ESTIMATING THE DISEASE PARAMETERS FOR SMALLPOX IN LONDON OVER THE PERIOD 1708 TO 1748

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Abstract: When predicting the spread of a disease such as smallpox, knowledge of the transmission parameter, R_0, is important. Previous studies have estimated R_0 from outbreaks of the disease, but these estimates are prone to uncertainties because of the small population sizes and the short data runs. This study uses data from smallpox deaths in London over the period 1708 to 1748. Although smallpox was endemic in the population at this time, by using an estimator based upon a second order Gaussian filter to fit a nonlinear model to the dynamics of the disease, the disease parameters are obtained, leading to an estimate of R_0. The model also reveals the importance of temperature and rainfall on the transmissibility of the disease. *Copyright©2005 IFAC*

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1. INTRODUCTION

Smallpox has been present in the world for over 3,000 years and is known to be one of the most infectious human diseases (Fenner *et al.* 1988). In the 1630's, there are accounts that a particularly virulent strain began to emerge, with a gradual but significant rise in the fatality rate (Corfield 1987). The disease was greatly feared in Europe up until the end of the nineteenth century when it ceased to be endemic after the introduction of variolation, inoculation and vaccination. However, it was still prevalent in some parts of the world, for example India, until well into the twentieth century and it was not until 1980 that the World Health Organization declared that the disease had finally been eradicated (Fenner *et al.* 1988).

Following eradication, small stocks of the virus were kept in order to prepare vaccines in the event of the re-emergence of the disease and in recent times, concern has focussed on these stocks being used in bio-terrorism (Dove 2002).

In order to respond to an outbreak of smallpox, for example following a bio-terrorist attack, a knowledge of the transmissibility of the disease is fundamental. The transmissibility is usually expressed as the basic reproductive rate, R_0, which is defined as the mean number of secondary infections produced when one infected individual is introduced into a host population, where everyone is susceptible (Diekmann and Heesterbeek 2000, Anderson and May 1992). Few people under the age of 25 today have been vaccinated against smallpox and the protective effects of vaccination would have lapsed for most of the older members of the population and it is reasonable to assume that almost all of the present day population is susceptible to the disease. If a single infective individual enters a

population consisting solely of susceptibles, he will infect R_0 other individuals. After a latent period, D', where the disease is dormant within the host, these R_0 individuals will become infectious and will each infect a further R_0 susceptibles during their infectious period, D. The serial generation time for the disease is defined as $(D' + D/2)$ and if the disease is allowed to spread unchecked, there will be will be R_0^n infectives after n generations.

Previous studies have estimated R_0 from the increase in the number of infectives during the early stages of an epidemic, but because smallpox has been eradicated, researchers have relied upon historical data and there have been a number of estimates of R_0, which have varied from 1.5 to 20 (Gani and Leach 2001). The difficulty with deriving R_0 from the start of an epidemic is that a significant (but unknown) proportion of the population would have previously been exposed to the disease and hence would be immune, which will distort the estimate of R_0. Consequently, estimates of R_0 have been attempted from the rising phase of epidemics in more modern times (Gani and Leach 2001), when only a small proportion of the population would be immune, leading to estimates for R_0 between 3.5 and 6. However, these studies involved relatively small numbers of people (so that the analysis is sensitive to statistical fluctuations) and there were significant medical interventions and isolation of infectives, which reduced the spread of the disease.

The approach described in this paper uses historical data from London over the first half of the 18th century when smallpox was endemic within the population. The data comes from the Bills of Mortality, which recorded weekly burials resulting from smallpox deaths for each parish within London over a 250 year period (Creighton 1894). Figure 1 shows the weekly burials over the period 1708 to 1748, which is used here, primarily because both the total size of the population and the mean number of weekly smallpox burials remain constant over this period (Landers 1986). It is clear from this plot that there are significant dynamics within the data series. Although the disease is endemic over this period, so that a large proportion of the population is immune, it is still possible to estimate R_0, the transmissibility of the disease in a population where no one is immune. This is done by fitting a Gaussian second order filter to a non-linear dynamic model of the variations and using this to identify the key disease parameters. The intention was to use the estimated model to provide prior distributions for a particle filter, but the second order filter gave good results, primarily because the underlying model of the disease dynamics is bilinear and because the noises entering the system were found to be Gaussian.
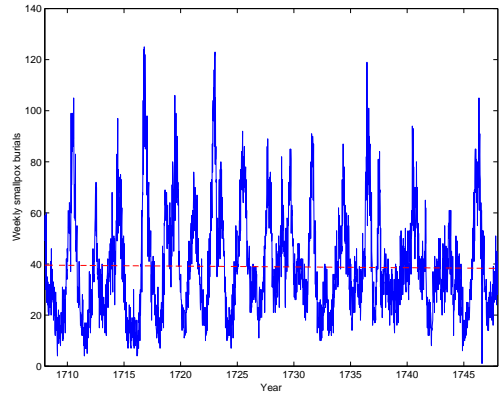

Fig. 1. Weekly burials due to smallpox over period 1708 to 1748. Dashed line shows linear fit to data

2. THE SEIR MODEL OF DISEASE DYNAMICS

A population of size $N(t)$ can be separated into four classes

$$N(t) = X(t) + H(t) + Y(t) + Z(t) \qquad (1)$$

where $X(t)$ is the number of susceptibles within the population, $H(t)$ is the number of latents (those who have been infected with the disease, but are not yet infectious), $Y(t)$ is the number of infectives and $Z(t)$ is the number of people who have recovered after being infected. The standard SEIR model for the aggregated population (ignoring the age structure of the population), is given by a set of coupled ordinary differential equations (Anderson and May 1992)

$$\dot{X}(t) = \gamma N(t) - \mu X(t) - \beta(t)X(t)Y(t) \quad (2)$$
$$\dot{H}(t) = \beta(t)X(t)Y(t) - \mu H(t) - \sigma H(t) \quad (3)$$
$$\dot{Y}(t) = \sigma H(t) - \mu Y(t) - \nu Y(t) \qquad (4)$$
$$\dot{Z}(t) = (1 - \alpha)\nu Y(t) - \mu Z(t) \qquad (5)$$

where γ is the birth rate, μ is the death rate due to causes other than the disease and α is the fraction of the infectives who die from the disease. The rate at which latents move to infectives is denoted by σ and ν is the rate at which infectives either recover or die from the disease. Usually, σ and ν are taken as the reciprocal of the latent period, D', and infectious period, D, respectively, so that $\sigma = 1/D'$ and $\nu = 1/D$. The term, $\beta(t)$, is the transmission parameter associated with the disease and describes the probability that the disease will be transmitted when a susceptible comes into contact with an infective. The probability of transmission is a parameter associated with disease, but it does depend on external factors, such as temperature and humidity, so $\beta(t)$ can vary over time (Anderson and May 1992).

Summing the differential equations in the SEIR model and using (1) leads to

$$\dot{N}(t) = (\gamma - \mu)N(t) - \alpha\nu Y(t) \qquad (6)$$

It is more convenient to use this equation in place of the expression for $\dot{Z}(t)$ in (5).

3. STEADY STATE ANALYSIS

From the plot of smallpox burials from 1708 to 1748 in Figure 1, the mean annual number of deaths due to smallpox, $\bar{B}$, for this period is 2,028. If ν, the rate at which infectives either recover or die from the disease, is expressed in units of year^{-1} (which can be obtained by setting $\nu = 1/D$, where the infectious period, D, is measured as a fraction of a year), then

$$\bar{B} = \alpha\nu\bar{Y} \qquad (7)$$

The mean values of susceptibles, latents, infectives and the total population size, $\bar{X}$, $\bar{H}$, $\bar{Y}$ and $\bar{N}$, satisfy steady state versions of the the SEIR equations, (2) to (4) and (6). Using the values of $\bar{N} = 660,000$ and $\mu = 1/30$ years^{-1} from historical records (Landers 1986), the steady state equations represent five equations in eight unknowns ($\bar{X}$, $\bar{H}$, $\bar{Y}$, γ, β, α, σ and ν). However, if three of the parameters are known, for example, α, σ and ν, then the other five values can be calculated. Once $\bar{X}$ is known, the value of R_0 is obtained from $R_0 = \bar{N}/\bar{X}$. The procedure also produces an estimate of the average transmission parameter, $\bar{\beta}$.

The difficulty is that in order to estimate $\bar{X}$ and hence R_0, it is necessary to have values for three unknown parameters. In principle, estimates of α, σ and ν are available. For example, Anderson and May (Anderson and May 1992) state that the latent period for smallpox lasts between 8 and 11 days, while the infectious period is between 2 and 3 days, although other authors extend the latent period to 13 days and the infectious period to 6 days (Gani and Leach 2001). From records obtained primarily from studies of smallpox outbreaks in 20th Century India, between 15% and 20% of infectives died from the disease. Although these values can be used to estimate R_0, the estimate of $\bar{X}$ is very sensitive to uncertainties in α and ν. It is also possible that the values of the parameters α, σ and ν obtained from relatively recent data records may not be applicable to the disease in the early 18th Century. For this reason, the approach adopted in this study is to use the dynamics of the smallpox outbreaks evident in the London data over this period, to estimate α, σ and ν. It is then possible to calculate the corresponding value of $\bar{X}$, leading to an estimate of R_0.

However, the estimation procedure also provides an estimate of $X(t)$ on a weekly basis and $\bar{X}$ can be obtained directly by taking the mean of these estimates.

4. NONLINEAR DYNAMIC MODEL

Previous work (Duncan *et al.* 1996) has shown that the oscillations in the number of smallpox deaths are driven by variations in the transmission parameter, $\beta(t)$. By examining monthly records for temperature (Manley 1974) and rainfall (Wales-Smith 1971) over the same period, it can be shown that there is a strong positive correlation between smallpox deaths and temperature and a negative correlation between smallpox deaths and rainfall. These correlations reflect the fact that because infection occurs via the airborne transmission of the virus, the disease tends to thrive in warm, dry conditions. As a result, variations in the transmission parameter are taken to have the form

$$\beta(t) = \bar{\beta} + \beta_\mathrm{T} T(t) + \beta_\mathrm{R} R(t) + w(t) \qquad (8)$$

where $T(t)$ and $R(t)$ denote the temperature and the rainfall respectively. In principle, the parameter $\bar{\beta}$ could be estimated from the steady state analysis of the previous section, but the parameters, β_T and β_R are unknown. The historical records only provide the monthly averages for temperature and rainfall, so interpolation is used to find the values of $T(t)$ and $R(t)$ at any given time, t. The $w(t)$ term represents a stochastic variation in the transmission parameter, which is taken to be a zero-mean, Gaussian, white noise signal, whose variance is unknown. It is convenient to combine the deterministic part of $\beta(t)$ into a single variable by defining

$$\beta_d(t) = \bar{\beta} + \beta_\mathrm{T} T(t) + \beta_\mathrm{R} R(t) \qquad (9)$$

so that $\beta(t) = \beta_d(t) + w(t)$.

Since the total size of the population, $N(t)$, is constant over the period being considered, the system can be described by $X(t)$, $H(t)$ and $Y(t)$. If $\mathbf{q}(t)$ is defined as

$$\mathbf{q}(t) = \begin{bmatrix} X(t) \\ H(t) \\ Y(t) \end{bmatrix} \qquad (10)$$

then the nonlinear model in (2), (3) and (4) can be written as

$$\dot{\mathbf{q}}(t) = \mathbf{f}\left(\mathbf{q}(t), \beta_d(t), \theta\right) + \mathbf{g}\left(\mathbf{q}(t)\right) w(t) \qquad (11)$$

where

$$\mathbf{f}\left(\mathbf{q}(t), \beta_d(t), \theta\right) = \begin{bmatrix} \gamma\bar{N} - \mu q_1(t) - \beta_d(t)q_1(t)q_3(t) \\ \beta_d(t)q_1(t)q_3(t) - (\mu+\sigma)q_2(t) \\ \sigma q_2(t) - (\mu+\nu)q_3(t) \end{bmatrix}$$
(12)

$$\mathbf{g}\left(\mathbf{q}(t)\right) = \begin{bmatrix} -q_1(t)q_3(t) \\ q_1(t)q_3(t) \\ 0 \end{bmatrix}$$
(13)

with $\theta^{\mathrm{T}} = [\sigma,\ \nu,\ \alpha,\ \beta_{\mathrm{T}},\ \beta_{\mathrm{R}}]$ representing the unknown model parameters. Other parameters in the model, namely $\bar{N}$ and μ, are obtained from historical data (Landers 1986) and given values of σ and ν, $\bar{\beta}$ can be obtained from the steady state analysis. The model is completed by the discrete time, linear measurement equation relating B_k, the number of burials over the period $kT_s \le t < (k+1)T_s$, to the state

$$B_k = \mathbf{c}^{\mathrm{T}}\mathbf{q}_k + e_k$$
(14)

where $\mathbf{c}^{\mathrm{T}} = [0,\ 0,\ \alpha\nu T_s]$, $\mathbf{q}_k = \mathbf{q}(kT_s)$ and e_k represents the measurement noise.

For a given set of parameters, θ, using the number of burials at each time step, the underlying state $\mathbf{q}(t)$ can be estimated using a continuous-discrete nonlinear filter (Jazwinski 1970). Since the system contains bi-linear terms in both $\mathbf{f}(\mathbf{q}(t),\beta_d(t),\theta)$ and $\mathbf{g}(\mathbf{q}(t))$, a second order filter, which includes terms involving up to the second derivatives of $\mathbf{f}(\mathbf{q}(t),\beta_d(t),\theta)$ and $\mathbf{g}(\mathbf{q}(t))$ with respect to $\mathbf{q}(t)$, is appropriate, since the higher order derivatives vanish. If it is assumed that both the underlying state noise, $w(t)$, and the measurement noise, e_k, are Gaussian, then a suitable estimator is the Gaussian second order filter (Jazwinski 1970). The state update part of the filter is given by

$$\dot{\hat{\mathbf{q}}}(t) = \mathbf{f}\left(\hat{\mathbf{q}}(t), \beta_d(t), \theta\right) + \frac{1}{2}\partial^2\left(\mathbf{f}, \mathbf{P}(t)\right)$$
(15)

where $\mathbf{P}(t)$ is the covariance matrix and $\partial^2\left(\mathbf{f}, \mathbf{P}(t)\right)$ is a vector whose ith element is (Gelb 1974)

$$\partial_i^2\left(\mathbf{f}, \mathbf{P}(t)\right) = \mathrm{trace}\left\{ \left. \frac{\partial^2 f_i}{\partial q_m \partial q_n}\right|_{\hat{q}_m, \hat{q}_n} \mathbf{P}(t) \right\}$$
(16)

From (12), the only nonlinear terms in the state evolution equation are $q_1(t)q_3(t)$, so $\partial_1^2\left(\mathbf{f}, \mathbf{P}(t)\right)$ and $\partial_2^2\left(\mathbf{f}, \mathbf{P}(t)\right)$ depend only on $\beta_d(t)$, while $\partial_3^2\left(\mathbf{f}, \mathbf{P}(t)\right)$ is the zero matrix. The initial conditions for the state estimate evolution in (15) are taken to be $\hat{\mathbf{q}}(0) = E[\hat{\mathbf{q}}(t)] = [\bar{X}, \bar{H}, \bar{Y}]^{\mathrm{T}}$.

The evolution of the covariance matrix between samples is given by (Jazwinski 1970)

$$\dot{\mathbf{P}}(t) = \mathbf{F}(t)\mathbf{P}(t) + \mathbf{P}(t)\mathbf{F}^T(t) + \widehat{\mathbf{GQG}}^{\mathrm{T}}$$
(17)

where $\mathbf{Q} = E[\mathbf{w}(t)\mathbf{w}(t)^T]$ is the covariance of the state noise and

$$\mathbf{F}(\hat{\mathbf{q}}) = \left.\frac{\partial f_i}{\partial q_j}\right|_{\hat{\mathbf{q}}}$$
(18)

$$= \begin{bmatrix} -\mu - \beta_d(t)\hat{q}_3 & 0 & -\beta_d(t)\hat{q}_1 \\ \beta_d(t)\hat{q}_3 & -(\mu+\sigma) & \beta_d(t)\hat{q}_1 \\ 0 & \sigma & -(\mu+\nu) \end{bmatrix}$$
(19)

For the case of a Gaussian second order filter

$$\begin{aligned}\widehat{\mathbf{GQG}}^{\mathrm{T}} = &\ \mathbf{g}(\hat{\mathbf{q}})\mathbf{Q}\mathbf{g}(\hat{\mathbf{q}})^{\mathrm{T}} + \mathbf{G}(\hat{\mathbf{q}})\mathbf{P}(t)\mathbf{G}(\hat{\mathbf{q}})^{\mathrm{T}}\mathbf{Q} \\ &+ \mathbf{g}(\hat{\mathbf{q}})\mathbf{Q}\partial^2\left(\mathbf{P}(t), \mathbf{g}\right) \\ &+ \frac{3}{4}\mathbf{Q}\partial^2\left(\mathbf{P}(t), \mathbf{g}\right)\partial^2\left(\mathbf{g}, \mathbf{P}(t)\right)^{\mathrm{T}}\end{aligned}$$
(20)

where

$$\mathbf{G}(\hat{\mathbf{q}}) = \left.\frac{\partial g_i}{\partial q_j}\right|_{\hat{\mathbf{q}}} = \begin{bmatrix} -\hat{q}_3 & 0 & -\hat{q}_1 \\ \hat{q}_3 & 0 & \hat{q}_1 \\ 0 & 0 & 0 \end{bmatrix}$$
(21)

The term $\partial^2(\mathbf{P}(t), \mathbf{g})$ takes the same form as in (16).

Since the measurement equation in (14) is linear, the update to the state and covariance matrix at each sample interval is (Jazwinski 1970)

$$\hat{\mathbf{q}}_k(+) = \hat{\mathbf{q}}_k(-) + \mathbf{k}_k[B_k - \mathbf{c}^{\mathrm{T}}\hat{\mathbf{q}}_k(-)]$$
(22)

$$\mathbf{k}_k = \mathbf{P}_k(-)\mathbf{c}^{\mathrm{T}}\left[\mathbf{c}\mathbf{P}_k(-)\mathbf{c}^{\mathrm{T}} + r\right]^{-1}$$
(23)

$$\mathbf{P}_k(-) = \left[\mathbf{I} - \mathbf{k}_k\mathbf{c}^{\mathrm{T}}\right]\mathbf{P}_k(-)$$
(24)

where $r = E[e_k^2]$.

Estimates of the unknown parameters θ are obtained by finding

$$\arg\min_\theta \sum_{k=1}^{N}\left[B_k - \mathbf{c}^{\mathrm{T}}\hat{\mathbf{q}}_k(+)\right]^2$$
(25)

where N is the number of data points. In practice, this is done by fixing θ, running the second order Gaussian filter to calculate the sum of the squared residuals and then using the simplex method to update θ. This process is repeated until a local minimum is found. The optimization procedure is started using estimates of θ obtained from the steady-state analysis and a linearized version of the model. In theory, the estimates could be improved by using a non-linear smoother in place of the second order filter, but in practice, it was found that it was difficult to maintain the stability of the smoother when passing backwards through the data.

5. RESULTS

The parameter estimates were obtained by applying the optimization procedure to the first half of the data record over the period from 1708 to

1729.5 years, which corresponds to 1,121 data points, and Figure 2 shows the fit to a portion of this data (only part of the data has been shown in order to improve the clarity of the plot). The values of the parameters used to obtain this fit are given in Table 1, which also includes the values used in the algorithm for q, the state noise variance, and r, the measurement noise variance. The residuals, $B_k - \mathbf{c}^{\mathrm{T}} \hat{\mathbf{q}}_k(+)$, were found to include a low frequency variation with a wavelength of around 20 years. This long-term variation has not been included in the SEIR model and was removed by subtracting a cubic polynomial from the residuals. Figure 3(a) plots a histogram of the modified residuals, which indicates that the residuals are normally distributed and applying a Lilliefors test (Conover 1971) shows that the hypothesis that the residuals are drawn from a normal distribution can be accepted at the 95% confidence level. Figure 3(b) gives the autocorrelation plot of the residuals along with the 95% confidence intervals (dashed lines), indicating that the residuals can be taken as white at this confidence level. Figures 3(c) and (d) shows the cross-correlation between the residuals and the temperature and rainfall respectively. Although the plots indicate that there is no correlation between the residuals and the variations in rainfall, some correlation between the residuals and temperature is evident. However, this is almost within the 95% confidence interval (shown by the dashed line).

Parameter	Estimated Value
σ	28.3 year^{-1}
ν	125.9 year^{-1}
α	0.094
β_{T}	9.5×10^{-6}
β_{R}	-2.0×10^{-5}
q	1.0×10^{-9}
r	81.0

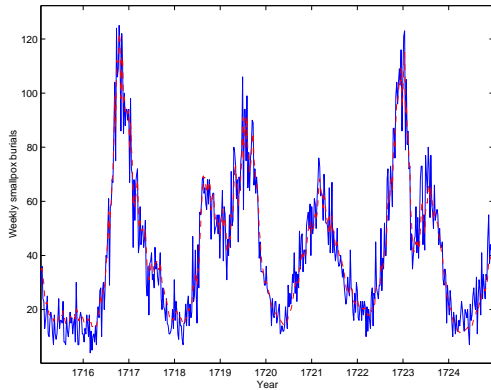Table 1. Parameter estimates identified from model

Fig. 2. Fit (dashed line) of non-linear model to part of test data

Using the parameters that were estimated from the first half of the data, corresponding to the
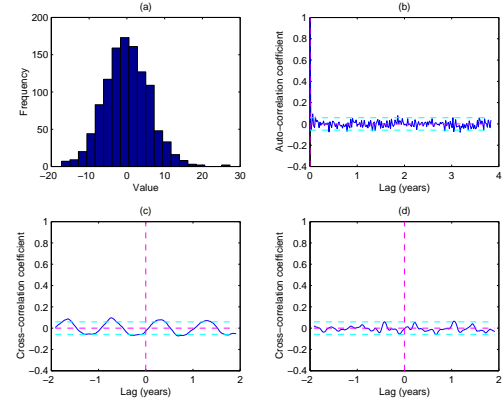

Fig. 3. (a) Histogram of residuals from test data. (b) Autocorrelation of residuals. (c) Cross-correlation between residuals and temperature. (d) Cross-correlation between residuals and rainfall

period 1708 to 1729, the Gaussian second order filter was then applied to the smallpox burials for 1729.5 to 1748 (1,123 data points) in order to validate the model. A portion of the fitted model is shown in Figure 4, while the statistics of the residuals are given in Figure 5. Although the fit to the validation data is good, Figure 5(b) shows that compared with the test data, there was a higher level of autocorrelation in the residuals from the validation data and that there is correlation between the residuals and the temperature data. Also, the Lilliefors test indicates that the hypothesis that residuals are normally distributed cannot be accepted at the 95% confidence level, although when an outlier data point is removed, this hypothesis can be accepted. This suggests that the influence of the exogenous variables, in particular the temperature, on the spread of the disease may have changed over the period being considered, so that β_{T} was not constant. Despite this, the quality of the fit is good, with the standard deviation of the residuals being 8.31 burials per week, which is considerably less than the standard deviation of the full burials records, which is 20.4 burials per week.
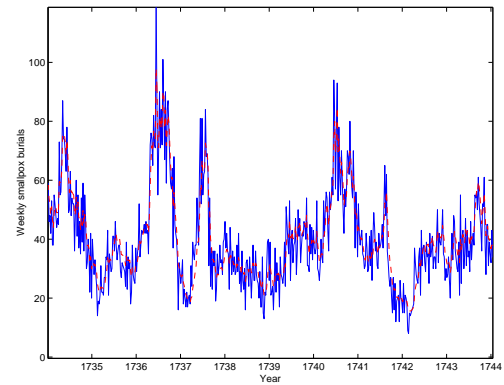

Fig. 4. Fit (dashed line) of non-linear model to part of validation data
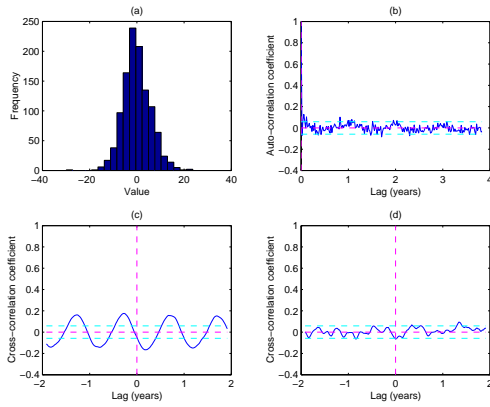
Fig. 5. (a) Histogram of residuals from validation data. (b) Autocorrelation of residuals. (c) Cross-correlation between residuals and temperature. (d) Cross-correlation between residuals and rainfall

The estimated parameters given in Table 1 are reasonable. The values of σ and ν correspond to latent and infectious periods of 12.9 days and 2.9 days respectively. The value of q used for the variance of the state noise shows that the random component of $\beta(t)$ is smaller than the deterministic, exogenous portion, since the variance of $\beta_{\mathrm{T}} T(t) + \beta_{\mathrm{R}} R(t)$ is 2.53×10^{-9}. This indicates the importance of temperature and rainfall on the spread of the disease.

On the basis of these of the model, the estimate of $\bar{X}$ is 8.9×10^4, which gives a value of $R_0 = 7.41(\pm 0.57)$. This is at the higher end of the published figures. However, the estimated value of α, the fraction of infectives dying from the disease is lower than expected. The estimated value suggests that less than 10% of infectives died, but values published in the literature indicate that the death rate exceeds 15% for both contemporary and historical outbreaks of the disease. The most likely reason for this discrepancy lies with the assumption that the non-disease induced death rate, μ, is constant throughout the population. In practice, the childhood mortality was so high that almost 50% of children died in the first year of birth. Since smallpox is primarily a disease of childhood, the high childhood mortality reduces the size of the pool of susceptibles, meaning that the fraction of the infectives dying from the disease will need to be higher in order to match the observed number of smallpox burials. Current work is focussing on incorporating the age dependent death rate and the resultant age-structure of the population into the nonlinear model.

6. CONCLUSION

This paper has presented an estimator based upon a second order Gaussian filter, to estimate the parameters of a nonlinear SEIR model of the disease dynamics. The nonlinear model is driven by variations in the transmission parameter, $\beta(t)$, which is affected by both temperature and rainfall, plus a noise term. The resultant model was fitted to half of the data, giving residuals that are Gaussian and white, and uncorrelated with both the temperature and rainfall variations. The model was validated against the second half of the data. The model gave an estimate of 7.41 for R_0, which is higher than expected, although it is suspected that this may be because the model does not take into account the age structure of the population.

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