult to obtain. Dushoff et al. (2004) suggested that a low $e = 4\%$ was enough to explain influenza seasonality but their endemic model required a special choice of parameter values to get some resonance phenomenon. Cauchemez et al. (2008) estimated that winter school breaks reduced transmission to children by about 25%, suggesting that $a(t)$ may exhibit large variations. Shaman and Kohn (2009) recently found a strong correlation between vapor pressure and transmission of influenza among guinea pigs. Given the monthly

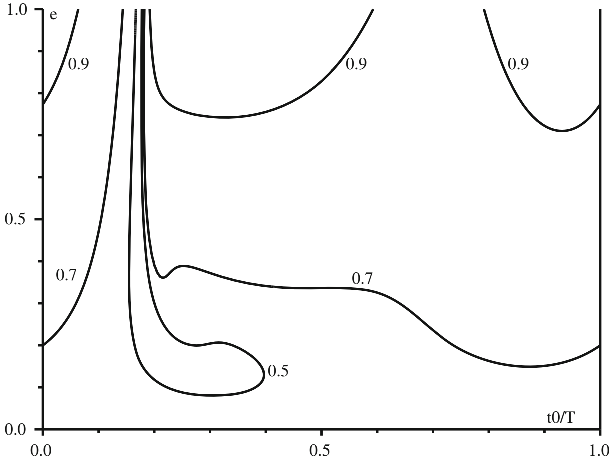

Fig. 1 Level curves of the final epidemic size $R(\infty)$ when the time t_0 of introduction of the first infected case (*horizontal axis*) and the level e of seasonality (*vertical axis*) vary. In all this diagram, we have $R_0 = 1.5$

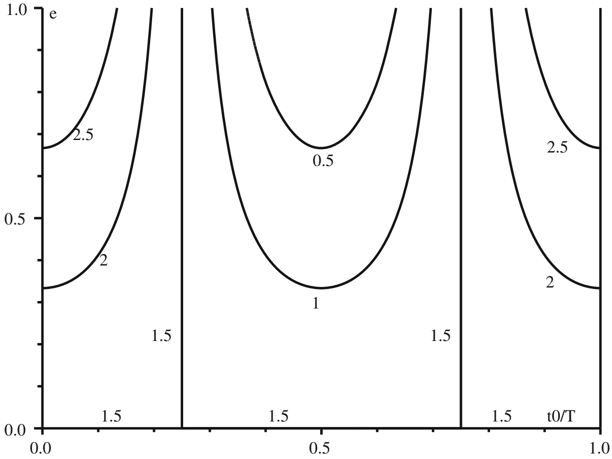

Fig. 2 Level curves of $a(t_0)/b$ when the time t_0 of introduction of the first infected case (*horizontal axis*) and the level e of seasonality (*vertical axis*) vary

variations of the indoor and outdoor vapor pressure in Sweden (Shaman and Kohn 2009, Fig. 4) (outdoor vapor pressure varying from 5 mb in winter to 15 mb in summer) and the variation of influenza transmission as a function of vapor pressure (Shaman and Kohn 2009, Fig. 1) (transmission decreasing from 80 to 20% as the vapor pressure increases from 5 to 15 mb), we would expect relatively large values of the seasonal factor e (say at least 20%) to be common.

6 Conclusion

The present paper shows that the basic reproduction number R_0 in a periodic environment [as defined or used in Bacaër and Guernaoui (2006), Bacaër (2007), Bacaër and Ouifki (2007), Bacaër and Abdurahman (2008), Bacaër and Gomes (2009), Bacaër (2009), Nakata and Kuniya (2010), Thieme (2009), Wang and Zhao (2008)] has the same biological meaning as in the classical theory of R_0 in a constant environment: it is an asymptotic per generation growth rate.

Section 5 compared this theoretical R_0 with the estimated "reproduction number" that can be obtained by fitting an exponential to the beginning of an epidemic curve. It turned out that both numbers are poor predictors of the final epidemic size. Recent estimates of the "reproduction number" for the ongoing H1N1 influenza pandemic did not take seasonality into account even though seasonality is certainly important for such an air-borne disease. Predictions based on these estimates and comparisons with previous pandemics should therefore be considered with caution. The question of defining and estimating R_0 correctly would be of no practical consequence if the estimates did not have some kind of influence on public health decisions such as spending large sums of money in buying in advance stocks of vaccines.

Appendix 1

Here is a proof of Lemma 1.

(i) Boundedness of L_s. Assumption (9) implies that $\|e^{-s\tau} K(t,\tau)\, V(t-\tau)\| \leq \alpha\,\gamma\, e^{-(s+\beta)\tau}\, \|V\|_\infty$. So the continuity of the function $t \mapsto (L_s V)(t)$ follows from Lebesgue's dominated convergence theorem. If $\|L_s\|_\infty$ stands for the operator norm on the space $\mathcal{L}(\mathcal{P})$ of bounded linear operators, then

$$\|L_s\|_\infty \leq \max_{0\leq t\leq T} \int_0^\infty e^{-s\tau}\, \|K(t,\tau)\|\, d\tau \leq \frac{\alpha\,\gamma}{s+\beta}. \tag{23}$$

(ii) Compactness of L_s. As pointed out in Bacaër (2007) (see also Jagers and Nerman 1985, p. 260), a simple computation using the periodicity of $K(t,\tau)$ with respect to t and of $V \in \mathcal{P}$ gives $(L_s V)(t) = \int_0^T \widehat{K}_s(t,\theta)\, V(\theta)\, d\theta$ for all $0 \leq t \leq T$, where $\widehat{K}_s(t,\theta) = \sum_{n=0}^\infty K_s(t, t-\theta+nT)$ if $0 \leq \theta \leq t$, $\widehat{K}_s(t,\theta) = \sum_{n=1}^\infty K_s(t, t-\theta+nT)$ if $t < \theta \leq T$, and $K_s(t,\tau) = e^{-s\tau} K(t,\tau)$. Since for all $t, \theta \in [0,T]$, $0 \leq \|K_s(t, t-\theta+nT)\| \leq \alpha\,\gamma\, e^{-(\beta+s)(t-\theta+nT)} \leq \alpha\,\gamma\, e^{-(\beta+s)(n-1)T}$, it follows that the function $\widehat{K}_s(t,\theta)$ is continuous on the set $\{(t,\theta) \in [0,T] \times [0,T];\ t \neq \theta\}$ and bounded on the set $[0,T] \times [0,T]$. So $\widehat{K}_s(t,\theta)$ is a "weakly singular" kernel and the integral operator L_s is compact (Kress 1999, Theor. 2.22).

(iii) Monotonicity of $s \mapsto \rho(s)$. The matrix kernel $K(t,\tau)$ is nonnegative so the operator L_s is also nonnegative ($V \geq 0$, meaning $V_i \geq 0$ for all i, implies $L_s V \geq 0$). Moreover $s \leq s'$ implies $L_s \geq L_{s'}$. Recall that the space $\mathcal{P}$ is a Banach space with the norm $\|\cdot\|_\infty$ and also a Banach lattice ($|V_i| \leq |V_i'|$ for all i implies $\|V\|_\infty \leq \|V'\|_\infty$). The monotonicity of the spectral radius for nonnegative operators in Banach lattices implies that $s \mapsto \rho(s)$ is nonincreasing (see, e.g., Burlando (1991)).

(iv) Continuity of $s \mapsto \rho(s)$. The mapping $s \mapsto L_s$ from $(-\beta, +\infty)$ to $\mathcal{L}(\mathcal{P})$ is continuous since

$$\|L_s - L_{s'}\|_\infty \le \max_{0\le t\le T} \int_0^\infty |e^{-s\tau} - e^{-s'\tau}|\, \|K(t,\tau)\|\, d\tau$$
$$\le \alpha\gamma \int_0^\infty |e^{-s\tau} - e^{-s'\tau}| e^{-\beta\tau}\, d\tau$$

and since the right-hand side tends to 0 when $s' \to s$. The spectral radius is continuous on the space of compact linear operators (see, e.g., Degla (2008)). So $s \mapsto \rho(s)$ is continuous.

(v) Existence of r. Inequality (23) shows that $\|L_s\|_\infty \to 0$ as $s \to +\infty$. Since $\rho(s) \le \|L_s\|_\infty$, we also have $\rho(s) \to 0$ as $s \to +\infty$. The continuity of $s \mapsto \rho(s)$ and the assumption $\rho(s_0) > 1$ imply that there exists $r \ge s_0$ such that $\rho(r) = 1$.

(vi) Log-convexity of $s \mapsto \rho(s)$. One could use (Kato 1982, Theor. 2.5) and argue that $s \mapsto L_s$ is “completely monotonic” and thus “superconvex” (Thieme 1998, Theor. 2.5). However a somewhat different proof inspired from the finite-dimensional case (Bapat and Raghavan 1997, Theor. 3.3.4) might be of interest. Assume that $-\beta < s_1 < s_2$ and that $s = \lambda s_1 + (1-\lambda)s_2$ with $0 < \lambda < 1$. We would like to show that $\rho(s) \le \rho(s_1)^\lambda \rho(s_2)^{1-\lambda}$. Because of the continuity of the spectral radius on the space of compact linear operators and by considering the operator associated to the modified kernel $K^\varepsilon_{i,j}(t,\tau) = K_{i,j}(t,\tau) + \varepsilon\, e^{-\beta\tau}$, it is enough to prove the log-convexity with the extra assumption that L_s is “strongly positive” (if $\mathcal{C}$ is the closed convex cone of nonnegative functions in $\mathcal{P}$, then $L_s(\mathcal{C} \setminus \{0\}) \subset \mathrm{Int}(\mathcal{C})$). The “strong version” of the Krein–Rutman theorem (see, e.g., Drábek and Milota 2007, Theor. 5.4.33) then says that there is a strictly positive eigenfunction $V^{(1)}(t)$ (resp. $V^{(2)}(t)$) associated with the eigenvalue $\rho(s_1)$ (resp. $\rho(s_2)$) of the operator L_{s_1} (resp. L_{s_2}). Set $W_i(t) = (V_i^{(1)}(t))^\lambda\, (V_i^{(2)}(t))^{1-\lambda}$. Then the discrete-version of Hölder’s inequality (with $p = 1/\lambda$ and $q = 1/(1-\lambda)$) shows that

$$(L_s W)_i(t) = \int_0^\infty \sum_j \left[e^{-s_1\tau} K_{i,j}(t,\tau) V_j^{(1)}(t-\tau)\right]^\lambda$$
$$\times \left[e^{-s_2\tau} K_{i,j}(t,\tau) V_j^{(2)}(t-\tau)\right]^{1-\lambda} d\tau$$
$$\le \int_0^\infty \left[\sum_j e^{-s_1\tau} K_{i,j}(t,\tau) V_j^{(1)}(t-\tau)\right]^\lambda$$
$$\times \left[\sum_j e^{-s_2\tau} K_{i,j}(t,\tau) V_j^{(2)}(t-\tau)\right]^{1-\lambda} d\tau.$$

The continuous-version of Hölder's inequality implies that

$$(L_s W)_i(t) \le \left\{ \int_0^\infty \left[\sum_j e^{-s_1 \tau} K_{i,j}(t,\tau) V_j^{(1)}(t-\tau) \right] d\tau \right\}^\lambda$$
$$\times \left\{ \int_0^\infty \left[\sum_j e^{-s_2 \tau} K_{i,j}(t,\tau) V_j^{(2)}(t-\tau) \right] d\tau \right\}^{1-\lambda}$$
$$= \left[\rho(s_1) V_i^{(1)}(t)\right]^\lambda \left[\rho(s_2) V_i^{(2)}(t)\right]^{1-\lambda} = \rho(s_1)^\lambda \rho(s_2)^{1-\lambda} W_i(t).$$

Finally, (Drnovšek 2000, Theor. 2.4) (Collatz–Wielandt upper bound) implies that $\rho(s) \le \rho(s_1)^\lambda \rho(s_2)^{1-\lambda}$.

(vii) Assume there is $r_1 < r_2$ such that $\rho(r_1) = \rho(r_2) = 1$. Since $s \mapsto \rho(s)$ is decreasing and (log-)convex, it follows that $\rho(s) = 1$ for all $s \ge r_1$. This contradicts the fact that $\rho(s) \to 0$ as $s \to +\infty$. So there is a unique $r > -\beta$ such that $\rho(r) = 1$. Moreover, we have shown that the mapping $s \mapsto \rho(s)$ is either strictly decreasing on the interval $(-\beta, +\infty)$ or strictly decreasing on some interval $(-\beta, r_0)$ with $\rho(s) = 0$ for all $s \ge r_0$. This proves corollary 1.

Appendix 2

We check that the proof given in Michel et al. (2005) for the asymptotic behavior of a single-type population in a periodic environment can be generalized to the case of multi-type populations. Alternatively, this can be seen as a generalization to PDEs of (Perthame 2007, Remark 6.2) concerning multi-type populations modeled by ODEs. Let $A'(t,\tau)$ (resp. $B'(t,\tau)$, $K'(t,\tau)$) be the transpose of the matrix $A(t,\tau)$ (resp. $B(t,\tau)$, $K(t,\tau)$). Generalizing (Michel et al. 2005, Theor. 5.1), we start by the following lemma:

Lemma 5 *There is a unique triplet* (r, N, ϕ) *solution of the dual eigenvalue problems*

$$\frac{\partial N}{\partial t}(t,\tau) + \frac{\partial N}{\partial \tau}(t,\tau) + r\,N(t,\tau) + B(t,\tau)N(t,\tau) = 0\ , \quad \forall t,\ \forall \tau > 0, \quad (24)$$

$$N(t,0) = \int_0^\infty A(t,\tau)\,N(t,\tau)\,d\tau \quad (25)$$

$$N(t+T,\tau) = N(t,\tau), \quad N(t,\tau) \ge 0, \quad \sum_i \int_0^T \int_0^\infty N_i(t,\tau)\,d\tau\,dt = 1,$$

$$\frac{\partial \phi}{\partial t}(t,\tau) + \frac{\partial \phi}{\partial \tau}(t,\tau) - r\,\phi(t,\tau) - B'(t,\tau)\,\phi(t,\tau) = -A'(t,\tau)\,\phi(t,0), \quad (26)$$

$$\phi(t+T,\tau) = \phi(t,\tau), \quad \phi(t,\tau) \geq 0, \quad \sum_i \int_0^\infty N_i(t,\tau)\,\phi_i(t,\tau)\,d\tau = 1.$$

Proof (24)–(25) on one side and (26) on the other side reduce to the dual eigenvalue problems

$$N(t,0) = \int_0^\infty e^{-r\tau}\,K(t,\tau)\,N(t-\tau,0)\,d\tau\ ,$$

$$\phi(t,0) = \int_0^\infty e^{-r\tau}\,K'(t+\tau,\tau)\,\phi(t+\tau,0)\,d\tau,$$

whose properties follow from Appendix 1 and from the Krein–Rutman theorem.

Generalizing (Michel et al. 2005, Eq. (5.11)), we have the following lemma:

Lemma 6 *Let $H : \mathbb{R} \to \mathbb{R}$ be a convex function. Assume that $P(t,\tau)$ satisfies (5)–(6). Set*

$$\mathcal{H}(t) = \sum_i \int_0^\infty \phi_i(t,\tau)\,N_i(t,\tau)\,H\left(\frac{P_i(t,\tau)e^{-rt}}{N_i(t,\tau)}\right)d\tau. \quad (27)$$

Then $\frac{d\mathcal{H}}{dt} \leq 0$ for all t.

Proof A tedious computation similar to those in Michel et al. (2005), Perthame (2007) gives

$$\frac{d\mathcal{H}}{dt} = \sum_i \phi_i(t,0)\,N_i(t,0)\left\{H\left(\int_0^\infty \sum_j \mu_{i,j}\,g_j\,d\tau\right) - \int_0^\infty \sum_j \mu_{i,j}\,H(g_j)\,d\tau\right\}$$
$$+\sum_{i,j}\int_0^\infty \phi_i\,B_{i,j}\,N_j\left\{H(g_j) - H(g_i) + (g_i - g_j)H'(g_i)\right\}d\tau\ , \quad (28)$$

where for convenience we do not repeat that the functions depend on (t,τ) and where we set

$$\mu_{i,j}(t,\tau) = \frac{A_{i,j}(t,\tau)\,N_j(t,\tau)}{N_i(t,0)}\ , \quad g_j(t,\tau) = \frac{P_j(t,\tau)\,e^{-rt}}{N_j(t,\tau)}. \quad (29)$$

Indeed, the derivative of (27) is

$$\frac{d\mathcal{H}}{dt} = \sum_i \int_0^\infty \Bigg\{ \left[\frac{\partial \phi_i}{\partial t}\, N_i + \phi_i\, \frac{\partial N_i}{\partial t} \right] H\left(\frac{P_i\, e^{-rt}}{N_i} \right) \\ + \phi_i\, N_i\, H'\left(\frac{P_i\, e^{-rt}}{N_i} \right) \left[\frac{\partial P_i}{\partial t} - r\, P_i - \frac{P_i}{N_i} \frac{\partial N_i}{\partial t} \right] \frac{e^{-rt}}{N_i} \Bigg\}\, d\tau.$$

Replacing $\partial P_i/\partial t$, $\partial N_i/\partial t$ and $\partial \phi_i/\partial t$ with (5), (24) and (26), we get

$$\frac{d\mathcal{H}}{dt} = \sum_i \int_0^\infty \Bigg\{ \left[-\frac{\partial \phi_i}{\partial \tau} + r\, \phi_i + \sum_j \phi_j\, B_{j,i} - \sum_j \phi_j(t,0) A_{j,i} \right] N_i\, H\left(\frac{P_i\, e^{-rt}}{N_i} \right) \\ - \phi_i \left[\frac{\partial N_i}{\partial \tau} + r\, N_i + \sum_j B_{i,j}\, N_j \right] H\left(\frac{P_i\, e^{-rt}}{N_i} \right) \\ - \phi_i\, N_i\, H'\left(\frac{P_i\, e^{-rt}}{N_i} \right) \left[\frac{\partial P_i}{\partial \tau} + \sum_j B_{i,j}\, P_j \right] \frac{e^{-rt}}{N_i} \\ + \phi_i\, N_i\, H'\left(\frac{P_i\, e^{-rt}}{N_i} \right) \frac{P_i}{N_i} \left[\frac{\partial N_i}{\partial \tau} + \sum_j B_{i,j}\, N_j \right] \frac{e^{-rt}}{N_i} \Bigg\}\, d\tau.$$

Introducing the notation g_j from (29), grouping the terms involving derivatives with respect to τ on one side and the terms involving $B_{i,j}$ on the other side, and exchanging the indices i and j in the sums involving $B_{j,i}$ and $A_{j,i}$ gives

$$\frac{d\mathcal{H}}{dt} = -\sum_i \int_0^\infty \frac{\partial}{\partial \tau} \left[\phi_i N_i H(g_i) \right] d\tau - \sum_{i,j} \phi_i(t,0) \int_0^\infty A_{i,j} N_j H(g_j)\, d\tau \\ + \sum_{i,j} \int_0^\infty \phi_i\, B_{i,j}\, N_j \left\{ H(g_j) - H(g_i) + (g_i - g_j) H'(g_i) \right\} d\tau.$$

Integrating the first integral, we arrive at

$$\frac{d\mathcal{H}}{dt} = \sum_i \phi_i(t,0) N_i(t,0) \left\{ H(g_i(t,0)) - \int_0^\infty \sum_j \frac{A_{i,j} N_j}{N_i(t,0)}\, H(g_j)\, d\tau \right\} \\ + \sum_{i,j} \int_0^\infty \phi_i\, B_{i,j}\, N_j \left\{ H(g_j) - H(g_i) + (g_i - g_j) H'(g_i) \right\} d\tau.$$

This yields (28) if we take into account the boundary condition (6), which shows that

$$g_i(t,0) = \frac{P_i(t,0)\,e^{-rt}}{N_i(t,0)} = \int_0^\infty \sum_j \frac{A_{i,j}(t,\tau)\,N_j(t,\tau)}{N_i(t,0)}\,\frac{P_j(t,\tau)\,e^{-rt}}{N_j(t,\tau)}\,d\tau.$$

Back to the proof of Lemma 6, Jensen's inequality—using $\int_0^\infty \left(\sum_j \mu_{i,j}\right) d\tau = 1$—and its discrete form show that

$$\begin{aligned} H\left(\int_0^\infty \sum_j \mu_{i,j}\, g_j\, d\tau\right) &\le \int_0^\infty H\left(\frac{\sum_j \mu_{i,j}\, g_j}{\sum_j \mu_{i,j}}\right)\left(\sum_j \mu_{i,j}\right) d\tau \\ &\le \int_0^\infty \sum_j \mu_{i,j}\, H(g_j)\, d\tau. \end{aligned}$$

So the first line in (28) is nonpositive. The second line of (28) is also nonpositive because the term corresponding to $i = j$ vanishes and because for $i \ne j$, the convexity of H implies that the expression inside the brackets $\{\cdots\}$ is nonnegative while $B_{i,j} \le 0$, $\phi_i \ge 0$, and $N_j \ge 0$. So $\frac{d\mathcal{H}}{dt} \le 0$.

We now arrive at the generalization of Michel et al. (2005, Theor. 5.2).

Lemma 7 *Let $P(t,\tau)$ be the solution of (5)–(6) with the initial condition $P(t_0,\tau)$. Set $c = \sum_i \int_0^\infty P_i(t_0,\tau)\,\phi_i(t_0,\tau)\,d\tau$. Then*

$$\sum_i \int_0^\infty |P_i(t,\tau)\,e^{-r(t-t_0)} - c\,N_i(t,\tau)|\,\phi_i(t,\tau)\,d\tau \xrightarrow[t\to+\infty]{} 0. \qquad (30)$$

Proof Notice that $e^{rt_0} P_i(t,\tau) - c\,N_i(t,\tau)\,e^{rt}$ is also a solution of the linear equations (5)–(6). Applying lemma 6 to this solution with the convex function $H(x) = |x|$, we get that $\mathcal{H}(t)$—the left-hand side of (30)—decreases with time t and thus converges to a limit ℓ. The fact that $\ell = 0$ can be proved following arguments similar to those used in Michel et al. (2005, p. 1259) or Perthame (2007, Sect. 3.6).

Corollary 2 $\|P(t,0)\| \sim c\,e^{r(t-t_0)}\|N(t,0)\|$ *as* $t \to +\infty$.

References

Aronsson G, Kellogg RB (1978) On a differential equation arising from compartmental analysis. Math Biosci 38:113–122

Bacaër N, Guernaoui S (2006) The epidemic threshold of vector-borne diseases with seasonality. J Math Biol 53:421–436

Bacaër N (2007) Approximation of the basic reproduction number R_0 for vector-borne diseases with a periodic vector population. Bull Math Biol 69:1067–1091

Bacaër N, Ouifki R (2007) Growth rate and basic reproduction number for population models with a simple periodic factor. Math Biosci 210:647–658

Bacaër N, Abdurahman X (2008) Resonance of the epidemic threshold in a periodic environment. J Math Biol 57:649–673

Bacaër N, Gomes MGM (2009) On the final size of epidemics with seasonality. Bull Math Biol 71:1954–1966

Bacaër N (2009) Periodic matrix population models: growth rate, basic reproduction number, and entropy. Bull Math Biol 71:1781–1792

Bapat RB, Raghavan TES (1997) Nonnegative matrices and applications. Cambridge University Press, London

Berman A, Plemmons RJ (1979) Nonnegative matrices in the mathematical sciences. Academic Press, New York

Boëlle PY, Bernillon P, Desenclos JC (2009) A preliminary estimation of the reproduction ratio for new influenza A (H1N1) from the outbreak in Mexico, March–April 2009. Euro Surveill 14(19):pii=19205

Burlando L (1991) Monotonicity of spectral radius for positive operators on ordered Banach spaces. Arch Math 56:49–57

Cauchemez S, Valleron AJ, Boelle PY, Flahault A, Ferguson NM (2008) Estimating the impact of school closure on influenza transmission from Sentinel data. Nature 452(7188):750–754

Coale AJ (1970) The use of Fourier analysis to express the relation between time variations in fertility and the time sequence of births in a closed human population. Demography 7:93–120

Coale AJ (1972) The growth and structure of human populations, a mathematical investigation. Princeton University Press, Princeton

Degla G (2008) An overview of semi-continuity results on the spectral radius and positivity. J Math Anal Appl 338:101–110

Diekmann O, Heesterbeek JAP (2000) Mathematical epidemiology of infectious diseases. Wiley, Chichester

Drábek P, Milota J (2007) Methods of nonlinear analysis applications to differential equations. Birkhäuser, Basel

Drnovšek R (2000) Bounds for the spectral radius of positive operators. Comment Math Univ Carol 41:459–467

Dushoff J, Plotkin JB, Levin SA, Earn DJD (2004) Dynamical resonance can account for seasonality of influenza epidemics. Proc Natl Acad Sci USA 101:16915–16916

Ediev D (2003) On monotone convergence to stability. Demogr Res 8:31–60

Feller W (1941) On the integral equation of renewal theory. Ann Math Stat 12:243–267

Fraser C, Donnelly CA, Cauchemez S et al (2009) Pandemic potential of a strain of influenza A (H1N1): early findings. Science 324:1557–1561

Grassly NC, Fraser C (2006) Seasonal infectious disease epidemiology. Proc R Soc B 273:2541–2550

Heesterbeek JAP, Roberts MG (1995) Threshold quantities for helminth infections. J Math Biol 33:415–434

Inaba H, Nishiura H (2008) The basic reproduction number of an infectious disease in a stable population: the impact of population growth rate on the eradication threshold. Math Model Nat Phenom 3(7):194–228

Jagers P, Nerman O (1985) Branching processes in periodically varying environment. Ann Probab 13:254–268

Kato T (1982) Superconvexity of the spectral radius, and convexity of the spectral bound and the type. Math Z 180:265–273

Kermack WO, McKendrick AG (1927) A contribution to the mathematical theory of epidemics. Proc R Soc A 115:700–721

Kress R (1999) Linear integral equations, 2nd edn. Springer, New York

Lipsitch M, Viboud C (2009) Influenza seasonality: lifting the fog. Proc Natl Acad Sci USA 106:3645–3646

Lotka AJ (1939) Théorie analytique des associations biologiques, 2e partie. Hermann, Paris

Michel P, Mischler S, Perthame B (2005) General relative entropy inequality: an illustration on growth models. J Math Pures Appl 84:1235–1260

Munayco CV, Gomez J, Laguna-Torres VA et al (2009) Epidemiological and transmissibility analysis of influenza A(H1N1)v in a southern hemisphere setting: Peru. Euro Surveill 14(32 pii):19299

Nakata Y, Kuniya T (2010) Global dynamics of a class of SEIRS epidemic models in a periodic environment. J Math Anal Appl 363:230–237

Nishiura H, Castillo-Chavez C, Safan M, Chowell G (2009) Transmission potential of the new influenza A (H1N1) virus and its age-specificity in Japan. Euro Surveill 14(22):pii–19227

Perthame B (2007) Transport equations in biology. Birhäuser, Basel

Pourbohloul B, Ahued A, Davoudi B et al (2009) Initial human transmission dynamics of the pandemic (H1N1) 2009 virus in North America. Influenza Other Respi Viruses 3(5):215–222

Shaman J, Kohn M (2009) Absolute humidity modulates influenza survival, transmission, and seasonality. Proc Natl Acad Sci USA 106:3243–3248

Thieme HR (1984) Renewal theorems for linear periodic Volterra integral equations. J Integral Equ 7:253–277

Thieme HR (1998) Remarks on resolvent positive operators and their perturbation. Discret Contin Dyn Syst 4:73–90

Thieme HR (2009) Spectral bound and reproduction number for infinite population structure and time-heterogeneity. SIAM J Appl Math 70:188–211

Wang W, Zhao XQ (2008) Threshold dynamics for compartmental epidemic models in periodic environments. J Dyn Differ Equ 20:699–717

Wesley CL, Allen LJS (2009) The basic reproduction number in epidemic models with periodic demographics. J Biol Dyn 3:116–129

Williams BG, Dye C (1997) Infectious disease persistence when transmission varies seasonally. Math Biosci 145:77–88