2022 SISMID Module 9
Lecture 6: Spatial Infectious Diseases

Jon Wakefield and Lance Waller

Departments of Statistics and Biostatistics
University of Washington

Overview

Infectious Disease Data

The aims of infectious disease modeling include:

- Understanding the mechanisms of spread.
- Estimating the durations of the latent and infectious periods.
- Determining strategies for disease control.
- Forecasting the future space-time course of the epidemic, including estimating the cumulative number of cases.

The modeling of infectious disease data has a huge literature, though spatial models are less well-developed than temporal models.

Overview

- Keeling and Rohan (2008, Chapter 7) give an overview of spatial modeling.
- For directly transmitted diseases, individuals have to be in the same geographical location, and spread will occur when individuals move in space.
- The type of model used will depend on:
  - the host organism (human, animal, plant),
  - what is known about the organism's behavior, and
  - the geographical scale that is considered.
- A big distinction concerns the form of the data we receive; do we see individuals, with point locations, or aggregated counts with respect to some administrative regions?
- If infection can only be passed to a small number of individuals (as is the case for sexually transmitted diseases) then network models are advantageous, if the required data are available (which is rare).

Infectious Disease Data

- A starting dichotomy is in terms of deterministic versus stochastic models.
- The classic text on deterministic models is Anderson and May (1991).
- Books that consider both include Daley and Gani (1999) and Bailey (1975).
- Books on stochastic modeling include Becker (1989), Andersson and Britton (2000) and Halloran *et al.* (2010).
- The SIR model is popular.
- Let $x(t)$, $y(t)$, $z(t)$ be the number of susceptibles, infectives, recovered at time t in a closed population.

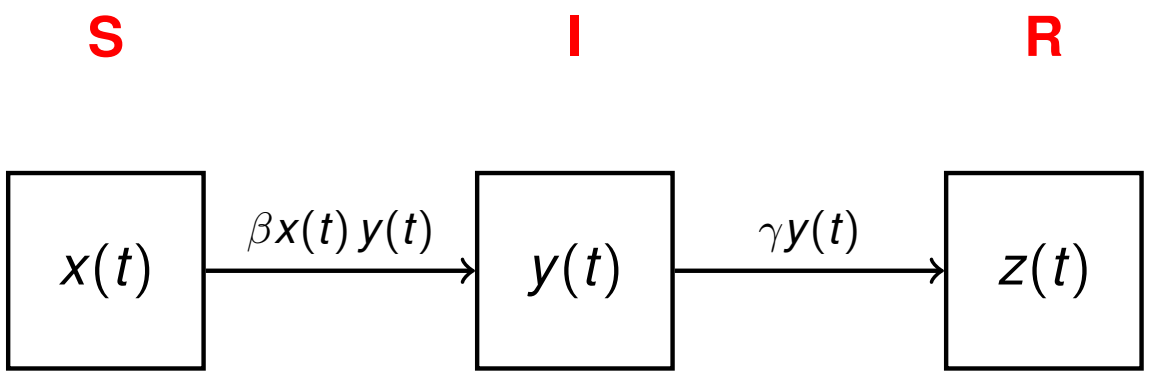


Figure 1: Solid arrows show the movement from S to I to R.

Categories of infectious disease transmission models

Deterministic Models based on Differential Equations:

- Computation is efficient so system can be complex.
- Fit to data using ordinary least squares or variants, inference dicey.
- Interpretable parameters.
- Poor for small populations or when the disease is rare.

Discrete-Time Stochastic Models:

- Fitting via likelihood/Bayes is relatively straightforward.
- Interpretability of parameters depends on the exact form.
- Computational efficiency not greatly affected by population size.
- Rigid data form (equally-spaced) typically required.

Continuous-Time Stochastic Models:

- Interpretable parameters.
- Computation not yet feasible in large populations.

Deterministic Models

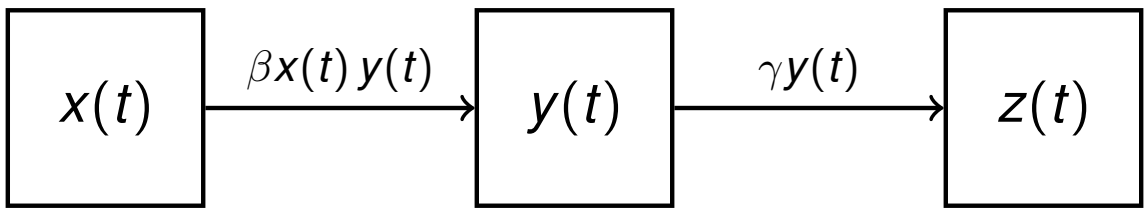
- The law of mass action is central to modeling (both deterministic and stochastic).
- In a population context, if the individuals in a population mix homogeneously, the rate of interaction between two different subsets of the population is proportional to the product of the numbers in each of the subsets concerned.
- Groups of individuals defined by their disease status are described in continuous time (usually) via differential equations and there is no randomness — may be thought of as producing the mean of a random process.

Deterministic SIR model

- Kermack and McKendrick (1927) proposed the following classic mass-action equations to describe the dynamics of the general epidemic (where we assume frequency dependent transmission):

$$\begin{aligned}
\frac{dx(t)}{dt} &= -\beta x(t) y(t) \\
\frac{dy(t)}{dt} &= \beta x(t) y(t) - \gamma Y(t) \\
\frac{dz(t)}{dt} &= \gamma y(t),
\end{aligned}$$

  subject to initial conditions $(X(0), Y(0), Z(0))$ with $Z(0) = 0$.
- Per-contact infection rate is β and the recovery rate is γ.
- Deterministic models can be embedded within a statistical framework for inference, or a stochastic approach can be taken from the onset.



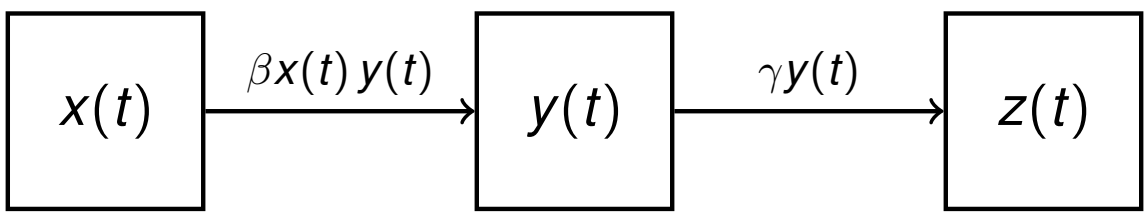
Continuous-time stochastic SIR model

- In the SIR model, deterministic differential equations are replaced by probabilistic descriptions of the transitions.
- Continuous-time Markov chain $\{X(t), Y(t), t \geq 0\}$ with transition probabilities for a susceptible becoming infective and an infective becoming recovered being:

$$\Pr\left(\begin{bmatrix} X(t+h) \\ Y(t+h) \end{bmatrix} = \begin{bmatrix} x-1 \\ y+1 \end{bmatrix} \,\middle|\, \begin{bmatrix} X(t) \\ Y(t) \end{bmatrix} = \begin{bmatrix} x \\ y \end{bmatrix} \right) = \beta h x y + o(h)$$

$$\Pr\left(\begin{bmatrix} X(t+h) \\ Y(t+h) \end{bmatrix} = \begin{bmatrix} x \\ y-1 \end{bmatrix} \,\middle|\, \begin{bmatrix} X(t) \\ Y(t) \end{bmatrix} = \begin{bmatrix} x \\ y \end{bmatrix} \right) = \gamma h y + o(h)$$

  where the remainder term $o(h)$ is small.
- The most appealing (at least to a statistician!) but quickly gets computationally hideous as populations increase in size given the usual surveillance data, see references in Fintzi *et al.* (2017).



Computation for compartmental models

To address the inference problem, various approaches have been suggested:

- For small populations, auxiliary variable approaches are tractable (Gibson and Renshaw, 1998; O'Neill and Roberts, 1999; O'Neill and Becker, 2001; Neal and Kypraios, 2015).
- Discrete approximations (Lekone and Finkenstädt, 2006).
- Diffusion process approximation (Cauchemez and Ferguson, 2008).
- Particle filtering, for likelihood or Bayesian inference (He *et al.*, 2010; Koepke *et al.*, 2016).
- Gaussian process approximate Bayesian inference (Jandarov *et al.*, 2014).
- Approximate Bayesian Computation (ABC) (McKinley *et al.*, 2009; Toni *et al.*, 2010; Neal, 2012).

The last three require simulation from the model, which is straightforward.

Disease mapping type models ignore the infectious aspect (Mugglin *et al.*, 2002; Knorr-Held and Richardson, 2003; Bauer *et al.*, 2016).

Discrete-Time Stochastic Models

An epidemic/endemic framework

- We describe in some detail, a statistical framework for analyzing spatio-temporal, aggregated infectious disease data originally proposed by Held *et al.* (2005).
- The framework was extended by Paul *et al.* (2008), Paul and Held (2011), Held and Paul (2012), Meyer and Held (2014) and Geilhufe *et al.* (2014)
- These models are implemented within the `surveillance` package in `R` (Meyer *et al.*, 2017) and have been applied to a variety of diseases; see, for example, Höhle *et al.* (2011) and Herzog *et al.* (2011).
- Notably the implementation does not provide a straightforward way to allow age/gender and space to be in the model, though Meyer and Held (2017) use survey information on contact rates in the epidemic/endemic model.

A Discrete Time SIR Model

- We focus on the situation in which we have disease counts Y_{it} in area i and in time observation period t.
- It is common to use time steps relative to the disease of interest, meaning that we are assuming the sum of incubation and infectious times is approximately that of the observation times.
- For example, for measles, the data are often aggregated over 1 or 2 week periods.
- Let S_{it} be the size of the susceptible population.
- We denote the force of infection (risk) of an individual who was susceptible at time $t-1$ becoming infected by time t in area i, by λ.

A Discrete Time SIR Model

- Assuming a constant hazard of infection between time steps, the probability of a susceptible individual in area i and time $t-1$ becoming infected by time t is determined by the hazard rate λ_{it}. That is,

$$\Pr\left(\text{infection in } (t-1,t] \,|\, \text{no infection by } t-1,\ \text{area } i\right) \quad = \quad 1-e^{-\lambda_{it}}.$$

- Additionally assume that time until infection is independent for all susceptible individuals; hence, the number of new infectives in area i at time t can be modeled as

$$Y_{it}|\lambda_{it} \sim \text{Binomial}\left(S_{i,t-1}, 1-e^{-\lambda_{it}}\right).$$

- When λ_{it} is small, the Taylor expansion,

$$1-\exp(-\lambda_{it}) \approx \lambda_{it}.$$

- When the number of susceptibles, $S_{i,t-1}$ is large, and the probability of infection is small, the binomial distribution can be approximated by a Poisson distribution so that

$$Y_{it}|\lambda_{it} \sim \text{Poisson}\left(S_{i,t-1}\lambda_{it}\right).$$

Measles in Germany

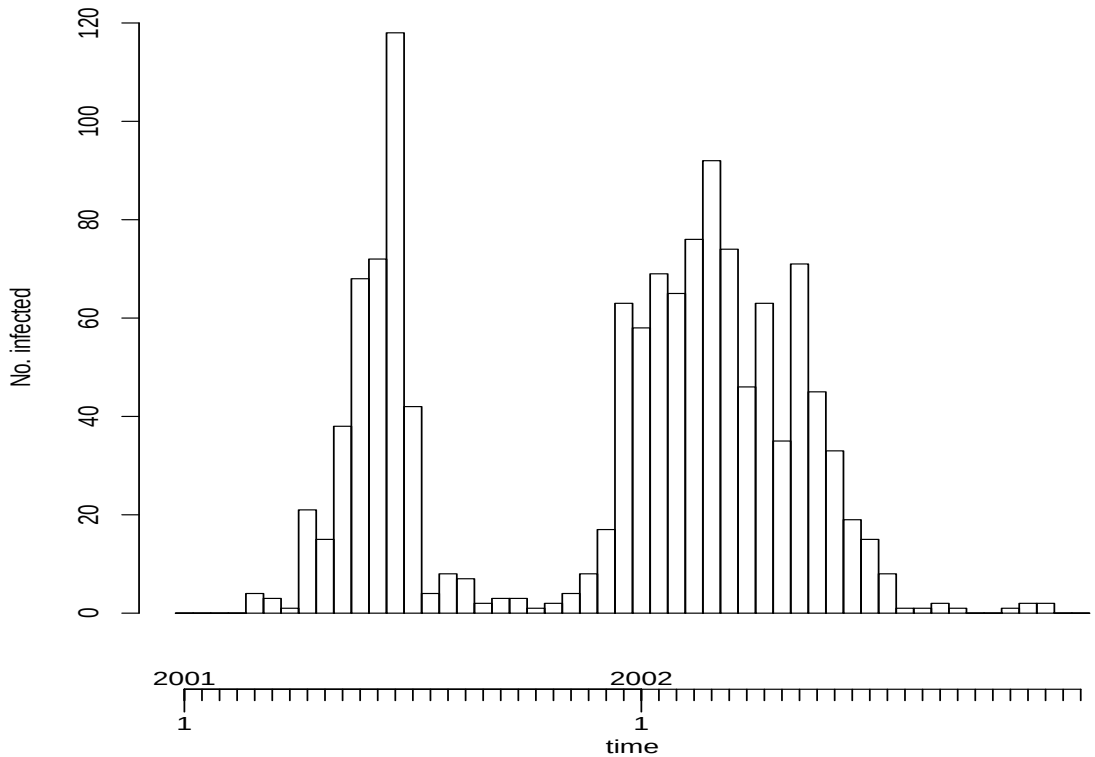


Figure 2: Weekly counts of measles infections by district in the Weser-Ems region of Lower Saxony, Germany, 2001–2002, from the `surveillance` package.

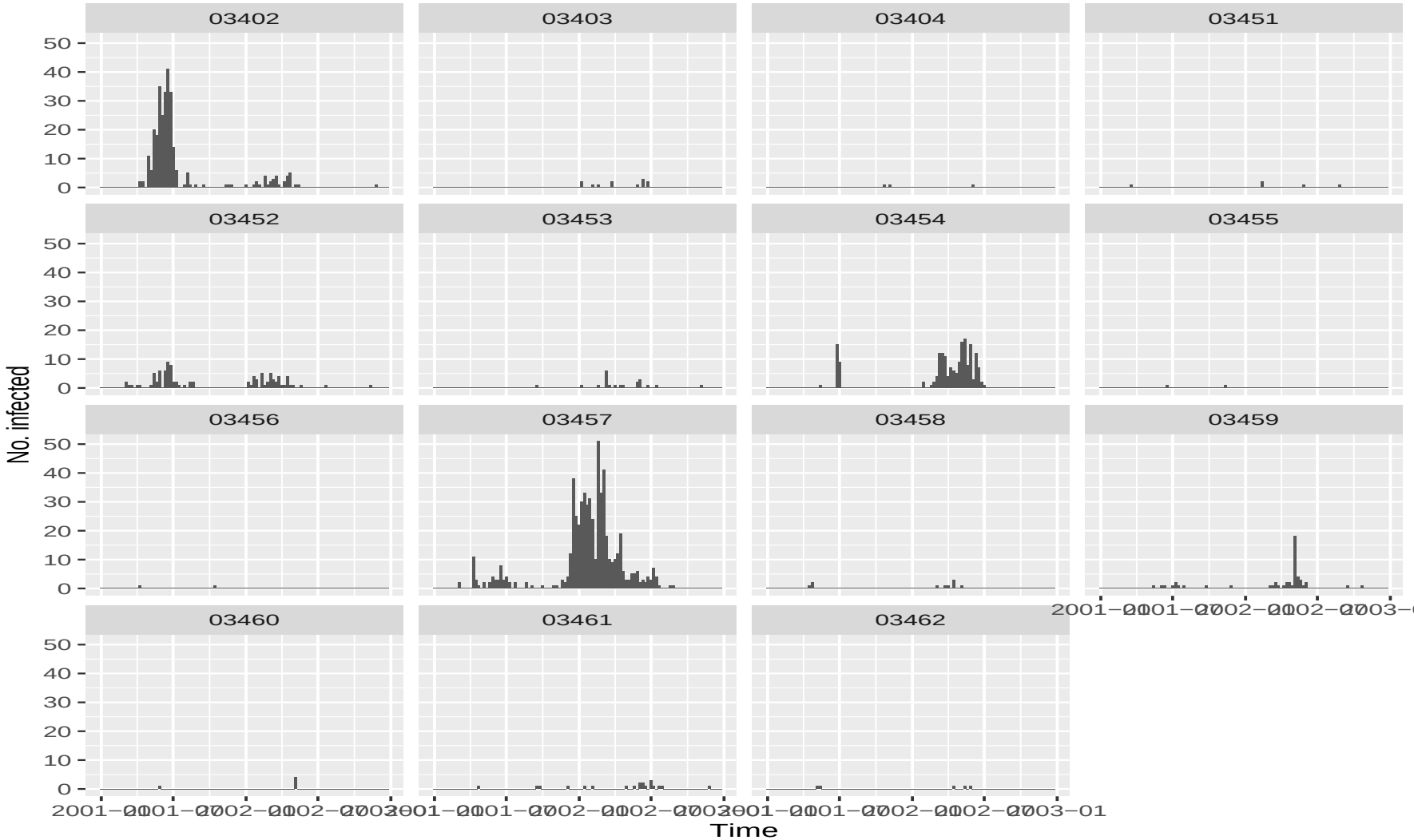


Figure 3: Time series of measles infections by district in the Weser-Ems region of Lower Saxony, Germany, 2001–2002. Only those areas with cases are shown (two areas have zero counts throughout).

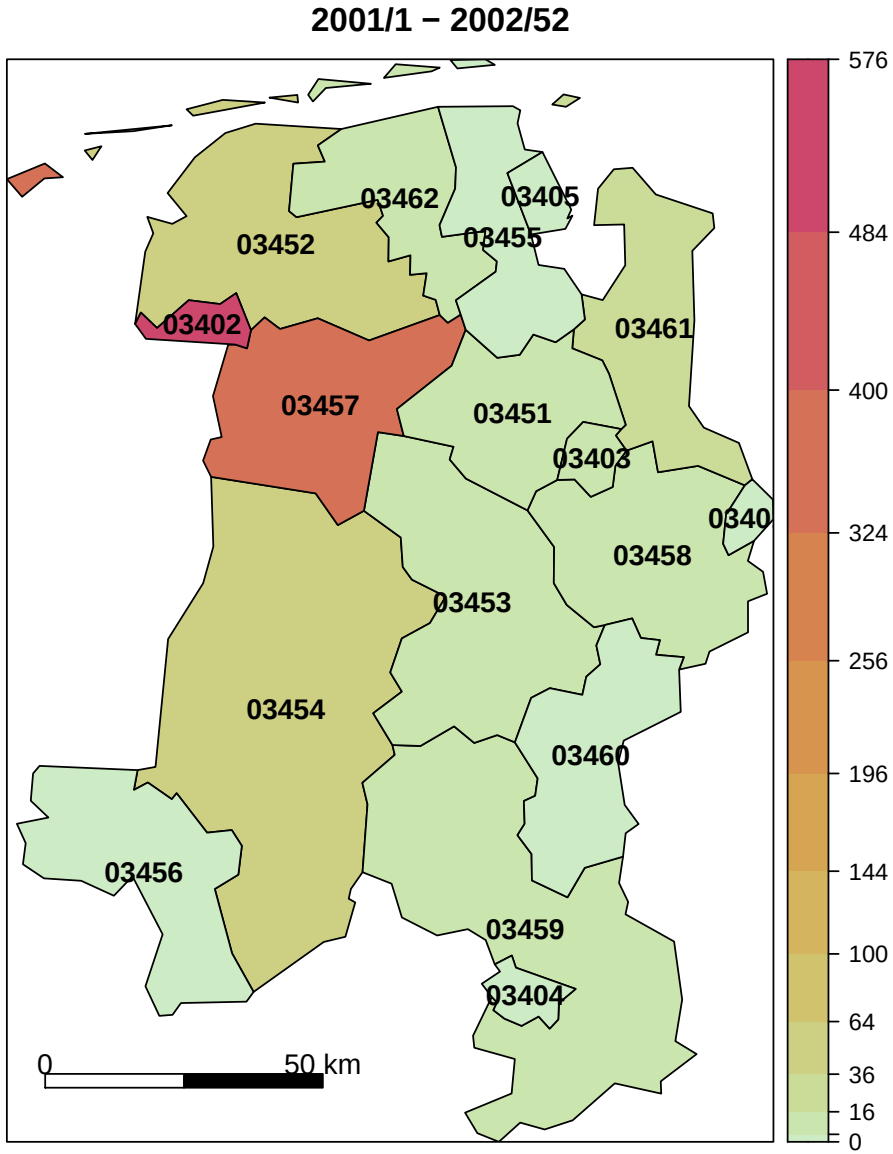


Figure 4: Map of measles infections by district in the Weser-Ems region of Lower Saxony, Germany, 2001–2002.

Decomposition of Risk

- In general, a susceptible may become infected from:
  - an infective in their own area,
  - an infective in another area, or
  - an environmental reservoir or infective external to the study region.
- One specific model (Held *et al.*, 2005) takes a linear combination of three terms that are labeled autoregressive, neighborhood and endemic.
- A competing risk framework gives,

$$\lambda_{it} = \lambda_{it}^{AR\star} + \lambda_{it}^{NE\star} + \lambda_{it}^{EN\star}$$

and under the approximation

$$\begin{aligned} 1 - \exp(-\lambda_{it}) &\approx \lambda_{it} \\ &= \lambda_{it}^{AR\star} + \lambda_{it}^{NE\star} + \lambda_{it}^{EN\star}. \end{aligned}$$

Decomposition of Risk

- For the self-area term:

$$\lambda_{it}^{\mathrm{AR}\star} = c(S_{i,t-1}) \times \frac{y_{i,t-1}}{N_i} \times p,$$

  where
  - $c(S_{i,t-1})$ is the rate of contact between a susceptible and the infective,
  - $y_{i,t-1}/N_i$ is the current prevalence,
  - p is the per-contact probability of infection.
- Assume density dependent transmission, i.e., $c(S_{i,t-1}) \propto S_{i,t-1}$, and suppose $S_{i,t-1} \approx N_i$, then

$$\lambda_{it}^{\mathrm{AR}\star} = \lambda_{it}^{\mathrm{AR}} y_{i,t-1}$$

- Similarly, assume the model

$$\lambda_{it}^{\mathrm{NE}\star} = \lambda_{it}^{\mathrm{NE}} \sum_{i'=1}^{n} w_{i'i} y_{i,t-1}$$

- The neighborhood rate λ_i^{NE} determines the contribution from the neighboring areas.

An epidemic/endemic model

Under the model of Held *et al.* (2005) it is assumed that

$$Y_{it}|\mu_{it} \sim \text{Poisson}(\mu_{it}).$$

This was later extended to,

$$Y_{it}|\mu_{it} \sim \text{NegativeBinomial}(\mu_{it}, \psi)$$

to allow for overdispersion via:

$$\text{var}(Y_{it}) = \mu_{it}(1 + \mu_{it}/\psi),$$

with parameter $\psi > 0$.

In either case the mean μ_{it} is decomposed into the three terms: autoregressive (AR), neighborhood (NE) and endemic (EN)

An epidemic/endemic model

Specifically,

$$\mu_{it} = \lambda_{it}^{\text{AR}} y_{i,t-1} + \lambda_i^{\text{NE}} \sum_{i'=1}^{n} w_{i'i} y_{i',t-1} + N_i \lambda_{it}^{\text{EN}}, \tag{1}$$

where:

- The autoregressive rate λ_i^{AR} dictates the contribution to the risk from the cases in area i in the previous time period.
- The neighborhood rate λ_i^{NE} determines the contribution from the neighboring areas.
- The endemic component λ_{it}^{EN} is a catch all term for contributions not catered for by the autoregressive and neighborhood components and, for example, includes seasonality. Note the N_i population multipliers.

An epidemic/endemic model

For the autoregressive self area rate, a general model is:

$$\log \lambda_{it}^{\text{AR}} = \alpha_0^{\text{AR}} + \boldsymbol{z}_{it}^{\text{T}} \boldsymbol{\beta}^{\text{AR}} + b_i^{\text{AR}},$$

where

- $\boldsymbol{z}_{it}$ represent a $q \times 1$ vector of area-time specific bases,
- $\boldsymbol{\beta}^{\text{AR}}$ is a $q \times 1$ vector of association parameters, and
- $b_i^{\text{AR}} \sim_{iid} \text{N}(0, \sigma^2_{\text{AR}})$ is an area-level autoregressive random effect.

For the neighborhood area rate a general model is:

$$\log \lambda_i^{\text{NE}} = \alpha_0^{\text{NE}} + b_i^{\text{NE}},$$

with

- $b_i^{\text{NE}} \sim_{iid} \text{N}(0, \sigma^2_{\text{NE}})$ an area-level neighborhood random effect.

An epidemic/endemic model

For the endemic component we might include seasonality:

$$\log \lambda_{it}^{\text{EN}} = \alpha_0^{\text{EN}} + b_i^{\text{EN}} + \beta_{\sin} \sin\left(\frac{t}{52} 2\pi\right) + \beta_{\cos} \cos\left(\frac{t}{52} 2\pi\right),$$

where

- $b_i^{\text{EN}} \sim_{iid} \text{N}(0, \sigma^2_{\text{EN}})$ is the area-level endemic random effect.
- Seasonality is modeled via the sin/cos terms.

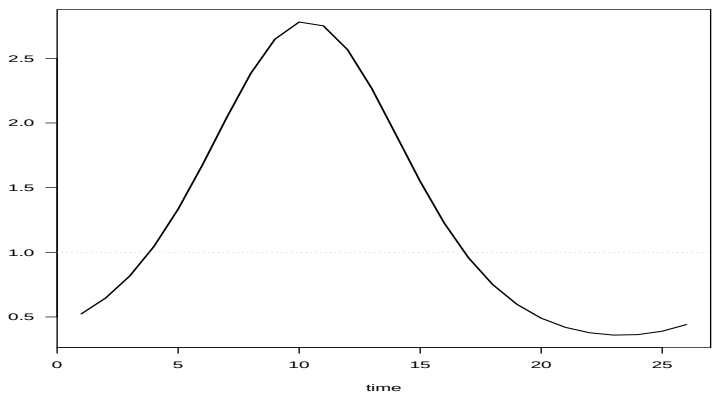


Figure 5: Seasonality estimate for measles data.

Modeling the weights

- The weights may be taken as simply 1 for neighbors (defined through a common boundary) and 0 otherwise.
- Paul *et al.* (2008) use,

$$w_{i'i} = \frac{1}{|\text{ne}(i')|} \quad \text{for } i' \in \text{ne}(i),$$

where ne(i) is the set of neighbors of area i, and $w_{i'i} = 0$ for $i' \notin \text{ne}(i)$.

Modeling the weights

- Alternatively, the weights can be assumed to follow a power law (Meyer and Held, 2014),

$$w_{i'i} = \frac{o_{i'i}^{-\theta}}{\sum_{k=1}^{n} o_{ki}^{-\theta}}$$

  where $o_{i'i}$ is the number of areas that must be crossed when moving between areas i and i', and θ is a power which may be estimated.
- The limit $\theta \to \infty$ corresponds to first-order dependency, and $\theta = 0$ gives equal weight to all areas.
- The normalization ensures that $\sum_{k=1}^{n} w_{ki} = 1$ for all rows of the weight matrix (infecteds are being allocated to neighbors).
- The power law allows "contact" between areas that are a large distance apart since it is "heavy-tailed".

Basic model

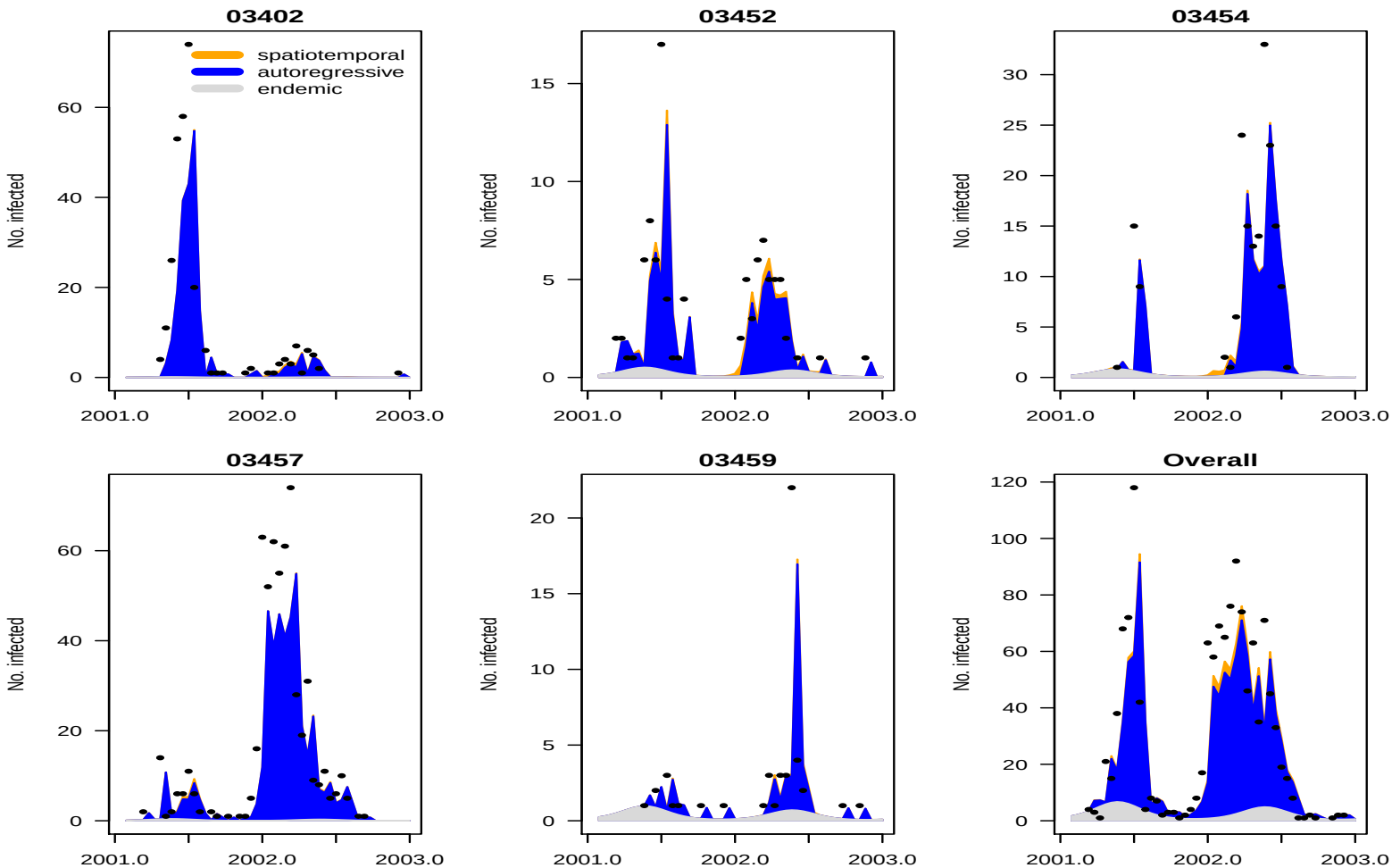


Figure 6: Fits from simple model with no random effects. The AR component dominates. We only show fits for areas with more than 50 cases, and for all areas combined.

Model Comparison

- The above model is very flexible and so in practice many models may be fitted.
- In terms of interpretation it is difficult to assess what is “big”
- Interval estimates on regression coefficients β may be examined to assess significance (do the intervals contain zero?).
- Seeing if random effects are needed is more difficult.
- Using AIC or BIC is not straightforward in a mixed model framework – alternatives include DIC and WAIC, or CPO (all available in `INLA`, but the epidemic/endemic models can’t be fitted in this software).
- Paul and Held (2011) compare models by assessing one-step ahead predictions (with the point to be predicted removed) with the observed value.

Relationship to TSIR Model

- In the Xia *et al.* (2004) time series SIR (TSIR) framework with a gravity model for movement between areas:

$$\begin{aligned} \mathrm{E}[Y_{it}|y_{i,t-1}] &= \lambda_{it} \\ \lambda_{it} &= \frac{\beta_t S_{it}(y_{i,t-1}+\delta_{it})^{\alpha}}{N_i} \\ \delta_{it} &\sim \mathrm{Gamma}(m_{it},1) \\ \mathrm{E}[\delta_{it}] &= m_{it} \\ &= \theta N_{it}^{\tau_1} \sum_{i'=1}^{n} \frac{y_{i',t-1}^{\tau_2}}{d_{i'i}^{\rho}} \end{aligned}$$

- So with $\alpha = \tau_1 = \tau_2 = 1$ and $S_{it} \approx N_i$, we could write

$$\lambda_{it} = \lambda_t^{\mathrm{AR}} y_{i,t-1} + \lambda^{\mathrm{NE}} N_{it} \sum_{i'=1}^{n} \frac{y_{i',t-1}}{d_{i'i}^{\rho}}$$

where $\lambda_t^{\mathrm{AR}} = \beta_t$, $\lambda^{\mathrm{NE}} = \theta$ and we have a distance-based weighting scheme.

Space-Time Models for Point Data

A model for plantation data

- We now turn our attention to the situation in which point data are available.
- Brown *et al.* (2014) describe a spatial susceptible-infectious (SI) model in which the intensity at time t and location $\boldsymbol{x}_i$ is

$$\lambda(\boldsymbol{x}_i, t) = \mu + \sum_{j:\tau_j<t} \theta f(\boldsymbol{x}_i - \boldsymbol{x}_j; \sigma)$$

where τ_j is the infection time of individual j and

$$\theta f(\boldsymbol{x}_i - \boldsymbol{x}_j; \sigma)$$

is the transmission rate from individual j to individual i, and μ is the environmental contribution.

A model for plantation data

- The data concern plant infections transmitted by aphids and the Gaussian function is chosen to represent spatial connection:

$$f(d;\sigma) = (2\pi\sigma^2)^{-1/2} \exp\left(-\frac{d^2}{2\sigma^2}\right).$$

- As usual with models such as these, the likelihood is not straightforward to calculate, and an auxiliary variable method is used.

A model for plantation data

Point data:

- A Bayesian approach to inference is taken.
- The likelihood, given known infection times $\tau_1, \ldots, \tau_n$ (total observation period is $[0, T]$), is

$$
\begin{aligned}
L(\mu, \theta, \sigma^2) &= \left[\prod_{i:\tau_i \leq T} \exp\left\{ - \int_0^{\tau_i} \lambda(\boldsymbol{x}_i, t) dt \right\} \lambda(\boldsymbol{x}_i, \tau_i) \right] \\
&\times \prod_{i:\tau_i > T} \exp\left\{ - \int_0^{\tau_i} \lambda(\boldsymbol{x}_i, t) dt \right\}
\end{aligned}
$$

- The data are interval censored (plants are surveyed on six occasions) and so the unobserved times are imputed via an auxiliary variable scheme.
- Much of Brown *et al.* (2014) concerns computation.

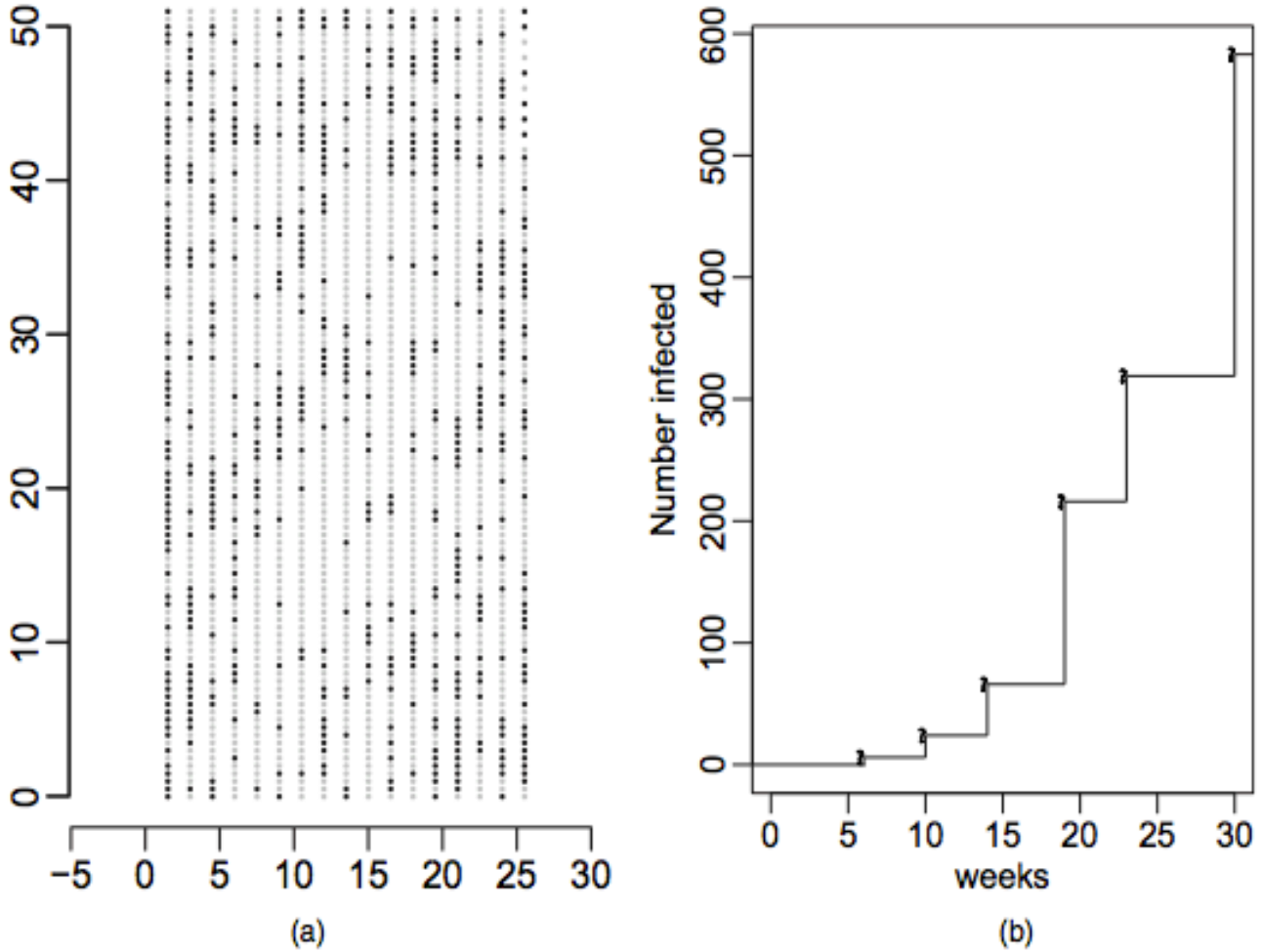


Fig. 1. (a) Location of 1742 sugar canes which are infected (•) or uninfected (•) at the end of the study period, along with (b) the cumulative number of infections over time

Figure 7: Raw data, from Brown *et al.* (2014).

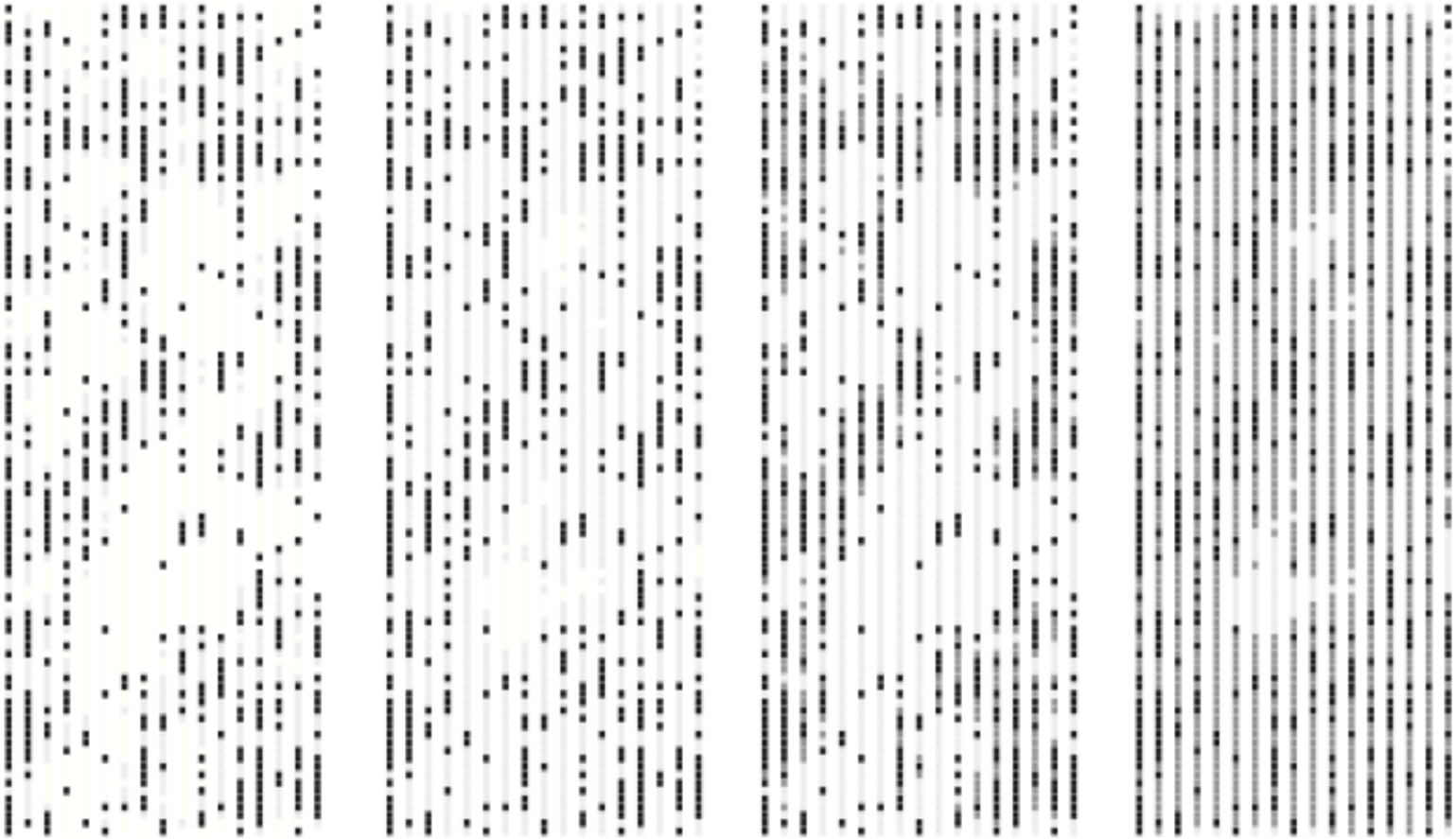


Fig. 5. Probabilities forecast at week 30 of each plant being infected by (a) week 35, (b) week 40, (c) week 50 and (d) week 60: the probabilities are 0–19% (□), 20–79% (▒), 80–99% (▓) and 100% (■) (colour versions are available in the on-line supplement)

Figure 8: Predictions, from Brown *et al.* (2014).

Animal applications

- Animal disease epidemics: A number of authors have considered data in the form of the infectious status of farms.
- For example, data on foot and mouth disease (FMD) have been analyzed by a number of authors including Keeling *et al.* (2001), Lawson and Zhou (2005), Diggle (2006) and Jewell *et al.* (2009).
- In the latter, a Susceptible-Infected-Notified-Removed model is assumed.
- Likelihood is constructed from a time inhomogenous Poisson point process with rates that depend on the states of each farm over time.
- Spatial transmission is modeled using a Cauchy-type kernel and computation is via RJMCMC, again with auxiliary variables.

Conclusions

- This lecture has largely concentrated on spatio-temporal models for aggregated count data (though we touched on point data at the end) – with such data much fine detail is lost and so biologically motivated models are difficult to fit.
- The full SIR formulation (and its spin offs, such as SEIR) are computationally hard to fit since the likelihood is analytically intractable.
- Spatio-temporal methods may be used to assess the effect of intervention programs, see for example Azman *et al.* (2012).
- The space-time models within the `surveillance` package do not currently allow adjustment for age and gender, i.e. different transmission dynamics for different stratum, which is problematic.
- Much work to be done!!!

References

Anderson, R. and May, R. (1991). *Infectious Diseases of Humans: Dynamics and Control*. Oxford University Press.

Andersson, H. and Britton, T. (2000). *Stochastic Epidemic Models and their Statistical Analysis*. Springer Lecture Notes.

Azman, A., Luquero, F., Rodrigues, A., Palma, P., Grais, R., Banga, C., Grenfell, B., and Lessler, J. (2012). Urban cholera transmission hotspots and their implications for reactive vaccination: evidence from Bissau City, Guinea Bissau. *PLoS Neglected Tropical Diseases*, **6**, 1–11.

Bailey, N. (1975). *The Mathematical Theory of Infectious Diseases*. Oxford University Press.

Bauer, C., Wakefield, J., Rue, H., Self, S., Feng, Z., and Wang, Y. (2016). Bayesian penalized spline models for the analysis of spatio-temporal count data. *Statistics in Medicine*, **31**, 1848–1865.

Becker, N. (1989). *Analysis of Infectious Disease Data*. Chapman and Hall.

Brown, P., Chimard, F., Remorov, A., Rosenthal, J., and Wang, X. (2014). Statistical inference and computational efficiency for spatial infectious disease models with plantation data. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, **63**, 467–482.

Cauchemez, S. and Ferguson, N. (2008). Likelihood-based estimation of continuous-time epidemic models from time-series data: application to measles transmission in London. *Journal of the Royal Society Interface*, **5**, 885–897.

Daley, D. and Gani, J. (1999). *Epidemic Modelling: An Introduction*. Cambridge University Press.

Diggle, P. (2006). Spatio-temporal point processes, partial likelihood, foot and mouth disease. *Statistical Methods in Medical Research*, **15**, 325–336.

Fintzi, J., Cui, X., Wakefield, J., and Minin, V. (2017). Efficient data augmentation for fitting stochastic epidemic models to prevalence data. *Journal of Computational and Graphical Statistics*, **26**, 918–929.

Geilhufe, M., Held, L., Skrøvseth, S., Simonsen, G., and Godtliebsen, F. (2014). Power law approximations of movement network data for modeling infectious disease spread. *Biometrical Journal*, **56**, 363–382.

Gibson, G. and Renshaw, E. (1998). Estimating parameters in stochastic compartmental models using Markov chain methods. *Mathematical Medicine and Biology*, **15**, 19–40.

Halloran, M., I.M. Longini, J., and Struchiner, C. (2010). *Design and Analysis of Vaccine Studies*. Springer, New York.

He, D., Ionides, E., and King, A. (2010). Plug-and-play inference for disease dynamics: measles in large and small populations as a case study. *Journal of the Royal Society Interface*, **7**, 271–283.

Held, L. and Paul, M. (2012). Modeling seasonality in space-time infectious disease surveillance data. *Biometrical Journal*, **54**, 824–843.

Held, L., Höhle, M., and Hofmann, M. (2005). A statistical framework for the analysis of multivariate infectious disease surveillance counts. *Statistical Modelling*, **5**, 187–199.

Herzog, S., Paul, M., and Held, L. (2011). Heterogeneity in vaccination coverage explains the size and occurrence of measles epidemics in German surveillance data. *Epidemiology and Infection*, **139**, 505–515.

Höhle, M., Siedler, A., Bader, H.-M., Ludwig, M., Heininger, U., and von Kries, R. (2011). Assessment of varicella vaccine effectiveness in Germany: a time-series approach. *Epidemiology and Infection*, **139**, 1710–1719.

Jandarov, R., Haran, M., Bjornstad, O., and Grenfell, B. (2014). Emulating a gravity model to infer the spatiotemporal dynamics of

an infectious disease. *Journal of the Royal Statistical Society, Series C*, **63**, 423–444.

Jewell, C., Kypraios, T., Neal, P., and Roberts, G. (2009). Bayesian analysis for emerging infectious diseases. *Bayesian Analysis*, **4**, 465–496.

Keeling, M. and Rohani, P. (2008). *Modeling Infectious Diseases in Humans and Animals*. Princeton University Press, Princeton and Oxford.

Keeling, M., Woolhouse, M., Shaw, D., Matthews, L., Chase-Topping, M., Haydon, D., Cornell, S., Kappey, J., Wilesmith, J., and Grenfell, B. (2001). Dynamics of the 2001 uk foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape. *Science*, **294**, 813–817.

Kermack, W. and McKendrick, A. (1927). A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society of London Series A, Containing Papers of a Mathematical and Physical Character*, **115**, 700–721.

Knorr-Held, L. and Richardson, S. (2003). A hierarchical model for space-time surveillance data on meningococcal disease incidence. *Journal of the Royal Statistical Society: Series C*, **52**, 169–183.

Koepke, A., Longini Jr, I., Halloran, M., Wakefield, J., and Minin, V. (2016). Predictive modeling of cholera outbreaks in Bangladesh. *Annals of Applied Statistics*, **10**, 575–595.

Lawson, A. and Zhou, H. (2005). Spatial statistical modeling of disease outbreaks with particular reference to the uk foot and mouth disease (fmd) epidemic of 2001. *Preventive Veterinary Medicine*, **71**(3), 141–156.

Lekone, P. and Finkenstädt, B. (2006). Statistical inference in a stochastic epidemic SEIR model with control intervention: Ebola as a case study. *Biometrics*, **62**, 1170–1177.

McKinley, T., Cook, A., and Deardon, R. (2009). Inference in epidemic models without likelihoods. *The International Journal of Biostatistics*, **5**, 24.

Meyer, S. and Held, L. (2014). Power-law models for infectious disease spread. *Annals of Applied Statistics*, **8**, 1612–1639.

Meyer, S. and Held, L. (2017). Incorporating social contact data in spatio-temporal models for infectious disease spread. *Biostatistics*, **18**, 338–351.

Meyer, S., Held, L., and Höhle, M. (2017). Spatio-temporal analysis of epidemic phenomena using the R package `surveillance`. *Journal of Statistical Software*, **77**.

Mugglin, A., Cressie, N., and Gemmell, I. (2002). Hierarchical statistical modelling of influenza epidemic dynamics in space and time. *Statistics in Medicine*, **21**, 2703–2721.

Neal, P. (2012). Efficient likelihood-free bayesian computation for household epidemics. *Statistics and Computing*, **22**, 1239–1256.

Neal, P. and Kypraios, T. (2015). Exact bayesian inference via data augmentation. *Statistics and Computing*, **25**, 333–347.

O'Neill, P. and Becker, N. (2001). Inference for an epidemic when susceptibility varies. *Biostatistics*, **2**, 99–108.

O'Neill, P. and Roberts, G. (1999). Bayesian inference for partially observed stochastic epidemics. *Journal of the Royal Statistical Society, Series A*, **162**, 121–129.

Paul, M. and Held, L. (2011). Predictive assessment of a non-linear random effects model for multivariate time series of infectious disease counts. *Statistics in Medicine*, **30**, 1118–1136.

Paul, M., Held, L., and Toschke, A. M. (2008). Multivariate modelling of infectious disease surveillance data. *Statistics in Medicine*, **27**, 6250–6267.

Toni, T., Welch, D., Strelkowa, N., Ipsen, A., and Stumpf, M. (2010). Approximate Bayesian computation scheme for parameter

inference and model selection in dynamical systems. *Journal of the Royal Society Interface*, **6**, 187–202.

Xia, Y., Bjørnstad, O. N., and Grenfell, B. (2004). Measles metapopulation dynamics: a gravity model for epidemiological coupling and dynamics. *The American Naturalist*, **164**, 267–281.