Recurrent epidemic cycles driven by intervention in a population of two susceptibility types

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Abstract. Epidemics have been known to persist in the form of recurrence cycles. Despite intervention efforts through vaccination and targeted social distancing, infectious diseases like influenza continue to appear intermittently over time. I have undertaken an analysis of a stochastic epidemic model to explore the hypothesis that intervention efforts actually drive epidemic cycles. Time series from simulations of the model reveal oscillations exhibiting a similar temporal signature as influenza epidemics. The power-spectral density indicates a resonant frequency, which approximately corresponds to the apparent annual seasonality of influenza in temperate zones. Asymptotic solution to the backward Kolmogorov equation of the dynamics corresponds to an exponentially-decaying mean-exit time as a function of the intervention rate. Intervention must be implemented at a sufficiently high rate to extinguish the infection. The results demonstrate that intervention efforts can induce epidemic cycles, and that the temporal signature of cycles can provide early warning of imminent outbreaks.

1. Introduction
Sentinel surveillance of influenza-like illnesses (ILI) done in several countries have gathered and presented evidence for recurrent epidemics [1, 2, 3, 4, 5]. Prevailing models based on the Susceptible-Infected-Recovered or SIR framework, however, do not inherently predict the cycle-like variation of $R_0$ with time unless exogenous seasonal forcing is assumed [6]. The problem with that assumption is the weak correspondence of seasonal forcing with recurrent epidemic activity [7]. On the contrary, the apparent seasonality may emerge endogenously from the host-pathogen feedback interaction. The host’s natural immunity along with intervention efforts induce a feedback loop with the pathogen’s mutations via antigenic drift. Demographic noise is a likely feature of that interaction. In models of resonant amplification, endogenous forcing due to demographic stochasticity has been demonstrated [8]. However, those models do not clearly address how epidemic cycles can be extinguished through intervention initiatives. Here, I propose and analyze a mathematical model that generates epidemic cycles and could account for the observed time variation in $R_0$. The model illustrates how intervention promotes epidemic cycles, and how a time-varying $R_0$ could serve as a lead indicator of an imminent outbreak.

2. Mathematical model
Consider an infected population of size $N = N_1 + N_2$ with two susceptibility types of subpopulation sizes $N_1$ and $N_2$. The population dynamics of both types are similar in all respects but one: type–1 gets infected at a faster rate than type–2. The population dynamics
can be further described in terms of reactions. Recruitment processes are: 1. \( \frac{\mu}{2} \to 11 \) or 2. \( \frac{\mu}{2} \to 21 \); and 2. \( \frac{\lambda}{2} \to 22 \) or 1. \( \frac{\lambda}{2} \to 12 \), wherein \( \mu \) and \( \lambda \) are per-capita rates of infection of type 1 and 2, respectively. Density-dependent removal are: \( k_1 \frac{\delta}{\rho} \to k \) or \( k_2 \frac{\delta}{\rho} \to k \) where \( k = 1, 2 \). Intervention-induced removal is expressed as: \( k \frac{\nu}{\Omega} \), occurring at the rate \( \nu \Phi \), which may be related to vaccine efficacy [9]. The function \( \Phi = \sum_{k \in \{1, 2\}} N_k (N_k - 1) / [N(N - 1)] \) encapsulates the susceptibility structure of the community relevant to targeted vaccination.

The population size of both types are random variables drawn from a joint probability density function \( P(N_1, N_2; t) \) that evolves over time. The exact time evolution of \( P \) is given by the master equation constructed from the recruitment and removal processes. Assuming a community size \( \Omega \gg 1 \), a diffusion approximation of the master equation is the Fokker-Planck equation:

\[
\frac{\partial P(n_1, n_2; t)}{\partial t} = -\sum_{j=1}^{2} \left\{ \frac{\partial}{\partial n_j} [b_j(n_1, n_2)P] + \frac{1}{2\Omega} \frac{\partial^2}{\partial n_j^2} [a_j(n_1, n_2)P] \right\},
\]

where \( n_1 = N_1 / \Omega \) and \( n_2 = N_2 / \Omega \) are dimensionless concentrations. The drift terms are: \( b_1 = [\mu - n_1 - \nu \Phi](n_1 + n_2) \) and \( b_2 = [\lambda - n_2 - \nu \Phi](n_1 + n_2) \); and the diffusion terms are: \( a_1 = [\mu + n_1 + \nu \Phi](n_1 + n_2) \) and \( a_2 = [\lambda + n_2 + \nu \Phi](n_1 + n_2) \). A further simplification of the model is made by setting \( \mu + \lambda = 1 \), with \( \mu \in (\frac{1}{2}, 1) \) and \( \lambda \in (0, \frac{1}{2}) \).

Linking the variables in the model with measurement requires a rescaling of dimensions. The time unit \( t \) in the model is set at the clinical-onset serial interval, which is the period between the onset of symptoms in the index case and the onset of symptoms in any secondary cases. The serial interval is \( \approx 3.6 \) days from careful estimates supplemented by laboratory testing [10]. The carrying capacity is set at \( \Omega = 10^6 \), which is the order of the size of a typical community. But the timescale of the system is set using a small dimensionless parameter \( \varepsilon \approx 0.01 \), such that the effective capacity is \( \varepsilon \Omega \approx 10^4 \).

A transcritical bifurcation of the model occurs when \( \mu \) is a function of \( \nu \), as follows:

\[
\mu = \mu_0(\nu) = \frac{1}{2} + \frac{1}{3} \sqrt{\frac{(1 - \nu)^2}{3\nu}}.
\]

On this manifold, it can be shown that the equilibrium concentration vector \( \tilde{n} = (\tilde{n}_1, \tilde{n}_2) \) is asymptotically stable, where \( \tilde{n}_1 = \left( \frac{1 - \nu}{3} \right) \left( 1 + \sqrt{\frac{1 - \nu}{3\nu}} \right) \) and \( \tilde{n}_2 = \left( \frac{1 - \nu}{3} \right) \left( 1 - \sqrt{\frac{1 - \nu}{3\nu}} \right) \).

3. Epidemic cycle and resonant frequency

The model is examined in a region of the parameter space denoted by the set of ordered pairs, \( (\nu, \mu) \in \mathbb{K} = [0, 1] \times (\frac{1}{2}, 1) \). Let \( \mathcal{B} \) denote the drift Jacobian, which is evaluated at the stable equilibrium \( \tilde{n} \). The power spectral density \( S(\omega) \) of the epidemic time series is inversely proportional to the expression \( (\omega^2 - \text{det} \mathcal{B})^2 + (\text{Tr} \mathcal{B})^2 \omega^2 \), the real zero of which corresponds to the square of the resonant frequency [8]:

\[
\omega_0(\mu, \nu)^2 = 2(2\mu - 1) \nu \sqrt{\frac{1 - \nu}{3\nu}} - \frac{2}{3}(1 - \nu)^2.
\]

The cycle exists if \( \omega_0^2 > 0 \), which is satisfied in \( \mathcal{J} = \{ (\nu, \mu) \mid \mu \in (\frac{1}{2}, 1) ; \nu > \nu_0 = \mu_0^{-1}[\mu(\nu)] > 0 \} \subset \mathbb{K} \), where \( \nu_0 \) is the inverse function from Eq. (2). Figure 1 illustrates the cycles generated by the model (using a stochastic simulation algorithm [11]) compared with a real time-series of ILI activity in the U.S. from 1997 to 2010. ILI activity reported in other settings exhibit similar time series (not shown): Hong Kong, 1998-2006 [1]; Melbourne, 1999-2008 [2]; Réunion Island, 2009-2011 [3]; and several countries in continental Europe [4, 5]. Resonance is indicated by the peak in the spectral density.
4. Mean extinction time and stochastic amplification

Extinguishing the epidemic is the primary objective of intervention. Extinction refers to the state wherein \( n_1 = n_2 = 0 \). The mean time of such occurrence is represented by \( T \), which is a solution to the 2D backward Kolmogorov equation (BKE) [12]. The asymptotic solution for \( \Omega \gg 1 \) is the mean extinction time given by:

\[
T = -\sqrt{\frac{\pi}{\Omega \varphi''(\tilde{n}_2) A(\tilde{n}_2)\varphi'(0)}} e^{2\Omega \varphi(0)}.
\]

At the bifurcation manifold, where \( \mu = \mu_b(\nu) \) as in Eq. (2), the mean extinction time in Eq. (4) only depends explicitly on \( \nu \) [see Fig. 2(a)], which simplifies the analysis. Figure 2(b), inset, illustrates how extinction time is determined for a time series from the simulations.

The mean extinction time is measured at the bifurcation manifold, where only \( \nu \) is the free parameter, in the region \( J \) of resonance. The observed extinction time for different \( \Omega \) is presented in figure 2b. The trend is consistent with the existence of a singularity of \( T(\nu) \).
at $\nu = \tilde{\nu} = \frac{1}{4} \left[ 2 - (1 + \sqrt{2})^{-1/3} + (1 + \sqrt{2})^{1/3} \right] \approx 0.649$. Cycles persist longer at resonant frequencies for which $\nu \approx \tilde{\nu}$. The value of $\mathcal{T}$ is confirmed to diverge as $\nu \rightarrow \tilde{\nu}^\pm$. This is indicated by the higher $\mathcal{T}$ for higher $\Omega$. It is expected that for $\nu < \tilde{\nu}$ the extinction time is very large as the epidemic persists in time. On the other hand, for $\nu > \tilde{\nu}$ the epidemic is extinguished in finite time which is shorter for larger $\nu$.

5. Reproduction number and outbreak prediction

The reproduction number denoted as $R_0$ is commonly employed as a measure of the capability of a disease to spread as an epidemic. Based on the definition of $R_0$, the model finds a dynamic reproduction number given by

$$R_0(t) = \frac{1}{n(t) + 2\nu \Phi(t)}, \quad (5)$$

Figure 3 shows $R_0(t)$ superimposed with the $n(t)$ time series. The range of values is $0.6 < R_0 < 2.2$ which is consistent with typical ranges known empirically via parameter estimation methods [13]. Generally, the time evolution of $R_0(t)$ in relation to $n(t)$ is consistent with those found in empirical studies [14].

![Figure 3](image)

**Figure 3.** Reproduction number $R_0$ varies in time. Equation 5 is calculated for each time $t$ and superimposed the concentrations $n_1$ and $n_2$. Remarkably, $R_0(t)$ peaks along with $n_2(t)$ and thus may serve as a suitable leading indicator for an imminent outbreak when the epidemic has spread to the more susceptible subpopulation of the community.

6. Conclusion

The proposed model predicts an extinction time that decreases with increasing $\nu$ above a threshold value $\tilde{\nu}$. Epidemic cycles emerge from the confluence of decreasing extinction time and presence of a resonant frequency. Thus, the path to extinction is in the form of cycles. Indeed, epidemic cycles are counterintuitively driven by intervention efforts, which are meant to extinguish the infection. Future work may focus on the analysis, using the proposed model, on epidemics of other communicable diseases requiring person-to-person transmission. One may also address the demographic effects of migration which in the present model is neglected. Moreover, the inclusion of susceptibility structure should enhance the design of existing community surveillance protocols. Consequently, early detection for outbreaks is made possible, which is especially relevant in the tropics where influenza does not display any apparent seasonality.

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