Statistical modelling and inference for spatio-temporal disease processes

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Disease, Prediction and Chance

- Spread of infectious disease is a complex process typically involving a plethora of factors.
- Some are explicable/predictable.
- Others are essentially random.
- Plenty of work for statisticians deciding which is which.

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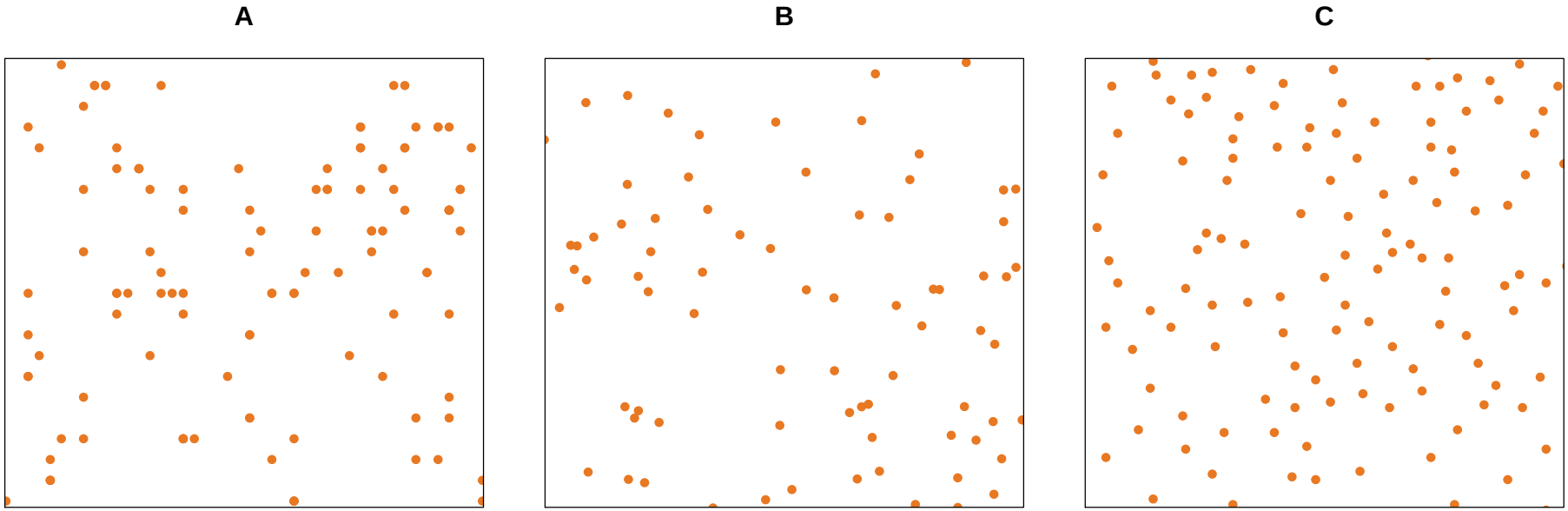
Spatial Patterns ... of Disease?



- Complete spatial randomness
- Locations of gastroenteritis cases
- Mystery spatial point pattern

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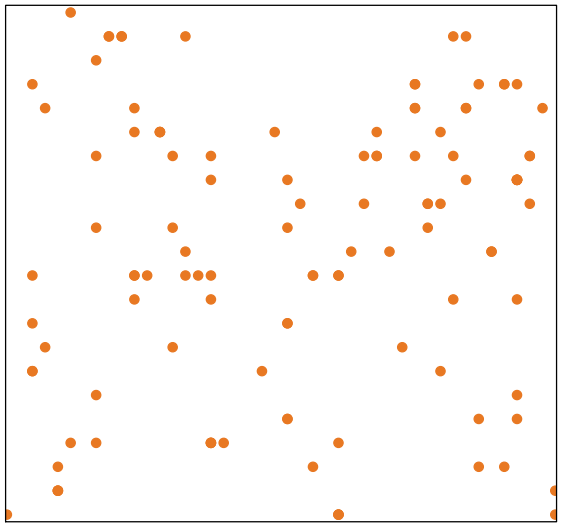
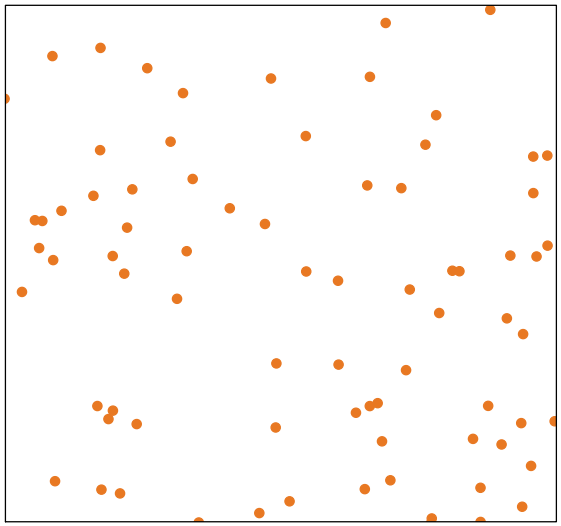
Spatial Patterns ... of Disease?

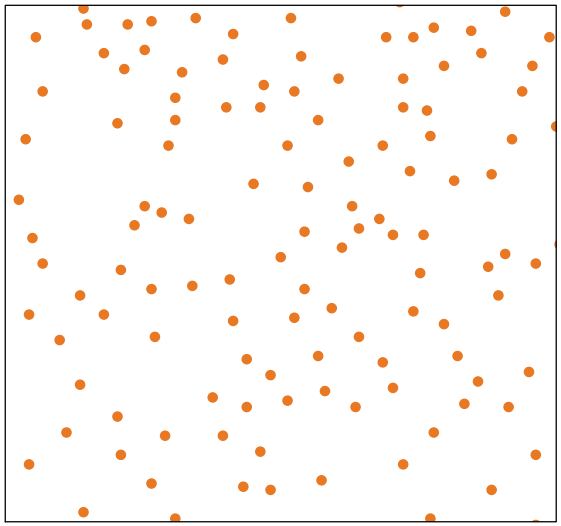
Gastroenteritis cases



Complete spatial randomness



Sea anemone locations



- Complete spatial randomness (B)
- Locations of gastroenteritis cases (A)
- Mystery spatial point pattern (C)

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Measuring Spatial Risk

- To understand spatial patterns of disease we must adjust for underlying population density.
- To this end, Bithell (1990) defined the **relative risk function**:

$$r(\boldsymbol{z}) = \frac{f(\boldsymbol{z})}{g(\boldsymbol{z})} \qquad \boldsymbol{z} \in \mathcal{R}$$

  where f is density of cases and g density of controls.
- Usual to work on log-scale:

$$\rho(\boldsymbol{z}) = \log\{r(\boldsymbol{z})\} = \log\{f(\boldsymbol{z})\} - \log\{g(\boldsymbol{z})\}$$

Bithell J.F. (1990). An application of density estimation to geographical epidemiology. *Statistics in Medicine* **9**:691–701.

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Kernel Estimation

- Straightforward approach to estimation of r is to replacing unknown densities by kernel estimates thereof:

$$\hat{r}(\boldsymbol{z}) = \frac{\hat{f}(\boldsymbol{z})}{\hat{g}(\boldsymbol{z})} \qquad \boldsymbol{z} \in \mathcal{R}$$

- **Kernel density estimate** constructed from bivariate data $\boldsymbol{x}_1, \ldots, \boldsymbol{x}_n$:

$$\hat{f}(\boldsymbol{z}) = n^{-1} \sum_{i=1}^{n} K_h(\boldsymbol{z} - \boldsymbol{x}_i)$$

  - $K_h(\boldsymbol{z}) = h^{-2} K(\boldsymbol{z}/h)$, with kernel K being spherically symmetric;
  - h is the bandwidth, controlling degree of smoothing.

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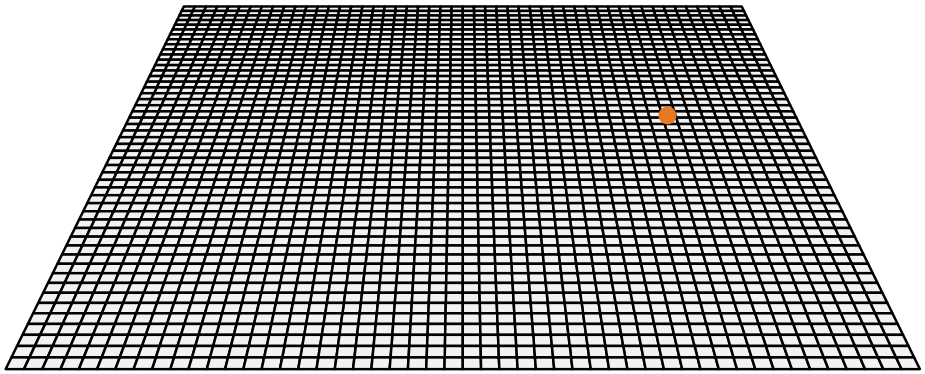
Constructing Kernel Density Estimates

An example using the gastroenteritis data



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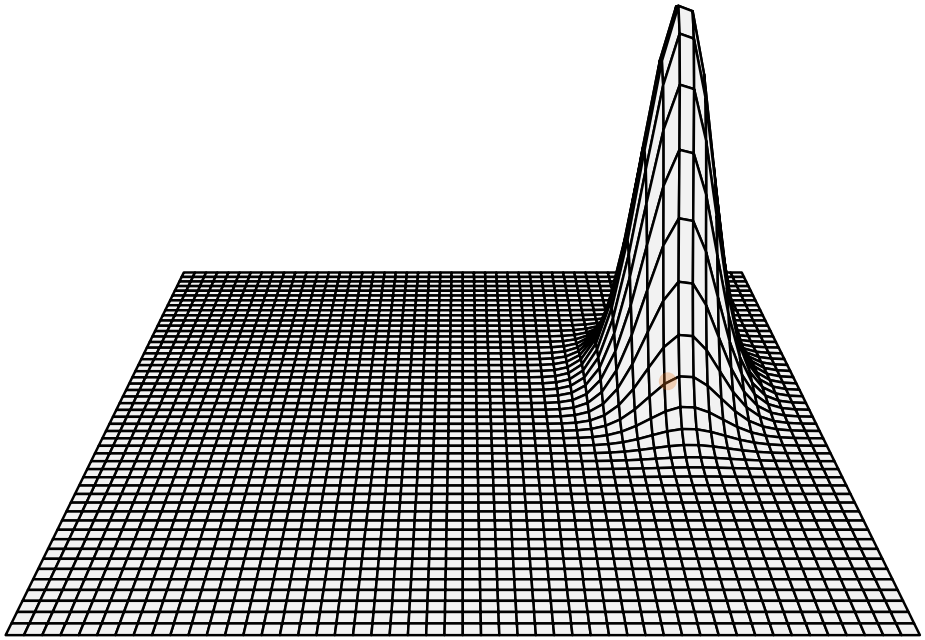

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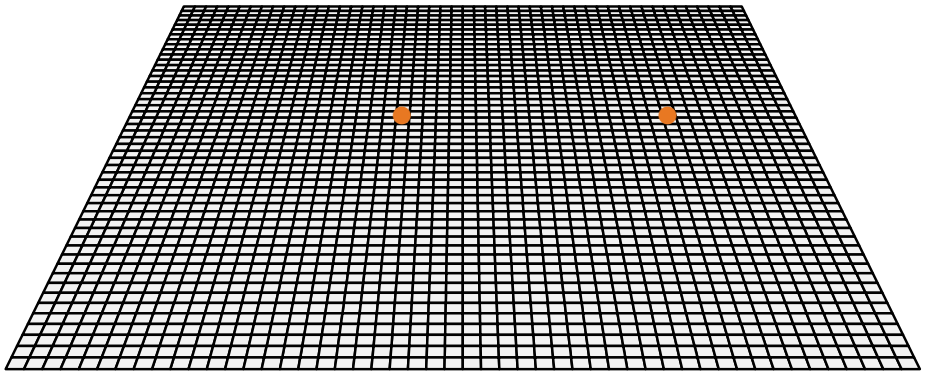

Constructing Kernel Density Estimates

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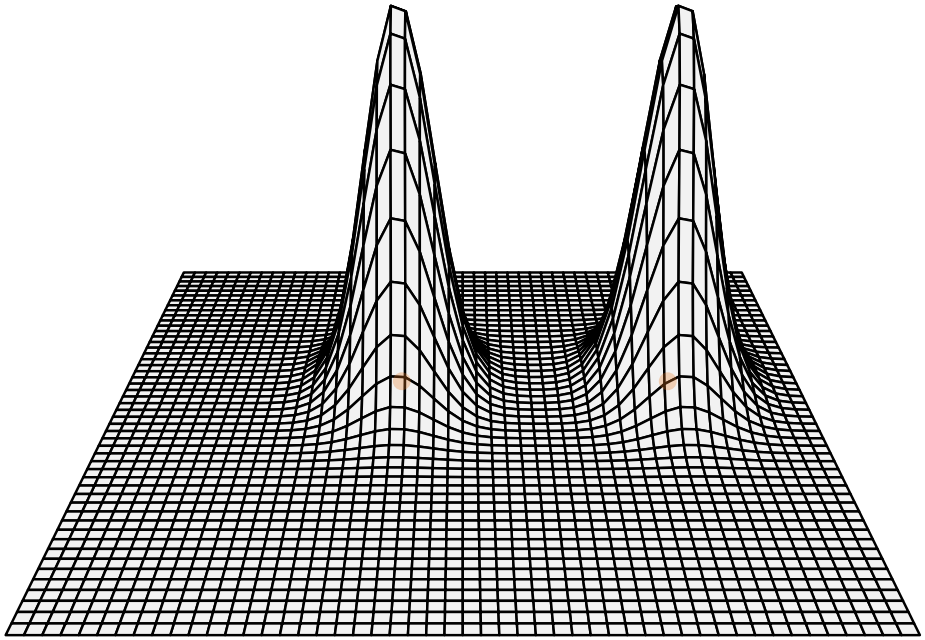

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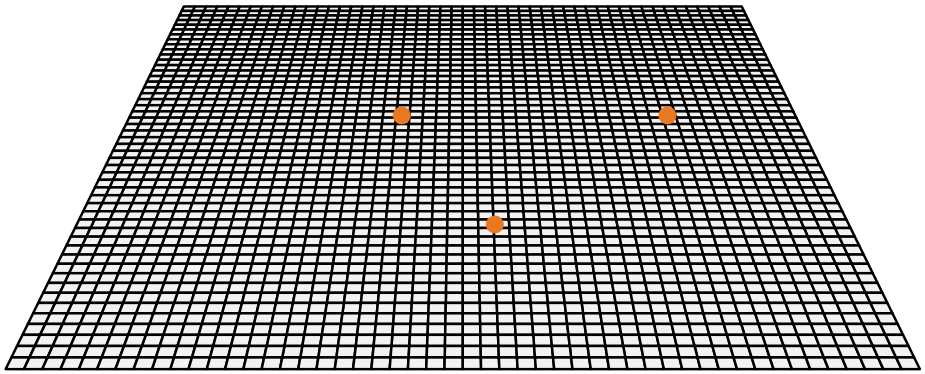

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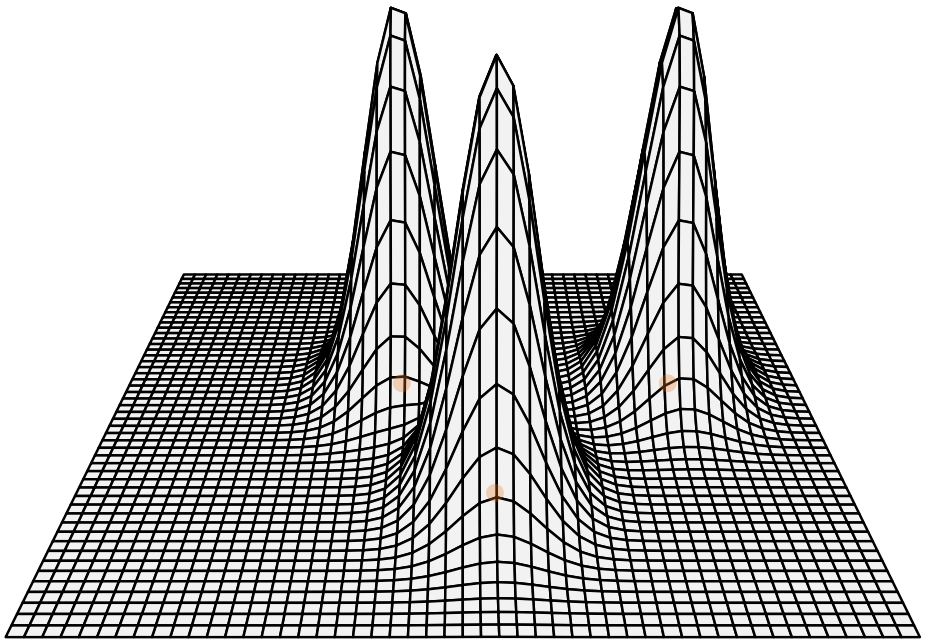

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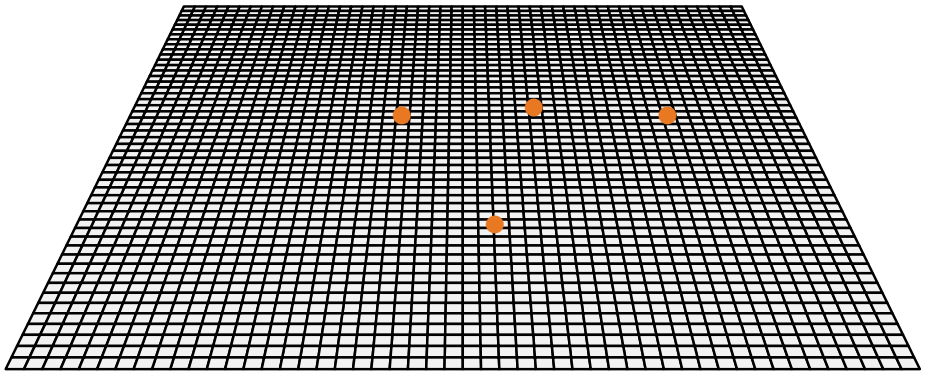

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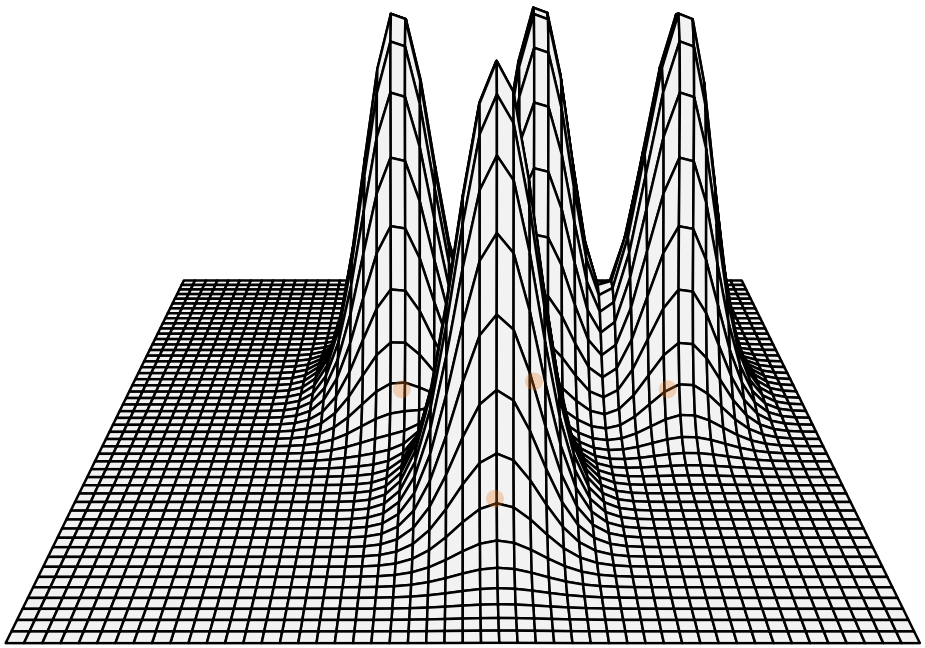

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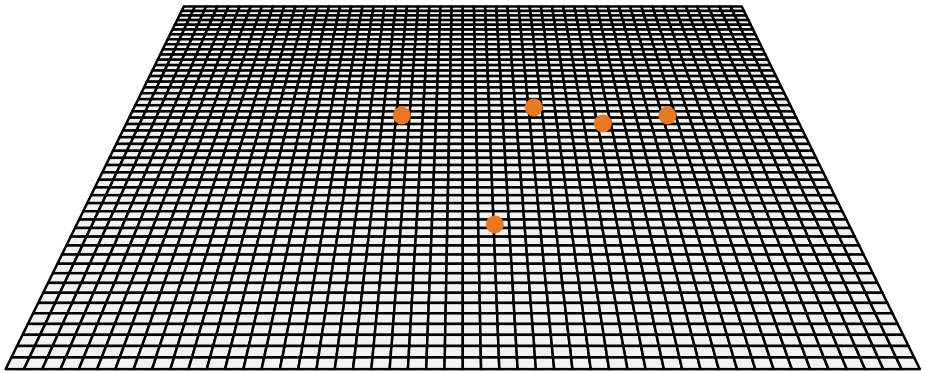

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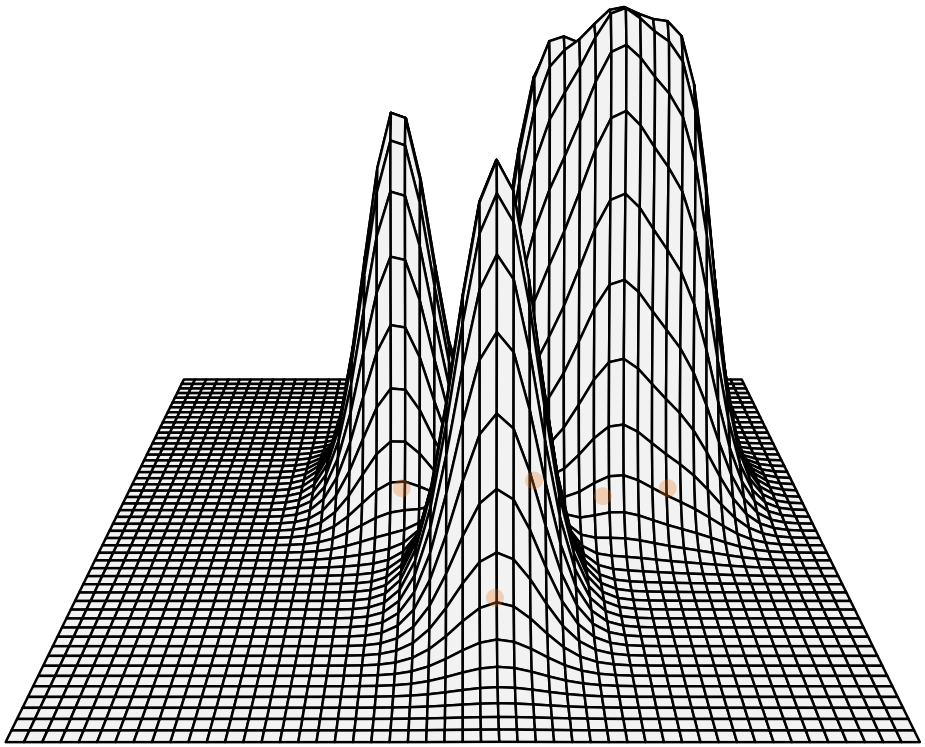

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Constructing Kernel Density Estimates

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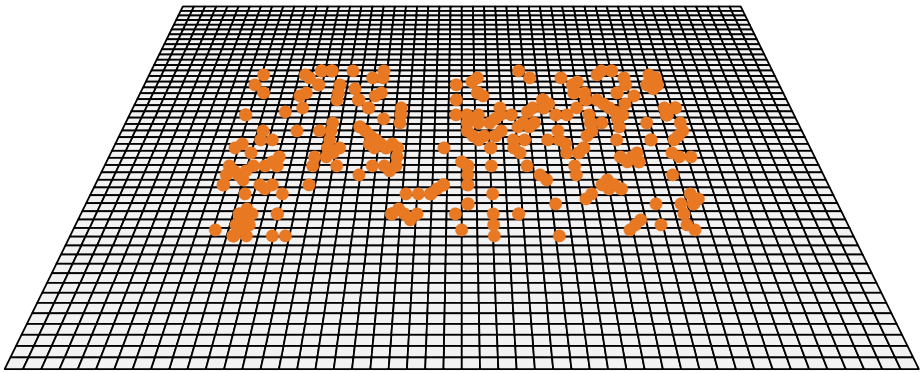

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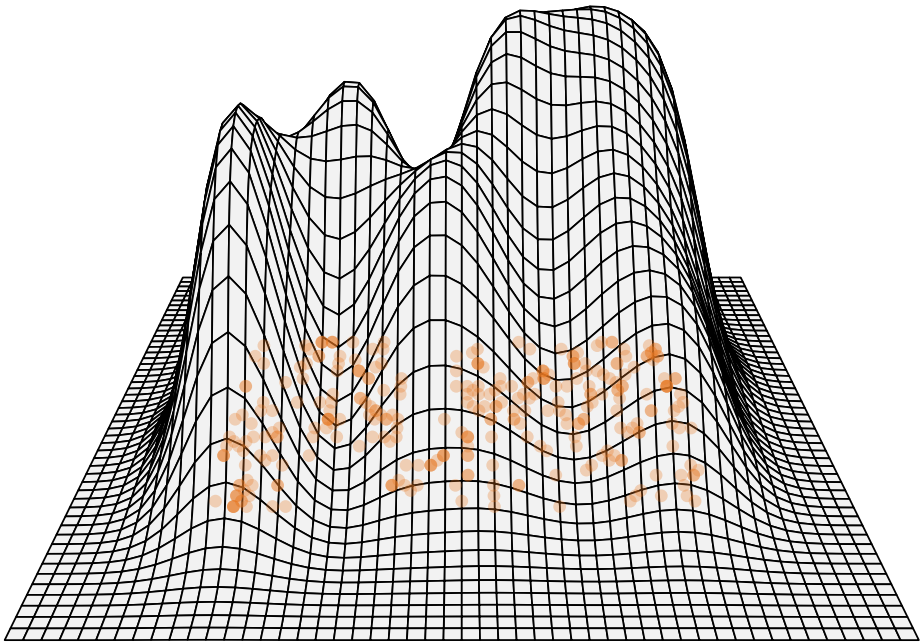
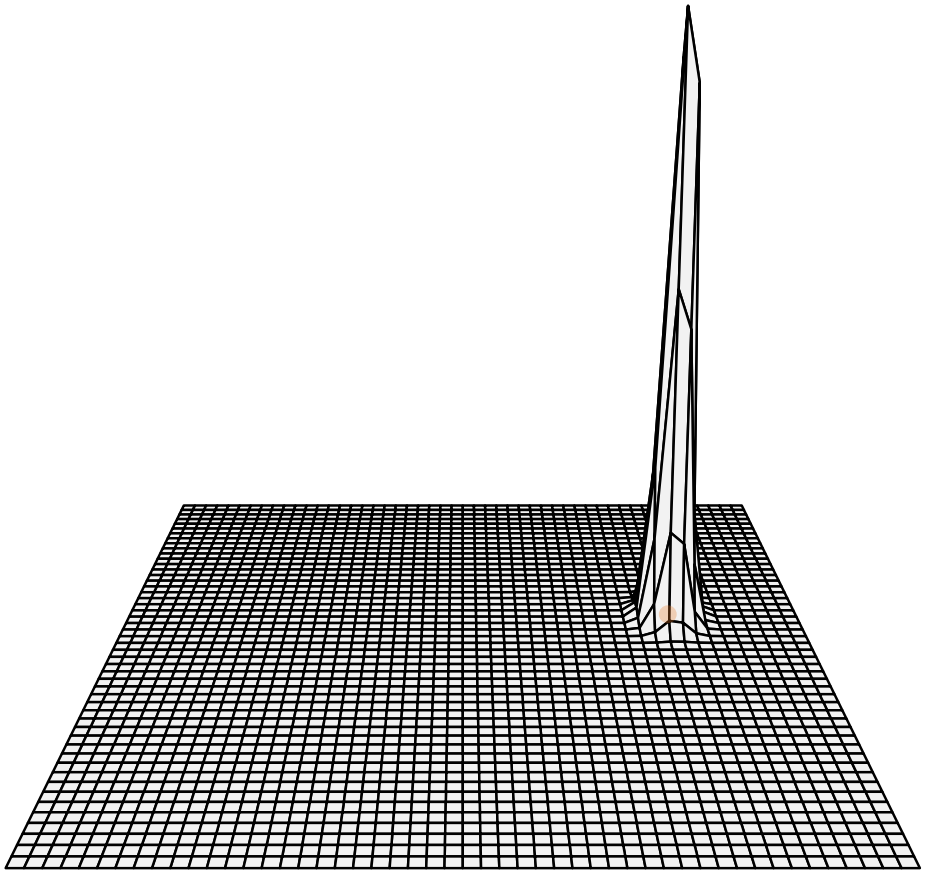


Smoothing of Kernel Density Estimates

Small bandwidth (undersmoothing)



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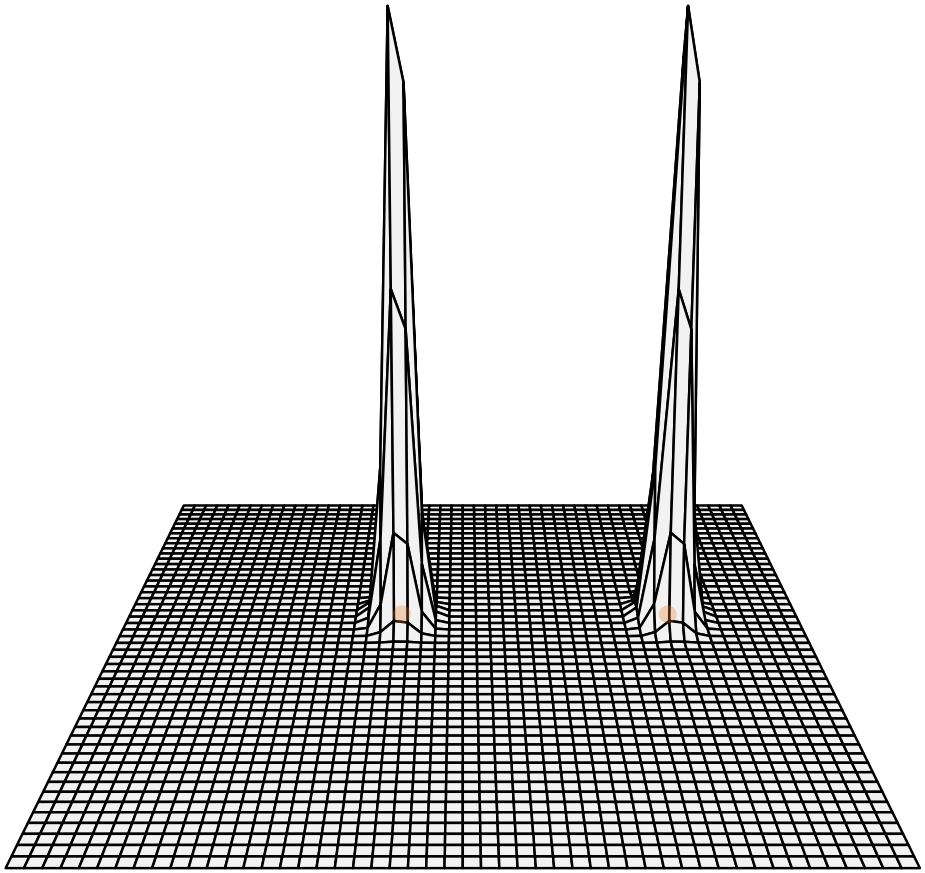

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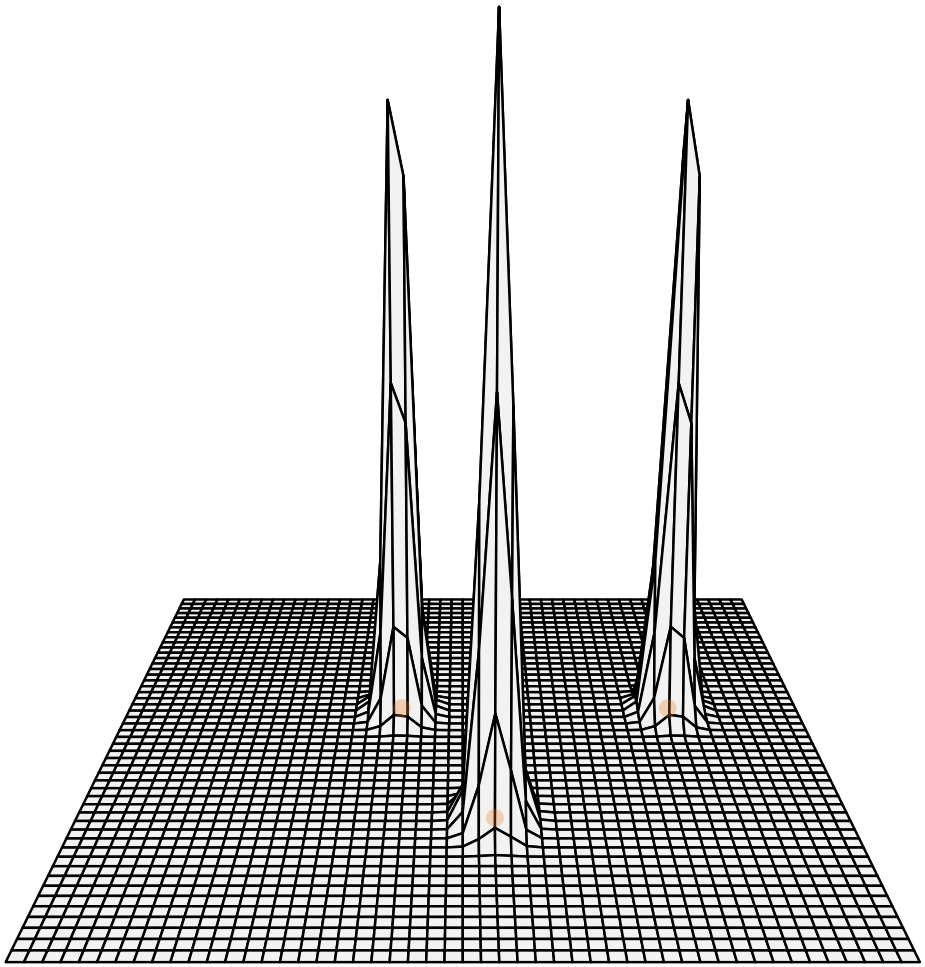

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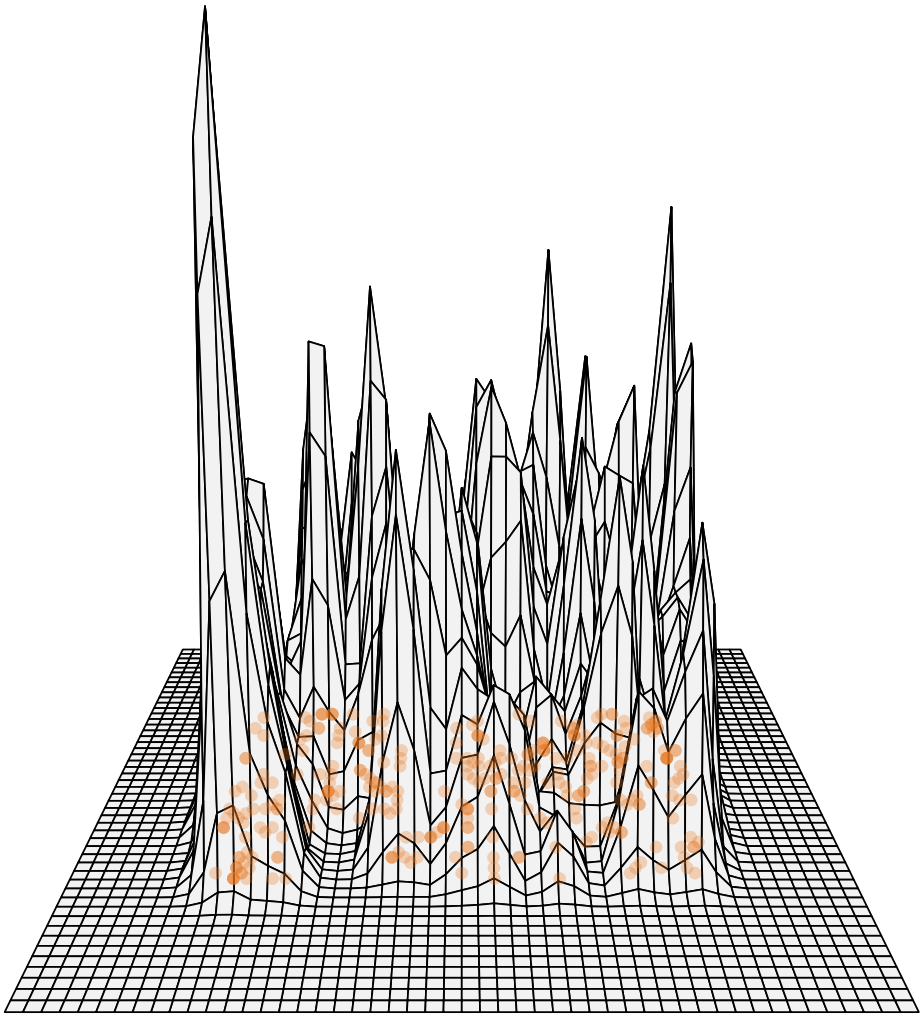

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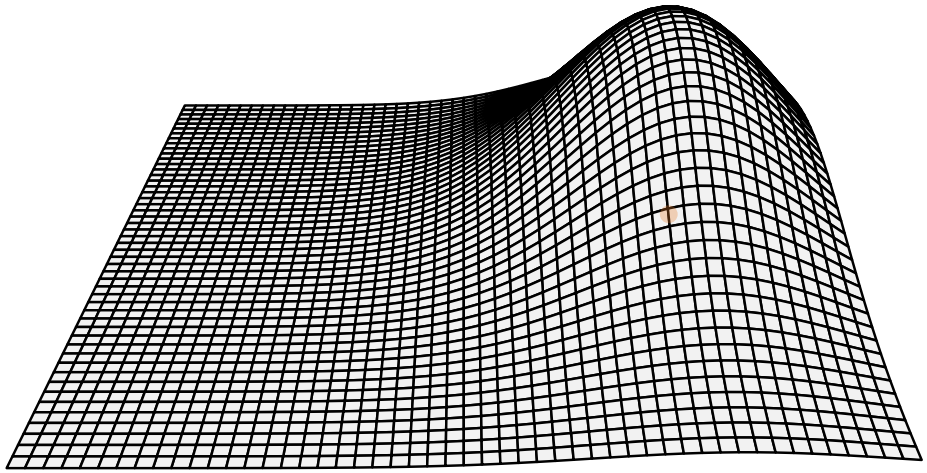

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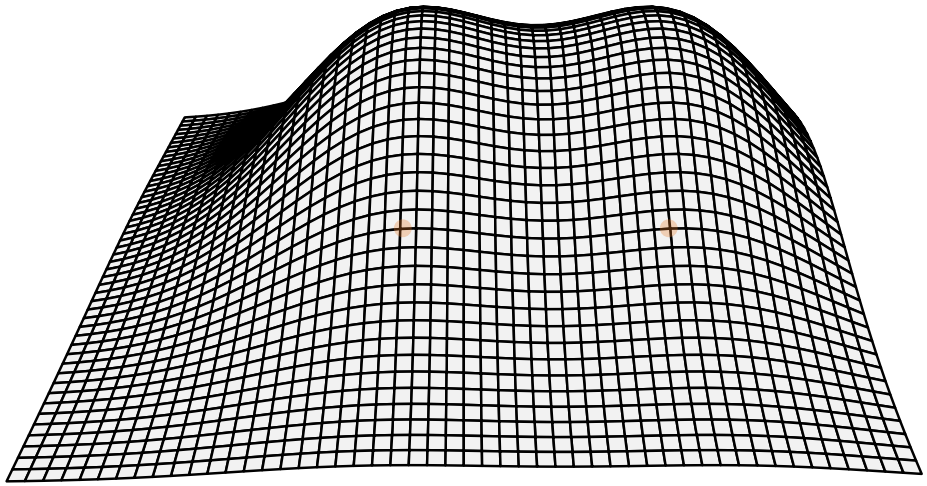

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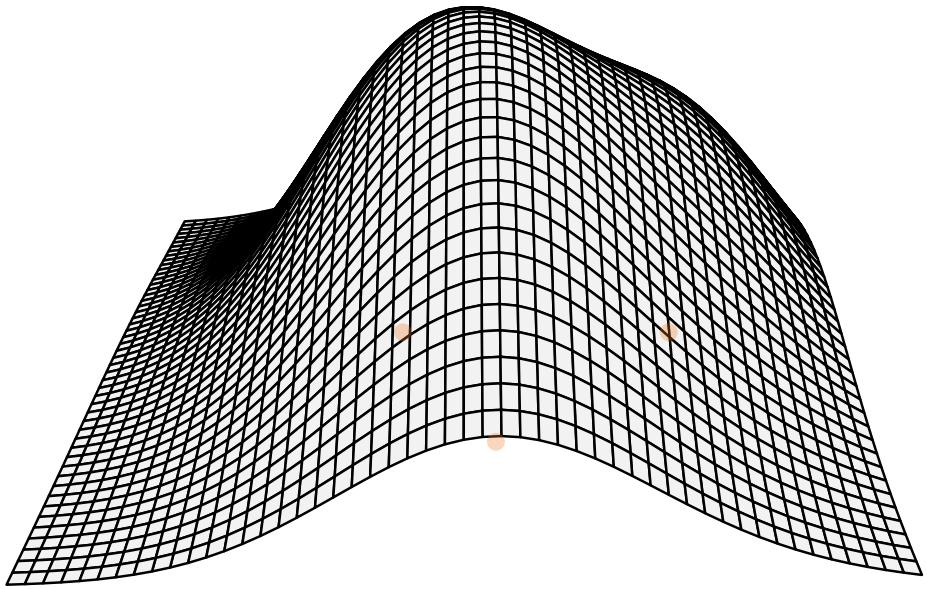

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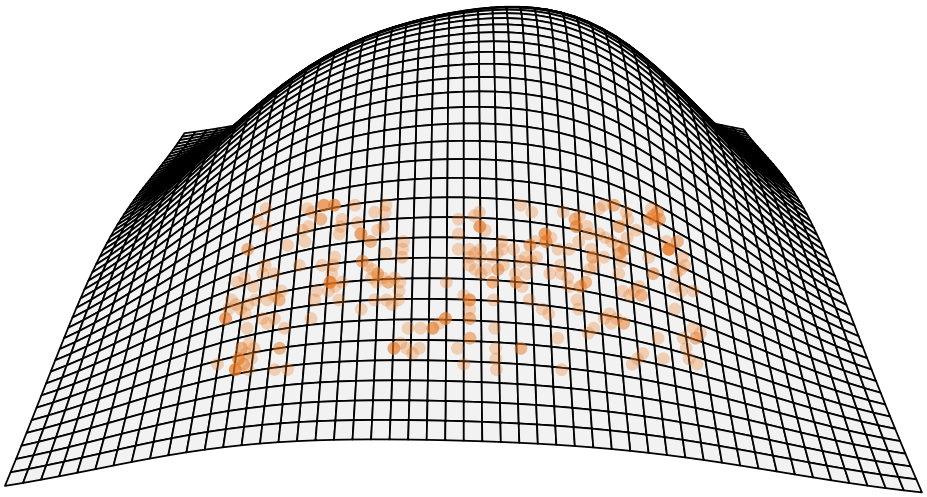

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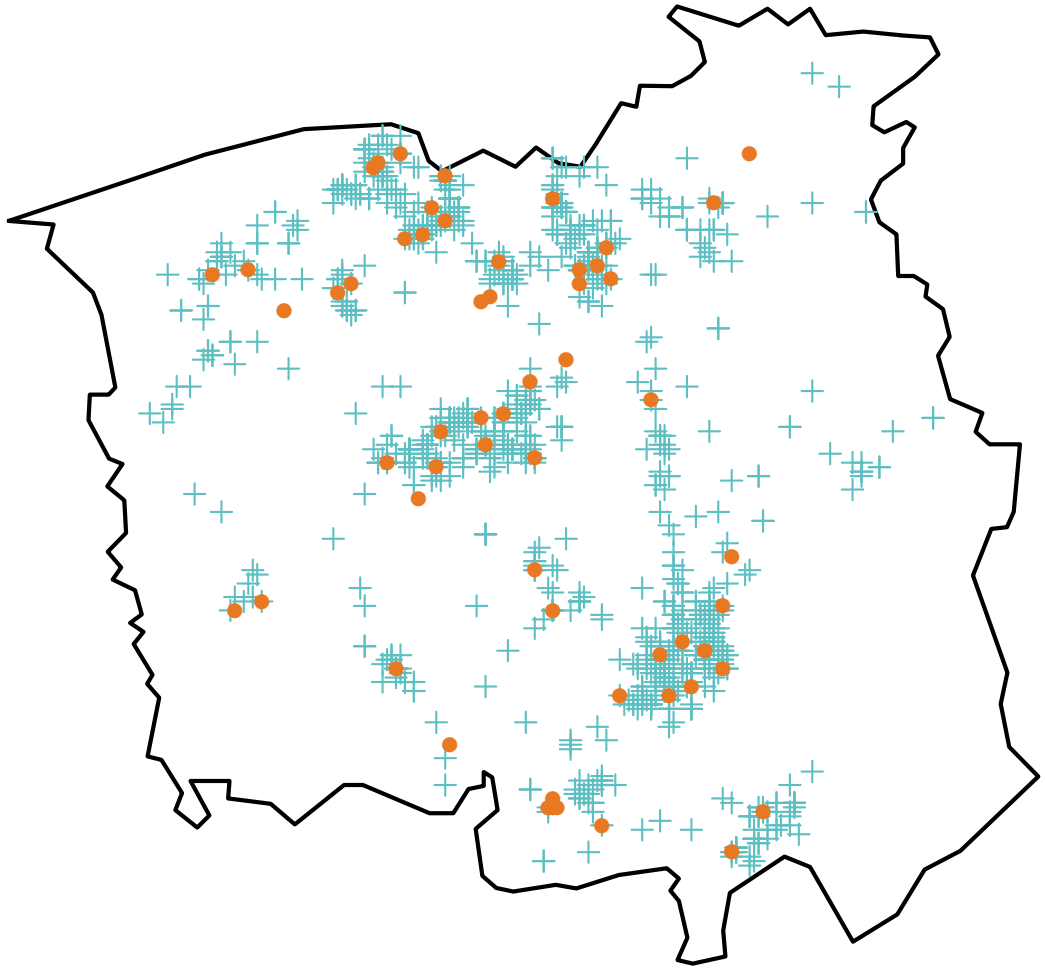
Example: Cancer of the Larynx in South Lancashire

- Data are geographical coordinates for 58 cases of cancer of the larynx, and 978 controls (cases of lung cancer).
- Data collected between 1974 and 1983 by Chorley and South Ribble Health Authority in Lancashire, England.



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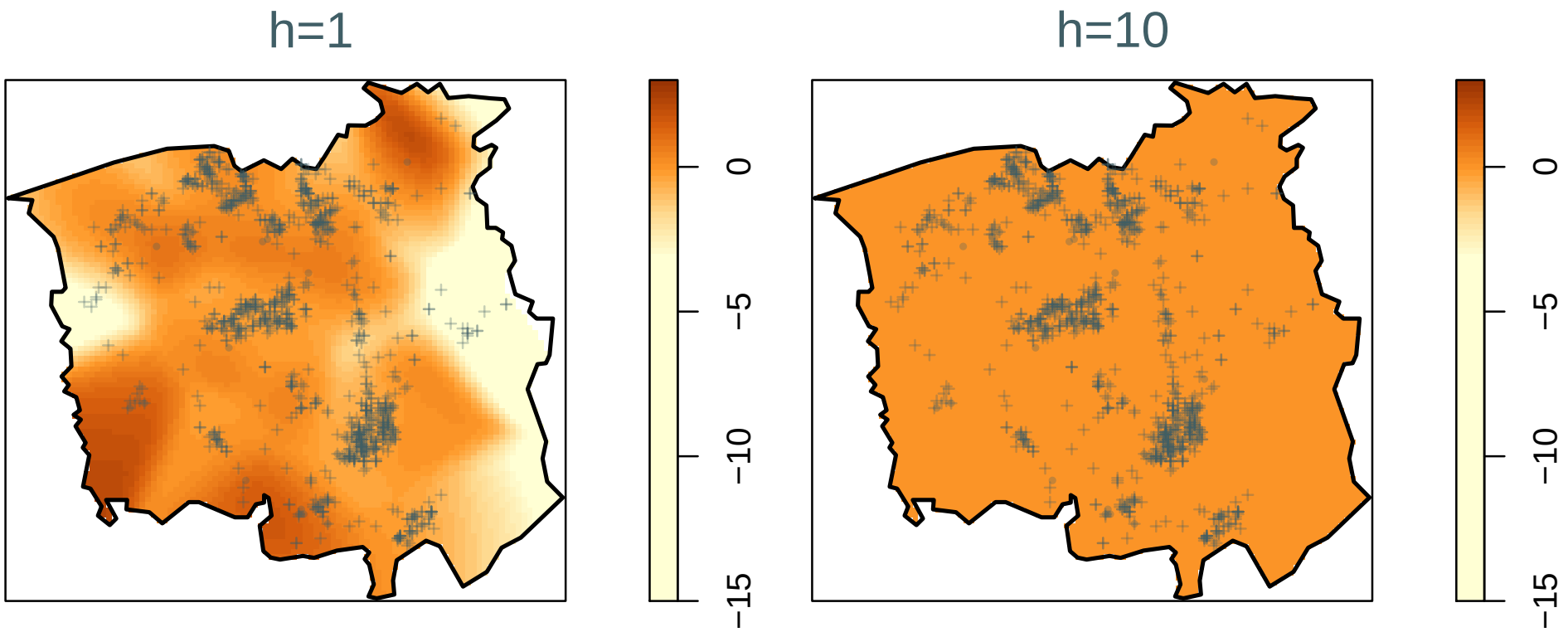
The Effect of Bandwidth Selection

For the log-relative risk function



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Research on Bandwidth Selection

- Bandwidth selection is a challenging problem for both theoretical and practical reasons.
  - Typical inhomogeneity of populations.
  - Want stable estimates of risk even where data are sparse.
  - Asymptotic theory very delicate.
- Recent progress on spatially adaptive smoothing regimens Davies & Hazelton (2010).

Davies, T.M. and Hazelton, M.L. (2010). Adaptive kernel estimation of spatial relative risk. *Statistics in Medicine* **29**, 2423–2437.

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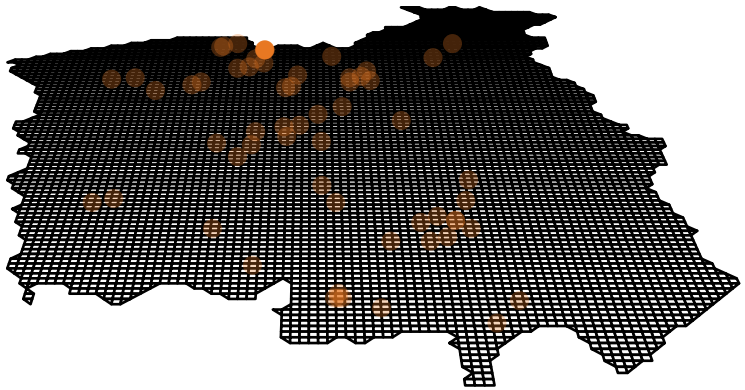
Estimation with Spatially Adaptive Bandwidths

Estimation of case density



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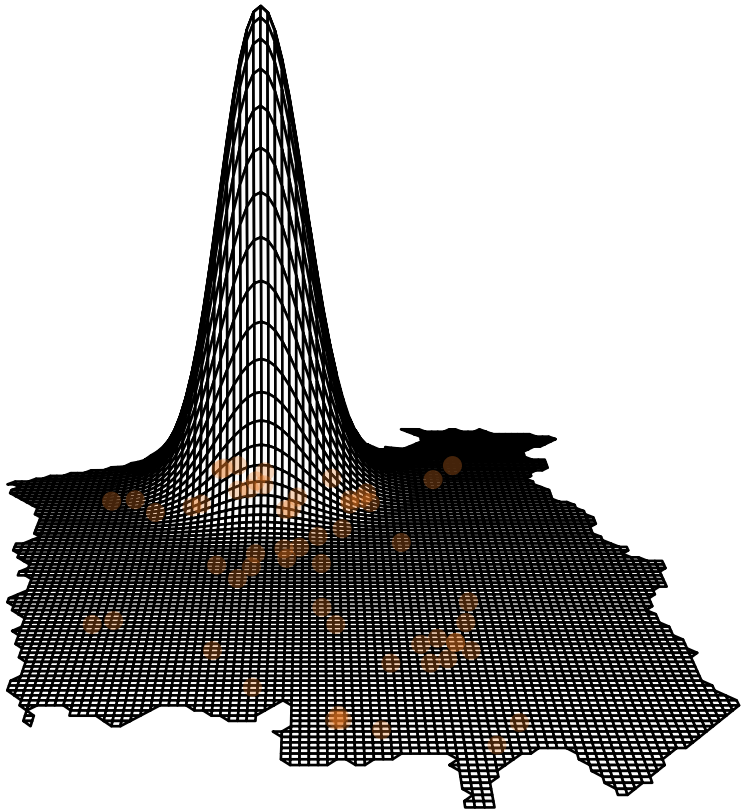

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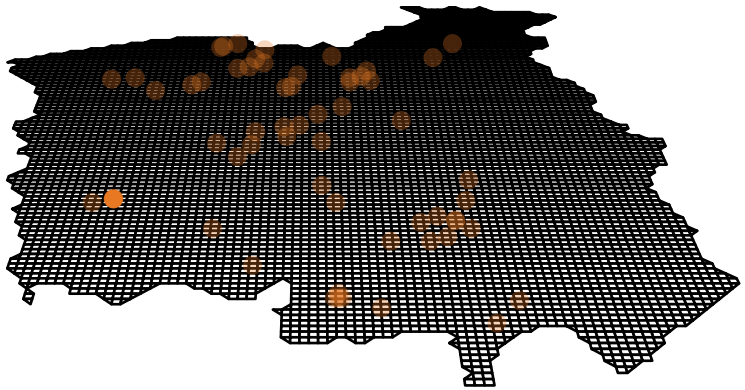

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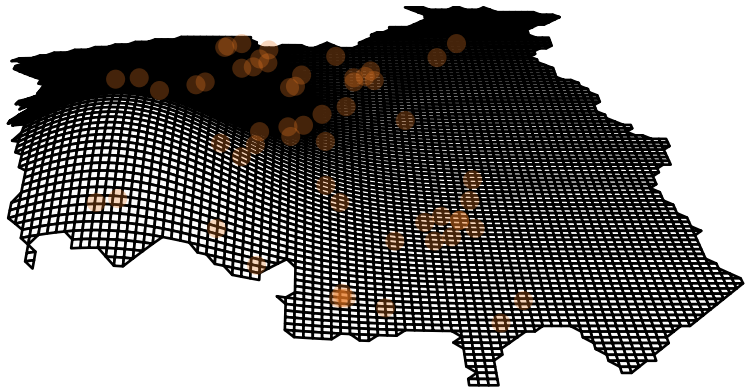

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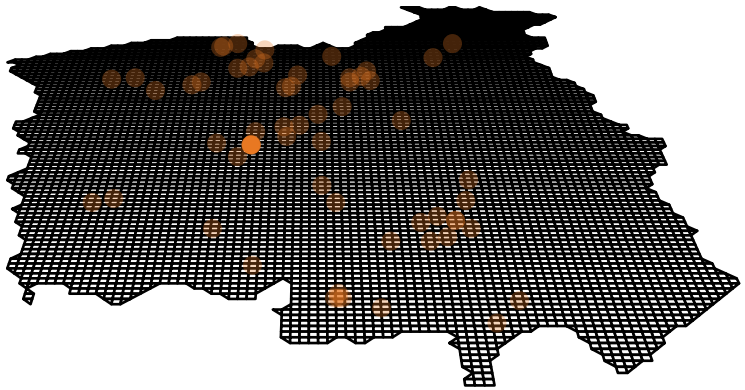

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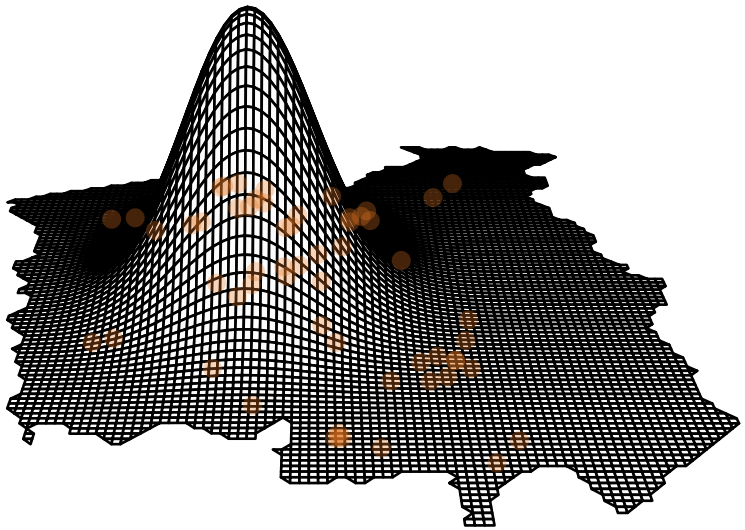

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Estimation with Spatially Adaptive Bandwidths

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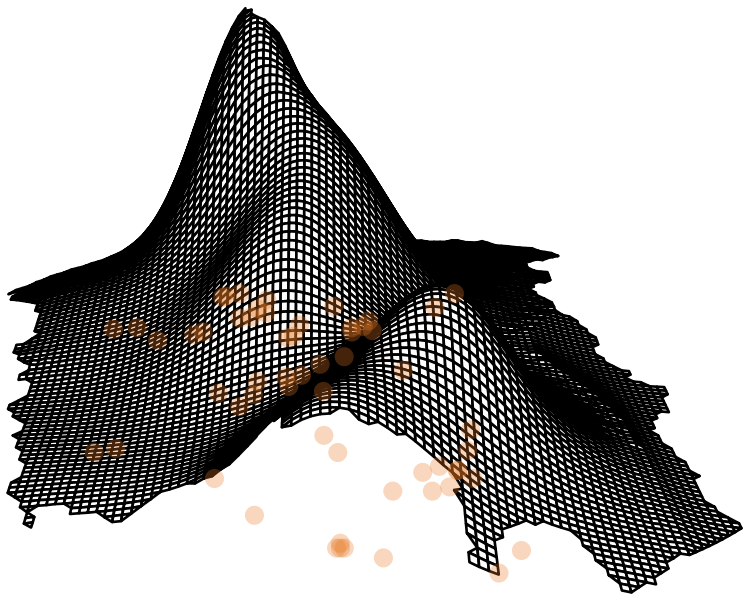

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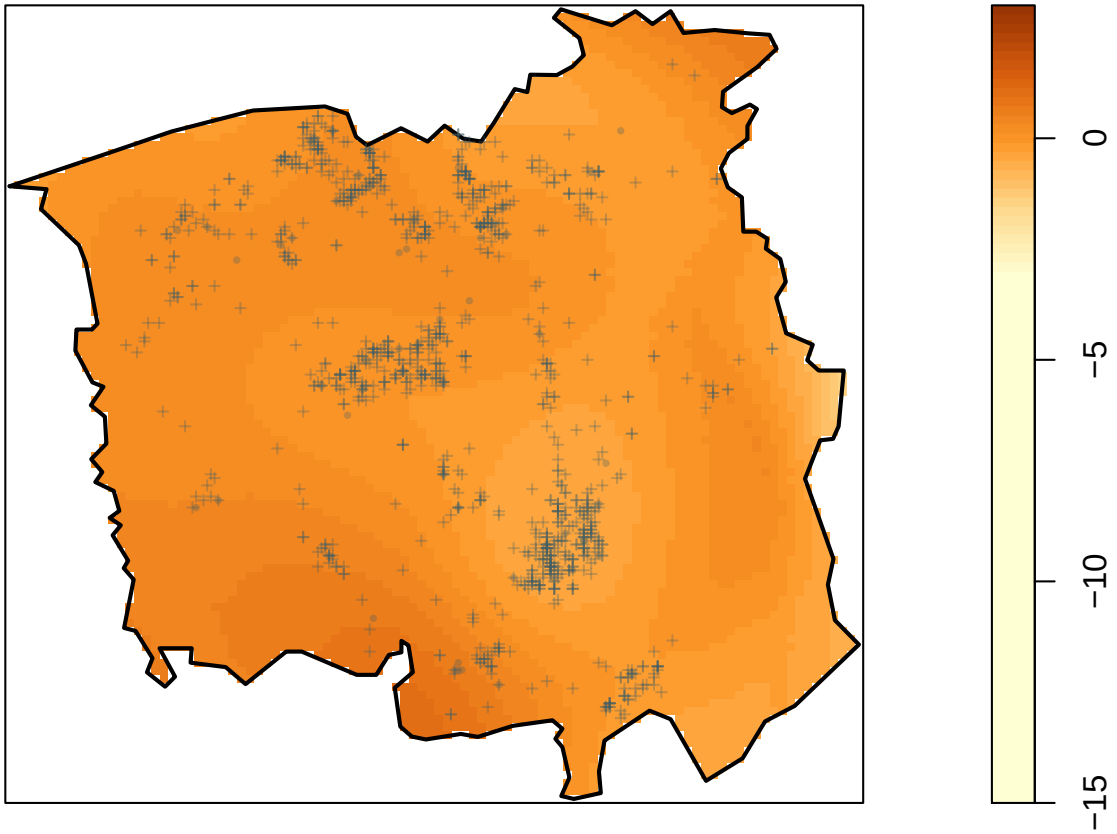
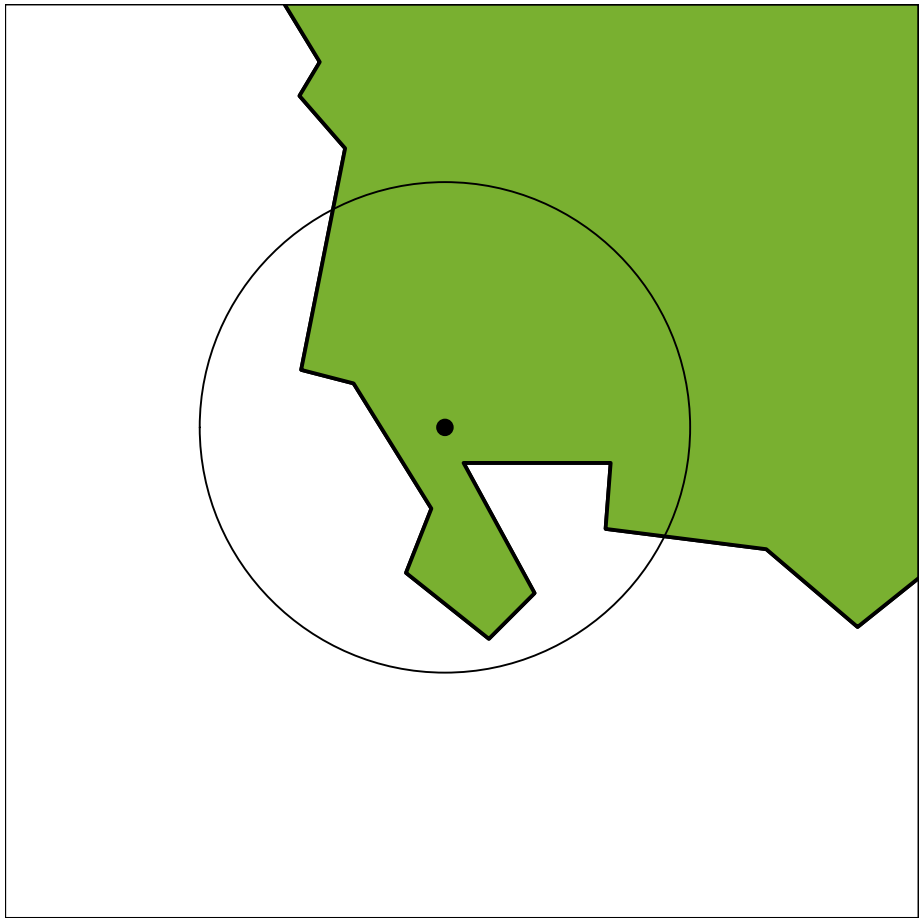
Estimation with Spatially Adaptive Bandwidths

Estimation of log-relative risk surface



Boundary Bias

- Disease data collected over finite region.
- For points near edge, some of kernel weight spills over boundary and is lost.
- Has significant impact on kernel estimates.
- Theoretical analysis is intricate.



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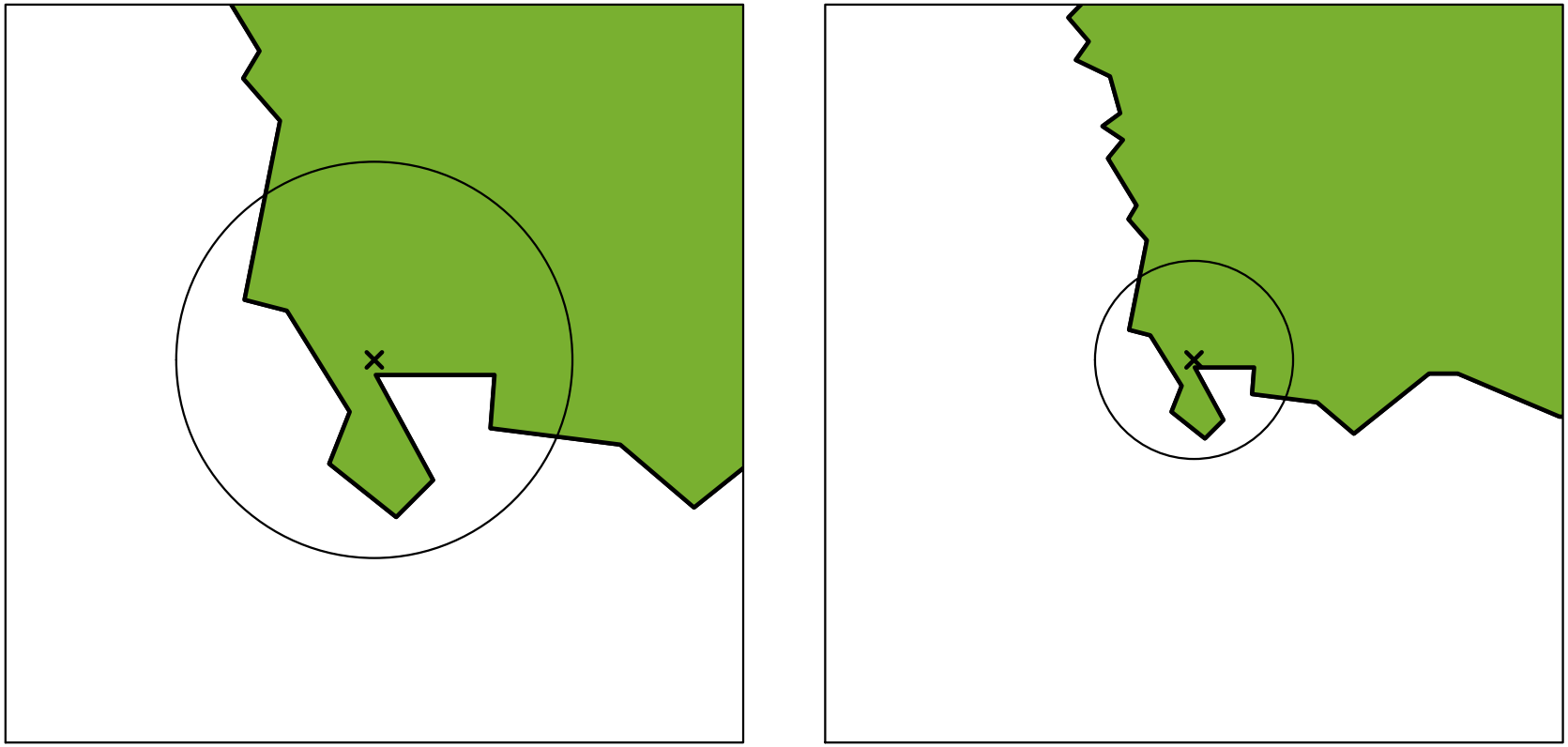
Foundations of Asymptotic Analysis of Boundary Bias



Asymptotics with Adaptive Boundary Kernel

Or ... Why Postdocs are Great

$$
\begin{aligned}
\frac{\text{bias}(\hat{f}(z))}{h_0^2} = \frac{[D^{10}f(z)]^2}{4f(z)} \Bigg[& \frac{b_0}{q}\left(a_{40}^{(20)} + 2a_{31}^{(11)} + a_{22}^{(02)} + 7a_{30}^{(10)} + 7a_{21}^{(01)} + 8a_{20}\right) \\
& + \frac{b_1}{q}\left(a_{50}^{(20)} + 2a_{41}^{(11)} + a_{32}^{(02)} + 9a_{40}^{(10)} + 9a_{31}^{(01)} + 15a_{30}\right) \\
& + \frac{b_2}{q}\left(a_{41}^{(20)} + 2a_{32}^{(12)} + a_{23}^{(02)} + 9a_{31}^{(10)} + 9a_{22}^{(01)} + 15a_{21}\right)\Bigg] \\
+ \frac{D^{10}f(z)D^{01}f(z)}{4f(z)} \Bigg[& \frac{b_0}{q}\left(2a_{31}^{(20)} + 4a_{22}^{(11)} + 2a_{13}^{(02)} + 14a_{21}^{(10)} + 14a_{12}^{(01)} + 16a_{11}\right) \\
& + \frac{b_1}{q}\left(2a_{41}^{(20)} + 4a_{22}^{(11)} + 2a_{23}^{(02)} + 18a_{31}^{(10)} + 18a_{22}^{(01)} + 30a_{21}\right) \\
& + \frac{b_2}{q}\left(2a_{32}^{(20)} + 4a_{23}^{(11)} + 2a_{14}^{(02)} + 18a_{22}^{(10)} + 18a_{13}^{(01)} + 30a_{12}\right)\Bigg] \\
+ \frac{[D^{01}f(z)]^2}{4f(z)} \Bigg[& \frac{b_0}{q}\left(a_{22}^{(20)} + 2a_{13}^{(11)} + a_{04}^{(02)} + 7a_{12}^{(10)} + 7a_{03}^{(01)} + 8a_{02}\right) \\
& + \frac{b_1}{q}\left(a_{32}^{(20)} + 2a_{23}^{(11)} + a_{14}^{(02)} + 9a_{22}^{(10)} + 9a_{13}^{(01)} + 15a_{12}\right) \\
& + \frac{b_2}{q}\left(a_{23}^{(20)} + 2a_{14}^{(11)} + a_{05}^{(02)} + 9a_{13}^{(10)} + 9a_{04}^{(01)} + 15a_{03}\right)\Bigg] \\
+ \frac{D^{20}f(z)}{4} \Bigg[& \frac{b_0}{q}\left(2a_{30}^{(10)} + 2a_{21}^{(01)} + 8a_{20}\right) + \frac{b_1}{q}\left(2a_{40}^{(10)} + 2a_{31}^{(01)} + 10a_{30}\right) \\
& + \frac{b_2}{q}\left(2a_{31}^{(10)} + 2a_{22}^{(01)} + 10a_{21}\right)\Bigg]
\end{aligned}
$$

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Computer Implementation

- Important practical problems in spatial epidemiology can quickly lead to fascinating theoretical work.
- Need to make this stuff available to users.
- Released R package `sparr`. See Davies, Hazelton & Marshall (2011).

Davies, T.M., Hazelton, M.L. and Marshall, J.C. (2011). sparr: Analyzing spatial relative risk using fixed and adaptive kernel density estimation in R. *Journal of Statistical Software* **39**, 1–14.

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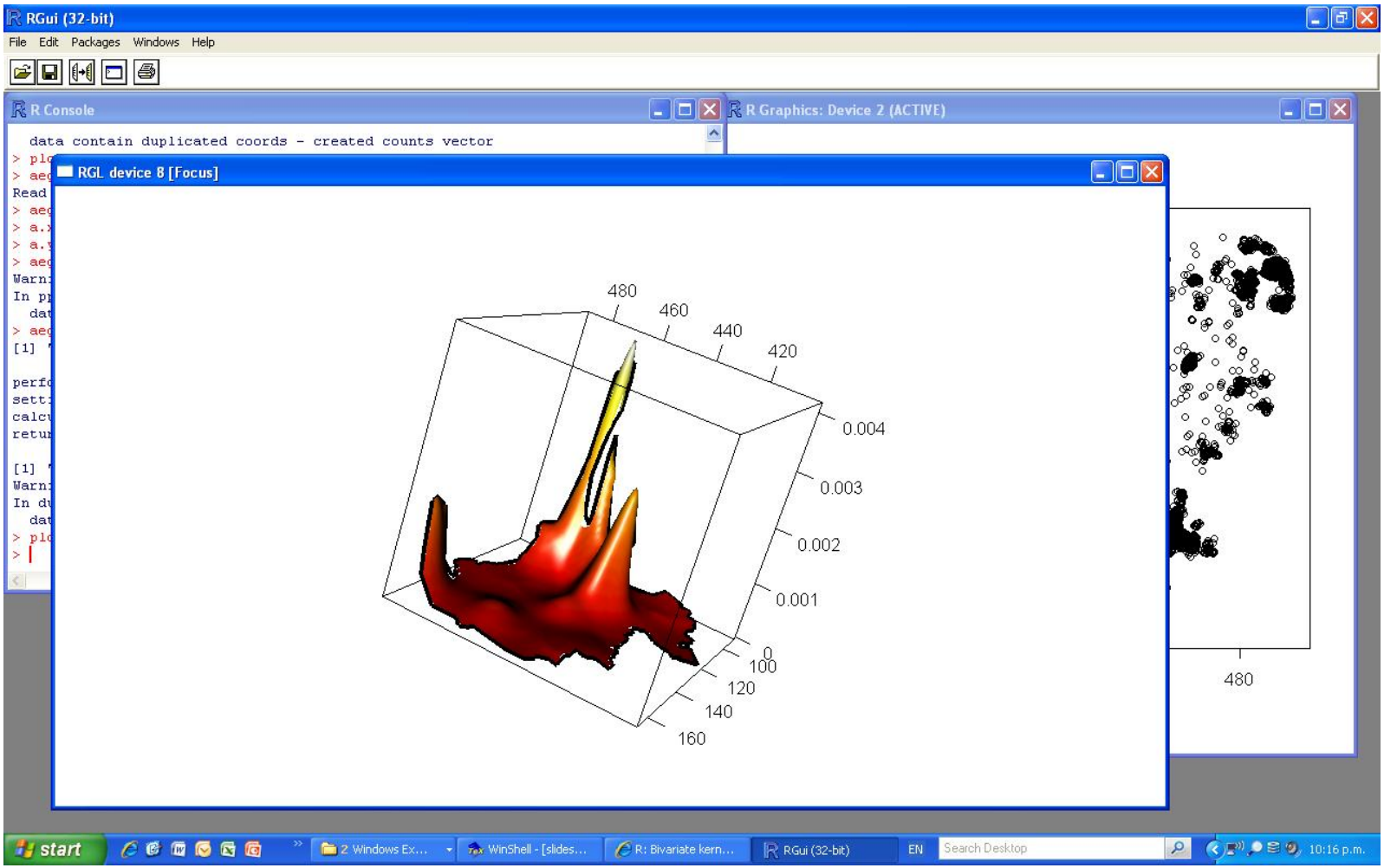
Screenshot of R Package `Sparr`



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Statistics and Bioinformatics Group Research

- Methodological research with applications to infectious disease
  - Spatial statistics
  - Markov chain Monte Carlo methods
  - Simulation based inference
  - Smoothing methods
  - Semiparametric modelling
  - Statistical software development
- Variety of applications

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Some Members of the Research Group

Postgraduate students

Sarojinie Fernando
PhD (recently submitted)

Kate Richards
PhD (year 2)

Lyndal Henden
Honours

Brigid Betz-Stablein
PhD (year 3)

Khair Jones
PhD (year 1)

Staff with interest in infectious disease applications

Prof Martin Hazelton
A/Prof Geoff Jones
Dr Chris Jewell
Dr Jonathan Marshall

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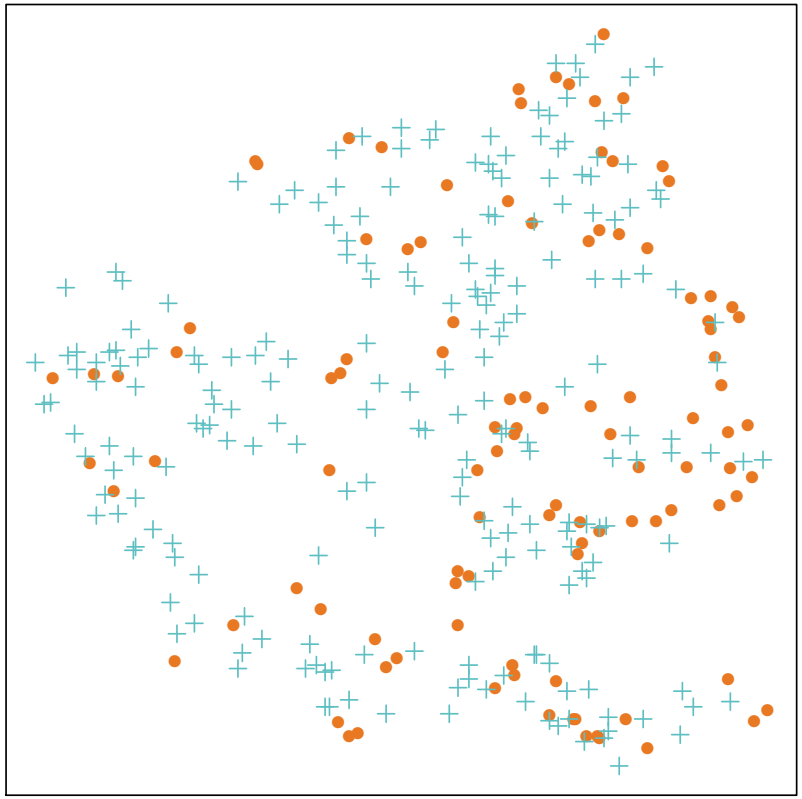
Improved Spatio-Temporal Risk Estimation



- Local linear versus density ratio estimation of relative risk.
- Application to myrtle wilt in Tasmanian myrtle beech (*Nothofagus cunninghamii*).

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Dr Jonathan Marshall

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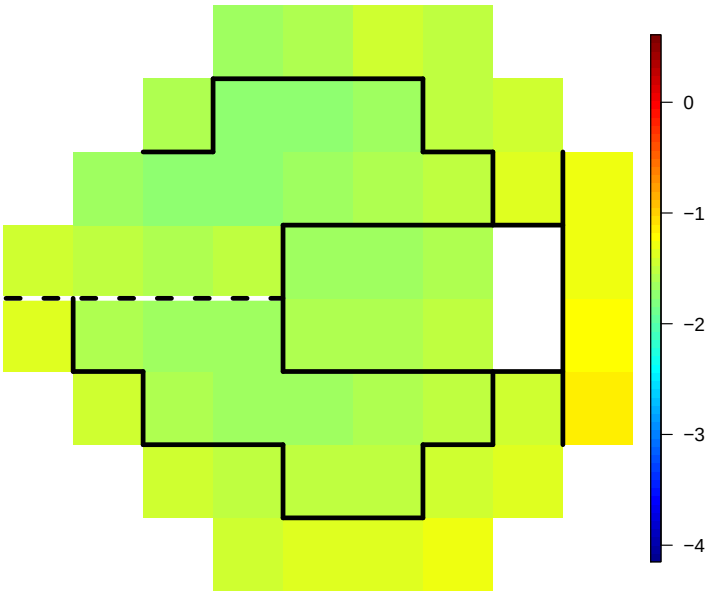
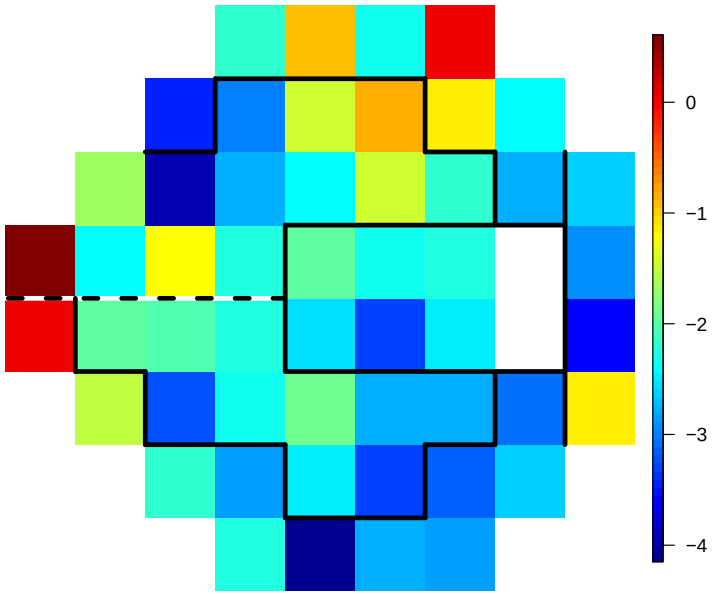
Modelling Progression of Eye Disease



(a) SPROG method



(b) PLR method

- Using ideas from geographical disease mapping to examine spatial patterns of damage over retina.
- Interpretation of visual field data must account for physiology and optics.

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Some Members of the Research Group

Postgraduate students

Sarojinie Fernando
PhD (recently submitted)

Kate Richards
PhD (year 2)

Lyndal Henden
Honours

Brigid Betz-Stablein
PhD (year 3)

Khair Jones
PhD (year 1)

Staff with interest in infectious disease applications

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A/Prof Geoff Jones
Dr Chris Jewell
Dr Jonathan Marshall

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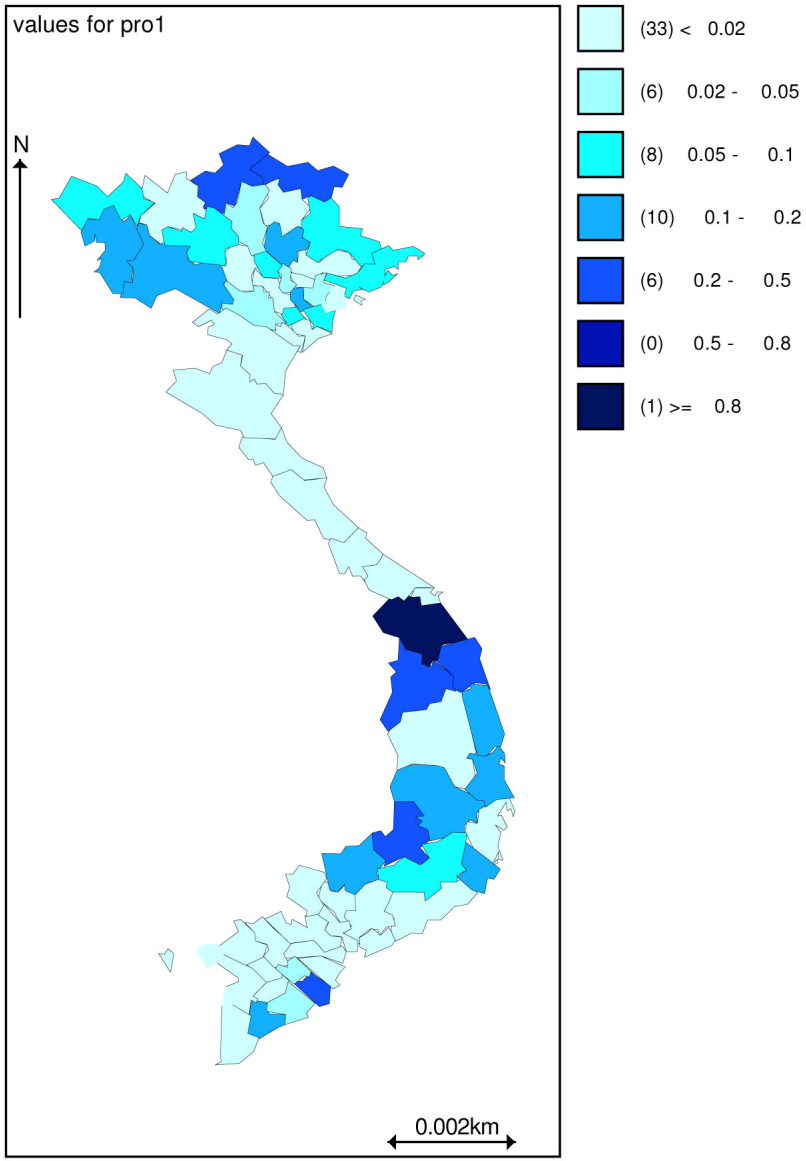
Modelling Foot and Mouth Disease in Vietnam



- Data quality issues for FMD in Vietnam.
- Appropriate level of data aggregation for modelling?
- Developing methods for identifying anomalies
  - High risk provinces.
  - Under-reporting.

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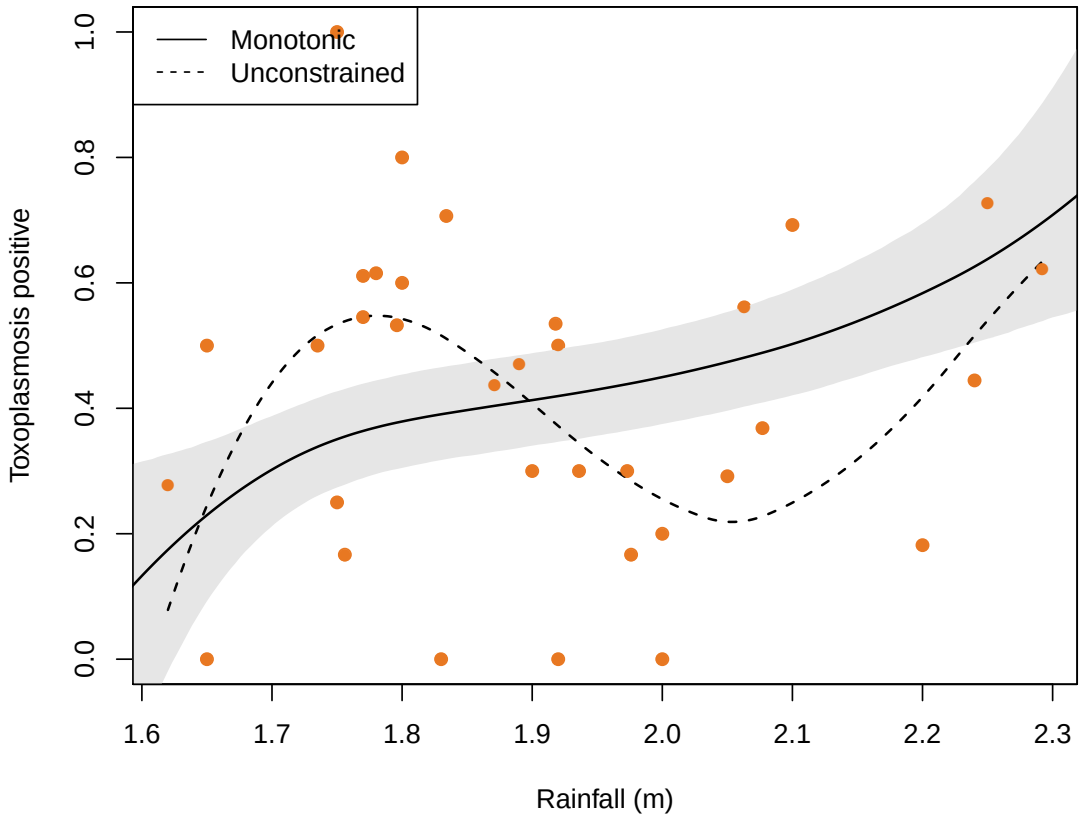
Bayesian Constrained Smoothing Problems



- In some problems want flexible smooth fit under shape constraints.
- Application to toxoplasmosis data from 34 cities in El Salvador.

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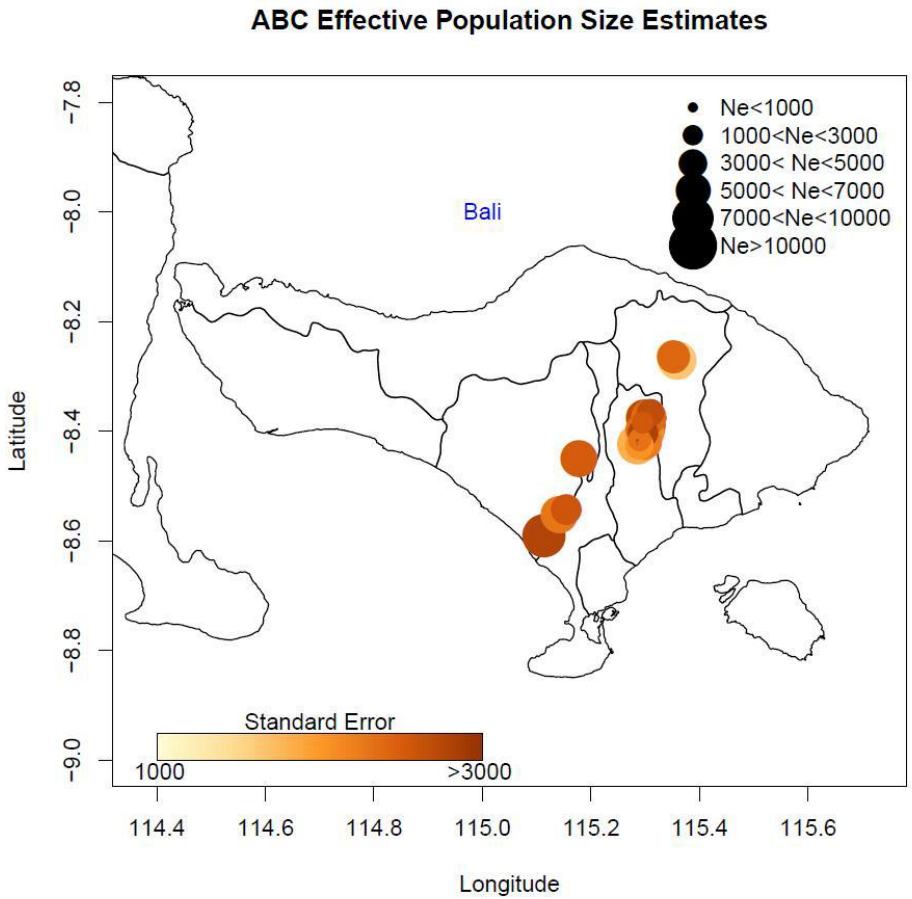
Methods of Simulation Based Inference



- Modern complex stochastic models often have intractable distribution theory.
- Standard methods of inference infeasible.
- We are working on improving simulation based approaches (e.g. ABC).
- Application is estimation of effective population sizes in Bali using coalescent model.

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TO BE CONTINUED...