

Applying Bayesian Hierarchical Models to N-of-1 Trials

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Introduction

N-of-1 trials in clinical practice are multiple crossover trials conducted on a single patient, where treatment periods are formed into multiple blocks each containing at least one period of each treatment under consideration [1]. By comparing the measurements taken during different treatment regimes over multiple blocks, the most suitable treatment option can be chosen for the particular patient studied.

In the following pages we will go through a concise explanation of the experimental design of N-of-1 trials and how we can statistically model them given the kinds of challenges their design poses. I then follow up with how we can apply Bayesian methods in estimating the effectiveness of different treatments, highlighting how these methods can give needed flexibility when running N-of-1 trials by not relying on hypothesis testing tied to a prespecified study design. We then consider the case when there are multiple similar N-of-1 trials and show how it is possible to pool the information from these with hierarchical Bayesian methods, without losing sight of the goal of N-of-1 trials: to find the best treatment for each individual patient. Finally we end by with a complete example of analyzing multiple N-of-1 trials with hierarchical Bayesian methods with Python using PYMC3-package with simulated data.

Chapter 1

What Are N-of-1 Trials?

In the assessment of any medical treatment the “gold standard” is a randomized controlled trial (RCT), where subjects are randomized to two or more groups that are given different treatments or no treatment at all. The measurement from these groups are then compared and a result derived about which treatment is most effective on average. This design takes into account unknown factors that might make some patients more susceptible to certain treatments by forming the groups randomly and thus, on average, distributing these patients evenly between groups. By comparing the groups against each other and not just to the same patients at the beginning and end of the study, it also takes into account time related effects like natural progression of disease. Despite its unquestionable value in finding general effects, this method can run into problems when we actually try to apply its results to individual patients in clinical practice.

Knowing the best treatment in average might not help much in finding right treatment for a particular patient if the variability in treatment effectiveness between patients is high. Although we can use covariates like age, gender, or a certain gene variant to explain the variance between patients in RCT:s, there usually is still much unexplained variance left after this (TODO source). Some of this variance is of course caused by random factors like measurement error, but a significant part might be caused by real differences between the patients. In other words, there might be individual factors that explain the variability of the efficacy of different treatments between patients that might either be too specific to be considered in a RCT study or unknown and thus impossible to analyze in this kind of experimental design.

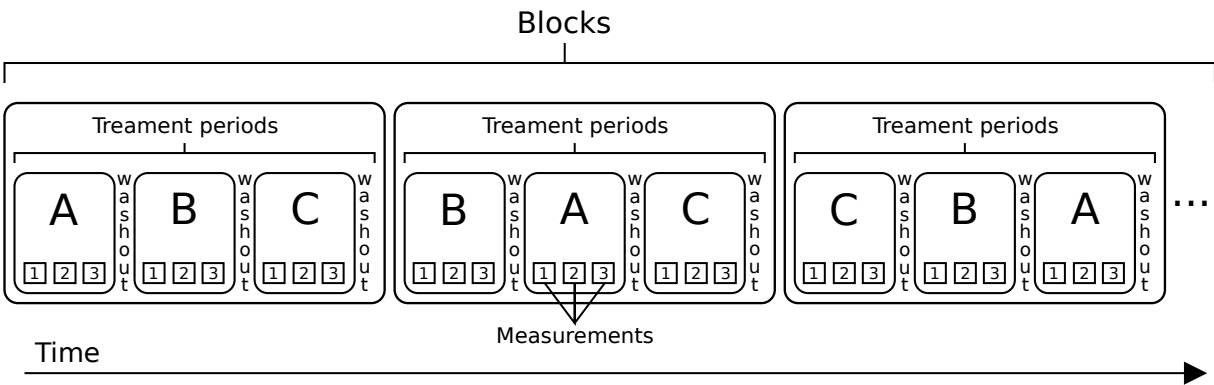
Another problem with RCT:s is the peculiarity of their participants. It is common practice to accept patients to RCT:s only if they don’t suffer from any medical issue besides the one that is being studied. This lack of comorbidity makes it easier to get clear results by removing confounding factors, but at the same time this lowers the external validity of the results, because in the real world patients often suffer from multiple medical issues

simultaneously (TODO source?). Because of this, it might be possible that even when the scientific literature provides clear results about the relative effectiveness of different treatments, these results don't actually generalize that well to the kinds of patients the clinical practitioner sees daily in her office.

N-of-1 trials can be used to patch the holes in the knowledge that RCT:s cannot fill by changing the focus of the study from group averages to the individual patients. In N-of-1 studies, instead of comparing groups with different treatments, the comparisons are made across time with a single patient using different treatments. In this design multiple treatments are tried sequentially in periods that are formed into blocks each of which contains a treatment period of each treatment option under consideration at least once. Measurements are taken throughout the study and, depending on the ease of measuring the outcome of interest, these could be taken just once per treatment period, or even multiple times per day. Each block includes a period of each treatment under consideration in random or balanced order to take into account time related effects. A simple example would be an ABBA design that includes two blocks within which the two treatments A and B are assigned in a balanced order.

Depending on the treatments considered, there might be also be a so called "washout" period between treatments, where the patient does not receive any treatment and her state is allowed to return to baseline. This method is used to prevent treatment interactions that could make it difficult to analyze the results or could be dangerous to the patient. If the treatments under study allow, N-of-1 trial can also use the double-blind method, where both the patient and the person administering the treatment don't know which treatment is currently used, and placebo treatment, where one of the treatments only resembles treatment, but does not contain any active ingredient (pharmacological or otherwise).

Below is schema of a more complex N-of-1 trial with three treatments A, B and C, random assignment of treatments within blocks, three measurements within each treatment period and a washout periods between treatments:



The stated aim of N-of-1 trials is quite different from RCT:s: where the latter tries

to generalize results to population and find which treatment is best in general, the N-of-1 trial tries to only generalize to the patient in question. This means that whereas comorbidity and other factors that cause systematic variation between the patients in treatment outcomes are a problem in RCT:s, these are not an issue in N-of-1 trials because there is no need to generalize beyond the one patient. There is also often no actual need to know what is causing a certain treatment to work better or worse, as long as it is not because of measurement errors or time related effect.

Use of N-of-1 trials is appropriate in situations where there are multiple treatment options but there is no prior knowledge of which of these would be best, when there is known to be considerable variability between patients in treatment efficacy, or when there is reason to doubt that the results from scientific literature generalize to the patient in question [1]. This would seem to make n-of-1 trials applicable to many situations, but there are also multiple factor restricting their use [1].

Firstly, N-of-1 trials can only be used to study illnesses that are chronic, progress slowly and are at least somewhat stable. Also the treatments options available must have a noticeable treatment responses within a short timeframe. Running the trials needs time to complete and fast changing illness or slowly effecting treatment make it either impossible to distinguish true effects from the natural progression of the disease or make the length of the trials impractically long. N-of-1 trials are also unsuitable for testing of preventative treatments because the effects of these treatments are often impossible to assess without comparisons to other patients who are not receiving the treatment.

Secondly, running a N-of-1 trial is costly because of added expenses of training the medical staff in the method, running the trial with all its measurements and analyzing the data. This is means that it can be hard to find cases where using this method is cost effective and studies trying to make these kind calculations have given mixed results [2].

These limitations have kept the use of N-of-1 trials rare in clinical use, even though they could potentially both increase the life quality of the patients and lower the health-care costs by finding most suitable medications to patients that might end up potentially using them for years. This state of affairs might be changing fast though. Aging and environmental factors are changing worlds disease burden so that a growing proportion of it is constituted by chronic diseases [5], of which common ones like non-acute cardiovascular diseases and diabetes are excellent candidates for N-of-1 trials. Also the cost of administering N-of-1 trials are dropping with advent of cheap and reliable health sensors like smartwatches and connected blood pressure monitors. For example in diabetic patients it is now possible to get real time readings of blood insuline levels with minimal effort from the patient [6]. These factors mean that the popularity of this method could potentially rise significantly in the future.

Chapter 2

Statistical Modeling of N-of-1 Trials

Even though the data created by the N-of-1 trials resembles traditional time series data with autocorrelation between observations and repeated measurements from the same study unit, there are additional complexities from the structure of repeating treatment periods. Trying to take into account all the peculiarities of the study design could end up with model too complicated to the small amount of data generated by a single study, so one must consider carefully what factors actually need to be incorporated in to the model.

Simplest model that we could employ is to just count the number of blocks where a treatment is considered “better” than others. The precise definition of “better” doesn’t matter here. This way we arrive to a simple binomial model where the number of “successes” X is the number of blocks where a treatment is considered the “best” follows binomial distribution and the probability of each treatment option of having k successes is given by:

$$(2.1) \quad P(X = k) = \binom{n}{k} p^k (1 - p)^{(n-k)},$$

where k = number of blocks, where the treatments is considered the “best”, n = total number of blocks and p = the probability of being considered the “best”.

This type of model is rudimentary at best, because it fails to consider the magnitude of the differences between treatment effects and does not take into account the actual number of measurements within each treatment period. To take these factors into account, more complex models are in order.

2.1 Basic Models

Before going further we make the assumption that the measurements are continuous as this is probably the most common use case. Lets first look at a model where we assume that there are no time-trends and no autocorrelation between measurements. Let y_{mbpt} represent the outcome measured while on treatment m within treatment block b within treatment period p at time t . The treatment periods are indexed within each block and time is indexed within each treatment period:

$$(2.2) \quad y_{mbpt} = \mu_m + \gamma_b + \delta_{p(b)} + \epsilon_{t(p(b))},$$

where $\gamma_b \sim N(0, \sigma_\gamma^2)$, $\delta_{p(b)} \sim N(0, \sigma_\delta^2)$, and $\epsilon_{t(p(b))} \sim N(0, \sigma_\epsilon^2)$

This model assumes all treatment effects μ_m to be constant. Within the normally distributed terms γ_b represents random block effects, $\delta_{p(b)}$ random period effects and $\epsilon_{t(p(b))}$ random within period errors. We could choose one of the blocks as a reference and set $\gamma_1 = 0$ and assume that within each block the between period effects follow the same pattern, e.g. the difference between treatment period one and two is the same within each block.

The random effects between blocks and treatment periods could represent for example the random variations in the motivation of the patient and possible changes in treating personnel within each block and treatment period. The random within period errors represents the measurement error of single measurements within treatment periods. The relative size of these terms is important for effective design of the trial, because they determine if it is more beneficial for the statistical power of the study to add more measurements, treatment periods or blocks.

If the measurements within blocks and within periods do not correlate, the model 2.2 can be simplified by dropping γ_b and $\delta_{p(b)}$:

$$(2.3) \quad y_{mbpt} = \mu_m + \epsilon_{t(p(b))},$$

where $\epsilon_{t(p(b))} \sim N(0, \sigma_\epsilon^2)$.

This simple model is a natural fit in scenarios where there is just one measurement within each treatment period.

2.2 Incorporating time-trends into the model

As the symptoms of the patient might not be completely stable (e.g. because symptoms get worse with the progression of the disease) fitting some kind of time-trend to the model

is usually advisable. We can modify the model 2.3 from previous chapter to include a linear time-trend by adding an intercept and slope of the time-trend. In this case the model can be expressed more concisely just in terms of the measurement y_t taken at time t , where time is indexed from the start of the study:

$$(2.4) \quad y_t = \beta_0 + \beta_1 t + \mu_t + \epsilon_t,$$

where $\epsilon_t \sim N(0, \sigma^2)$.

Here β_0 is the intercept, β_1 the slope of the time trend, μ_t the effect of the treatment given during time t and ϵ_t is the residual error at time t . More complex time-trends can be introduced by modifying the slope, for example by adding the term $\beta_2 t^2$ to introduce a quadratic trend.

Another effect dependent on time to take into consideration are period effects. There might be some part of the trial that falls within a period that we presume to have its own effect. An example of this kind of effect is if we study asthma medications and part of the trial falls within the pollen season. A simple way to model this is to use a dummy variable that takes the value 1 within the period and 0 outside it. Extending the model 2.4 with a period of constant effect β_2 we end up with:

$$(2.5) \quad y_t = \beta_0 + \beta_1 t + \beta_2 Z_t + \mu_t + \epsilon_t,$$

where $\epsilon_t \sim N(0, \sigma^2)$ and dummy variable $Z_t = 1$ when $t \in (t_{\text{period start}} \dots t_{\text{period end}})$ and 0 otherwise.

Lastly, to take into account that treatment effects themselves can vary with time, for example because treatment works better during periods of greater disease severity, we can add a time-by-treatment interaction effect into the model. For example in the case where we expect that the illness gets steadily (linearly) worse with time, but the treatments compensate this by being similarly more effective, we can extend the simple linear time-trend model 2.4 by adding a second time related treatment term $\gamma_t t$:

$$(2.6) \quad y_t = \beta_0 + \beta_1 t + \mu_t + \gamma_t t + \epsilon_t,$$

where $\epsilon_t \sim N(0, \sigma^2)$

2.3 The Problem of Autocorrelation

A common occurrence in time-series data is the autocorrelation between measurements, so that there is similarity between observations defined by a function of time lag between

them. Often a good first response to this problem is to add a time-trend to the model like we did previously. This often removes a substantial proportion of the autocorrelation that could be caused for example by the natural progression of disease or seasonal variations in its symptoms [3]. Unfortunately in N-of-1 trials the carryover effects from previous treatments and slow onset of treatment effects can lead to very complex autocorrelation patterns that are hard to remove with just a simple time-trend.

Carryover effects refer to the lingering effects of the treatment even after it has been stopped. This can make the treatment effects in next treatment period with a different treatment seem larger than they actually are or smaller in the unfortunate and hopefully rare case where the previous treatment was actually harmful. Carryover effects also encompass the effects of interactions between sequential treatments, which could even be dangerous depending on the nature of the treatments. On the other hand treatment effects that manifest slowly can often give the opposite effect of carryover effects by making the treatments look less effective than they really are during the first measurements of each treatment period.[3]

To deal with these more devious sources of autocorrelation in our model we can take two routes: moving average models and autoregressive models. In moving average models the error is represented as depending on the previous error(s), by expressing the measurement at time t as function of one or more previous errors:

$$(2.7) \quad y_t = \mu_t + \epsilon_t + \rho\epsilon_{(t-1)},$$

where μ_t is the effect of the treatment given at time t , ρ is the correlation between consecutive errors and all errors $\epsilon \sim N(0, \sigma^2)$. Instead of making the measurement dependent on just the previous error the model can be adjusted to include more a complex lag by adding more error terms with bigger lag and including more ρ terms to denote the correlations between them ($\rho_1\epsilon_{t-1} + \dots + \rho_x\epsilon_{t-x}$).

In autoregressive models approach we express the autocorrelation in the measurements themselves so that the measurement at time t is a function of the measurement at $t - 1$:

$$(2.8) \quad y_t = \rho y_{t-1} + \mu_t + \epsilon_t,$$

where μ_t is the effect of the treatment given at time t , ρ is the correlation between consecutive measurements and $\epsilon_t \sim N(0, \sigma^2)$ is the error term. Like with moving average model we could also include more than just one lag by adding more lagged terms and correlation terms.

Although it can make more intuitive sense to make whole observation dependent on the previous observation, it is important to recognize that in this case the treatment

effects μ_t must be interpreted differently as they are in this case conditioned on previous measurements.

Moving average models and autoregressive models are often combined by using both methods of taking the autocorrelation in to account simultaneously (ARMA-models), but as amount of data produced in N-of-1 studies is often so small, taking this approach might not be advisable as it might make the model unnecessarily complex.

Although we can try to solve problems created by carryover effect and slow manifestation of treatment effect with modelling, a better way could be to take measures to mitigate the effects in the study design itself. By having long enough washout period between different treatments, we can minimize the carryover effect. If there are no harmful interactions between the treatment the next treatment can be started within the washout period so that we minimize the problem of slow treatment effects. If there are interactions to be taken into consideration, the first few measurement at the beginning of each treatment period could also just be dropped. By doing this we are of course throwing away data, but we must remember that if the measurements at the beginning of the treatment period are mangled, this will also mangle our parameter estimates. Trying to take these effects into account in our model will probably not eliminate these effects completely and will increase the complexity of our model.

2.4 Non-continuous Measurements

Up to this point we have assumed that the measurement used are continuous, but we could of course have measurements that are binary, counts of events or categorical. With these kind of measurement the models need to be reformatted so that they don't presume normal distributions. Despite this the models still don't have to differ much from the models presented above and the principals covered before can be applied.

To modify previously presented models to work when measurements are not continuous, we need to formulate them as generalized linear models. We do this by keeping the right-hand sides in the same form but expressing the left-hand side in terms of link function of the mean of the probability distribution of the outcomes. So instead of expressing the model in terms of individual observations y_t , we express it as the expected value of these measurements conditional on the data $E(Y|D)$ that we feed to the link function. The link function allows us to model measurements with arbitrary distributions, as now the link function can linearly depend on the parameters of the model, rather than needing the measurements themselves to do so. We need to do this to prevent the models from giving impossible predictions, e.g. negative counts or probabilities.

Let's work with an example of a binary outcome measurements. In this case the measurements y at time t follow the Bernoulli distribution $y_t \sim \text{Bernoulli}(p)$ where

the the expected value of the distribution is the probability p of observing the event in measurement y_t . In this case the suitable link function is the logit function $\text{logit}(p) = \log_e(\frac{p}{1-p})$. With this information we can now formulate a simple model with a linear time trend:

$$(2.9) \quad \log_e\left(\frac{p_t}{1-p_t}\right) = \beta_0 + \beta_1 t + \mu_t,$$

where p_t is the the probability of observing the event at time t and $\log_e(\frac{p_t}{1-p_t})$ are the log-odds of this event, β_0 is the intercept, β_1 the slope of the time trend and μ_t the effect of the treatment given during time t .

By first exponentiating and then using simple algebraic manipulation we can express the model in terms of the probability p_t :

$$(2.10) \quad \frac{p_t}{1-p_t} = e^{\beta_0 + \beta_1 t + \mu_t}$$

$$(2.11) \quad p_t = \frac{e^{\beta_0 + \beta_1 t + \mu_t}}{e^{\beta_0 + \beta_1 t + \mu_t} + 1} = \frac{1}{1 + e^{-(\beta_0 + \beta_1 t + \mu_t)}}$$

We notice that there are no error terms in this model. This is because we are not modelling individual observations, but the expected value of these values (probability of observing the event under treatment used at time t in this case). Even though there is random variations in the individual observations, when we talk about their expected value, there is just a single value with no random errors. Apart from this difference we can see that we find the same model from the denominator that we used when modelling a continuous measurement with a linear time-trend in model 2.4, but without the aforementioned error term. This means that to build the models described before, we would just insert the right side of the equations into the denominator, apart from the error term.

With numbers of events as measurements, instead of expressing the model in terms of time, we can express it in terms of periods p that are of equal length and indexed from the beginning of the experiment. The number of events during period p follows a Poisson distribution $y_p \sim \text{Poisson}(\lambda)$ and the expected value of the distribution is the rate λ_p of the events during period p . For link function we use the natural log that is we have $\log_e(\lambda_p)$ on the left side of the equation. Once again using the same simple model with linear time trend we end up with a model:

$$(2.12) \quad \log_e(\lambda_p) = \beta_0 + \beta_1 r + \mu_p,$$

where λ_p is the the rate of events between measurements during period p , β_0 is the intercept, β_1 the slope of the time trend and μ_p the effect of the treatment given during period p . By simply exponentiating both sides we can express the model in terms of rate of events:

$$(2.13) \quad \lambda_t = e^{\beta_0 + \beta_1 t + \mu_t},$$

where we now have the familiar linear model formula in the exponent on the right side of the equation.

The case of categorical measurements is more complex as there are multiple possible link functions depending on which way we want to model the measurements, so we don't go through all of them here. The one that is probably the most relevant is the case when categorical measurements are ordinal, that is they have a natural ordering (like in a Likert-scale). In this case we can use the cumulative logit as the link function. So if we assume that our ordinal measurement has J categorical choices ordered from 1 to J , we can model the cumulative probability of getting a response y at time t that is at least as "severe", by putting this to the logit function and using the same basic model as before:

$$(2.14) \quad \log_e \left(\frac{P(y_i \leq j)}{1 - P(y_i \leq j)} \right) = \beta_0 + \beta_1 t + \mu_t,$$

where β_0 is the intercept, β_1 the slope of the time trend and μ_t the effect of the treatment given during time t . By exponentiating and algebraic manipulation we end up with similar model as with binary outcomes where we once again find the familiar linear model formula in the exponent:

$$(2.15) \quad \frac{P(y_i \leq j)}{1 - P(y_i \leq j)} = e^{\beta_0 + \beta_1 t + \mu_t}$$

$$(2.16) \quad P(y_i \leq j) = \frac{e^{\beta_0 + \beta_1 t + \mu_t}}{e^{\beta_0 + \beta_1 t + \mu_t} + 1} = \frac{1}{1 + e^{-(\beta_0 + \beta_1 t + \mu_t)}}$$

Chapter 3

Bayesian Estimation

Now that we have some models defined, we need to move into the next part of the analysis and actually give estimates to the parameters in these models. There are two broad ways to approach this task by using two different definitions of probability. The first is frequentist inference, where we consider the “true” parameters of our model fixed, but unknown, and randomness only applies to the process of creating our data. The second way is Bayesian inference, where we consider the data to be fixed and instead of thinking about the parameters as fixed parts of nature, we conceptualize them as probability distributions that express our internal uncertainty about their true values.

Although both of these inference methods work for all the models covered before, there are several factors that favor the use of Bayesian inference in N-of-1 studies that are related to their design and use context. We will return to these later when we have first gone through the principles of Bayesian inference.

3.1 Principles of Bayesian Inference

Bayesian inference is based on the Bayes’ Theorem that states the probability of an event conditional on another event:

$$(3.1) \quad P(A|B) = \frac{P(B|A)P(A)}{P(B)},$$

where A and B are events and $P(B) \neq 0$. $P(A|B)$ is the conditional probability of event A happening given that event B happened and is called the posterior. $P(A)$ is our initial probability estimate for the event A called the prior. The quotient $\frac{P(B|A)}{P(B)}$ represent how much information event B gives about event A happening. If this number is greater

than 1, then event B happening makes event A more likely and if it less than 1 is less likely. If the quotient is 1, event B gives no information about the probability of event A . Breaking the quotient down further $P(B|A)$, called the likelihood, is the reverse of the posterior and tells us how believable it is to see the event B given that event A happened. Finally $P(B)$ in the denominator is called marginal likelihood and tells us the probability of observing event B with or without event A .

Instead of events, in our case we want to formulate the theorem with parameters Θ and the data D , so that the we get can estimate the posterior probability (or likelihood in case of continuous parameter values) of our parameters having certain values:

$$(3.2) \quad P(\Theta|D) = \frac{P(D|\Theta)P(\Theta)}{P(D)},$$

where $P(D) \neq 0$. We could make it more explicit what the marginal likelihood $P(D)$ stands for by writing it as $\sum_{\Theta} P(D|\Theta)P(\Theta)$ in the case when parameter value takes discrete values and $\int_{\Theta} P(D|\Theta)P(\Theta)d\Theta$, if they are continuous. That is, the possibility of observing the data with all different combinations of the possible values of the parameters, taking into account our prior belief in the probability of these value combinations.

To tie this formula into the models we introduced previously we can demonstrate how this applies to a simple model with only the treatment effects μ of the given treatment and a random error ϵ at time t :

$$(3.3) \quad y_t = \mu_t + \epsilon_t,$$

where $\epsilon_t \sim N(0, \sigma^2)$. Time t is indexed from the beginning of the study. In this case when we want to estimate the parameters of the effects of the treatments μ_t . For simplicity lets assume that only one treatment was given so μ_t is constant. Let's refer to this treatment effect simply as μ . According to our model single observations follow a normal distribution defined by constant μ and the error term ϵ_t . As our model assumes that the observations y_t are independent (no autocorrelation included in the model) individual observations are defined as $y_t \sim N(\mu, \sigma^2)$ and the likelihood term in the bayesian formula is a simple product of the probability density functions of a normal distribution with mean μ and variance σ^2 that the observations are independent:

$$(3.4) \quad P(Y|\mu, \sigma) = \prod_Y \frac{1}{\sqrt{2\pi\sigma^2}} \exp \left\{ -\frac{(y_t - \mu)^2}{2\sigma^2} \right\},$$

where Y represents all the observations.

To avoid the complexity of dealing with multiple unknown variables we assume that σ is known. We will later come back to the case of multiple unknown variables. Now we have to define only one prior distribution as there is just one unknown parameter. We choose a normal distribution for the prior of μ that is defined by mean λ_0 and variance δ_0^2 , whose values we define ourself based on our previous knowledge and beliefs:

$$(3.5) \quad P(\mu) = \frac{1}{\sqrt{2\pi\delta_0^2}} \exp \left\{ \frac{-(\mu - \lambda_0)^2}{2\delta_0^2} \right\}$$

We could of course choose whatever distribution best matches our previous knowledge and uncertainty about the parameter, but using a normal distribution for prior when the likelihood also follows a normal distribution, we get some nice algebraic properties that we will soon see.

Now the only missing term from our bayesian equation is the marginal likelihood $P(Y)$. When we express the term more precisely as the probability of getting the data we observed over possible values of our unknown parameter $\int P(Y|\mu)P(\mu)d\mu$, we can see that as we integrate over all the possible values of μ , the term is not dependent on the specific values of μ . This means that the marginal likelihood is just a constant and as such does not affect shape of the posterior distribution, So the shape of posterior distribution is defined by just by the likelihood and the prior $P(\mu|Y) \propto P(Y|\mu, \sigma^2)P(\mu)$. With some arithmetic manipulation we can see that the posterior probability is actually a normal distribution with mean $\lambda_1 = \delta_1^2 (\lambda_0 \delta_0^{-2} + \sum_Y y \sigma^{-2})$ and standard deviation $\delta_1^2 = \frac{1}{\delta_0^{-2} + n\delta^{-2}}$:

(3.6)

$$\begin{aligned}
P(\mu|Y) &\propto P(Y|\mu, \sigma)P(\mu) \\
&= \prod_{t=1}^n \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left\{-\frac{(y_t - \mu)^2}{2\sigma^2}\right\} \frac{1}{\sqrt{2\pi\delta_0^2}} \exp\left\{-\frac{(\mu - \lambda_0)^2}{2\delta_0^2}\right\} \\
&= \frac{1}{(2\pi)^{\frac{n+1}{2}} \sqrt{\delta_0^2 \sigma^{2n}}} \exp\left\{-\frac{\mu^2 + 2\mu\lambda_0 - \lambda_0^2}{2\delta_0^2} - \sum_{t=1}^n \frac{y_t^2 - 2\mu y_t + \mu^2}{2\sigma^2}\right\}
\end{aligned}$$

Dropping the constant terms

$$\begin{aligned}
&\propto \exp\left\{-\frac{\mu^2(\sigma^2 + t\delta_0^2) + 2\mu(\lambda_0\sigma^2 + \delta_0^2 y_1 + \dots + \delta_0^2 y_n) - (\lambda_0^2\sigma^2 + \delta_0^2 y_1^2 + \dots + \delta_0^2 y_n^2)}{2\delta_0^2\sigma^2}\right\} \\
&\propto \exp\left\{-\frac{\mu^2 + 2\mu\frac{\lambda_0\sigma^2 + \sum_{t=1}^n \delta_0^2 y_t}{\sigma^2 + n\delta_0^2} - \left(\frac{\lambda_0\sigma^2 + \sum_{t=1}^n \delta_0^2 y_t}{\sigma^2 + n\delta_0^2}\right)^2}{2\frac{\delta_0^2\sigma^2}{\sigma^2 + n\delta_0^2}}\right\} \times \exp\left\{-\frac{\lambda_0\sigma^2 + \sum_{t=1}^n \delta_0^2 y_t}{2\delta_0^2\sigma^2}\right\} \\
&\propto \exp\left\{-\frac{\left(\mu - \frac{\lambda_0\sigma^2 + \sum_{t=1}^n \delta_0^2 y_t}{\sigma^2 + n\delta_0^2}\right)^2}{2\frac{\delta_0^2\sigma^2}{\sigma^2 + n\delta_0^2}}\right\} \\
&= \exp\left\{-\frac{\left(\mu - \frac{\lambda_0\delta_0^{-2} + \sum_{t=1}^n y_t\sigma^2}{\delta_0^{-2} + n\sigma_0^{-2}}\right)^2}{2\frac{1}{\sigma^{-2} + n\delta_0^{-2}}}\right\}
\end{aligned}$$

Recognizing that we have the "right" part of normal distribution and adding the constant part back in

$$\begin{aligned}
&\propto \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left\{-\frac{(\mu - \lambda_1)^2}{2\delta_1^2}\right\}, \text{ where} \\
\delta_1^2 &= \frac{1}{\delta_0^{-2} + n\delta_0^{-2}} \quad \text{and} \quad \lambda_1 = \frac{\lambda_0\delta_0^{-2} + \sum_{t=1}^n y_t\sigma^2}{\delta_0^{-2} + n\sigma_0^{-2}} = \delta_1^2 \left(\lambda_0\delta_0^{-2} + \sum_{t=1}^n y_t\sigma^{-2}\right)
\end{aligned}$$

So we ended up with a posterior distribution that has the shape of a normal distribution. The trick where we ignored the marginal likelihood can be used anywhere, but the fact that we could arithmetically solve that the posterior follows a well defined distribution is not a general occurrence. Usually we need to go beyond arithmetic methods and solve the problem algorithmically.

3.1.1 Challenges of Bayesian Inference

Although the Bayes formula is conceptually simple, but when actually utilizing it we run into two big difficulties. First is the common case when the probability distributions of the prior and/or the likelihood or their product are not well defined distributions with known properties. This can make the integral in the marginal likelihood impossible to solve analytically like we did above. Even with discrete distributions similar problems emerge if the number of possible parameter value combinations is very large (this can happen easily when there are multiple parameters) as this makes just calculating the posterior probability for each individual value unfeasible. The second problem is how we should define our priors. If we have prior knowledge, we need to be able to formulate our beliefs in a precise mathematic form and when we do not have prior knowledge we still need to define a prior, but in this case it has to be defined so that it has minimal effects on the posterior distribution.

Dealing with the Marginal Likelihood

As mentioned before, the marginal likelihood can often be impossible or unfeasible to calculate analytically even in the case parameters with discrete values where we don't need to solve a complex integral. Common solution to this, that has been historically the only option, is to rely on so called "conjugate priors". These are priors that follow distribution which multiplied by suitable likelihood function produce posterior distribution that has the same form as the prior distribution. A good example of this is our example above (3.6) using a normal distribution for the prior when the likelihood is also normally distributed. If the likelihood function belongs to exponential family of distributions, there exists at least one corresponding conjugate prior distribution (often also in the exponential family). For likelihood functions outside the exponential family there are some cases where a conjugate prior exists, but these are rare.

The conjugate function method makes the denominator analytically solvable, but is in practice very limiting. First, we need to restrict ourselves when modelling to only use models that create a suitable likelihood function with an existing conjugate prior. Second, it limits our options in defining our prior beliefs as we have to be able to express them with the conjugate function. To have a more general solution we need to abandon the search for an analytical solution and tackle the problem algorithmically. We start this by noticing that as marginal likelihood is calculated over all possible parameter values, it is not dependent on particular values of the parameter and is thus constant across them. Therefore we can drop it from the Bayes' formula (3.2) and state that the posterior distribution follows the shape of the distribution of likelihood times prior:

$$(3.7) \quad P(\Theta|D) \propto P(D|\Theta)P(\Theta)$$

Even though we can't calculate the exact posterior probability any set value of values for our parameters because we don't know the correct denominator, we now have distribution whose shape is identical to the posterior. If we could take samples from this distribution we could approximate the posterior distribution with the probability distribution of the values of the samples. The general method to get this kind of sample is the following:

1. Pick a set of values for our parameters as our starting position in the parameter space. The starting location has to be a plausible set of values. We can check this As we can know that $P(D|\Theta)P(\Theta)$ has the same shape as our posterior and so if the value of the this function is zero when we pluck our set of parameter values in it, these values are impossible and should not be use as a starting point.
2. Pick a second set values for our parameters with some random method.
3. Calculate the probability of moving from our current position in the parameter space to the second set of parameter values with the following formula:

$$(3.8) \quad p_{move \text{ to new location}} = \min \left(\frac{P(D|\Theta = \text{proposed set})P(\Theta = \text{proposed set})}{P(D|\Theta = \text{current set})P(\Theta = \text{current set})}, 1 \right)$$

In other words, if the value calculated with the proposed parameter value set is higher than the value for the current set we always move to the new proposed location in the parameter space and if the value is lower we move there with a probability defined by the ratio of the two values.

4. Generate a random number between 0 and 1 and move to the proposed location in the parameter space if the number is lower than the probability that we calculated in the previous step. Otherwise we stay in the same place.
5. Mark down the values of our current location in the parameter space.
6. Repeat from step 2.

This method takes us on a random walk on the distribution with the steps defined by the likelihood times prior, but as this is distribution has identical shape with the posterior function we indirectly end up with representative sample of values from the posterior distribution. So in actuality we have taken a random walk in the posterior probability distribution, where we spend more steps in parts of the distribution where the values are more likely. To end up with an estimate of the posterior distribution we can now just divide the parameter space in to parts, calculate how many times we visited each of these parts and divide this by the number of steps taken in total. We now have a proper probability distribution that approximates the true posterior distribution. If we want a more precise estimate, we can just take more steps and divide the parameter space into smaller and smaller parts.

This algorithm is general description of a group of algorithms called Metropolis-Hastings algorithms. All of these methods follow the principles above, but they differ in the way they decide where to move next. Although with even very simple rules of picking a random proposed value the described will end up exploring the whole posterior distribution eventually, more clever algorithms can make this process much more efficient. By proposing steps that are more likely in posterior distribution a clever algorithm can lower the chance of proposing steps that have high probability of being rejected and so assure efficient moving trough the parameter space with less steps.

Metropolis-Hastings algorithms themselves are a part of a more broader group of algorithms called Markov chain Monte Carlo methods that all are methods of sampling from a probability distribution. The development of these method has been pushed forward by the need to have the sampling be as efficient as possible, as even with the computational power of modern computer, more complex models can run into unfeasible long computational times. On top of choosing the right algorithm, there are lots other things related to the computation to consider when implementing bayesian inference, but we will return to these later with the example of practical implementation of this kind of calculation with Python and PYMC3 package.

How to Define the Priors?

For the Bayesian formula to work we have to define a prior and this can be trickier that it seems at first glance. Ideally the prior would codify our prior beliefs and knowledge [8, 7], but trying to actually codify all we know is a fool's errand, because of how complex this is and we are anyway working with a model that is a simplified representation of reality. Even if we aim for a more limited goal, codifying what we know (or think we know) to mathematic formulas can be a tricky business. But it gets more difficult when we consider that we are doing the study not just to convince ourselves but also other people and we should try to capture the beliefs of our target audience. Unless this target audience is

easily available for questions and is highly mathematically minded, this leads to multiple layers of uncertainty as we try guess what others believe and then codify these beliefs with mathematical precision.

To avoid this hurdle the other option is to try to define some non-informative priors that “let the data speak for itself”, but this approach also has problems. Firstly, defining priors that have no effects on the posterior can be mathematically very difficult when we move beyond simple models [8] and if we would need to invest a lot of time finding these priors we should instead probably spend this time to define proper informed priors. Second, non-informative priors do not always seem so non-informative, when we actually know something about the issues. Consider a case where are trying to predict if a patient has a rare disease and we assign a uniform prior from 0 to 1 as this seems non-informative. This prior will have the effect of moving the posteriors towards the possibility of the patient actually having the disease. So if we definitely know something about the phenomenon, a non-informative prior can work against these beliefs.

Considered more broadly, chasing after truly non-informative prior is also somewhat of a fool’s errand if the data actually has “something to say”. If the data is informative, then lots of different priors that are somewhat weak should lead to almost identical posterior distributions. On the other hand if the data is weak and we have a weak prior, why are we even doing the analysis if we know that it will give us almost no information?

As a compromise between having strong priors based on previous beliefs and knowledge and letting the data stand on its own, Gelman et al. suggest using weakly informative priors [8]. These can be defined in two different ways. First we can start with non-informative prior (when it is easily available) and then add minimum information constraining the posterior results to reality (e.g. object cannot move faster than light or the height of an adult human must be between 50 and 300 cm). The other way is to start with strong informative priors and then broaden these to take into account the uncertainty of how applicable our priors knowledge is to the question at hand.

Because of how complex defining priors can get, this problem can act as an additional limiter on how complex bayesian models we can build. The more complex model, the more priors we have to define and the more prior information and beliefs we could codify and the more difficult this problem gets.

3.2 Why Bayesian Inference Fits N-of-1 Studies

As mentioned at beginning the previous chapter, both the more traditional frequentist inference and Bayesian inference can be used to estimate the parameter values of models described in. This choice is not just a technical one as both methods come with different conceptions about the nature of probability and assumptions related to this conception.

Unfortunately for frequentist inference, its assumptions fit the reality the N-of-1 trials poorly and its estimates, and especially their uncertainty, can be hard to communicate to a lay audience. Because of these issues Bayesian inference can usually be recommended over frequentist inference when analyzing and communicating the results of N-of-1 studies even though it comes with its own complexities that we previously went over.

3.2.1 Flexibility of Experimental Design

The central tenet of frequentist inference is the assumption that the experiment could be in theory repeated with statistically independent results. Probability is defined in relation to these hypothetical repetitions as a proportion of them that include some event of interest. To repeat the same experiment its design needs to be defined precisely and this definition needs to be made before the study has begun because the changes made to the design during the experiment might be influenced by its results.

Lets take for example an experiment where we are trying to find out if a coin is fair. For this purpose we decide to flip the coin 20 times and count the number of heads. Then we can model how “typical” the result we got for a fair coin. We do this by calculating the distribution of heads for repeated similar 20 coin toss trials assuming that the coin is fair. Then we can measure our actual result against this distribution. If the result seems plausible (depending how strict we want to be) then we would say that the null hypothesis stand and the coin is fair. The problem comes if did not actually decide to throw the 20 times before, but first threw it 10 times, looked at the results, and thought that we should get some more data. Now what kind of distribution should we compare our results against? The length of the trials seems to now hinge in some undefined way from the results of the first 10 coin tosses.

This demand of precisely predefined design can be especially problematic in N-of-1 studies used in a clinical setting. There might be cases when some treatment seems clearly better in the middle of an experiment and the patient (or the clinician) wants to stop the experiment. As the subjects are real people, it would be unethical to force them to continue the study just for the sake of statistical rigor. There might also be a situation where a couple of treatments seem promising, but the rest seem completely useless and we would want to change the design of the experiment on the fly to focus just on the promising treatments. These changes to the predefined experimental design will brake frequentist assumptions and make the inferences made with it very difficult.

The possibility to stop the study or change the experimental design can be incorporated to frequentist inference, if we predefine the rules of when to stop the experiment and under what circumstances the design should be altered and how. Then we need to take these rules into account when performing the estimation calculations and this complicates the analysis. But is questionable if we can actually define and stick to these stopping rules

because of the human element: we would need to convince the patient that she should stop the experiment only in these predefined circumstances. This seems quite unrealistic, as if there are any unforeseen problems with the treatments, it is more than likely that the patient will want to stop whatever rules she sign to follow before hand.

With Bayesian inference on the fly modifications of the study design do not cause such problems as with frequentist inference, as there is no assumption about repeating the experiment. Instead of hypothesizing about future experiment, we just take into account our prior information and the data created by the current experiment. The changes to the experimental design modify what data we get out of it, but don't brake any assumptions of Bayesian inference. This adaptability is a big benefit when applying N-of-1 designs in a clinical setting, as the unpredictable nature of the patients and treatment effects and all the other practical considerations that could force changes to our experiment design don't break the assumptions of our inference method.

3.2.2 Richness and Communicability of the Estimates

In N-of-1 studies much consideration has to be given to the communication of the results, both to the patient and the clinician administering the experiment. We would like to portray not just the estimates of the effects of the treatments, but also the uncertainty associated with these estimates. In frequentist inference there are two options to communicate these facts. The first one is maximum likelihood estimates combined with confidence intervals. Maximum likelihood estimates are just point estimates of the parameters and don't communicate any uncertainty. Confidence intervals communicate uncertainty, but don't actually mark the most likely values of the estimate. A 95 % confidence interval, is often interpreted wrongly as including the true value of the parameter with 95 % change, but the real meaning is that if we repeated the experiment indefinitely 95 % of the 95 % confidence intervals, would include the true parameter value. This is because in frequentist interpretation of probability, true parameter values are not random but fixed, so a single confidence interval either does or does not include this value. This confusing definition makes confidence intervals a bad choice of presenting the uncertainty of the estimates as they might create lots of misinterpretations and even when interpreted correctly are hard to grasp.

The second frequentist communication tool are p-values of hypothesis tests. We might define a null hypothesis that the parameters of the effects of different treatments are equal and calculate the likelihood to obtain the data or a more extreme version of it, if this would be the case. This would give us a more easily communicable number of the probability to obtain the data if the null hypothesis would be true. If the p-value is low we could say with confidence that there is real differences between the effectiveness of the treatments. The problem is that this actually gives us very little useful information, as

we would also like to know how big the differences in treatments effectiveness could realistically be.

A Bayesian approach to inference gives us richer and more easily communicable information about the estimates because it actually gives us a distribution as a result. With this we can easily communicate point out the plausible values with the tops of this distribution and the uncertainty with how flat the distribution is. The usual misinterpretation of the confidence intervals as containing the true value of the parameter with certain probability is actually the right interpretation for bayesian credible intervals, that contain certain percentage of the probability mass of the posterior distribution and so have a defined chance of containing the true value of the parameter. Bayesian method itself also seems to fit really well with the ways that clinicians conceptualize their practice of arriving to diagnosis for a patient as updating their beliefs (i.e. priors) with the new information gained from new observation such as test results [4].

Chapter 4

Combining Information From Several N-of-1 Trials With Hierarchical Models

Conducting a individual N-of-1 trials is expensive but if we notice that there is some treatment or certain population that benefits greatly from this kind of design, we could lower the cost significantly by conducting multiple similar trials. If this is possible, we would also like some option for pooling the information from the separate trials to achieve greater statistical power and to answer more general questions than just finding the best treatment for an individual patient.

By applying Bayesian statistics we could achieve this by using hierarchical models where each model parameter is imagined to come from “higher” distributions that is controlled by its own parameters. For example we could assume that the effectiveness of a certain treatment to be normally distributed within a population and the effectiveness of this treatment for a single patient is sample from this distribution.

picture

The question now becomes how we apply the bayesian formula in this case?

To start exploring this lets first look in more details to the case when we have more than one parameter in our model. We alluded to this already previously when we talked about multiple parameters, but we did not go into details there about how this affects the formulas practically. Lets take example where we have two parameters instead of one, slot them into the familiar Bayes’ rule and see how it applies to the joint parameter space:

TODO: explain the steps in more details

$$(4.1) \quad p(\theta, \sigma|D) \propto p(D|\theta, \sigma)p(\theta, \sigma) = p(D|\theta)p(\theta|\sigma)p(\sigma)$$

We start from the basic definition of the posterior and the apply bayes rule, but ignore the denominator as we learned previously that if we just want to know the shape of the posterior these has no effect on it can be dropped. Next we applied

We can see that the data D depends only on the value of parameter θ , so that if the value of θ is set, then the data are independent of all other parameter values. Similarly, the value of θ depends conditionally only the value of σ and σ is an independent variable.

These kind of dependencies among parameters are useful in several respects. First, the dependencies are meaningful for the given application, e.g. we can model that the treatment effect for a single patient as an instance from a broader population distribution of this effectiveness. Second, because of the dependencies across parameters, all the data can now jointly inform all the parameter estimates. The reduction of variance in the estimators that this effect causes, is the generally referred by the term “shrinkage”.

In general, shrinkage in hierarchical models causes lower-level parameters to shift toward the modes of the higher-level distribution. If the higher-level distribution has multiple modes, then the low-level parameter values cluster more tightly around those multiple modes, which might actually pull some low-level parameter estimates apart instead of together. The greatest thing is that if we don’t explicitly set the parameter values of the higher-level distributions, the amount of shrinkage is actually informed by the data so that similar observed data points from lower-level distributions lead to “tighter” estimates for the higher-level distributions and in this in turn leads to greater shrinkage.

Chapter 5

Example of a Hierarchical Bayesian Analysis Using Simulated Data

Imagined experimental design

5.0.1 Simulating the Data

$$(5.1) \quad y_t = \mu_i + t\beta_i + Z_t\theta_i + \epsilon_t + \rho_i\epsilon_{t-1}$$

where μ_i is the baseline of the patient i , β_i is the trend, θ_i is the treatment effect with Z_t being an indicator variable that is 1 when t is within a period where treatment was applied and 0 otherwise. $\epsilon_t \sim N(0, \sigma_i^2)$ is the error term at t and ρ_i is the correlation between consecutive errors.

So we have a data generating model with both trend and lag 1 autocorrelation making the generated model more complex. The trend and autocorrelation are parts of the generation process that likely cannot be modeled with the generated data because of limited observations. This way the example tries to be more realistic by having the data generation function to be such complexity that it cannot be fully modeled and some decisions have to be made of how to try to approximate the process with a simpler model.

These patient level terms are generated from population level distributions

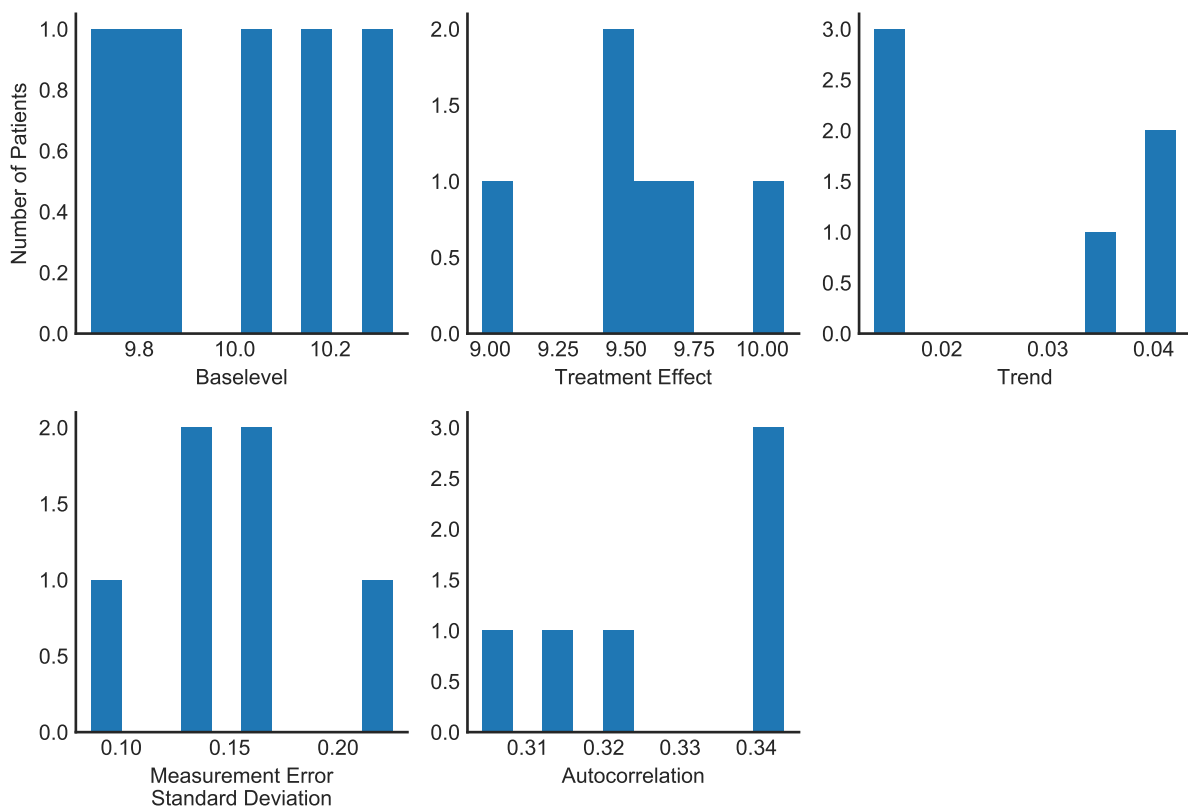
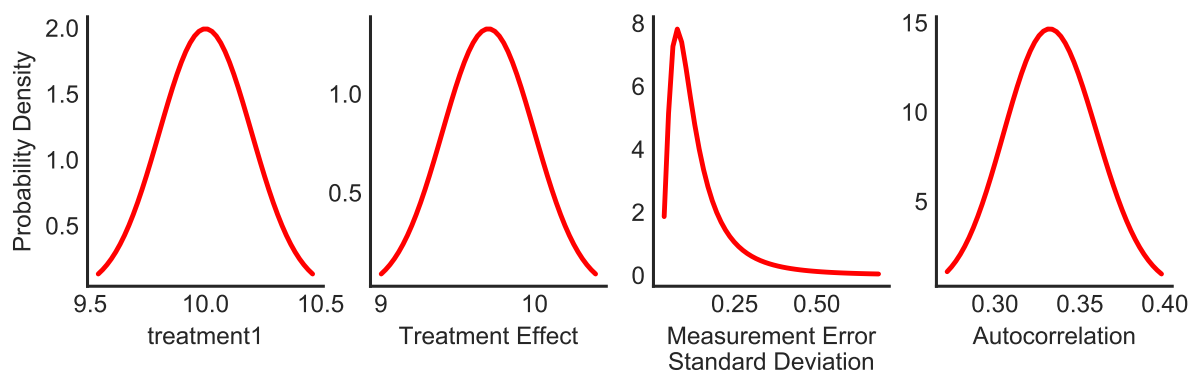
$$(5.2) \quad \mu_i \sim \mathcal{N}(\mu, \sigma^2)$$

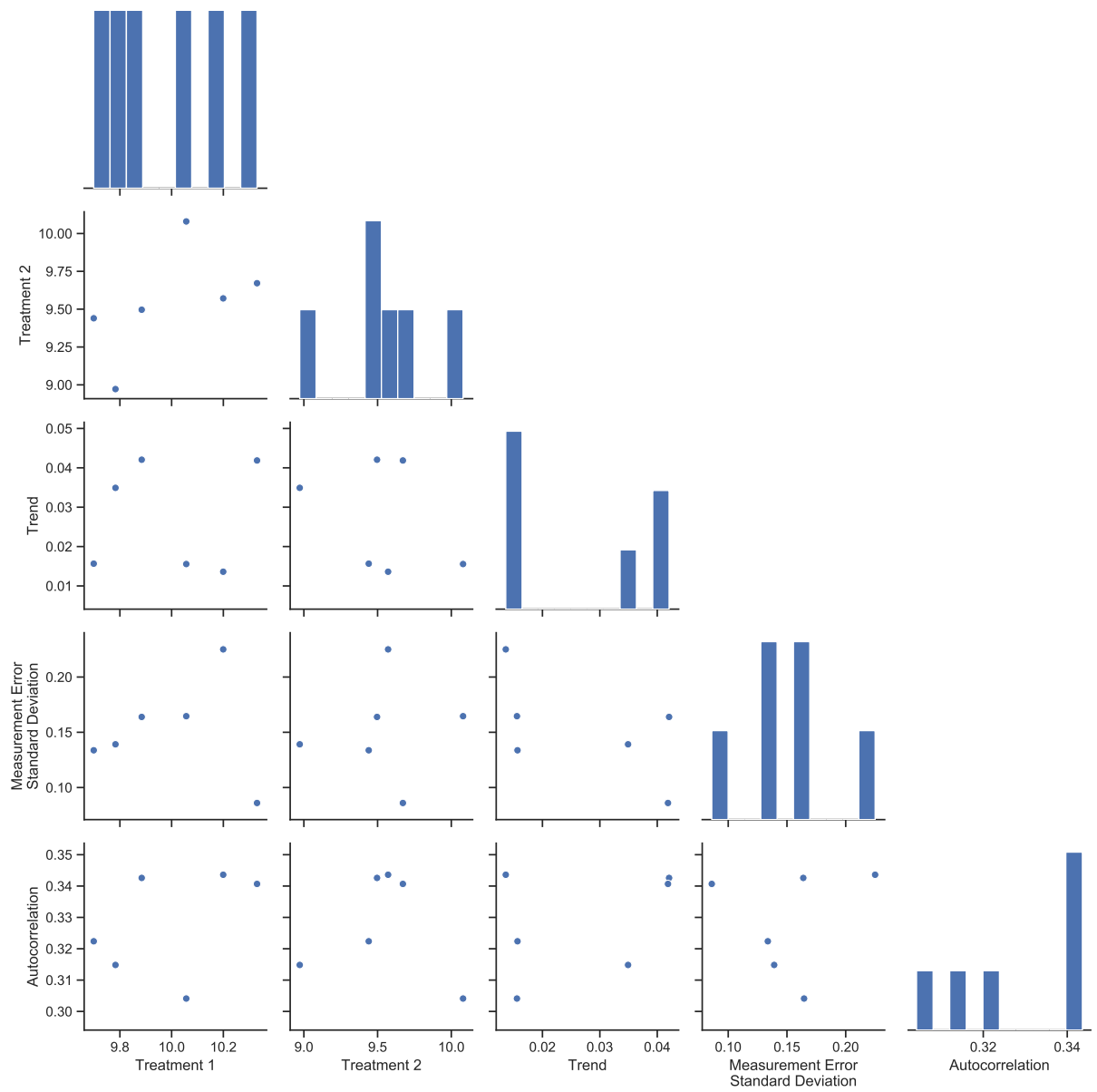
$$(5.3) \quad \theta_i \sim \mathcal{N}(\theta, \sigma^2)$$

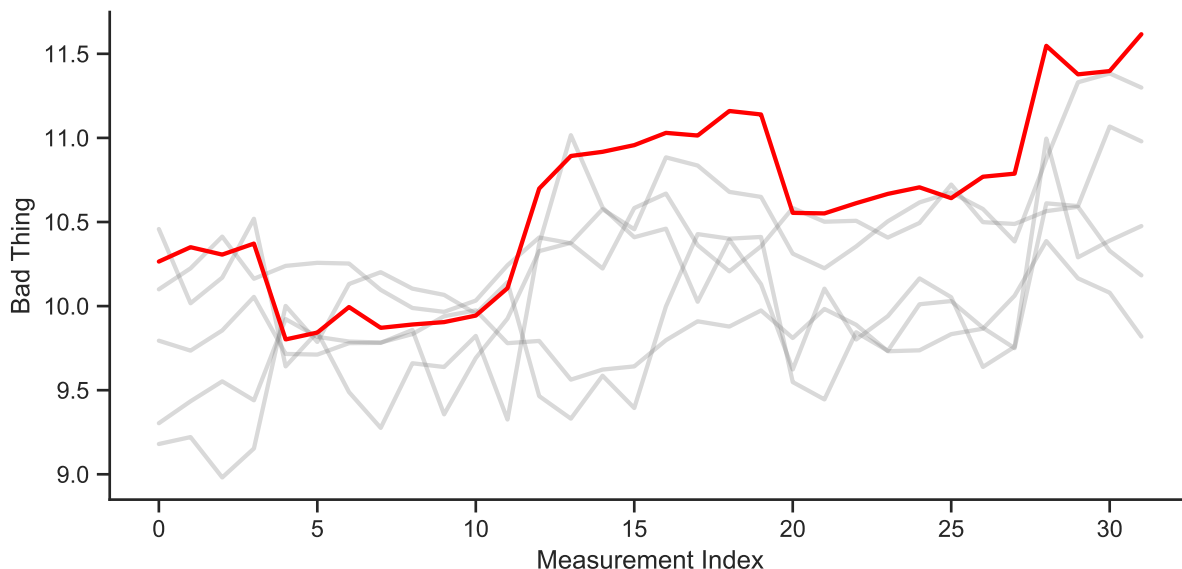
$$(5.4) \quad \sigma_i \sim \text{Beta}(\alpha, \beta)$$

(5.5)

$$\rho_i \sim \text{InvGamma}(\alpha, \beta)$$







What makes the simulated data hierarchical?

picture of the hierarchical parameter structure used to create the data

5.1 Analyzing a Single Trial

PYMC3 requires that we appropriately give it functional forms for likelihoods to represent the information from the data. This can be bit tricky when it is clear that likelihood does not take form a well known distribution. For these cases we must define the log-likelihood function of the likelihood manually.

Theano is a package that allows us to define functions involving array operations and linear algebra

5.1.1 Defining the Model

$$(5.6) \quad y_t = \mu + Z_t\theta + \epsilon_t$$

where μ is the baseline θ is the treatment effect with Z_t being an indicator variable that is 1 when t is within a period where treatment was applied and 0 otherwise and finally $\epsilon_t \sim N(0, \sigma^2)$ is the error term.

Priors:

$$(5.7) \quad \mu \sim N(10, 3^2)$$

$$(5.8) \quad \theta \sim N(0, 1^2)$$

$$(5.9) \quad \epsilon \sim \text{HalfCauchy}(\text{loc} = 0, \text{scale} = 10)$$

Defining the priors and incorporating our previous knowledge.

Defining the model in a technical sense with STAN, with mention of the problems that have to be considered

5.1.2 Results

5.2 Analyzing Multiple Trials With Hierarchical Models

With the shape parameter we can initialise the parameters as vectors with the length of out number of patients. This way each patient get her own parameter.

5.2.1 Defining the Model

$$(5.10) \quad y_t = \mu_i + Z_t \theta_i + \epsilon_i$$

where μ_i is the baseline of the patient i , θ_i is the treatment effect with Z_t being an indicator variable that is 1 when t is within a period where treatment was applied and 0 otherwise and finally $\epsilon_i \sim N(0, \sigma_i^2)$ is the error term.

Individual parameters relation to population distribution:

$$(5.11) \quad \mu_i \sim N(\mu_{pop}, \sigma_{pop}^2)$$

$$(5.12) \quad \theta_i \sim N(\theta_{pop}, \sigma_{pop}^2)$$

$$(5.13) \quad \sigma_i \sim \text{HalfCauchy}(\text{loc} = 0, \text{scale} = \sigma_{pop})$$

Defining priors for the population distribution:

$$(5.14) \quad \mu_{pop} \sim N(10, 3^2)$$

$$(5.15) \quad \sigma_{pop} \sim HalfCauchy(loc = 0, scale = 10)$$

$$(5.16) \quad \theta_{pop} \sim N(0, 1^2)$$

$$(5.17) \quad \sigma_{pop} \sim HalfCauchy(loc = 0, scale = 10)$$

$$(5.18) \quad \sigma_{pop} \sim HalfCauchy(loc = 0, scale = 10)$$

5.2.2 Results

Visualization of the shrinkage

Bibliography

- [1] Richard L. Kravitz, Naihua Duan, Sunita Vohra, Jiang Li: Introduction to N-of-1 Trials: Indications and Barriers in Design and Implementation of N-of-1 Trials: A User's Guide, AHRQ, 2014.
- [2] Wilson D. Pace, Elizabeth W. Staton, Eric B. Larson: Financing and Economics of Conducting N-of-1 Trials in Design and Implementation of N-of-1 Trials: A User's Guide, AHRQ, 2014.
- [3] Christopher H. Schmid, Naihua Duan: Statistical Design and Analytic Considerations in Design and Implementation of N-of-1 Trials: A User's Guide, AHRQ, 2014.
- [4] Christopher J. Gill, Lora Savin, Christopher H. Schmid: Why clinicians are natural Bayesians, *British Medical Journal* 2005;330(7499):1080-1083.
- [5] Colin D. Mathers, Dejan Loncar: Projections of global mortality and burden of disease from 2002 to 2030, *PLoS medicine* 2016;3.11:e442.
- [6] Irl B. Hirsch, et al.: Clinical application of emerging sensor technologies in diabetes management: consensus guidelines for continuous glucose monitoring (CGM). *Diabetes Technology and Therapeutics* 2018;10.4:232-246.
- [7] John K. Kruschke: *Doing Bayesian Data Analysis: A Tutorial With R, JAGS, and Stan* (2nd), Academic Press, 2014.
- [8] Andrew Gelman, John B. Carlin, Hal Stern, David Dunson, Aki Vehtari, Donald B. Rubin: *Bayesian Data Analysis*, CRC press, 2013