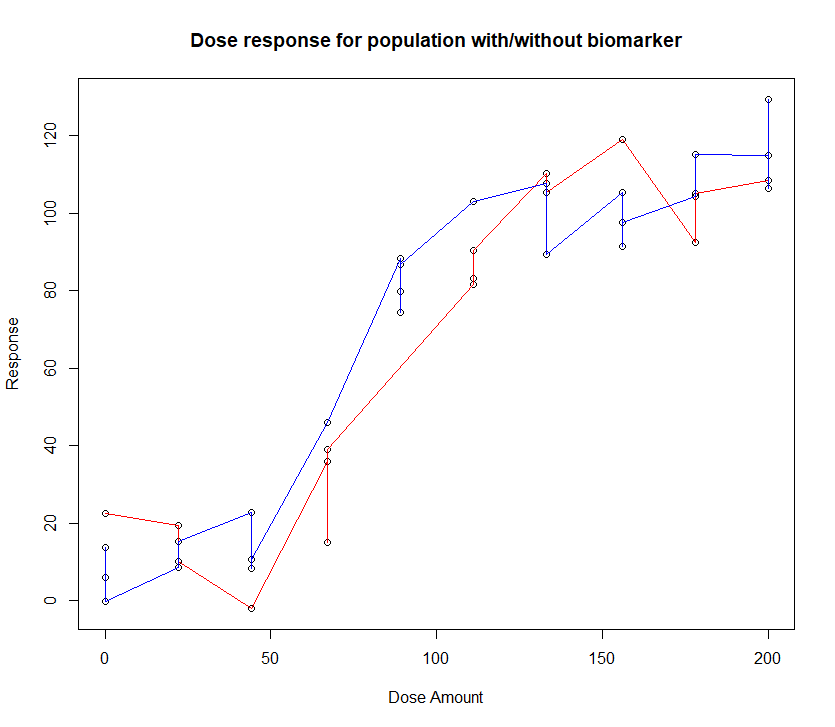
MA40198 Coursework

Introduction and Aim

This statistical report explores the capabilities of a new pharmaceutical treatment; primarily finding the maximum safe dosage of the treatment. The collated data is from a Phase one clinical trial where only a few patients (40 in total) are tested on and, if deemed safe, the treatment will pass onto the next stage of the clinical trial. Three observations were measured in each of the patients: the dose received, the measured response of the dose and the presence of a certain biomarker.

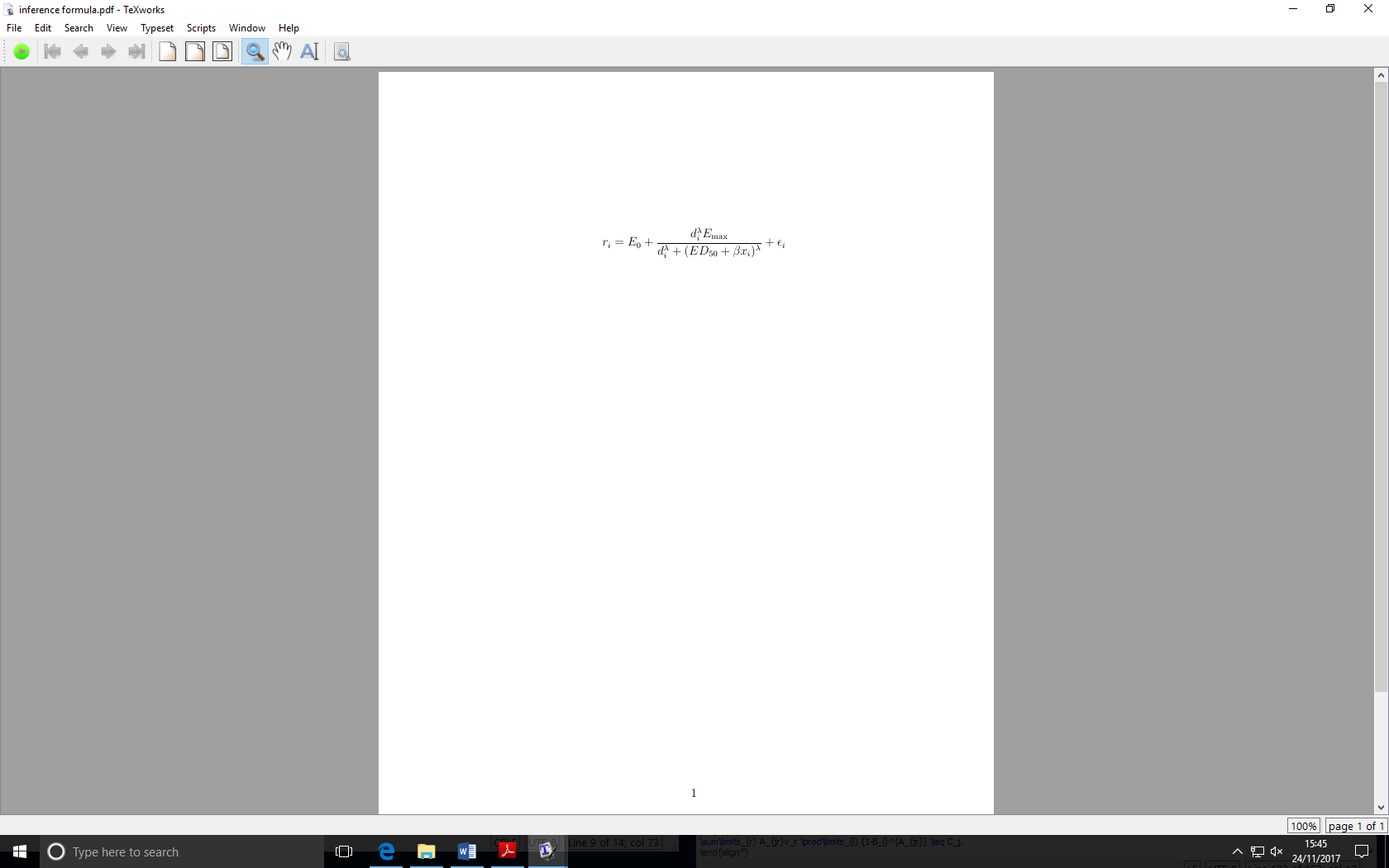
The second part of this analysis is to study whether the biomarker, identified by clinicians, will raise the tolerance of the patient in response to the treatment. Therefore, the hypothesis test for this analysis is as follows: the null hypothesis is that the biomarker does not affect the tolerance of the patient to the treatment against the alternative hypothesis whereas the biomarker does affect the tolerance to the treatment. However from our initial analysis of the data, we plotted a graph (shown below) of the response of the individuals against the dose amount with the biomarker (in red) and without the biomarker (in blue). From this graph we expect to accept the alternative hypothesis and be able to fit a model to the data



Finally, the third part of this analysis is to know more about giving 30 percent of the maximum dosage in order to set the maximum safe dosage for the treatment; denoted as ED30 here and defined in full below where the clinicians want to use the highest available dose below ED30.

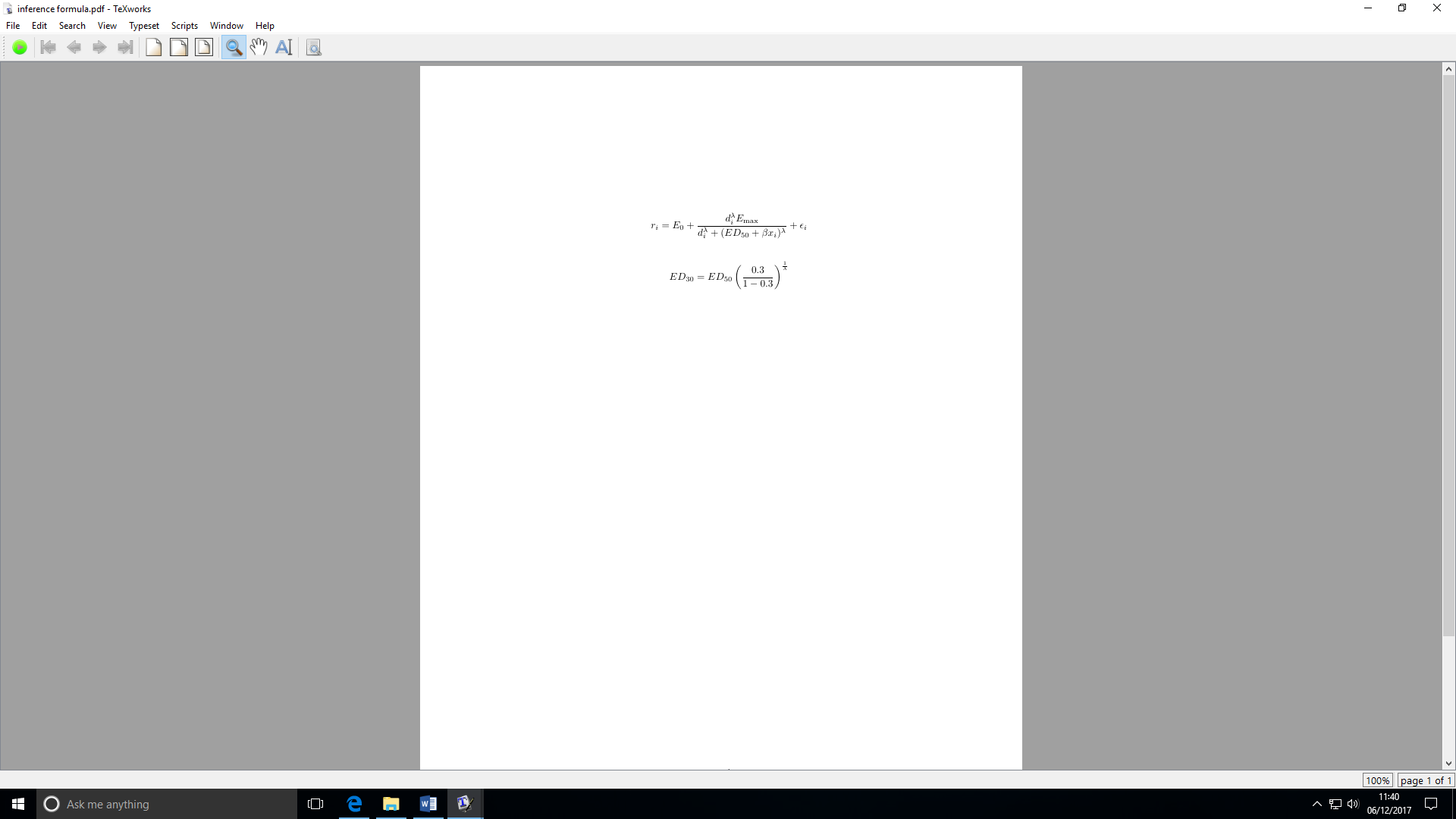
The model considered

To model the response of the dose, we use the four parameter Emax model. This model is shown below:



Where the terms can be defined as follows: ri := is the measure response for the dose for the ith patient; di := is the dose given to the ith patient; xi:= indicates whether the ith patient has the biomarker (given as 1) or not (given as 0); E0:= this is the response when the drug is not given, sometimes given as the placebo effect the patient has when given the treatment in which the model adjusts for this; λ:= is known as the slope factor defined as sensitivity measured to the dose of the treatment; ED50:= the dose of the treatment which is half of Emax; β:= measures the change in ED50  with the biomarker is present in the patient; εi:= is the error term for patient ith for εi~N(0,σ2).

Furthermore, ED30 is defined as:



The Emax model can be deemed suitable for analysing this trial in several ways. Firstly, this model adapts to the placebo effect, E0, therefore the model shifts around E0 meaning that this will not lead to a distortion in the results and giving more credit to the treatment. Secondly, the model accounts for the presence of the biomarker, denoted by xi, so it is possible to determine how and if the biomarker affects the patients’ tolerance to the treatment; which is one of the aims if this analysis. Thirdly, the use of the slope factor coefficient, λ, accounts for the sensitivity to the dose of the treatment and is helpful to understand the relative differences between the levels of dosage given.

The function ll returns the log likelihood of the four parameter Emax model. An output is only calculated if ED50+beta1 is greater than zero else the output is minus infinity. This ensures that we are only using real numbers and positive doses. In physical terms, the patient would have an unlimited tolerance to the treatment which is not possible. Therefore the function would just return out which is defined as negative infinite.

The function pri returns the prior of our parameters where E0 has a normal distribution with mean 0 and standard deviation 10. Emax also has a normal distribution with mean 100 and standard deviation 10. ED50 has a beta distribution with shape parameters 2.5 and 5. Lambda has a uniform distribution between the interval 0.5 and 3. The standard deviation has a proposed truncated normal distribution with mean 3 and standard deviation 5. Finally beta has a normal distribution with mean 10 and standard deviation 4. Then we are returning the log likelihood of our proposed distribution making sure ED50+beta1 is greater than zero.

Metropolis-Hastings: Results

After performing a first run of the Metropolis-Hastings algorithm, we tested for correlation between the posterior distribution of each parameter in the model. To do this, we calculated the sample correlation between each parameter and also performed Pearson’s product-moment correlation test, to assess whether the sample correlation is significantly different than zero. The results of these tests determined that the correlations between each pair of parameters is significant, though close to zero in some cases. Thus, a second Metropolis-Hastings sampled is proposed, but now we will take into consideration this correlation between parameters and sample multivariate normal distributions at each step, using the covariance matrix from the posterior distributions as an input for the second attempt.

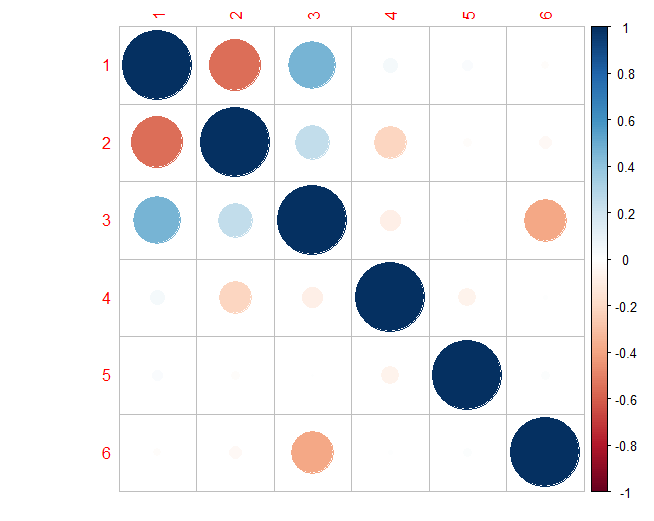


Figure 2: A pictorial diagram of the Pearson’s product-moment correlation test between the six parameters

Now, having generated two different proposals for the posterior distribution of the parameters, we perform tests to decide which proposal provides a better description of the model.

First, we need to test for convergence of the parameters, by subsampling independent observations of each parameter, for each of the two proposals. This independent subsampling is done by calculating the autocorrelation length, , of the -th parameter and keeping the -th element of the vector of observed values for each parameter. Afterwards, we divide our independent samples into two populations and perform the two-sample Kolmogorov-Smirnov to test if the populations follow the same distribution. (Remark: This procedure is performed on the two proposals for the posterior distribution). We say that the proposal for the posterior distribution converged if, for each parameter, the Kolmogorov-Smirnoff test yielded a p-value greater than 5%.

The following results were observed:

* The samples of the posterior distribution obtained from the first Metropolis-Hastings sampler converged.
* The samples of the posterior distribution obtained from the second Metropolis-Hastings sampler, which took into consideration the correlation between the parameters, converged.

Having two feasible proposals for the posterior distribution of the parameters, we have to decide which provides a better fit. We do this by calculating the Deviance Information Criterion (DIC) on each proposal, we will keep the one with the lowest DIC. After computing the DIC for both proposals we observe these results:

* The samples of the posterior distribution from the first Metropolis-Hastings sampler have a DIC of 127.9149
* The samples of the posterior distribution from the second Metropolis-Hastings sampler have a DIC of 127.7179

Even though the difference is small, including the correlations from the posterior distribution provides a better fit and this is the model we shall use.

Conclusion

Having considered the tolerance levels of the individuals in the phase one of the trial with and without the biomarker, it would be advisable for the clinicians to set the maximal safe dose to ED30 for future trials.

<http://www.math.chalmers.se/~rootzen/finrisk/reportwriting0315.pdf> : for how to write a report

<https://www.wikihow.com/Write-a-Statistical-Report>

<http://file.zums.ac.ir/ebook/75-Dose%20Finding%20in%20Drug%20Development%20(Statistics%20for%20Biology%20and%20Health)-Naitee%20Ting-0387290745-Sp.pdf>