Statistical approaches to the temporal and spatio-temporal surveillance of infectious diseases

Leonhard Held[1] Michael Höhle[2] Michaela Paul[1]

[1]Biostatistics Unit
Institute of Social and Preventive Medicine
University of Zurich

[2]Department of Statistics
University of Munich

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Outline

1. Introduction

- This talk is about the statistical analysis of routinely collected surveillance data seen as multiple time series of counts
- Our aim is to explain concepts behind prospective and retrospective statistical surveillance and illustrate use and potential in veterinary epidemiology
- The statistical methods of this talk are implemented in the R-package `surveillance` available from the Comprehensive R Archive Network (CRAN) (Höhle, 2007)

Examples of disease surveillance applications

In human epidemiology

- Monitoring of congenital malformations (Chen, 1978)
- Surveillance of notifiable diseases (Robert Koch Institute, 2007; Widdowson et al., 2003)
- Monitoring surgical outcomes (Steiner et al., 2000)

In veterinary epidemiology

- Salmonella in livestock reports, Veterinary Laboratories Agency, UK (Kosmider et al., 2006)
- Rabies Surveillance (WHO Collaboration Centre for Rabies Surveillance and Research, 2007)
- Monitoring of abortions in dairy cattle (Carpenter et al., 2007)

Animal surveillance vs. surveillance for humans

- Zonoses underline the connection between animal and human surveillance
- Differences between animal and humans:
  - Diverse species (cattle, pig, sheep, fox, bat, etc)
  - Character of living (pet, industry, wild)
  - Herd vs. the individual (isolation vs. incident)
- Consequences:
  - Possibility and cost of investigation depends heavily on character of living and species
  - Control strategies differ

The quality of surveillance data

Issues complicating statistical analysis of the time series

- Lack of clear case definition
- Under-reporting and reporting delays
- Often no denominator data
- Seasonality
- Low number of disease cases
- Presence of past outbreaks

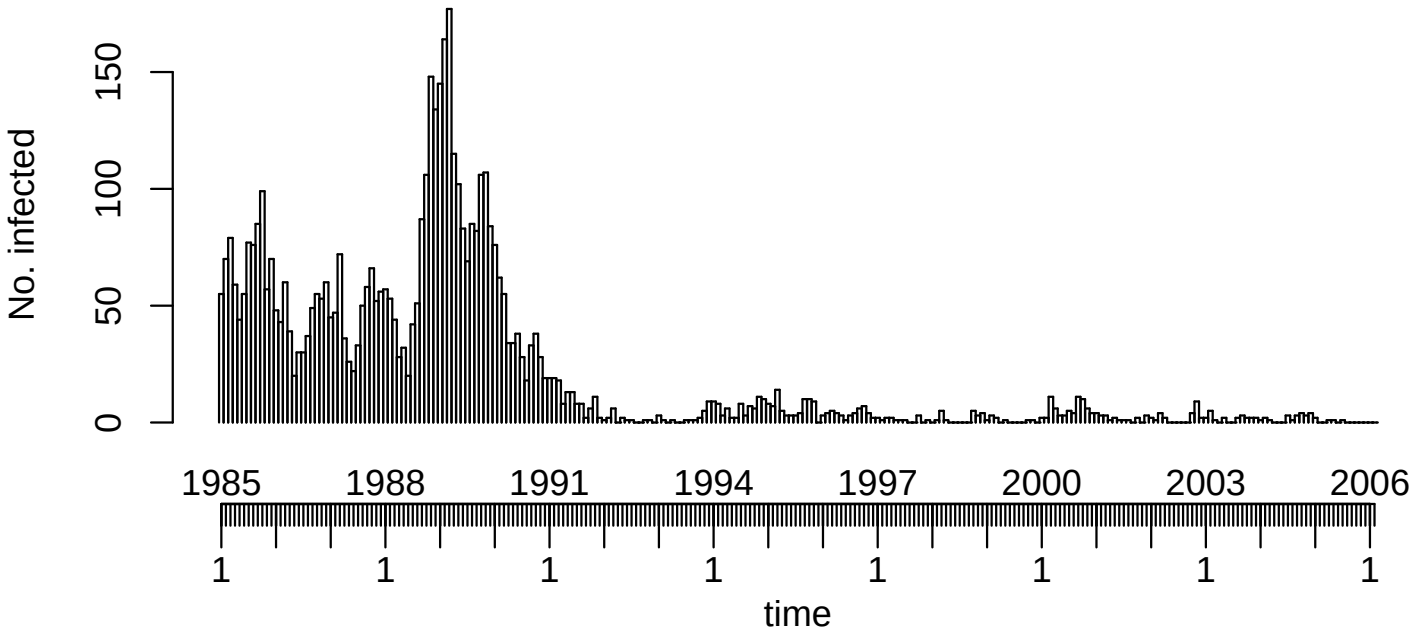
2. Statistical outbreak detection in univariate time series

Contents of this section:

- Example of animal disease surveillance
- Short introduction to three surveillance methods for count data
  - The Farrington algorithm (Farrington et al., 1996)
  - Cumulative sum (CUSUM) likelihood ratio detectors
  - Generalized likelihood ratio detectors
- Evaluating performance

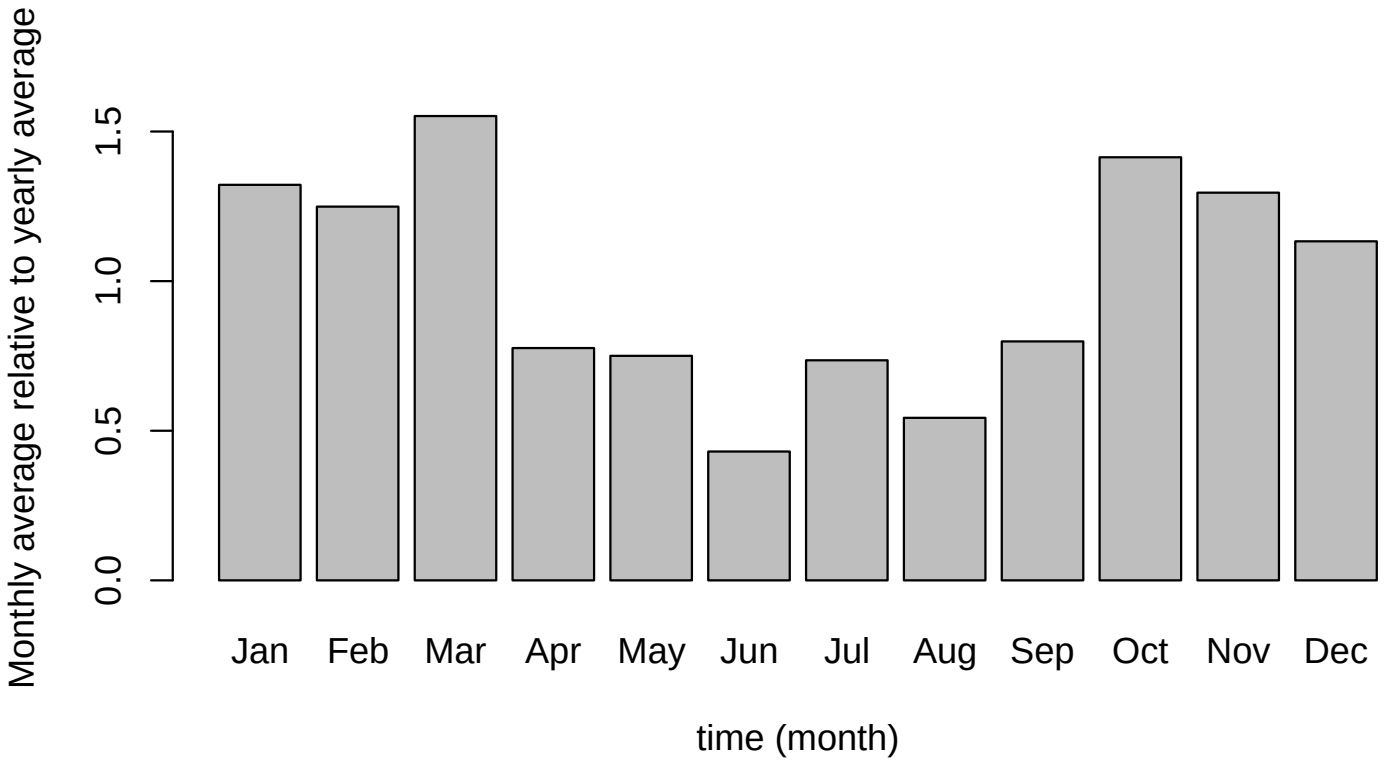
Example – Rabies among foxes in Hesse 1985-2006 (1)

Monthly counts are provided by the WHO Collaboration Centre for Rabies Surveillance and Research. Thanks to Christoph Staubach, Federal Research Institute for Animal Health, Germany



The observed count time series is $\{y_t\}_{t=1}^{254} = \{y_{1:1985}, \ldots, y_{2:2006}\}$.

Example – Rabies among fox in Hesse 1985-2006 (2)



To illustrate seasonality:

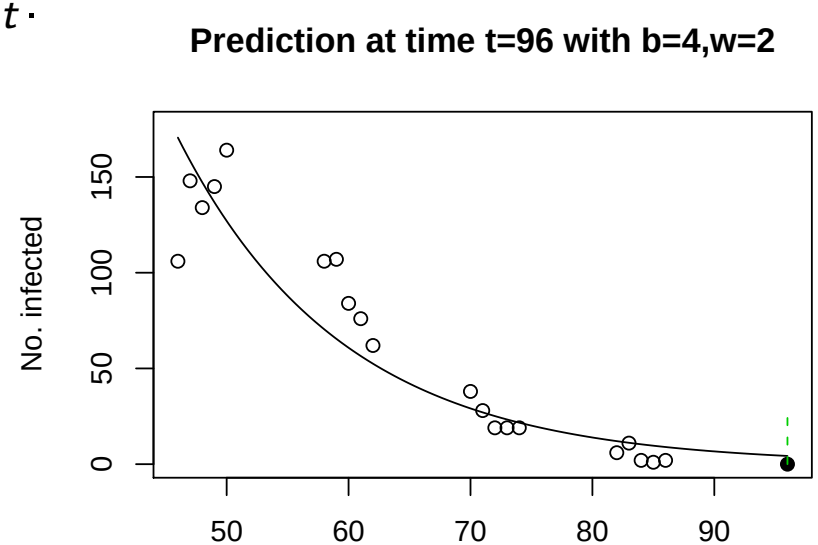
1. divide monthly cases by the respective yearly average
2. compute monthly mean of this detrended time series

Farrington algorithm (1) – model

- Predict value y_{t_0} at time $t_0 = (t_0^m, t_0^y)$ using a set of reference values from window of size $2w + 1$ up to b years back:

$$R(w, b) = \left(\bigcup_{i=1}^{b} \bigcup_{j=-w}^{w} y_{t_0^m + j : t_0^y - i} \right)$$

- Fit a Poisson GLM with overdispersion to the $b(2w + 1)$ reference values, i.e. $\mathrm{E}(y_t) = \mu_t$, where $\log \mu_t = \alpha + \beta t$ and $\mathrm{Var}(y_t) = \phi \mu_t$.



Farrington algorithm (2) – outbreak detection

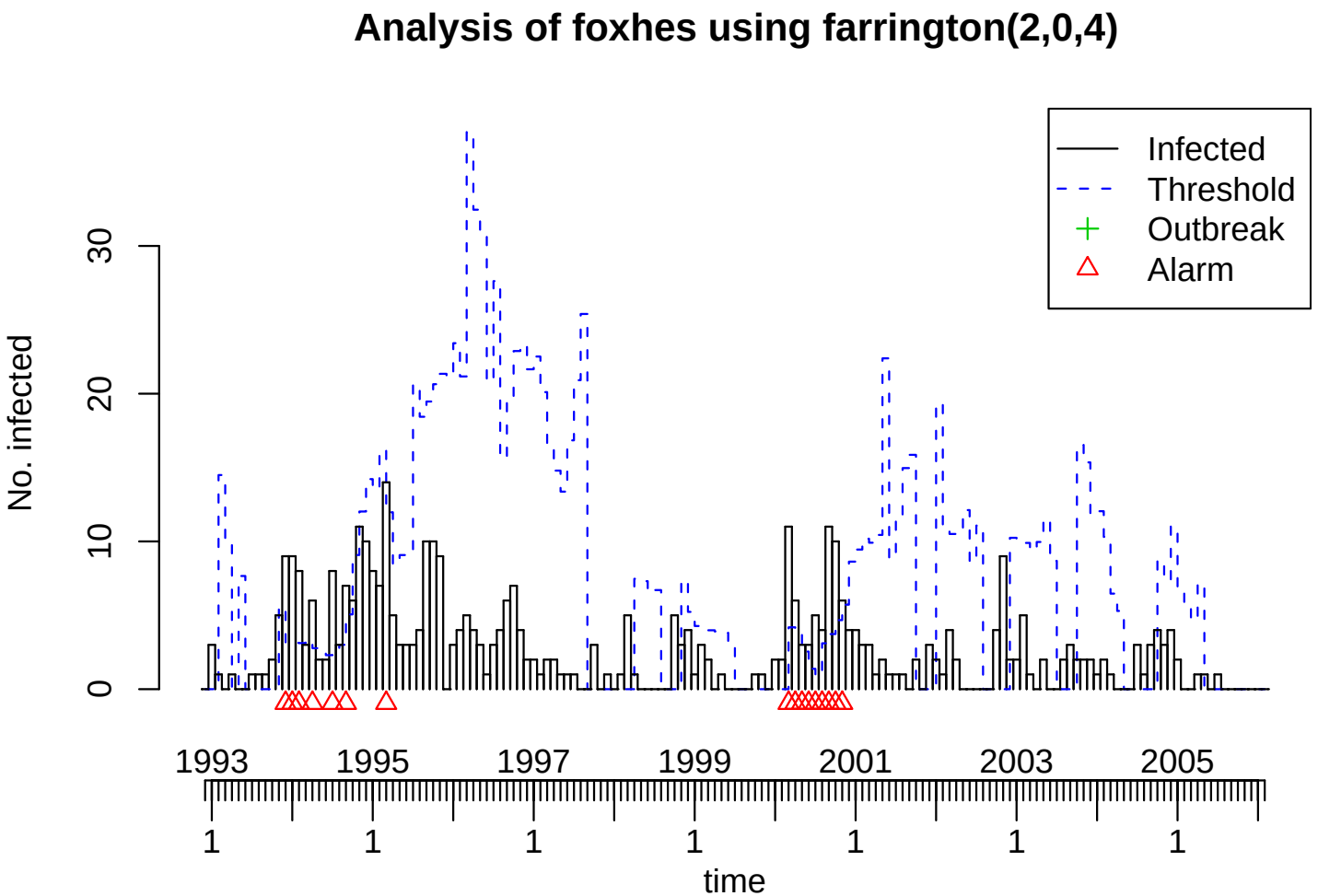
Predict and compare:

- An approximate $(1 - \frac{\alpha}{2})\%$ prediction interval for y_{t_0} based on the GLM has upper limit $U = \hat{\mu}_{t_0} + z_\alpha \sqrt{\text{Var}(y_{t_0} - \hat{\mu}_{t_0})}$
- If observed y_{t_0} is greater than U then flag t_0 as outbreak

Remarks:

- Linear trend is only included if significant at 5% level, $b \geq 3$ and no over-extrapolation occurs
- Automatic correction for past outbreaks by computing Anscombe residuals for reference values and re-fit GLM assigning lower weights to values with large residuals
- Low count protection – the algorithm raises an alarm only if more than 5 cases in past 4 weeks

Farrington algorithm (3) – example



CUSUM likelihood ratio detectors (1)

Assume that given change-point τ

$$y_t|z_t,\tau \sim \begin{cases} f_{\theta_0}(\cdot|z_t) & \text{for } t = 1,\ldots,\tau-1 \text{ (in-control)} \\ f_{\theta_1}(\cdot|z_t) & \text{for } t = \tau,\tau+1,\ldots \text{ (out-of-control)} \end{cases}$$

where z_t denotes known covariates at time t and f_θ is e.g. the Poisson probability function parametrized by θ.

Likelihood ratio (LR) based stopping time

$$N = \inf\left\{ n \geq 1 : \max_{1\leq k\leq n} \left[\sum_{t=k}^{n} \log\left\{ \frac{f_{\theta_1}(y_t|z_t)}{f_{\theta_0}(y_t|z_t)} \right\} \right] \geq c_\gamma \right\}.$$

CUSUM likelihood ratio detectors (2)

With no covariates and pre-specified θ_0 and θ_1 the stopping rule can be written in recursive form:

Cumulative Sum (CUSUM)

$$l_0 = 0, \quad l_n = \max\left(0, l_{n-1} + \log\left\{\frac{f_{\theta_1}(x_n)}{f_{\theta_0}(x_n)}\right\}\right), \; n \geq 1$$

with stopping-rule $N = \inf\{n : l_n \geq c_\gamma\}$.

- The CUSUM detector is optimal (in some technical sense) for the detection from θ_0 to θ_1.
- CUSUM for Poisson distribution described by Lucas (1985)

CUSUM likelihood ratio detectors (3) – seasonality

What if in-control observations originate from seasonal Poisson GLM, i.e. $Y_t \sim \text{Po}(\mu_{0,t})$ with

$$\log \mu_{0,t} = \alpha + \beta t + \sum_{s=1}^{S} \Big(\gamma_s \sin(\omega_s t) + \delta_s \cos(\omega_s t) \Big)$$

and $\omega_s = \frac{2\pi}{p} s$ with period p.

- Rossi et al. (1999) suggest a Poisson CUSUM for such time varying mean data by transformation to normality

$$x_t = \frac{y_t - 3\mu_{0,t} + 2\sqrt{\mu_{0,t} \cdot y_t}}{2\sqrt{\mu_{0,t}}}$$

and applying a Gaussian CUSUM to these transformed values

CUSUM likelihood ratio detectors (4) – seasonality cnt'ed

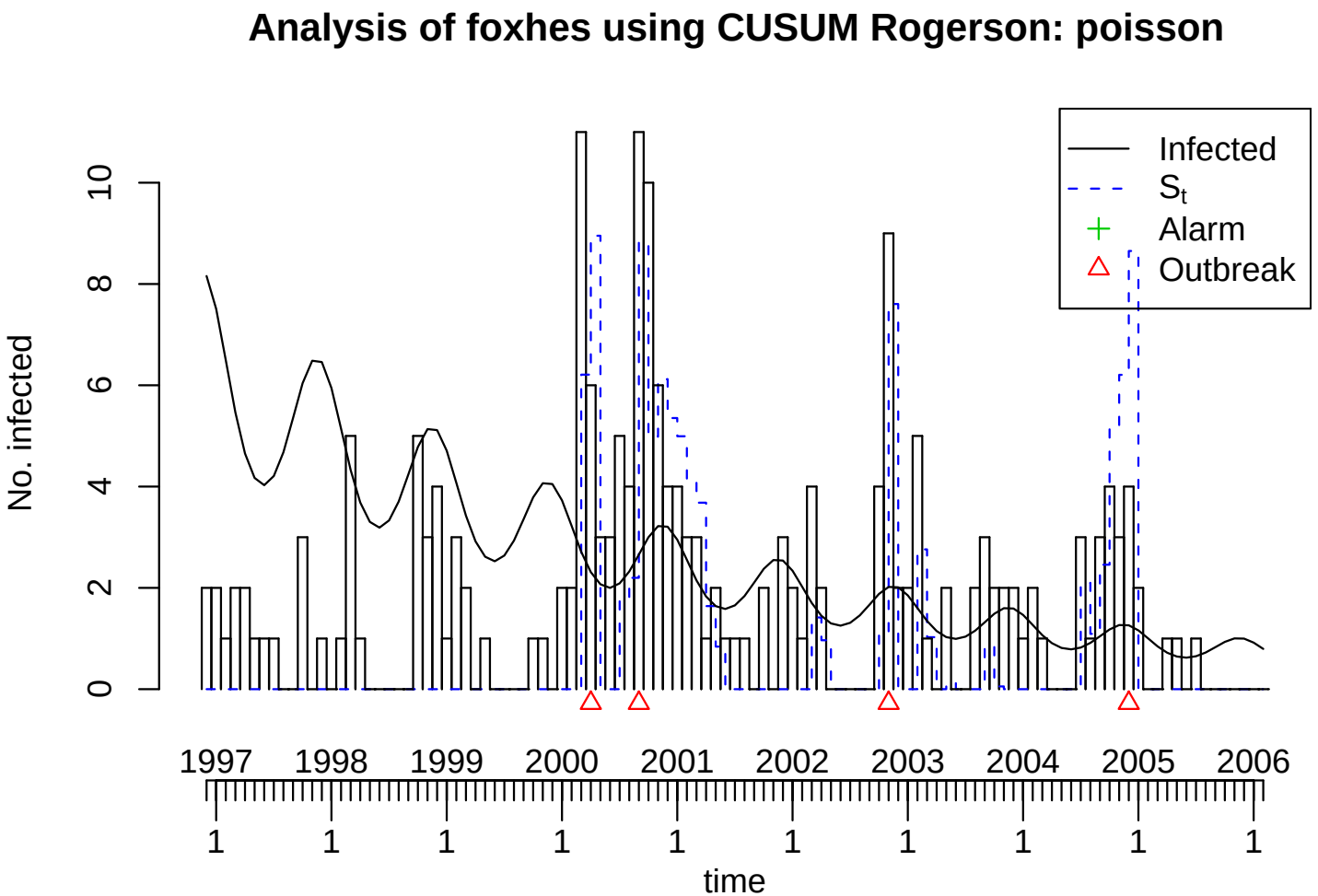
- Rogerson and Yamada (2004) compute time-varying parameters of the Poisson CUSUM to keep in-control ARLs fixed:

$$S_t = \max\{0, S_{t-1} + c_t(x_t - k_t)\}, \quad \text{with}$$

$$k_t = \frac{\mu_{1,t} - \mu_{0,t}}{\log(\mu_{1,t}) - \log(\mu_{0,t})},$$

with $\mu_{1,t} = \mu_{0,t} + s\sqrt{\mu_{0,t}}$ and $c_t = h/h_t$ scales the contribution of $(x_t - k_t)$. The decision interval h_t is determined at each time point as the decision interval of a Poisson CUSUM with reference value k_t having ARL_0.

CUSUM likelihood ratio detectors (5) – example



Generalized likelihood ratio detector (1) – model

- A problem of the LR scheme is that detection is only optimal for pre-specified θ_1. Generalization:

Generalized likelihood ratio (GLR) based stopping rule

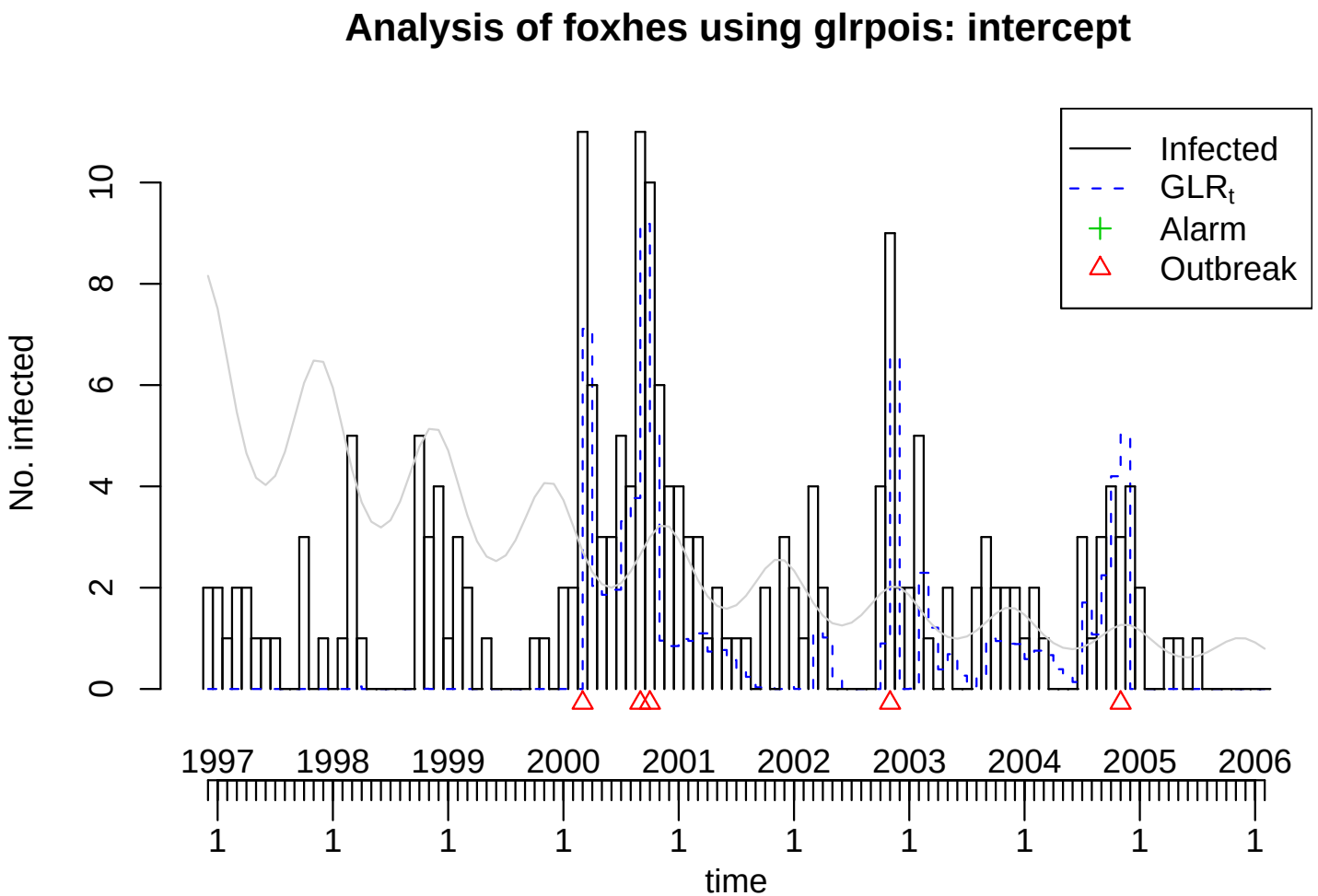
$$N_G = \inf\left\{ n \geq 1 : \max_{1\leq k\leq n} \sup_{\theta_1\in\Theta_1} \left[\sum_{t=k}^{n} \log\left\{ \frac{f_{\theta_1}(y_t|z_t)}{f_{\theta_0}(y_t|z_t)} \right\} \right] \geq c_\gamma \right\}$$

- No recursive updating as in CUSUM possible
- However, for Poisson case with

$$\log \mu_{1,t} = \log \mu_{0,t} + \kappa$$

efficient computations are possible (Höhle, 2006)

Generalized likelihood ratio detector (2) – example



Evaluating the performance of a surveillance algorithm

Choice of threshold in surveillance algorithms should be based on performance measure:

- Location parameters of the run length distribution, e.g. the ARLs $\mathrm{E}(N|\tau = 0)$ or $\mathrm{E}(N|\tau = \infty)$.
- Conditional expected delay $E(N - \tau|\tau, N \geq \tau)$
- Probability of false alarm within first m time points, i.e. $P(N \leq m|\tau = \infty)$.
- Sensitivity, Specificity, ROC-Curves

Computation of measures rarely available as closed formulas. Instead Monte-Carlo sampling is used.

3. Model-based surveillance

Philosophy so far:

1. Use of a simple statistical model to describe the incidence, e.g. a Poisson GLM
2. No modelling of epidemic behaviour

$\longrightarrow$ Attempt to detect outbreaks instead of predicting them

$\longrightarrow$ Implicit assumption that no outbreak has happened in the past (except ad-hoc adjustment in Farrington et al. (1996))

Modelling surveillance data

Goal: Development of a realistic stochastic model for the statistical analysis of surveillance data of infectious disease counts

Features that should be taken into account:

- Count data, possibly overdispersion
- Epidemic nature
- No information about number of susceptibles
- Seasonality
- Dependencies between time series

Our model approach

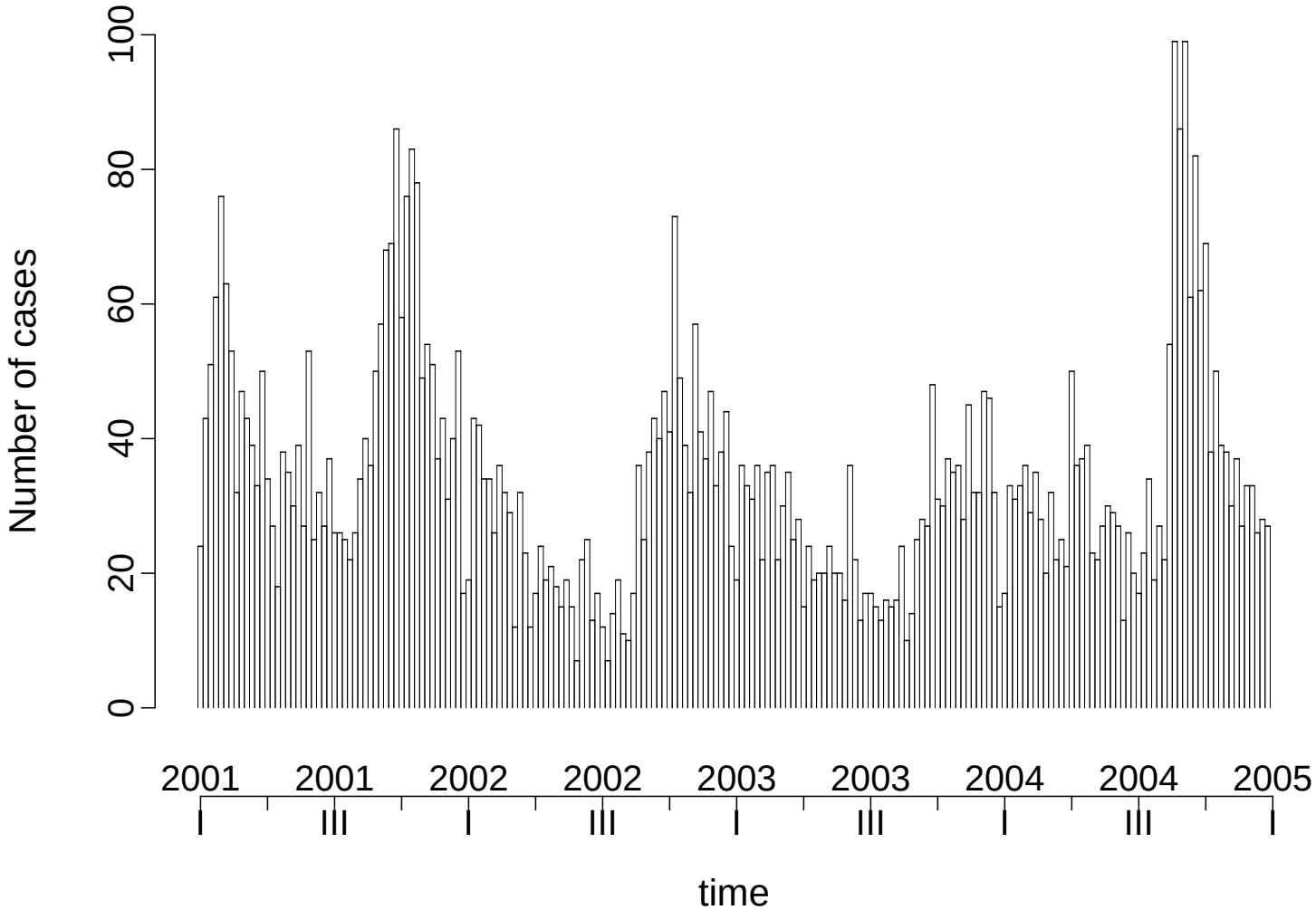
- A compromise is needed between mechanistic and empirical modelling
- Our model is based on a generalized branching process with immigration
- Note: Branching process is a useful approximation of SIR-models in the absence of information on susceptibles
- Explicit decomposition of the incidence in endemic and epidemic component (Held et al., 2005)
- Past counts act additively on disease incidence
  $\longrightarrow$ model is not a GLM

Model

$$
\begin{aligned}
y_t &\sim \text{Po}(\mu_t) \\
\mu_t &= \nu_t + \lambda y_{t-1} \\
\log(\nu_t) &= \alpha + \sum_{s=1}^{S} (\gamma_s \sin(\omega_s t) + \delta_s \cos(\omega_s t))
\end{aligned}
$$

- Autoregressive coefficient $\lambda < 1$ determines stationarity of y_t, can be interpreted as epidemic proportion
- $\log \nu_t$ is modelled parametrically as in log-linear Poisson regression; includes terms for seasonality
- Adjustments for overdispersion straightforward: Replace $\text{Po}(\mu_t)$ by $\text{NegBin}(\mu_t, \psi)$-Likelihood
- Model can be fitted by Maximum-Likelihood in `surveillance`

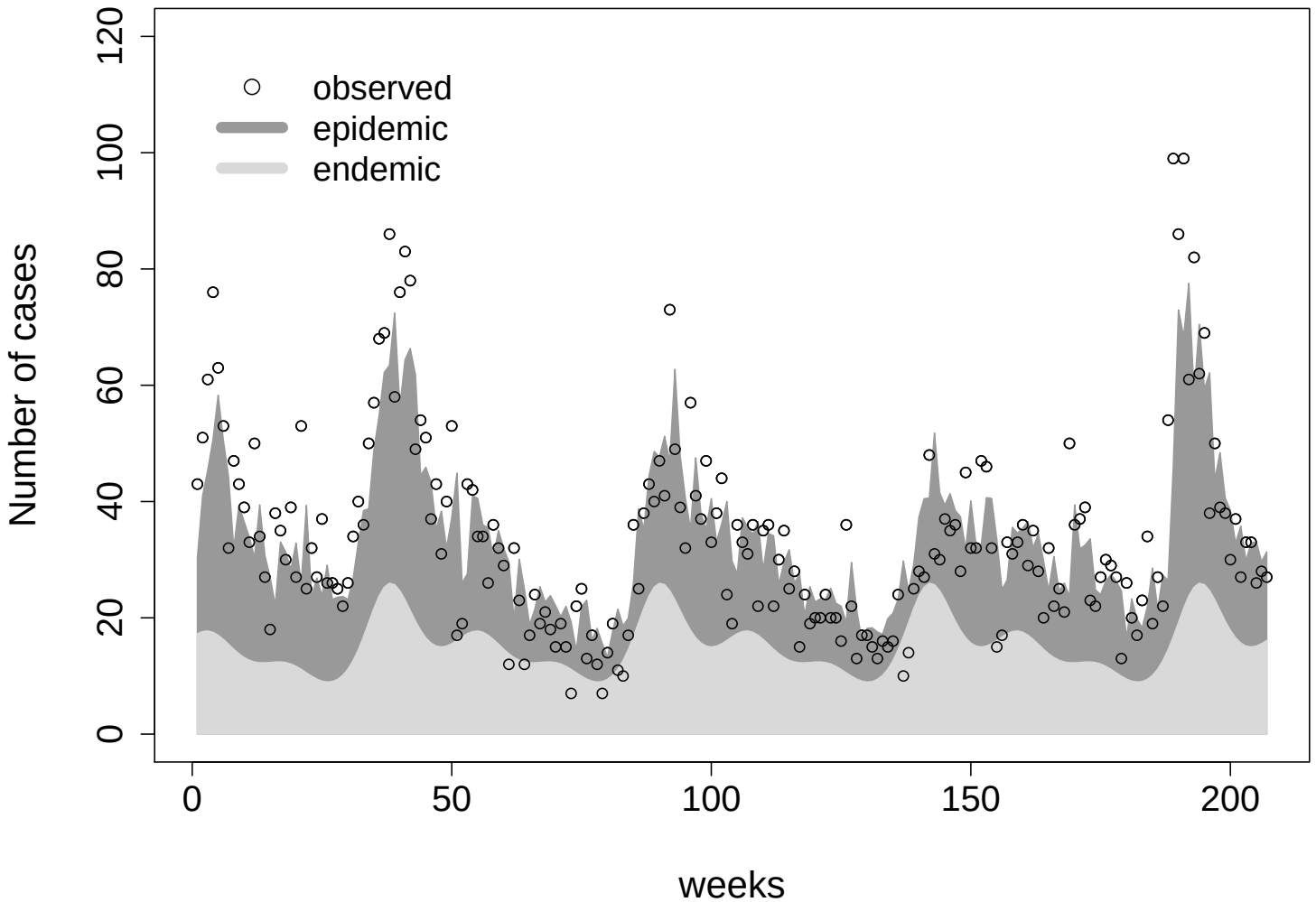
Example: Hepatitis A in Germany 2001-2005



Parameter estimates

S	$\hat{\lambda}_{ML}$ (se)	$\hat{\psi}_{ML}$ (se)	$\log L(\mathbf{y}, \boldsymbol{\theta})$	$\lvert\boldsymbol{\theta}\rvert$	AIC
1	0.65 (0.03)	-	-893.9	4	1795.8
1	0.62 (0.06)	13.94 (1.98)	-770.6	5	1551.2
2	0.57 (0.06)	14.70 (2.13)	-767.0	7	1548.0
3	0.54 (0.06)	15.36 (2.26)	-763.8	9	1545.6
4	0.54 (0.06)	15.42 (2.27)	-763.4	11	1548.9

Fitted values



Multivariate modelling

- Suppose now multiple time series $i = 1, \ldots, n$ are available over the same time horizon $t = 1, \ldots, T$
- Notation: $y_{i,t}$ is the number of disease cases made from the i-th time series at time t
- Examples:
  - Incidence in different age groups
  - Incidence of related diseases
  - Incidence in different geographical regions
- Idea: Include now also the number of counts from other time series as autoregressive covariates
  $\longrightarrow$ multi-type branching process

Bivariate modelling

Joint analysis of two time series $i = 1, 2$

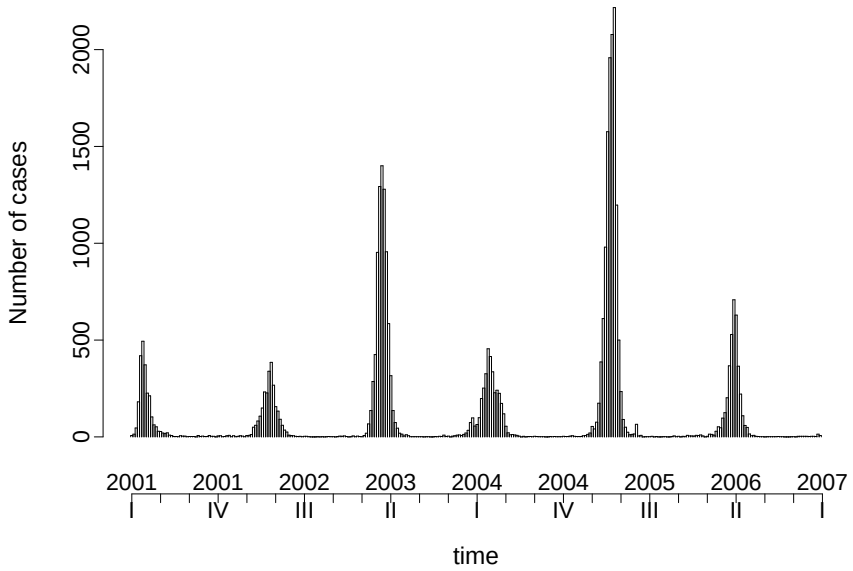
$$\begin{aligned} y_{i,t} &\sim \text{NegBin}(\mu_{i,t}, \psi) \\ \mu_{i,t} &= \nu_t + \lambda y_{i,t-1} + \phi y_{j,t-1} \qquad \text{where } j \neq i \end{aligned}$$

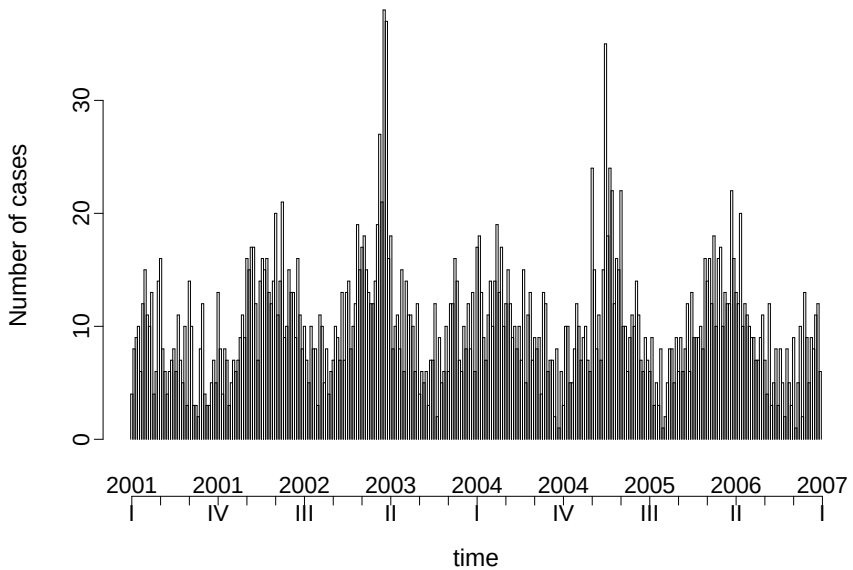
Note: ψ, ν_t, λ and ϕ may also depend on i

Example: Influenza and meningococcal disease

- Interdependencies between disease cases caused by different pathogens might be of particular interest to further understand the dynamics of such diseases
- For example, several studies describe an association between influenza and meningococcal disease (Cartwright et al., 1991; Hubert et al., 1992; Makras et al., 2001; Jensen et al., 2004)
- We analyse routinely collected surveillance data from Germany, 2001-2006

Data


Number of cases
0
500
1000
1500
2000
2001 I
2001 IV
2002 III
2003 II
2004 I
2004 IV
2005 III
2006 II
2007 I
time


Number of cases
0
10
20
30
2001 I
2001 IV
2002 III
2003 II
2004 I
2004 IV
2005 III
2006 II
2007 I
time

Univariate analysis of influenza infections

S	$\hat{\lambda}_{ML}$ (se)	$\hat{\psi}_{ML}$ (se)	$\log L(\mathbf{y}, \boldsymbol{\theta})$	$\lvert\boldsymbol{\theta}\rvert$	AIC
0	0.99 (0.01)	-	-4050.9	2	8105.9
0	0.98 (0.05)	2.41 (0.27)	-1080.2	3	2166.5
1	0.86 (0.05)	2.74 (0.31)	-1064.1	5	2138.2
2	0.76 (0.05)	3.12 (0.37)	-1053.3	7	2120.6
3	0.74 (0.05)	3.39 (0.41)	-1044.1	9	2106.3
4	0.74 (0.05)	3.44 (0.42)	-1042.2	11	2106.3

Univariate analysis of meningococcal infections

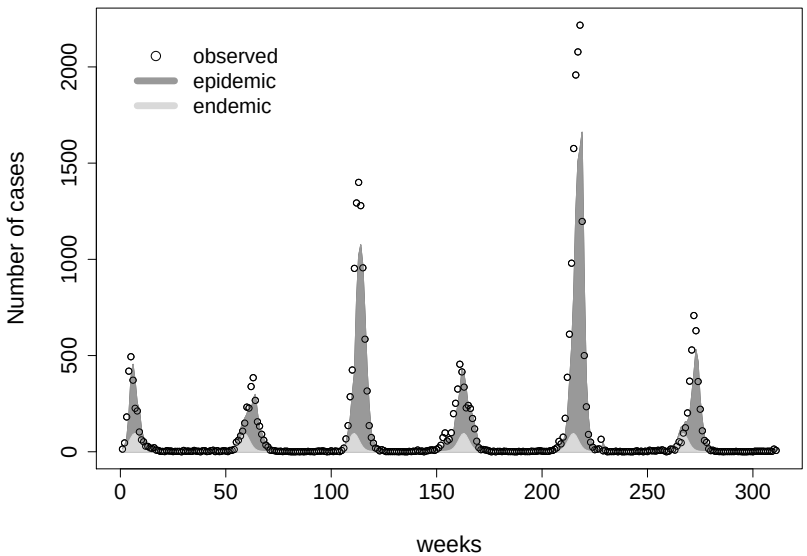
S	$\hat{\lambda}_{ML}$ (se)	$\hat{\psi}_{ML}$ (se)	$\log L(\mathbf{y}, \boldsymbol{\theta})$	$\lvert\boldsymbol{\theta}\rvert$	AIC
0	0.50 (0.04)	-	-919.2	2	1842.4
0	0.48 (0.05)	11.80 (2.09)	-880.5	3	1767.0
1	0.16 (0.06)	20.34 (4.83)	-845.6	5	1701.2
2	0.16 (0.06)	20.41 (4.86)	-845.5	7	1705.0

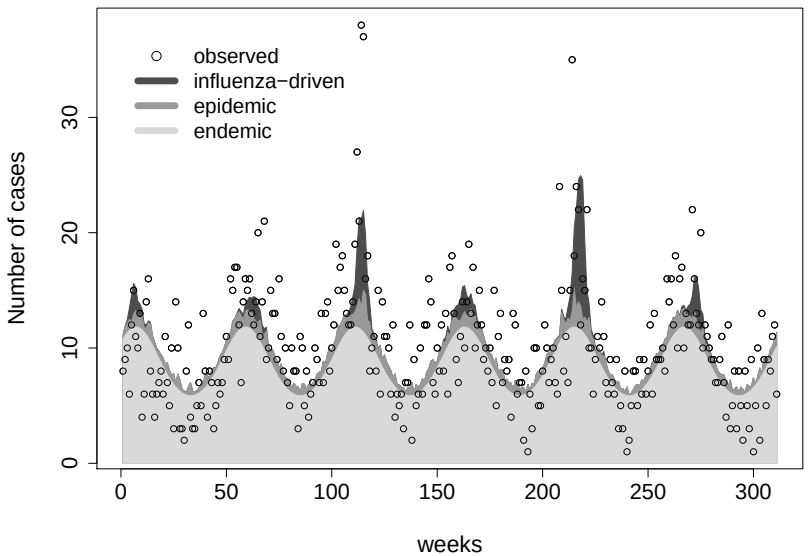
Multivariate analyses

Model	S		$\hat{\lambda}_{ML}$ (se)		$\hat{\phi}_{ML}$ (se)	
	flu	men	flu	men	flu	men
1	3	1	0.74 (0.05)	0.16 (0.06)	-	
2	3	1	0.74 (0.05)	0.16 (0.06)	0.000 (0.000)	-
3	3	1	0.74 (0.05)	0.10 (0.06)	-	0.005 (0.001)
4	3	1	0.74 (0.05)	0.10 (0.06)	0.000 (0.000)	0.005 (0.001)

Model	$\hat{\psi}_{ML}$ (se)		$\log L(\mathbf{y}, \boldsymbol{\theta})$	$\lvert\boldsymbol{\theta}\rvert$	AIC
	flu	men			
1	3.39 (0.41)	20.34 (4.83)	-1889.7	14	3807.5
2	3.39 (0.41)	20.34 (4.83)	-1889.7	15	3809.5
3	3.39 (0.41)	25.32 (6.98)	-1881.0	15	3791.9
4	3.40 (0.41)	25.32 (6.98)	-1881.0	16	3793.9

Fitted time series





Spatio-temporal models

- Suppose surveillance data on the same pathogen are available for several geographical locations $i = 1, \ldots, n$
- A possible model extension is:

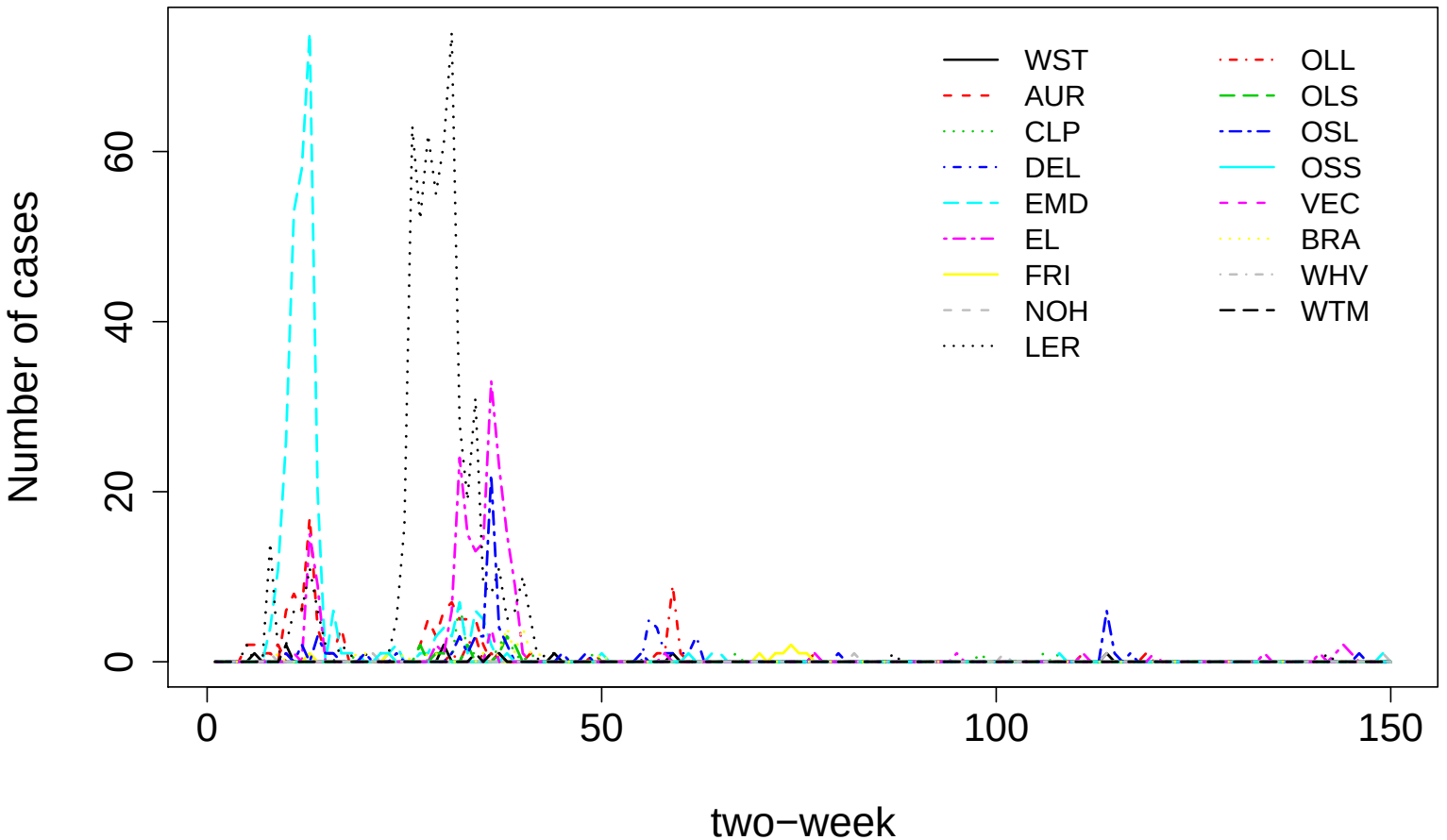
$$\mu_{i,t} = \nu_t + \lambda y_{i,t-1} + \phi \sum_{j \neq i} w_{ji} y_{j,t-1}$$

- A possible choice for the weights w_{ji} is $w_{ji} = \mathbb{1}(j \sim i)$, i.e. only regions adjacent to region i are taken into account
- Perhaps more natural is $w_{ji} = 1/n_j \cdot \mathbb{1}(j \sim i)$, where n_j denotes the number of neighbours of region j
- Note: λ and ϕ may also depend on i

Example: Measles in Lower Saxony

- In the administrative district "Weser-Ems", located in the eastern part of the German state Lower Saxony, two measles epidemics occurred in the years 2001 and 2002
- Measles has an incubation period of 9-12 days
- Here we analyse bi-weekly surveillance counts from the corresponding $m = 17$ areas of this district in the years 2001-2005
- The data showed a better fit for the aggregated bi-weekly data

Data


Number of cases
0
20
40
60
0
50
100
150
two−week
WST
AUR
CLP
DEL
EMD
EL
FRI
NOH
LER
OLL
OLS
OSL
OSS
VEC
BRA
WHV
WTM

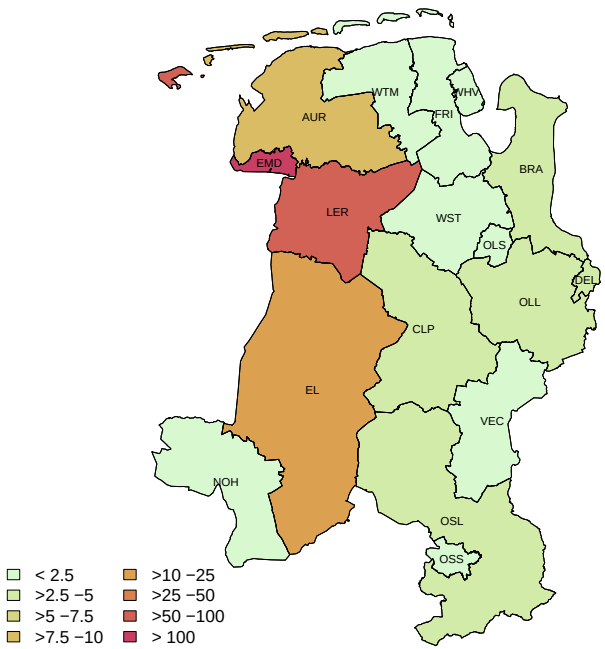
Parameter estimates

Model	w_{ji}	S	$\hat{\lambda}_{ML}$ (se)	$\hat{\phi}_{ML}$ (se)
1	-	1	0.73 (0.10)	-
2	$\mathbb{1}(j \sim i)$	1	0.61 (0.09)	0.029 (0.007)
3	$1/n_j \cdot \mathbb{1}(j \sim i)$	1	0.59 (0.09)	0.149 (0.034)
4	$1/n_j \cdot \mathbb{1}(j \sim i)$	1	0.00 (0.00) - 1.04 (0.59)	0.142 (0.032)
5	$1/n_j \cdot \mathbb{1}(j \sim i)$	1	0.49 (0.07)	0.000 (0.000) - 0.859 (0.361)
6	$1/n_j \cdot \mathbb{1}(j \sim i)$	1	0.00 (0.00) - 0.97 (0.54)	0.000 (0.000) - 0.788 (0.328)

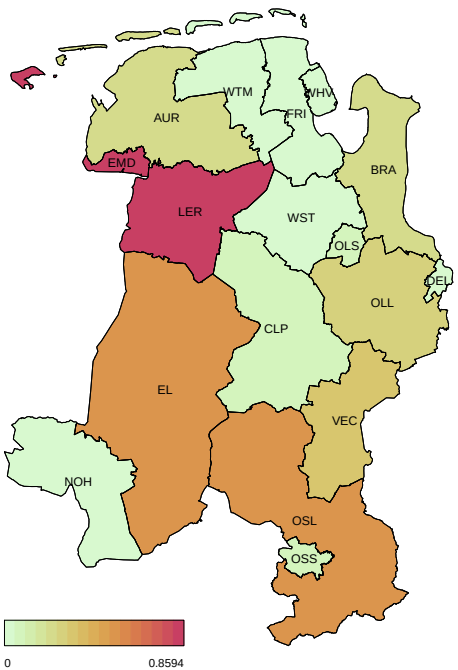
Model	$\hat{\psi}_{ML}$ (se)	$\log L(\mathbf{y}, \boldsymbol{\theta})$	$\lvert\boldsymbol{\theta}\rvert$	AIC
1	0.34 (0.05)	-961.8	21	1965.7
2	0.38 (0.05)	-933.4	22	1910.9
3	0.41 (0.06)	-929.2	22	1902.4
4	0.46 (0.07)	-917.9	38	1911.9
5	0.51 (0.07)	-897.6	38	1871.3
6	0.59 (0.09)	-884.3	54	1876.5

Spatio-temporal coefficients

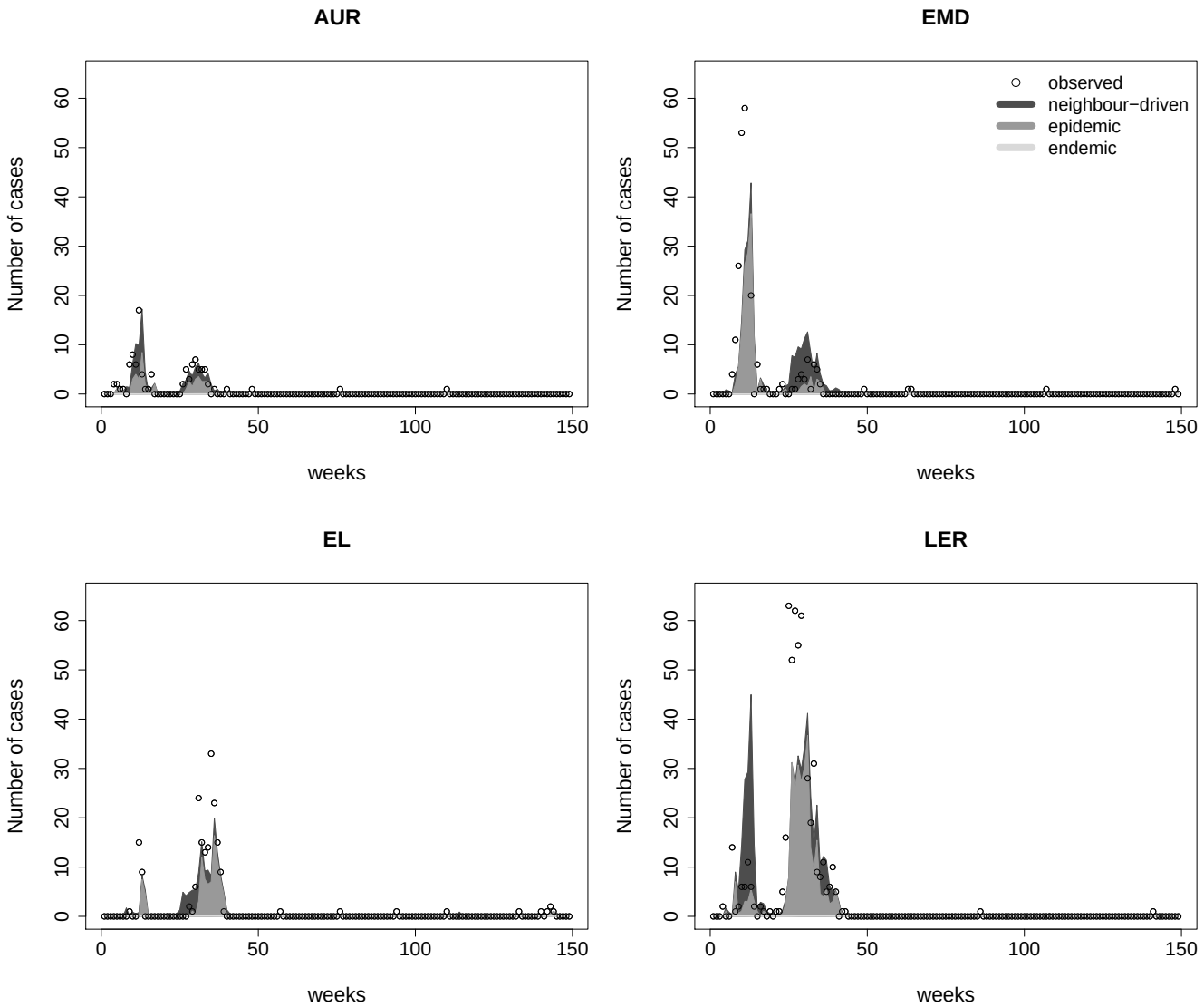
Yearly incidence



Spatio-temporal coefficient



Fitted values



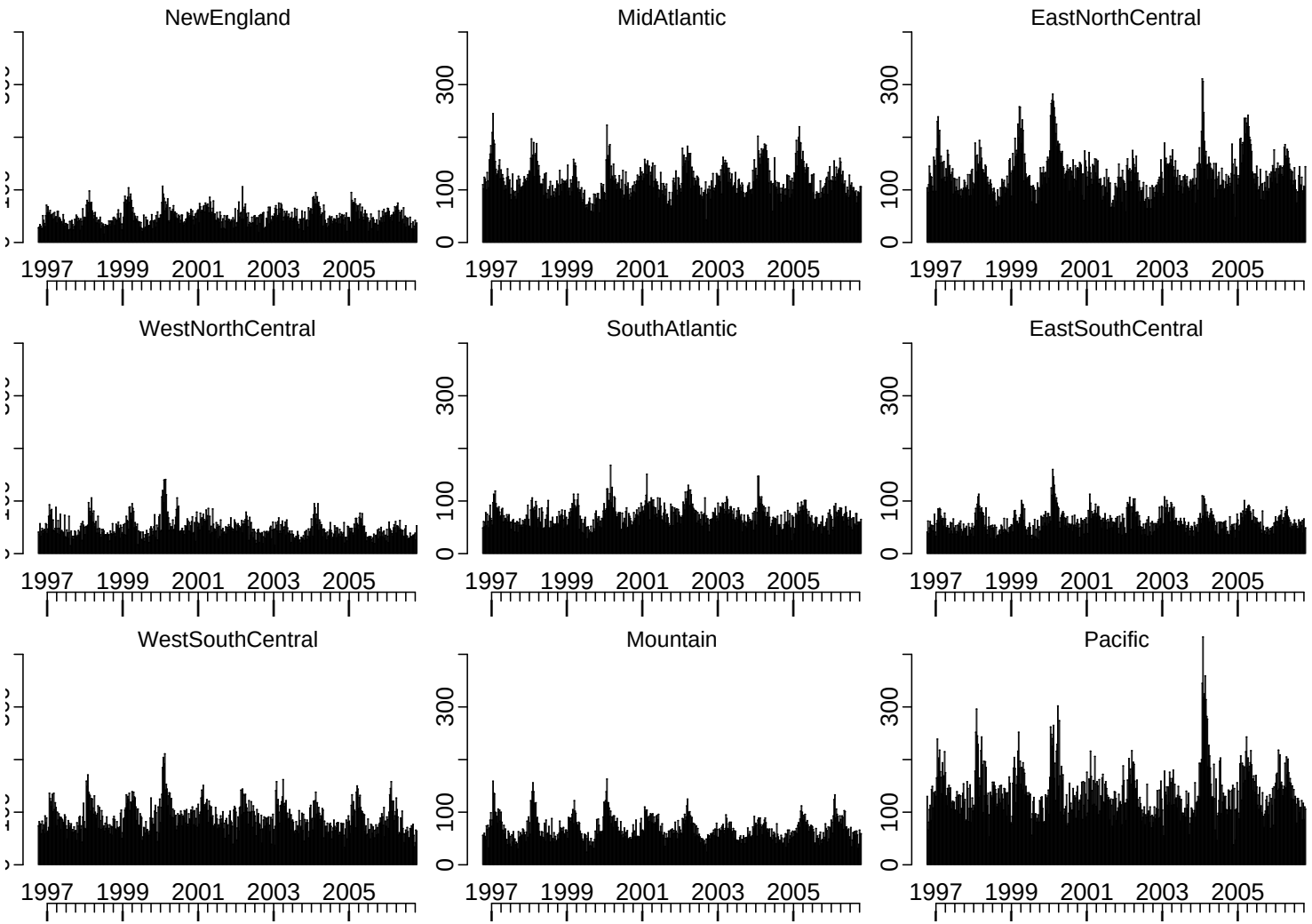
Incorporating travel information

- Linking of parallel time series based on adjacencies $w_{ji} = \mathbb{1}(j \sim i)$ or $w_{ji} = 1/n_j \cdot \mathbb{1}(j \sim i)$ may be unrealistic in a globalized world
- Alternative: Include (air) travel information, if available
- Convincing example: SARS epidemic, as analysed in Hufnagel et al. (2004)
- Our example: Influenza in USA, as analysed in Brownstein et al. (2006)

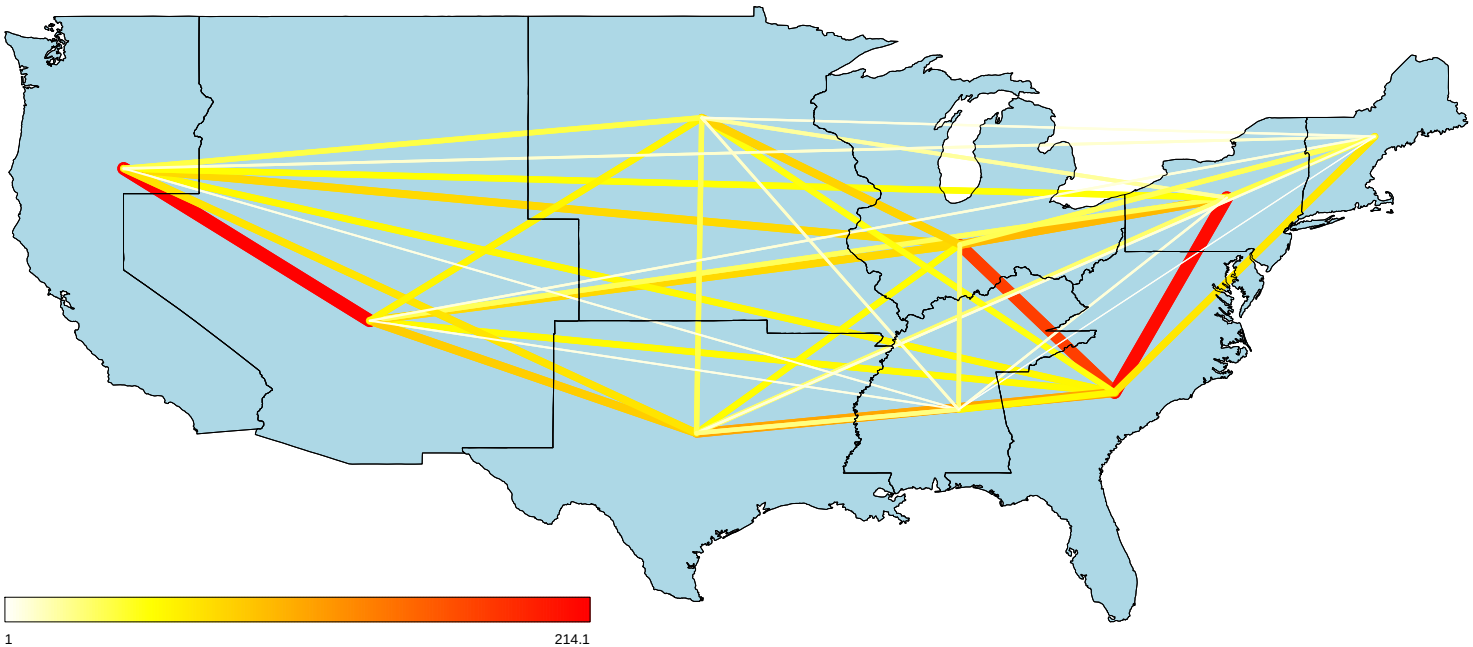
Example: Influenza in USA, 1997-2007

- Data on weekly mortality from pneumonia and influenza obtained from the CDC 121 Cities Mortality Reporting System
- These reports summarize the total number of deaths due to pneumonia and influenza in 9 geographical regions
- Data on the average/yearly number of passengers travelling by air obtained from TranStats database, U.S. Department of Transportation

Data


NewEngland
MidAtlantic
EastNorthCentral
WestNorthCentral
SouthAtlantic
EastSouthCentral
WestSouthCentral
Mountain
Pacific
0
100
300
1997
1999
2001
2003
2005

Air travel data, 1997-2007



Shown is the average yearly number of passengers per 100,000

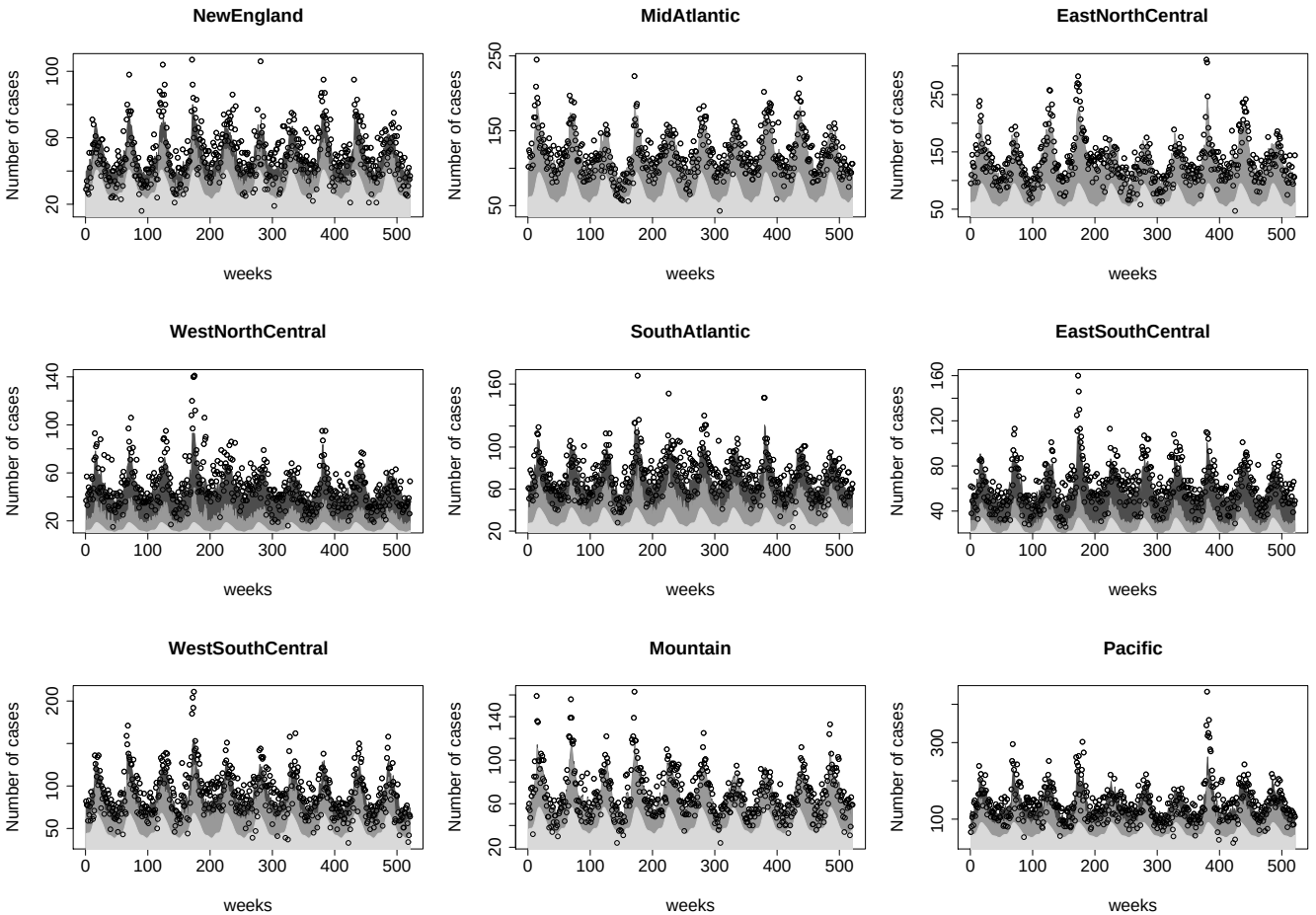
Parameter estimates

Model	w_{ji}	S	$\hat{\lambda}_{ML}$ (se)	$\hat{\phi}_{ML}$ (se)
1	-	4	0.23 (0.04) - 0.47 (0.04)	-
2	$1/n_j \cdot \mathbb{1}(j \sim i)$	4	0.17 (0.05) - 0.47 (0.04)	0.001 (0.011) - 0.650 (0.253)
3	p_{ji} (average)	4	0.16 (0.05) - 0.47 (0.04)	0.000 (0.001) - 0.805 (0.137)
4	p_{ji} (yearly)	4	0.14 (0.05) - 0.44 (0.05)	0.001 (0.032) - 0.725 (0.113)

Model	$\hat{\psi}_{ML}$ (se)	$\log L(\mathbf{y}, \boldsymbol{\theta})$	$\lvert\boldsymbol{\theta}\rvert$	AIC
1	31.82 (0.93)	-19817.2	27	39688.5
2	32.80 (0.97)	-19766.6	36	39605.3
3	32.95 (0.97)	-19758.6	36	39589.3
4	33.15 (0.98)	-19746.6	36	39565.1

Here p_{ji} denotes the relative proportion of persons travelling from region j to region i

Fitted values



Outlook

- Validation through out-of-sample predictions
- Comparison of predictions with actually observed data based on proper scoring rules (Gneiting and Raftery, 2007)
- Model-based approach can also be used for outbreak detection using time varying λ (Held et al., 2006)

Discussion/Summary

- Distinction between prospective and retrospective surveillance
- The focus of prospective surveillance is on outbreak detection
- Retrospective surveillance tries to explain temporal and spatio-temporal pattern in the data through statistical modelling
- We have emphasized the time series aspect of surveillance as an alternative to spatial and spatio-temporal cluster detection methods, e.g. scan statistics

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