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PERIODICITY IN EPIDEMIOLOGICAL MODELS

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Periodicity in Epidemiological Models

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Contents

Various epidemiological mechanisms have been shown to lead to periodic solutions. The most direct way in which periodicity arises is through extrinsic forcing by a parameter such as the contact rate, but periodicity can also arise autonomously. Cyclic models of SIRS or SEIRS type can have periodic solutions if there is a large time delay in the removed class. Epidemiological models with nonlinear incidence of certain general forms can have periodic solutions. Some models with variable population size and disease-related deaths have periodic solutions; most of these are host-parasite models where the parasite lifetime is much shorter than that of the host. Recently, periodic solutions have been found numerically in age structured models with cross immunity between two viral strains.

1. Introduction

Periodicity and other oscillatory behaviors have been observed in the incidence of many infectious diseases, including measles, mumps, rubella, chickenpox, poliomyelitis, diphtheria, pertussis and influenza. In some locations the incidence of some diseases such as chickenpox, mumps and poliomyelitis goes up and down every year. For example, there were yearly outbreaks of chickenpox and mumps from 1929 to 1970 in New York City (London and Yorke, 1973). The reported incidence of gonorrhea in the United States has oscillated seasonally for at least the last forty years (Hethcote and Yorke, 1984). This period of one year appears to be due to a seasonal variation in some factor such as the contact rate. Contact

ates may vary seasonally due to weather changes and the periodic aggregation of children in schools.

The observed interepidemic periods are longer for some diseases. For example, measles outbreaks occurred every two to three years in New York City and Baltimore from 1929 to 1970 (London and Yorke, 1973). Fine and Clarkson (1982, 1983) found that, although measles incidence oscillates biennially in England and Wales, the contact rate varies annually with increases at the openings of school terms and decreases at the closings. In many countries the interepidemic period is 2 to 6 years for infectious diseases such as whooping cough, poliomyelitis, chickenpox, rubella, mumps, diphtheria and scarlet fever (Anderson, 1982).

Although the periodic outbreaks may look like epidemics, the disease often remains endemic in the country or continent by low-level transmission between the major outbreaks. The susceptible fraction may be low after an outbreaks, but usually increases as new susceptibles are born or as recovered people lose their immunity. When the susceptible fraction is sufficiently large, a new outbreak may be triggered by the low-level background transmission or by a case from outside the country. A related phenomenon (Liu, 1987) occurs when the disease has a refuge in a second host population, which can serve as a source to trigger an epidemic when the susceptible fraction of the original host population is sufficiently large.

Because of the observed periodicity in the incidence of many diseases, there has been great interest in the ways in which periodic solutions can arise in epidemiological models. In a survey of epidemic models, Hethcote et al. (1981c) found that the mathematical epidemiology literature up to 1981 supported the conjecture that without external forcing or time-dependent coefficients, a single-population epidemiological model with bilinear incidence rates, constant population size and constant parameter values can have periodic solutions if and only if the model is cyclic of SIRS or SEIRS type and individuals can be "significantly delayed" in the removed class by a mechanism such as a large constant period of temporary immunity.

This was a useful way to organize and unify the conclusions from the mathematical epidemiology literature up to 1981. However, the conjecture was based on models with bilinear incidence λIS; recent work (Liu, Levin and Iwasa, 1986; Liu, Hethcote and Levin, 1987) described in Sect. 4 shows that nonlinear incidence can lead to periodic solutions even in models that are not cyclic. Furthermore, other modifications of the basic assumptions also can lead to periodicity and other sustained oscillations. Therefore, rather than trying to patch the 1981 conjecture with additional qualifications, we have chosen to survey the known ways in which periodicity can arise. Undoubtedly, this list will be enlarged in the future. The benefit of having such a catalogue available goes beyond simply demonstrating that similar phenomena in nature can have distinct causes, it also provides a systematic way to organize investigations of the mechanisms underlying observed patterns.

Models with periodic coefficients are described in Sect. 2 and models with delays in the removed class are considered in Sect. 3. Section 4 is devoted to models with nonlinear incidence and Sect. 5 considers models with variable population

sizes. Models with age structure are presented in Sect. 6. It is useful to classify the various mechanisms as follows. Periodicity can arise from causes related to the structure of the epidemiological model itself, including delays or periodicities in the parameters; such influences are considered in Sects. 2 to 4. Alternatively, periodicity may have little to do with epidemiology and may arise from demographic or other causes. For example, any model with variable population size or age structure, if based on an underlying demographic model that has an oscillatory character, can be expected to demonstrate the same character when the population is subdivided into epidemiological classes. Thus, as discussed to some extent in Sects. 5 and 6, epidemiological models with variable population size or age structure can exhibit oscillations that have nothing to do with the epidemiology. Perhaps most intriguing are the class of models, only recently investigated, that exhibit oscillations due to an interplay between epidemiological and demographic features. Examples include the interplay between age specific mortality and the existence of multiple strains in models of fixed population size; the influence of alternative host species in influenza and other diseases and the oscillatory and chaotic behavior that can arise indirectly when epidemiological models are forced by periodic parameter variation.

The paper complements the 1981 survey by focusing exclusively on periodicity and related sustained oscillations in epidemiological models and by including recent results. It must be recognized that recurrent epidemics in nature often are damped in magnitude in successive outbreaks. Many models such as those with age-dependent contact rates do exhibit slowly damped oscillations, and cannot be eliminated as explanations of observed natural variations.

In the models that follow, let $S(t)$ be the fraction of the population that is susceptible at time t, $E(t)$ be the fraction that is latent (i.e., infected but not yet infectious), $I(t)$ be the fraction that is infectious, and $R(t)$ be the fraction that is removed by immunity (i.e., removed from the susceptible-infective interactions, but not removed from circulation in the population). Models are usually named according to the flow between classes in the model; for example, in an SEIRS model, an individual is susceptible, then exposed (latent), then infectious, then immune upon recovery and finally susceptible again when the temporary immunity disappears. See Hethcote (1976, 1988) for the three basic epidemiological models and Hethcote, Stech and van den Driessche (1981c) for the formulation of functional differential and integral equation models. Pitfalls in the formulation of models for heterogeneous populations are explained in Hethcote and Van Ark (1987).

2. Models with Periodic Coefficients

In a chapter on recurrent epidemics and endemicity, Bailey (1975) described the deterministic models used in 1929 by Soper and the similar models used in the early 1940's by Wilson and Worcester (1945a, b). These models have damped oscillations; however, a periodic infection rate leads to periodic solutions with the same period as the infection rate. Using stochastic models, Bartlett (1956, 1960)

presented the concept of a critical community size above which oscillations in disease incidence can be maintained in a community.

Many authors have found that periodic coefficients in deterministic epidemiological models lead to periodic solutions. For an SIS model, Hethcote (1973) found explicit periodic solutions for a differential equation with a periodic contact rate. Cooke and Kaplan (1976) proved that periodic solutions exist for a scalar delay integral equation describing an SIS model with periodic coefficients. Their proof used fixed points on cones in Banach spaces. Similar methods were used by Nussbaum (1977, 1978), Smith (1977, 1978, 1979) and Busenberg and Cooke (1978a, b) to prove the existence of periodic solutions for a variety of models with periodic coefficients including an SEIRS model with three delays.

For n subgroups in an SIS model, Lajmanovich and Yorke (1976) proved global stability for the endemic equilibrium above the threshold. Aronsson and Mellander (1980) extended this result by proving that when the contact rates are periodic, the periodic solution is globally asymptotically stable. Hirsch (1984) generalized the Lajmanovich and Yorke result to a more general SIS model. Smith (1986) proved that when the Hirsch model is periodic, the periodic solution is globally stable above the threshold. These results of Hirsch and Smith are important since they imply that the Lajmanovich and Yorke, and Aronsson and Mellander results have a certain robustness; namely, the dynamical behavior is the same as long as the incidence and removal terms in the differential equations have the same general behavior. The Hirsch result suggests that any observed fluctuations in incidence are not due to the intrinsic dynamics of the disease so they must be due to fluctuations in epidemiological or environmental factors or in reporting.

Hethcote and Yorke (1984) analyzed an SIS gonorrhea model that subdivided the population into groups of men and women, and with contact rates that have a small periodic component. Using a perturbation analysis they found that a 5% oscillation in the contact rates leads to results consistent with the observed 6% and 10% oscillations in incidence in women and men, respectively. Moreover, the observed peak incidences in August to October are due to an earlier peak in the contact rate in the summer months.

Biennial Oscillations in Measles

Measles incidence has an approximately biennial oscillation in which the peak in the high year may be 80 times the peak in the low year. Numerous epidemiological models have been proposed as explanations of this two year period. London and Yorke (1973) used a delay-differential SEIR model with a contact rate that varied yearly by a factor of two. They found that the contact number and latent period for measles lead to periodic solutions with a two year period, but the parameter values for mumps and chickenpox yield one year periods. Stirzaker (1975) used perturbation methods to analyze a periodic SIR model with all births joining the susceptible class and all deaths in the removed class, but this model is not well posed (Hethcote et al. 1981c).

Dietz (1976) studied two well-posed models: an SIR model with births into the susceptible class and deaths in each class, and the SEIR model

$$S'(t) = -\lambda(t)IS + \mu - \mu S$$
$$E'(t) = \lambda(t)IS - (\varepsilon + \mu)E$$
$$I'(t) = \varepsilon E - (\gamma + \mu)I$$
$$R'(t) = \gamma I - \mu R$$
$$S + E + I + R = 1$$

where $\lambda(t)$ is periodic. The behaviors of the two models are essentially the same. For parameter values consistent with measles, Dietz found that the natural damping period with a constant contact rate is about 2 years; his numerical calculations with periodic contact rates yielded biennial oscillations, provided the contact rate oscillations percentage was not too small. Longer periods of oscillations of 3, 4 or 6 years were found numerically for other parameter ranges. Since the period of the damped oscillations is an integral multiple of the one year periodicity of the contact rate, the oscillations become undamped. This phenomenon, called subharmonic resonance, is a plausible explanation of the biennial oscillation in measles incidence; but it is probably too simplistic in view of the work of Schenzle (1984) described in Sect. 6.

Grossman, Gumowski and Dietz (1977) used formal perturbation methods on the model above the obtain biennial periodic solutions. Grossman (1980) extended this perturbation analysis to models with delays. Smith (1982a, 1982b) proved the existence of two-year periodic solutions of the SIR model with vital dynamics and showed that for many values of n, n-year periodic solutions coexist and are simultaneously stable. Schwartz (1983) found numerically that an SEIR measles model has coexisting solutions with periods of 1, 2 and 3 years. Schwartz and Smith (1983) showed both analytically and numerically that an SEIR model has coexisting stable, large-amplitude subharmonic solutions of period n for many values of n, including $n = 2$. They suggested that random environmental changes could perturb the system from the domain of attraction of one sub-harmonic to another so that the incidence would look aperiodic. As a possible example, they cited measles, which often exhibits either two or three year intervals between major outbreaks.

Aron and Schwartz (1984a, b) showed numerically for the SEIR model that small amplitude periodic solutions exhibit a sequence of period-doubling bifurcations as the amplitude of the seasonal variation in transmission increases: this predicts a transition to chaotic behavior. The period-doubled solutions all appear as alternating high- and low-incidence years; effectively only biennial epidemics can be explained by this model since the longer periods change only the low years, in ways that cannot be distinguished statistically. The appearance of period-doubling occurs for higher basic reproduction rates corresponding to measles, but not for lower rates corresponding to rubella. Thus they suggested that the seasonal mechanism generating biennial epidemics may not be able to account for small-amplitude recurrent epidemics of arbitrary periodicity. Schwartz (1985) numerically determined the basins of attraction for the coexisting small and large amplitude periodic solutions. The basins of attraction for two coexisting

stable periodic solutions are intertwined in a complicated (fractal) manner, so that it may not be possible to predict the outbreak type due to the uncertainty in the initial data

A seasonally-forced SEIR model can have a sequence of period doubling subharmonic bifurcations such that the dynamical system can exhibit chaos (Aron and Schwartz, 1984a). Schaffer (1985) and Schaffer and Kot (1985) have studied epidemiological data and models related to periodic childhood diseases by using time series analysis and recent dynamical systems methods. They have sought to determine if the epidemiological dynamics are 1) damped oscillations maintained by noise, or 2) stable cycles with noise where the period is some multiple of the seasonal (yearly) forcing, or 3) inherently chaotic fluctuations.

Nonlinear systems of differential equations can exhibit a variety of dynamic behaviors including point attractors, stable limit cycles, toroidal flow (including quasiperiodic and phase-locked trajectories) and various sorts of chaotic attractors. Chaotic systems are deterministic, yet their solutions can look like stochastic systems. Some chaotic systems have maximal algorithmic complexity in the sense that the solutions are indistinguishable from a set of random numbers and the most economical description is the time series of the solution. Other chaotic systems have some structure and methods have been developed to detect this structure

Plotting the orbit in phase space can reveal whether the system corresponds to a known kind of chaos. Takens (1981) showed how to construct the phase portrait for a system with n state variables from a univariate time series. Orbits of fractal or Hausdorff dimension almost 2 or between 2 and 3 often occur for ecology and epidemiological models. Lyapunov exponents are generalized eigenvalues that average the motion over an attractor. A fractal dimension (computed from the Lyapunov exponents) near 2 means the flow is essentially two-dimensional so that the Poincaré section (a cross section perpendicular to the flow) is thin. A difference equation corresponding to the Poincaré or time-1 map may turn out to be a standard type about which much is known.

Schaffer and Kot (1985) using the methods above analyzed measles data in New York City and Baltimore and found essentially two-dimensional chaos in the presence of noise (the fractal dimension is about 2.5). Chickenpox data from New York City did not yield a one dimensional map so they suggested that there is a simple yearly cycle with noise. Schaffer (1985) not only analyzed actual data for diseases such as measles and chicken-pox, but also analyzed simulated data. For example, data with noise were generated using a seasonally forced SEIR model with parameter values in the chaotic region. When this simulated data set was analyzed, the phase space reconstruction, Poincaré section and time-1 map were similar to those obtained from actual data. Thus the chaotic theory is not inconsistent with the commonly accepted SEIR model. Unfortunately, there does not seem to be any precise statistical measure of goodness of fit, so the similarities observed are only visual. Schaffer also showed that Bartlett's (1956, 1960) hypothesis that recurrent epidemics are sustained by chance perturbations did not lead to data that yield phase space reconstructions, Poincaré sections and time-1 maps that were similar to those for measles data.

Schwarz (1988) provides further numerical results on the seasonally forced

SEIR model. As the amplitude of the yearly periodic forcing increases from zero, the following behavior with parameter values for measles is found numerically: 1) a stable period-2 orbit bifurcates off the period-1 orbit which becomes unstable, 2) then a stable period-3 branch of orbits and an unstable orbit branch appear at a saddle-node bifurcation, 3) a stable period-4 branch of orbits and an unstable orbit branch appear at a saddle-node bifurcation, 4) the period-3 branch of attractive orbits undergo period doubling bifurcations leading to a chaotic attractor, 5) the period-4 saddle orbit branch appears to be the cause of the disappearance of the period-3 branch chaotic attractor and to lead to a period-4 branch chaotic attractor. No chaos is observed along the period-1 branch for fluctuations of the seasonal forcing that are less than 20%.

Myxomatosis

In an analysis of the interaction between European rabbits and the viral disease myxomatosis, Dwyer, Levin and Buttel (preprint, 1988) considered a very detailed SIR model involving age structure, demographic seasonality, and detailed accounting of the etiology of disease. With demographic seasonality suppressed, they examined the sensitivity of the model to parameter variation. At low natural mortalities, the typical behavior of the model is rapidly damped oscillation to a stable equilibrium. However, as natural mortality is increased, there is a bifurcation to periodic behavior determined by the maturation delay that is incorporated in the population's life table. As the natural mortality is increased further, the period of the oscillation increases; the amplitude first increases and then decreases, and ultimately the population crashes.

When demographic seasonality is introduced into the model above, the annual period used to force the demographic parameters interacts in fascinating ways with the natural oscillatory dynamics represented in the analysis above. When the natural period of oscillation is much less than a year, as it is at low natural mortalities, the intrinsically and extrinsically induced fluctuations remain separable: there is a dominant annual period, with several shorter and less pronounced oscillations superimposed upon it. At the other extreme, that of a long natural period, a complementary situation exists: annual fluctuations are superimposed on the broader trends that are exhibited by the unforced model. In the middle regions, in which the natural fluctuations appear with a period not too different from 12 months, a complicated interference pattern results in apparently chaotic dynamics. In general, computer simulations provide us a powerful tool to explore the interplay between multiple sources of fluctuation and should lead to new insights in years to come.

3. Models with Delays in the Removed Class

Numerical simulations by Hoppensteadt and Waltman (1971), Mosevich (1975), and Boland and Powers (1977) of an integral equation SEIRS model with three

time delays suggested the existence of nontrivial periodic solutions. Periodic solutions do not exist for the ordinary differential equation SIRS model since solutions always approach equilibrium points (Hethcote, 1976). Green (1978) considered the SIRS model with constant time delays in the infectious and removed classes and showed, using a combination of numerical and Hopf bifurcation techniques, that the associated system of delay-differential equations has nontrivial periodic solutions. Busenberg and Cooke (1980) subsequently pointed out that this approach could be used to prove the existence of a periodic bifurcation from the endemic equilibrium for this SIRS model.

After all of the numerical studies above, it seemed that some epidemiological models with delays could have periodic solutions; but the essential structure causing the periodicity was unknown. In particular, it was not known if any models with one delay or no delays could have periodic solutions. Since it is important for those who use models for specific diseases to known which models lead to periodic solutions, answers to the questions above became a goal of much research.

Hethcote, Stech and van den Driessche (1981a) considered an SIRS model with an infective removal rate proportional to the infectious fraction and a constant length of immunity w. For $t > w$ the system is:

$$\begin{aligned} I'(t) &= \lambda IS - \gamma I \\ R(t) &= \int_{t-w}^{t} \gamma I(u)du \\ S(t) + I(t) + R(t) &= 1 \end{aligned} \tag{3.1}$$

They showed that as the ratio of the period of immunity w to the average infectious period $1/\gamma$ increases the endemic equilibrium for (3.1) loses its asymptotic stability and there is a Hopf bifurcation to a locally asymptotically stable periodic solution. Similarly, they showed that for particular parameter values, the ordinary differential equation $SIR_1R_2\cdots R_nS$ model has periodic solutions whenever $n \geq 3$. This model corresponds to an SIRS model with a gamma-distributed time delay in the removed class. They also showed that the endemic equilibrium for the SIRS model with an arbitrarily distributed time delay in the infectious class and an exponentially distributed delay in the removed class is always locally asymptotically stable; hence, periodic solutions cannot arise by Hopf bifurcation.

Thus, a large constant length of immunity or a delay induced by a sequence of at least three removed classes is sufficient for the existence of periodic solutions. Stech and Williams (1981) considered the SIRS model with an arbitrarily distributed time delay in the removed class and obtained qualitative conditions implying stability of the endemic equilibrium, as well as qualitative conditions implying its instability. Their results suggest that at a change in stability there is generically a Hopf bifurcation from the endemic equilibrium. Van den Driessche (1981) incorporated the effects of vital dynamics into (3.1) and showed that this tends to have a stabilizing effect on the endemic equilibrium.

At about the same time Gripenberg (1980) used a bifurcation method to show that a class-age SIRS model has periodic solutions. Also, Diekmann and Montijn (1982) showed that periodic solutions arise by Hopf bifurcation for a class-age

model equivalent to an SEIRS model. Smith (1986) also showed that periodic solutions can occur in an SEIRS model. For SEIS models with distributed time delays in the exposed and infectious class, Hethcote, Stech and van den Driessche (1981b) proved that above the threshold the endemic equilibrium is always locally asymptotically stable if both time delays are constant or if any one delay is exponentially distributed. For SIR and SEIR models with permanent immunity, vital dynamics and distributed infectious period, Hethcote and Tudor (1980) showed that periodic solutions do not occur.

The experience gained from the papers above and others led Hethcote, Stech and van den Driessche (1981c) to the conjecture already mentioned regarding when periodic solutions can occur in epidemiological models. This conjecture, however, did not consider that periodic solutions could arise in models with nonlinear incidence as described in the next section.

4. Models with Nonlinear Incidence

The incidence rate is the rate of new infections. In most epidemiological models, the incidence rate is assumed to be bilinear in the infective fraction I and the susceptible fraction S. This bilinear incidence rate of λIS is consistent with the law of mass action in chemistry, in which a chemical reaction occurs during a collision between two active molecules which are moving randomly in the gas or liquid. Epidemiological models assume that individuals are moving around in a community and that the infection is transmitted when a susceptible and an infective come into contact or "collide". The bilinear incidence rate λIS is certainly a reasonable assumption; however, nonlinear incidence rates that include saturation or that are nearly bilinear are also reasonable. Some models with nonlinear incidence can have periodic solutions without seasonal variation in the parameters.

The use of bilinear incidence is so well entrenched in the literature that many researchers feel very strongly that it should be accepted as the null hypothesis unless there is a compelling reason to the contrary. Dietz (personal communication) has argued to us that nonlinear incidence rates do not represent reasonable epidemiological models, and that their consideration should be actively discouraged and replaced by heterogeneous population models built on the assumption of bilinear incidence within and between groups. Our view is different. Certain functional forms other than bilinear incidence can be motivated on first principles; and indeed, at high densities of infectives, saturation effects seem to us as much a logical necessity as are saturation effects in population growth models. Nonlinearities of the other form, in which infection rates increase disproportionately as the density of infectives increases, represent more special situations that can only hold over limited ranges of variables. Analyses of such models are nonetheless very suggestive and are likely to be qualitatively correct near bifurcation points.

A variety of nonlinear incidence rates have been used. Wilson and Worcester (1945a, b) used λIS^q, but concluded that $q = 1$ fits the data best. Severo (1969) formulated models with incidence rates kI^pS^q where $q < 1$, but did not analyse

them. Yorke and London (1973) simulated measles outbreaks and found that an incidence rate given by $g(I)S = \beta I(1 - CI)S$ with positive C and time dependent β gives good agreement with observation. Capasso and Serio (1978) used $g(I)S$ where $g(I)$ tends to a saturation level when I gets large, e.g., $g(I) = \beta I/(1 + \beta\delta I)$. May and Anderson (1979) derived a similar form using different time scales to approximate complex transmission processes of parasitic infections with indirect life cycles. Gani (1978) argued that similar modifications should be used in a model of myxomatosis in rabbits. General functions to represent contact rates were used by Wang (1978) and Cooke (1979).

Hethcote, Stech and van den Driessche (1981b) used the incidence rate $g(I)S$ in an SEIS model. They assumed that $g(I)$ is $C^1[0, 1]$, $g(I)$ is positive on $(0, 1]$, $g(0) = 0$ and $g(I)/I$ is nonincreasing. Clearly, no incidence rate of the form kI^pS can satisfy these assumptions unless $p = 1$; however, more general forms such as those given in the previous paragraph qualify. For incidence rates of the form $g(I)S$ where $g(I)$ satisfies the assumptions, there is still a threshold value such that the disease dies out below the threshold and approaches an endemic equilibrium above the threshold. Thus these nonlinear incidence rates do not lead to periodic solutions arising through Hopf bifurcation.

Cunningham (1979) indicated that incidence rates of the form $k(IS)^p$ with $p > 1$ may lead to periodic solutions. Gabriel, Hanisch and Hirsch (1981) used a nonlinear incidence rate in a helminth disease model where reproduction depends on the probability of pairing worms within the host. In a model with a delay in the intermediate host, they found several positive equilibrium points and periodic solutions. Liu, Levin and Iwasa (1986) discussed possible mechnisms that could lead to nonlinear incidence and showed that an SIRS model with nonlinear incidence kI^pS^q can have periodic solutions for $p > 1$.

Liu, Hethcote and Levin (1987) considered the following SEIRS model with vital dynamics and nonlinear incidence.

$$S'(t) = -\lambda I^pS^q + \mu - \mu S + \delta R$$
$$E'(t) = \lambda I^pS^q - (\varepsilon + \mu)E$$
$$I'(t) = \varepsilon E - (\gamma + \mu)I$$
$$R'(t) = \gamma I - (\delta + \mu)R$$
$$S + E + I + R = 1$$

They also considered the SIS, SIR, SIRS, SEIS and SEIR models that are limiting cases of the SEIRS model above. The phase space portrait of the system above changes greatly as p changes, but does not change significantly when q changes. For $p = 1$ this SEIRS model has the usual behavior in the sense that the disease disappears below the threshold and approaches an endemic equilibrium above the threshold. Thresholds seem reasonable in infectious disease models; in particular, the notion that a contact number or reproductive number (Hethcote, 1976; Hethcote, 1987; Anderson and May, 1982) must exceed unity fits biological intuition. For $0 < p < 1$ the trivial equilibrium is always unstable and the positive equilibrium is asymptotically stable. An unrealistic aspect when $0 < p < 1$ is that there is no threshold so that the disease always remains endemic.

For $p > 1$, the disease disappears below the threshold. Above the threshold, there are three equilibria for $p > 1$ due to a saddle-node bifurcation of the positive equilibrium at the threshold. The trivial equilibrium is always locally asymptotically stable, and the small positive equilibrium always is a saddle; however, the large positive equilibrium can be stable or unstable depending on the values of p and the contact number $\sigma = \lambda\varepsilon/[(\gamma + \mu)(\varepsilon + \mu)]$. Liu, Hethcote and Levin (1987) showed that both stable and unstable periodic solutions can arise by Hopf bifurcation.

Note that periodic solutions can occur in the SEIR model ($\delta = 0$) with nonlinear incidence if $p > 1$. Thus nonlinear incidence can lead to periodicity, even if the model is not cyclic due to temporary immunity as in Sect. 3. Let us consider a typical childhood disease such as measles, mumps, rubella or chickenpox with average latent period $1/\varepsilon = 12$ days $= 1/30$ year, average (death-adjusted) infectious period $1/(\gamma + \mu) = 6$ days $= 1/60$ year, average lifetime $1/\mu = 75$ years and permanent immunity so that $\delta = 0$. Then Hopf bifurcation can occur for $p > p_1 = 1.00067$. If we choose $p = 1.01$ and $q = 1$, then there are three equilibria for $\sigma > \sigma^* = 1.15053$, and Hopf bifurcation occurs at $\sigma = \sigma^{**} = 20.667$. Note that the threshold value σ^* is approximately 1.

If $\sigma < \sigma^* = 1.15053$ then there is only the trivial equilibrium and the disease disappears. For any $\sigma > 2$ the infectious fraction I at the small positive equilibrium is less than 10^{-30} so that it is practically indistinguishable from $I = 0$ and the basin of attraction for this trivial equilibrium point is very small. The large positive equilibrium has an infectious fraction I that is approximately 0.000222 times $(1 - 1/\sigma)$. The stability of the periodic solutions around this large positive equilibrium for σ near σ^{**} can be determined by calculating the sign of a stability constant A given by (42) in Liu, Hethcote and Levin (1987). If A is positive, then there is a subcritical Hopf bifurcation and an unstable periodic solution surrounds the large positive equilibrium for $\sigma > \sigma^{**}$. If A is negative, then there is a supercritical Hopf bifurcation and a stable periodic solution surrounds the large positive equilibrium for $\sigma < \sigma^{**}$. The radius r of these periodic solutions is approximated for σ near σ^{**} by

$$r = 4\left[\frac{d(\sigma - \sigma^{**})}{-A}\right]^{1/2}$$

where d is the derivative with respect to σ of the real part of the complex eigenvalues evaluated at $\sigma = \sigma^{**}$. Thus periodic solutions can occur for realistic parameter values and for p values very near 1; however, these periodic solutions might be so small that they are indistinguishable from the positive equilibrium.

Hethcote, Lewis and van den Driessche (1988) analyzed an SIRS epidemiological model with a time delay in the removed class and a nonlinear incidence rate. They found the thresholds and number of equilibria and evaluated stability. For some parameter values, periodic solutions arise by Hopf bifurcation from the large nontrivial equilibrium state. For this model periodic solutions occur for $1/2 < p < 1$ while they did not occur for $p \leqq 1$ in the nonlinear incidence model of Liu, Hethcote and Levin (1987). Moreover, periodic solutions can occur for any $p \geqq 1$, while they only occurred for $p \geqq p_1 > 1$ in the model of Liu, Hethcote and Levin (1987).

5. Models with Variable Population Size

Many epidemiological models assume that the total population size is constant. Thus if these models include vital dynamics, the birth rate must be equal to the death rate in the population. This assumption is reasonable in human populations for diseases where death due to the disease is rare. Even if the population is growing a few percent per year, this change is often considered to be insignificant and is ignored. However, if the death rate due to the disease is significant, then this must be incorporated and the total population cannot be considered to be constant. Indeed, in animal populations disease-related deaths may regulate the population size.

Anderson and May (1979) and Ross (1916) considered models with disease-related death and variable population size. For example, if $N(t)$ is the total population size and $X(t)$, $Y(t)$ and $Z(t)$ are the numbers in the susceptible infectious and removed classes, then one SIRS model is

$$\begin{aligned} X'(t) &= -\beta XY + aN - bX + \gamma Z \\ Y'(t) &= \beta XY - (\nu + b + \alpha)Y \\ Z'(t) &= \nu Y - (\gamma + b)Z \\ N'(t) &= (a - b)N - \alpha Y \end{aligned} \tag{5.1}$$

where a is the birth rate, b is the natural death rate, and α is the disease-related death rate. For this model, Anderson and May (1979) found that the disease dies out if $r = a - b < 0$ and it persists if $r > 0$. If $0 < r < \alpha(1 + \nu/(b + \gamma))$, then an equilibrium is approached since the disease-related death regulates the population size. If $r > \alpha(1 + \nu/(b + \gamma))$, then the sizes of the infectious class, the removed class and the total population grow exponentially while the susceptible class approaches a constant size as $t \to \infty$. Other models for microparasitic (viruses, bacteria, protozoans) infections are also formulated in Anderson and May (1979). One of these models gives good fits to two diseases in laboratory mice populations. Except for the fox rabies model below, the variable population size models of Anderson and May (1979) with direct transmission do not seem to have periodic solutions.

Anderson et al. (1981) proposed the following model for fox rabies in Europe.

$$\begin{aligned} X'(t) &= \beta XY + aX - (b + \gamma N)X \\ I'(t) &= \beta XY - (\alpha + b + \gamma N)I \\ Y'(t) &= \alpha I - (\alpha + b + \gamma N)Y \\ N'(t) &= aX - (b + \gamma N)N - \alpha Y \end{aligned} \tag{5.2}$$

Here N is the total population size and X, I and Y are the numbers in the susceptible, exposed and infective classes. For certain parameter values, they found numerically that this model has stable periodic limit cycles. The periodicity may occur because the exposed and infectious foxes do not reproduce in this model.

May and Anderson (1979) developed models for both microparasites and macroparasites (helminths and arthropods) transmitted either directly or indirectly by one or more intermediate hosts. They considered the overall dynamics and the mechanisms that yield cyclic states or multiple stable states in the prevalence of the host population. In most of their models for microparasitic and macroparasitic infections, the host population either is regulated to a stable size by the disease or else it grows exponentially. However, May and Anderson (1978) found numerically that the model 5.1 with nonlinear incidence of the form $\lambda XY/(H_0 + X)$ can lead to stable limit cycles. This term is the result of a host-parasite model where the free-living infective stage of the parasite "collapses" due to a quasi-steady-state assumption. This "collapse" is due to the differences in the time scales of the host and parasite lifetimes.

Anderson and May (1981) presented a variety of models for microparasites and their invertebrate hosts. One model includes dynamical equations for the populations of free-living infective stages of microparasites:

$$\begin{aligned} X'(t) &= -\nu WX + a(X + Y) - bX + \gamma Y \\ Y'(t) &= \nu WX - (\alpha + b + \gamma)Y \\ H'(t) &= rH - \alpha Y \\ W'(t) &= \lambda Y - (\mu + \nu H)W \end{aligned} \tag{5.3}$$

where the total host population size H is divided into X susceptibles and Y infectives, and W is the number of free-living infective stages of the microparasites. They found numerically that this model has stable limit cycles for some parameter values.

Hence it seems that a variety of host-parasite models with disease-related deaths and variable population sizes can lead to periodic solutions. These host-parasite models are somewhat like predator-prey models that have periodic solutions.

Mena (1988) has analyzed rigorously various models with disease-related deaths, including the models above of Anderson and May. For these models he has determined thresholds, proved local and global stability, determined neutral stability surfaces (where the real part of conjugate pairs of characteristic roots changes sign) and proved that periodic solutions exist by Hopf bifurcation.

6. Models with Age Structure

For many diseases the susceptible fraction of age a decreases as the age a increases. Moreover, the number of contacts of an infective with susceptibles often depends not only on the age of the infective, but also on the ages of the susceptibles. School children tend to have a high contact rate since they mix a lot in school while preschool children, adults and older people often have lower contact rates. Thus it is important to consider epidemiological models with age structure.

Age-structured models were formulated by some of the pioneers in epidemiological modeling such as Ross and Hudson (1917) and Kermack and McKendrick (1927). Dietz (1975) presented the following SIR model with age structure:

$$\frac{\partial x}{\partial a} + \frac{\partial x}{\partial t} = -\lambda(t)x - \mu x$$

$$\frac{\partial y}{\partial a} + \frac{\partial y}{\partial t} = \lambda(t)x - (\gamma + \mu)y$$
$$\frac{\partial z}{\partial a} + \frac{\partial z}{\partial t} = \gamma y - \mu z \tag{6.1}$$
$$\lambda(t) = \beta \int_0^a y(s,t)ds$$

with initial and boundary conditions

$$x(a,0) = x_0(a), \quad y(a,0) = y_0(a), \quad z(a,0) = z_0(a)$$
$$x(0,t) = N\mu, \quad y(0,t) = 0, \quad z(0,t) = 0$$

where x, y and z are the susceptibles, infectives and removeds, respectively, N is the total population size, μ is the birth and death rate, $\lambda(t)$ is the total infectivity and γ is the removal rate. Similar models with a chronological age a and a class age c in the infectious class were formulated and analysed by Hoppenstadt (1975). Longini et al. (1978) used an ordinary differential equation SIR model with the population divided into age groups to compare vaccination programs for influenza.

Although age-structured models with a proportionate mixing contact matrix or a symmetric contact matrix do not seem to have periodic solutions, it appears that an asymmetric contact matrix can lead to periodic solutions. Enderle (1980) used a discrete Reed-Frost type model with three age groups for measles. When he used an asymmetric contact matrix between his age groups, he numerically obtained periodic solutions with a period of about eight years.

Age-structured models have been used to compare the USA and UK strategies for rubella vaccination (Knox, 1980; Dietz, 1981; Hethcote, 1983; Anderson and May, 1983). The implications of these modeling studies of rubella vaccination were summarized in Hethcote (1986). Age-structured models were applied to a variety of diseases in Anderson and May (1982). None of these models with age-specific incidence seems to have periodic solutions.

Ordinary differential equation models with age groups have been used to study measles. Schenzle (1984) used 21 age groups and a symmetric contact matrix which changes when school opens and closes. His model with its seasonally varying contact matrix fits the biennial data for measles in England and Wales. Moreover, his model fits data from Hamburg in 1900–1913 when new children started school in the spring and there were two peaks per year. As in Sect. 2, it is the periodic contact matrix in the Schenzle model that leads to periodic solutions. Tudor (1985) used a model with 5 age groups and a proportionate mixing contact matrix to study measles vaccination in the USA.

Other age-structured models are described in Dietz and Schenzle (1985a). Dietz and Schenzle (1985b) derived the threshold for a general SEIR model with proportionate mixing, chronological age, class age, and vaccination. El-Doma (1986) proved global stability of the steady-state age distribution for an SIS model with age structure and both horizontal and vertical transmission. Thus the current status for periodicity in age-structured models of constant population size is as follows: sustained periodic solutions have occurred only when the contact matrix

is asymmetric (Enderle, 1980) or the contact matrix is periodic (Schenzle, 1984).

Castillo-Chavez et al. (1988a, 1988b) used various models to gain some insight into the observed multiyear periodicities in influenza and into the roles of cross-immunity and age-dependence. Their simulations and analyses with cross immunity between two strains, but without any age structure, suggest that periodic solutions do not occur. On the other hand, when age-structure is introduced for a single viral strain, again only slowly damped oscillations are observed. However, when two strains are coupled by cross immunity, periodic solutions are found numerically for some age structures; in effect, the weakly damped oscillations due to age structure and those due to the interaction between strains mutually excite one another. In particular, if the survivorship is a negative exponential function of age (approximately true in a developing country), then their two-strain model does not seem to have periodic solutions; however, if the survivorship is constant until age 75 years when everyone dies (approximately true in a developed country), then numerical simulations suggest the existence of periodic solutions (Andreasen, 1987). Thus the multiyear periodicities that are observed in influenza incidence could be due to cross immunity between related strains of an influenza subtype. However, the sensitivity of the observed period to the time step used leaves open many questions concerning the robustness of this conclusion.

7. Conclusion

The list of ways in which periodic behavior and related sustained oscillatory behavior can arise in epidemiological models is a growing one; but these can be grouped into a number of categories. The principal dichotomy is between periodicities that are forced externally and those that arise autonomously, although interesting phenomena occur when both factors are present in the same model.

Autonomous oscillations can arise in a variety of ways, all of which involve some sort of delay. For a single host population without age structure and without periodic coefficients, explicit delays in the removed class can be introduced in ways that give rise to oscillations. Such models introduce a time delay operating through the internal structure of the population. Similarly, delays introduced through age-specific contact rates can lead to sustained oscillations, but apparently only if contacts are not symmetric in transmission effectiveness. These restrictions may be relaxed if the population size is allowed to vary, in which case various mechanisms (such as age-specific fecundities) can lead to oscillations. Finally, a somewhat surprising deviation from these generalizations occurs if the usual assumption of bilinear incidence rates is relaxed. The important ecological relevance of the particular incidence functions that lead to sustained oscillations can be debated, but it is clear that the investigation of the mathematical properties of models with nonlinear incidence functions has raised our awareness of the importance of the form of this term.

With the consideration for various diseases of the interactions between multiple host populations, multiple disease types and multiple groups, including age classes,

a whole new set of possibilities is opened up. Preliminary investigation of age-structured models with multiple disease types suggest that sustained oscillations are possible even with constant population size. It should not be a surprise if further investigations of multiple-type models demonstrate a variety of ways in which oscillations can be maintained, since interactions between types provide another way that delays can be introduced.

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