Modelling the MESS Data

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Introduction

Th MESS data comes from a randomised controlled trial about treatments for epilepsy. The subjects in the study are patients who have had only one seizure or hve not had epilepsy for long. There are two treatments; either immediate or deferred. Patients assigned the deferred treatment are not prescribed anti-epileptic drugs after their first seizure, but the decision is revisited if they have further seizures.

Because many people have only one seizure in their life, we don't necessarily want to put patients on anti-epileptic drugs after just one seizure. However, we also don't want patients going on to have further seizures that could have been prevented or reduced by starting treatment immediately.

We are therefore interested in the level of benefit associated with immediate treatment relative to deferred treatment. Ultimately we could weigh this up against the costs of ongoing medication in order to decide whether a new patient should be given immediate treatment or not. This decision could depend on other data about the patient; for instance the trial recorded demographic details, results of some medical tests, and information about previous seizures.

Our aim is to construct a model considering some of these factors, which can be used to predict the outcome for a specific type of patient under immediate and deferred treatment. The model could then be used with some loss function to make optimal decisions about how to treat new patients.

Exploratory analysis

Change data types

We first format as factors those variables that should be factors, format the dates as dates, and change the 1/2-coded binary variables to 0/1.

Check censoring indicator

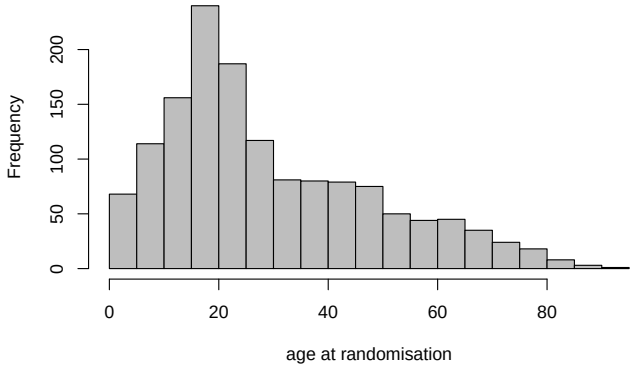
Next we want to see which way round the censoring indicator is used. We see that where the censoring indicator `ind1yr` is 1, the time to one year remission `int1yr` has minimum 365, whereas where `ind1yr` is 0, the minimum is 1. From this we deduce that the indicator is 1 when the variable is observed and 0 if the variable is censored.

Missing data

We verify that the same data are missing from `d1seiz` and `period`. These were probably subjects who couldn't remember the date of their first seizure, and/or whose medical records were missing. This suggests they are missing not at random - for instance if the subject can't remember the date it is likely to be a long time ago, i.e. higher values of `period`. However, since they are only 5 out of 1425 observations, we suspect it will not make much difference to treat them as if missing at random.

Investigate some variables

Plotting the age at randomisation `ager` we see that it is positively skewed. This is plausible since it is a study of people with single seizure or recent diagnosis of epilepsy, and it is more likely that an individual has their first seizure at a younger age.



We see that the number of subjects having each treatment is roughly equal, in accordance with the design of the study.

```
## treatment
## Immediate  Deferred
##       712       713
```

There is a mystery as to how some patients who have not had an EEG have recorded an abnormal EEG result. There are several possible explanations (different types of recording error), but we will assume the patients with an abnormal EEG have had an EEG. We adjust the `eeg` varaible accordingly. Since there are only five subjects in this category it shoudln't substantially affect any results.

```
##    abEEG
## EEG   0   1
##   0  80   5
##   1 554 786
```

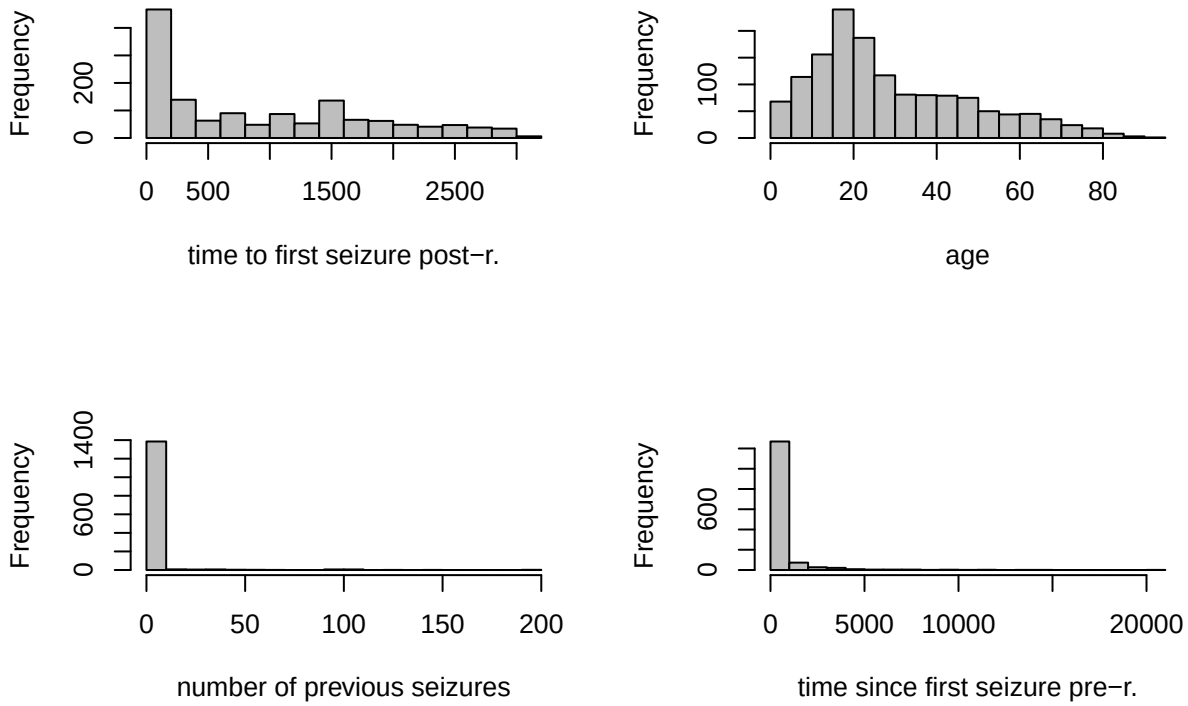
Split age into bins

We use the age categories referred to in Marson et al. (2005).

```
## agecategory
##   [0,5]   (5,9]  (9,19] (19,29] (29,39] (39,49] (49,59] (59,69] (69,92]
##      68      90     379     327     166     150     105      72      68
```

Transform some variables

We plotted histograms of each of the key (non-binary) variables. The variables `nseiz` and `period` are very positively-skewed. This is not surprising since this is a study on early epilepsy, so most subjects have only had one seizure and the first seizure was not long before entering the study.



We will try transforming `period` and `nseiz`. For `nseiz`, we simply use the indicator of whether it is 1 or more than 1, since over half of the patients have `nseiz==1`. We take the logarithm of `period` to reduce the skew.

Select initial set of covariates

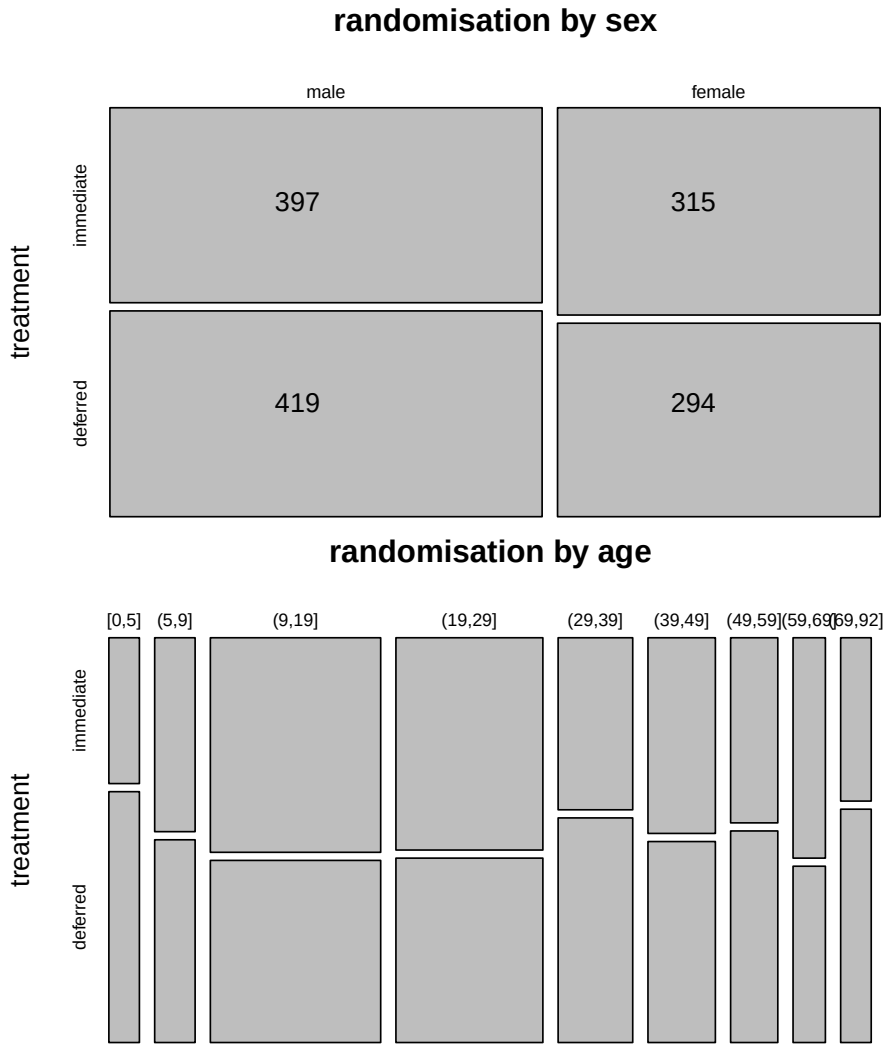
For the purposes of the initial exploratory model fitting, we use a small subset of the covariates. We address the issue of variable selection later on.

We drop all of the date variables because we suspect the absolute time does not matter; relative times are available for many of the events. We also drop the sub-categories for different types of seizures, retaining just the number of tonic-clonic seizures (the most severe type) and the overall number of seizures. We also drop the sub-categories of EEG abnormality, retaining just the overall indicator. We do not include the centre, since there are so many levels it adds too many degrees of freedom, and we have no information about how they might be grouped e.g. geographically.

```
covars1 <- transmute(mess, ager, sex, trt, ntc, nseiz.tr, period.tr, eeg, abeeg)
```

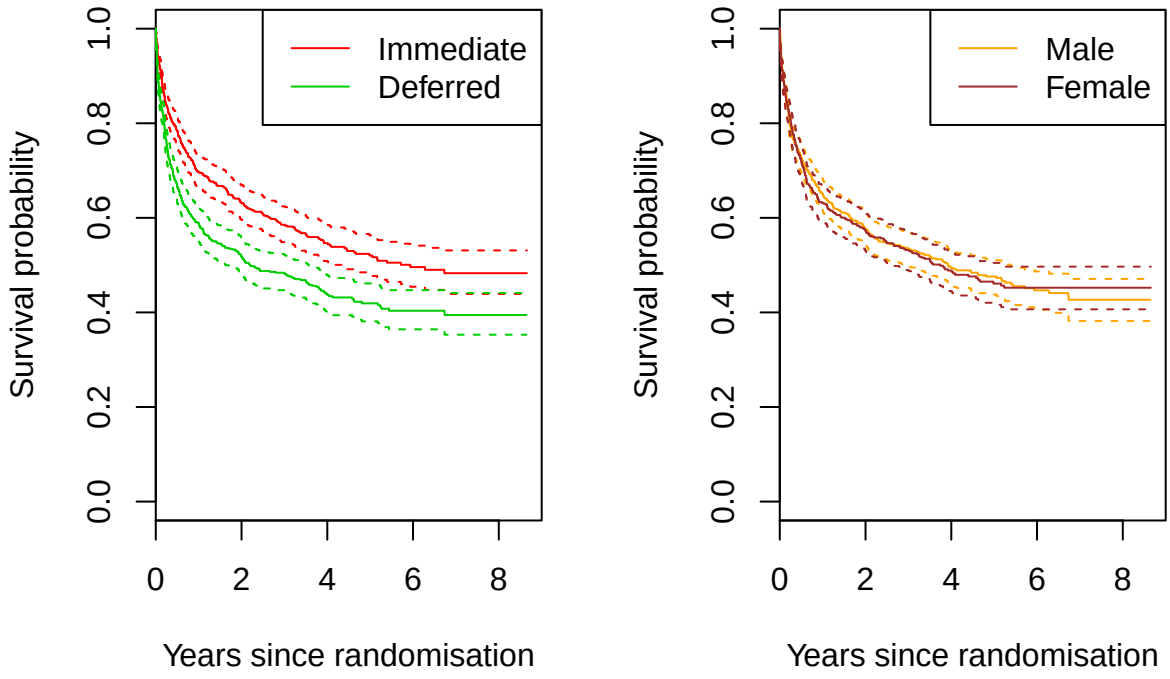
Check balance of randomisation

We check that the randomisation is balanced over sex and age. There is a noticeable deviation from an even split in some categories, but the deviation is not systematic and the overall sample size is large so it should not make a big difference to our results.



Exploratory Kaplan-Meier curves

We plot Kaplan-Meier curves of the first seizure after randomisation, grouped by treatment and sex. The first plot shows that the survival probability for those who received a deferred treatment is lower than for those immediately treated, at least for the first 5 years after the randomisation. From the second plot it seems that sex does not have a significant effect on the survival probability.



Cox proportional hazards model

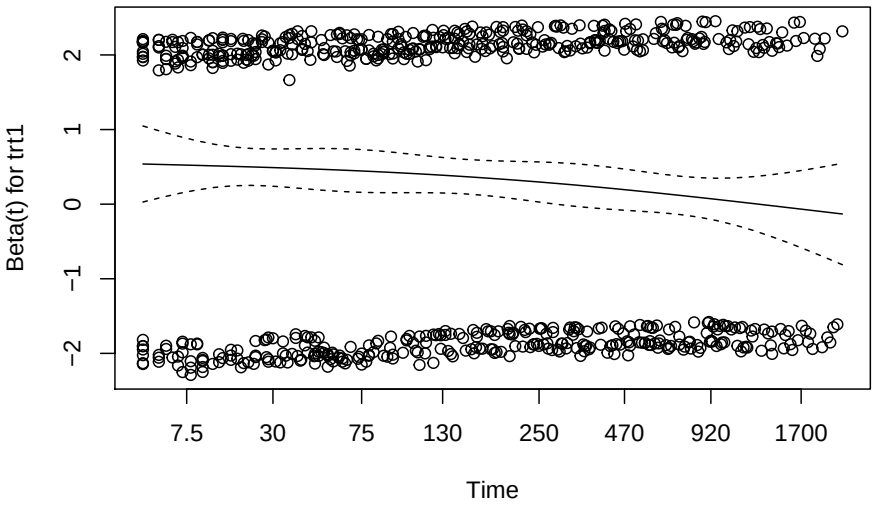
The Cox model relies on the strong assumption of *proportional hazards*, that is that a unit increase in a certain covariate has a multiplicative effect on the hazard rate. In particular, the hazard function λ has the form

$$\lambda(t|X) = \lambda_0(t) \exp(X^T \beta)$$

where X is the matrix of covariates and β is the vector of coefficients to be estimated, and $\lambda_0(t)$ is the baseline hazard (i.e. when all covariates are zero). The exponential of a coefficient $\exp(\beta_i)$ represents the multiplicative effect on the hazard resulting from a unit increase in the corresponding covariate.

First we fit a naive proportional hazards model with the covariates of interest. We see that the treatment `trt` is significant, as is the number `nseiz` of seizures prior to entering the study. This is to be expected since subjects with a tendency for more frequent seizures are likely to go less time before the first post-randomisation seizure regardless of treatment. The elapsed time `period` between the subject's first seizure and their entry into the trial is slightly significant, which is also unsurprising.

Next we assess whether proportional hazards is a suitable assumption for these data. We see from the residual plots that the treatment seems to have a decreasing effect over time and the residuals have mean consistently greater than zero. The residuals of the other covariates don't seem to vary over time. This is confirmed by the small p-value for `trt` in the test of the proportional hazards assumption. The treatment effect decreasing over time is indicative that a proportional hazards model is not suitable, but we will try a few fixes before abandoning the Cox model completely.



Next we try adding into the model an interaction term of treatment with time, to correct for the problem with the first model. We see, as expected, that the interaction term is very significant. However the proportional hazards model is still rejected.

Next we fit the model using the transformed versions of `period` and `nseiz`. The significant covariates are largely the same as in the first model, however the assumption of proportional hazards is not supported in the `trt` and `nseiz` terms.

	coef	exp(coef)	p.coef	p.PH
trt1	0.351	1.420	0.000	0.024
ager	-0.003	0.997	0.193	0.904
sex1	-0.040	0.960	0.604	0.576
nseiz.trTRUE	0.633	1.882	0.000	0.034
period.tr	-0.044	0.957	0.046	0.130

Finally, in the next model we include an interaction term between `trt` and `nseiz`, since it is plausible that the treatment may have a different effect on people who suffer more severely (indicated by having had more seizures previously). With this model the proportional hazards assumption appears to be satisfied. However we find that the interaction term is only slightly significant, and including the interaction drastically reduces the estimated treatment effect.

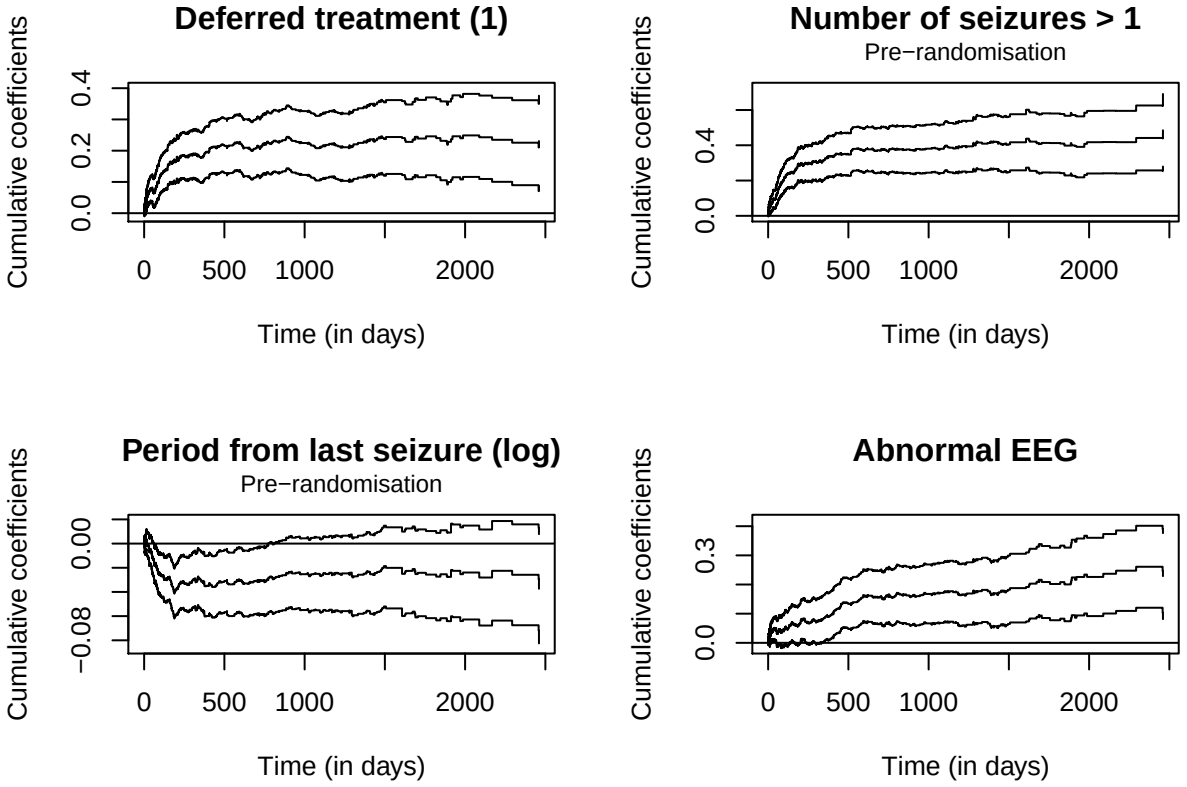
	coef	exp(coef)	p.coef	p.PH
trt1	0.218	1.244	0.047	0.412
ager	-0.003	0.997	0.178	0.901
sex1	-0.045	0.956	0.564	0.584
nseiz.trTRUE	0.494	1.638	0.000	0.386
period.tr	-0.045	0.956	0.043	0.140
trt1:nseiz.trTRUE	0.256	1.292	0.095	0.384

Aalen's additive model

The proportional hazards assumption underlying Cox model might be in many cases too strict and lead to unrealistic conclusions. Moreover, it is not uncommon to consider that the effect of one or more covariates might change over time. In these cases the model proposed by Aalen (1989) provides a flexible way to tackle

these issues. Unlike Cox model, in Aalen's model the effect of the covariate on the hazard function at time t is additive. In other words, the hazard function at time t is a linear function of the covariates. Each coefficient is a function allowed to vary over time; in this sense, the model is fully nonparametric. At time t, the value of the coefficient function is to be read as the variation with respect to the baseline hazard function induced by a change of one unit (level in case of categorical variables) in the covariates.

Aalen's additive model is widely used because of the easiness in the interpretation of the graphical results, that report the cumulative regression coefficient over time with 95% confidence bands. The slope of the cumulative coefficient function gives indeed some information about the effect of a variable on the outcome of interest. For what concerns the effect of deferring the treatment, the cumulative coefficient increases in the first two years approximately after randomisation, then remains flat: this suggests that the hazard ratio is fairly stable until that breakpoint and then it gets closer to 1. In other words, after two years having received the treatment immediately or not has no effect on the time to the next seizure. A similar conclusion can be drawn on the number of seizures pre-randomisation. In addition, the time from the last seizure .... has not a significant effect after approximately 2 years, while the effect of an abnormal EEG is quite constant over time



Parametric survival models

An alternative to the Cox model is to consider a parametric specification for the distribution of survival times. In particular, the class of accelerated failure time (AFT) models provides the natural extension in case the proportional hazard assumption does not work. Following the introduction provided by Hosmer, Lemeshow, and May (2008), it is possible to write the distribution of the time to event for the i-th subject as

$$\log(t_i) = \mu + \beta^T x_i + \sigma\epsilon_i$$

where σ is a scale parameter and ϵ_i is an error term with a prespecified distribution (its choice determines the type of model). The effects in this model are multiplicative on the time scale: in other words, the time to

the event depends on the exponential of the linear combination of the covariates weighted by the coefficients. The name "accelerated failure time" arises from the fact that given

$$t_i = \exp\left[\beta^T x_i\right] \exp\left[\sigma \epsilon_i\right]$$

the effect of the covariates is to "accelerate" or decelerate the time to the event of interest with respect to a subject with baseline characteristics (i.e., the one for which all the covariates assume value zero). This means that if for a given variable the coefficient is positive, the time to the event will increase, hence the effect of the covariate will be protective. Therefore, the sign of the coefficient has to be read in opposite way with respect to the proportional hazards models.

In this report we proposed 4 parametric regression models: exponential, Weibull, lognormal (where ϵ and therefore $ln(t)$ are normally distributed) and loglogistic. The same set of covariates has been used for all of them: namely, `trt`, `sex`, `age`, `nseiz.tr`,`period.tr`, `abeeg`. The selection of the most suitable parametric form is done on the basis of the lowest AIC, that is reached by the lognormal model among the accelerated failure time (AFT) ones considered.

	N.obs	Loglik	df	AIC
exponential	1420	-5900.726	7	11692.63
weibull	1420	-5548.895	8	11024.34
lognormal	1420	-5511.851	8	10950.74
loglogistic	1420	-5527.916	8	10979.20

Once the parametric form has been established, we might consider to include other covariates in the model in order to discover whether they may have an influence on the phenomenon under study. In particular, we fitted a new lognormal model by adding to the previous set of covariates all the variables referring to the type of seizures experienced before randomization (`nsp`, `nps`, `nps`, `nmyo`, `nab`, `naab`, `ntc`, `noth`) and the type of EEG abnormality (`nsab`, `gparsp`, `gparnsp`, `fparsp`, `fparnsp`). In addition, we insert an interaction term between the treatment and the number of seizures pre-randomisation. For comprehensibility we display only the significant covariates here. We point out that many of the variables included in the model (especially those referring to an EEG abnormality) seems to be not significant.

	Value	Std. Error	z	p
(Intercept)	7.096	0.491	14.441	0.000
trt1	-0.502	0.234	-2.147	0.032
nsp	-0.050	0.021	-2.406	0.016
ncp	-0.049	0.015	-3.369	0.001
nps	-0.087	0.032	-2.718	0.007
nmyo	-0.027	0.009	-3.015	0.003
nseiz.trTRUE	-0.988	0.283	-3.490	0.000
period.tr	0.141	0.054	2.621	0.009
abeeg1	-1.199	0.364	-3.294	0.001
nsab1	0.924	0.419	2.207	0.027
trt1:nseiz.trTRUE	-0.732	0.346	-2.117	0.034
Log(scale)	1.042	0.030	35.160	0.000

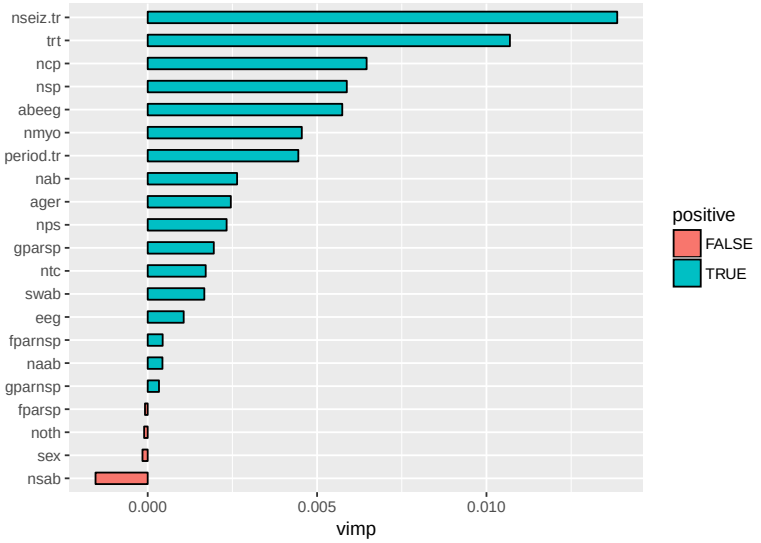
Random survival forests

We would like to ensure that the set of covariates we include in the model is relatively stable. Up to now we have only selected covariates insofar as the fitted log-normal model has some significant and some insignificant

covariates. We now compare the set of significant covariates in the log-normal model to those obtained using a non-parametric variable selection technique, namely random survival forests.

Again we omit the `centre` variable since it destabilises the model, having a large number of levels many of which correspond to only one observation. If we had some additonal information say about suitably groupings of centres it would be sensible to include it. For instance, in Marson et al. (2005) the authors distinguish between UK and non-UK centres. However we do not have any information linking the number of a centre to its location. However we now include the counts of every type of seizure, and the results of all tests, as possible covariates.

We still omit date variables. we found that the error rate didn't really decrease by creating more than 100-200 trees, so we use `ntree = 200`. There is not a universal threshold on the `vimp` above which variables should be considered selected, but in the literature `vimp=0.002` has been suggested as a rule-of-thumb.



As we found in our exploratory analysis, `nseiz` and `trt` are the most important covariates, with `abeeg` also significant. We also see the counts of several particular types of seizure are important, which weren't included in our initial analysis.

The six most important variables in random forests were all significant in the log-normal model, which is encouraging. On the whole, random forests has selected roughly the same variables as the log-normal model, with only a few discrepancies. For instance, `nps` (one of the seizure counts) was significant in the log-normal model (p=0.009) but was not selected by random forests.

For the purposes of our model, we will include only the covariates which the parametric and non-parametric approaches have both selected, namely `nseiz`, `trt`, `ncp`, `nsp`, `abeeg`, and `nmyo`. This captures the most important covariates of each approach.

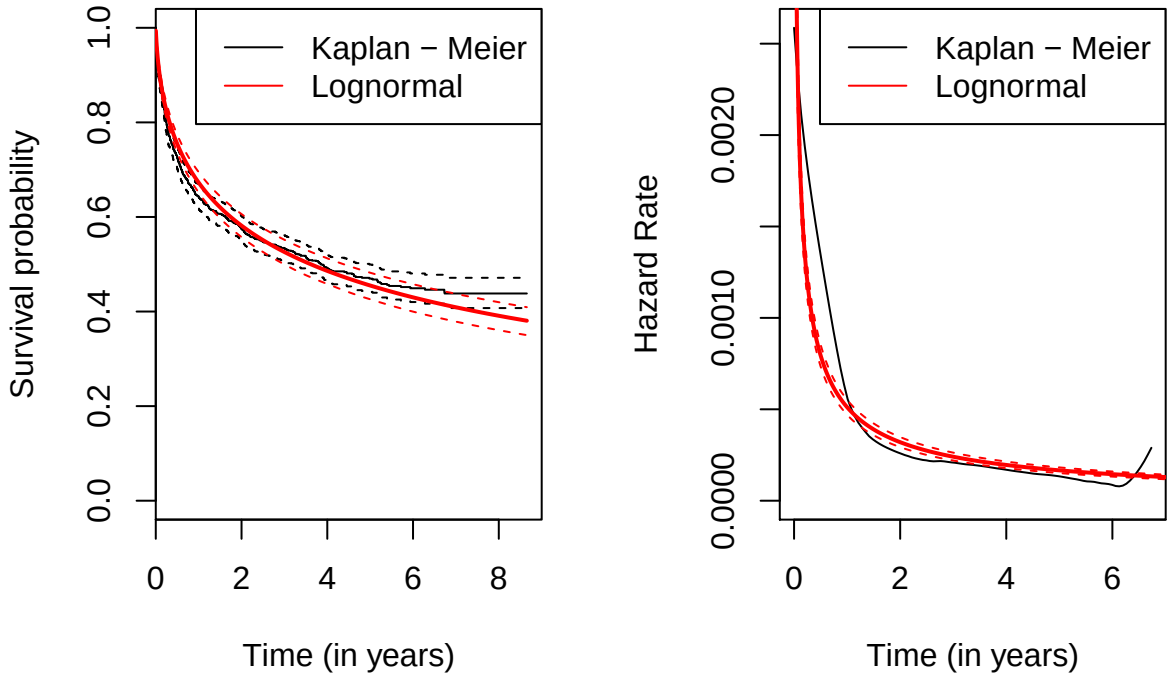
Final model

Given a parametric specification for the model and a restricted set of covariates, we can fit the final model for the data at hand. We are interested in checking also the significance of the interaction term between the treatment and the number of seizures pre-randomisation. The fundamental advantages of such model are the parsimony and the fact that, thanks to the full parametric representation, we can easily predict the survival function for a subject given its characteristics. To make the interpretation simpler and consistent with what observed before, we report also the hazard ratio for each coefficient β, that can be shown to correspond to $HR = \exp[-\beta]$.

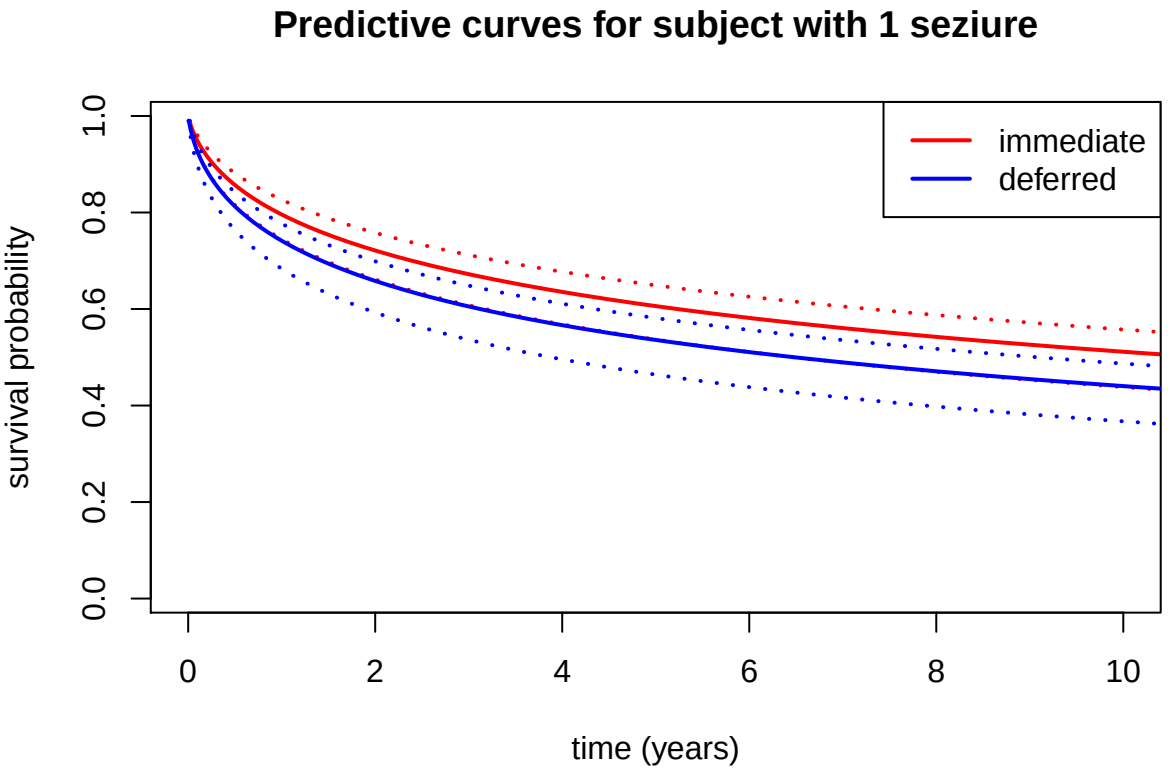
	Coefficient	HR	Std. Error	z	p
(Intercept)	8.286		0.202	41.07	0
trt1	-0.516	1.676	0.236	-2.183	0.029
nseiz.trTRUE	-0.708	2.03	0.253	-2.795	0.005
abeeg1	-0.596	1.815	0.176	-3.378	0.001
ncp	-0.049	1.05	0.015	-3.339	0.001
nsp	-0.046	1.047	0.021	-2.184	0.029
nmyo	-0.026	1.026	0.009	-2.895	0.004
trt1:nseiz.trTRUE	-0.633	1.882	0.348	-1.815	0.069
Log(scale)	1.06		0.03	35.79	0

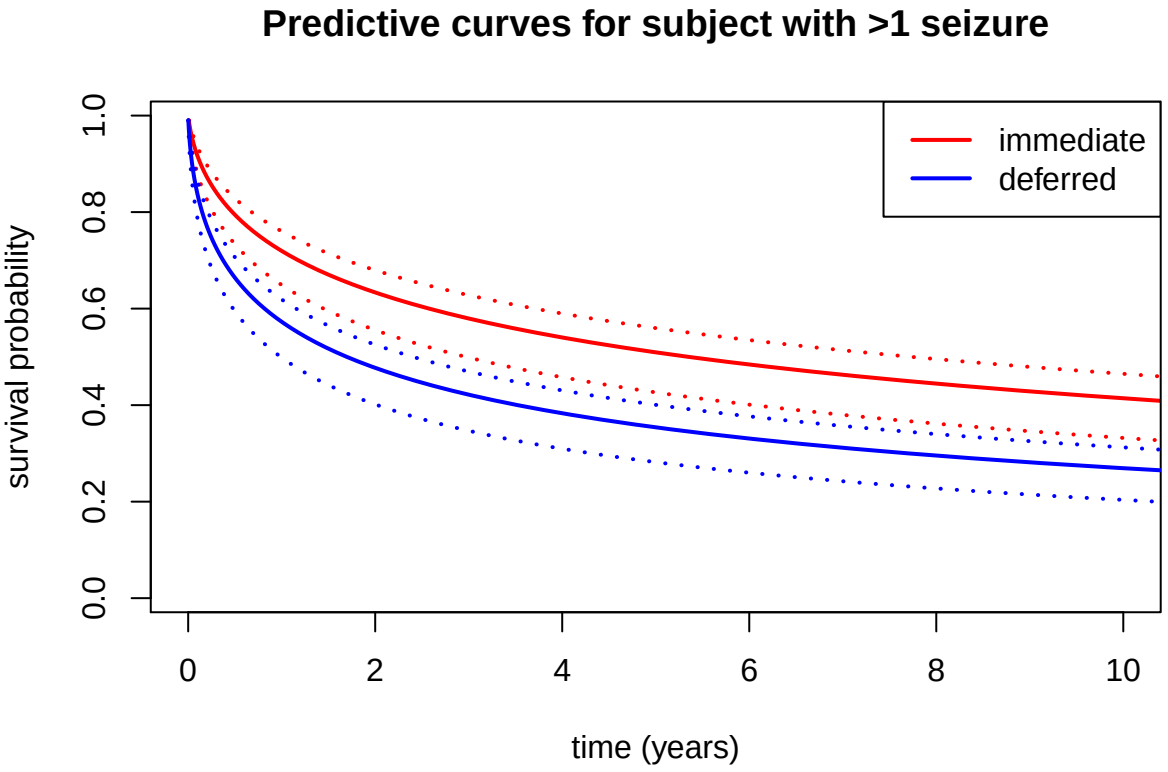
Having a deferred treatment increases the hazard of a new seizure by around 68%; the hazard for a subject with more than a seizure pre-randomisation is approximately double than the one for those with only a seizure, *ceteris paribus*. At a 0.05 significance level, the interaction between the two variables is not significant therefore we can remove this effect. The other variable that induces a relevant change in the hazards is the presence of an abnormal EEG, while the other variables concerning the type of seizures pre-randomisation give a hazard ratio close to 1 but significant.

In this model we assumed that only the location parameter of the lognormal distribution depends on the covariate and we estimated the scale parameter, that is equal to 2.8850143 (we tried to estimate the scale as a function of the treatment, but it turned out to be not significant). The hazard function for this model is non monotonic: it increases up to a maximum value (that depends on the scale parameter - in this case it will be very close to 0 because of the magnitude of this parameter) then decreases as time passes. The fit of our model is assessed graphically by comparing the survival function and hazard function estimated with our model (and the corresponding 95% confidence bands) to the Kaplan-Meier estimates. The two plots indicates that the lognormal model captures the main behaviour of the observed curves after 2 years, but it overestimates the survival probability prior to that time point.



Prediction


Predictive curves for subject with 1 seziure
survival probability
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
time (years)
immediate
deferred


Predictive curves for subject with >1 seizure
survival probability
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
time (years)
immediate
deferred

Further research

The parametric model considered seems to be a good choice for the data at hand. Nevertheless, there are some .... in the first years that may indicate the need for introducing a frailty term that takes into account the variability between subject. Another potential source of variability not addressed in the model is the `centre` variable that may account for some correlation between subjects. Even in this case we might consider to include it as a random effect.

We have considered as our outcome the time to first seizure post-randomisation. The dataset also contains information about the time to second and fifth seizure, and the time to the first tonic-clonic seizure. Additionally investigating these outcomes could enrich the results and establish the longevity of the treatment effect.

Alternatively, working with the first seizure outcome, we could transform the outcome to an indicator "seizure free for first six months Y/N" or similar, and fit a logistic model. This outcome is of interest because it determines whether or not a patient is allowed to drive again.

Another way to look at the data is to consider each patient as having their own unobserved seizure rate λ_i pre-randomisation, and consider the treatment effect in terms of how this compares to their post-treatment seizure rate, say γ_i. This is quite different to the standard medical statistics approaches we have used, but makes sense from a modelling perspective. This approach was treat in Cowling, Hutton, and Shaw (2006).

References

Aalen, Odd O. 1989. "A Linear Regression Model for the Analysis of Life Times." *Statistics in Medicine* 8 (8). Wiley Online Library: 907–25.

Cowling, BJ, JL Hutton, and JEH Shaw. 2006. "Joint Modelling of Event Counts and Survival Times." *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 55 (1). Wiley Online Library: 31–39.

Hosmer, David W., Stanley Lemeshow, and Susanne May. 2008. "Parametric Regression Models." In *Applied Survival Analysis*, 244–85. John Wiley & Sons, Inc. doi:10.1002/9780470258019.ch8.

Marson, A, A Jacoby, A Johnson, L Kim, C Gamble, D Chadwick, Medical Research Council MESS Study Group, and others. 2005. "Immediate Versus Deferred Antiepileptic Drug Treatment for Early Epilepsy and Single Seizures: A Randomised Controlled Trial." *The Lancet* 365 (9476). Elsevier: 2007–13.