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DClusterm: Model-based detection of disease clusters

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Abstract

The detection of regions with unusual high risk plays an important role in disease mapping and the analysis of Public Health data. In particular, the detection of groups of areas (i.e., clusters) where the risk is significantly high is often conducted by Public Health authorities.

Many methods have been proposed for the detection of disease clusters, most of them based on moving windows, such as, Kulldorff's Spatial Scan Statistics (SSS). Here we describe a model-based approach for the detection of disease clusters implemented in the **DClusterm** package. Our model-based approach is based on representing a large number of possible clusters by dummy variables and then fitting many genralized linear models to the data wherethese covariates are included one at a time. Cluster detection is done by performing a variable or model selection among all fitted models using different criteria.

Because of our model-based approach, cluster detection can be performed using different types of likelihoods anf latent effects. We cover the detection of spatial and spatio-temporal clusters, as well as how to account for covariates, deal with zero-inflated datasets and overdispersion in the data.

Keywords: disease cluster, spatial statistics, R.

1. Introduction

The analysis of epidemiological data at small area level often involves accounting for possible risks factors and other important covariates using different types of regression models. How-

ever, it is not uncommon that after a number of covariates have been accounted for, residuals show a spatial distribution that defines some groups of areas with unusual high epidemiological risk. Hence, in many ocassions it is not clear whether all spatial risk factors have been included in our model.

Public health data are often aggregated over small administrative areas becasue of confidentiality issues, but it is not uncommon that individual data are available. Generalised Linear Models (GLM,) are a common framework for disease mapping to model aggregated and individual data. GLMs not only model Poisson or Binomial responses, but they can also link the outocome to a linear predictor on the covariates (and, possibly, other effects). However, until recently, it was not clear how to use GLMs to detect clusters of disease, i.e., a group of contiguous areas with significant high risk.

In order to detect disease clusters, probably the most widely used method is the one proposed by Kulldorff (1997). This is called the Spatial Scan Statistic and it will find the most likely cluster. Significance is assessed via a Monte Carlo test using a test statistic based on a likelihood ratio test for the following hypotheses:

$$\begin{aligned} H_0: &\quad \theta_z = \theta_{\bar{z}} \\ H_1: &\quad \theta_z > \theta_{\bar{z}} \end{aligned}$$

Here, z represents a cluster (i.e., a set of contiguous areas), θ_z the relative risk in the cluster and $\theta_{\bar{z}}$ the relative risk outside the cluster. Many different clusters are tested in turn. The most likely cluster is the one with the highest value of the test statistic. Then a Monte Carlo test is used to compute the p-value of the most likely cluster.

In this paper we will summarise the work by several authors that have established a link between GLMs and SSS, so that the detectiopn of disease clusters is approached from a regression point of view. As described later, this will involved fitting many different GLMs for which dummy variables that represent possible clusters are included one at a time. Cluster detection is based on selecting a number of dummy cluster variables using variable selection methods. Furthermore, we will describe how these methods have been implemented in the **DClusterm** package for the R software.

This paper is organised as follows. Section 2 will introduce the link between GLM and SSS. Next, in Section 3 we describe how to extend these ideas to dectect clusters in space and time. The detection of disease clusters for zero-inflated data is discussed in Section 4. Section 5 shows how to include random effects in the detection of disease clusters. A multivariate approach for the detection of disease clusters of two diseases has been included in Section 6. Finally, a discussion and some final remarks are provided in Section 7.

{sec:GLM}

2. Generalised Linear Models for cluster detection

Jung (2009); Zhang and Lin (2009) provide a explicit link between GLMs and the SSS, and show that the test statistic for a given cluster is equivalent to fitting a Generalised Linear Model using a cluster variable as a predictor. This cluster variable is a dummy variable which is 1 for the areas in the cluster and 0 for the areas outside the cluster.

Firstly, given that we are using GLM's we could include covariates in the model. For example, for a Poisson model with expected counts E_i we could have:

$$O_i \sim Po(E_i\theta_i)$$

$$\log(\theta_i) = \log(E_i) + \alpha + \beta x_i$$

Fitting this model will provide estimates $\hat{\alpha}$ and $\hat{\beta}$. This will account for the (spatial) effects of the covariates. In order to include the cluster variable the effects of the covariates will be keep fixed. Hence, the clusters covariates will be used in a model with fixed coefficients for the covariates:

$$\log(\theta_i) = \log(E_i) + \hat{\alpha} + \hat{\beta} x_i + \gamma CLUSTER_i$$

This means that the offset now is $\log(E_i) + \hat{\alpha} + \hat{\beta} x_i$. γ is a measure of the difference of the risk in the cluster. We are only interested in clusters whose coefficient is higher than 0 (i.e., increased risk), hence those with a significant negative coefficient will be ignored.

Testing different clusters will produce many different cluster covariates. We can use model selection techniques to select the most important cluster in the area. In particular, the log-likelihood can be used to compare the model with the cluster variable to the null model (i.e., the one with the covariates only). Note that we are interested in clusters with a high risk and, because of that, we are only interested in clustes whose associated coefficient is significantly higher than zero.

Regarding the effect of the covariates, it is possible to perform a cluster dection without considering covariates in the model. Then a cluster detection accouting for the covariates will likely provide a different number of clusters. By comparing the clusters detected in both cases we will be able to find what clusters are linked to underlying risk factors included in the model and what clusters remain unexplained by the covariates. In the examples that we included in this paper we will always consider both scenarios to better understand how cluster detection works with these methods.

Bilancia and Demarinis (2014); Gómez-Rubio, Moraga, and Molitor (2015) describe a similar approach to the detection of disease cluster using Bayesian hierarchical models. The Integrated Nested Laplace Approximation is used in both cases for model fitting as it provides computational benefits over other computationally expensive methods, such as Markov Chain Monte Carlo.

2.1. Leukemia in upstate New York

The `NY8` dataset is avaialble in package `DClusterm` and it provides cases of leukemia in different census tracts in upstate New York. This data set has been analysed by several authors (Waller, Turnbull, Clark, and Nasca 1992; Waller and Gotway 2004). The location of leukemia is thought to be linked to the use of Trichloroethene (TCE) by several companies in the area. Figure 1 shows the Standardised Mortality Ratios of the census tracts and the locations of the industries using TCE.

In order to measure exposure, the inverse of the distance to the nearest TCE site has been used (PEXPOSURE). In addition, two other socioeconomic covariates have been used: the percentage of people aged 65 or more (PCTAGE65P) and the percentage of people who own their home (PCTOWNHOME).

This dataset is included in package **DClusterm** as `NY8`. Hence, our first action is to load some required packages and the dataset itself.

```
> library(DClusterm)
> library(snowfall)
> library(xts)
> data(NY8)
```

A number of cases could not be linked to their actual location and they were distributed uniformly over the study are, making the counts real numbers instead of integers. We have rounded these values as we intend to use a Poisson likelihood for the analysis. Furthermore, expected counts are computed using the overall incidence ratio (total number of cases divided by the total population). Age-sex standarisation is not possible in this case as this information is not available in our dataset.

```
> NY8$Observed <- round(NY8$Cases)
> NY8$Expected <- NY8$POP8 * sum(NY8$Observed)/sum(NY8$POP8)
> NY8$SMR <- NY8$Observed/NY8$Expected
> NY8$x <- coordinates(NY8)[, 1]
> NY8$y <- coordinates(NY8)[, 2]
```

Finally, a `STFDF` object is created to store all the data. Functions in **DClusterm** will take object for space-time data as defined in package **spacetime**. Note that in this case we do not have a truly space-time dataset.

```
> NY8st <- STFDF(as(NY8, "SpatialPolygons"), xts(1, as.Date("1972-01-01")),
+     NY8@data, endTime = as.POSIXct(strptime(c("1972-01-01"),
+         "%Y-%m-%d"), tz = "GMT"))
```

2.2. Cluster detection

Cluster detection with no covariates

First of all, a model with no covariates will be fitted and used as a starting point.

```
> m0 <- glm(Observed ~ offset(log(Expected)) + 1, family = "poisson",
+     data = NY8)
> idxcl <- c(120, 12, 89, 139, 146)
> cl0 <- DetectClustersModel(NY8st, thegrid = as.data.frame(NY8)[idxcl,
+     c("x", "y")], fractpop = 0.15, alpha = 0.05, radius = Inf,
+     step = NULL, typeCluster = "S", R = NULL, numCPUS = 2, model0 = m0)
```

Below is a summary of the clusters detected with this method. The dates can be ignored as this is a purely spatial cluster.

```
> cl0
```

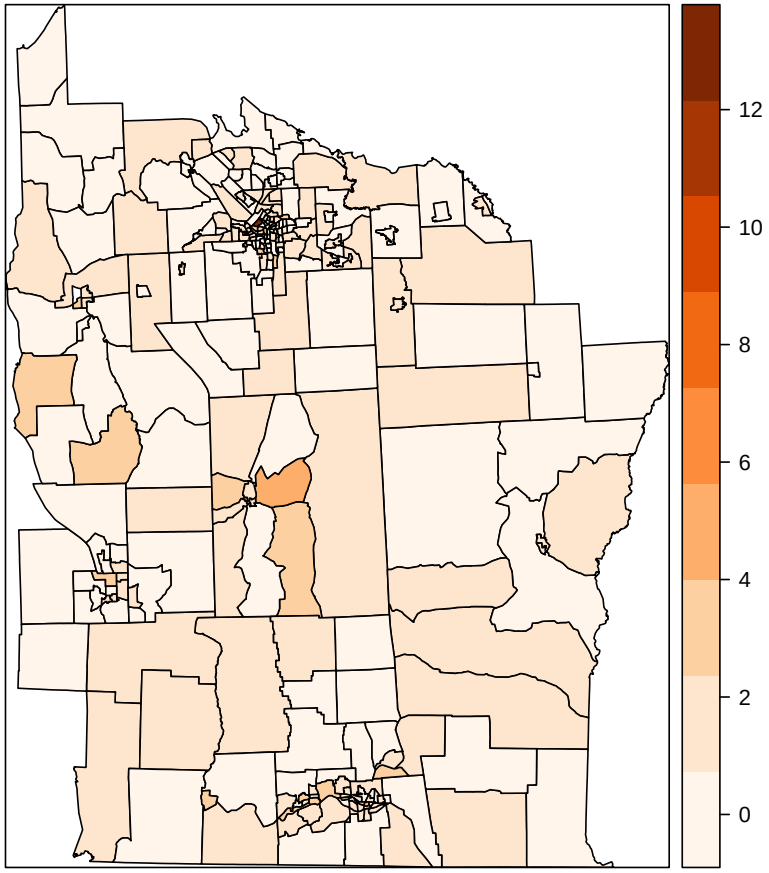


Figure 1: **INCLUDE TCE LOCATIONS** SMR of the incidence of Leukemia in upstate New York.

{fig:NYmap}

```
           x       y size      minDateCluster      maxDateCluster statistic
11  424728.9 4661404   39 1972-01-01 01:00:00 1972-01-01 01:00:00  8.044846
88  409430.4 4720092    9 1972-01-01 01:00:00 1972-01-01 01:00:00  6.967107
119 404710.7 4768346   24 1972-01-01 01:00:00 1972-01-01 01:00:00  3.254824
          pvalue      risk cluster
11  0.0000604120 0.3916904    TRUE
88  0.0001893208 0.6455613    TRUE
119 0.0107290781 0.4445236    TRUE
```

The centre of the clusters detected are shown in Figure 2.

Cluster detection after adjusting for covariates

Similarly, clusters can be detected after adjusting for significant risk factors. First we will fit a GLM with the 3 covariates mentioned earlier. As it can be seen, all three are significant:

```
> m1 <- glm(Observed ~ offset(log(Expected)) + PCTOWNHOME + PCTAGE65P +
```

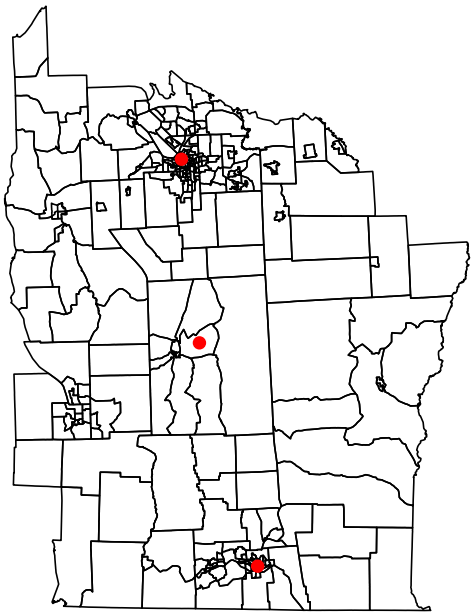


Figure 2: Clusters detected when no covariates are included in the model. {fig:NYcl0}

```
+     PEXPOSURE, family = "poisson", data = NY8)
> summary(m1)


Call:
glm(formula = Observed ~ offset(log(Expected)) + PCTOWNHOME +
    PCTAGE65P + PEXPOSURE, family = "poisson", data = NY8)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.9099  -1.1294  -0.1768   0.6385   3.2426

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -0.65507    0.18550  -3.531 0.000413 ***
PCTOWNHOME  -0.36472    0.19316  -1.888 0.058998 .
PCTAGE65P    4.05031    0.60559   6.688 2.26e-11 ***
PEXPOSURE    0.15141    0.03165   4.784 1.72e-06 ***
```

```
---
Signif. codes:  0 âĂŸ***âĂŹ 0.001 âĂŸ**âĂŹ 0.01 âĂŸ*âĂŹ 0.05 âĂŸ.âĂŹ 0.1 âĂŸ âĂŹ 1

(Dispersion parameter for poisson family taken to be 1)

    Null deviance: 459.05  on 280  degrees of freedom
Residual deviance: 384.01  on 277  degrees of freedom
AIC: 958.97

Number of Fisher Scoring iterations: 5
```

The cluster detection method is run as before, but now we use the previous model instead:

```
> cl1 <- DetectClustersModel(NY8st, thegrid = as.data.frame(NY8)[idxcl,
+     c("x", "y")], fractpop = 0.15, alpha = 0.05, typeCluster = "S",
+     R = NULL, numCPUS = 2, model0 = m1)

> cl1

           x       y size      minDateCluster      maxDateCluster statistic
88  409430.4 4720092    9 1972-01-01 01:00:00 1972-01-01 01:00:00  5.861204
119 404710.7 4768346   20 1972-01-01 01:00:00 1972-01-01 01:00:00  3.160591
          pvalue      risk cluster
88  0.0006175202 0.5869176    TRUE
119 0.0119304026 0.4882633    TRUE
```

Figure 3 shows the clusters detected after adjusting for covariates.

3. Spatio-temporal clusters

{sec:spaceti

Jung (2009) discusses how to extend model-based approaches for the detection of spatial disease clusters to space and time. Gómez-Rubio *et al.* (2015) propose the following model:

$$\log(\mu_{i,t}) = \log(E_{i,t}) + \gamma_j c_{i,t}^{(j)} \quad (1)$$ {eq:stcluste

where $\mu_{i,t}$ is the mean of area i at time t and $c_{i,t}^{(j)}$ a cluster dummy variable for cluster j.

3.1. Brain Cancer in New Mexico

The `brainNM` data set contains yearly cases of brain cancer in New Mexico from 1973 to 1991 (inclusive). The data set has been taken from the SatScan website and the area boundaries from the U.S. Census Bureau. In addition, the location of Los Alamos National Laboratory has been included (from the Wikipedia). Inverse distance to this site can be used to test for increased risk in the areas around the Laboratory as no other covariates are available.

```
> library(DClusterm)
> library(snowfall)
> data(brainNM)
```

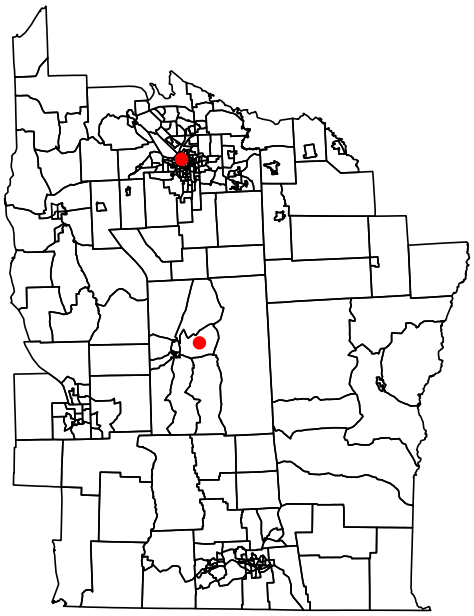


Figure 3: Clusters detected after adjusting for covariates. {fig:NYcl1}

Expected counts have been obtained using age and sex standardisation over the whole period of time. Hence, yearly differences are likely to bee seen when plotting the data. The SMR's have been plotted in Figure 3.1.

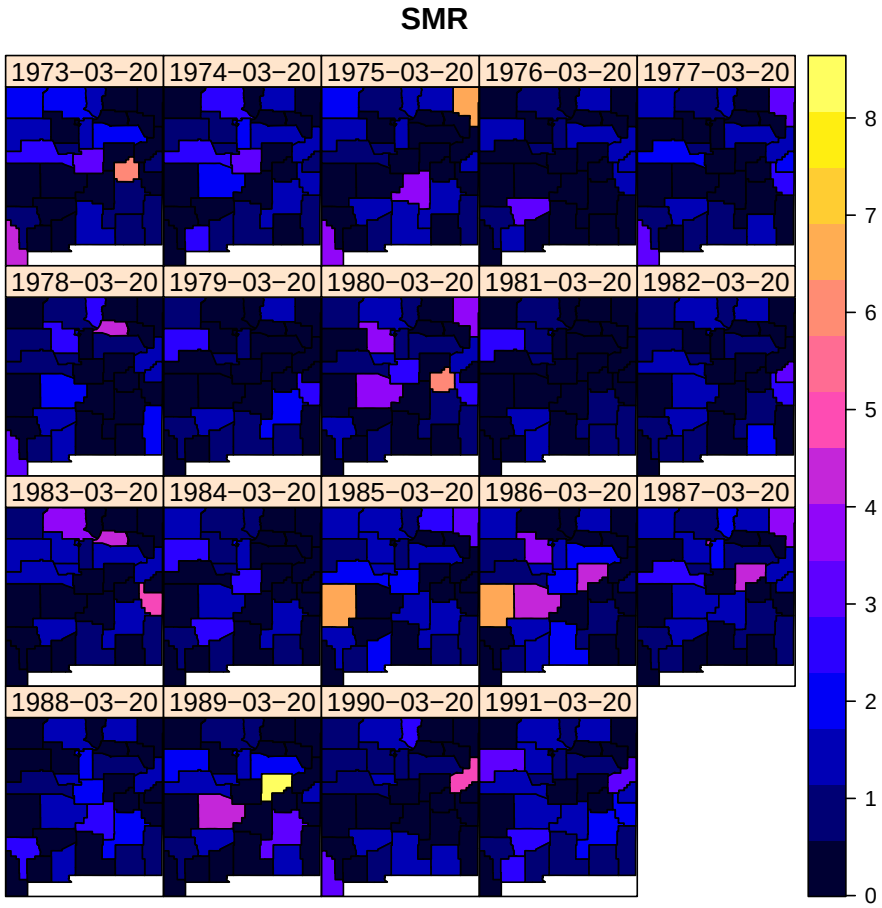
3.2. Cluster detection

Cluster detection with no covariates

Similarly as in the spatial case, a GLM

```
> m0 <- glm(Observed ~ offset(log(Expected)) + 1, family = "poisson",
+     data = brainst@data)
> summary(m0)

Call:
glm(formula = Observed ~ offset(log(Expected)) + 1, family = "poisson",
    data = brainst@data)
```



{fig:NMSMR}

Figure 4: SMR of brain cancer in New Mexico.

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.4874  -0.9998  -0.4339   0.3773   3.1321

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) 2.834e-16  2.917e-02       0        1

(Dispersion parameter for poisson family taken to be 1)

    Null deviance: 631.64  on 607  degrees of freedom
Residual deviance: 631.64  on 607  degrees of freedom
AIC: 1585.6

Number of Fisher Scoring iterations: 5
```

```
> cl0 <- DetectClustersModel(brainst, coordinates(brainst@sp),
+     minDateUser = "1985-01-01", maxDateUser = "1989-01-01", fractpop = 0.15,
+     alpha = 0.05, typeCluster = "ST", R = NULL, numCPUS = 2,
+     model0 = m0)

> nrow(cl0)

[1] 180

> cl0[1:5, ]

             x        y size      minDateCluster      maxDateCluster statistic
0286 -106.3073 35.86930    3 1986-03-20 01:00:00 1988-03-20 01:00:00  7.493492
0496 -105.9761 35.50684    2 1986-03-20 01:00:00 1988-03-20 01:00:00  6.438221
0531 -106.9303 34.00725    9 1985-03-20 01:00:00 1986-03-20 01:00:00  6.378992
0498 -105.9761 35.50684    2 1987-03-20 01:00:00 1988-03-20 01:00:00  6.331113
0288 -106.3073 35.86930    2 1987-03-20 01:00:00 1988-03-20 01:00:00  6.331113
           pvalue      risk cluster
0286 0.0001082553 0.6814588    TRUE
0496 0.0003327442 0.6970405    TRUE
0531 0.0003544929 0.3838756    TRUE
0498 0.0003731179 0.8070901    TRUE
0288 0.0003731179 0.8070901    TRUE
```

Cluster detection after adjusting for covariates

We will use the inverse of the distance to Los Alamos National Laboratory as a covariate.

```
> dst <- spDistsN1(coordinates(brainst@sp), losalamos, TRUE)
> nyears <- length(unique(brainst@data$Year))
> brainst@data$IDLANL <- rep(1/dst, nyears)

> m1 <- glm(Observed ~ offset(log(Expected)) + IDLANL, family = "poisson",
+     data = brainst)
> summary(m1)

Call:
glm(formula = Observed ~ offset(log(Expected)) + IDLANL, family = "poisson",
    data = brainst)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.4832  -0.9982  -0.4280   0.3775   3.1424

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
```

```
(Intercept) -0.005721   0.029897  -0.191    0.848
IDLANL       0.338194   0.364900   0.927    0.354

(Dispersion parameter for poisson family taken to be 1)

    Null deviance: 631.64  on 607  degrees of freedom
Residual deviance: 630.84  on 606  degrees of freedom
AIC: 1586.8

Number of Fisher Scoring iterations: 5

> cl1 <- DetectClustersModel(brainst, coordinates(brainst@sp),
+     fractpop = 0.15, alpha = 0.05, minDateUser = "1988-01-01",
+     maxDateUser = "1989-01-01", typeCluster = "ST", R = NULL,
+     numCPUS = 2, model0 = m1)

> nrow(cl1)

[1] 6

> cl1[1:5, ]

            x        y size      minDateCluster      maxDateCluster statistic
049 -105.9761 35.50684    2 1988-03-20 01:00:00 1988-03-20 01:00:00  2.433451
028 -106.3073 35.86930    2 1988-03-20 01:00:00 1988-03-20 01:00:00  2.433451
057 -105.8508 34.64048    2 1988-03-20 01:00:00 1988-03-20 01:00:00  2.431998
013 -106.8328 32.35265   17 1988-03-20 01:00:00 1988-03-20 01:00:00  2.010047
027 -105.4592 33.74524    3 1988-03-20 01:00:00 1988-03-20 01:00:00  2.007057
        pvalue      risk cluster
049 0.02737662 0.7122467    TRUE
028 0.02737662 0.7122467    TRUE
057 0.02742274 0.7475794    TRUE
013 0.04496121 0.2594413    TRUE
027 0.04512090 0.7512120    TRUE
```

We can easily display the most significant cluster as follows:

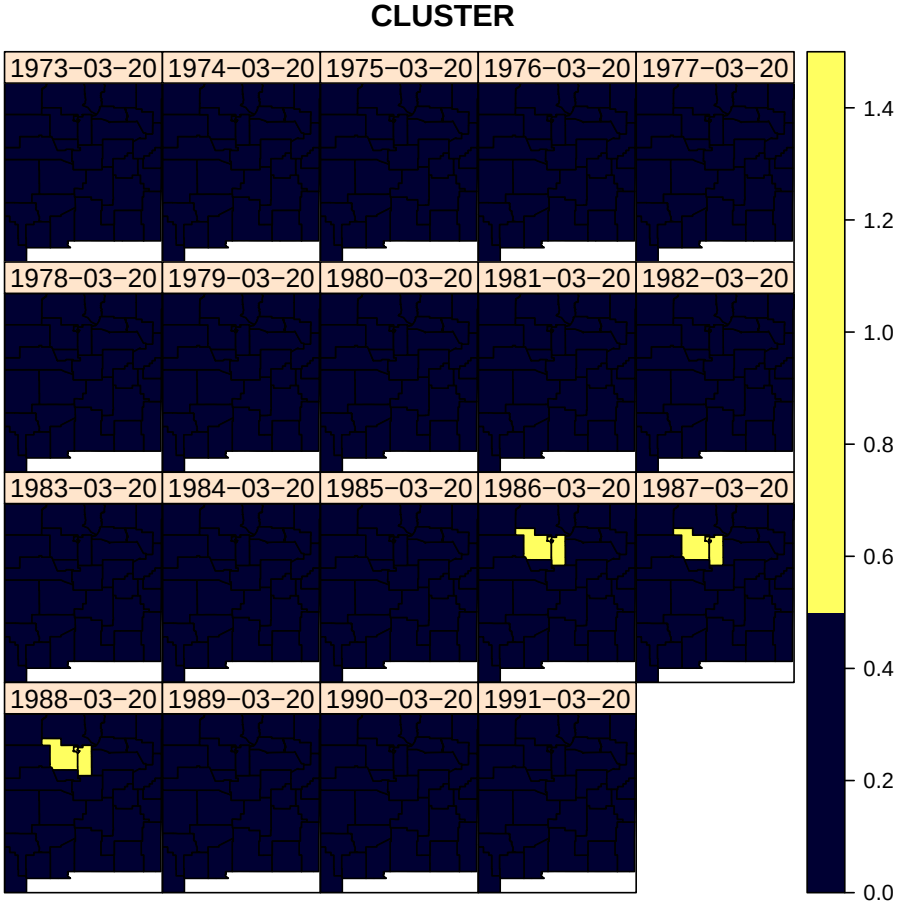
```
> stcl <- get.stclusters(brainst, cl0)
> brainst$CLUSTER <- 0
> brainst$CLUSTER[stcl[[1]]] <- 1
```

4. Zero-inflated models for cluster detection

{sec:zeroinf

Gómez-Rubio and López-Quílez (2010) extend this method to account for zero-inflation. In this case the observed number of cases come from a mixture distribution:

```
> print(stplot(brainst[, , "CLUSTER"], at = c(0, 0.5, 1.5)))
```



{fig:NMclust

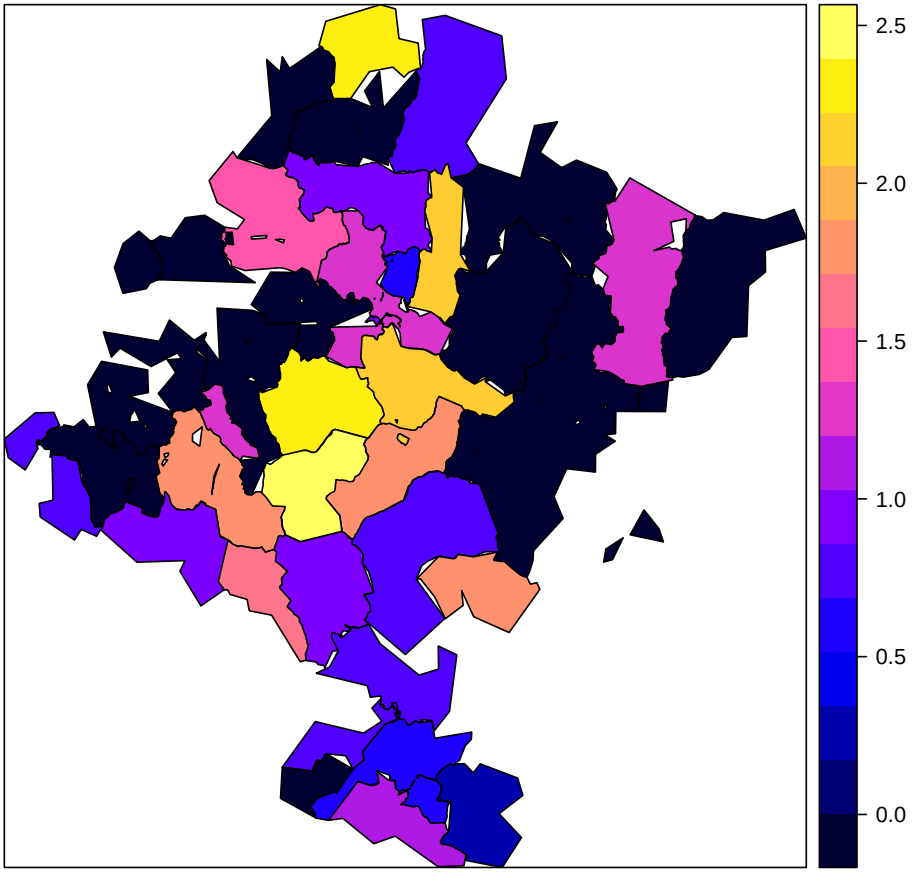
Figure 5: Spatio-temporal cluster of brain cancer detected in New Mexico.

$$Pr(O_i = n_i) = \begin{cases} \pi_i + (1-\pi_i)Po(0|\theta_i E_i) & n_i = 0 \\ (1-\pi_i)Po(n_i|\theta_i E_i) & n_i = 1, 2, \ldots \end{cases}$$

The relative risk θ_i can be modelled using a log-linear model to depend on some relevant risk factors. Also, it is common that all π_i's are taken equal to a single value π.

4.1. Brain Cancer in Navarre (Spain)

Ugarte, Ibáñez, and Militino (2006) analyse the incidence of brain cancer in Navarre (Spain). The aggregation level is the health district. Figure 4.1 shows the SMR. As it can be seen there are many areas where the SMR is zero because there are no cases in those areas. Ugarte, Ibáñez, and Militino (2004) also tested for positive zero-inflation of these data compared to a Poisson distribution. The method implemented in this package is similar to the one used in Gómez-Rubio and López-Quílez (2010) for the detection of disease clusters of rare diseases.



{fig:Navarre}

Figure 6: SMR of brain cancer in Navarre (Spain).

4.2. Cluster detection

Cluster detection with no covariates

Before starting our cluster detection methods, we will check the appropriateness of a Poisson GLM for this data. Fitting a log-linear model (with no covariates) gives the following model:

```
> m0 <- glm(OBSERVED ~ offset(log(EXPECTED)) + 1, family = "poisson",
+     data = brainnav)
> summary(m0)

Call:
glm(formula = OBSERVED ~ offset(log(EXPECTED)) + 1, family = "poisson",
    data = brainnav)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
```

```
-2.5227  -1.4783  -0.3203   0.7042   1.6393

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -7.752e-06  8.805e-02       0        1

(Dispersion parameter for poisson family taken to be 1)

    Null deviance: 63.733  on 39  degrees of freedom
Residual deviance: 63.733  on 39  degrees of freedom
AIC: 145.02

Number of Fisher Scoring iterations: 5
```

Furthermore, a quasipoisson model has been fit in order to asses any extra-variation in the data:

```
> m0q <- glm(OBSERVED ~ offset(log(EXPECTED)) + 1, family = "quasipoisson",
+     data = brainnav)
> summary(m0q)


Call:
glm(formula = OBSERVED ~ offset(log(EXPECTED)) + 1, family = "quasipoisson",
    data = brainnav)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.5227  -1.4783  -0.3203   0.7042   1.6393

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept) -7.752e-06  9.703e-02       0        1

(Dispersion parameter for quasipoisson family taken to be 1.214555)

    Null deviance: 63.733  on 39  degrees of freedom
Residual deviance: 63.733  on 39  degrees of freedom
AIC: NA

Number of Fisher Scoring iterations: 5
```

The dispersion parameter in the previous model seems to be higher than 1, which may mean that the Poisson distribution is not appropriate.

For this reason, and following Ugarte *et al.* (2004), a zero-inflated Poisson model has been fit. Here is the resulting model:

```
> m0zip <- zeroinfl(OBSERVED ~ offset(log(EXPECTED)) + 1 | 1, data = brainnav,
+     dist = "poisson", x = TRUE)
> summary(m0zip)


Call:
zeroinfl(formula = OBSERVED ~ offset(log(EXPECTED)) + 1 | 1, data = brainnav,
    dist = "poisson", x = TRUE)

Pearson residuals:
    Min      1Q  Median      3Q     Max
-1.3585 -0.9137 -0.1378  0.7137  1.8091

Count model coefficients (poisson with log link):
            Estimate Std. Error z value Pr(>|z|)
(Intercept)  0.09347    0.09459   0.988    0.323

Zero-inflation model coefficients (binomial with logit link):
            Estimate Std. Error z value Pr(>|z|)
(Intercept)  -1.6158     0.6435  -2.511    0.012 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Number of iterations in BFGS optimization: 9
Log-likelihood: -69.08 on 2 Df
```

Hence, the zero-inflated Poisson model will be used now to detect clusters of disease:

```
> brainnav$Expected <- brainnav$EXPECTED
> brainnavst <- STFDF(as(brainnav, "SpatialPolygons"), xts(1, as.Date("1990-01-01")),
+     brainnav@data, endTime = as.POSIXct(strptime(c("1990-01-01"),
+         "%Y-%m-%d"), tz = "GMT"))
> cl0 <- DetectClustersModel(brainnavst, coordinates(brainnav),
+     fractpop = 0.25, alpha = 0.05, typeCluster = "S", R = NULL,
+     numCPUS = 2, model0 = m0zip)


Library spdep loaded.
Library splancs loaded.
Library spacetime loaded.
Library DCluster loaded.
Library pscl loaded.
Library INLA loaded.
Library DClusterm loaded.
[1] 1 1

> cl0
```

```
          x       y size      minDateCluster      maxDateCluster statistic
31 596886.8 4710520    4 1990-01-01 01:00:00 1990-01-01 01:00:00  2.520092
30 611795.5 4713762    3 1990-01-01 01:00:00 1990-01-01 01:00:00  2.016942
       pvalue      risk cluster
31 0.02476587 0.5987255    TRUE
30 0.04459518 0.6139100    TRUE
```

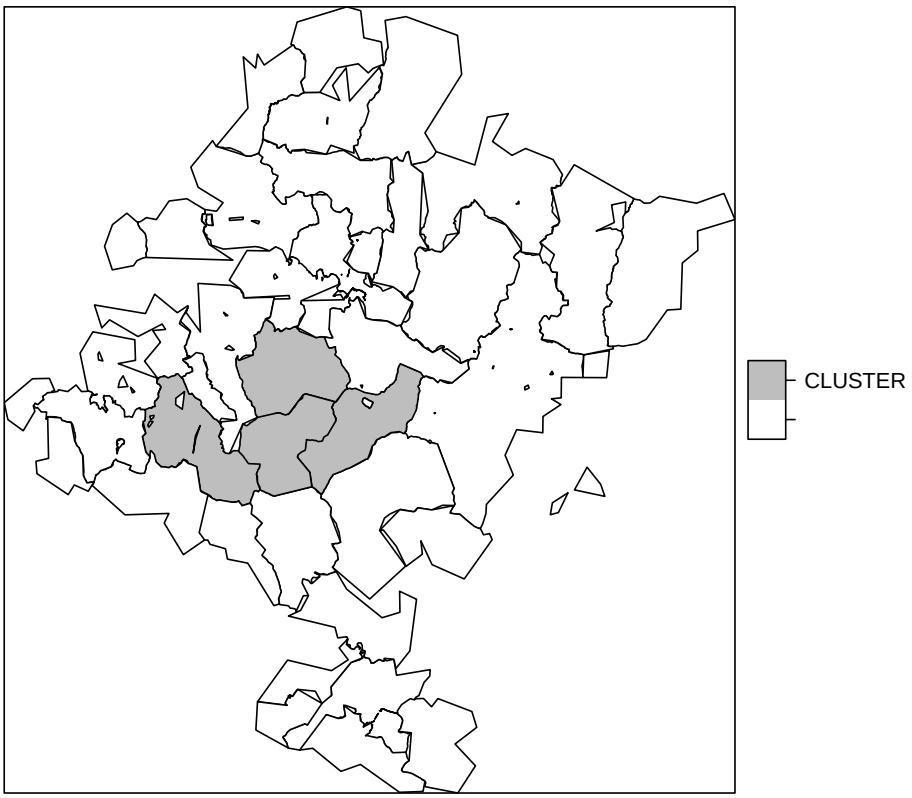
As it can be seen, two clusters (with a p-value lower than 0.05) are detected. However, they overlap and we will just consider the one with the lowest p-value, which is shown in Figure 4.2.1

```
> names(cl0)[3] <- "size"
> knbinary(brainnav, cl0)
```

```
   CL1 CL2
1    0   0
2    0   0
3    0   0
4    0   0
5    0   0
6    0   0
7    0   0
8    0   0
9    0   0
10   0   0
11   0   0
12   0   0
13   0   0
14   0   0
15   0   0
16   0   0
17   1   0
18   0   1
19   0   0
20   0   0
21   0   0
22   0   0
23   0   0
24   1   0
25   0   0
26   0   0
27   0   0
28   0   0
29   0   0
30   1   1
31   1   1
32   0   0
```

```
33    0    0
34    0    0
35    0    0
36    0    0
37    0    0
38    0    0
39    0    0
40    0    0
```

```
> brainnav$CLUSTER <- as.factor(knbinary(brainnav, cl0)[, 1])
> levels(brainnav$CLUSTER) <- c("", "CLUSTER")
```



{fig:Navarre

Figure 7: Cluster of brain cancer detected in Navarre (Spain).

5. Mixed-effects models for cluster detection

{sec:mixed}

6. Bivariate models for cluster detection

{sec:bivar}

7. Discussion

{sec:disc}

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