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Modelling the different smallpox epidemics in England

S. R. DUNCAN[1], S. SCOTT[2] AND C. J. DUNCAN[3]†

[1]*Control Systems Centre, Department of Electrical Engineering and Electronics, UMIST, P.O. Box 88, Manchester M60 1QD, U.K.*
[2]*Department of Economic and Social History, University of Liverpool, Liverpool L69 3BX, U.K.*
[3]*Department of Environmental and Evolutionary Biology, University of Liverpool, Liverpool L69 3BX, U.K.*

SUMMARY

Time series analysis has revealed two different patterns of smallpox epidemics in Britain in the seventeenth and eighteenth centuries: in large conurbations (exemplified by London) the disease was endemic whereas medium-sized rural towns (exemplified by Penrith, Cumbria) suffered from 5 year epidemics with no cases of smallpox in the inter-epidemic years. The oscillations (epidemics) persisted for over 150 years and it is suggested that both systems were pumped up by regular fluctuations in susceptibility ($\delta\beta$). Modelling suggests that: (i) the natural frequency of oscillations in large cities is two years and the system is pumped up by a 1 year, seasonal input; (ii) it takes five years to build up a pool of susceptibles in medium-sized towns by new births and epidemics are then triggered by a 5 year input. The equations represent a system that has two components, a basic linear element with the remainder of the system being nonlinear; modelling a progressive increase in $\delta\beta$ in London illustrates theoretically how a predominantly linear response changes to a nonlinear response and ultimately to chaos. A variation in susceptibility is a theoretical condition for inducing chaos; the undriven system cannot become chaotic. Modelling populations of progressively increasing size/density and applying a 1 year or 5 year sinusoidal oscillation in $\delta\beta$ illustrates the fundamental distinction in the response of medium-sized rural towns and large cities.

1. INTRODUCTION

Smallpox has been described as the most infectious human disease but was rarely lethal until the 1630s (Appleby 1981) when many accounts suggest that a particularly virulent strain began to afflict people (Corfield 1987) with a gradual but significant increase in the case fatality rate (Razzell 1977). It was greatly feared in England from the time of the final visitation of bubonic plague in 1666 until the end of the nineteenth century, when it ceased to be endemic (Smith 1987) because of variolation, inoculation and vaccination.

We have used the burial series of parish registers to study child mortality, analysing the results by conventional time-series analysis: we have described short-wavelength oscillations in mortality (Duncan *et al.* 1992) and have suggested that the peaks are composed, in part, of child deaths resulting from smallpox epidemics (Duncan *et al.* 1993*a*). We have also analysed smallpox deaths directly by time-series analysis in the Bills of Mortality series (Duncan *et al.* 1993*b*). It is evident that the dynamics of this viral disease during the seventeenth and eighteenth centuries were different in different population centres, as follows.

1. Scattered communities where the population size/density was below a critical level: no smallpox epidemics were detectable. In some smaller communities, the population increased rapidly after about 1750 and regular epidemics began once numbers had increased above a critical size (Duncan *et al.* 1993*a*).

2. Medium-sized rural towns where smallpox epidemics with a 5-year periodicity began to be firmly established after about 1640. The disease was not endemic at any time. We have studied the dynamics of smallpox epidemics in Penrith, Cumbria, in detail (Duncan *et al.* 1993*a*,*b*).

3. Large cities, e.g. London (Duncan *et al.* 1993*b*), Chester, Glasgow and Edinburgh (Duncan *et al.* 1994), where smallpox was endemic with superimposed epidemics at a frequency of 2 to 3 years.

In this paper we present computer modelling of populations (ii) and (iii) to illustrate the different dynamics of the disease.

2. METHODS

Time-series analysis was carried out by the time-series comuting method of Shumway (1988) with an IBM PC AT, as previously described (Duncan *et al.* 1992). Modelling was developed using the SIMULINK module in the PRO-MATLAB package and run on a Sun Workstation. The differential equations were solved by using the function in SIMULINK, which is based on fourth-order Runge–Kutta–Fehlberg methods (Forsythe *et al.* 1977).

† To whom correspondence should be addressed.

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3. THE DYNAMICS OF SMALLPOX INFECTIONS

Anderson & May (1991) have provided a mathematical study of the theory of infectious, viral epidemics; their analysis as applied to smallpox is summarised in appendix 1. There are two important conclusions that can be drawn from this analysis.

(i) After an epidemic of smallpox in a medium-sized rural town almost all the children will have been infected, so that the population will be largely composed of immune survivors (Z) from the latest or earlier epidemics. The 5 year inter-epidemic interval detected by time-series analysis of the burials in the parish registers is the time taken to build up the density of susceptibles by new births to a critical threshold level.

(ii) A model of these four basic equations, determining the fraction of susceptibles (X) as a function of time, exhibits a damped oscillation, i.e. the epidemics are predicted to die out rapidly (Anderson & May 1991). This prediction is clearly at variance with our study of smallpox epidemics at London (Duncan *et al.* 1993*b*), Chester (Duncan *et al.* 1994) and Penrith and other rural towns (Duncan *et al.* 1993*a*), where the oscillatory outbreaks clearly do not decay over a period of 150 years.

Smallpox in the sixteenth and seventeenth centuries in England was almost wholly a disease of children; the mean age at death has been calculated as 2.6 years (Razzell 1977) and 4.5 years (Scott & Duncan 1993). The equations derived in the Appendix predict that the inter-epidemic period (T) would be 2 years, a value that agrees with the period of smallpox epidemics detected in large conurbations (Duncan *et al.* 1993*b*). We conclude, therefore, that smallpox epidemics occurred at approximately 5 year intervals in medium-sized towns because of the absolute requirement that the susceptibles needed to build up by fresh births to exceed the critical threshold density. On the other hand, in large cities, where the disease was endemic, the system oscillated at its natural frequency.

Anderson & May (1991) have suggested that stochastic effects could perpetuate and pump up a decaying oscillation, so locking the system into sustained cycles; they have explored a variety of different mechanisms by which epidemics in different diseases may be perpetuated. What external factors would act to pump up the oscillations (smallpox epidemics) both in large conurbations and in rural towns, where T is clearly different, in England during 1650–1800? We have suggested that a periodic fluctuation in susceptibility to this disease (β) could provide the necessary trigger to maintain the oscillations (Duncan *et al.* 1993*a*). Short-wavelength oscillations in annual total deaths with a period of approximately 5 years have been described in the parish of Penrith, Cumbria (Duncan *et al.* 1993*a*) and in other parishes in N. W. England (Duncan *et al.* 1993*b*) throughout the period 1550–1800, and these have been shown to synchronize with corresponding oscillations in wheat prices, which also have a periodicity of about 5 years. The thesis that wheat prices drive child deaths at Penrith has been tested by examining the input–output relations of the two series (Shumway 1988); the squared coherence function showed that the two series are coherent in the frequency bands of wavelength 5–6 years after 1650 (Duncan *et al.* 1993*b*). We suggest that periodic high grain (wheat and barley) prices caused malnutrition and famine, resulting in higher mortality, particularly among infants and young children. These oscillations in mortality became established after 1550 and, it is suggested, caused an associated fluctuation in susceptibility to disease. These oscillations in susceptibility to smallpox established the 5 year epidemics after 1640 and were superimposed on the pre-existing mortality cycle.

Another possible periodic oscillation in susceptibility to infection is the annual seasonal fluctuation. A small-amplitude, seasonal mechanism has been suggested to produce period-doubling bifurcations, so causing the biennial measles epidemics (Dietz 1976; Aron & Schwartz 1984).

We consider here the theoretical effect of a sinusoidal variation in susceptibility (or transmission coefficient, β) on the population dynamics of two model communities, a large city and a medium-sized rural town (see Olsen *et al.* 1988; Olsen & Schaffer 1990).

4. THEORETICAL EFFECT OF A VARIATION IN SUSCEPTIBILITY TO SMALLPOX (β)

Three changes have been applied to the four basic equations described in the Appendix.

(i) The latent stage of the infection is ignored and the latents are incorporated into infectives.

(ii) The death rate from smallpox, α, is included in the equations.

(iii) The variables X, Y and Z give the absolute numbers in each class but, using the approach described in Anderson & May (1991), the equations are written in terms of the fraction of the population in each class by defining three new variables:

$$x = X/N; = Y/N; \quad z = Z/N.$$

Incorporation of these changes reduces the basic equations to:

$$\mathrm{d}x/\mathrm{d}t = \mu - \mu x - N\beta xy; \tag{1}$$

$$\mathrm{d}y/\mathrm{d}t = N\beta xy - (\mu + \alpha + \gamma)y. \tag{2}$$

Note that it is necessary to solve only two equations because the fraction of the population which is immune, Z, can be deduced from the fact that $x + y + z = 1$.

Equations (1) and (2) describe the response of a nonlinear equation in terms of a pair of coupled first-order differential equations. Because this system can be described by only two differential equations, it is not possible for the system to display chaotic behaviour. However, it is proposed that the model is driven by periodic variations in the susceptibility to infection. This variation is represented by:

$$\beta(t) = \beta\left[1 + \delta\beta \sin\frac{(2\pi t)}{\lambda}\right], \quad (3)$$

where λ = the wavelength of the periodic variation and β = the nominal or steady state value of the susceptibility. The amplitude of the variation is determined by $\delta\beta$, which represents the change in the susceptibility, expressed as a fraction of β.

An alternative description of the dynamic response of the system can be obtained by defining Φ as the phase of the periodic variation,

$$\Phi = (2\pi t)/\lambda; \quad (4)$$

then equation (3) can be written as

$$\beta(t) = \beta[1 + \delta\beta \sin(\Phi)] \quad (5)$$

and equations (1), (2) and (5) can be arranged to give

$$dx/dt = \mu - \mu x - N\beta xy[1 + \delta\beta \sin(\Phi)], \quad (6)$$

$$dy/dt = N\beta xy[1 + \delta\beta \sin(\Phi)] - (\mu + \alpha + \gamma)y, \quad (7)$$

$$d\Phi/dt = 2\pi/\lambda. \quad (8)$$

In this form it can be seen that the response of the system that is driven by periodic variations in susceptibility can be described by three coupled, first-order, nonlinear differential equations. Because there are three equations, the dynamics of this system can exhibit a chaotic response, as will be shown below.

Further insight into the response of the model can be obtained by considering equations (6) and (7) as consisting of the sum of a linear component and the nonlinear term,

$$N\beta xy[1 + \delta\beta \sin(\Phi)].$$

The amplitude of the variation in the force of the infection, $\delta\beta$, determines whether the linear or nonlinear term dominates.

If a linear system is driven by a sinusoidal variation, the output in both number of susceptibles and number of infectives is sinusoidal where: (i) the frequency of the output variation is the same as the frequency of the driving variation; (ii) the amplitude of the output variation will be different from that of the amplitude of the driving term; and (iii) the output variation will be phase shifted relative to the driving variation.

For given values of death rate (μ), smallpox death rate (α) and recovery rate (γ), the natural frequency of the system is determined by the value of $N\beta$ (where N = population size and β = the steady state value of susceptibility or transmission coefficient before any oscillations are applied). The natural frequencies of the two populations under consideration are 2 years (large cities) and 5 years (medium-sized rural towns)

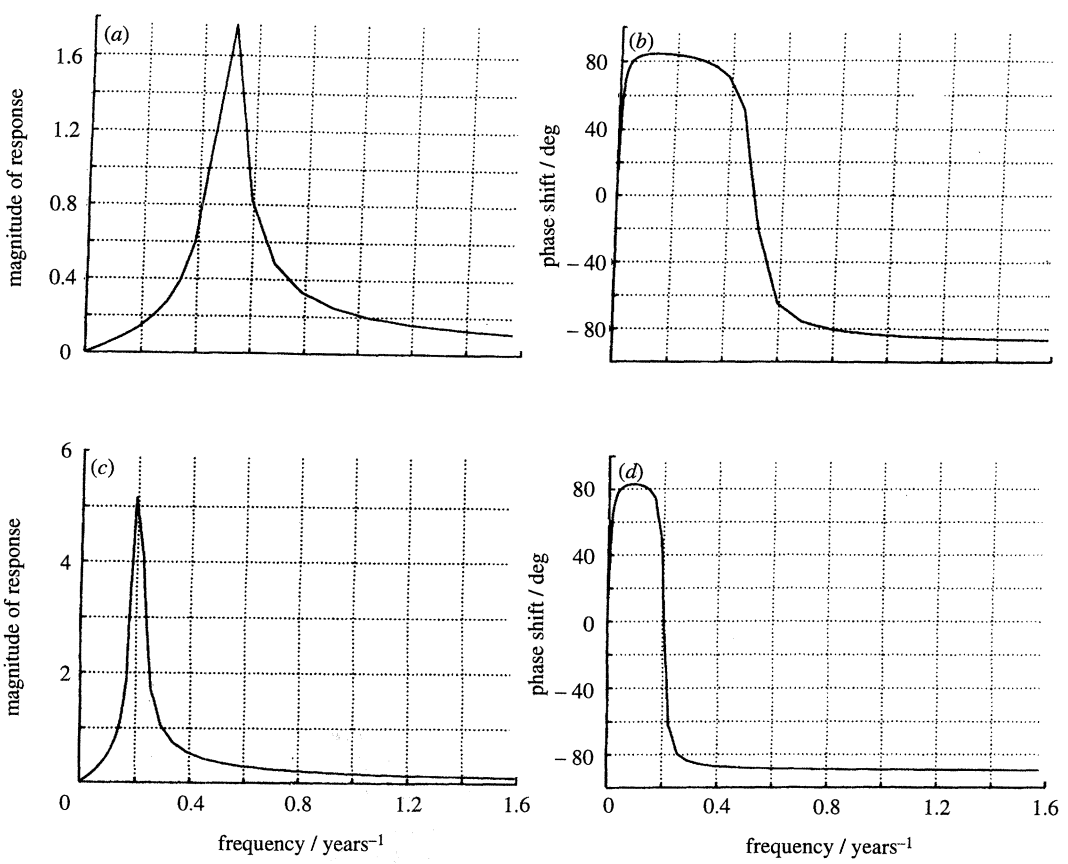

Figure 1(*a*,*c*) Amplitude of the response of model systems plotted against the frequency of the input. (*b*,*d*) Phase shift in degrees (ordinate) plotted against input frequency (1/years). (*a*,*b*) $N\beta = 270$ ('London'), maximum output amplitude generated at a frequency of 0.5.(*c*,*d*) $N\beta = 65$ ('Penrith'), natural frequency of 0.2.

and can be characterised by using frequency response plots (or Bode diagrams) of the linear portion of the systems.

Figure 1*a*,*b* illustrates the response of the linear portion where $N\beta = 270$; figure 1*a* plots the amplitude of the output variation generated by a unit input variation against frequency. The maximum output amplitude is generated by an input frequency of 0.5 (i.e. period = 2 years; figure 1*a*). Figure 1*b* shows the corresponding phase shift in degrees; for frequencies below 0.5 the output leads the input and for frequencies above 0.5 the output lags the input.

Figure 1*c* (magnitude of response) and figure 1*d* (phase shift) illustrate the corresponding responses where $N\beta = 65$. The system has a natural frequency of 0.2 (period = 5 years).

The foregoing applies to the linear element of the system. For small amplitudes of the variation ($\delta\beta$) the response is approximately linear, so that the output is sinusoidal for a sinusoidal variation in $\delta\beta$ at the same frequency, but different in amplitude and phase. As $\delta\beta$ is increased the nonlinear effects begin to become significant (see below).

A fourth-order Runge–Kutta–Fehlberg method is used to integrate the differential equations. However, using the equations in the form given in (6)–(8), the integration procedure proved to be susceptible to numerical errors, particularly in regions where the number of infectives is small (i.e. between epidemics). The robustness of the integration procedure can be improved by transforming equations (6) and (7) by using the substitutions $u = \log_e x$ and $v = \log_e y$, so that $du/dx = 1/x$ and $dv/dy = 1/y$.

This leads to

$$du/dt = \mu e^{-u} - \mu - N\beta[1 + \delta\beta \sin(\Phi)]e^{v}; \quad (9)$$

$$dv/dt = N\beta[1 + \delta\beta \sin \Phi]e^{u} - (\mu + \alpha + \gamma). \quad (10)$$

5. SINUSOIDAL VARIATION IN SUSCEPTIBILITY

In the modelling described below, the system is assumed to start out in steady-state, the original oscillations being damped out. The dynamics of model populations are simulated by assuming $\mu = 0.04$, $\alpha = 4.0$, $\gamma = 20.0$ (i.e. the average age at death = 25 years and 1/6 of those infected die of the disease), the latent plus infectious periods = 15 days. The dynamics of the two model populations are defined as follows: $N\beta = 270$ in a large city (e.g. London or Chester; see figure 1*a*,*b*) and $N\beta = 65$ in rural towns (e.g. Penrith; see figure 1*c*,*d*). When comparing different populations, it is evident that N is

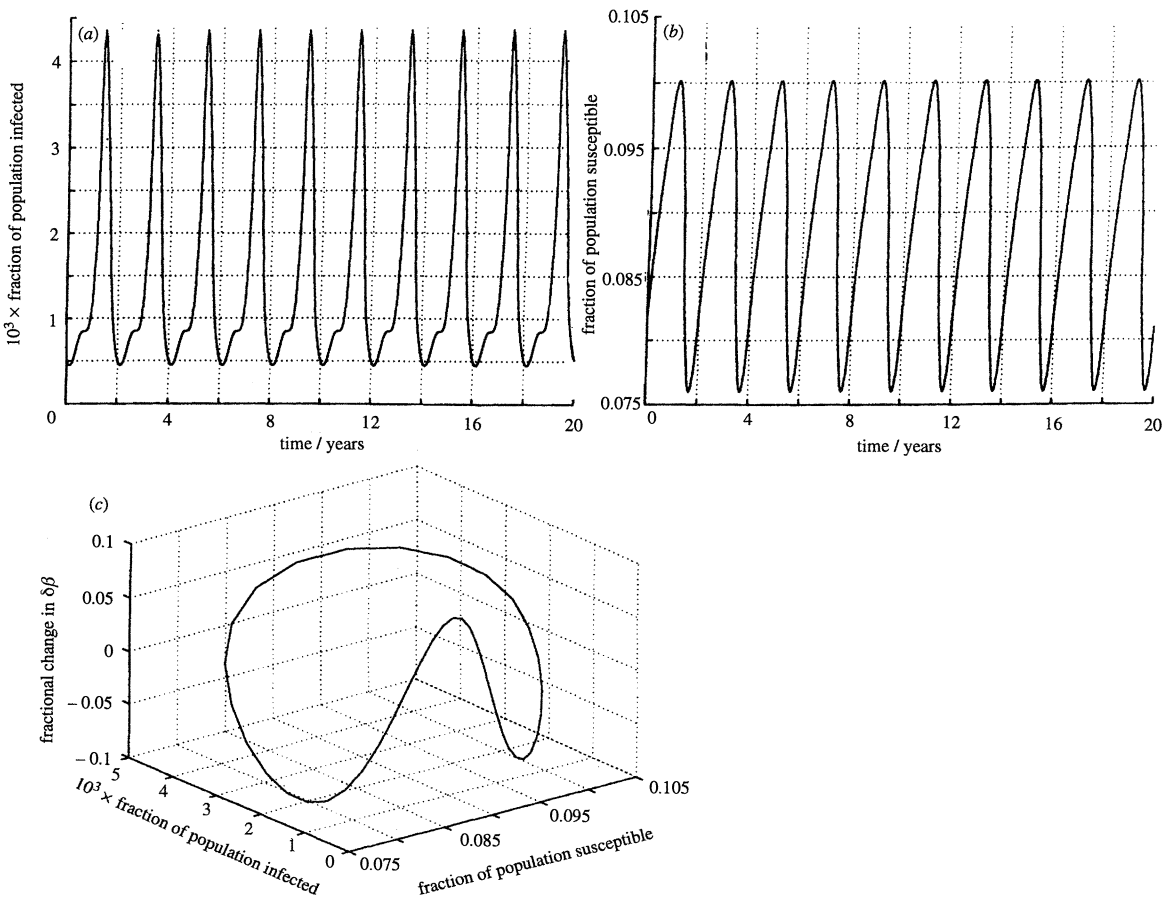

Figure 2. London model. $N\beta = 270$; $\delta\beta = 0.08$; period of sinusoidal input = 1 year. (*a*) Fraction of population infected; note dominant 2 year oscillation; smallpox is endemic. (*b*) Fraction of population susceptible. (*c*) Phase diagram of fraction of population susceptible vs. fraction of population infected vs. fractional change in $\delta\beta$.

not simply the total size of the population but is also related to the average population density.

The driving force is a sinusoidal variation in susceptibility; the input is either (i) an annual seasonal cycle as has been suggested for driving the biennial measles epidemics (Dietz 1976; Aron & Schwartz 1984) or (ii) a 5 year cycle associated with grain prices, famine and hardship. The model is run for 250 years and all figures show the results for the last 20 years (fraction of population infected or susceptible) or the last 50 years (phase diagrams).

Example 1. London: $\delta\beta = 0.08$, period of sinusoidal input = 1 year. The results of modelling are shown in figure 2. The small annual fractional change in β (8%) generates a 2 year oscillation in the fraction of the population infected although there is evidence of the effects of the annual input in the inter-epidemic years. The number of infectives does not drop to zero in the inter-epidemic periods, i.e. the disease is endemic (figure 2*a*). The progressive rise in the number of susceptibles, which crashes at the epidemic, is shown in figure 2*b*. The phase plane of susceptibles vs. infectives vs. the fractional change in $\delta\beta$ after the system has stabilized is shown in figure 2*c*. The fraction of the population infected in the phase diagram does not fall to zero, indicating that smallpox was endemic. There is no indication of chaos; the phase diagram is simply the result of driving a nonlinear system with a sinusoidal input. We conclude that a small (8%) annual variation in β is sufficient pump up the system, so that the system oscillates at its natural frequency (2 years).

Example 2. London: $\delta\beta = 0.11$, but the sinusoidal input is compounded of 75% 1 year cycle, 25% 5 year cycle (i.e. the annual cycle is modified by a small component of the wheat price cycle). The change in the fraction of the population infected is shown in figure 3*a* and the change in the fraction of the population susceptible to smallpox is shown in figure 3*b*. Again, the number of infectives does not drop to zero in the inter-epidemic periods. The oscillation generated is less regular than that shown in figure 2*a* and superficially more closely resembles the London smallpox epidemics that have been determined by filtering the Bills of Mortality series (Duncan *et al*, 1993*b*). This is illustrated by the phase diagram (fraction of the population infected plotted vs. fraction susceptible vs. $\delta\beta$) in figure 3*c*.

Spectral analysis of smallpox deaths recorded in the London Bills of Mortality shows clearly that only the

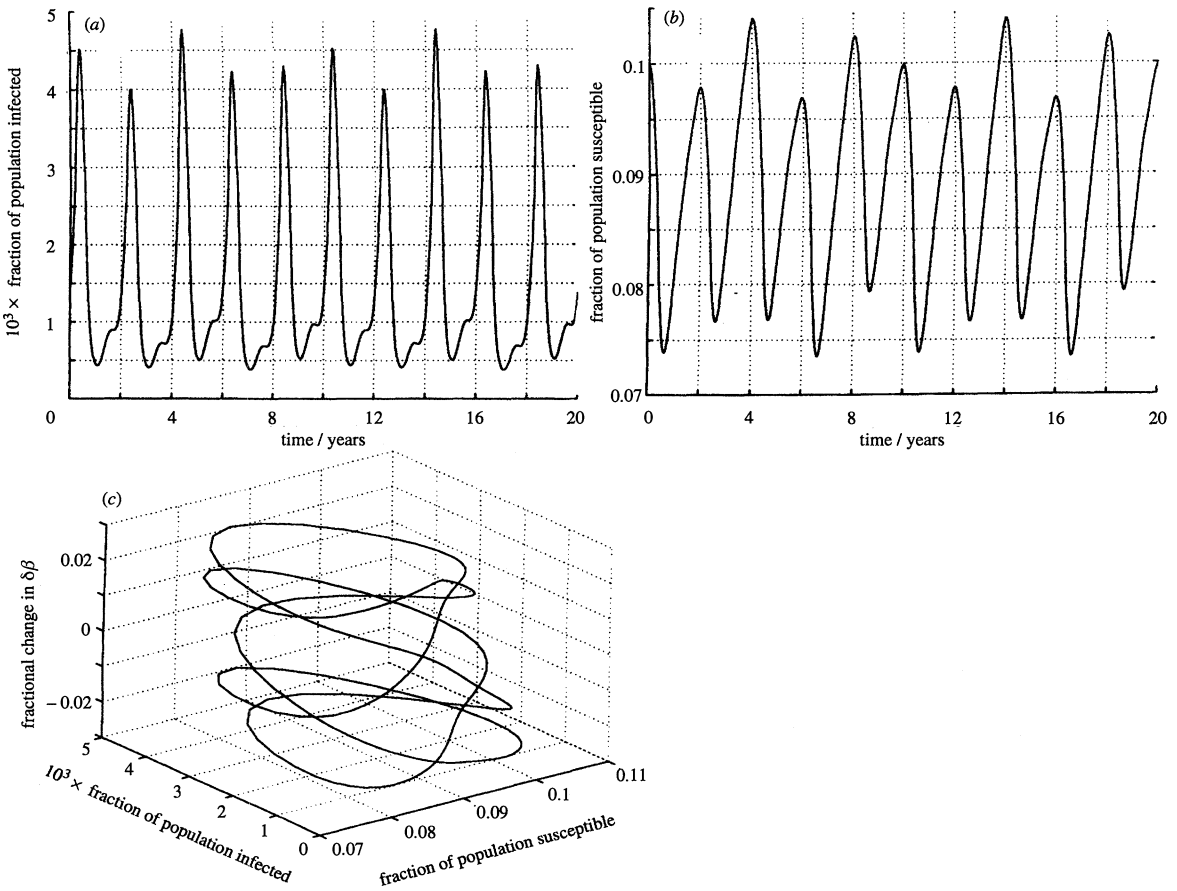

Figure 3. London model driven by a compound input $\delta\beta = 0.11$, 75% 1 year cycle and 25% 5 year cycle; $N\beta = 270$. (*a*) Fraction of population infected. Smallpox is endemic. (*b*) Fraction of population susceptible. (*c*) Phase diagram, fraction infected vs. fraction susceptible vs. fractional change in $\delta\beta$; smallpox endemic.

2 and 3 year cycles are significant, although minor peaks at a wavelength of 5 years can be detected. Filtering the London Bills of Mortality smallpox series (filter window = 4–8 years) to exclude the 2–3 year cycles reveals clear 5 year oscillations (a.c.f. at 5 years = 0.6). When this series is run against wheat prices, using the same filter, there is a good cross-correlation at zero lag (c.c.f. = 0.49). The coherence between wheat prices (input) and London smallpox mortality (output) is significant ($p < 0.025$) only in the 5 year cycles. We conclude that there is evidence that the 5 year oscillation in wheat prices may produce a secondary 5 year oscillation in β, which modulates the response of the system in London to its 1 year driving sinusoidal input.

Example 3. Penrith: $\delta\beta = 0.05$; period of sinusoidal input = 5 years. The natural period of the system is close to 5 years and with only this small $\delta\beta$ (5%) very large epidemics are generated at a periodicity of 5 years. There are virtually no infectives in the inter-epidemic period (figure 4*a*), i.e. the disease was not endemic. The response is non-sinusoidal. The corresponding simulation for the number of susceptibles (figure 4*b*) shows the progressive build-up by new births during the inter-epidemic period and the dramatic fall at the epidemic. The phase diagram of susceptibles vs. infectives vs. $\delta\beta$ is shown in figure 4*c*.

We conclude that the dynamics at Penrith are simply explained; the population takes 5 years to build up the pool of susceptibles to threshold size/density ($X > N_T$); i.e. the natural frequency of the system is determined by $N\beta = 65$, whereupon an epidemic is triggered by a very small change in β so that smallpox oscillations become phase-locked to the 5-year oscillations in wheat prices.

Example 4. Penrith: $\delta\beta = 0.08$; the sinusoidal input is compounded of 75% 1 year cycle, 25% 5 year cycle. The resulting oscillation is less regular, but strongly retains its 5 year periodicity. However, the number of infectives does not fall to zero in the inter-epidemic period (figure 5*a*) and this is not a completely satisfactory model of the conditions at Penrith. We conclude that, with $N\beta = 65$, the Penrith model is robust so that even when only 25% of the input is a 5 year oscillation the epidemics are established at 5 year intervals. Indeed, with $N\beta = 65$, the model locks onto the 5 year component, even if the ratio of the 1 year cycle to the 5 year cycle is 9 : 1.

Example 5. Penrith: $\delta\beta$ is raised to 0.13; the sinusoidal input is compounded of 75% 1 year cycle, 25% 5 year

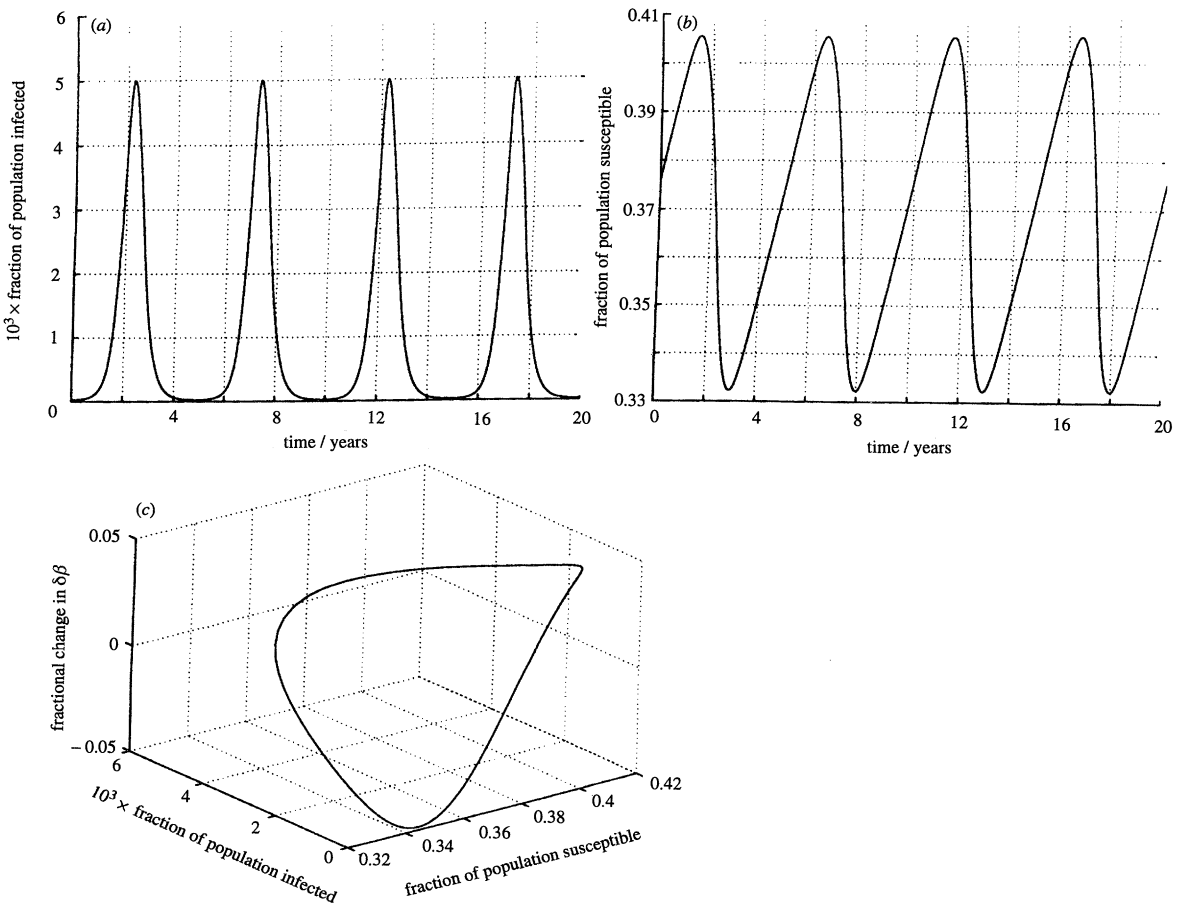

Figure 4. Penrith model. $N\beta = 65$; $\delta\beta = 0.05$; period of sinusoidal input = 5 years. (*a*) Fraction of population infected; 5 year, non-sinusoidal oscillatory output; smallpox is not endemic. (*b*) Fraction of population susceptible. (*c*) Phase diagram, fraction infected vs. fraction susceptible vs. fractional change in $\delta\beta$.

cycle. The 5 year oscillation in infectives shows clearly with this higher $\delta\beta$ of 13% (figure 6*a*) even though the 5 year driving input has again been reduced to 25% of $\delta\beta$. The build-up of the number of susceptibles during the interepidemic periods is shown in figure 6*b*. We conclude from examples 4 and 5 that the 1 year seasonal cycle has little effect on the dynamics of the Penrith model, which is robust and primarily responds with 5 year epidemics.

Compared with the changes induced by variations in the susceptibility, $\delta\beta$, the model system is markedly less sensitive to fluctuations in the disease-induced death rate, α, and the non-diseased induced mortality rate, μ.

7. THE RESPONSE OF THE SYSTEM TO A PROGRESSIVE INCREASE IN $\delta\beta$

Equations (6) and (7) represent a nonlinear system that is defined by the value of $N\beta$; the foregoing examples illustrate how populations with differing values of $N\beta$ have different fundamental characteristics, including the period of their natural frequency. The system has two components: there is a basic linear element, with the remainder of the system being nonlinear. As $\delta\beta$ (which is the amplitude of the variation driving the system) is increased, the nonlinear effects become more significant. This effect of progressively raising $\delta\beta$ has been studied in the London model ($N\beta = 270$) driven by a sinusoidal 1 year input; the results are summarised in table 1. At very low levels of $\delta\beta$ (< 0.055) the 1 year input generates a regular 1 year output cycle (figure 7*a*), but at $\delta\beta = 0.055$ the response of the system changes and, within the broad range of $\delta\beta = 0.055$ to 0.25, a regular 2 year cycle is generated. At the lower end of this range (e.g. $\delta\beta = 0.059$), the 1 year component of the output is clearly evident; however, at values of $\delta\beta > 0.065$ the 1 year component is of little importance (see figure 2; $\delta\beta = 0.08$). As $\delta\beta$ is increased to around 0.25 there is a bifurcation (revealed on the phase diagram) so that the pattern repeats every 4 years although the dominant oscillation remains at 2 years (figure 7*b*). Further bifurcations occur at $\delta\beta = 0.285$ (figure 7*c*) and at $\delta\beta = 0.293$ (note narrow ranges of $\delta\beta$ in table 1). The system becomes chaotic at $\delta\beta = 0.3$ (figure 7*d*) and remains so until, at $\delta\beta = 0.435$, it abruptly switches back to a condition of steady, 4 year epidemics with virtually no infectives between outbreaks. This abrupt transition is clearly illustrated by comparing figures 7*d* ($\delta\beta = 0.434$) and 7*e*

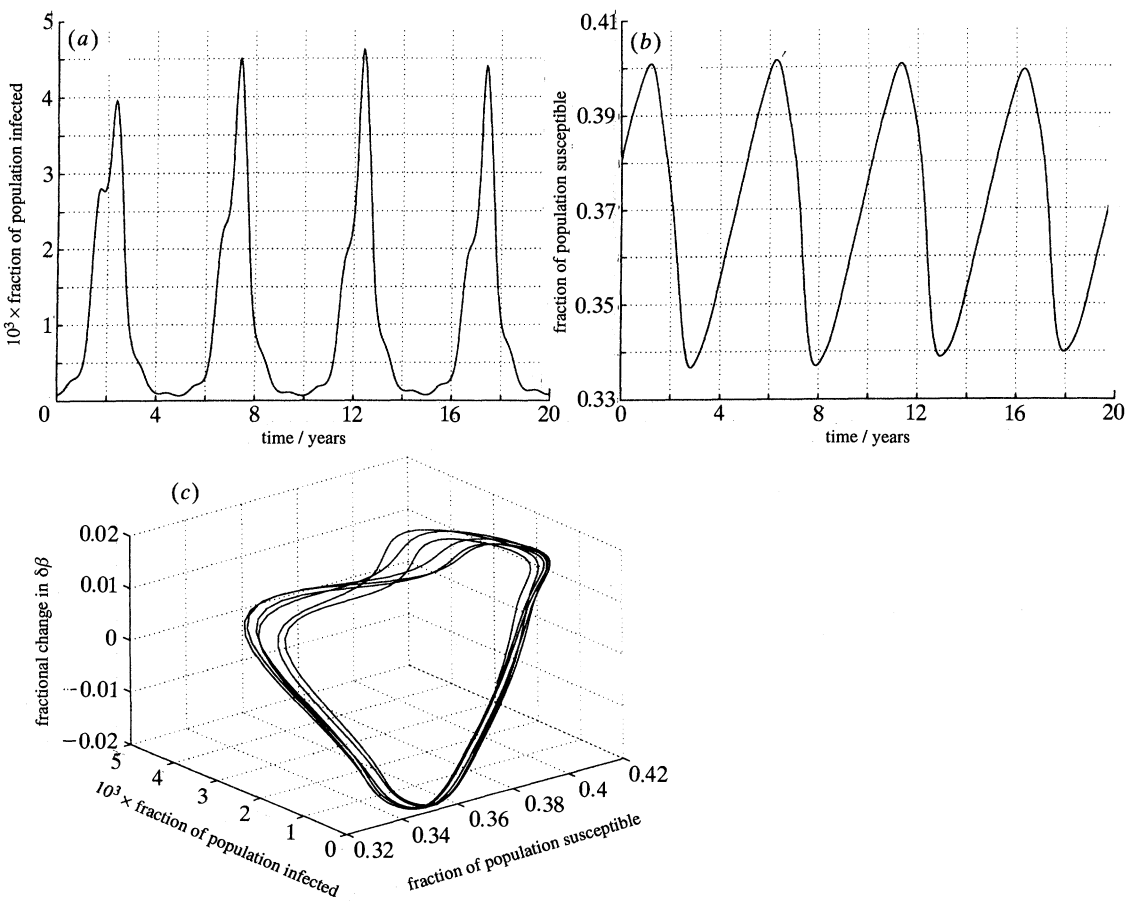

Figure 5. Penrith model driven by a compound input, $\delta\beta = 0.08$, 75% 1 year cycle and 25% 5 year cycle; $N\beta = 65$. (*a*) Fraction of population infected; 5 year, non-sinusoidal oscillatory output; number of infectives does not fall to zero in inter-epidemic years. (*b*) Fraction of population susceptible. (*c*) Phase diagram, fraction infected vs. fraction susceptible vs. fractional change in $\delta\beta$ due to 5 year cycle.

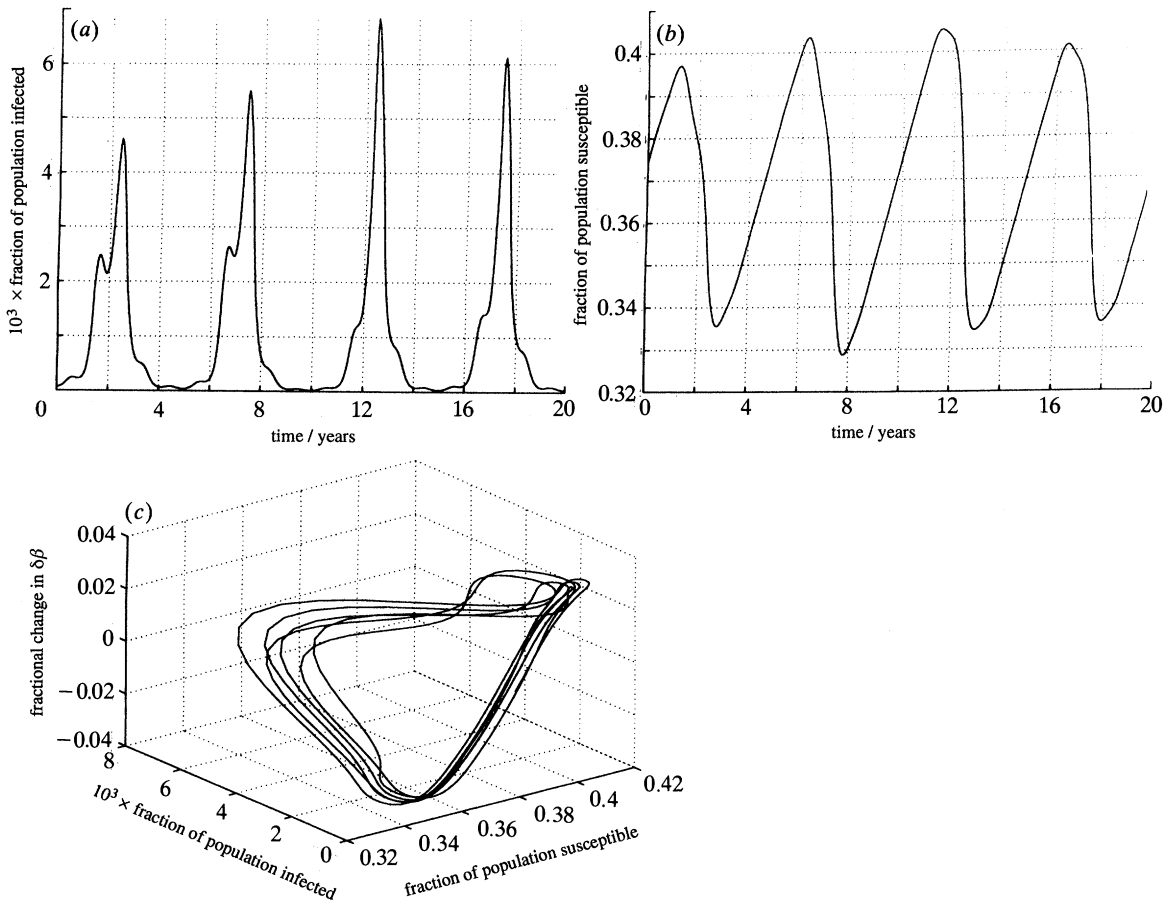

Figure 6. Penrith model driven by a compound input, $\delta\beta = 0.13$, 75% 1 year cycle, 25% 5 year cycle; $N\beta = 65$. (*a*) Fraction of population infected. (*b*) Fraction of population susceptible; abscissa = years. (*c*) Phase diagram, fraction infected vs. fraction susceptible vs. fractional change in $\delta\beta$ due to five year cycle.

($\delta\beta = 0.435$). It seems that chaos in the model system is related to the transition from the endemic to the epidemic condition.

As $\delta\beta$ increases further (> 0.63), bifurcations occur; see figure 7*f* (note the narrow ranges of $\delta\beta$ for changes in the character of the response of the system, table 1), and the system again becomes chaotic although the underlying 4 year oscillation remains visible.

We conclude from this modelling (i) that if $N\beta = 270$ is accepted as a description of conditions in London (see figure 1), the annual variation in susceptibility that will trigger the 2 year epidemics lies in the range of $\delta\beta = 5\%$ to 25%; and (ii) that chaos may be associated with the transition from the disease being endemic with major superimposed epidemics to the condition of regular epidemics with virtually no infectives in the inter-epidemic years.

8. THE EFFECT OF A VARIATION IN $N\beta$

The two model systems studied here, London and Penrith, differ in $N\beta$, i.e. in population size or density. In this section we briefly summarize the effects produced when either a 1 year or a 5 year sinusoidal driver is applied to a population with a progressive increase in $N\beta$. The amplitude of $\delta\beta$ is arbitrarily fixed at 0.1, within the range that generates a 2 year cycle in the London model (table 1) and a 5 year cycle in the

Table 1. *Regions of response of London system to variation in* $\delta\beta$

($N\beta = 270$; $\gamma = 1$ year)

$\delta\beta$	behaviour	figure
0 – 0.055	Regular 1 year cycle	7*a*
0.055 – 0.25	Regular 2 year cycle (with 1 year component detectable)	2
0.25 – 0.285	1st bifurcation; regular 4 year pattern repeat, although 2 year spikes dominate	7*b*
0.285 – 0.293	2nd bifurcation; regular 8 year pattern repeat	7*c*
0.293 – 0.297	3rd bifurcation; 16 year pattern repeat	
0.3 – 0.434	Chaotic	7*d*
0.435 – 0.62	Regular 4 year pattern: true epidemics with 'zero' infectives between outbreaks (not endemic)	7*e*
0.63	1st bifurcation; 8 year pattern repeat	7*f*
0.64	2nd bifurcation; 16 year pattern repeat	
0.66	Chaos (although 4 year peaks are still discernible)	7*g*

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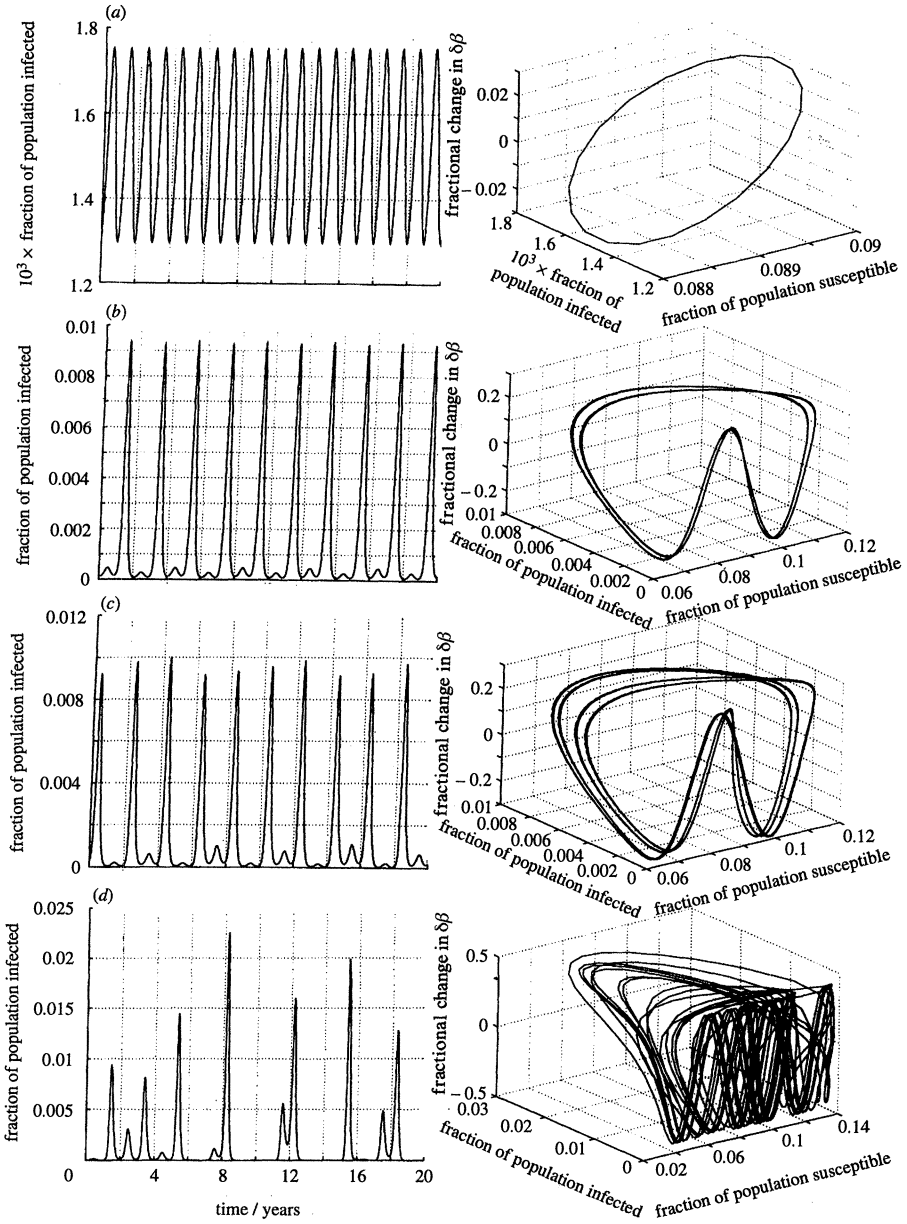

Figure 7. Different steady-state responses of a nonlinear system, the London model, to a progressive increase in $\delta\beta$. $N\beta = 270$; $\gamma = 1$ year. Figures illustrate the fraction of the population infected when the system has settled after the introduction of the oscillation in $\delta\beta$ (left-hand column) and the corresponding phase diagram, fraction infected vs. fraction susceptible vs. fractional change in $\delta\beta$ (right-hand column). Values for $\delta\beta$: (*a*) 0.03, (*b*), 0.26, (*c*) 0.292, (*d*) 0.434, (*e*) 0.435, (*f*) 0.63, (*g*) 0.8.

Penrith model. The results for $N\beta = 65$ to 600 are shown in table 2. The 1 year sinusoidal input produces an endemic response throughout the range of $N\beta$ but, with $\delta\beta = 10\%$, the two-yearly epidemics characteristic of London are found over a finite range of $N\beta$: $250 < N\beta < 330$. The characteristic 2 year epidemics superimposed on an endemic condition for London are shown at $N\beta = 270$. The system reverts to 1 year oscillations above $N\beta = 330$. $N\beta = 90$ corresponds to a population where the natural frequency of oscillations is four-yearly; however, no such oscillations in response to a 1 year driver were detectable in the model, although they might exist at a different value of $\delta\beta$.

The response of the model to a 5 year driver switches from epidemic to endemic around $N\beta = 180$ (table 2). The 5 year epidemics at $N\beta = 65$ to 130 are characteristic of Penrith.

The results summarized in table 2 are applicable only to $\delta\beta$ around 10%; different responses may be obtained if markedly different values of $\delta\beta$ are chosen (see table 1). Nevertheless, these responses illustrate the fundamental difference between medium-sized rural towns ($N\beta < 180$) and cities and larger conurbations ($N\beta > 250$).

9. CONCLUSIONS

The existing literature on smallpox epidemics in England is, inevitably, anecdotal; statistics of smallpox deaths are provided in Bills of Mortality and a

number of quite detailed accounts have been given of major, sporadic outbreaks of the disease in different parts of England during the seventeenth and eighteenth centuries. We have attempted to provide the first detailed, quantitative description of these smallpox epidemics in two very different, representative situations in England (Duncan *et al.* 1992, 1993*a*,*b*), namely a large city where smallpox was endemic and a rural town where the disease did not persist between epidemics. Mathematical theory of infectious diseases predicts that: (i) the inter-epidemic period (T) for smallpox is 2–3 years; and (ii) oscillatory epidemics die out unless the system is perturbed. We have shown clearly for the first time that these oscillations were not damped out and that regular smallpox epidemics persisted in Britain for 150 years in both these contrasting situations (Duncan *et al.* 1992, 1993*a*). The inter-epidemic period is approximately 2 years in large conurbations whereas it is 5 years in Penrith and other rural towns. We explain these apparent discrepancies as follows. The foregoing simulations illustrate how different patterns of epidemics can theoretically be generated by a fluctuation in susceptibility in a system described by equations (1) and (2); they show that a periodic variation in susceptibility can pump up and produce persistent oscillations in a steady-state system. Each system will tend to resonate at its natural frequency, determined by its population size and density (which govern the birth rate of new susceptibles and the ease of spread of the disease) and by its sensitivity to external factors. If the external factors fluctuate regularly (1 year or 5 year cycles) they are sufficient to pump up and maintain the oscillatory epidemics. These dynamics of smallpox can be demonstrated by mathematical modelling: the London model naturally oscillates with a 2 year periodicity and requires only a minor perturbation of a 1 year sinusoidal input ($\delta\beta$), whereas in Penrith it

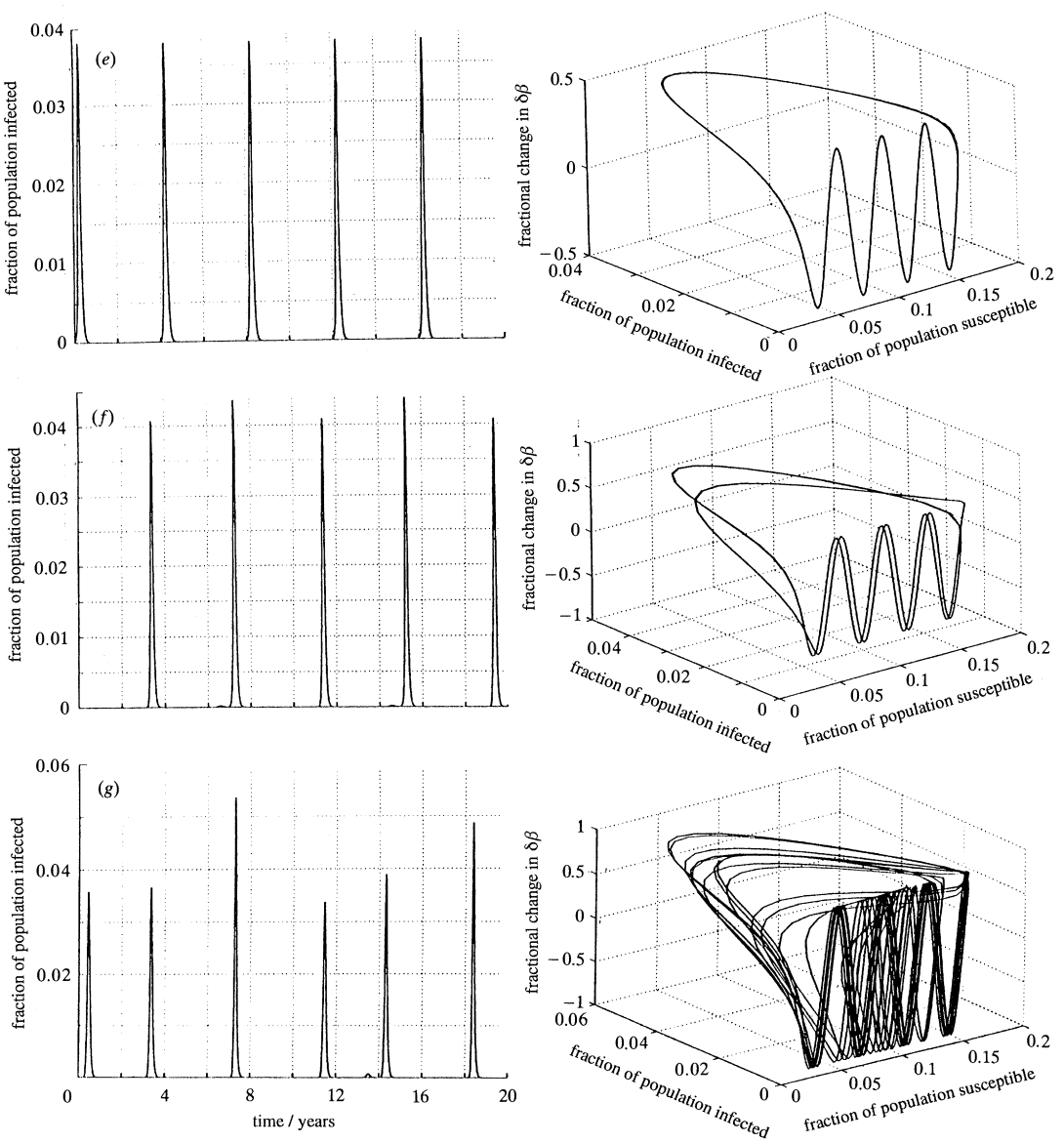

Figure 7. Continued.

Table 2. *Responses shown by a progressive increase in $N\beta$ to a 1 year or 5 year sinusoidal change in $\delta\beta$*
(Value of $\delta\beta = 0.1$.)

Wavelength of driver	$N\beta$						
	65	130	200	270	330	350	600
1 year	1 yr Endemic	1 yr Endemic	1 yr Endemic	2 yr Endemic	2 yr Endemic	1 yr Endemic	1 yr Endemic
5years	5 yr Epidemic	5 yr Epidemic	5 yr[a] Endemic	5 yr Endemic	5 yr Endemic	5 yr Endemic	5 yr Endemic

[a]Intermediate, small oscillations seen, two years after each 5 year epidemic.

takes approximately 5 years for an adequate build-up of susceptibles, whereupon an epidemic can be triggered by a periodic small change in β.

We have now completed an intensive family reconstitution study of the population at Penrith. Studies of coherence functions show that the 5-year oscillation in the child burial series synchronizes with the wheat price index from 1560 to 1650 and it was on this pre-existing cycle of child mortality that the virulent outbreaks of smallpox epidemics were established in 1650. The principal hazard in the northern province at that time was the meagre corn harvest, which placed the whole economy upon a precarious footing. The main crop in Cumberland was barley or bigg, a poorer and hardier variety of barley (Thirsk 1967) and diets deficient in multiple nutrients frequently lead to a lower resistance to infection (Scrimshaw *et al.* 1968). From about 1650 to 1710 the child mortality cycles synchronized most closely with the barley price index, whereas from 1750 to 1812 they again cross-correlate with the wheat price index. Although the smallpox epidemics and child mortality cycles continued strongly during the intervening period, 1710–1750, they did not synchronize with the grain price indices. By this time, Penrith was a thriving market town (Furness 1894) and we have detected oscillations in immigration from surrounding parishes where the population size or density was too small for the establishment of smallpox epidemics. Such incomers would add to the pool of susceptibles, thereby effectively providing a periodic variation in N and x, i.e. the system can be driven by fluctuations in $N\beta xy$ (equation (2)). Because births were also fluctuating on a 5 year cycle, 180° out of phase with deaths (Duncan *et al.* 1992), this feature of the population dynamics will also contribute to the variation in x. Oscillations in food shortages and malnutrition, as well as modifying susceptibility to disease (Scrimshaw *et al.* 1968) and initiating immigrations and fluctuations in $N\beta xy$, could have other possible effects; for example, the mortality rate from smallpox could rise, so exacerbating the records in the burial series.

It is evident that the basic equations given in appendix 1 are probably not strictly applicable to the conditions at Penrith where the disease was not endemic (unlike London) and hence where there was not a continuous chance of infection. The minimum inter-epidemic period (5 years) was critically dependent on the time taken to build up a supply of susceptibles by new births and immigration, whereupon only a small change in the dynamics is necessary to trigger an epidemic although this would not explode unless an infective came into the community. Penrith was on the main road to Scotland, so travellers and drovers would contribute to the movement of infectives. We have shown that smallpox epidemics in the adjacent towns in the north-west were largely synchronized, a feature that would exacerbate the five-yearly cycle. In the Penrith model (figure 4) the fraction of the population does not drop completely to zero in the inter-epidemic years, but the modelling shows a fraction of an individual infected, which is obviously impossible in reality. However, the sum of these fractions over 5 years probably represents stray infectives coming into the community.

The modelling shows that an annual fluctuation of only 5% in susceptibility is sufficient to trigger the 2 year epidemics in the London model and, if $N\beta = 270$ is accepted as a description of this population, it can be seen from table 1 that $\delta\beta$ lay in the range 0.055–0.25. It has been suggested that the 2 year measles epidemics that were experienced nationally in the twentieth century, when the population (in comparison with the seventeenth and eighteenth centuries) was extremely mobile, could have been pumped up by the introduction of a noisy signal to β (Bartlett 1990; Rand & Wilson 1991; Grenfell 1992; Bolker & Grenfell 1993). We have introduced broad-band noise from a random noise generator with zero mean as a source of variation in susceptibility ($\delta\beta$) into the London and Penrith models. The 2 year epidemics can be generated in London but only if the input is of large amplitude; we conclude that an annual oscillatory input is the more probable explanation for pumping up these epidemics. An oscillatory driver is a requirement for the simulation of the conditions of smallpox epidemics in rural towns.

Landers (1986, 1987, 1990) has studied smallpox deaths in Quakers in London, 1675–1825, and concluded that epidemic episodes were precipitated by the immigration of young adult susceptibles from the countryside in search of work during periods of

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food shortages and hardship. Such a suggestion can be incorporated into the London model; fluctuations in x and N could contribute to a secondary oscillation in $N\beta xy$. The periodicity of this immigration is not given but it was probably associated with the fluctuations in the grain price index; we have shown that there is a secondary 5 year oscillation in London smallpox deaths which contributes to the complex dynamics of the disease.

Table 1 shows that if $\delta\beta$ is raised progressively above 0.25 in the London model the dynamics alter dramatically with bifurcations and chaos which then switches sharply at $\delta\beta = 0.435$ to a pattern of 4 year epidemics with virtually no infectives between outbreaks. This theoretical finding suggests that chaos may be associated with the transition from the endemic condition to the strictly epidemic condition. The modelling shows that if the amplitude of the variations in susceptibility ($\delta\beta$) are sufficiently high, the system exhibits a chaotic response. However, the presence of the variation in susceptibility (the driver) is a sufficient condition for inducing this chaos; the undriven system defined solely by equations (1) and (2) cannot become chaotic. Such chaotic conditions are probably of only theoretical interest since presumably $\delta\beta$ will not normally be at such high levels and the London smallpox mortality series confirms that the disease was endemic throughout the period of study.

APPENDIX 1

The basic equations concerning the theory of viral epidemics (Anderson & May 1991) can be summarized as follows. The population, N, is assumed to remain constant where the net input of susceptibles (births) equals the net mortality, μN (where $\mu =$ death rate; life expectancy $= 1/\mu$). The population is divided into susceptibles (X), latents (infected, not yet infectious, H), infectious (Y) and recovered and hence immune (Z). Thus, $N = X + H + Y + Z$. It is assumed that the net rate at which infections occur is proportional to the number of encounters between susceptibles and infectious, βXY (where β is a transmission coefficient). Individuals move from latent to infectious at a *per capita* rate, σ, and recover, so becoming immune, at rate γ. The dynamics of the infection are then described by the following equations:

$$dX/dt = \mu N - \mu X - \beta XY; \qquad A(1)$$

$$dH/dt = \beta XY - (\mu + \sigma)H; \qquad A(2)$$

$$dY/dt = \sigma H - (\mu + \gamma)Y; \qquad A(3)$$

$$dZ/dt = \gamma Y - \mu Z. \qquad A(4)$$

The criterion for triggering an epidemic is the requirement (Anderson & May 1991) that the susceptibles (X) exceed a threshold density, $X > N_T$, where

$$N_T = (\gamma + \mu)(\sigma + \mu)\beta\sigma. \qquad A(5)$$

The oscillation shown by the model has a period (T) where

$$T \approx 2\pi(AD)^{0.5}, \qquad A(6)$$

where A is the mean age at mortality once the infection is endemic and D is the sum of the latent and infectious periods and is approximately 12 days for smallpox (Anderson & May 1991).

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