L04 Latencies and Delays[1]

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Outline

1. Back-calculation method
   - Back-projection for the 2011 STEC/HUS outbreak
   - Discussion and Extensions
2. Nowcasting

Overview

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    - Back-projection for the 2011 STEC/HUS outbreak
    - Discussion and Extensions
2. Nowcasting

STEC/HUS Outbreak in Germany 2011 (1)

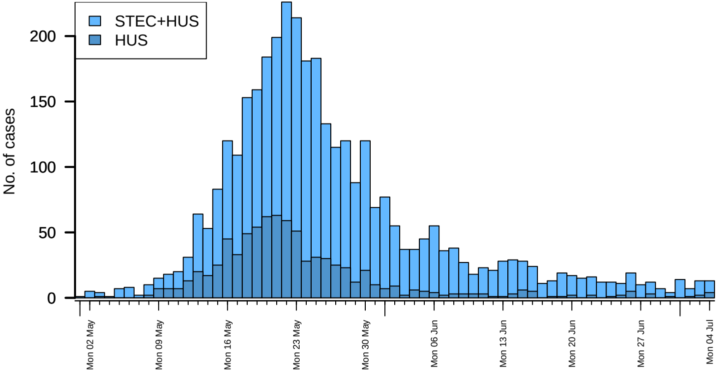
- Outbreak of Shiga toxin-producing *E. coli* (STEC) O104:H4 in Germany May–July 2011 associated with sprouts

	STEC	HUS
N (% of total)	2987 (78)	855 (22)
Median age (years)	46	42
Female (%)	58	68
Deaths	18	35
Case-fatality-ratio (%)	0.6	4.1

- Hemolytic-uremic syndrome (HUS) is a disease characterized by hemolytic anemia, thrombocytopenia and acute kidney failure.
- HUS can be a complication of an STEC infection.
- Onset of HUS occurs a median of 5 days (IQR: 4–7) days after onset of the STEC related diarrhea.

STEC/HUS Outbreak in Germany 2011 (2)

- Retrospective curve illustrating the onset of diarrhea of confirmed patients per day (where available: STEC 2715, HUS 783



STEC/HUS Outbreak in Germany 2011 (2)

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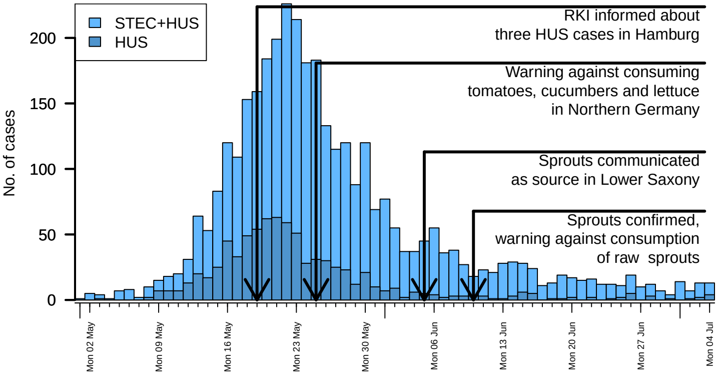

Example: STEC/HUS Outbreak in Germany 2011 (3)

- However, during the outbreak the situation is not as clear.
- Incubation period and reporting delays complicate real-time tracking of key indicators for detecting epidemic trends.
- Illustration: Day of hospitalization of HUS cases and the day the HUS case arrives at the RKI.

[Animated curve of reporting delay of HUS cases]

Focus on implication of time lags

Time lags during the STEC outbreak, e.g.,

- the delay between exposure to the disease and onset of diarrhea in cases
- the inherent reporting delay present in any public health surveillance system

Goal of back-projection:

Infer exposure times of HUS patients from the retrospective epidemic curve of diarrhea onsets in order to reconstruct the infection curve.

Goal of nowcasting:

Extrapolate currently available counts by taking the reporting delay from the past into account. Add uncertainty indication to this extrapolation.

Outline

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Motivation for back-projection

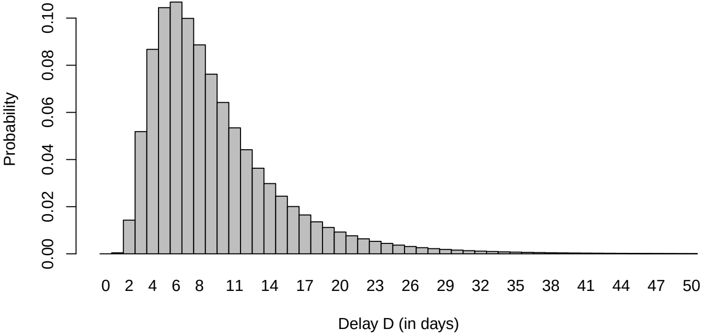
- There is a time delay between time of infection and the onset of the disease. This time delay is often denoted *incubation time*.
- Usually, only onset of disease can be observed. Examples:
  - Time to AIDS onset after HIV infection
  - Onset of diarrhea after consumption of sprouts (STEC/HUS)
- Let D be a discrete random variable describing the delay in number of time units. Assuming this delay is constant over time let $f(d), d = 0, 1, 2, \ldots,$ be the PMF of D.

Back-projection

Interest is often in the time of exposure of individuals, but data is only available about their time of disease onset.

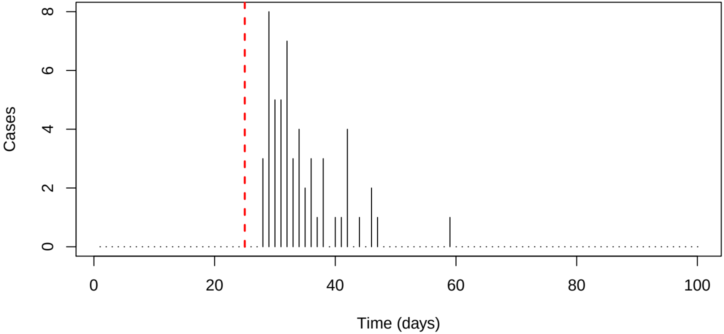
Incubation time as a random variable

- Example: D as discretized version of a log-normal distribution with $\log \mu = 2$, $\log \sigma = 0.6$ and $d_{\max} = 50$.



Example 1: Point source outbreak at time t_0

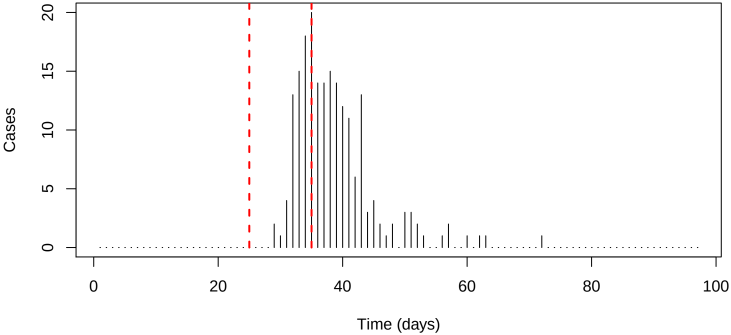
- Assume a point source is active on day $t_0 = 25$ infecting a total of $n = 55$ individuals and f_D as in the previous example.
- The following time series for disease onsets is observed:



- To identify the possible source, interest is in inferring infection times from the onset times.

Example 2: Point source during an interval

- Assume a point source is active for l days from day t_0 on infecting a total of n individuals, where individuals are equally likely to be infected within $[t_0, t_0 + l - 1]$.
- Example $t_0 = 25$, $l = 10$ and $n = 200$.



Simple back-projection methods (1)

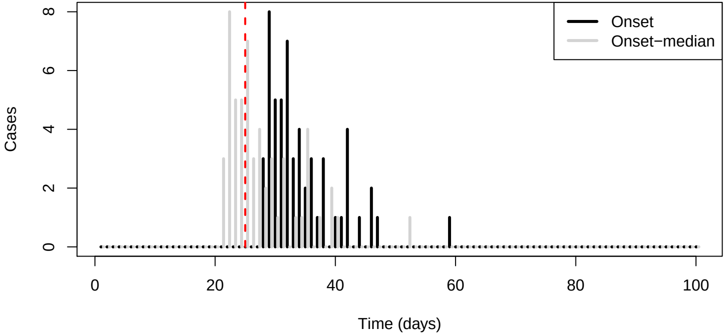
- Method 1: Determine the exposure interval by subtracting the shortest incubation time from the first case and the longest incubation from the last case of the epidemic curve
- R-code for outbreak Examples 1 & 2

```
subtract.minmax <- function(y, d.pmf,eps=1e-3) {
  exposure.left <- head(which(y>eps),n=1) - ((0:d.max)[head(which(d.pmf>eps),n=1)])
  exposure.right <- tail(which(y>eps),n=1) - ((0:d.max)[tail(which(d.pmf>eps),n=1)])
  structure( c(exposure.left,exposure.right-exposure.left),names=c("t0","l"))
}
subtract.minmax(y.ts, d.pmf)
## t0  l
## 26  1
subtract.minmax(y.l.ts, d.pmf)
## t0  l
## 27 13
```

Simple back-projection methods (2)

- Method 2: Subtract the median incubation time from each onset.

```r
subtract.median <- function(y,d.pmf) {
  d.median <- (0:length(d.pmf)-1)[which(cumsum(d.pmf)>0.5)][1]
  structure(c(tail(y,n=-d.median),rep(0,d.median)),names=names(y))
}
subtract.median(y.ts,d.pmf)
```



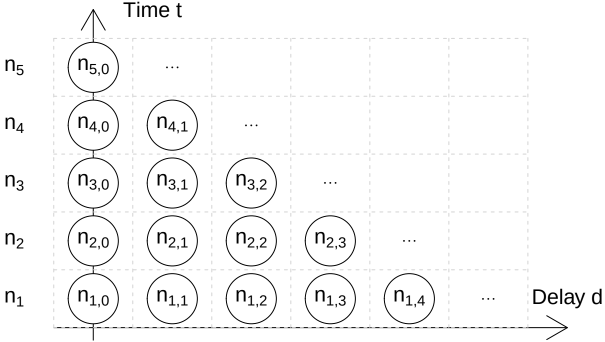
- This method is not recommendable since it ignores the order of events in the epidemic curve.

Non-parametric back-projection by Becker et al. (1991)

- Becker et al. (1991) proposed a non-parametric back-projection method for discrete time interval data.
- Their motivating application was a back-projection of AIDS cases to HIV incidence (before the use of antiretroviral therapy).
- The method differs from the the individual based continuous time parametric back-calculation of Brookmeyer et al. (1988).
- However, it equally presumes a fixed and known incubation time distribution.

Model and notation (1)

$n_{t,d}$ – Number of individuals exposed in interval $t = 1, \ldots, T$ having an incubation of time d (i.e. observed at time $t + d$)



y_t – The observed number of incident cases in interval t

$$y_t = \sum_{i=1}^{t} n_{i,t-i}, \quad t = 1, \ldots, T.$$

Model and notation (2)

n_t – Number of individuals infected in interval t, i.e.

$$n_t = \sum_{d=0}^{\infty} n_{t,d}.$$

- Assume $n_t \sim \mathrm{Po}(\lambda_t)$ and as a consequence

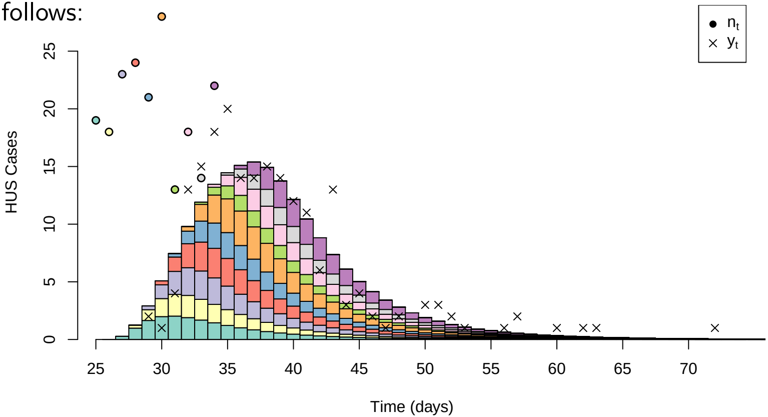
  $$n_{t,d} \sim \mathrm{Po}(f(d)\lambda_t),$$

  where $f(\cdot)$ is the PMF of the incubation time.
- As a consequence $y_t \sim \mathrm{Po}(\mu_t)$, where

  $$\mu_t = \sum_{i=1}^{t} E(n_{i,t-i}) = \sum_{i=1}^{t} f(t-i)\lambda_i.$$

Model and notation (3)

- The convoluted μ_t from the previous foil can be illustrated as follows:



- Thus backprojection is the inverse problem of deducing the λ_t's given the observed y_t's.

Expectation Maximization Smoothing (EMS) Algorithm

- Interest is in estimating $\boldsymbol{\theta} = (\lambda_1, \ldots, \lambda_T)'$, i.e. the expected daily number of new exposures
- Estimation can be done by using an expectation-maximization (EM) algorithm, where for $t \in \{1, \ldots, T\}$ the update step is

$$\lambda_t^{(k+1)} = \frac{\lambda_t^{(k)}}{F(T-t)} \sum_{d=0}^{T-t} \frac{y_{t+d} f_d}{\sum_{j=1}^{t+d} \lambda_j^{(k)} f_{t+d-j}},$$

  where $F(T-t) = \sum_{d=0}^{T-t} f_d$ is the CDF of the incubation time.
- To stabilize the estimation a smoothing step of $\boldsymbol{\lambda}^{(k)}$ is introduced, i.e.

$$\tilde{\lambda}_t^{(k+1)} = \sum_{i=0}^{k} w_i \cdot \lambda_{t+i-k/2}^{(k+1)},$$

  with symmetric binomial weights w_i, e.g. $\frac{1}{4}, \frac{1}{2}, \frac{1}{4}$ for $k = 2$.

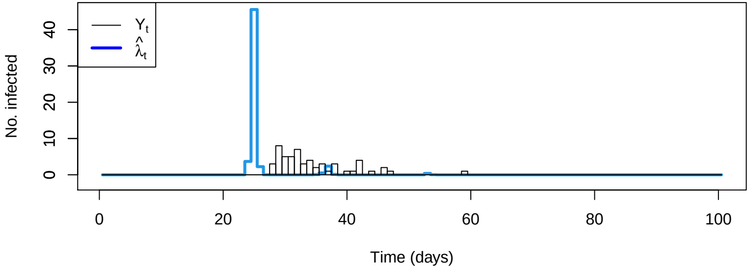
Implementation in surveillance

- Code:

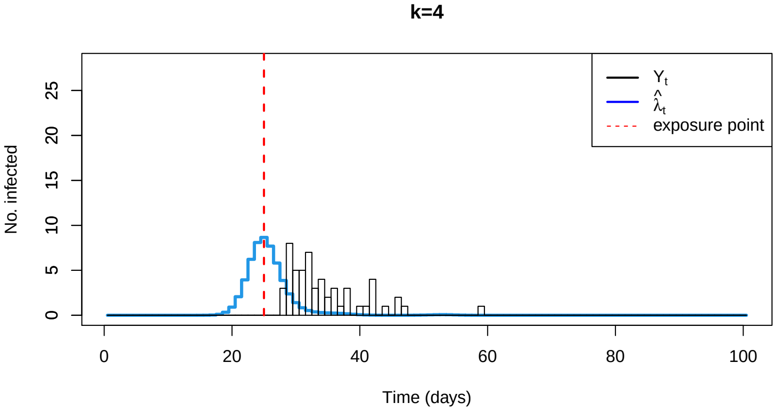
```r
#Create vector with incubation time PMF values on (0,...,d_max)
incu.pmf <- c(0, (plnorm(1:d.max,logmu,logsd) - plnorm(0:(d.max-1),logmu,logsd))/plno
#Create sts object
require("surveillance")
sts <- new("sts",epoch=1:length(y.ts),observed=matrix(y.ts,ncol=1))
#Backproject using the method by Becker et al. (1991)
bp.control <- list(k=0,eps=1e-3,iter.max=100,verbose=TRUE,eq3a.method="C")
sts.bp.k0 <- backprojNP(sts, incu.pmf=incu.pmf, control=bp.control)
```

- Plotting code:

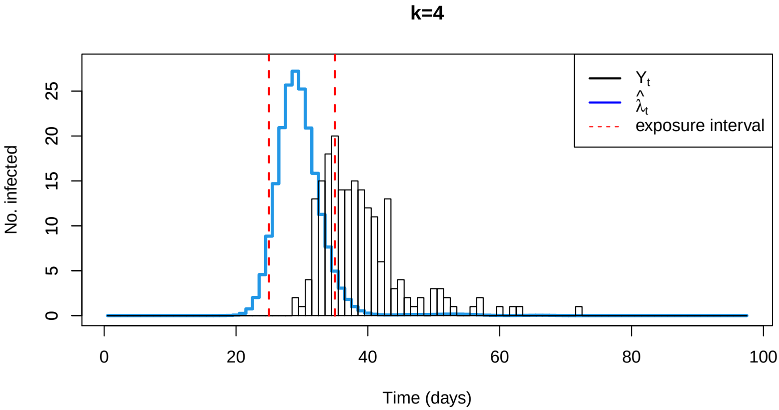
```r
plot(sts.bp.k0,xaxis.labelFormat=NULL)
```



Back-projection for outbreak Example 1



Back-projection for outbreak Example 2

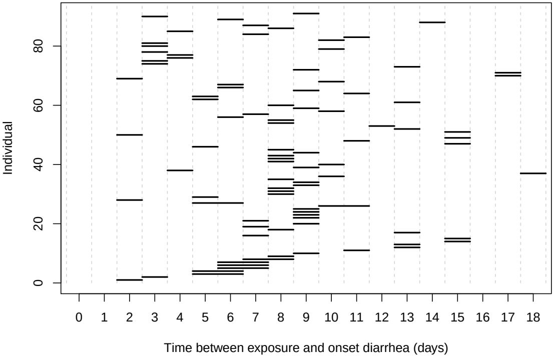


Uncertainty of the estimates

- Problem: The non-parametric back-projection (NPBP) does not provide any measures of uncertainty for the estimate $\hat{\boldsymbol{\lambda}}$
- Two sources of uncertainty exists:
  - Sampling variation in the observed y_t
  - Uncertainty in the estimation of the incubation time

Estimation of the incubation time (1)

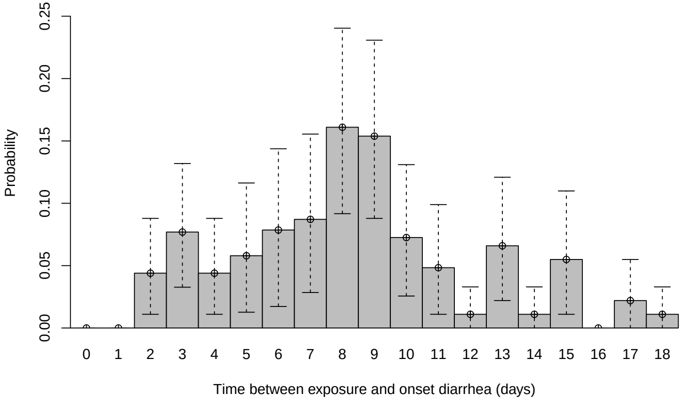
- Determination of the incubation time PMF from 91 cases with a well known exposure time (foreign cases, restaurant cluster, etc.)



- Goal: Non-parametric estimate of the probability mass function

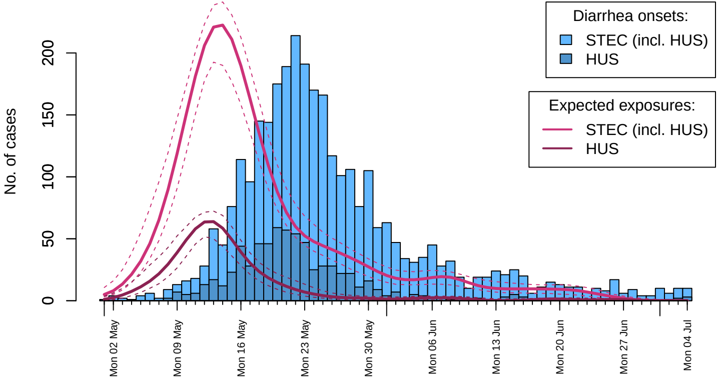
Estimation of the incubation time (2)

- Estimated PMF using Turnbull's method (Turnbull 1976) for interval censored data and point-wise 95% CIs by the percentile method on $R = 999$ additional bootstrap samples



Back-projection for the 2011 STEC/HUS outbreak (4)

- Werber et al. (2013) refines the incubation time estimation by using a Weibull interval censored regression model adjusting for age, sex and HUS in 114 symptomatic adults from six cohorts.



Discussion

- The non-parametric method needs no underlying assumptions about the mode of transmission (person to person, point source, etc.).
- During an outbreak one should choose T such that the incidence cases observed at time y_T are reliable (i.e. sufficiently complete), i.e. T should not be too close to “now”.
- A good recent review of back-projection methods can be found in Egan et al. (2015).

Outline

1 Back-calculation method

2 Nowcasting

Nowcasting – what's the situation?

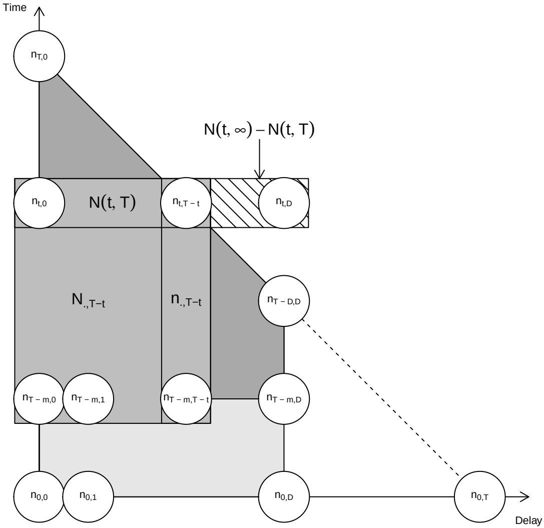
- Opposite to forecasting, we just want to know what the situation is "now" during an outbreak, i.e. in a ideal setup of no reporting delay → nowcasting.
- The term is basically a revival of what has been extensively studied as *reporting delay* during the AIDS/HIV epidemic, see e.g. Kalbfleisch et al. (1989) and Harris (1990).
- Nowcasting was used for real-time tracking daily hospitalizations during the 2009 A/H1N1 influenza (Donker et al. 2011).
- There is a close connection between nowcasting and *claims reserving* in actuarial sciences (England et al. 2002).

Nowcasting Notation (1)

- Let $n_{t,d}$ be the number of cases which occur on day t and become available with a delay of d days, where $t = 0, \ldots, T$ – with T being *now* – and $d = 0, \ldots, D$.
- Problem: $n_{t,d}$ is unknown when $d > T - t$ – see reporting triangle
- $N(t, T) = \sum_{d=0}^{\min(T-t,D)} n_{t,d}$ is the number of cases which occured on t and who are reported until time T
- Aim of nowcasting: predict the total number of cases, i.e.

$$N(t, \infty) = \sum_{d=0}^{\infty} n_{t,d} = \sum_{d=0}^{D} n_{t,d}.$$

Nowcasting Notation (2) – Reporting triangle



Nowcasting Methods (1)

- Alternative: The reporting delay for an event follows a distribution with probability mass function $f(d) = f_d$, $d = 0, 1, \ldots, D$.
- We will assume time homogeneity of the delay distribution
- Let $F(d) = \sum_{x=0}^{d} f(x)$ be the CDF of the delay distribution.
- Lawless (1994) presents the following nowcast procedure

$$\hat{N}(t, \infty) = \frac{N(t, T)}{\hat{F}(T - t)},$$

where the CDF F is estimated taking the right-truncation of the data into account, for example by using the reverse time hazard function.

Nowcasting Methods (2)

- Alternative model in Donker et al. (2011)

$$N(t,T) \sim \mathrm{Bin}\left(N(t,\infty), \hat{F}(T-t)\right)$$

- In this model inference is about estimating the size parameter in a binomial distribution, i.e.

$$\hat{N}(t,\infty) = \underset{n\geq N(t,T)}{\arg\max} \left\{ f_{\text{Bin}}(n, \hat{F}(T-t)) \right\}$$

Nowcasting Methods (3)

- The counts of the reporting triangle can also be thought of as an incomplete contingency table with

$$n_{t,d} \sim \mathrm{Po}(\lambda_t \cdot f_d), \quad t = 0, \ldots, T,\ 0 \leq d \leq \min(T-t, D),$$

where λ_t is the expected number of new events occuring at time t.

- Altogether, $T + D + 2$ parameters are to be estimated.
- The above presentation lends itself to log-linear modeling, i.e. with parametric, semi-parametric or non-parametric linear predictor

$$\log \mu_{t,d} = \log(\lambda_t) + \log(f_d) = s(t;\beta) + v(d;\theta),$$

where $E(n_{t,d}) = \mu_{t,d}$.

Example: AIDS registry data from the CDC (1)

- Zeger et al. (1989) contains an analysis of 6190 homosexual AIDS cases classified by quarter of diagnosis and the number of quarters between diagnosis and report to the CDC

```
##         0   1  2  3  4  5  6  7  8  9 10 11 12
## 03-87 244 138 NA NA NA NA NA NA NA NA NA NA NA
## 02-87 217 165 35 NA NA NA NA NA NA NA NA NA NA
## 01-87 317  80 54 13 NA NA NA NA NA NA NA NA NA
## 04-86 353  64 32 17 14 NA NA NA NA NA NA NA NA
## 03-86 345  53 35 18 10  6 NA NA NA NA NA NA NA
## 02-86 313  60 29 15 10  9  7 NA NA NA NA NA NA
## 01-86 294  71 27 10 13  5  5  6 NA NA NA NA NA
## 04-85 216  68 23 21 10  5  2  6  3 NA NA NA NA
## 03-85 206  58 36 23  9  7  2  6  0  4 NA NA NA
## 02-85 215  61 26 19 15  3  4  4  1  0  1 NA NA
## 01-85 188  70 36 22 11  6  2  3  1  0  0  0 NA
## 04-84 159  36 20 14  9  1  4  2  2  1  1  3  2
## 03-84 149  51 26 16 10  6  3  0  1  0  0  0  3
## 02-84 140  51 16 12  3  5  1  3  1  1  0  1  0
## 01-84 119  41  9  4  8  2  3  2  0  1  0  0  1
## 04-83  94  26  9  8  4  0  2  0  0  1  2  0  2
## 03-83  80  24  5  3  3  2  1  1  0  0  0  1  2
## 02-83  97  23  9  0  1  1  1  2  0  1  0  1  0
## 01-83  67  25  7  7  1  1  0  1  0  2  0  0  0
## 04-82  52  10  6  1  2  0  1  0  0  0  0  0  1
## 03-82  59  11  7  1  2  1  1  0  0  0  0  0  1
## 02-82  36   4  1  0  3  1  1  0  1  0  0  0  1
## 01-82  24   8  5  0  4  2  0  2  0  0  0  0  4
```

Example: AIDS registry data from the CDC (2)

- They use a semi-parametric log-linear model with truncated power splines for $s(t, \beta)$.
- We shall use a more simple non-parametric setup, but will also focus on prediction uncertainty

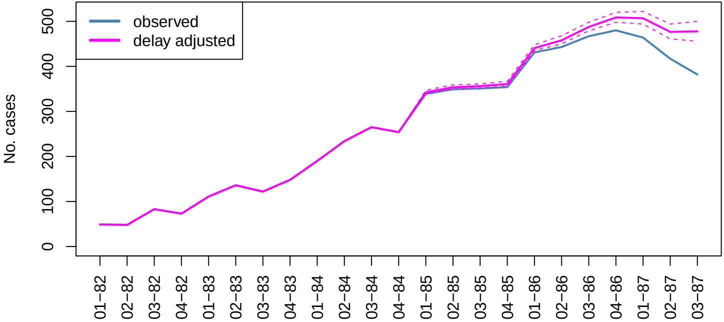
```r
#Function to convert reporting triangle matrix into data.frame
matrix2df <- function(zeger) {
  data.frame(n=as.numeric(as.matrix(zeger)),
             t=as.numeric(as.matrix(row(zeger)-1)),
             d=as.numeric(as.matrix(col(zeger)-1)))
}

#Convert to data.frame
zeger.df <- matrix2df(zeger)
#Fit log-linear model.
m <- glm( n ~ as.factor(t) + as.factor(d), data=zeger.df, subset=!is.na(n), family=poisson)

#Prediction m_{t,d} for ALL cells in the contingency table
mu.mle <- predict(m, newdata=zeger.df, type="response")
```

Example: AIDS registry data from the CDC (3)

```r
#Function to compute our target statistic
NtInf <- function(data) {
    as.numeric(with(data, tapply(n, t, sum, na.rm=TRUE)))
}

#Function to generate new data by parametric bootstrap
rntd <- function(data, mle) {
    #Indicator vector of what is observed
    observed <- !is.na(data$n)
    #Extra data copies (one to estimate, one to predict)
    data.estimate <- data.predict <- data

    #Make a new data matrix with observed values replaced
    data.estimate$n[observed] <- rpois(n=nrow(data),lambda=mle)[observed]

    #Fit Poisson GLM to the data to obtain estimates
    m.star <- glm( n ~ as.factor(t) + as.factor(d), data=data.estimate, subset=!is.na(n), family=poisson)

    #Add sampled values where missing
    data.predict$n[!observed] <- rpois(n=nrow(data), predict(m.star,newdata=data,type="response"))[!observed]
    #Done - return new data.frame
    return(data.predict)
}

set.seed(123)
b <- boot::boot(zeger.df, statistic=NtInf,sim="parametric",R=999, ran.gen=rntd,mle=mu.mle)

#Simple percentile intervals
predIntervals <- apply(rbind(b$t0,b$t),2,quantile,prob=c(0.025,0.975))
```

Example: AIDS registry data from the CDC (4)

- The model is an instance of a generalized linear model, which can be fitted in R using the function `glm`
- Point estimate for the delay adjusted $N(t, \infty)$'s in the AIDS example ($+$ pointwise predictive distributions).



Discussion (1)

- A natural framework for handling predictive distributions is within a Bayesian context (→ predictive posterior)
- In Höhle et al. (2014) a non-MCMC approach based on a Dirichlet prior for the delay distribution is used to nowcast the HUS reports during the STEC outbreak.
- In practice the delay distribution often time-inhomogeneous. In this situation a proportional hazards model for the reverse time hazard function can be used (Kalbfleisch et al. 1991; Pagano et al. 1994).
- Back-projection based on registry data for an ongoing epidemic is often to be seen concurrently with delay adjustments (Brookmeyer et al. 1989; Zeger et al. 1989; Kalbfleisch et al. 1989).

Discussion (2)

- Nowcasting approaches are in heavy use during the COVID-19 pandemic and are particularly useful for the mortality time series (Günther et al.; Schneble et al. 2020)
- Example: Up2date picture of the situation in Bavaria

  `https://corona.stat.uni-muenchen.de/nowcast/`
- Back-projection is a non-parametric alternative to SIR modelling in order to assess the effect of interventions (Küchenhoff et al. 2021)
- Nowcasting and back-projection can be combined in order to provide real-time assessment of epidemic trends[2]

[2] E.g. `https://www.covid19.statistik.uni-muenchen.de/pdfs/codag_bericht_10.pdf`

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