

Automated and Early Detection of Disease Outbreaks

AEDDO

Master Thesis



Automated and Early Detection of Disease Outbreaks
AEDDO

Master Thesis
August, 2023

By
Kasper Schou Telkamp

Copyright: Reproduction of this publication in whole or in part must include the customary bibliographic citation, including author attribution, report title, etc.

Cover photo: Vibeke Hempler, 2012

Published by: DTU, Department of Applied Mathematics and Computer Science,
Richard Petersens Plads, Building 324, 2800 Kgs. Lyngby Denmark
www.compute.dtu.dk

ISSN: [0000-0000] (electronic version)

ISBN: [000-00-0000-000-0] (electronic version)

ISSN: [0000-0000] (printed version)

ISBN: [000-00-0000-000-0] (printed version)

Approval

This thesis has been prepared over six months at the Section for Dynamical Systems, Department of Applied Mathematics and Computer Science, at the Technical University of Denmark, DTU, in collaboration with Epidemiologisk Forskning / Modelgruppen at Statens Serum Institut, SSI, in partial fulfilment for the degree Master of Science in Engineering, MSc Eng., Quantitative Biology and Disease Modelling.

It is assumed that the reader has a basic knowledge in the areas of statistics.

Kasper Schou Telkamp - s170397

.....
Signature

.....
Date

Abstract

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

Acknowledgements

Lasse Engbo Christiansen, Senior Researcher, Statens Serum Institut

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

Jan Kloppenborg Møller, Associate Professor, Technical University of Denmark

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

Notation

All vectors are column vectors. Vectors and matrices are emphasized using a bold font. Lowercase letters are used for vectors and uppercase letters are used for matrices. Transposing is denoted with the upper index T . Random variables are always written using uppercase letters. Thus, it is not possible to distinguish between a multivariate random variable and a matrix. However, variables and random variables are assigned to letters from the last part of the alphabet (X, Y, Z, U, V, \dots), while constants are assigned to letters from the first part of the alphabet (A, B, C, D, \dots). From the context it should be possible to distinguish between a matrix and a random vector.

Contents

Preface	ii
Abstract	iii
Acknowledgements	iv
Notation	v
1 Introduction	1
2 Literature	3
3 Dataset	5
3.1 Case studies	5
4 Methods	9
4.1 Novel outbreak detection algorithm	9
4.2 General mixed effects models	9
4.3 Hierarchical generalized linear models	11
4.4 Implementation in R using TMB	15
5 Results	17
5.1 Case studies	17
5.2 Simulation study	17
6 Discussion	19
7 Conclusion	21
Bibliography	23
A Some probability functions	25
A.1 The Poisson distribution model	25
A.2 The Gamma distribution model	25
A.3 The Negative Binomial distribution model	25
A.4 The Normal distribution model	26
B Proofs	27
B.1 Hierarchical Poisson Gamma model	27

1 Introduction

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

All the methods are open-source and can be found at <https://github.com/telkamp7/AEDDO>

2 Literature

In recent years, there has been a notable increase in the interest surrounding statistical methods for automated and early detection of infectious disease outbreaks. These methodologies encompass a wide range of statistical techniques, including regression analysis, time series methodology, methods inspired by statistical process control, approaches incorporating spatial information, and multivariate outbreak detection. A comprehensive review of these methods can be found in Buckeridge (2007) and Unkel et al. (2012).

In addition to the aforementioned studies, state-of-the-art methods for aberration detection are presented in Salmon, Schumacher, and Höhle (2016). These methods have been implemented in the R package called **surveillance**, which can be accessed from the Comprehensive R Archive Network (CRAN) at <https://cran.r-project.org/web/packages/surveillance/index.html>. The **surveillance** package provides various techniques for detecting aberrations in disease surveillance data, including the Farrington method initially introduced by Farrington et al. (1996) and subsequent improvements proposed by Noufaily et al. (2013). These methods offer advanced statistical tools for detecting and monitoring disease outbreaks and are currently *the* method choice at European public health institutes (Hulth et al. 2010).

Therefore, in this master's thesis, these established methods will be compared to a novel outbreak detection algorithm based on generalized mixed effects models and hierarchical generalized linear models respectively. The thesis introduces this new algorithm as an innovative approach to outbreak detection and aims to assess its performance in comparison to existing methods.

3 Dataset

In Denmark, the surveillance of infectious diseases is conducted by Statens Serum Institut (SSI). This surveillance system plays a pivotal role in national and international disease preparedness. It encompasses more than just the collection and registration of disease data; it also involves the prompt and ongoing dissemination of knowledge to the relevant authorities responsible for treatment, prevention, and control. This comprehensive approach ensures efficient communication and facilitates appropriate measures to address infectious diseases. The quality of the Danish surveillance registers is maintained at a high standard, thanks to The National Board of Health Statutory Order on Physicians' Notification of Infectious Diseases. This order specifies that several diseases¹ are individually notifiable by physicians and general practitioners. Notifications consist of essential patient information and are submitted in paper form to both the Ministry of Health and to SSI. This rigorous notification process ensures accurate and comprehensive data collection for disease surveillance purposes in Denmark.

In addition to the individually notifiable diseases, SSI has implemented a laboratory notification system for numerous microorganisms. Clinical-microbiological laboratories are obligated to report the identification of specific microorganisms, along with relevant patient information. The national surveillance system focuses on diseases of a severe nature, those that are highly contagious, and the majority of vaccine-preventable diseases. This comprehensive approach allows for effective monitoring and control of infectious diseases in Denmark.

3.1 Case studies

For the scope of this master's thesis, only a specific subset of diseases from the mandatory notification system will be considered. This subset consists of *Listeriosis*, *Shigellosis*, Shiga toxin (verotoxin)-producing *Escherichia coli* (STEC), and *Salmonellosis*. These diseases have been chosen for analysis and investigation based on various factors, such as seasonality, incidence, and severity. Additionally, these diseases have been associated with documented outbreaks observed by SSI (<https://www.ssi.dk/sygdomme-beredskab-og-forskning/sygdomsudbrud/arkiv>) in the past decade, which adds to their relevance for the study.

¹For a full list of diseases see https://www.ssi.dk/sygdomme-beredskab-og-forskning/anmeldelse-af-sygdomme/lovpligtige-meldesystemer/individ_anmeldelses_sygdomme

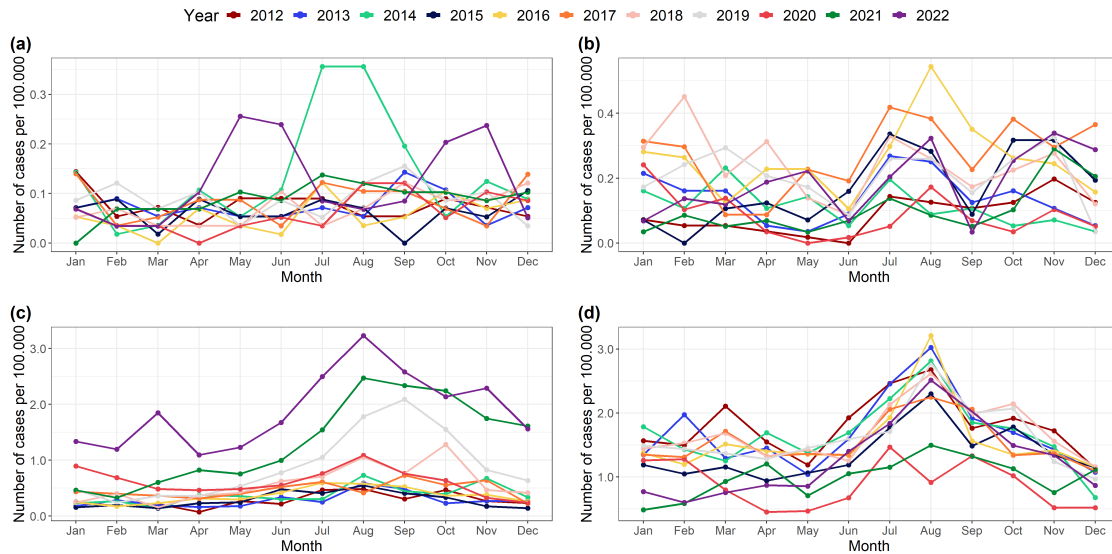


Figure 3.1: Epidemic curve showing the incidence per 100,000 in Denmark, 2012-2022, for the subset of diseases considered in this master thesis. (a) Listeriosis, (b) Shigellosis, (c) STEC, and (d) Salmonellosis.

All the diseases within the selected subset pose a significant risk of infection and can vary in terms of severity for affected individuals. Therefore, early identification of disease outbreaks is of utmost importance in order to promptly implement necessary interventions. Timely detection allows for swift and targeted actions to control the spread of these diseases and mitigate their impact on public health.

3.1.1 Listeriosis

Listeriosis is a foodborne illness that is caused by consuming food contaminated with *Listeria monocytogenes*. This disease primarily affects pregnant women, unborn or newborn babies, the elderly, and individuals with weakened immune systems. *Listeriosis* is associated with high mortality (Goulet et al. 2012) and manifests in three ways: sepsis, meningitis, and mother-to-child transmission. Pregnancy-associated *Listeriosis* can have severe consequences for the fetus or newborn, including miscarriage, stillbirth, neonatal sepsis, and meningitis (Awofisayo et al. 2015). *Listeriosis* is uncommon among individuals in other demographic groups. The bacteria is ubiquitous in the environment, found in moist environments, soil, water, decaying vegetation, and animals. Furthermore, it can survive and even grow under refrigeration and other food preservation measures.

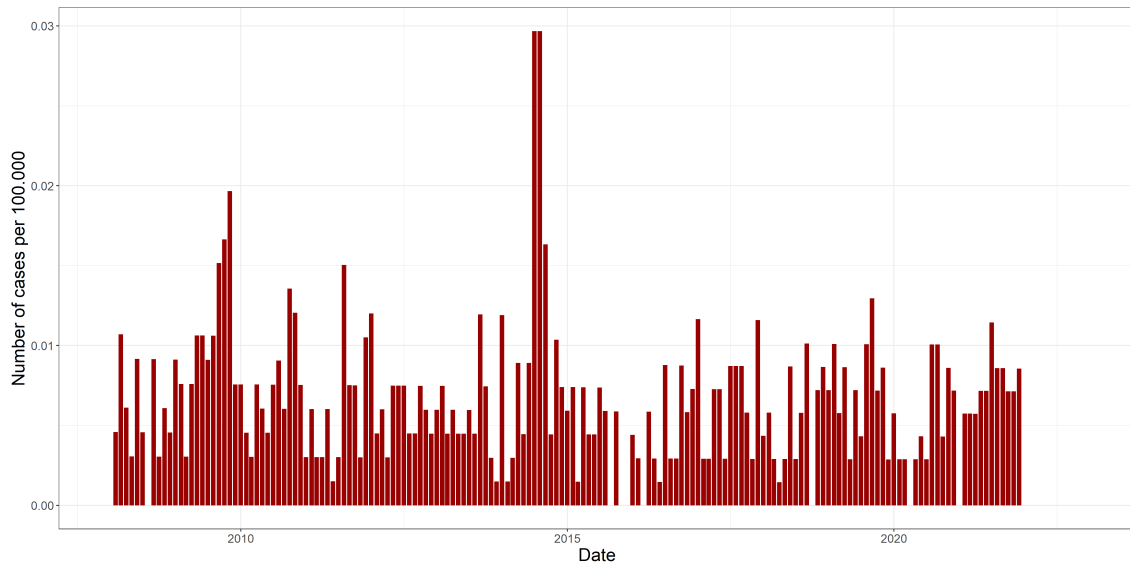


Figure 3.2: Placeholder caption

3.1.2 *Shigellosis*

Shigellosis is a diarrheal illness that is caused by a group of bacteria called *Shigella*. The bacteria are highly contagious and can be transmitted through direct person-to-person contact, consumption of contaminated food, or ingestion of water contaminated with human feces. *Shigella* infections are most commonly observed in children under the age of 5, individuals traveling to regions with poor sanitation and unsafe water and food practices, as well as gay, bisexual, and other men who have sex with men. In Denmark, another significant cause of *Shigellosis* outbreaks is the importation of contaminated vegetables. This was evident in several incidents, including a 2007 outbreak where 215 individuals fell ill after consuming imported contaminated baby corn, a smaller outbreak in 2009 linked to sugar snap peas from Kenya, and a 2020 outbreak associated with fresh mint as the source of infection².

3.1.3 Shiga toxin (verotoxin)-producing *Escherichia coli*

STEC primarily spreads through contaminated food. Less common sources of infection include contaminated drinking and bathing water, as well as direct or indirect contact with infected animals. Cattle and other ruminants are primary reservoirs for STEC serotypes that are frequently associated with human disease (Menge 2020). Therefore, in Denmark, the source of infection is often products derived from beef, non-heat-treated dairy products, or other foods such as ready-to-eat vegetables, leafy greens, vegetable sprouts, and berries contaminated with feces from cows. *Hemolytic uremic syndrome* is a severe complication that, in some cases, particularly in children, can develop following an infection with STEC.

²See EPI-NYT 35/07, EPI-NYT 36/09, and EPI-NYT 41/20 respectively

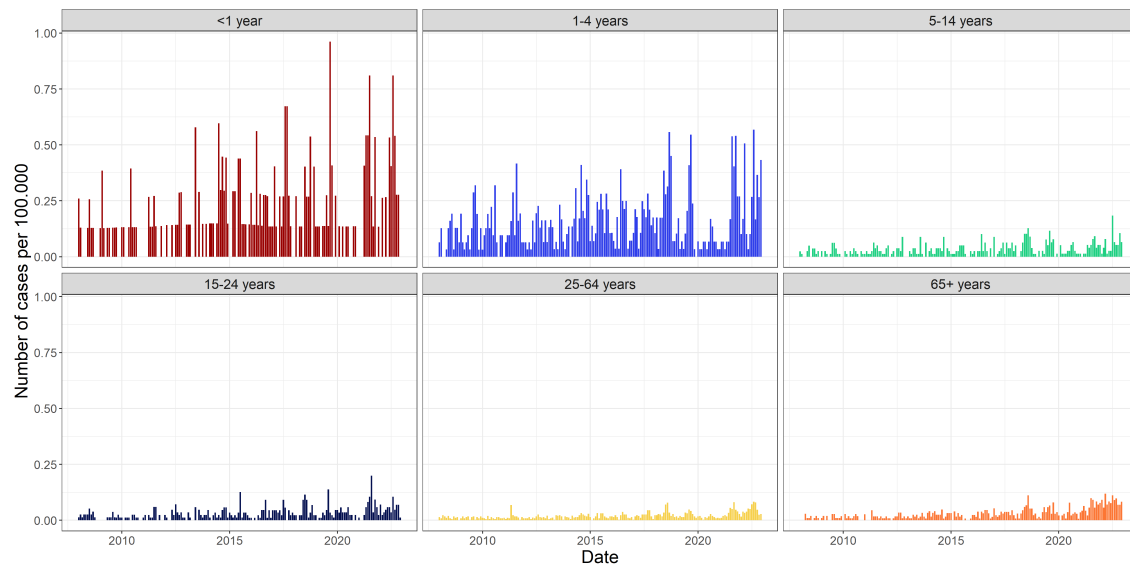


Figure 3.3: Placeholder caption

3.1.4 *Salmonellosis*

Salmonellosis is a bacterial disease that primarily affects the intestinal tracts of humans. The *Salmonella* bacteria are commonly found in the intestines of animals and humans and are excreted in feces. Human infection typically occurs through the consumption of contaminated food or water. *Salmonella* infections are often associated with the consumption of raw or undercooked meat, poultry, eggs or egg products, as well as unpasteurized milk. It is worth noting that an increasing proportion of infections in Denmark are now observed in connection with international travel, particularly since *Salmonella* has been eliminated from commercial chicken flocks in Denmark, making Danish eggs and poultry meat free from the bacteria. However, imported meat products can still pose a risk of contamination.

4 Methods

In this chapter the novel outbreak detection algorithm together with theory related to generalized mixed effects models and hierarchical generalized linear models is presented. These models are used in this master thesis to model the count observations y , but more importantly they are used to assess the unobserved random variables or random effects u , which are used directly in the detection algorithm to characterize an outbreak. In general it is impossible to obtain closed form solutions for generalized mixed effects models and hence an outline of the Laplace approximation is included in this chapter. Moreover, the implementation of aforementioned models in R is presented. The presentation of this chapter is mostly inspired by Madsen and Thyregod (2011).

4.1 Novel outbreak detection algorithm

The novel method for the prospective detection of disease outbreaks utilize a generalized mixed effects model or a hierarchical generalized linear model to model the count observations y and to assess the unobserved random effects u . These random effects are used directly in the detection algorithm to characterize an outbreak.

4.2 General mixed effects models

In this section selected theory related to generalized mixed effects models is presented. The general mixed effects model can be represented by its likelihood function

$$L_M(\theta; y) = \int_{\mathbb{R}^q} L(\theta; u, y) du \quad (4.1)$$

where y is the observed random variable, θ is the model parameters to be estimated and U is the q unobserved random variables. The likelihood function L is the joint likelihood of both the observed and the unobserved random variables. The likelihood function for estimating θ is the marginal likelihood L_M obtained by integrating out the unobserved random variables. In general it is difficult to solve the integral in (4.1) if the number of unobserved random variables is more than a few and hence numerical methods must be used.

4.2.1 Hierarchical models

It is useful to formulate the model as a hierarchical model containing a *first stage model*

$$f_{Y|u}(y; u, \beta) \quad (4.2)$$

which is a model for the observed random variables given the unobserved random variables, and a *second stage model*

$$f_U(u; \Psi) \quad (4.3)$$

which is a model for the unobserved random variables. Here β represent the fixed effects parameters and Ψ is a model parameter. The total set of parameters is $\theta = (\beta, \Psi)$. Hence the joint likelihood is given as

$$L(\beta, \Psi; u, y) = f_{Y|u}(y; u, \beta) f_U(u; \Psi) \quad (4.4)$$

To obtain the likelihood for the model parameters (β, Ψ) the unobserved random variables are integrated out. The likelihood function for estimating (β, Ψ) is as in (4.1) the marginal likelihood

$$L_M(\beta, \Psi; y) = \int_{\mathbb{R}^q} L(\beta, \Psi; u, y) du \quad (4.5)$$

where q is the number of unobserved random variables, and β and Ψ are the parameters to be estimated.

4.2.2 Laplace Approximation

The Laplace approximation will be outlined in the following. A thorough description of the Laplace approximation in nonlinear mixed effects models is found in Wolfinger and Lin (1997).

For a given set of model parameters θ the joint log-likelihood $\ell(\theta, u, y) = \log(L(\theta, u, y))$ is approximated using a second order Taylor approximation around the optimum $\tilde{u} = \hat{u}_\theta$ of the log-likelihood function w.r.t. the unobserved random variables u , i.e.,

$$\ell(\theta, u, y) \approx \ell(\theta, \tilde{u}, y) - \frac{1}{2}(u - \tilde{u})^T H(\tilde{u})(u - \tilde{u}) \quad (4.6)$$

where the first-order term of the Taylor expansion disappears since the expansion is done around the optimum \tilde{u} and $H(\tilde{u}) = -\ell''_{uu}(\theta, u, y)|_{u=\tilde{u}}$ is the negative Hessian of the joint log-likelihood evaluated at \tilde{u} .

It is readily seen that the joint log-likelihood for the hierarchical model specified in Section 4.2.1 is

$$\ell(\theta, u, y) = \ell(\beta, \Psi, u, y) = \log f_{Y|u}(y; u, \beta) + \log f_U(u; \Psi) \quad (4.7)$$

which implies that the Laplace approximation becomes

$$\ell_{M,LA}(\theta, y) = \log f_{Y|u}(y; \tilde{u}, \beta) + \log f_U(\tilde{u}, \Psi) - \frac{1}{2} \log \left| \frac{H(\tilde{u})}{2\pi} \right| \quad (4.8)$$

4.2.3 Formulation of the hierarchical Poisson Normal model

In order to simplify the notation, the probability density functions are presented for a specific observation and hence the subscripts indicating the group and time are omitted. The conditional distribution of the count observations is assumed to be a Poisson distribution with intensities λ

$$f_{Y|u}(y; u, \beta) = \frac{\lambda \exp(u)^y}{y!} \exp(-\lambda \exp(u)) \quad (4.9)$$

Also, it is assumed that the count is proportional to the population size x . Hence, in terms of the canonical link for the Poisson distribution the model for the fixed effects is

$$\log(\lambda_{it}) = \mathbf{X}_t^T \boldsymbol{\beta} + \log(x_{it}), \quad i = 1, \dots, k, \quad t = 1, \dots, n \quad (4.10)$$

Here \mathbf{X}_t and $\boldsymbol{\beta}$ are p -dimensional vectors of covariates and fixed effects parameters respectively, where p denotes the number of fixed effects parameters, k denotes the number of groups, and n denotes the length of the period. Moreover, the probability density function for the distribution of the random effects is assumed to follow a Gaussian distribution, $\mathbf{u} \sim \mathbf{N}(\mathbf{0}, \sigma^2)$, i.e.

$$f_U(u; \sigma) = \frac{1}{\sigma \sqrt{2\pi}} \exp \left(-\frac{u^2}{2\sigma^2} \right) \quad (4.11)$$

where σ is a model parameter.

Henceforth, the total set of parameters are $\boldsymbol{\theta} = (\boldsymbol{\beta}, \sigma)$ and the model can be formulated as a two-level hierarchical model

$$\mathbf{Y} | \mathbf{u} \sim \text{Pois}(\lambda \exp(\mathbf{u})) \quad (4.12a)$$

$$\mathbf{u} \sim \mathbf{N}(\mathbf{0}, \sigma^2) \quad (4.12b)$$

The joint likelihood for the count observations \mathbf{y} and the random effects \mathbf{u} becomes

$$L(\boldsymbol{\beta}, \sigma; u_{it}, y_{it}) = \prod_{t=1}^n \prod_{i=1}^k \frac{(\lambda_{it} \exp(u_{it}))^{y_{it}}}{y_{it}!} \exp(-\lambda_{it} \exp(u_{it})) \prod_{t=1}^n \prod_{i=1}^k \frac{1}{\sigma \sqrt{2\pi}} \exp \left(-\frac{u_{it}^2}{2\sigma^2} \right) \quad (4.13)$$

4.3 Hierarchical generalized linear models

In this section selected theory related to hierarchical generalized linear models is presented. The model class was initially formulated by Lee and Nelder (1996) as a natural generalization of the generalized linear models to also incorporate random effects. A starting point in hierarchical modelling is an assumption that the distribution of random effects may be modeled by an exponential dispersion family. This family of models were first introduced by Fisher and Russell (1922), and has proven to play an important role in mathematical statistics because of their simple inferential properties. The exponential dispersion family considers a family of distributions, which can be written on the form

$$f_Y(y; \theta) = c(y, \lambda) \exp(\lambda \{\theta y - \kappa(\theta)\}) \quad (4.14)$$

Here the parameter $\lambda > 0$ is called the *precision parameter*, which in some cases represents a known shape parameter as for the Gamma distribution. In other cases the precision parameter represents an over-dispersion that is not related to the mean. These distributions combine with the so-called *standard conjugate distributions* in a simple way, and lead to marginal distributions that may be expressed in a closed form suited for likelihood calculations.

4.3.1 Standard conjugate distribution

Now the general notion of a *standard conjugate distribution* for an exponential dispersion family is introduced.

Consider an exponential dispersion family $\text{ED}(\mu, V(\mu)/\lambda)$ with density (4.14) for $\theta \in \Omega$. Let $\mathcal{M} = \tau(\Omega)$ denote the mean value space for this family. Let $m \in \mathcal{M}$ and consider

$$g_\theta(\theta; m, \gamma) = \frac{1}{C(m, \gamma)} \exp\left(\frac{\theta m - \kappa(\theta)}{\gamma}\right) \quad (4.15)$$

with

$$C(m, \gamma) = \int_{\Omega} \exp\left(\frac{\theta m - \kappa(\theta)}{\gamma}\right) d\theta \quad (4.16)$$

for $\gamma \in \mathbb{R}_+$ for which the integral converges. Then (4.15) defines the density function of a probability distribution for θ . This distribution is called the *standard conjugate distribution* for θ corresponding to (4.14).

4.3.2 Definition of the hierarchical generalized linear model

Consider a set of observations $\mathbf{Y} = (Y_1, Y_2, \dots, Y_k)^T$ such that for a given value of a parameter θ the distribution of Y_i is given by an exponential dispersion model with density (4.14) and with canonical parameter space Ω (for θ), mean value $\mu = \kappa'(\theta)$, mean value space \mathcal{M} (for μ) and canonical link $\theta = g(\mu)$.

Let the *conjugate distribution* of θ be given by (4.15), and the corresponding conjugate distribution of μ , (e.g., $f_Y(y)$ Poisson distribution; $g_\mu(\mu)$ Gamma distribution; link $g(\mu) = \log(\mu)$).

The variables in a hierarchical generalized linear model are

- i) the observed responses $y_1, y_2, \dots, y_k \quad (\in \mathcal{M})$
- ii) the unobserved random effects $u_1, u_2, \dots, u_q \quad (\in \mathcal{M})$
- iii) and the corresponding unobserved canonical variables $v_i = g(u_i) \quad (\in \Omega)$

The *linear predictor* is of the form

$$\theta = g(\mu|v) = \mathbf{X}\beta + \mathbf{Z}v \quad (4.17)$$

The distribution of $\mathbf{V} \in \Omega$ is a conjugated distribution to the canonical parameter θ . The derived distribution of $\mathbf{U} \in \mathcal{M}$ is the corresponding conjugated distribution to the mean value parameter μ such that $E[\mathbf{U}] = \psi$. When the conditional distribution of $\mathbf{Y}|\mu$ is a Poisson distribution, and the distribution of \mathbf{V} is constructed in such a way that the distribution of $\mathbf{U} = \log(\mathbf{V})$ is a Gamma distribution with mean value $E[\mathbf{U}] = \psi = 1$, then it follows that the distribution of \mathbf{Y} is a negative binomial distribution with parameters determined by $\mathbf{X}\beta$ and $\mathbf{Z}v$.

4.3.3 Formulation of the hierarchical Poisson Gamma model

In the compound Poisson Gamma model the conditional distribution of the count observations are assumed to be a Poisson distribution with intensities λ

$$f_{Y|u}(y; u, \beta) = \frac{(\lambda u)^y}{y!} \exp(-\lambda u) \quad (4.18)$$

The model for the fixed effects is specified as

$$\log(\lambda_{it}) = \mathbf{X}_t^T \beta + \log(x_{it}), \quad i = 1, \dots, k, \quad t = 1, \dots, n \quad (4.19)$$

Here \mathbf{X}_t and β are p -dimensional vectors of covariates and fixed effects parameters respectively, where p denotes the number of fixed effects parameters, k denotes the number of groups, and n denotes the length of the period. Additionally, the probability density function for the random effects u are assumed to follow a reparametrized Gamma distribution with mean 1, $u \sim G(1/\phi, \phi)$ that is

$$f_u(u; \phi) = \frac{1}{\phi \Gamma(1/\phi)} \left(\frac{u}{\phi} \right)^{1/\phi-1} \exp(-u/\phi) \quad (4.20)$$

Subsequently, the model can be formulated as a two-level hierarchical model

$$\mathbf{Y}|\mathbf{u} \sim \text{Pois}(\lambda \mathbf{u}) \quad (4.21a)$$

$$\mathbf{u} \sim G(1/\phi, \phi) \quad (4.21b)$$

Given (4.18) and (4.20), the probability function for the marginal distribution of \mathbf{Y} is determined from

$$\begin{aligned} g_Y(y; \beta, \phi) &= \int_{u=0}^{\infty} f_{Y|u}(y; u, \beta) f_u(u; \phi) du \\ &= \int_{u=0}^{\infty} \frac{(\lambda u)^y}{y!} \exp(-\lambda u) \frac{1}{\phi \Gamma(1/\phi)} \left(\frac{u}{\phi} \right)^{1/\phi-1} \exp(-u/\phi) du \\ &= \frac{\lambda^y}{y! \Gamma(1/\phi) \phi^{1/\phi}} \int_{u=0}^{\infty} u^{y+1/\phi-1} \exp(-u(\lambda\phi + 1)/\phi) du \end{aligned} \quad (4.22)$$

In (4.22) it is noted that the integrand is the *kernel* in the probability density function for a Gamma distribution, $G(y + 1/\phi, \phi/(\lambda\phi + 1))$. As the integral of the density shall equal one, we find by adjusting the norming constant that

$$\int_{u=0}^{\infty} u^{y+1/\phi-1} \exp\left(-u\left(\phi/(\lambda\phi + 1)\right)\right) du = \frac{\phi^{y+1/\phi} \Gamma(y + 1/\phi)}{(\lambda\phi + 1)^{y+1/\phi}} \quad (4.23)$$

Therefore, it can be shown that the marginal distribution of Y is a negative binomial distribution, $Y \sim \text{NB}(1/\phi, 1/(\lambda\phi + 1))$. The probability function for Y is

$$\begin{aligned}
P[Y = y] &= g_Y(y; \beta, \phi) \\
&= \frac{\lambda^y}{y! \Gamma(1/\phi) \phi^{1/\phi}} \frac{\phi^{y+1/\phi} \Gamma(y+1/\phi)}{(\lambda\phi + 1)^{y+1/\phi}} \\
&= \frac{\Gamma(y+1/\phi)}{\Gamma(1/\phi) y!} \frac{1}{(\lambda\phi + 1)^{1/\phi}} \left(\frac{\lambda\phi}{\lambda\phi + 1} \right)^y \\
&= \binom{y+1/\phi-1}{y} \frac{1}{(\lambda\phi + 1)^{1/\phi}} \left(\frac{\lambda\phi}{\lambda\phi + 1} \right)^y, \quad \text{for } y = 0, 1, 2, \dots
\end{aligned} \tag{4.24}$$

where we have used the convention

$$\binom{z}{y} = \frac{\Gamma(z+1)}{\Gamma(z+1-y) y!} \tag{4.25}$$

for z real and y integer values. Consequently, the mean and variance of Y are given by

$$E[Y] = \lambda \quad V[Y] = \lambda(\lambda\phi + 1) \tag{4.26}$$

The likelihood function for estimating (β, ϕ) is

$$L(\beta, \phi; y_{it}) = \prod_{t=1}^n \prod_{i=1}^k \binom{y_{it} + 1/\phi - 1}{y_{it}} \frac{1}{(\lambda_{it}\phi + 1)^{1/\phi}} \left(\frac{\lambda_{it}\phi}{\lambda_{it}\phi + 1} \right)^{y_{it}} \tag{4.27}$$

Inference on individual groups

In order to simplify the notation, the subscript indicating the group and time are omitted. Consider the compound Poisson Gamma model in (4.21), and assume that a value $Y = y$ has been observed. Then the conditional distribution of u for given $Y = y$ is a Gamma distribution.

$$u|Y = y \sim G(y + 1/\phi, \phi/(\lambda\phi + 1)) \tag{4.28}$$

The mean of the conditional distribution is given by:

$$E[u|Y = y] = \frac{y\phi + 1}{\lambda\phi + 1} \tag{4.29}$$

And the variance of the conditional distribution is:

$$V[u|Y = y] = \frac{(\phi^2 + \phi)}{(\lambda\phi + 1)^2} \tag{4.30}$$

These formulas provide the mean and variance of the conditional distribution of u given the observed value $Y = y$.

Why do we choose the Gamma distribution to represent the variation between days?

The choice of the Gamma distribution for modeling the random effects has been motivated by several reasons. Firstly, the support of the Gamma distribution, which ranges from 0 to infinity, aligns with the mean-value space, denoted as \mathcal{M} , for the Poisson distribution. This ensures that the random effects are constrained within a meaningful range for the underlying Poisson process.

Secondly, the two-parameter family of Gamma distributions offers considerable flexibility, encompassing a wide range of shapes and distributions that can span from exponential-like distributions to fairly symmetrical distributions on the positive real line. This flexibility allows the model to capture various patterns and characteristics observed in the data.

Additionally, the choice of the Gamma distribution has benefits in terms of the derivation of the marginal distribution of the response variable Y . The kernel $u^{\alpha-1} \exp(-u/\beta)$ of the Gamma distribution used for modeling the random effects exhibits a similar structure to the kernel $u^y \exp(-u)$ of the likelihood function corresponding to the sampling distribution of Y . This similarity facilitates the analytical computation of the integral involved in deriving the marginal distribution, as it can be expressed in terms of known functions.

Overall, the Gamma distribution is selected due to its alignment with the mean-value space of the Poisson distribution, its flexibility in capturing diverse distributions, and its analytical convenience in computing the marginal distribution of the response variable.

4.4 Implementation in R using TMB

The models described in equations (4.12) and (4.21) have been implemented in R using the open-source R package called **TMB** (Template Model Builder) developed by Kristensen et al. (2016). This package facilitates maximum likelihood estimation and uncertainty calculations for the parameters θ and random effects u in an efficient manner. **TMB** achieves this by maximizing a user-provided objective function in the form of a C++ template. The likelihood maximization or a Laplace approximation for the marginal likelihood is then performed using conventional R optimization routines.

Furthermore, **TMB** utilizes Automatic Differentiation (AD) techniques (Griewank and Walther 2008) to evaluate first, second, and potentially third-order derivatives. For a comprehensive introduction to the concept of AD, it is recommended to read sections 2.1 and 2.2 of Fournier et al. (2012). This approach enhances the computational efficiency and accuracy of the parameter estimation process in the implemented models.

5 Results

In this chapter...

5.1 Case studies

In this section, the results of applying the novel outbreak detection algorithm to the subset of diseases will be presented. The performance of the algorithm in detecting outbreaks in the selected diseases will be thoroughly discussed and analyzed. Additionally, a comparative analysis will be conducted, evaluating the performance of the novel outbreak detection algorithm against the current state-of-the-art methods, namely the Farrington method (Farrington et al. 1996) and the improved Noufaily method (Noufaily et al. 2013). This comparative analysis will provide valuable insights into the strengths and limitations of the novel algorithm, as well as its potential contributions to the field of outbreak detection.

5.1.1 *Listeriosis*

Consider the models given in (4.12) and (4.21)

5.1.2 *Shigellosis*

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

5.1.3 *Shiga toxin (verotoxin)-producing Escherichia coli*

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

5.1.4 *Salmonellosis*

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

5.2 Simulation study

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest

gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

6 Discussion

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

7 Conclusion

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

Bibliography

- Buckeridge, David L. (2007). "Outbreak detection through automated surveillance: A review of the determinants of detection". In: *Journal of Biomedical Informatics* 40.4. Public Health Informatics, pp. 370–379. ISSN: 1532-0464. DOI: <https://doi.org/10.1016/j.jbi.2006.09.003>. URL: <https://www.sciencedirect.com/science/article/pii/S1532046406000980>.
- Unkel, Steffen et al. (2012). "Statistical methods for the prospective detection of infectious disease outbreaks: a review". In: *Journal of the Royal Statistical Society. Series A (Statistics in Society)* 175.1, pp. 49–82. ISSN: 09641998, 1467985X. URL: <http://www.jstor.org/stable/41409708> (visited on 02/15/2023).
- Salmon, Maëlle, Dirk Schumacher, and Michael Höhle (2016). "Monitoring Count Time Series in R: Aberration Detection in Public Health Surveillance". In: *Journal of Statistical Software* 70.10, pp. 1–35. DOI: 10.18637/jss.v070.i10. URL: <https://www.jstatsoft.org/index.php/jss/article/view/v070i10>.
- Farrington, C. P. et al. (1996). "A Statistical Algorithm for the Early Detection of Outbreaks of Infectious Disease". In: *Journal of the Royal Statistical Society. Series A (Statistics in Society)* 159.3, pp. 547–563. ISSN: 09641998, 1467985X. URL: <http://www.jstor.org/stable/2983331> (visited on 01/27/2023).
- Noufaily, Angela et al. (Mar. 2013). "An Improved Algorithm for Outbreak Detection in Multiple Surveillance Systems". en. In: *Online Journal of Public Health Informatics* 32.7, pp. 1206–1222.
- Hulth, A. et al. (2010). "Practical usage of computer-supported outbreak detection in five european countries". In: *Eurosurveillance* 15.36. Cited by: 31, pp. 1–6. URL: <https://www.scopus.com/inward/record.uri?eid=2-s2.0-77957607700&partnerID=40&md5=ff916d06bcf38218b2388d0874eed9f8>.
- Goulet, Véronique et al. (2012). "Incidence of listeriosis and related mortality among groups at risk of acquiring listeriosis". In: *Clinical infectious diseases* 54.5, pp. 652–660.
- Awofisayo, A. et al. (Jan. 2015). "Pregnancy-associated listeriosis in England and Wales". In: *EPIDEMIOLOGY AND INFECTION* 143.2, pp. 249–256. ISSN: 0950-2688. DOI: 10.1017/S0950268814000594.
- Menge, Christian (2020). "The Role of Escherichia coli Shiga Toxins in STEC Colonization of Cattle". In: *Toxins* 12.9. ISSN: 2072-6651. DOI: 10.3390/toxins12090607. URL: <https://www.mdpi.com/2072-6651/12/9/607>.
- Madsen, Henrik and Poul Thyregod (2011). *Introduction to general and generalized linear models*. English. Texts in statistical science. CRC Press. ISBN: 9781420091557.
- Wolfinger, Russell D. and Xihong Lin (1997). "Two Taylor-series approximation methods for nonlinear mixed models". In: *Computational Statistics and Data Analysis* 25.4. Cited by: 87, pp. 465–490. DOI: 10.1016/S0167-9473(97)00012-1. URL: <https://www.scopus.com/inward/record.uri?eid=2-s2.0-0031222254&doi=10.1016%2fS0167-9473%2897%2900012-1&partnerID=40&md5=dbf7ca1e47d836029af4044ff9880463>.
- Lee, Y. and J. A. Nelder (1996). "Hierarchical Generalized Linear Models". In: *Journal of the Royal Statistical Society. Series B (Methodological)* 58.4, pp. 619–678. ISSN: 00359246. URL: <http://www.jstor.org/stable/2346105> (visited on 05/16/2023).
- Fisher, R. A. and Edward John Russell (1922). "On the mathematical foundations of theoretical statistics". In: *Philosophical Transactions of the Royal Society of London. Series A, Containing Papers of a Mathematical or Physical Character* 222.594-604, pp. 309–368. DOI: 10.1098/rsta.1922.0009. eprint: <https://royalsocietypublishing.org/doi/pdf/10.1098/rsta.1922.0009>.

1098/rsta.1922.0009. URL: <https://royalsocietypublishing.org/doi/abs/10.1098/rsta.1922.0009>.

Kristensen, Kasper et al. (2016). “TMB: Automatic Differentiation and Laplace Approximation”. In: *Journal of Statistical Software* 70.5, pp. 1–21. DOI: 10.18637/jss.v070.i05.

Griewank, Andreas and Andrea Walther (2008). *Evaluating Derivatives*. Second. Society for Industrial and Applied Mathematics. DOI: 10.1137/1.9780898717761. eprint: <https://epubs.siam.org/doi/pdf/10.1137/1.9780898717761>. URL: <https://epubs.siam.org/doi/abs/10.1137/1.9780898717761>.

Fournier, David A. et al. (2012). “AD Model Builder: using automatic differentiation for statistical inference of highly parameterized complex nonlinear models”. In: *Optimization Methods and Software* 27.2, pp. 233–249. DOI: 10.1080/10556788.2011.597854. eprint: <https://doi.org/10.1080/10556788.2011.597854>. URL: <https://doi.org/10.1080/10556788.2011.597854>.

A Some probability functions

This chapter serves as a reference, specifying notation, properties, and moments related to the various distributions used in this master thesis.

Name	Support	Density	$E[Y]$	$V[Y]$
Poisson $\text{Pois}(\lambda)$	$0, 1, 2, \dots$ $\lambda \in \mathbb{R}_+$	$\frac{\lambda^y}{y!} \exp(-\lambda)$	λ	λ
Gamma $G(\alpha, \beta)$	\mathbb{R}_+ $\alpha \in \mathbb{R}_+, \beta \in \mathbb{R}_+$	$\frac{1}{\Gamma(\alpha)\beta} \left(\frac{y}{\beta}\right)^{\alpha-1} \exp(-y/\beta)$	$\alpha\beta$	$\alpha\beta^2$
Neg. Bin. $\text{NB}(r, p)$	$0, 1, 2, \dots$ $r \in \mathbb{R}_+, p \in]0, 1]$	$\binom{r+y-1}{y} p^r (1-p)^y$	$\frac{r(1+p)}{p}$	$\frac{r(1-p)}{p^2}$
Normal $N(\mu, \sigma^2)$	\mathbb{R} $\mu \in \mathbb{R}, \sigma^2 \in \mathbb{R}_+$	$\frac{1}{\sigma\sqrt{2\pi}} \exp\left(-\frac{(y-\mu)^2}{2\sigma^2}\right)$	μ	σ^2

Table A.1: Density, support, mean value, and variance for a number of distributions used in this master thesis.

A.1 The Poisson distribution model

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

A.2 The Gamma distribution model

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

A.3 The Negative Binomial distribution model

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

A.4 The Normal distribution model

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

B Proofs

B.1 Hierarchical Poisson Gamma model

This section is a collection of proofs for the derivation of the compound Poisson Gamma model in (4.21).

B.1.1 Conditional distribution of Y

The conditional distribution is found using Bayes Theorem

$$\begin{aligned}
 g_u(u|Y = y) &= \frac{f_{y,u}(y, u)}{g_Y(y; \lambda, \phi)} \\
 &= \frac{f_{y|u}(y; u)g_u(u)}{g_Y(y; \lambda, \phi)} \\
 &= \frac{1}{g_Y(y; \lambda, \phi)} \left(\frac{(\lambda u)^y}{y!} \exp(-\lambda u) \frac{1}{\phi \Gamma(1/\phi)} \left(\frac{u}{\phi} \right)^{1/\phi-1} \exp(-u/\phi) \right) \\
 &\propto u^{y+1/\phi-1} \exp(-u(\lambda\phi + 1)/\phi)
 \end{aligned} \tag{B.1}$$

We identify the *kernel* of the probability density function

$$u^{y+1/\phi-1} \exp(-u(\lambda\phi + 1)/\phi) \tag{B.2}$$

as the kernel of a Gamma distribution, $G(y + 1/\phi, \phi/(\lambda\phi + 1))$

Hello, here is some text without a meaning. This text should show what a printed text will look like at this place. If you read this text, you will get no information. Really? Is there no information? Is there a difference between this text and some nonsense like “Huardest gefburn”? Kjift – not at all! A blind text like this gives you information about the selected font, how the letters are written and an impression of the look. This text should contain all letters of the alphabet and it should be written in of the original language. There is no need for special content, but the length of words should match the language.

Technical
University of
Denmark

Richard Petersens Plads, Building 324
2800 Kgs. Lyngby
Tlf. 4525 1700

www.compute.dtu.dk