Analysis of Recurrent Spasticity Due to Spinal Cord Injury

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Introduction

Spasticity is a side effect of paralysis that varies from mild muscle stiffness to severe, uncontrollable movements. It may occur as a result of spinal cord injury, multiple sclerosis, cerebral palsy, or brain trauma. Symptoms of spasticity may include increased muscle tone, rapid muscle contractions, exaggerated deep tendon reflexes, muscle spasms, scissoring (involuntary crossing of the legs) and fixed joints.

Spasticity is usually caused by damage to the portion of the brain or spinal cord that controls voluntary movement. Since the normal flow of nerve messages from the brain to the desired location below the level of injury is interrupted, those messages may not reach the reflex control center of the brain. As a result, the spinal cord then attempts to moderate the body's response. Unfortunately, the spinal cord is not as efficient as the brain, so the signals that are sent back to the site of the sensation are often over-exaggerated in an overactive muscle response or spastic event.

Studies have shown that about 65% of individuals living with spinal cord injury experience some spasms. Those with cervical injuries and incomplete injuries are more likely than those with paraplegia and/or complete injuries to have recurrent spasticity. There are many treatments for spasticity, but the most often prescribed is a regiment of medication meant to relax the spastic muscles.[1]

I myself am an individual suffering from muscle spasticity as a result of a complete C-5 spinal cord injury. Additionally, the severity of my symptoms has increased as a result of a cyst or cavity forming in my spinal cord (post-traumatic syringomyelia), which I underwent additional surgery to treat. This study is therefore motivated by my desire to understand the factors contributing to my muscle spasticity. Specifically, I would like to know the effect of my muscle relaxant medication (baclofen), weather conditions (bad or changing weather is often considered to cause additional spasticity), and daily lifestyle trends on the amount of muscle spasticity I experience.

[1] Christopher Reeve Foundation, *What is Spasticity?*

Data and Experimentation

In order to understand the causes of muscle spasticity, I conducted an experiment on myself and recorded the resulting data. This experiment lasted 26 days and was carried out as follows. Each day was split into two time periods, a morning to afternoon time and afternoon to evening time. Distribution of baclofen was then randomized within each day, so that every day one random time period began by taking baclofen and the other time period began by taking a placebo. Each time period lasted six hours, the claimed amount of time that baclofen is effective for. During these blocks, every time I experienced spasticity I recorded the time and then calculated how long it had been since the time period started.

I also used available data to approximate the temperature, barometric pressure and humidity. I have heard claims that each of these factors has effects on spasticity. Additionally, I recorded the amount of sleep I had from the previous night and the amount of time driving that day. Those five quantitative variables, along with the response time and indicator variables for treatment and time period make up a total of 618 observations of 8 variables in the dataset. Figure 1 shows density plots of overall spasm times as well as gap times, defined as time since last spasm.

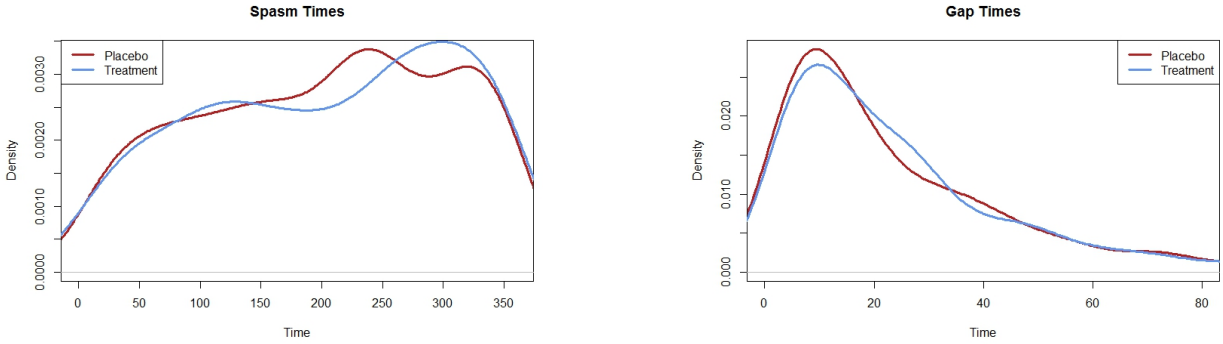

Figure 1: An initial glance at the time of event and time since last event data shown here shows that there does not seem to be much separation between the placebo and treatment group, although there is some motivation for a belief that the placebo group experienced spasms faster and sooner.

Methods

There are several approaches to carrying out this analysis, of which can can be split up into univariate and multivariate models. Some approaches are more or less appropriate than others, so this analysis fits several models and then compares the results of each approach.

Univariate Methods

Poisson Regression: The dataset was rearranged by counting the number of spasms in each time block and carrying out a Poisson Regression as follows.

$$Y_i \sim \text{Poisson}(\mu_i)$$

$$\log(\mu_i) = x_i'\beta$$

This model carries assumptions of Poisson distributed count data, independence, and linearity on the log scale, all of which are met. However, use of this univariate model discards the information on the timing of the events and is therefore an inefficient use of data.

Cox Proportional Hazards Regression: Survival analysis methods, such as proportional hazards regression model the incidence or hazard rate, the number of new cases of disease per population at-risk per unit time. In this context, the hazard function λ is the probability that if I have made it to a time t without a spasm, I will experience a spasm in the next instant. The model is as follows.

$$\log\left(\frac{\lambda\left(t|X_{1i}, X_{2i}, ..., X_{Ki}\right)}{\lambda_0(t)}\right) = \beta_1 X_{1i} + \beta_2 X_{2i} + ... + \beta_K X_{Ki}$$

Proportional hazards refers to the important assumption that the hazard for any individual is a fixed proportion of the hazard for any other individual. In this study, individuals are the time period blocks. This assumption is met, but in order to meet the additional assumption of independence only the first failure time within each time period block can be used. This is again an inefficient use of data as all the later observations are discarded.

Multivariate Methods

The following models treat the several spasm time observations as multivariate responses within each time period and thus make much more appropriate use of the recurrent events data.

Anderson-Gill Model: Also known as the intensity model, this is a counting process approach that generalizes the Cox model. Each subject is treated as a multiple event counting process with independent increments. These times between successive events must be conditionally independent given all observables up to the event times.[2] This assumption appears to hold in this study. The model is given as follows.[3]

[2] Therneau and Hamilton (1997)
[3] Anderson and Gill (1982)

Consider a sequence of models indexed by n and an n-component multivariate counting process $N^{(n)}$ which counts observed events in the life of individuals over the time interval [0,1]. The assumption is then that for each n, $N^{(n)}$ has a random intensity process $\lambda^{(n)}$ such that:

$$\lambda_i^{(n)}(t) = Y_i^{(n)}(t)\lambda_0(t)\exp\{\beta_0' Z_i^{(n)}(t)\}$$

β_0 and λ_0 are both fixed, the former being a vector of p coefficients and the latter an underlying hazard function. $Y_i^{(n)}$ is a predictable process taking values in 0,1 indicating when the ith individual is under observation. $Z_i^{(n)}$ is a predictable vector of p covariate processes for the ith individual.

Prentice, Williams and Peterson Models: These models analyze multiple events using stratification. They model all participants as at risk for the first stratum, but only those with an event in the previous stratum are at risk for the successive one. PWP models can be designated in terms of total time or gap time, the time since the previous event. The total time model evaluates the effect of a covariate for the ith event since the time began and the gap time model evaluates the effect of a covariate for the ith event since the previous event. Unlike the A-G model, the effect of covariates are allowed to vary from event to event. Therefore, these PWP models might be preferable to the A-G model when the effects of covariates are different in subsequent events.[4] The model is given as follows.[5]

This model relies on similar counting and covariate processes, N and Z, respectably. The total time model and gap time model below are notated as:

$$\lambda\{t|N(t), Z(t)\} = \lambda_0(t)\exp\{z(t)\beta\}$$

$$\lambda\{t|N(t), Z(t)\} = \lambda_0(t - t_{n(t)})\exp\{z(t)\beta\}$$

Results

Tables 1 and 2 display the results of the univariate models. Both models show that the difference in time period (either morning to afternoon or afternoon to evening) has a significant effect in that I am experiencing a much higher rate of spasms as the day progresses. Treatment appears to have at least a marginal effect, but not a significant one, at least in these models. No other covariates appear notable, although the high standard error for barometric pressure in the Cox model calls for further investigation in the multivariate models.

[4] Amorim and Cai (2014)
[5] Prentice, Williams and Peterson (1981)

	β	HR	SE	95% HR CI
Time Period	2.517	12.393	0.491	(4.735, 32.434)
Treatment	0.087	1.091	0.332	(0.569, 2.090)
Driving	0.008	1.008	0.013	(0.983, 1.033)
Sleep	-0.006	0.994	0.005	(0.984, 1.004)
Temperature	-0.014	0.986	0.029	(0.931, 1.044)
Barometer	0.386	1.471	1.088	(0.174, 12.409)
Humidity	-0.002	0.998	0.013	(0.972, 1.024)

Table 1: Results from univariate Cox regression

	β	$\exp(\beta)$	SE	p-value
Intercept	2.713	15.078	0.569	1.84e-06
Time Period	0.353	1.423	0.083	2.22e-05
Treatment	-0.107	0.898	0.083	0.196
Driving	0.001	1.001	0.002	0.67
Sleep	-0.002	0.998	0.001	0.171

Table 2: Results from univariate Poisson regression

Tables 3, 4 and 5 display the results of the multivariate models. The second column, the exponentiated β shows the hazard ratios, which can be considered the result of interest. This ratio can be interpreted as the ratio of spasm probabilities. For example, the hazard ratio of 1.434 for time period in Table 3 indicates that a spasm is that much more likely in the second time block than the first. Since the 95% confidence interval does not contain 1, this is a significant effect.

The multivariate models all give somewhat similar results, but each PWP model has a shortcoming that the A-G model does not. In Table 4, the total time PWP model has not only time period as significant, but also driving time. This is a curious result because driving time did not appear to be influential in any other model. Contrastingly, the gap time PWP results in Table 5 do not show any significance. Because of these discrepancies in the PWP models, the assumption of varying covariates from event to event needs to be examined further. Overall, the A-G model is preferred. It efficiently models the multivariate nature of the recurrent events data and correctly shows the significance of the time of day covariate. No other variables contributed significantly, including treatment, although there appears to be at least a marginal decrease in the hazard ratio when the treatment is taken. Perhaps additional amounts of data would validate this affect.

	β	HR	SE	95% HR CI
Time Period	0.360	1.434	0.089	(1.197, 1.1716)
Treatment	-0.119	0.888	0.088	(0.729, 1.082)
Driving	0.004	1.004	0.003	(0.998, 1.010)
Sleep	-0.002	0.998	0.001	(0.995, 1.001)
Temperature	0.009	1.009	0.007	(0.997, 1.022)
Barometer	-0.002	.998	0.007	(0.998, 0.999)
Humidity	-0.002	0.998	0.004	(0.9983, 1.003)

Table 3: Results from the multivariate A-G model

	β	HR	SE	p-value
Time Period	0.389	1.477	0.131	0.003
Treatment	-0.134	0.874	0.104	0.195
Driving	0.008	1.008	0.004	0.024
Sleep	-0.002	0.998	0.001	0.106
Temperature	0.001	1.002	0.009	0.836
Barometer	-0.002	.998	0.011	0.826
Humidity	-0.004	0.996	0.004	0.267

Table 4: Results from the multivariate total time PWP model

	β	HR	SE	p-value
Time Period	0.168	1.183	0.099	0.093
Treatment	-0.097	0.908	0.093	0.299
Driving	0.005	1.005	0.004	0.168
Sleep	-0.001	0.999	0.001	0.352
Temperature	0.005	1.005	0.008	0.412
Barometer	-0.002	.998	0.007	0.837
Humidity	-0.001	0.999	0.004	0.822

Table 5: Results from the multivariate gap time PWP model

Conclusion

This analysis successfully modeled recurrent spasticity data and showed that multivariate models, specifically the Anderson-Gill approach, provide more meaningful results than competing univariate models. The time period during the day was shown to have a significant effect on my spasticity, while other factors including treatment, were not. However this statement brings to light several shortcomings of the analysis. First, although it is interesting to know about this time of day effect, it would be more valuable to know specifics of this trend over time. Further research should include a time variable directly. Second, although times of over 600 spasms were recorded, there were only 26 observations in the study due to the multivariate nature of the data. With more data, effects such as treatment might become more clear. Finally, although these results are enlightening for me, they are useless to anyone else interested in spasticity because the study was only done on one subject. Future research with multiple individuals would be much more informative in terms of determining factors that effect spasticity and the effectiveness of treatments.

Appendix

R Code

```
library(survival)

#ag model

cox.ag <- coxph(Surv(Tstart,Tstop,Status) ~ WithinDay + Treatment + Driving + Sleep + Temperature +
        Barometer + Humidity + cluster(Date),data=spasms)
summary(cox.ag)

#pwp model

coxph(Surv(Tstart,Tstop,Status) ~ WithinDay + Treatment + Driving + Sleep + Temperature +
        Barometer + Humidity + cluster(Date) + strata(Enum),data=spasms)

#poisson regression (univariate)

pois.mod <- glm(Count~WithinDay+Treatment+Sleep+Driving,family=poisson,data=spasms.total)
summary(pois.mod)

#first time (univariate) Cox regression

spasms.first <- spasms[which(spasms$Tstart==0),]
survObj <- with(spasms.first,Surv(Tstop,Status==1))
unv <- coxph(survObj ~ WithinDay + Treatment + Driving + Sleep + Temperature +
               Barometer + Humidity,data=spasms.first)
summary(unv)
```

SAS Code

```
/* A-G (Intensity) Model */
```

```
proc phreg data=spasm;
model (Tstart,Tstop)*Status(0)= WithinDay Trt Drive Sleep Temp Barm Hum;
run;

/* Total Time PWP with common terms for each stratum */

proc phreg data=spasm;
model (Tstart,Tstop)*Status(0)= WithinDay Trt Drive Sleep Temp Barm Hum;
    strata Enum;
run;

/* Gap Time PWP with common terms for each stratum */

proc phreg data=spasm;
model Tgap*Status(0)= WithinDay Trt Drive Sleep Temp Barm Hum;
    strata Enum;
run;
```