Treatment effects in single-subject count data

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Introduction

In this document I explain various ways of estimating treatment effects in single-subject designs with blinded treatment allocation over time. The motivating example is a patient with seizures, followed over 84 days, where treatment was allocated in 4 periods using an ABAB design.

The goal is to obtain an estimate of the treatment effect for this patient. I will show several ways of obtaining this estimate, first by simple visualization and summary statistics, and then by using a count data model (Poisson regression). I will show how to do inference both in the frequentist and in the Bayesian way, first by correcting the standard errors and confidence intervals of the treatment effect for potential model misspecification, and then by performing full Bayesian inference.

Over the course of this document, we will use the following packages:

I have simulated some example data for illustrative purposes. This data has three variables: the day of measurement (`treat`), the number of seizures on that day (`y`), and whether treatment was administered on that day (`treat`). A small sample of the data is shown below. The script that generates the data is found in `gen_dat.R` in this folder.

```
df <- readRDS("example_data.rds")
head(df)
```

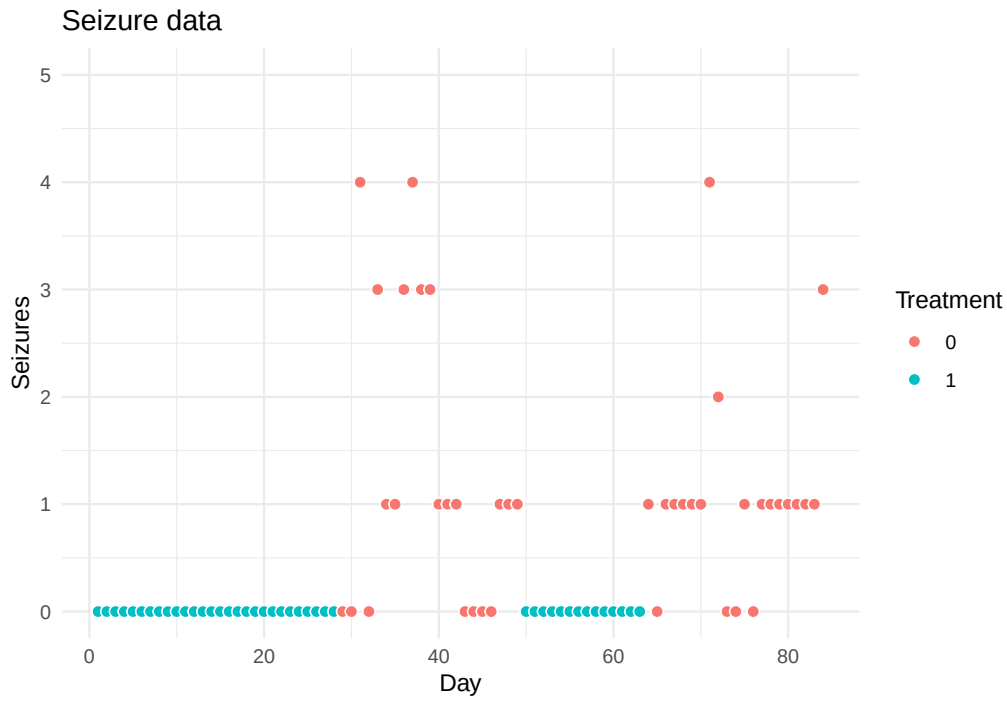
```
##   day y treat
## 1   1 0     1
## 2   2 0     1
```

```
## 3   3 0     1
## 4   4 0     1
## 5   5 0     1
## 6   6 0     1
```

Visual analysis and summary statistics

The simplest way of getting an idea of the treatment effect is through visual analysis and summary statistics. First, we create a plot of the data over time, where the treatment periods are indicated:

```
ggplot(df, aes(x = day, y = y, fill = treat)) +
  geom_point(pch = 21, colour = "white", size = 2.3) +
  theme_minimal() +
  labs(x = "Day", y = "Seizures", fill = "Treatment",
       title = "Seizure data") +
  ylim(0, 5)
```



Using summary statistics, we can estimate the rate of seizures in both the treatment and control periods

```
df |>
  group_by(treat) |>
  summarize(seizure_rate = mean(y))
```

```
## # A tibble: 2 x 2
##   treat seizure_rate
##   <fct>        <dbl>
## 1 0             1.21
## 2 1             0
```

This table shows that the expected seizure rate in the control condition is 1.2 seizures per day, and the expected seizure rate in the treatment condition is 0. Thus, we observe a difference in seizure rate of 1.2, which is our first naïve estimate of the treatment effect.

However, we do not know anything yet about the uncertainty around this effect. For this, we need a statistical model.

Poisson regression for estimating the treatment effect

We will perform regression for estimating the treatment effect. Specifically, we estimate the following model:

$$y \sim Poisson(\lambda)$$
$$log(\lambda) = \beta_0 + \beta_1 \cdot \text{treat}$$

In other words, we model the seizures y using a Poisson distribution with seizure rate λ. Then, the logarithm of this rate is the sum of a base rate β_0 and a treatment effect β_1. We use the logarithm for technical reasons – it is the "canonical" link function of the Poisson distribution – so we need to deal with this in interpreting our parameters later.

The model can be estimated in R and summarized like so:

```
fit <- glm(y ~ 1 + treat, family = poisson(), data = df)
summary(fit)
```

```
##
## Call:
## glm(formula = y ~ 1 + treat, family = poisson(), data = df)
##
## Deviance Residuals:
##      Min        1Q    Median        3Q       Max
## -1.55839  -0.20065  -0.00006  -0.00006   1.99140
##
## Coefficients:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept)    0.1942     0.1400   1.387    0.166
## treat1       -20.4967  2398.1616  -0.009    0.993
##
## (Dispersion parameter for poisson family taken to be 1)
##
##     Null deviance: 119.899  on 83  degrees of freedom
## Residual deviance:  49.198  on 82  degrees of freedom
```

```
## AIC: 124.57
##
## Number of Fisher Scoring iterations: 18
```

Here, we can see that our base rate (the rate in the control condition) is $e^{\beta_0} = e^{0.19} = 1.21$ like before. The estimated treatment effect is -20.49. Converting this into an estimated treatment effect on the rate scale leads to $e^{\beta_0+\beta_1} = e^{-20.3} \approx 0$. In other words, the estimated rate difference $1.21 - 0$ is very similar to before.

So the parameter estimates make sense, but we see a huge uncertainty around the estimate: the standard error is > 2000! This is another technical issue: because the treatment condition has *no seizures*, it is hard to estimate the log-rate and its uncertainty. Theoretically, the maximum likelihood estimate for the rate is $-\infty$ (as $e^{-\infty} = 0$)!

Penalized estimation of the Poisson model

There are several solutions for this which "regularize" the estimates to be within a more reasonable range. One of the solutions is penalized maximum likelihood estimation. In cases such as this one, penalized estimation is shown to have better frequentist properties (such as better calibrated standard errors and confidence intervals). Here we refit the model with penalized estimation as implemented in the package `brglm2`.

```
fit_pen <- glm(y ~ 1 + treat, family = poisson(), data = df,
               method = "brglmFit")
summary(fit_pen)
```

```
##
## Call:
## glm(formula = y ~ 1 + treat, family = poisson(), data = df, method = "brglmFit")
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -1.5660  -0.2111  -0.1543  -0.1543   1.9777
##
## Coefficients:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept)   0.2039     0.1393   1.463  0.14337
## treat1       -4.6347     1.4211  -3.261  0.00111 **
## ---
## Signif. codes:
## 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##     Null deviance: 119.904  on 83  degrees of freedom
## Residual deviance:  50.203  on 82  degrees of freedom
## AIC:  125.57
##
```

```
## Type of estimator: AS_mixed (mixed bias-reducing adjusted score equations)
## Number of Fisher Scoring iterations: 1
```

Now the estimate and standard error are much more reasonable! The treatment effect is estimated at -4.6, meaning a rate ratio of $e^{-4.6} = 0.0097$. The confidence interval is as follows:

```
confint(fit_pen)
```

```
##                    2.5 %     97.5 %
## (Intercept) -0.06920213  0.4770265
## treat1      -7.41995951 -1.8494985
```

This means that the treatment is expected to reduce the seizure rate by a factor of $e^{-7.42} = 0.0006$ to $e^{-1.85} = 0.15$. Thus, according to this model, not treating this patient leads to between 6.36 and 1670 times higher seizure rate for this patient.

However, in this model we are making an assumption which does not necessarily hold: that of uncorrelated residuals. We are assuming that the seizure rates for each day are independent (conditional on treatment). This would be the case if this were a randomized controlled trial, but since this is a single-subject design we cannot make this assumption. For example, it could be the case that a high seizure rate on day 1 leads to a similarly high seizure rate on day 2. This would lead to "serial correlation" or "autocorrelation". As a result, we cannot trust the confidence interval or the p-values in this section. In the next section, I show how to compute standard errors which are robust to mild model misspecification of this type.

Robust inference for the Poisson model

Instead of using the default estimator for the standard errors, we will now estimate a type of standard error which is robust to heteroskedasticity and autocorrelation, the so-called "HAC" estimator[1]. This is implemented in the `sandwich`package:

```
coeftest(fit_pen, vcov. = vcovHAC)
```

```
##
## z test of coefficients:
##
##             Estimate Std. Error z value  Pr(>|z|)
## (Intercept)  0.20391    0.09809  2.0788   0.03763 *
## treat1      -4.63473    0.74917 -6.1865 6.153e-10 ***
## ---
## Signif. codes:
## 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Note that in this case, the robust standard errors are smaller than the default standard errors. This may not be the case (in fact usually they are larger than the default ones!). Now we can perform our inference.

[1] this is very common in econometrics, where researchers have to deal with such time-series and within-subject changes all the time!

Inference on rate ratio scale

According to the model, treatment significantly reduces the rate of seizures (p < .05). Not treating the patient is estimated to increase the seizure rate by a factor $e^{4.63} = 103$, which is our estimated effect size on the rate ratio scale. We can compute robust 95% confidence intervals for this effect as follows:

```
se_robust <- sqrt(diag(vcovHAC(fit_pen)))
lo <- round(exp(4.63473 - 1.96*se_robust[2]), 2)
hi <- round(exp(4.63473 + 1.96*se_robust[2]), 2)
cat("Robust 95% CI: [", lo, ", ", hi, "]", sep = "")
```

```
## Robust 95% CI: [23.72, 447.25]
```

This effect size seems very large (and it is!) but this is partially due to the fact that there are no seizures at all in the treatment condition. Because of this, it is sometimes better to look at the absolute difference in rates.

Inference on rate difference scale

To compute the rate difference, we compute expectations for the treatment and the control conditions and then we subtract these. On the rate difference scale, not treating the patient means a rate increase of $e^{0.20} - e^{0.20-4.63} = 1.21$. We can compute approximate robust 95% confidence intervals for this effect size measures as follows:

```
se_robust <- sqrt(diag(vcovHAC(fit_pen)))
lo <- round(exp(0.20391 - 1.96*se_robust[1]) -
            exp(0.20391 - 1.96*se_robust[1] -
                4.63473 - 1.96*se_robust[2]), 2)
hi <- round(exp(0.20391 + 1.96*se_robust[1]) -
            exp(0.20391 + 1.96*se_robust[1] -
                4.63473 + 1.96*se_robust[2]), 2)
cat("Approx. robust 95% CI: [", lo, ", ", hi, "]", sep = "")
```

```
## Approx. robust 95% CI: [1.01, 1.42]
```

Bayesian inference for the Poisson model

In order to obtain a Bayes factor for this treatment effect, we need to estimate a Bayesian version of the "null model" – the model without treatment effect – and the "alternative model" which includes the treatment effect. Using the package `rstanarm` we can do this as follows:

```
fit_null <- stan_glm(
  formula = y ~ 1,
  family = poisson(),
  data = df,
  diagnostic_file = "chains/null.csv"
)
```

```
fit_altr <- stan_glm(
  formula = y ~ 1 + treat,
  family = poisson(),
  data = df,
  diagnostic_file = "chains/altr.csv"
)
```

This performs fully Bayesian estimation, which also includes regularizing non-informative priors which perform a similar job to the penalized estimation in the frequentist setting. We can display the parameter estimates of the alternative model like so:

```
coef(fit_altr)
```

```
## (Intercept)      treat1
##   0.1815866  -5.4660703
```

Note that these estimates are reasonably similar: a seizure rate of $e^{0.18} = 1.20$ for the control condition, and a seizure rate of $e^{-5.46} = 0.004$ for the treatment condition.

We can get a Bayes factor for the treatment effect by comparing the two models. Using the package `bridgesampling`, we first estimate the "marginal likelihood" of each model[2]:

```
mlik_null <- bridge_sampler(fit_null)
mlik_altr <- bridge_sampler(fit_altr)
```

And then we can get a Bayes Factor by using the `bf()` function:

```
bf(mlik_altr, mlik_null)
```

```
## Estimated Bayes factor in favor of mlik_altr over mlik_null: 199825959748978.34375
```

This shows overwhelming evidence in favour of the alternative model.

Bayesian inference accounting for autoregression

In the Bayesian setting, we cannot easily perform autoregression-corrected inference like we do in the frequentist setting. What we can do, however, is estimate our null and alternative models with an explicit autoregression parameter, and then redo our inference. For this, we include a "lagged" version of our outcome variable `y` in the model.

First, we compute the lagged variable:

```
df <-
  df |>
  mutate(yl = lag(y))

head(df)
```

[2] In order to estimate Bayes factors with `bridgesampling`, in `rstanarm` we need to save the model diagnostics somewhere. Hence the use of the `diagnostic_file` in the model fitting process.

```
##   day y treat yl
## 1   1 0     1 NA
## 2   2 0     1  0
## 3   3 0     1  0
## 4   4 0     1  0
## 5   5 0     1  0
## 6   6 0     1  0
```

Then, we can redo our model and marginal likelihood estimation including this lagged variable:

```
fit_null_ar <- stan_glm(
  formula = y ~ 1 + yl,
  family = poisson(),
  data = df,
  diagnostic_file = "chains/null_ar.csv"
)
fit_altr_ar <- stan_glm(
  formula = y ~ 1 + treat + yl,
  family = poisson(),
  data = df,
  diagnostic_file = "chains/altr_ar.csv"
)
mlik_null_ar <- bridge_sampler(fit_null_ar)
mlik_altr_ar <- bridge_sampler(fit_altr_ar)
```

Lastly, we can compute the Bayes Factor for the treatment effect:

```
bf(mlik_altr_ar, mlik_null_ar)
```

```
## Estimated Bayes factor in favor of mlik_altr_ar over mlik_null_ar: 2834836854.85245
```

So even in this case, there is overwhelming evidence in favour of the treatment effect.