Prospective Detection of Outbreaks

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\textbf{Chapter Abstract}

This chapter surveys univariate and multivariate methods for infectious disease outbreak detection. The setting considered is a prospective one: data arrives sequentially as part of the surveillance systems maintained by public health authorities, and the task is to determine whether to ‘sound the alarm’ or not, given the recent history of data. The chapter begins by describing two popular detection methods for univariate time series data: the EARS algorithm of the CDC, and the Farrington algorithm more popular at European public health institutions. This is followed by a discussion of methods that extend some of the univariate methods to a multivariate setting. This may enable the detection of outbreaks whose signal is only weakly present in any single data stream considered on its own. The chapter ends with a longer discussion of methods for outbreak detection in spatio-temporal data. These methods are not only tasked with determining \textit{if} and \textit{when} an outbreak started to emerge, but also \textit{where}. In particular, the scan statistics methodology for outbreak cluster detection in discrete-time area-referenced data is discussed, as well as similar methods for continuous-time, continuous-space data. As a running example to illustrate the methods covered in the chapter, a dataset on invasive meningococcal disease in Germany in the years 2002–2008 is used. This data and the methods covered are available through the R packages \texttt{surveillance} and \texttt{scanstatistics}. 

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Chapter 0

Prospective Detection of Outbreaks

An essential aspect of infectious disease epidemiology is the timely detection of emerging infectious disease threats. To facilitate such detection, public health authorities maintain surveillance systems for the structured collection of data in humans, animals and plants. In this chapter we focus on the prospective, i.e. as-data-arrive, detection of outbreaks in such data streams obtained as part of the routine surveillance for known diseases, symptoms or other well-defined events of interest. The organization of this chapter is as follows: In Section 0.2 we briefly present methods for outbreak detection in purely temporal data streams, which is followed by a more extensive presentation of methods for spatio-temporal detection in Section 0.3.

0.1 Motivation and Data Example

Surveillance data is nowadays collected in vast amounts to support the analysis and control of infectious diseases. As a consequence, the data volume, velocity and variety exceeds the resources to look at each report individually and thus statistical summaries, insightful visualizations and automation are needed (Höhle 2017). In response to this, semi-automatic systems for the screening and further investigation of outbreaks have been developed. This screening typically consists of identifying emerging spikes in the monitored data streams and flagging particular cases for further inspection. For foodborne diseases, for example, this inspection could consist of attempts to identify and remove the food source consumed by all cases.

Our aim is thus to develop data mining tools to support the sequential decision making problem (to react or not) for pathogens with quite heteroge-
neous features, differing in e.g., data collection, prevalence and public health importance. As an example, even a single Ebola case constitutes a serious public health threat, whereas only larger clusters of Campylobacter jejuni infections will trigger public health actions. It is also worth to point out that large accumulations of cases in a short time period are almost surely noticed at the local level. Automatic procedures nonetheless provide a safety net ensuring that nothing important is missed, but the added value lies predominantly in the detection of dispersed cross-regional outbreaks. Another added value is that the quantitative nature of the algorithms allows for a more objective approach, which can be a helpful addition to epidemiological intuition. However, alarms are useless if they are too frequent to be investigated properly. On the other hand, missing an important outbreak is also fatal.

0.1.1 Invasive Meningococcal Surveillance in Germany

As an illustration we use 2002-2008 data from the routine monitoring of invasive meningococcal disease (IMD) by the National Reference Centre for Meningococci (NRZM) in Germany
\footnote{http://www.meningococcus.de} as motivating example. Figure 1 shows the number of new cases of two particular finetypes described in more detail in Meyer et al. (2012) and available as dataset imdepi in the R package surveillance (Salmon et al., 2016b; Meyer et al., 2017).

![Figure 1: Time series of monthly number of IMD cases of the two finetypes.](image)

From the figure and its context we observe a number features which make the statistical modelling and monitoring of surveillance time series a challenge. From the time series in the figure we see that we deal with a low
integer number of reported cases, which can contain secular trends, seasonality, as well as past outbreaks. In the IMD example a microbiological investigation provides a pretty clear definition, however, having a clear case definition can otherwise be a challenge. Furthermore, it is common to only report positive test outcomes with no information on how many tests were actually performed. Spikes in the incidence of new cases might very well be due to an increased testing behaviour. This brings us to the important issues of under-ascertainment and under-reporting often reflected as stages in a surveillance pyramid of which only the top stage are the reported cases. Another issue, which we shall ignore in this chapter, is the problem of reporting delays; depending on the aims it can be necessary to adjust the detection for this phenomena, c.f. the chapter written by Angela Noufaily. Instead, we move on to a statistical description and solution of the detection problem.

0.2 Univariate Surveillance Methods

Assume data have been pre-processed such that a univariate time series of counts is available. Denote by \( y_1, \ldots, y_t \) the time series of cases with the time index representing, e.g., daily, weekly or monthly time periods and \( y_t \) being the observation under present consideration. Different statistical approaches can now be used to detect an outbreak at the last instance \( t \) of the series. Such approaches have a long tradition and comprehensive review articles exist (Farrington and Andrews, 2003; Unkel et al., 2012; Sonesson and Bock, 2003; Le Strat, 2005; Woodall, 2006; Höhle and Mazick, 2011). An implementational description of many of these algorithms can be found in the R package \texttt{surveillance} (Salmon et al., 2016b). We therefore keep this account short and just present two of the most commonly used algorithms, in particular because their approach fits well into that of the multivariate approaches covered in Section 0.3. Both algorithms presented compute a prediction for \( y_t \) based on a set of historic values, under the assumption that there is no outbreak at \( y_t \), and then assess how extreme the actually observed value is under this assumption.

0.2.1 EARS Algorithm

The Early Aberration Detection System (EARS) method of the CDC as described in Fricker et al. (2008) is a simple algorithm convenient in situations when little historic information is available and, hence, trends and seasonality are not of concern. In its simplest form, the baseline is formed by the last \( k = 7 \) timepoints before the assessed timepoint \( t \), which is particularly meaningful
when monitoring a time series of daily data. The simplest version of the method is based on the statistic \( C_t = \frac{y_t - \bar{y}_t}{s_t} \), where

\[
\bar{y}_t = \frac{1}{7} \sum_{s=t-7}^{t-1} y_s \quad \text{and} \quad s_t^2 = \frac{1}{k-1} \sum_{s=t-k}^{t-1} (y_s - \bar{y}_t)^2
\]

are the usual unbiased estimators for the mean and variance of the historic values. For the null hypothesis of no outbreak, it is assumed that \( C_t \sim N(0,1) \). The threshold for an extreme observation, under the assumption of no outbreak, is now defined as \( U_t = \bar{y}_t + 3 \cdot s_t \). Consequently, an alarm is raised if the current observation \( y_t \) exceeds this upper limit.

The simplicity of the method makes it attractive, and variants of this Gaussian approach can be found in different contexts, e.g., as an approximation when the underlying distribution is binomial (Andersson et al., 2014). However, from a statistical point of view the method has a number of shortcomings. In particular the distributional \( N(0,1) \) assumption is likely to be inaccurate in case of counts below 5-10, because the distribution is discrete, non-negative and hence right-skewed. As easy as the three times standard deviation is to remember, the appropriate comparison of \( y_t \) should be with the upper limit of a prediction interval. Assuming that the \( y \)'s are identical and independent variables from a Gaussian distribution with both mean and standard deviation unknown, such a one-sided \( (1 - \alpha) \cdot 100\% \) interval has upper limit

\[
\bar{y}_t + t_{1-\alpha}(k-1) \cdot s_t \cdot \sqrt{1 + \frac{1}{k}},
\]

where \( t_{1-\alpha}(k-1) \) denotes the \( 1 - \alpha \) quantile of the t-distribution with \( k - 1 \) degrees of freedom. Note that for \( k \) larger than 20-30, this quantile is very close to that of the standard normal distribution, which is why some accounts, e.g., Farrington and Andrews (2003), use \( z_{1-\alpha} \) instead. However, when \( k = 7 \) the \( \alpha \) corresponding to a multiplication factor of 3 is not \( \alpha = 1 - \Phi(3) = 0.0013 \), as one might think, but \( \alpha = 1 - F(3/\sqrt{1+1/k}) = 0.0155 \), where \( F \) denotes the cumulative distribution function of the t-distribution with \( k - 1 \) degrees of freedom. In other words, using a factor of 3 means that the probability of false discoveries is notably higher than one might naively expect. From an epidemiologist’s point of view, this might seem as yet another instance of statistical nitpicking, however, in the next section we provide an example illustrating how misaligned the \( 3 \cdot s_t \) rule can be in the case of few and low count data.

The more historic values are available, the larger \( k \) one can choose in practice. However, seasonality and secular trends then become an issue. A
simple approach to handle seasonality suggested by Stroup et al. (1989) is to just pick time points similar to the currently monitored time point. For example: When working with weekly data and looking at week 45 in year 2017 then one could take the values of, say, weeks 43 to 47 of the previous years as historic values. Another approach is to handle seasonality and trends explicitly in a linear regression model framework, e.g.,

$$
\mu_t = \mathbb{E}(y_t) = \beta_0 + \beta_1 \cdot t + \sum_{i=1}^{L} \left\{ \beta_{2i} \sin \left( \frac{2\pi it}{P} \right) + \beta_{2i+1} \cos \left( \frac{2\pi it}{P} \right) \right\},
$$

where $P$ is the period, e.g., 52 for weekly data. This has the advantage that all historic values are used to infer what is expected. As an alternative to the above superposition of harmonics one could instead use (penalized) cyclic splines (Wood, 2006) or factor levels for the individual months or days.

### 0.2.2 Farrington Algorithm

An extension of the above approaches is the so called Farrington algorithm [Farrington et al., 1996; Noufaily et al., 2013], which explicitly uses an underlying count data distribution and handles possible trends through the use of an (over-dispersed) Poisson regression framework. The algorithm is particularly popular at European public health institutions as its easy to operate and handles a large spectrum of time series with different characteristics without the need of particular tuning.

Assuming, as before, that one wants to predict the number of cases $y_t$ at time $t$ under the assumption of no outbreak by using a set of historic values from a window of size $2w + 1$ up to $b$ periods back in time. With weekly data and assuming 52 weeks in every year the set of historic values would be $\cup_{i=1}^{b} \cup_{j=-w}^{w} y_{t-i \cdot 52+j}$. We then fit an over-dispersed Poisson generalized linear model (GLM) with $\mathbb{V}(y_s) = \phi \cdot \mu_s$ and log-linear predictor

$$
\mathbb{E}(y_s) = \mu_s, \quad \text{where} \quad \log(\mu_s) = \beta_0 + \beta_1 \cdot s
$$

to the historic values. In the above, $s$ denotes the $b(2w + 1)$ time points $t - i \cdot 52 + j$ of the historic values and $\phi > 0$ is the over-dispersion parameter. If the dispersion parameter in the quasi-Poisson is estimated to be smaller than one a Poisson model (i.e. $\phi = 1$) is used instead. Based on the estimated GLM model we compute the upper of limit of a $(1 - \alpha) \cdot 100\%$ one-sided prediction interval for $y_t$ by

$$
U_t = \hat{\mu}_t + z_{1-\alpha} \cdot \sqrt{\mathbb{V}(y_t - \hat{\mu}_t)},
$$
where $V(y_t - \hat{\mu}_t) = V(y_t) + V(\hat{\mu}_t) - 2\text{Cov}(y_t, \hat{\mu}_t) = \phi\mu_t + V(\hat{\mu}_t)$, because the current observation is not used as part of the estimation. We know that asymptotically $\hat{\beta} \sim N(\beta, I^{-1}(\beta))$, where $I^{-1}$ denotes the inverse of the observed Fisher information. Therefore, $\hat{\eta}_t = \log(\hat{\mu}_t)$ is normally distributed with variance $V(\hat{\eta}_t) = V(\beta_0) + t^2V(\beta_1) + 2t\text{Cov}(\beta_0, \beta_1)$. Through the use of the delta method we find that $V(\hat{\mu}_t) \approx \exp(\hat{\eta}_t)V(\hat{\eta}_t)$.

Figure 2 displays the fitted GLM and the limits of a corresponding two-sided $(1 - 2\alpha) \cdot 100\%$ prediction interval for the first observation in 2008 when $b = 3$, $w = 3$ and $\alpha = 0.00135$. Because the upper limit 21.1 of the prediction interval is larger than the observed value of 13 no alarm is sounded.

Note that the above is a somewhat simplified description of the Farrington procedure. For example, a trend is only included, if the following three conditions are all fulfilled: it is significant at the 0.05 level, there are at least 3 years of historic values and including it does not lead to an over-extrapolation (i.e. $\hat{\mu}_t$ is smaller than the maximum of the historic values). Additional refinements of the algorithm include the computation of the prediction interval in (2) on a $\sqrt{y}$ or $y^{2/3}$ power transformation scale and then back-transform the result. This would for example fix the obvious problem in (2) that the prediction includes negative values: using the $2/3$-power transformation the resulting upper limit would be 24.5 instead. If the historic values contain outliers in form of previous outbreaks the Farrington algorithm suggests to instead base the prediction on a re-weighted second fit with weights based on Anscombe residuals. Noufaily et al. (2013) suggest a number of additional improvements to the algorithm. Instead of using the window based approach to select the historic values, all past data are utilized in the regression model by adding a cyclic 11-knot zero-order spline consisting of a
7-week historic period and nine 5-week periods. Furthermore, better results seem to be obtained when computing the prediction interval directly on a negative binomial assumption, i.e. by assuming $y_t \sim \text{NegBin} \left( \mu_t, \mu_t/(\hat{\phi} - 1) \right)$ where the first argument denotes the mean and the second argument the dispersion parameter of the distribution. By plug-in of the estimates $\hat{\mu}_t$ and $\hat{\phi}$ one obtains that the $1 - \alpha$ quantile of the negative binomial distribution in the example of Fig. 2 is 24.

For comparison: had we taken the 7 observations corresponding to Farrington’s $b = 1$ and $w = 3$ as historic values for the EARS approach we get $\bar{y}_t = 7.1$, $s_t = 2.6$, and an upper limit of 15.0. When using (1) with $\alpha = 1 - \Phi(3)$ for the same historic values the upper limit is 20.8. The corresponding upper limit of the Farrington procedure are 15.7 (untransformed), 17.2 (2/3-power transformation) and 16 (Poisson quantile) for the Quasi-Poisson approach. If we assume that a Po(7.1) is the correct null-distribution (the output of the Farrington algorithm in the example), the 3 times standard deviation rule thus produces too many false alarms—in this particular setting about 0.681% instead of the nominal 0.135%. Continuing this further: If the 7 observations would instead have been a quarter of their value (i.e. 2x1 and 5x2), the corresponding false alarm probability of the $3 \cdot s_t$ approach would raise as high as 9.53%, whereas the Farrington procedure with quantile threshold by construction keeps the nominal level. This illustrates the importance of using count response distributions when counts are small.

0.3 Multivariate Surveillance Methods

Surveillance of univariate data streams typically involves some type of spatial or temporal aggregation. For example, many of the detection algorithms discussed in the previous section assume the disease cases are counted on a daily or weekly basis, or monitor just the total sum of all cases that occur in a municipality, a county, or even a whole nation. If this aggregation is too coarse, it could result in the loss of information useful for the detection of emerging threats to public health. Similarly, the failure to monitor secondary data sources such as over-the-counter medicine sales may equate to a forfeiture of the same. These problems motivate the use of multivariate methods, which offer means to treat data at a finer spatial or temporal scale, or to include more sources of information. We start this section by reviewing some of the available extensions of univariate methods to multivariate settings, and then proceed to cover methods for cluster detection in spatio-temporal data. Naturally, our review cannot be all-encompassing, and we therefore direct the
reader to the books by Lawson and Kleinman (2005), Wagner et al. (2006), and Rogerson and Yamada (2008) for other takes on surveillance methods for spatio-temporal data.

0.3.1 Extensions of Univariate Surveillance Methods

An intuitive approach to the surveillance of multiple data streams is to apply one of the univariate methods from Section 0.2 to each time series monitored. For example, Höhle et al. (2009) applied the Farrington method to the monthly incidence of rabies among foxes in the 26 districts of the German state of Hesse, and did likewise to the aggregated cases for the state as a whole and for its subdivision into three administrative units. Data from the years 1990–1997 were available as a baseline, and the period 1998–2005 was used for evaluation. The authors were able to pinpoint the districts in which an outbreak occurred in March of 2000. Höhle et al. (2009) argue that using multiple univariate detectors in this hierarchical way is often a pragmatic choice, because many of the analogous multivariate changepoint detection methods used in the literature (see e.g. Rogerson and Yamada, 2004) assume continuous distributions for the data; an assumption hardly realistic for the low count time series often seen after partitioning the total number of cases by region, age, serotype, and so on.

The parallel application of univariate methods does have its downsides, however. Univariate methods such as the Farrington algorithm require either a false alarm probability (significance level) $\alpha$ or a threshold $c$ to be set prior to an analysis. These are often set to achieve some maximum number of false alarms per month or year (see e.g. Frisén, 2003, for other optimality criteria). If the same conventional $\alpha$ is used for $p \gg 1$ detection methods run in parallel, in the absence of an outbreak, the probability of raising at least one false alarm will be much greater than $\alpha$. On the other hand, lowering $\alpha$ will make outbreaks harder to detect. Multivariate methods, considered next, do not suffer from the same issues.

0.3.1.1 Scalar Reduction and Vector Accumulation

In the multivariate setting, we suppose that the process under surveillance can be represented as a $p$-variate vector $\mathbf{Y}_t = (Y_{t,1}, Y_{t,2}, \ldots, Y_{t,p})'$, where $t = 1, 2, \ldots$ are the time points under consideration. Each component $Y_{t,i}$ could represent the disease incidence (as a count) of a given region at time $t$, for example. One of the earliest control chart methods of multivariate surveillance is the use of Hotelling’s $T^2$ statistic (Hotelling, 1947). Under the null hypothesis for this method, $\mathbf{Y}_t$ is assumed to follow a multivariate normal
distribution with mean vector \( \mu \) and covariance matrix \( \Sigma \), both typically estimated from the data. Hotelling’s method then reduces the multivariate observation at each timepoint to a scalar statistic, given by

\[
T^2_t = (Y_t - \hat{\mu})' \hat{\Sigma}^{-1} (Y_t - \hat{\mu}), \quad t = 1, 2, \ldots, n. \tag{3}
\]

The Hotelling \( T^2 \) statistic is thus the squared Mahalanobis distance, which measures the distance between the observed data and the null hypothesis distribution while accounting for the different scales and correlations of the monitored variables. When properly scaled, the \( T^2 \) statistic has an \( F_{p,n-p} \) distribution under the null hypothesis of no outbreak; hence a detection threshold is given by a suitable quantile from this distribution. When dealing with disease count data, however, we know beforehand that the \( Y_{t,j} \)'s should increase in case of an outbreak. This prior knowledge is not reflected in the \( T^2 \) statistic, which penalizes deviations from the mean in either direction. With this motivation, O’Brien (1984) proposed several parametric and non-parametric tests that accommodate alternative hypotheses for consistent departures from the null hypothesis.

A problem with Hotelling \( T^2 \) statistic, and likewise the methods proposed by O’Brien (1984), is that they will fail to accumulate evidence for an outbreak over time. As noted by Sonesson and Frisén (2005) (in regard to the \( T^2 \) statistic), this will render the methods ineffective at detecting small to moderate changes in the monitored process. A solution suggested by Crosier (1988) is to first calculate the Hotelling \( T^2_t \) statistic for each timepoint \( t \) in the surveillance period, take its square root \( T_t \), and then apply a CUSUM scheme

\[
S_t = \max \{ 0, S_{t-1} + T_t - k \}, \quad S_0 \geq 0 \quad \text{and} \quad k > 0
\]

are chosen together with a threshold \( c \) to achieve a certain false positive rate, for example. Similarly, Rogerson (1997) devised a CUSUMized version of Tango’s (1995) retrospective spatial statistic, which assumes a Poisson distribution for the data, and calculates a quadratic form statistic using a distance matrix.

The parallel surveillance and scalar reduction methods can be combined by first calculating the ordinary alarm statistics for each data stream, and then apply a scalar reduction method to the vector of such statistics. A few such approaches are reviewed in Sonesson and Frisén (2005). We also point the reader to the important review papers by Frisén (1992), Sonesson and Bock (2003), Frisén et al. (2010), and Unkel et al. (2012). Finally, for a more general introduction to statistical quality control and the CUSUM method in particular, we recommend the book written by Montgomery (2008).
0.3.1.2 Illustration of Hotelling’s $T^2$ statistic

We now calculate the Hotelling $T^2$ statistic for the (monthly) Meningococcal data introduced in Section 0.1. Because this method assumes that the data follows a multivariate normal distribution, it is at an immediate disadvantage when applied to case data with low counts. We therefore aggregate this data, first over time to form monthly counts for all 413 districts of Germany, and then over space to obtain the corresponding time series for each of the country’s 16 states, i.e. $p = 16$. For the purposes of illustration, rather than epidemiological correctness, we also combine the cases across the two different finetypes B (MenB) and C (MenC). In Figure 3, we show the calculated $T^2$ statistics and the critical values at significance level corresponding to an ARLO of 3 years. The years 2002–2003 were used as a baseline period for the estimation of the mean vector and covariance matrix using the standard sample formulas (see e.g. Rencher and Christensen, 2012), and these parameter estimates were updated based on all available data at each time step. Note that it may be advisable to use robust estimators of the mean vector and covariance matrix in practice; we chose the standard estimators here because parameter estimation is not the focus of this illustration. Reinhardt et al. (2008) analyzed the meningococcal disease data for the years 2004–2005 using the EpiScanGIS (National Reference Centre for Meningococci, 2006) software and found one cluster in the period. For comparison, we therefore run our analysis in the same time interval. Figure 3 shows the monthly time series of the $T^2$ statistic (solid line), along with a critical value (dashed line).

![Figure 3: Hotelling’s $T^2$ statistic (solid) and critical values (dashed), calculated monthly in the years 2004–2005 for the German meningococcal disease data.](image)

As can be seen in Figure 3, Hotelling’s method fails to detect any outbreak at the chosen significance level (here $\alpha = 1/36$, corresponding to one expected
false detection every 3 years). An apparent flaw is that the detection threshold, which is based on an $F$ distribution with one of the degrees of freedom parameters increasing with $n$, will decrease monotonically with time, eventually reaching its asymptote. This happens regardless of significance level, and it may therefore be useful to explore other ways of obtaining detection thresholds—simulation-based, perhaps. Another drawback, which is not exclusive to Hotelling’s method, is that even if a detection is made, the method does not inform us of where (or which variables) caused the threshold to be exceeded. Methods that remedy this problem are the topic of the next section.

0.3.2 Spatio-temporal Cluster Detection

For some diseases, it may suffice to monitor the univariate time series of cases aggregated across a country, using the methods described in Section 0.2. A detection signal may then prompt further investigation into the time, location and cause of the potential outbreak. For many diseases however, a large increase in the case count of a small region can be drowned out by the noise in the counts of other regions as they are combined. In order to detect emerging outbreaks of such diseases before they grow large, the level of aggregation needs to be smaller, perhaps even at the level of individual cases—a tradeoff between variability and detecting a pattern. Despite the possibilities of long-range transmission enabled by modern means of transportation, transmission at a local level is still the dominant way in which most infectious diseases spread [Höhle 2016]. Thus, the statistical methods used to detect the clusters that arise should take into account the spatial proximity of cases in addition to their proximity in time. We begin this section by describing methods for area-referenced discrete-time data, in which counts are aggregated by region and time period. This is followed by Section 0.3.2.2, discussing methods for continuous space, continuous time data.

0.3.2.1 Methods for Area-Referenced Data

Aggregation by region and time period may in some cases be required by public health authorities due to the way the data collection or reporting works, or for privacy reasons. Legislation and established data formats may thus determine at what granularity surveillance data is available. For example, the CASE surveillance system [Cakici et al. 2010] used by the Public Health Agency of Sweden is limited to data at county (län) level, with the least populous of the 21 counties having a population of about 58,000 people. The monitored data in the area-referenced setting is typically of the form \{y_{it}\},
where \( i = 1, \ldots, N \) denotes the number of (spatial) regions, such as counties, and the index \( t = 1, \ldots, T \) denotes time intervals of equal length. Cluster detection in this setting involves identifying a set \( Z \) of regions in which a disease outbreak is believed to be emerging during the \( D = 1, 2, \ldots \) most recent time periods (weeks, for example). We will denote such a space-time window by \( W \), and its complement by \( \bar{W} \). A well-established methodology for cluster detection for this task is that of scan statistics, which dates back to the 1960’s with work done by Naus (1965), and that took on its modern form after the seminal papers by Kulldorff and Nagarwalla (1995) and Kulldorff (1997). These methods, which were extended from the spatial to the spatio-temporal context by Kulldorff (2001), are widely used amongst public health departments thanks to the free software SATScan™ (Kulldorff, 2016).

### 0.3.2.1.1 Example: Kulldorff’s prospective scan statistic

To illustrate the typical procedure of using a scan statistic designed for space-time cluster detection, we work through the steps of calculating and applying of the most popular such methods, often simply referred to as Kulldorff’s (prospective) scan statistic (Kulldorff, 2001). This method assumes that the count \( Y_{it} \) in region \( i \) and time \( t \) follows a Poisson distribution with mean \( q_{it} \cdot b_{it} \). Here, \( b_{it} \) is an ‘expected count’ or ‘baseline’, proportional to the population at risk in region \( i \) at time \( t \). For example, these could be constrained such that the sum of the expected counts over all regions and time periods equals the total of the observed counts during the time period under study. That is, \( \sum_{it} b_{it} = \sum_{it} y_{it} \). The factor \( q_{it} > 0 \), often called the relative risk, is assumed to be the same \( q_{it} = q \) for all \( i \) and \( t \) provided there is no outbreak. This constitutes the null hypothesis. In the case of an outbreak however, it is assumed that the relative risk is higher inside a space-time window \( W = Z \times \{ T - D + 1, \ldots, T \} \), consisting of a subset of regions \( Z \subset \{ 1, \ldots, N \} \) and stretching over the \( D \) most recent time periods. That is, for \( i \in Z \) and \( t > T - D \) we have \( E[Y_{it}] = q_W b_{it} \), while for \( i \notin Z \) or \( t \leq T - D \) it holds that \( E[Y_{it}] = \frac{q_W}{q_W} b_{it} \) with \( q_W > q_W \). Here, \( \bar{W} \) is the complement of \( W \). This multiplicative increase in the baseline parameters inside a space-time window is typically how outbreaks are modelled for scan statistics. For scan statistics applied to prospective surveillance, it is important to note that all potential space-time clusters have a temporal duration that stretches from the most recent time period backwards, without interruptions. This means that no inactive outbreaks are considered, and that any space-time window included in an analysis can be thought of as a cylinder with a base formed by the perimeter of the geographical regions covered by the window, and a
CHAPTER 0. PROSPECTIVE DETECTION OF OUTBREAKS

height equal to its length in time.

0.3.2.1.2 Definition and calculation of the scan statistic Of course, there could be many space-time windows \( W \) for which the alternative hypothesis is true. If one would conduct hypothesis tests for each window separately—and the number of such windows could well be in the thousands or hundreds of thousands in typical applications—this would result in a very large number of false positives for standard significance levels such as 0.05. This problem could be counteracted by lowering the nominal significance level to a miniscule value, or by using some other repeated testing strategy, but this would in turn allow only very large outbreaks (in terms of \( q_W \) relative to \( q_{\pi} \)) to be captured. The solution proposed by Kulldorff (2001) is to focus only on the window \( W \) that stands out compared to the others, as measured by the size of likelihood ratio statistics calculated for all windows \( W \) of interest. By calculating the maximum of all such statistics, and using the distribution of this maximum to calculate \( P \)-values, the ‘most anomalous’ space-time cluster can be identified. To calculate a likelihood ratio for a given space-time window \( W = Z \times \{1, 2, \ldots, D\} \), one must first calculate the maximum likelihood estimates of the relative risks \( q_W \) and \( q_{\pi} \). For Kulldorff’s Poisson scan statistic, these are easily computed as

\[
\hat{q}_W = \frac{Y_W}{B_W}, \quad \hat{q}_{\pi} = \frac{Y - Y_W}{Y - B_W} = \frac{Y_{\pi}}{B_{\pi}},
\]

(4)

where

\[
Y_W = \sum_{(i,t) \notin W} y_{it}, \quad B_W = \sum_{(i,t) \in W} b_{it}, \quad \text{and} \quad Y = \sum_{i=1}^{N} \sum_{t=1}^{T} y_{it} = \sum_{i=1}^{N} \sum_{t=1}^{T} b_{it}.
\]

(5)

Thus, the likelihood ratio statistic conditional on the window \( W \) is then given by

\[
\lambda_W = \left( \frac{Y_W}{B_W} \right)^{Y_W} \left( \frac{Y - Y_W}{Y - B_W} \right)^{Y - Y_W} I_{\{Y_W > B_W\}},
\]

(6)

up to a multiplicative constant not dependent on \( q_W \) or \( q_{\pi} \). Here, \( I_{\{\cdot\}} \) is the indicator function. This statistic is then calculated for all space-time windows \( W \) of interest, and the scan statistic is defined as the maximum of all such statistics: \( \lambda^* = \max_W \lambda_W \). The corresponding window \( W^* \), often called the most likely cluster (MLC), is thus identified.
0.3.2.1.3 Hypothesis testing  Because the distribution of $\lambda^*$ cannot be derived analytically, a Monte Carlo approach to hypothesis testing is often taken, whereby new data for each region $i$ and time $t$ is simulated under the null hypothesis using the expected counts $b_{it}$. For Kulldorff’s scan statistic, the sampling is made conditional on the total observed count $C$, leading to a multinomial distribution over regions and time intervals for the new counts. This sampling is repeated $R$ times, and for each sample $r$, a new scan statistic $\lambda^*_r$ is computed. A Monte Carlo $P$-value for the observed scan statistic can then be calculated in standard fashion using its rank amongst the simulated values:

$$P = \frac{1 + \sum_{r=1}^{R} \mathbf{1}\{\lambda^*_r > \lambda^*_\text{obs}\}}{1 + R}.$$ 

Typically, a number such as $R = 999$ or $R = 9999$ is used in order to get a fixed number of digits for the $P$-value. For prospective surveillance, past analyses—and potentially future ones—should also be accounted for when conducting hypothesis tests, in order to avoid a greater number of expected false positives than implied by the nominal significance value (i.e. a multiple testing problem). The solution suggested by [Kulldorff (2001)](Kulldorff2001) is to expand the set of replicates $\{\lambda^*_r\}_{r=1}^{R}$ above by including replicates calculated in past analyses. If too many past analyses are included however, the hypothesis tests could become too conservative. [Kulldorff (2001)](Kulldorff2001) therefore recommends including only the most recent $\ell$ analyses, where $\ell$ could be chosen to achieve a certain false positive rate during a given monitoring period, for example. This practice has been the subject of a heated debate recently, with [Correa et al. (2015a)](Correa2015a) asserting that any nominal significance level $\alpha$ used for prospective surveillance with Kulldorff’s scan statistic is unrelated to the average run length (ARL) and recurrence interval (RI) which are commonly used in prospective surveillance. Similar points have been raised earlier by [Woodall (2006)](Woodall2006), [Joner et al. (2008)](Joner2008), and [Han et al. (2010)](Han2010). In a rebuttal, [Kulldorff and Kleinman (2015)](Kulldorff2015) explain that in one of the three prospective cases considered by Correa et al. (2015a), the simulations performed actually show the expected result, and that in the other two cases the concerns raised are actually misunderstandings. [Correa et al. (2015b)](Correa2015b) later clarify that failure to account for future analyses remain a concern, despite the comments by Kulldorff and Kleinman (2015). In the latest reply to the debate, [Tango (2016)](Tango2016) states that both of the previous parties are in fact wrong: Correa et al. (2015a) for being unrealistic in their consideration of an indefinite number of future analyses and for focusing on the ARL in a setting for which the spatial component of outbreaks is at least as important as the temporal one (because the ARL does not inform us of the spatial spreading of the disease),
and [Kulldorff (2001) and Kulldorff and Kleinman (2015)] for performing a prospective analysis conditional on the total number of observed cases in any given study period. Rather, [Tango (2016)] reiterates the point made by [Tango et al. (2011)] that such an analysis should be unconditional on the total count. This last point will be expanded upon below, but the overall implication for those wishing to apply scan statistics in prospective settings is to carefully weigh the benefits and costs of setting the threshold for “sounding the alarm” at a particular level.

Given that the number of space-time windows to be included in the analysis can range in the thousands or hundreds of thousands, the calculation of Monte Carlo $P$-values means an $R$-fold increase of an already high computational cost. One way to reduce this computational cost is to calculate a smaller number of Monte Carlo replicates of the scan statistic, fit an appropriate distribution to these replicates, and then compute the tail probability of the observed scan statistic from the fitted distribution. [Abrams et al. (2010)] tested such a procedure for a number of different distributions (Gumbel, gamma, log-normal, normal) on Kulldorff’s scan statistic and others. The authors found that the Gumbel distribution yielded approximate $P$-values that were highly accurate in the far tails of the scan statistic distribution, in some scenarios making it possible to achieve the same rejection power with one tenth as many Monte Carlo replicates. Another possibility is to circumvent simulation altogether by comparing the value of the scan statistic computed on the current data to values calculated in the past, provided no outbreaks are believed have been ongoing in the data used for these past calculations. [Neill (2009a)] compared this approach to Monte Carlo simulation with standard and Gumbel $P$-values, and found that the latter two methods for calculating $P$-values gave misleading results on three medical data sets, requiring a much lower significance level than originally posited to reach an acceptable level of false positives.

### 0.3.2.1.4 Cluster construction

A second way of limiting the computational cost of running a scan statistic analysis is to limit the search to clusters with a compact spatial component (zone) $Z$, in the sense that all regions inside the cluster are close to one another geographically. This makes sense for both computational and practical reasons, since many of the $2^N - 1$ subsets of all $N$ regions are spatially disconnected and therefore not of interest for detection of diseases that emerge locally. For instance, one could limit the search to the $k$ nearest neighbors to each region $i = 1, \ldots, N$, for $k = 0, 1, \ldots, K_{\text{max}}$, where $K_{\text{max}}$ is some user-defined upper bound (as in [Tango et al. (2011)]), or automatically chosen such that the largest zone
with region \( i \) as center encompasses regions with a combined population that equals approximately 50% of the total population in the whole study area (as in Kulldorff, 2001). The set of zones obtained by these methods will be quite compact, which can be problematic if the true outbreak zone consists of regions that all lie along a riverbank, for example. To capture a richer set of zones, Tango and Takahashi (2005) propose a way to construct ‘flexibly shaped’ zones, by considering all connected subsets of the \( K_{\text{max}} \) nearest neighbors of each region \( i \), that still contain region \( i \) itself. This method can yield a vastly larger set of zones, but becomes impractical in terms of run-time for \( K_{\text{max}} > 30 \) when the number of regions is about 200 or more.

More data-driven approaches to finding the set of interesting zones can also be taken. For example, Duczmal and Assunção (2004) consider the set of all connected subgraphs as the set of allowable zones, and search the most promising clusters using a simulated annealing approach. Here, the nodes in the graph searched are the spatial regions, and edges exist between regions that share a common border. Another more holistic approach is taken by Neill et al. (2013), who propose a framework in which regions are first sorted by priority based on observed counts and estimated parameters, and the set of zones scanned then taken to be only the top \( n \) regions, for \( n = 1, 2, \ldots, N \). This method is discussed further in Section 0.3.2.1.7.

0.3.2.1.5 Illustration of Kulldorff’s scan statistic Once the set of clusters to be scanned have been determined, the analysis can take place. Here, we apply Kulldorff’s prospective scan statistic (Kulldorff, 2001) to the Meningococcal data considered earlier, now aggregated to monthly counts for each of Germany’s 413 districts (kreise). This scan statistic is implemented in the R package scanstatistics (Allévius, 2017) as the function \texttt{scan_pb_poisson}.

In Figure 4, we show the resulting scan statistics for each month of the study period (2004–2005). At each time step, the statistic was calculated using at most the latest 6 months of data, and the \( b_{it} \) for each district and time point was estimated as

\[
\hat{b}_{it} = \frac{Y}{T} \cdot \frac{\text{Pop}_i}{\text{Pop}_{\text{total}}}.
\]

(7)

Here, \( Y \) is the total observed count over all districts and time points, \( T = 6 \) is the length of the study period, and \( \text{Pop}_i \) and \( \text{Pop}_{\text{total}} \) are the 2008 populations for district \( i \) and all of Germany, respectively. Critical values (sample quantiles) for the significance level \( \alpha = 1/60 \) were obtained from Monte Carlo replication with \( R = 99 \) replicates, and previously generated replicates were included in the calculation at each new time step.
Figure 4: Observed value of Kulldorff’s prospective scan statistic, calculated monthly in the years 2004–2005 for the German meningococcal disease data.

The most likely cluster detected by Kulldorff’s prospective scan statistic, for most months scanned, corresponds well to the region of highest disease incidence in the years 2004–2005. The core cluster seems to be four districts in North Rhine-Westphalia, one of them the city (urban district) Aachen, and coincides with a confirmed cluster of Meningococcal disease discussed in Meyer et al. (2012). This cluster also matches that found by Reinhardt et al. (2008). In Figure 5, we show a map of the counties of North Rhine-Westphalia, with the detected cluster shaded in gray.

Figure 5: Districts of North Rhine-Westphalia, with the most likely cluster shaded in gray.

Figure 4 shows that the given significance level results in detection signals during much of the study period. This may not be entirely plausible, and one could see this as an inadequacy of the Monte Carlo method, as discussed...
CHAPTER 0. PROSPECTIVE DETECTION OF OUTBREAKS

in Section 0.3.2.1.3 (see in particular the issues of debate mentioned there). More likely however, is that the Poisson assumption of Kulldorff’s prospective scan statistic is ill-suited for data with such an abundance of zeros as the meningococcal data, considering that it assumes a Poisson distribution for the counts. For this type of data, a scan statistic based on e.g. the zero-inflated Poisson distribution (see Cançado et al., 2014; Allévius and Höhle, 2017) may perform better.

0.3.2.1.6 Developments in space-time scan statistics Kulldorff’s 2001 prospective scan statistic was introduced above to present the general procedure of using a scan statistic to detect space-time disease clusters. Of course, many more such methods have been devised since 2001, many to deal with the purported “flaws” of Kulldorff’s statistic. One such drawback of Kulldorff’s prospective scan statistic is that it requires data on the population at risk and its spatial (and possibly temporal) distribution over the study area. The notion of a population at risk may not be applicable in cases where the surveillance data consists of counts of emergency department visits and over-the-counter medicine sales, for example. Noting this fact, Kulldorff et al. (2005) formulate a space-time permutation scan statistic, which uses only the observed counts in the current study period and area to estimate the baselines. Under the assumption that the probability of a case occurring in region \( i \), given that it occurred at time \( t \), is the same for all times \( t = 1, \ldots, T \), the baseline (expected value) for the count in region \( i \) at time \( t \) is estimated by Kulldorff et al. (2005) as

\[
b_{it} = \frac{1}{Y} \left( \sum_{j=1}^{N} y_{jt} \right) \left( \sum_{\tau=1}^{T} y_{i\tau} \right).
\]  

The analysis is thus conditional on the marginal counts over regions and time points, leading to a hypergeometric distribution for the total count inside a space-time cluster \( W \). This distribution can in turn be approximated by a Poisson distribution when the marginal counts inside the cluster are small compared to the overall total count \( C \). Thus, a likelihood ratio statistic can be calculated using Equation (6), leading to a scan statistic of the same form as Kulldorff (2001). For hypothesis testing however, the random sampling is done such that the marginal counts over regions and time points are preserved, rather than just the total count.

The prospective (Kulldorff, 2001) and space-time permutation (Kulldorff et al., 2005) scan statistics both conduct hypothesis testing using expected counts that are conditional on the total or marginal counts in the observed data. This has been met with some critique, particularly from Tango et al.
who give a simple (albeit extreme) example showing that if counts are increased uniformly in all regions under surveillance, these types of scan statistics will fail to detect that something out of the ordinary has happened. Using less extreme circumstances, Neill (2009a) demonstrate that a ‘conditional’ scan statistic of this sort has low power to detect outbreaks that affect a large share of the regions under surveillance. When an outbreak actually is detected in such a scenario, that scan statistic takes longer to do so than the expectation-based scan statistics used for comparison. Introduced for Poisson-distributed counts by Neill et al. (2005) and Neill (2006), these scan statistics do not condition on the observed total count in their analysis. Neither do they use the most recent data for baseline parameter estimation; rather they calculate the baselines \( b_i \) and other non-outbreak parameters based on what we can expect to see from past data. In that sense, the analysis is split into two independent parts: First, parameters of the distribution are estimated on historical data believed to contain no outbreaks. This can be done by any method regression preferable; typically by fitting a GLM (McCullagh and Nelder, 1989) or a moving average to the data. Second, the estimated parameters are used for simulating new counts from the given probability distribution, and plugged into the calculation of the scan statistic on both the observed and simulated data in order to conduct Monte Carlo hypothesis testing. Expectation-based scan statistics have been formulated for the Poisson (Neill et al., 2005; Neill, 2009b), Gaussian (Neill, 2006), negative binomial (Tango et al., 2011), and zero-inflated Poisson (Allévius and Höhle, 2017) distributions, among others.

The drawback of these scan statistics, as well as those mentioned at the beginning of this section, is that they scan over a fixed set of space-time windows \( W \). If the true outbreak cluster is not among the windows scanned, the outbreak cannot be exactly identified. As also mentioned, the number of windows to be scanned poses a computational burden, particularly if Monte Carlo hypothesis is to be conducted. To overcome these issues, Neill (2012) proposes a ‘Fast Subset Scan’ framework for making fast searches for the top-scoring cluster, unconstrained by any pre-defined set of windows to be scanned. In particular, Neill introduces a ‘Linear Time Subset Scanning’ (LTSS) property, which is shown to hold for several members of the exponential family of distributions (or rather, scan statistics based thereon). For scan statistics with this property, a score function (such as the likelihood ratio in Equation (6)) is paired with a priority function, defined e.g. as the ratio of of count to baseline. The latter function is used to sort the data in order of priority, after which the former function only needs to be applied to increasing subsets of the ordered records. This allows an unconstrained search for the top-scoring subset in linear time (plus the cost of sorting the
data records); the method can also be modified to search only for clusters fulfilling spatial constraints, such as subsets of the $K$ nearest neighbors of each region. The Fast Subset Scan framework can also be extended to multivariate space-time data, as covered next.

### 0.3.2.1.7 Multivariate scan statistics

Until now, the scan statistics described have been univariate in the sense that the counts $\{y_{it}\}$ typically consist of cases of a single disease or symptoms thereof, each count having both spatial and temporal attributes. In practice however, public health authorities monitor a multitude of such data streams simultaneously. If each analysis is done without regard for the others, this will undoubtedly yield a number of false positives higher than desirable. Alternatively, if the significance level of each analysis is adjusted for the others, the power to detect an outbreak in any of the data streams diminishes. These issues can become by analyzing all data streams jointly, an endeavour that can be particularly fruitful when the streams pertain to the same phenomenon to be detected; typically a disease outbreak. For example, some diseases have multiple symptoms and patients may seek help in different ways. A simultaneous increase in over-the-counter flu medication sales at pharmacies and respiratory symptoms reported at a local clinic may in such a case be indicative of an influenza outbreak, but this signal of an outbreak may be missed if each of the two data streams are considered individually.

With this motivation and inspired by an idea of Burkom (2003), Kulldorff et al. (2007) formulate a multivariate scan statistic based on Kulldorff’s prospective scan statistic (Kulldorff 2001). The data in this setting can be represented as a collection of vector counts $\{y_{it}\}$, where $y = (y_{it}^{(1)}, \ldots, y_{it}^{(M)})'$ are the counts for each of the $M$ data streams monitored. The scan statistic is calculated by first processing each data stream separately, calculating a likelihood ratio statistic using Equation (6) for each space-time window, just as is done with the univariate scan statistic. For those windows whose aggregated count exceeds the aggregated baseline, the logarithm of these likelihood ratios are added to form a statistic for the window as a whole. The scan statistic is then defined as the maximum of all such statistics, so that the most likely cluster can be identified as the regions, time intervals and data streams making a positive contribution to the maximum statistic.

Building upon the Fast Subset Scan framework (Neill 2012) cited earlier, Neill et al. (2013) present two computationally efficient ways to detect clusters in space-time data, with and without spatial constraints on these clusters. The first method, Subset Aggregation, is an extension of the work done by Burkom (2003). It assumes that if an outbreak occurs, it has a
multiplicative effect on the baselines $b_{it}^m$ that is equal across all regions, time points and data streams affected by the outbreak. That is, for those regions, times and streams $(i,t,m)$ affected by the outbreak, the expected value of the count $y_{it}^{(m)}$ is $qb_{it}^{(m)}$ rather than $b_{it}^{(m)}$. This allows the counts and baselines within each subset (cluster) to be aggregated, so that the Subset Aggregation scan statistic can be reduced to a univariate scan statistic for the cluster.

The second method is the one previously proposed by Kulldorff et al. (2007), in which an outbreak affects each data stream separately through a stream-specific multiplicative factor $q_m$. Neill et al. (2013) then demonstrates how these methods can be combined with the Fast Subset Scan framework for scan statistics satisfying the LTSS property (Neill, 2012), yielding fast, exact detection algorithms when either the number of data streams or the number of regions are small, and fast approximate (randomized) algorithms when there are too many regions and streams for all subsets of each to be scanned. If hypothesis testing is to take place, this can be done using Monte Carlo replication as described earlier. Again, such replication can come at a high computational cost, and some efforts have therefore been made to avoid it altogether.

0.3.2.1.8 Bayesian scan statistics Neill et al. (2006) introduce the Bayesian Spatial scan statistic for cluster detection, based on Kulldorff’s 1997 original scan statistic. The method is easily extended to a spatio-temporal setting, which is that described below. In Kulldorff’s 2001 model, the data $\{y_{it}\}$ are assumed to be Poisson distributed with expected values $q \cdot b_{it}$, the relative risk $q$ varying depending on whether an outbreak is ongoing or not, and estimated by maximum likelihood. In the model of Neill et al. (2006), the parameters $q$ are instead given conjugate gamma distribution priors, with prior probabilities tuned to match the occurrence of an outbreak in each possible outbreak cluster considered. With the conjugate prior for the relative risks, and baselines $\{b_{it}\}$ estimated from historical data, simple analytical formulas can be derived for the marginal probabilities of the data (relative risks integrated out), in the end resulting in the posterior probability of an outbreak for each cluster considered, and for the non-occurrence of an outbreak. Thus, no Monte Carlo replications need to be made.

To exemplify the Bayesian scan statistic (Neill et al., 2006), suppose the null hypothesis of no outbreak states that each count is distributed as a Poisson random variable with mean $q \cdot b_{it}$, where $b_{it}$ is fixed and $q \sim \text{Gamma}(\alpha_{all}, \beta_{all})$. After marginalizing over the distribution of $q$, the likelihood under the null hypothesis becomes the negative binomial (a.k.a.
gamma-Poisson mixture) probability mass function:

$$
\mathbb{P}(y | H_0) = \frac{\Gamma(\alpha_{\text{all}} + Y)}{Y! \Gamma(\alpha_{\text{all}})} \left( \frac{\beta_{\text{all}}}{\beta_{\text{all}} + B} \right)^{\alpha_{\text{all}}} \left( \frac{B}{\beta_{\text{all}} + B} \right)^{\alpha_{\text{all}}},
$$

where \( y \) represents the entire data set, \( Y \) is the sum of all counts, and \( B \) the sum of all baselines \( b_{it} \). The alternative hypothesis states that an outbreak is occurring in a space-time window \( W \), with a prior distribution placed over all potential windows \( W \). For a given \( W \), it is assumed that counts inside \( W \) have a relative risk \( q \) distributed as \( q \sim \text{Gamma}(\alpha_W, \beta_W) \), while those counts outside have a corresponding distribution for \( q \) with parameters \( \alpha_W \) and \( \beta_W \). After marginalizing over the relative risk distributions, the likelihood becomes

$$
\mathbb{P}(y | H_1(W)) = \frac{\Gamma(\alpha_W + Y_W)}{Y_W! \Gamma(\alpha_W)} \left( \frac{\beta_W}{\beta_W + B_W} \right)^{\alpha_W} \left( \frac{B_W}{\beta_W + B_W} \right)^{\alpha_W} \times \frac{\Gamma(\alpha_{\text{all}} + Y_W)}{Y_W! \Gamma(\alpha_{\text{all}})} \left( \frac{\beta_{\text{all}}}{\beta_{\text{all}} + B} \right)^{\alpha_{\text{all}}} \left( \frac{B}{\beta_{\text{all}} + B} \right)^{\alpha_{\text{all}}},
$$

where \( Y_W \) and \( B_W \) is the sum of counts and baselines inside \( W \), respectively, \( Y_W = Y - Y_W \), and \( B_W = B - B_W \). With a prior \( \mathbb{P}(H_0) \) placed on the null hypothesis, and similarly \( \mathbb{P}(H_1(W)) \) for each outbreak scenario, one obtains the posterior probabilities

$$
\mathbb{P}(H_1(W) | y) = \frac{\mathbb{P}(y | H_1(W)) \mathbb{P}(H_1(W))}{\mathbb{P}(y)},
$$

$$
\mathbb{P}(H_0 | y) = \frac{\mathbb{P}(y | H_0) \mathbb{P}(H_0)}{\mathbb{P}(y)},
$$

where \( \mathbb{P}(y) = \mathbb{P}(y | H_0) \mathbb{P}(H_0) + \sum_W \mathbb{P}(y | H_1(W)) \mathbb{P}(H_1(W)). \) Neil et al. (2006) gives advice for eliciting the priors \( \mathbb{P}(H_0) \) and \( \mathbb{P}(H_1(W)) \), and also for specification of the hyperparameters of each relative risk distribution.

The space-time extension of the Bayesian spatial scan statistic [Neil et al. 2006] is available as the function \texttt{scan\_bayes\_negbin} in the \texttt{scanstatistics} R package (Allévius 2017). To illustrate, we run this scan statistic on the same data as in the illustration of Kulldorff’s scan statistic above. As hyperparameters, we set \( b_{it} \) to the estimate in Equation (8), and let all gamma distribution parameters \( \alpha_{(i)} \) and \( \beta_{(i)} \) be equal to 1. The exception is \( \alpha_W \), which we assume to be the same for all \( W \). We give this parameter a discrete uniform prior on equally spaced values between 1 and 15 in the first month, and let subsequent months use the posterior distribution from the previous month as a prior. We also set \( \mathbb{P}(H_1) = 1 - \mathbb{P}(H_0) = 10^{-7} \), which is...
on the order of magnitude of the incidence of meningococcal disease in Germany in 2002–2008. In Figure 6, we show the posterior outbreak probability \( P(H_1(W)|y) \) at each month of the analysis, for the space-time window \( W \) which maximizes this probability.

Figure 6 shows clear similarities to the scores calculated for Kulldorff’s scan statistic, shown in Figure 4. Further, half of all most likely clusters reported by each method are the same. The difference, as discussed earlier, is that the output of the Bayesian scan statistic is a posterior probability rather than the maximum of a likelihood ratio.

The Bayesian scan statistic was later extended to a multivariate setting by Neill and Cooper (2010). This Multivariate Bayesian Scan Statistic (MBSS) is also capable of detecting multiple event types, thus allowing it, for example, to assign probabilities to outbreaks of different diseases based on records of symptom data. A downside of this method is that the set of clusters to be searched must be specified, and the prior probability of an outbreak in each is (typically) uniform over all clusters, regardless of size and shape. To remedy this defect, Neill (2011) modify the MBSS by specifying a hierarchical spatial prior over all subsets of regions to be scanned. This method is shown to be superior to the MBSS in spatial accuracy and detection timeliness, yet remaining computationally efficient. More recently, for univariate data, a Bayesian scan statistic based on the zero-inflated Poisson distribution has been proposed by Cançado et al. (2017).

0.3.2.1.9 Alternative methods for cluster detection in areareferenced data Scan statistics are not the only option for cluster detection of the sort discussed above. To give an example, there is the What’s
Strange About Recent Events? (WSARE) ([Wong et al., 2005] method, available as software, which can detect outbreaks in multivariate space-time data sets by using a rule-based technique to compare the observed data against a baseline distribution. WSARE uses Bayesian networks, association rules and a number of other techniques to produce a robust detection algorithm. Other examples with more detail than space allows for here can be found e.g. in [Rogerson and Yamada, 2008].

0.3.2.2 Methods for Point Process Data

The methods discussed in the previous section were applicable to data which has been aggregated over space and time. While such an accumulation may be the inherent form of the data, the loss of granularity could impede both the timeliness and spatial accuracy with which outbreaks are detected. When data with exact coordinates and time stamps are available, it may thus be beneficial to analyze data in this format. In this section we therefore assume that the available data is of the form \( \{s_i, t_i\}_{i=1}^n \), where \( s = (x, y) \) are the coordinates (longitude and latitude) of the event (disease case, typically), and \( t \) the time of occurrence. We assume an ordering \( t_1 < t_2 < \ldots < t_n \), and that the study region is defined by the study area \( A \) and the surveillance timer interval \((0, T]\).

One starting point to analyze such data is to adapt a purely temporal surveillance method to a spatio-temporal setting. [Assunção and Correa, 2009] does so by combining a non-homogeneous Poisson point process partially observed on \( A \times (0, T] \) with the Shirayev-Roberts (SR) statistic ([Shirayev, 1963] [Roberts, 1966] [Kennet and Pollak, 1996]), utilizing the martingale property of the latter to establish a protocol for achieving a desired ARL with minimal parameter input by the user. Aside from the ARL, the user needs to specify a radius \( \rho \) defining the maximum spatial extent of the outbreak cluster, as well as a parameter \( \epsilon > 0 \) which measures the relative change in the density within the outbreak cluster as compared to the non-outbreak situation. The SR statistic in [Assunção and Correa, 2009] formulation is then defined as

\[
R_n = \sum_{k=1}^{n} \Lambda_{k,n}, \quad \text{where} \\
\Lambda_{k,n} = (1 + \epsilon)^{N(Y_{k,n})} I_{Y_{k,n}}(x, y, t) \exp \left(-\epsilon \mu(Y_{k,n})\right).
\]

Here, \( Y_{k,n} \) is the cylinder defined by the ball of radius \( \rho \) centered on the location of the \( k \)th event and the time interval \((t_k, t_n]\) between the \( k \)th and the \( n \)th event, \( N(Y_{k,n}) \) is the number of events inside that cylinder, \( \mu(Y_{k,n}) \)

is the expected number of events inside the cylinder if there is no space-time clustering, and \( I_{Y_{k,n}} \) is an indicator taking the value 1 if the \( k \)th event is inside \( Y_{k,n} \) and 0 otherwise. The outbreak signal goes off if \( R_n \) is larger than the specified ARL, and the outbreak cluster is identified as the cylinder \( Y_{k,n} \) for which \( \Lambda_{k,n} \) is maximized. The quantity \( \mu(Y_{k,n}) \) requires the specification of two densities related to the process’ intensity function, but since this is too much to ask from the user, \( \mu(Y_{k,n}) \) is instead replaced by the estimate

\[
\hat{\mu}(Y_{k,n}) = \frac{N(B(s_k, \rho) \times (0, t_{n})) \cdot N(A \times (t_k, t_{n}))}{n},
\]

i.e. the product of the number of events within the disk \( B(s_k, \rho) \), regardless of time of occurrence, and the number of events that occurred in the time interval \( (t_k, t_{n}) \) anywhere within the whole study region, divided by the total number of events. Every new incoming event thus requires the re-calculation of all terms in Equation (13), which Assunção and Correa (2009) demonstrate can be done in an efficient iterative procedure.

Assunção and Correa’s (2009) method was later extended by Veloso et al. (2013) to handle the detection of multiple space-time clusters. This is accomplished by (randomly) deleting excess events inside the detected clusters and re-running the method with a new ARL threshold corrected for the event deletion.

There have also been attempts to adapt retrospective methods for detection of space-time point event clusters to a prospective setting. For example, Rogerson (2001) formulate a local version of the (retrospective) Knox statistic (Knox, 1964) and combine it with a CUSUM framework to make the method suitable for prospective surveillance. However, Marshall et al. (2007) later concluded that it is certainly not, owing to a number of factors that strongly influence the performance of the method, and which a user has little power to regulate properly. A remedy is offered by Piroutek et al. (2014), who redefine the local Knox statistic by Rogerson (2001) to be prospective rather than retrospective. For a given observation indexed by \( i \), the local Knox statistic \( n_{st}(i) \) is defined as the number of observations that are closer than \( t \) units of time to \( t_i \), and whose coordinates are less than a distance \( s \) away from \((x_i, y_i)\). In Rogerson (2001), the closeness in the temporal dimension is measured in both directions, so that a \( n_{st}(i) \) counts nearby events both before and after the \( i \)th event. This account of future events is included in the CUSUM chart, which is not appropriate. Piroutek et al. (2014) instead let only past events enter into the calculation of \( n_{st}(i) \), which turns out to vastly improve the performance of the method in a prospective setting. As noted by Marshall et al. (2007), there are also problems with the normal distribution approximation made to the statistic calculated for the CUSUM
Namely, it can be very poor if the thresholds \( s \) and \( t \) are small, and this in turn makes it difficult to set the appropriate control limit to achieve a given ARL. Piroutek et al. (2014) instead propose to use a randomization procedure using past data to establish the correct control limit, obviating the need of an approximate distribution.

Paiva et al. (2015) later combines the modified local Knox statistic by Piroutek et al. (2014) with the Cumulative Surface method proposed by Simões and Assunção (2005), allowing for a visualization of clusters in three dimensions. In their method, the local Knox score of each event is smeared using a bivariate Gaussian kernel function, and a threshold for detection is defined through the distribution of the stochastic surfaces formed. In all, the method requires few parameters as input from users, and needs no information of the population at risk.

### Illustration of Assunção and Correa’s SR statistic

We now illustrate the method by Assunção and Correa (2009) on the meningococcal data (finetype B only) considered earlier, this time using the coordinates and time stamps of each event, rather than an aggregated count. The method is implemented as the function \texttt{stcd} in the R package \texttt{surveillance} (Salmon et al., 2016). As a validation of the method, we run the analysis for approximately the same period as Reinhardt et al. (2008), hoping that the results will be similar. We guide our choice of the parameter \( \rho \) required by this method by the analysis of the meningococcal data by Meyer et al. (2012); Figure 3 of this paper suggests that setting \( \rho = 75 \) km is adequate. For the choice of the parameter \( \epsilon \), which is the relative change of event-intensity within the to-be-detected cluster, we are guided by the simulation study by Assunção and Correa (2009) and set \( \epsilon = 0.2 \). Lastly, we set the desired ARL to 30 days.

In Figure 7, the detected cluster is shown, with all events up until the point of detection marked as triangles on the map.
Figure 7: Detected cluster (gray circle) and observed disease events for the cluster detection method by Assunção and Correa (2009).

The cluster detected by the \texttt{stcd} function is centered on the city of Aachen in the state North Rhine-Westphalia, which corresponds well to the cluster marked in Figure 3 of [Reinhardt et al.] (2008), and the dates also appear similar. The cluster was detected only one day after its estimated start date, showing the potential of Assunção and Correa's method in terms of timeliness. All in all, the ability to use the spatial and temporal attributes of each individual event for the detection of clusters is an attractive feature when greater exactness in the origins and spatial extent of outbreaks is important.

0.4 Summary and Outlook

This chapter presented temporal and spatio-temporal statistical methods for the prospective detection of outbreaks in routine surveillance data. Such data-driven algorithms operate at the intersection of statistical methodology, data mining and computational (big) data crunching. Simple methods have their virtues and speed of implementation can be of importance; however, this should never be an excuse for ignoring statistical facts when counts get small and sparse. Facts which might surprise the non-statisticians uncomfortable beyond the normal distribution.

Despite the many advances in the last 30 years, outbreak detection algorithms will never replace traditional epidemiological alertness. Nevertheless, they offer support for using the digital epidemiologist’s time more effectively. From a systems perspective, however, it is our impression that detection
algorithms have had limited impact on practical outbreak detection so far. One reason is that, historically, many algorithmic suggestions were not supported by accessible software implementations. Another reason is that their usefulness is questioned by the many false alarms and a misalignment between the users’ needs and presentation of the alarms found by the system. Statisticians—as part of interdisciplinary teams—need to worry more about how to roll-out the proposed algorithms in the public health organizations. As a step in this direction, all detection methods presented in this chapter are readily available from open-source packages in R. In particular, the \texttt{surveillance} and \texttt{scanstatistics} packages\(^2\). Examples of software supporting national surveillance systems by increased user focus are the Swedish CASE system (Cakici et al., 2010) and the German avoid@RKI (Salmon et al., 2016a).

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\(^2\)The R code producing the results and graphics of this manuscript is available from \url{https://github.com/BenjaK/ProspectiveDetectionChapter}
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