Applying Bayesian Hierarchical Models to N-of-1 Trials

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Introduction

In clinical practice, N-of-1 trials 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 walk trough 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. We then follow up with how to apply Bayesian inference with these models and estimate the effectiveness of different treatments, highlighting how Bayesian 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 loosing 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 and PyMC3-package using 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 measurements 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 suspectable 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 the natural progression of a disease. Despite its unquestionable value in finding general effects, this method can run into problems when we try to apply its results to individual patients in clinical practice.

Knowing the best treatment on average might not help much in finding the 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 can still be lots of unexplained between-patient variance left. 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 [9, 10, 11, 12]. 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 an RCT study or unknown and thus impossible to analyze in this kind of experimental design.

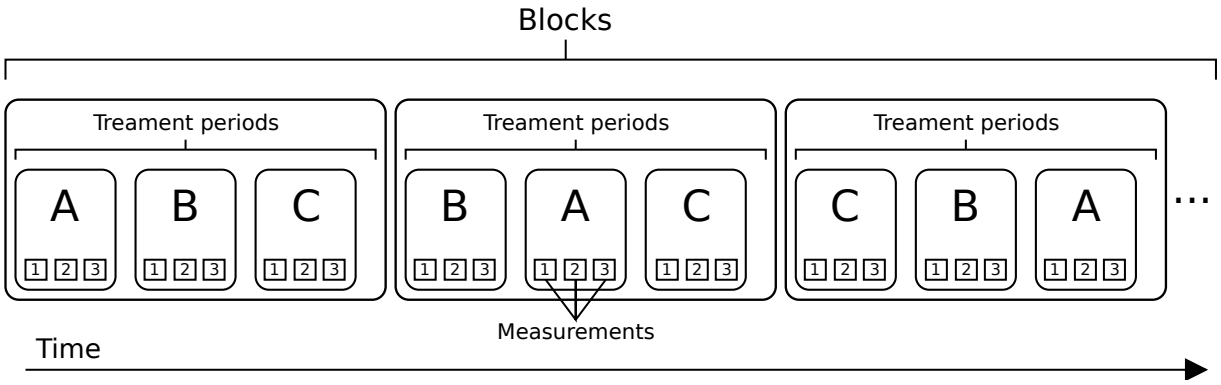
Another problem with RCTs is the peculiarity of their participants. It is a common practice to accept patients to RCTs only if they don't suffer from any medical issue besides the one that is being studied. This lack of comorbidity makes it easier to get clear results by removing confounding factors, 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. 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 generalize that well to the kinds of patients the clinical practitioner sees daily in her office. [9]

N-of-1 trials can be used to patch the holes in the knowledge that RCTs 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 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 being studied allow it, 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 a 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 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 effects.

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 factors 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 treatment options available must have 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 healthcare costs by finding the 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 the 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 the 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 insulin 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 into 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:

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

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:

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

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 be 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 $\delta_{p(b)}$:

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

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 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:

$$y_t = \beta_0 + \beta_1 t + \mu_t + \epsilon_t, \tag{2.4}$$

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:

$$y_t = \beta_0 + \beta_1 t + \beta_2 Z_t + \mu_t + \epsilon_t, \tag{2.5}$$

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

$$y_t = \beta_0 + \beta_1 t + \mu_t + \gamma_t t + \epsilon_t, \tag{2.6}$$

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 some similarity between observations defined by a function of the 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 the 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 the 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:

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

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 $(\rho_1\epsilon_{t-1} + \ldots + \rho_x\epsilon_{t-x})$.

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 $t-1$:

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

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 the 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 into account simultaneously (ARMA-models), but as amount of data produced in N-of-1 studies if 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 the carryover effect and the slow manifestation of treatment effect with modeling, a better way could be to take measures to mitigate the effects in the study design itself. By having a 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 measurements 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 be 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 kinds of measurement the models need to 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 a 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.

Lets work with an example of a binary outcome measurements. In this case the measurements y at time t follow the Bernoulli distribution $y_t \sim Bernoulli(p)$ 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 $logit(p) = \log_e(\frac{p}{1-p})$. With this information we can now formulate a simple model with a linear time trend:

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

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:

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

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

We notice that there are no error terms in this model. This is because we are not modeling 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 modeling 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 $y_p \sim Poisson(\lambda)$ 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:

$$\log_e(\lambda_p) = \beta_0 + \beta_1 r + \mu_p, \tag{2.12}$$

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:

$$\lambda_t = e^{\beta_0+\beta_1 t+\mu_t}, \tag{2.13}$$

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 trough 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 the 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:

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

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:

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

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

Chapter 3

Bayesian Estimation

Now that we have some models defined, we need to move into the next part of the analysis and 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 trough 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:

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

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 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 we get can estimate the posterior probability (or likelihood in case of continuous parameter values) of our parameters having certain values:

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

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 the 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:

$$y_t = \mu_t + \epsilon_t, \tag{3.3}$$

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:

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

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:

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

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 the 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 $\lambda_1 = \delta_1^2\left(\lambda_0\delta_0^{-2} + \sum_Y y\sigma^{-2}\right)$ 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

$$
\begin{aligned}
&\propto \exp\left\{\frac{-\mu^2(\sigma^2+t\delta_0^2)+2\mu(\lambda_0\sigma^2+\delta_0^2y_1+\cdots+\delta_0^2y_n)-(\lambda_0^2\sigma^2+\delta_0^2y_1^2+\cdots+\delta_0^2y_n^2)}{2\delta_0^2\sigma^2}\right\} \\
&\propto \exp\left\{\frac{-\mu^2+2\mu\frac{\mu_0\sigma^2+\sum_{t=1}^{n}\delta_0^2y_t}{\sigma^2+n\delta_0^2} - \left(\frac{\lambda_0\sigma^2+\sum_{t=1}^{n}\delta_0^2y_t}{\sigma^2+n\delta_0^2}\right)^2}{2\frac{\delta_0^2\sigma^2}{\sigma^2+n\delta_0^2}}\right\} \times \exp\left\{-\frac{\lambda_0\sigma^2+\sum_{t=1}^{n}\delta_0^2y_t}{2\delta_0^2\sigma^2}\right\} \\
&\propto \exp\left\{-\frac{\left(\mu-\frac{\lambda_0\sigma^2+\sum_{t=1}^{n}\delta_0^2y_t}{\sigma^2+n\delta_0^2}\right)^2}{2\frac{\delta_0^2\sigma^2}{\sigma^2+n\delta_0^2}}\right\} \\
&= \exp\left\{-\frac{\left(\mu-\frac{\lambda_0\delta_0^{-2}+\sum_{t=1}^{n}y_t\sigma^2}{\delta_0^{-2}+n\sigma_0^{-2}}\right)^2}{2\frac{1}{\sigma^{-2}+n\delta_0^{-2}}}\right\}
\end{aligned}
$$

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

$$
\propto \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left\{-\frac{(\mu-\lambda_1)^2}{2\delta_1}\right\}, \text{ where}
$$

$$
\delta_1^2 = \frac{1}{\delta_0^{-2}+n\delta^{-2}} \quad \text{and} \quad \lambda_1 = \frac{\lambda_0\delta_0^{-2}+\sum_{t=1}^{n}y_t\sigma^2}{\delta_0^{-2}+n\sigma_0^{-2}} = \delta_1^2\left(\lambda_0\delta_0^{-2}+\sum_{t=1}^{n}y_t\sigma^{-2}\right)
$$

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. A 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 a 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 the 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 it is in practice very limiting. First, we need to restrict ourselves when modeling 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 the 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:

$$P(\Theta|D) \propto P(D|\Theta)P(\Theta) \tag{3.7}$$

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 a 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 this function is zero when we pluck our set of parameter values in it, these values are impossible and should not be uses as a starting point.

2. Pick a second set of 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:

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

   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 probabilities.

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 an identical shape with the posterior function we indirectly end up with a 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 into 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 a 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 to be accepted. A clever algorithm can lower the chance of proposing steps that have a 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 (MCMC) that all are methods of sampling from a probability distribution. The development of these methods has been pushed forward by the need to have the sampling be as efficient as possible, as even with the computational power of a modern computer, more complex models can run into unfeasibly long computational times. On top of choosing the right algorithm, there are lots of other things related to the computation to consider when implementing Bayesian inference, but we will return to these later in 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 the beginning of the previous chapter, both frequentist and Bayesian inference can be used to estimate the parameter values of the models described. The choice between these two methods is not just a technical one as both come with different conceptions about the nature of probability and assumptions related to this conception

and these have serious implications on how we should interpret the results and run the studies. 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 (doctors and patients). 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 it 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 same 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 would have some event of interest (e.g. over 5 tails with 10 coin tosses). 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 would be for a fair coin. We do this by calculating the distribution of heads from multiple 20 coin toss trials assuming that the coin is fair. Then we can compare our actual result against this distribution. If the result would be typical within this distribution, then we can say that the null hypothesis stands and the coin is fair. The problem comes if we did not actually decide to throw the coin 20 times beforehand, but first threw it 10 times, looked at the results, though that we should get some more data, and then threw the rest 10. 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 that made us decide to keep tossing the coin some more.

This demand for predefined experiment designs 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 this method 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 which adds complexity is but is still possible. The problem is that it is questionable if we can actually define and stick to these 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 beforehand.

With Bayesian inference doing 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 the 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 most likely parameter values and don't communicate any uncertainty. Confidence intervals of these parameter values 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 the true value. This confusing definition makes confidence intervals a poor choice of presenting the uncertainty of the estimates to a lay audience 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 is indeed the case. This would give us a more easily communicable way to portray the probability to obtain the data if the null hypothesis is 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 how big the differences in the treatments' effectiveness could realistically be.

A Bayesian approach to inference gives us richer and more easily communicable information about the estimates because it gives us a distribution as a result in the form of the posterior distribution. With this is we can easily 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 a 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

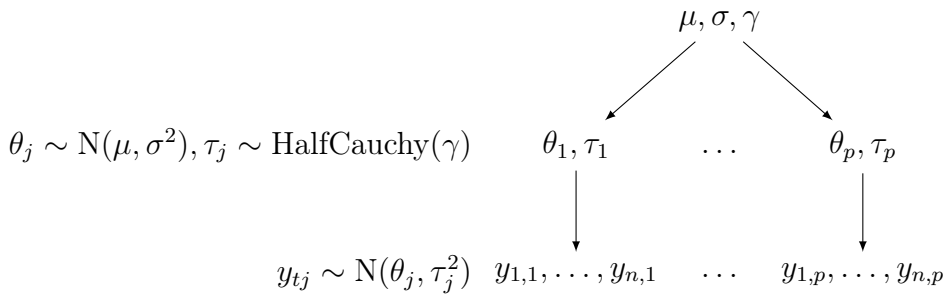
Let's say we have our N-of-1 trial set up nicely and we have a good model for analyzing the results. After running the first trials we continue to perform the same kind of setup with multiple patients as the treatments we are considering seem to have lots of individual variation in their effectiveness. Running these experiments separately is fine, but one might wonder if these separate trials could somehow be combined. Of course, we could pool the data and run a group-based analysis about what treatments seems to be the best in general, but there is a better way that keeps true to the goal of N-of-1 experiments of finding the best treatment for each *individual patient*.

4.1 How to Make a Model Hierarchical?

In the Bayesian framework we can pool information by making our models hierarchical. This means that instead of defining priors for our model variables, each model parameter is imagined to come from a "higher" distributions that is controlled by its own parameters. In the case of N-of-1 studies the individual lower-level parameters represent the individual patients, and the distribution where these parameters are taken from could represent the population which the patients are drawn. Priors are only defined for the higher-level distribution. Lets take a simple example where we have p patients with n measurements and, to make things simple just one treatment option. We can model this by a simple two-parameter model:

$$y_{tj} = \theta_j + \epsilon_{tj}, i \in (1 \dots n), j \in (1 \dots p) \tag{4.1}$$

where θ_j represents the effect of the treatment for patient j and $\epsilon_{tj} \sim N(0, \tau_j^2)$ is the error term for patient j at observation taken on time t. We can visualize this model as a tree:



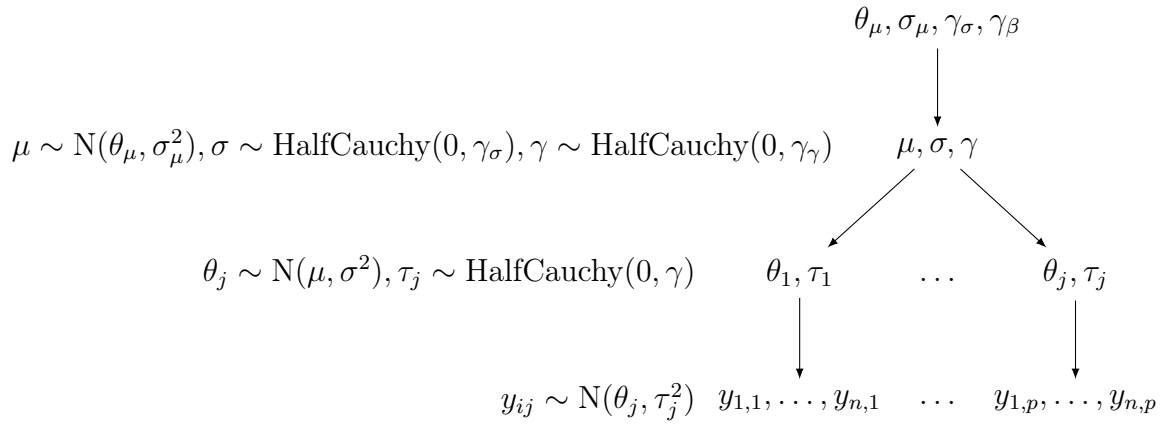
(4.2)

On top are the prior parameters that represent our existing knowledge and are shared by all patients. Next are actual prior distributions defined by these parameters from which the individual patient level patient parameters are drawn. At the bottom we describe the actual data generating process where values of individual observations are drawn from normal distributions defined by the patient level parameters. For the prior distributions we choose a normal distribution for the treatment effect and half-Cauchy distribution for the variance. The normal distribution for the treatment effect is a natural choice as probably the treatment effect is dependent on multiple factors which many could be independent. If this is the case, then the central limit theorem says that the treatment effect will follow a normal distribution. The variance parameters is more difficult and there are multiple reasonable distributions to choose, but half-Cauchy distribution is generally recommended for reasons we don't have space to go into here [15].

Even though each patient shares the same prior parameters, the estimates of the patient-level parameters are only affected by the data of the other patients as the shared prior parameter values are set beforehand and are not affected by the data. To change this we need to introduce some parameter that is shared by all patients and that is also being estimated based on the data. We can accomplish this by changing the priors from set values to distributions that are themselves affected by new higher level prior values. This new level of "uncertain priors" can be interpreted in this context as the population-level distribution of the treatment effectiveness:

hierarchical

(4.3)



Now instead of drawing the patient level parameters straight from distributions defined by the priors, these are drawn from the population-level distributions. The parameters population-level distributions themselves are taken from set distributions defined by the prior values. With the addition of this new layer, something very important happens: As the population-level parameters are not predefined, they are part of our estimation and as they are shared between the patients, they are informed by all the data we gather, and as estimated patient-level parameters are affected by the estimated shape of the population-level distribution, data from one patient can influence the estimated parameters for another patient trough this new higher level parameter layer. The elegance of this method comes from the fact that, even though we now have population-level parameters we still keep the individual patient-level parameters that can vary between the patients and the amount of effect that the data from one patient has on the other patients is itself influences by the data as the effects works trough the posteriors estimates we get for the population-level parameters.

4.2 Benefits of Hierarchical Models

The kinds of multilayered dependencies introduced with hierarchical models are useful in many ways. First, the dependencies can meaningful for the application, e.g. we can model the treatment effect for a single patient as an instance from a broader population distribution of this effectiveness. The population level is not just a mathematical curiosity, but it has a meaningful interpretation and the estimates we get for the population-level

parameters are interesting by themselves. Second, because of the dependencies across parameters, all the data can now jointly inform all the parameter estimates. As there is now more data used for the lower-level estimates trough intelligent pooling there is usually some reduction in the variance of these estimates. This reduction of variance is 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. This does not mean that estimates are always just pulled closer together, because if the higher-level distribution has multiple modes, then the low-level parameter values cluster more tightly around these modes, which might pull some low-level parameter estimates apart instead of together. The greatest thing is, that as we don't explicitly set the parameter values of the higher-level distributions, the amount of shrinkage is 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 (e.g. posterior estimates of the patient level parameters being more tightly clustered together). This means that using a hierarchical model in the case where the patients are actually are very different, does not force the estimates together as widely spread measurements leads to the estimates of the population level-distributions to have a large variance and thus to have little impact on the patient level estimates. So instead forcing similarity, the model "makes the decisions" if this is appropriate informed by the data.

4.3 Applying the Bayes Formula to Hierarchical Models

With all the parameters introduced by the new parameter levels in hierarchical models, the question now becomes, how we apply the Bayesian formula in these cases? Luckily this happens to be very simple as we just have to remember two rules of probability: the chain rule 4.4, that tells us that the probability of A and B is the probability of B on condition A times the probability of A, and the rule of independence 4.5 that states that the probability of A on condition B is just the probability of A if A and B are independent.

$$P(A \cap B) = P(B|A)P(A) \tag{4.4}$$

$$P(A|B) = P(A), \text{ if } P(A \cap B) = P(A)P(B) \tag{4.5}$$

Now lets see what happens when we apply write are our previously defined hierarchical model 4.3 in the Bayes formula 3.2 and apply these rules. For simplicity I assume that we only have two patients and leave out the prior parameters defining the shape of the population distributions for clarity.

$$
\begin{aligned}
posterior &= \frac{P(\theta_1, \tau_1, \theta_2, \tau_2, \mu, \sigma, \beta | Y)}{P(Y)} \\
&\text{(dropping the constant term)} \\
&\propto P(Y|\theta_1, \tau_1, \theta_2, \tau_2, \mu, \sigma, \beta) P(\theta_1, \tau_1, \theta_2, \tau_2, \mu, \sigma, \beta) \\
&\text{(using rule of independence as data Y depends only on parameters } \theta \text{ and } \tau) \\
&= P(Y|\theta_1, \tau_1, \theta_2, \tau_2) P(\theta_1, \tau_1, \theta_2, \tau_2, \mu, \sigma, \beta) \\
&\text{(using rule of independence to separate the two patients)} \\
&= P(Y_1|\theta_1, \tau_1)(Y_2|\theta_2, \tau_2) P(\theta_1, \tau_1, \mu, \sigma, \beta) P(\theta_2, \tau_2, \mu, \sigma, \beta) \\
&\text{(using the chain rule separate the patient and population parameters)} \\
&= P(Y_1|\theta_1, \tau_1)(Y_2|\theta_2, \tau_2) P(\theta_1, \tau_1|\mu, \sigma, \beta) P(\theta_2, \tau_2|\mu, \sigma, \beta) P(\mu, \sigma, \beta)^2 \\
&\text{(population parameters are independent of each other)} \\
&= P(Y_1|\theta_1, \tau_1)(Y_2|\theta_2, \tau_2) P(\theta_1, \tau_1|\mu, \sigma, \beta) P(\theta_2, \tau_2|\mu, \sigma, \beta) P(\mu)^2 P(\sigma)^2 P(\beta)^2 \\
&(\theta \text{ and } \tau \text{ are independent on each other and are dependent on different} \\
&\text{population level parameters)} \\
&= P(Y_1|\theta_1, \tau_1)(Y_2|\theta_2, \tau_2) P(\theta_1|\mu, \sigma) P(\tau_1|\beta) P(\theta_2|\mu, \sigma) P(\tau_2|\beta) P(\mu)^2 P(\sigma)^2 P(\beta)^2
\end{aligned}
$$

We can see that the measurements of each patient Y_1, Y_2 depend only on the patient level parameters $\theta_1, \theta_2, \tau_1, \tau_2$, so that if these values are set, then the measurements are independent of all other parameters. Similarly, the patient level parameters depend conditionally only on the population level parameters μ, σ, β. So we have now successfully expressed our hierarchical model in the Bayes formula. We could continue by writing the formula out by adding in the prior terms and replacing the abstract probability markings with the actual probability density functions given by our chosen distributions, but this gets messy and, in this case, no nice analytical solution can be found anyway, so we will leave it at this. It is also notable that we could add even more layers to the model and just apply the same rules we used here to write the formula out. Bayes formula makes no limitations on how complex and deep our hierarchical model can be.

Chapter 5

Example of a Hierarchical Bayesian Analysis Using Simulated Data

To put everything we learned into practice, lets go over an example Bayesian analysis of multiple N-of-1 trials, where we first analyze one trial separately and then combine multiple trials by using a hierarchical model. For the analysis we use Python and PyMC3 library [13] built for probabilistic programming. We will not go over each part of the code, but focus only on the critical parts where we see how the models and inference we went over in the previous chapters look like when implemented in practice. For those who want to see the full code, it is available from a GitHub repository [14] with instructions on how to run it.

As we now jump from theoretical and analytical considerations to practical consideration when doing this kind of analysis, we will need revisit the concept that we went over while talking about the problems of dealing with marginal likelihood 3.1.1 and introduce some new concepts related to how PyMC3 deals with this problem and what do we need to pay attention to make sure that the algorithmically derived results we get are actually reliable.

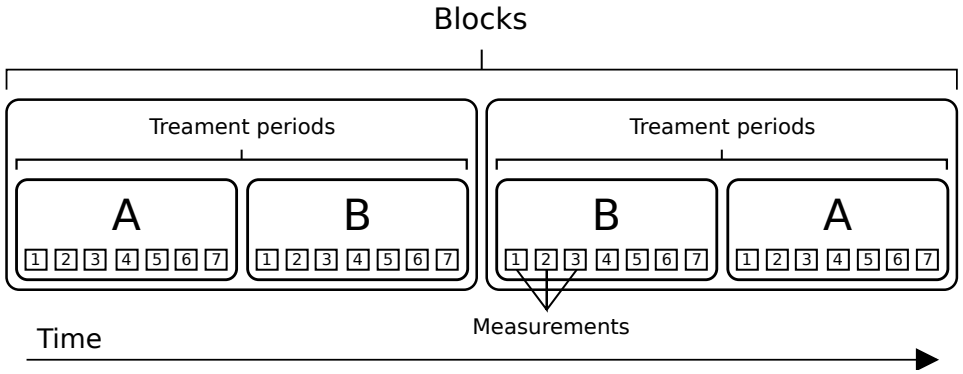
5.1 Defining the Experiment

Lets first describe our experiment design, as this is critical for understanding everything that comes later. Imagine that we have 6 patients that all suffer from the same medical condition to which there are two treatment options available (A) and (B). We know from the literature that there is clear patient-level variation in which treatment works better so we decide to test this with N-of-1 trials. We know that both of the treatments act very fast and that there are no known problems with interaction effects between them.

The state of the condition can also be easily measured at home so no visits to a hospital are needed to take the measurements. Higher measurements mean worse condition so we would like to find the treatment that gives the lowest measurements for each patient. The condition is usually steadily worsening with or without the treatment as the treatment is more for managing the disease and not curing it. Based on this information we come up with the following experiment design:

- The trial will run for 4 weeks with 2 weeks on each treatment
- Treatment periods will be one week long
- The week-long treatment periods will be organized into two blocks, each of which will run for 2 weeks and contain 1 week on each treatment
- The sequence of the treatments in the first block will be randomized and then the second block will have the treatments in reverse order creating a balanced design (ABBA or BAAB)
- Measurements will be taken by the patient at the end of each day so we end up with 28 measurements per patient with 14 for each of the treatments that are separated by roughly equal time-periods (one day)
- There will be no washout period when switching between the treatments

Figure 5.1: Example of the Experiment Design for a Single Patient



5.2 Simulating the Data

Next we simulate the data that we could get from our defined experiment with Python. As there should not be any interaction effects between the treatments, the treatment effect onset is immediate and there is no washout period, this is a fairly simple task. The benefit of having a relatively simple data generating process, is that it is easier to compare the results from out models with the actual parameters. We will not go over the code that creates the data in detail, but just look at the mathematical models used for it. The full code can be found in the GitHub repository [14]. For simulating each observation at time t for patient j we use the following model:

$$y_{tj} = Z_{tj}\theta_j + W_{tj}\eta_j + t\beta_j + \epsilon_t + \rho_j\epsilon_{t-1}, \tag{5.1}$$

where θ_j and μ_j are the treatment effects with Z_{tj} and W_{tj} being indicator variables that are 1 when observation t is within a period where treatment was applied and 0 otherwise. β_j is the trend representing the natural progress of the condition. $\epsilon_{tj} \sim N(0, \tau_j^2)$ is the error term at t and ρ_j is the correlation between consecutive errors.

This data generating model has both a trend and a lag-1-autocorrelation. The trend we are going to be modeling later, but also modeling autocorrelation would make the model too complex for the limited amount observations we will be dealing with. This way the example tries to be more realistic by having the data generation function to be of such complexity that it cannot be fully modeled and some decisions have to be made on how to try to approximate the process with a simplified version of reality.

"Above" the part creating the individual observations we have a population-level parameters that define the distribution from which the patient-level parameters are drawn from:

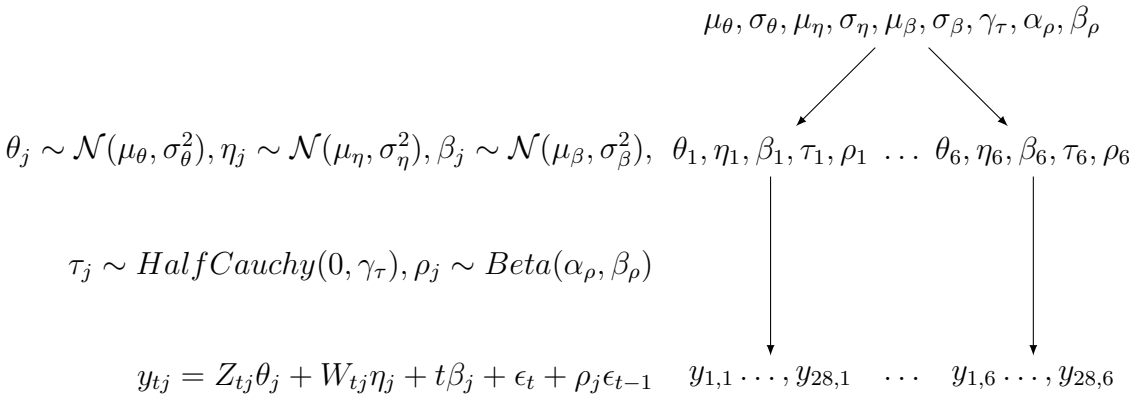


Table 5.1: Population Level Parameter Values for the Simulated Data

population treatment A mean:	$\mu_\theta = 10$
population treatment A standard deviation:	$\sigma_\theta = 0.2$
population treatment B mean:	$\mu_\eta = 9.7$
population treatment B standard deviation:	$\sigma_\eta = 0.3$
population trend mean:	$\mu_\beta = 0.02$
population trend standard error:	$\sigma_\beta = 0.01$
population measurement error scale:	$\gamma_\tau = 0.3$
population error autocorrelation alpha:	$\alpha_\rho = 100$
population error autocorrelation beta:	$\beta_\rho = 200$

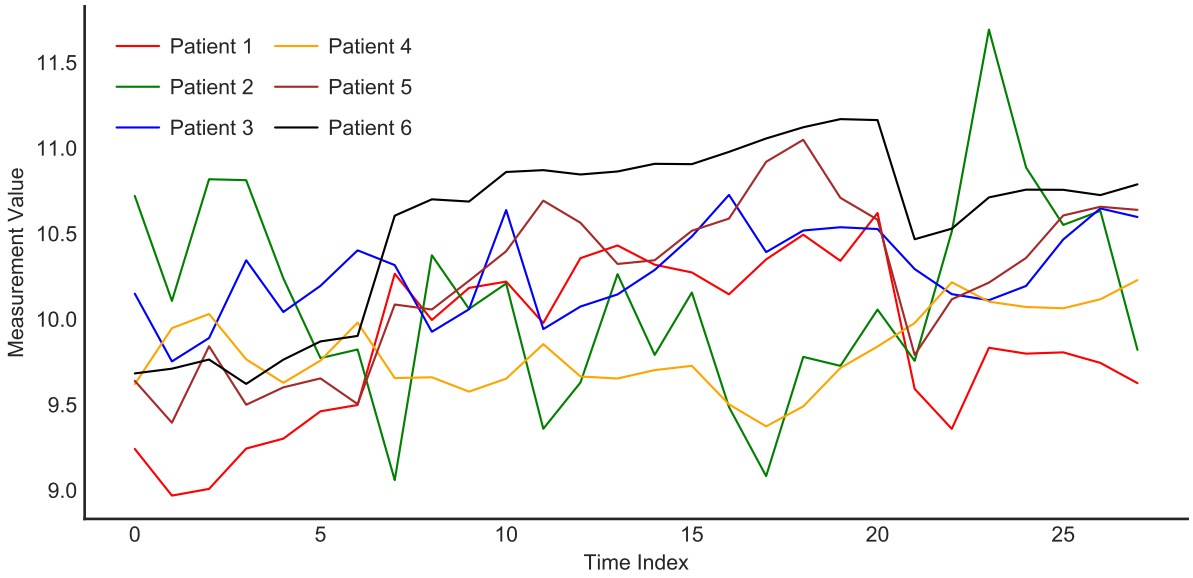
One noteworthy here is that we pick a beta distribution for the population autocorrelation as it is a natural choice as it limits the values nicely between 0 and 1.

To create the simulated data, we set the population parameters as follows and then run our data creation process:

There are some important things to note about these values. First, we defined the treatment A to usually have higher mean than treatment B meaning that the treatment B should perform better (lower measurement values) for most patients. Second, the mean of the trend β is positive and its variance is small. This means that almost all patient should have a steadily worsening condition (measurements get higher as the experiment progresses).

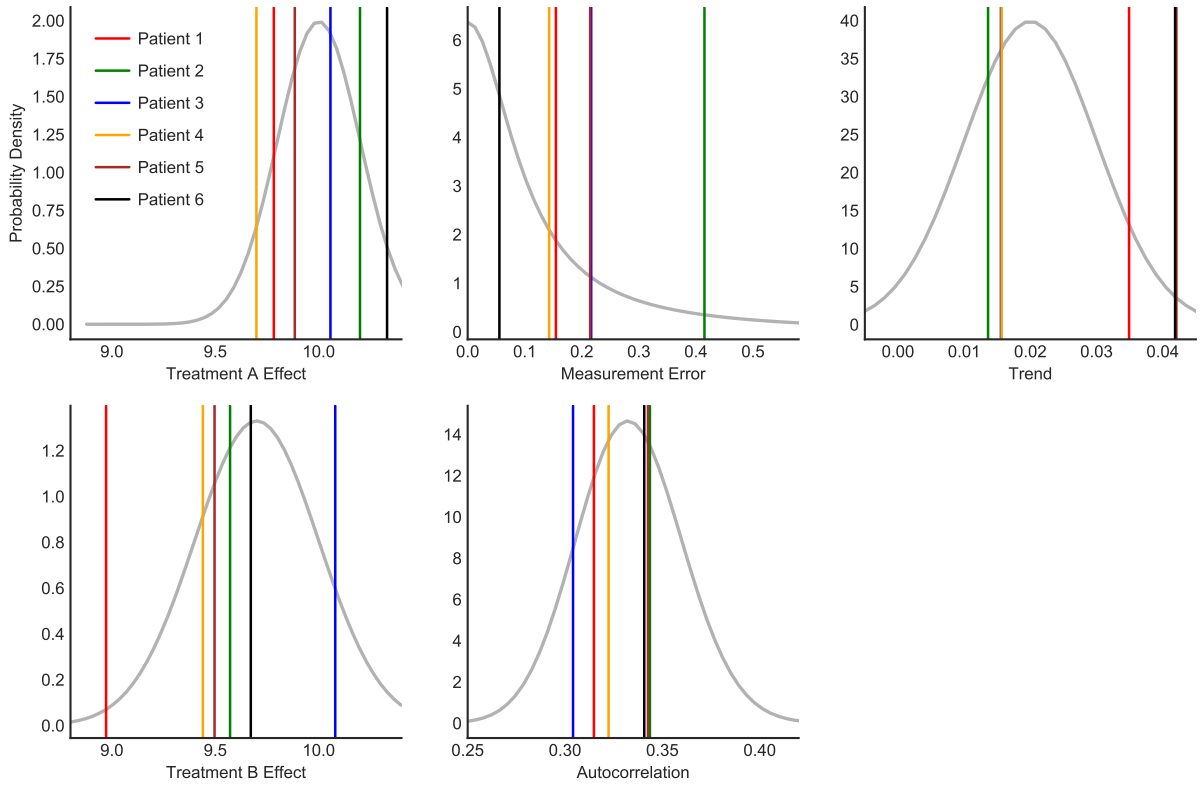
In figure 5.2 we see timelines of measurements for each patient. Just by looking at this plot, it seems pretty obvious that for patients 2 and 1 there is a clear difference in the efficacy of the treatments, with the treatment periods clearly visible. We also see more ambivalent cases. Patient 4 seems to have very stable measurement values regardless of the treatment, while patient 2 has lots of random fluctuations in the data making it hard to interpret the data just by looking at the plot. We can also see the upwards trend in the measurement as all patients except patient 2 end the experiment with higher measurement values that they started with (remember that because of the balanced design, patients start and end the experiment with the same treatment).

Figure 5.2: Timeline of Measurements for Each Patient



Let's next look at the actual parameters that created this data. In figure 5.3, we have all patient-level parameter values and population distributions which they where drawn from. On the left side we can see both of the treatment effect means. As these are plotted on an identical axis, we can easily compare them. We can see that for every patient, except patient for patient 3, treatment A is the better (higher parameter value). The second interesting finding is that for patient 1 the treatment B effectiveness is far better than for other patients. When we look at the hierarchical model these two patients are the ones to keep an eye out as we would expect the measurements from other patients to pull the treatment effectiveness of treatment B for patient 3 down (make it better) and conversely pull this up for patient 1. From the measurement error and autocorrelation there is less interesting things to see: the wild swings of the measurement for patient 2 are explained by her high measurement error and autocorrelation values are quite tightly grouped up for all patients. For the trend we see that patients 2, 4 and 5 are getting worse significantly slower than the other patients.

Figure 5.3: Parameter Used to Create Simulated Data

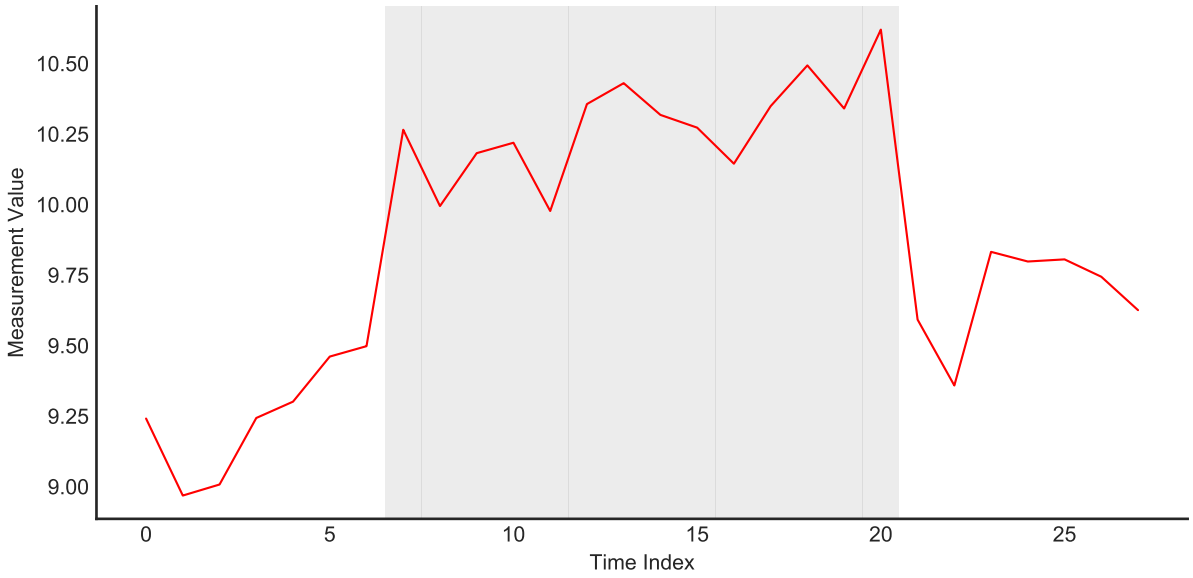


5.3 Analyzing a Single Trial

We start with the case of analyzing just a single patient. We pick patient 1 as we saw previously when looking at the parameter values 5.3 that this patient has a parameter value for treatment B that is significantly lower than for other patients. This makes for an interesting comparison as we can see how the estimates that we get for this parameter differs between the single patient model and the hierarchical model. We would expect the parameter value to be get pushed higher towards the other patients in the hierarchical model.

In figure 5.4 we have the timeline of observations for patient 1. We have highlighted the period where the patient was on treatment A with grey and can clearly see that this treatment is the inferior option for this patient.

Figure 5.4: Timeline of Measurements for Patient 1



Normally before we would start with a more extensive exploration of the data, but as teaching preliminary analysis is not the focus here and we created the data ourself and so know exactly what kind of distribution it follows, we will skip this step here. For analyzing any real-world data this proper data exploration would be *mandatory*.

5.3.1 Defining the Model

We use a model with the two treatment parameters and error term and a trend 5.2. We could start with a more simple model without the trend, but as we saw from figure 5.4 that there is a clearly trend in the data, so adding this parameter from the start seem appropriate:

$$y_t = Z_t\theta + W_t\eta + t\beta + \epsilon_t \tag{5.2}$$

where θ and η are the treatment effects with Z_t and W_t being indicator variables that is 1 when observation t is within a period where treatment was applied and 0 otherwise. β is the trend and $\epsilon_t \sim N(0, \tau^2)$ is the error term at t.

Our model assumes that the measurement values are distributed normally with variance τ^2 and with a mean of either θ or η depending on which treatment is applied at the observation $y_t \sim N(Z_t\theta + W_t\eta, \tau^2)$. This means that our likelihood function will have to

be a bit special as using a simple normal distribution will not do. We will see that this will cause use some headaches later when we try to implement the model.

Next we go to choose the prior distributions for our model. We choose normal distributions for the treatment effect parameters and the trend as it makes sense to think that these would depends on multiple independent biological and social factors (very reasonable assumption!) and the central limit theorem tells us the that the parameters should then be normally distributed. For the variance of the error term we choose a half-Cauchy distribution as this is a common recommendation for the prior of variance [15].

$$\mu_\theta, \sigma_\theta, \mu_\eta, \sigma_\eta, \mu_\beta, \sigma_\beta, \gamma_\tau$$

$$\downarrow$$

$$\theta \sim N(\mu_\theta, \sigma_\theta^2), \eta \sim N(\mu_\eta, \sigma_\eta^2), \qquad \theta, \eta, \beta, \tau$$

$$\downarrow$$

$$\beta \sim N(\mu_\beta, \sigma_\beta^2), \tau \sim HalfCauchy(0, \gamma_\tau)$$

$$\downarrow$$

$$y_t = Z_t\theta + W_t\eta + t\beta + \epsilon_t \qquad y_1 \ldots, y_{28}$$

Now that we have our model defined we should think about what kind of values we should give to our prior parameters. Lets say that for treatment A and B we know from existing literature that the typical measurements taken under these treatments are around 10. We can just slot this value in for the mean prior parameter values. The case for the standard deviance is harder as now we have to codify the strength of our belief in the treatment means. As we have actual (imagined) information available we can use the standard deviance of the means from different studies as our guidelines. Lets say that this value is 0.5, so that it is rare to values above 11 or under 9. We can tone down this certainty as we are not very sure that the patients on which the previous studies where conducted are that similar to our patients, so we double the standard deviance prior to 1 for both treatment options. For the trend we are not so certain, but we assume that it should be increasing slightly, so we set the mean to 0.1. Because of our uncertain we set the standard deviance to 0.3, giving this value a lot of flexibility and allowing the trend to be also positive without the patient being a huge outlier. For the scale of the half-Cauchy distribution we go with a non-informative prior as the error also depends on if on properly the measurement is performed (remember that the measurements are taken by the patients) and this is very hard to estimate so we set the value γ value to 1 for an non-informative prior. The set prior values can be seen in table 5.2.

Table 5.2: Single Patient Model Prior Values

treatment A mean prior:	$\mu_\theta = 10$
treatment A standard deviance prior:	$\sigma_\theta = 1$
treatment B mean prior:	$\mu_\eta = 10$
treatment B standard deviance prior:	$\sigma_\eta = 1$
trend mean prior:	$\mu_\beta = 0.1$
trend standard deviance prior:	$\sigma_\beta = 0.3$
measurement error scale prior:	$\gamma_\tau = 1$

5.3.2 Implementing the Model in PyMC3

PyMC3 is Python package built for probabilistic programming. Although it is not limited to Bayesian methods, that it is its main focus. Implementing Bayesian models in the package works so that you give it all the parts of the Bayesian formula except the marginal likelihood: the likelihood, prior distribution and the values defining the prior distributions. Then it automatically chooses a Markov Chain Monte Carlo method (MCMC) that it thinks can most efficiently algorithmically approximate the posterior distribution. This is very nice, as this takes out a huge chunk of work from us, namely choosing and implementing the approximation method ourself. But now that we have entered the territory of algorithmic solutions, we have introduced a new hurdle, namely checking that the algorithm is actually works for our model and gives us good approximations. On top of this we of course have all the usual stuff related to model accuracy and checking that our model itself is a good approximation of the reality. We will go over how these problems manifest themselves and how we can deal with them when these problems pop up, so lets us just jump in and implement the model in PyMC3 and then walk trough what the code is actually doing line by line[1].

[1]The code snippets that we will be showing are a slight simplification of the actual code that was used to calculate the results. The simplification does not mean that the code shown is not executable, but parts of it that are related to technical niceties (e.g. inter OS compatibility, saving the plots...) are taken out to focus on what is important for Bayesian calculations.

Full Model Implementation in PyMC3

```
# load in needed packages
import pymc3 as pm
import pandas as pd

# load measurement data and true parameter values
measurements_df = pd.read_csv("patient_measurements.csv")
parameters_df = pd.read_csv("patient_parameters.csv")

# convenience variable for easier indexing
patient_idx = measurements_df["patient"]

# define the model
with pm.Model() as single_patient_no_trend_model:

    # defing our prior beliefs of the distributions of parameters
    treatment_a = pm.Normal("Treatment A", mu=10, sigma=1)
    treatment_b = pm.Normal("Treatment B", mu=10, sigma=1)
    trend = pm.Normal("Trend", mu=0.1, sigma=0.3)
    gamma = pm.HalfCauchy("Gamma", beta=1)

    # creating a vector definig the expected means of the observations
    measurement_means = (
        treatment_a * measurements_df[patient_idx == 0]["treatment_a"]
        + treatment_b * measurements_df[patient_idx == 0]["treatment_b"]
        + trend * measurements_df[patient_idx == 0]["measurement"]
    )

    # likelihood is normal distribution with the same amount of dimensions
    # as the patient has measurements and and the means are defined by one of the
    # treatment priors + trend with always the same variance
    likelihood = pm.Normal(
        "y",
        measurement_means,
        sigma=gamma,
        observed=measurements_df[patient_idx == 0]["value"],
    )
```

```
    # adding the comparison between the treatments
    difference = pm.Deterministic(
        "Treatment Difference (A-B)", treatment_a - treatment_b
    )

    # running the model
    trace = pm.sample(800, tune=500, cores=3)

    # Checking diagnostic describing how the MCMC method performed
    pm.traceplot(
        trace, ["Treatment A", "Treatment B", "Trend", "Gamma"], divergences="top"
    )
    plt.show()
    pm.summary(trace)

    # checking the posterior distributions
    pm.plot_posterior(trace)
    plt.show()


# posterior sampling
with single_patient_no_trend_model as model:
    post_pred = pm.sample_posterior_predictive(trace, samples=500)
    predictions = post_pred["y"]

# visualizing posterior samples to check model match with reality
draw_posterior_checks(
    predictions=predictions,
    measurements_df=measurements_df[patient_idx == 0],
    parameters_df=parameters_df[parameters_df["patient"] == 0],
)
```

Loading in the Package and the Data

```
import pymc3 as pm
import pandas as pd

measurements_df = pd.read_csv("patient_measurements.csv")
parameters_df = pd.read_csv("patient_parameters.csv")
```

```
patient_idx = measurements_df["patient"]
```

The first thing we of course have to do is to load the package and get our data. There is not much to comment about loading the package, but lets show how our data looks like:

patient	measurement	period	block	treatement_a	treatment_b	value
0	0	0	0	0	1	9.241493
0	1	0	0	0	1	8.968412
0	2	0	0	0	1	9.007580
0	3	0	0	0	1	9.243449
0	4	0	0	0	1	9.301344
0	5	0	0	0	1	9.461129
0	6	0	0	0	1	9.498025
0	7	1	0	1	0	10.265324
0	8	1	0	1	0	9.994795
0	9	1	0	1	0	10.182349

All columns expect the last one are index columns. As is the standard in Python, everything zero-indexed. First column indexes the patient (0-5), second the measurement (0-27), third the treatment period (0-3), fourth the block (0-1) and fifth and sixth which treatment was applied during the particular measurement (0-1). Last column is the value of the measurements. PyMC3 does not require any particular format from the data and almost any format is possible as long as you can feed the right values into the right places in the model definition. Also using the Pandas package to handle the data as a dataframe is not necessary, but is very convenient.

The parameters_df dataframe contains the true parameter values of the patients. This data is used to check how accurate our predictions actually are. Each row is a patient and contains the true parameter values for each of the parameters we used to create the simulated data. Only a couple of the columns included in the dataset are shown here, because the full table would not fit.

patient	treatment_a	treatment_b	trend	measurement_error_sd
0	9.782874	8.971996	0.034914	0.154553
1	10.199469	9.571326	0.013611	0.414898
2	10.056596	10.079781	0.015560	0.216430
3	9.698741	9.439978	0.015656	0.142773
4	9.884280	9.496334	0.042059	0.214645
5	10.330287	9.671587	0.041868	0.055582

The last part of the code where we create the variable patient_idx is just for convenience so that we need to type less when referring to the data of a particular patient.

Initializing the Model

```
with pm.Model() as single_patient_no_trend_model:
```

PyMC3 models are usually defined within the Python context manager ("with" statements). This is not necessary, but makes the model definition much cleaner as when the model is defined in the context manager, all subsequent parts defined within the manager (indented parts of the code) are automatically associated with this particular model without need for manually defining this.

Defining the Priors

```
treatment_a = pm.Normal("Treatment A", mu=10, sigma=1)
treatment_b = pm.Normal("Treatment B", mu=10, sigma=1)
trend = pm.Normal("Trend", mu=0.1, sigma=0.3)
gamma = pm.HalfCauchy("Gamma", beta=1)
```

Now we start getting to the actual modeling. We start by defining our prior beliefs about out the parameter distributions. You could call these distributions the prior distributions, but this does not make much sense in PyMC3 as final output are these distributions with modified parameters. For both treatments and the trend we use a normal distribution and for the variance of the error term γ we use a half-Cauchy. For the half-Cauchy distribution we don't need to define the location term as it is by default zero, just like we want it. Something to note here is that the PyMC3 normal distribution sigma paramaters expects the standard deviation and not the variance. As all the distributions that we are using here are widely used, we can find functions implementing them

already built-in PyMC3. It is also possible to define completely custom distributions, but unfortunately this is quite complex, as you don't just have to worry about the math part, but also all you have to implement all the methods that PyMC3 relies on when making the calculations[2].

Defining the Likelihood

```
measurement_means = (
    treatment_a
    * measurements_df[patient_idx == 0]["treatment_a"]
    + treatment_b
    * measurements_df[patient_idx == 0]["treatment_b"]
    + trend
    * measurements_df[patient_idx == 0]["measurement"]
)

likelihood = pm.Normal(
    "y",
    measurement_means,
    sigma=gamma,
    observed=measurements_df[patient_idx == 0]["value"],
)
```

Defining the likelihood is the most difficult part our model definition because of the complexity introduced by the varying treatments. Because of this, the likelihood cannot be implemented as a simple normal distribution. We solve this problem by instead using a multivariate normal distribution with as many dimensions as the patient has measurements. We construct the vector of means for this distribution by multiplying the treatment distributions by the treatment indices (1 when treatment given, 0 when not) and add the trend multiplied by the index of the measurement (t). So instead of considering the observations separately we think of them as a single multidimensional sample from a multivariate normal distribution. This is not the only possible way to solve the problem, but is probably the most convenient. If we would have some dependencies between the measurements in our model (e.g. autocorrelation), this approach would not

[2]This complexity is a reason why the author would recommend using the Stan package for very complex models with lots of weird distributions. Although Stan requires to you to write model definition with its own language, this hurdle is worth in some cases as you just have worry about the math and there is no need to consider implementing any helper functions

work. In this case we would have to implement the likelihood function ourselves. One thing to note here is that even though we are using a multivariate normal distribution, we still use the same PyMC3 function for normal distribution and just give it a vector of means that matches the amount of our observations. This strategy works with all the inbuilt PyMC3 distributions: you can either have them using one set of parameters or a vector of parameters matching the data and PyMC3 will automatically change from using a single dimensional distribution with multiple observations to multidimensional distribution with one observation vector.

5.3.3 Defining the Parameter Comparison

```
difference = pm.Deterministic(
    "Treatment Difference (A-B)", treatment_a - treatment_b
)
```

As the estimate we are most interested is not actually any individual parameter, but the *difference* between the two treatment parameters, we have to add this comparison separately. We can do this before or after running our model, but here we have decided to do it beforehand. As the difference is actually determined by the values of the treatment parameters, we have to use PyMC3 pm.deterministic function that calculates the posterior by simple subtracting the value of treatment 2 parameter value from treatment 1 parameter value at each step in the chain.

Running the Model

```
trace = pm.sample(draw=800, tune=500, cores=3)
```

Now that we have defined our prior beliefs and our likelihood, we can move on to running the model. PyMC3 will now estimate the posterior with an automatically chosen Markov Chain Monte Carlo (MCMC) method (see chapter 3.1.1) that moves trough the posterior from point to point. We could also manually choose what algorithm to use, but unless we see problems when we evaluate the estimation efficiency, we should stick with the automatic selection. We also don't need to define the point in the posterior distribution where the estimation starts as this is also automatically chosen. This we could also define manually, but unless we run into problems, we should not need to.

The three parameters that we have to manually define are as follow:

draw = how many moves the MCMC chain should calculate

tune = how many moves the MCMC chain should take before it start to take the observations into account

cores = how many MCMC chains we will calculate in parallel

The total steps taken by each chain is draw+tune. The reason for the tuning steps is that the starting position of the chain is probably biased. We would want the starting position to be a sample from the posterior so that its probability of it being in a certain point would be defined by the posterior. We can do this by letting the chain first take a number of steps and as its moves trough the posterior its location distribution will start to reflect the actual posterior. If we would not have the tuning steps it would be possible that the chain starts in a weird position and the first steps it takes don't reflect the posterior as it might have to make lots of moves in a certain direction to get to the representative parts of the distribution. The more draws and tuning steps we take the better the estimation will be, but the more time the calculation will take. Finding the right number of draw and tuning steps involves usually some trial and error. It is hard to know how many steps you need before you try to run the model. Luckily PyMC3 will automatically alert us if it thinks that we need more tuning steps or draws and we can also diagnose this from metrics and plots that we will look at after we have run the model.

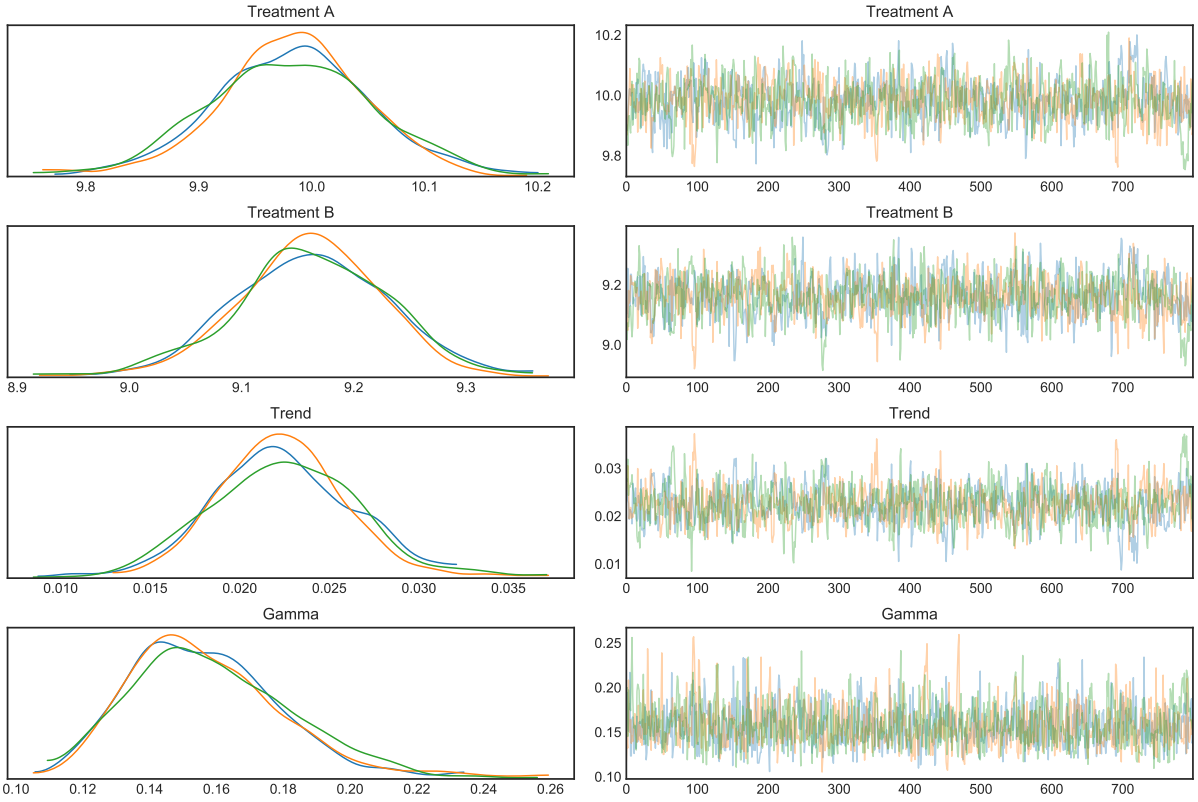
As modern CPUs have usually multiple cores, we can speed up the calculation by running multiple chains in parallel. Each chain will be independent of each other and each will take same amount of draws and tuning steps. As the chains can runs in parallel, having multiple chains running can dramatically speed up our estimation. The total number of steps that the posterior will be calculated with is the combined draws (not tuning steps) of the chains. So in our case we will use 3 cores and have 3 chains (running this on a 4 core CPU so we will leave 1 core free for other tasks), in total these chains will make (800 + 700) * 3 = 4500 steps, of which 800 * 3 = 2400 steps will be used for the posterior estimation.

Checking Algorithm Diagnostics

```
# Checking diagnostic describing how the MCMC method performed
pm.traceplot(
        trace, ["Treatment A", "Treatment B", "Trend", "Gamma"], divergences="top"
    )
plt.show()
pm.summary(trace)
```

Now that we have run the model we need to evaluate if the algorithm did a good job with the estimation. We can evaluate this by looking at diagnostic plots and from diagnostic metrics. Lets first look at the visualizations of the MCMC-chain steps called traceplots:

Figure 5.5: Single Patient Traceplots



On the right in figure 5.5 we can see the steps taken by each chain in our four parameters (remember from chapter 3.1.1 that each chain takes steps in all parameter values simultaneously. These are just the steps used for the posterior estimation and don't include the tuning steps. Each chain is portrayed with a different color. What we want to see here is that the timeseries looks like noise with no obvious patterns [3]. If we would see any patterns, like the chains moving values moving systematically up and down, it would mean that the chains had problems moving trough the posterior and ended up taking biased samples. These effects should be most pronounced at the beginning steps and if

[3]With this model it is hard to demonstrate this problem effectively in PyMC3 as not having enough tuning and and calculation steps often just leads the model to fail outright without any results

we would see these, we should increase the number of tuning steps.

On the right side of the figure, we can see the distribution of the posterior values for each chain. Here we would want to see that distributions from different chains more or less align with each other. If this is not the case, it means that the chains got stuck in different parts of the posterior. This would also show on the left side plots with the different chains staying in different parts of the posterior and being distinguishable from each other. If we see this problem the solution is once again to increase the tuning steps.

Besides looking at plots, we can also estimate the success of the estimation from diagnostic metrics. PyMC3 has an inbuilt method for printing the common metrics (pm.summary(trace)). Below 5.6 we can see the output from this methods:

Figure 5.6: Single Patient Traceplots

	mcse_mean	mcse_sd	ess_mean	ess_sd	ess_bulk	ess_tail	r_hat
treatment1	0.001	0.001	2712.0	2712.0	2724.0	1680.0	1.0
treatment2	0.001	0.001	2349.0	2348.0	2351.0	1830.0	1.0
gamma	0.001	0.001	2148.0	2140.0	2127.0	1703.0	1.0

If increasing the tuning steps does not seem to help we have to consider two things: the MCMC algorithm chosen by PyMC3 is not a good match for our model or our model might not be properly defined. The first thing is try to manually choose a different algorithm than PyMC3 automatically chose (can be seen from the model computation printout) and seeing if we get better results. If this does not seem to work, we have to over our model and think if the model is in some way improperly defined.

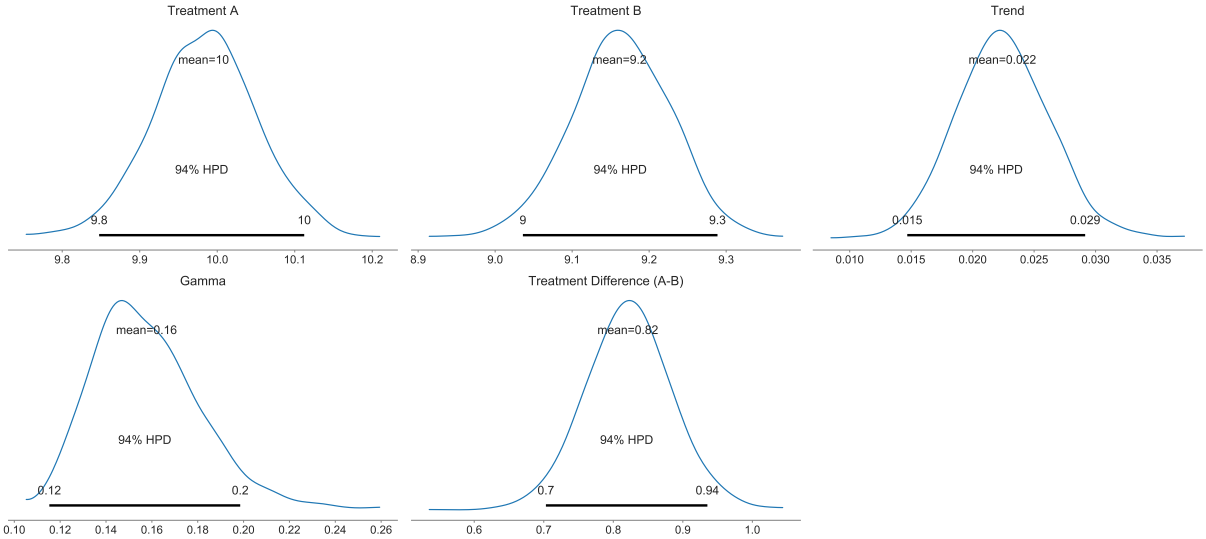
One thing that we should not here is that we only looked at diagnostic values for our parameters, but not the difference between the treatment means, that we are actually the most interested in. The reason for this, is that the difference is entirely determined by the individual treatment parameters, so if the estimation of these is in order, so will be the estimate of their difference.

Checking the Posterior

```
pm.plot_posterior(trace)
```

If the estimation looks fine, we can move on to checking the actual results and look at the computed posterior distributions 5.7:

Figure 5.7: Single Patient Posterior Distributions



The inbuilt PyMC3 method prints the posterior distribution for all of out parameters, with their posterior mean and highest posterior density interval (HPD) for approximately 95 % of the values. We can see that that the even though the posterior means between the two treatment options are clearly different, there is quite a lot of overlap for the HPD. Luckily we also defined the difference between these two parameters and can see this as a separate plot and this gives us the result we are interested in. We can see that the mean is positive and the HPD does not include zero, we can quite certain that treatment A is a worse option for this patient than treatment B, with the likely values of the difference falling between 0.71 and 0.94.

Checking Model Fit with Posterior Sampling

```
# posterior sampling
with single_patient_no_trend_model as model:
    post_pred = pm.sample_posterior_predictive(trace, samples=500)
    predictions = post_pred["y"]

draw_posterior_checks(
    predictions=predictions,
    measurements_df=measurements_df[patient_idx == 0],
```

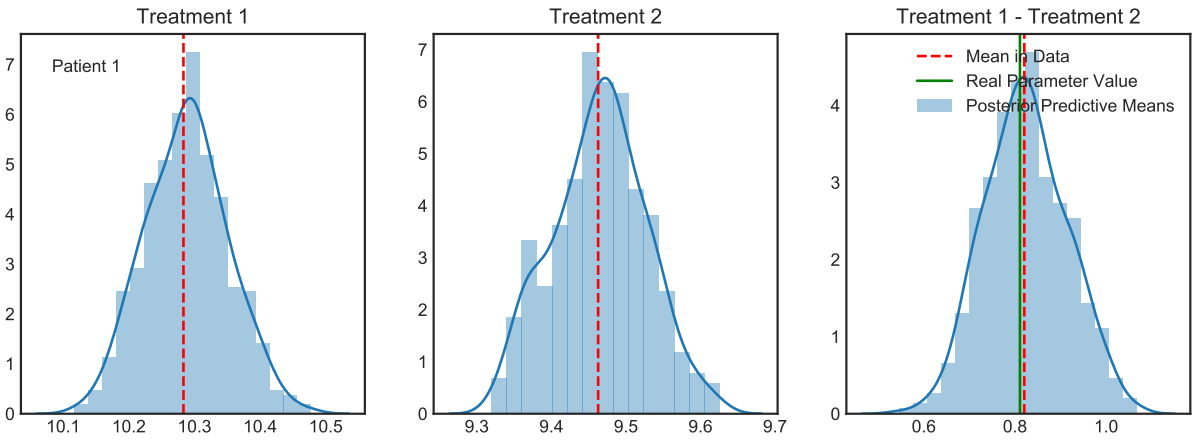
```
    parameters_df=parameters_df[parameters_df["patient_idx"] == 0],
    plot_name="single_patient_no_trend_posterior_sampling",
)
```

Even though we already checked that the estimation seems to be working correctly and saw that the posterior estimates clearly favor treatment option B for this patient, there is still one important thing that we should check before announcing our results. We should make sure that our model is actually a good fit for our data. We could have clear results with good estimation, but if our model does a poor job at reflecting the reality, we should not be very excited about our results.

Checking model fit for Bayesian models can be done with posterior sampling where we generate samples from the posterior distributions and for each of these samples we create a simulated dataset based on the chosen parameter values. Then we compare these simulated datasets to the actual data. What we want to see is that actual data looks like a typical case for a simulated dataset e.g. if our model where the exact way that the data was created, we would not be surprised to see the data that we got from the experiment.

PyMC3 has an inbuilt method for taking the posterior samples, but for comparing these samples to the real dataset we have to create our own function. We have written a special function called "draw posteriors" for this purpose. We don't go over the code of this function, but what it does is to use the datasets created by the PyMC3 inbuilt method and calculates the mean of the measurements under each treatment and difference between these means. It then plots these means as distribution against the mean treatment measures and the difference of these means between the treatment calculated from the original data. For the difference between the means it also adds in the actual difference of the true parameters. Normally we would not know this true value, but in this case we do as we generated the data ourselves. This makes it possible to see how accurate the model actually is.

Figure 5.8: Single Patient Posterior Sampling



In figure 5.8 we can see the plots generated by our function. We see that the distribution of mean treatment effectiveness calculated from the generated datasets matches nicely with the actual mean of the data. This means that our model seems to be good enough approximation of reality. Also when we look at the difference in the treatment effectiveness, we see that the posterior of difference between the treatments lines very nicely with the true parameter difference.

5.3.4 Final Results

After going trough the steps of:

1. Defining the model
2. Implementing the model in PyMC3
3. Calculating the results
4. Evaluating the estimation process
5. Checking the posterior values
6. Making sure that our model is an accurate enough description of reality

We can say that for this patient treatment B is recommended over treatment A with treatment B giving 0.82 points lower measurements. We can also easily communicate the uncertainty in our estimation by with the HPD by saying that the true difference of the treatments is with 95 % probability between 0.71 and 0.94.

5.4 Analyzing Multiple Trials With Hierarchical Models

Lets next add in all the other patients and connect the trials with a hierarchical model. We will still focus on patient 1 that we analyzed previously and pay special attention on how the posterior parameters estimates change when we pool all the data that we have. Our suspicion is that estimate of the difference in treatment effectiveness should be toned down as the treatment effectiveness for treatment B for patient 1 was an outlier compared to the other patients (see figure 5.3).

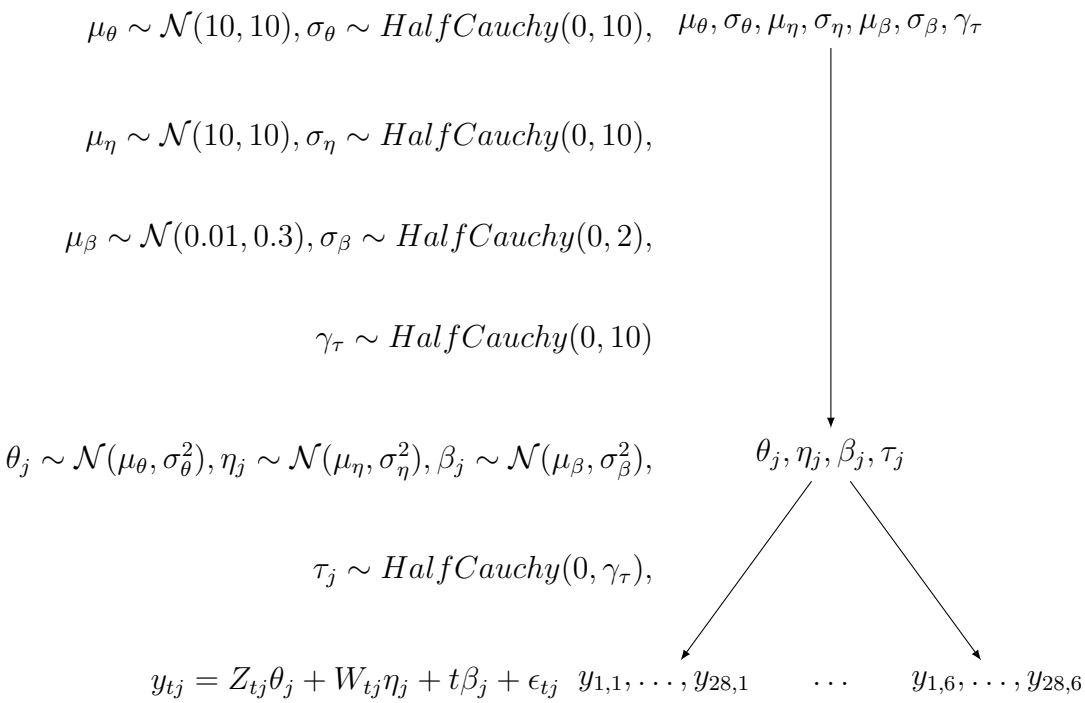
5.4.1 Defining the Model

We start with the same model that we used for the single patient, but now we index all our measurements not just by time t, but also by patient j:

$$y_{tj} = Z_{tj}\theta_j + W_{tj}\eta_j + t\beta_j + \epsilon_{tj} \tag{5.3}$$

where θ_j and η_j are the treatment effects with Z_{tj} and W_{tj} being indicator variables that is 1 when observation t is within a period where treatment was applied and 0 otherwise. β_j is the trend representing the natural progress of the condition. $\epsilon_{tj} \sim N(0, \tau_j^2)$ is the error term at t and ρ_j is the correlation between consecutive errors.

To make this model hierarchical we now add the population level distributions which the patient-level parameters are drawn from and the prior distributions for the parameters defining the population level distribution:



As the priors are defined on the population level we have to think about defining the parameters of these distributions in a bit different way

5.4.2 Implementing the Model in PyMC3

Next we move to implementing our hierarchical model in PyMC3. As by now we are already familiar with basics of PyMC3, we can now skip explaining the whole code and just focus on the difference from the single patient model.

```
patient_idx = measurements_df["patient_idx"]

with pm.Model() as hierarchical_model:

    # population priors
    pop_treatment_a_mean = pm.Normal(
        "Population Treatment A Mean", mu=10, sigma=1
    )
    pop_treatment_a_sd = pm.HalfCauchy("Population Treatment B Sd", beta=1)

    pop_treatment_b_mean = pm.Normal(
```

```
    "Population Treatment B Mean", mu=10, sigma=1
)
pop_treatment_b_sd = pm.HalfCauchy("Population Treatment B Sd", beta=1)

pop_trend_mean = pm.Normal("Population Trend Mean", mu=0.1, sigma=0.3)
pop_trend_sd = pm.HalfCauchy("Population Trend Sd", beta=2)

pop_gamma = pm.HalfCauchy(
    "Population Gamma", beta=10
)

# separate parameter for each patient
pat_treatment_a = pm.Normal(
    "Treatment A",
    mu=pop_treatment_a_mean,
    sigma=pop_treatment_a_sd,
    shape=6,
)
pat_treatment_b = pm.Normal(
    "Treatment B",
    mu=pop_treatment_b_mean,
    sigma=pop_treatment_b_sd,
    shape=6,
)
pat_gamma = pm.HalfCauchy(
    "Gamma", beta=pop_gamma, shape=6,
)
pat_trend = pm.Normal(
    "trend",
    mu=pop_trend_mean,
    sigma=pop_trend_sd,
    shape=6,
)

measurement_means = (
    pat_treatment_a[patient_idx] * measurements_df["treatment_a"]
    + pat_treatment_b[patient_idx] * measurements_df["treatment_a"]
    + pat_trend[patient_idx] * measurements_df["measurement"]
)
```

```
likelihood = pm.Normal(
    "y",
    measurement_means,
    sigma=pat_gamma[patient_idx],
    observed=measurements_df["value"],
)

# adding the comparison between the treatments
pop_difference = pm.Deterministic(
    "Population Treatment Difference (A-B)",
    pop_treatment_a_mean - pop_treatment_b_mean,
)
pat_difference = pm.Deterministic(
    "Treatment Difference (A-B)", pat_treatment_a - pat_treatment_b
)

trace = pm.sample(800, tune=300, cores=3)

# checking traceplots separately for population and patients
pm.traceplot(
    trace,
    [
        "Population Treatment A Mean",
        "Population Treatment A Sd",
        "Population Treatment B Mean",
        "Population Treatment B Sd",
        "Population Trend Mean",
        "Population Trend SD",
        "Population Gamma",
    ],
)
plt.show()
pm.traceplot(
    trace, ["Treatment A", "Treatment B", "Trend", "Gamma"],
)
plt.show()
pm.summary(trace)
```

```
    # plotting selected posteriors
    pm.plot_posterior(
        trace,
        [
            "Population Treatment A Mean",
            "Population Treatment B Mean",
            "Population Trend Mean",
            "Population Gamma",
            "Population Treatment Difference (A-B)",
        ],
    )
    plt.show()


# posterior sampling
with hierarchical_model as model:
    post_pred = pm.sample_posterior_predictive(trace, samples=500)
    predictions = post_pred["y"]

draw_posterior_checks(
    predictions=predictions,
    measurements_df=measurements_df,
    parameters_df=parameters_df,
    plot_name="hierarchical_model_posterior_sampling",
)
```

Defining the Population Level Priors

```
with pm.Model() as hierarchical_model:

    pop_treatment_a_mean = pm.Normal(
        "Population Treatment A Mean", mu=10, sigma=1
    )
    pop_treatment_a_sd = pm.HalfCauchy("Population Treatment B Sd", beta=1)

    pop_treatment_b_mean = pm.Normal(
        "Population Treatment B Mean", mu=10, sigma=1
```

```
)
pop_treatment_b_sd = pm.HalfCauchy("Population Treatment B Sd", beta=1)

pop_trend_mean = pm.Normal("Population Trend Mean", mu=0.1, sigma=0.3)
pop_trend_sd = pm.HalfCauchy("Population Trend Sd", beta=2)

pop_gamma = pm.HalfCauchy(
    "Population Gamma", beta=10
)
```

The first thing we do even before defining the population level priors is the create an index variable of the patient index. This is done just for clarity as referring to patient_idx instead of measurements_df["patient_idx"].

With the population priors we use the exact same method that we used when we were defining priors in the single patient model. All the distributions that we use are inbuilt in PyMC3, so now complex procedures are needed here.

Defining the Patient Level Parameters

```
pat_treatment_a = pm.Normal(
    "Treatment A",
    mu=pop_treatment_a_mean,
    sigma=pop_treatment_a_sd,
    shape=6,
)
pat_treatment_b = pm.Normal(
    "Treatment B",
    mu=pop_treatment_b_mean,
    sigma=pop_treatment_b_sd,
    shape=6,
)
pat_gamma = pm.HalfCauchy(
    "Gamma", beta=pop_gamma, shape=6,
)
pat_trend = pm.Normal(
    "trend",
    mu=pop_trend_mean,
    sigma=pop_trend_sd,
```

```
    shape=6,
)
```

When defining the patient level we run into bigger differences compared to the single patient model. As every parameter has to be defined for each patient, every distribution has to be multidimensional. As we saw when defining the single patient likelihood, PyMC3 can create multidimensional distributions if the distributions parameters are vectors instead of single values, but now the parameters are single values (we have only one population distribution), but we still want multidimensional distributions. We can do this by explicitly defining the shape parameter of the distribution. This, a bit confusingly named parameter (conflict with a commonly used terms for distribution parameters), takes an integer value and makes the distribution have that many dimensions, using the same parameter values for each dimensions. The parameter values for the distributions we get from the population distributions.

Defining the Likelihood

```
measurement_means = (
    pat_treatment_a[patient_idx] * measurements_df["treatment_a"]
    + pat_treatment_b[patient_idx] * measurements_df["treatment_b"]
    + pat_trend[patient_idx] * measurements_df["measurement"]
)

likelihood = pm.Normal(
    "y",
    measurement_means,
    sigma=pat_gamma[patient_idx],
    observed=measurements_df["value"],
)
```

Defining the likelihood is done very similarly as we did with the single patient model, but now we have to use indices to get separate values for each patient. The measurement means now becomes a 6X28 size matrix, where every patient get her own row with measurement means varying by the treatment given. For sigma we use a vector that is indexed the same way as the treatment means. This vector has one value for each patient and all the 28 observations of the patient will use this same value.

Running the Model

```
trace = pm.sample(800, tune=300, cores=3)
```

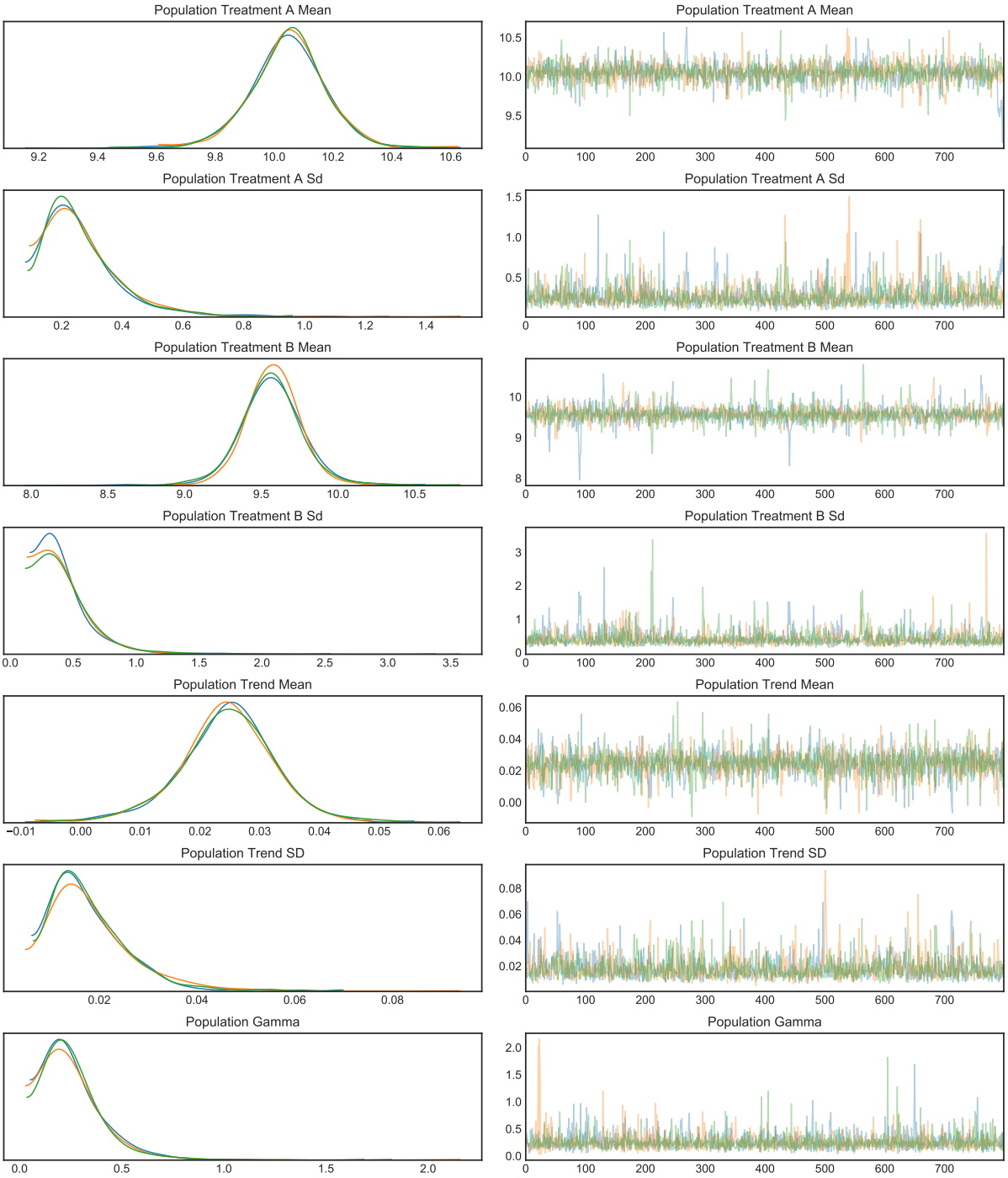
As our model is now much more complex than with the with the single patient model with more parameters, we need to use more tuning and calculation steps compared to our single patient model. Otherwise nothing changes. We still use 3 chains and now this chains take steps in the multidimensional posterior defined not just by patient parameters, but also population parameters, adding 7 more dimensions.

Checking Algorithm Diagnostics

```
pm.traceplot(
    trace,
    [
        "Population Treatment A Mean",
        "Population Treatment A Sd",
        "Population Treatment B Mean",
        "Population Treatment B Sd",
        "Population Trend Mean",
        "Population Trend SD",
        "Population Gamma",
    ],
)
plt.show()
pm.traceplot(
    trace, ["Treatment A", "Treatment B", "Trend", "Gamma"],
)
plt.show()
pm.summary(trace)
```

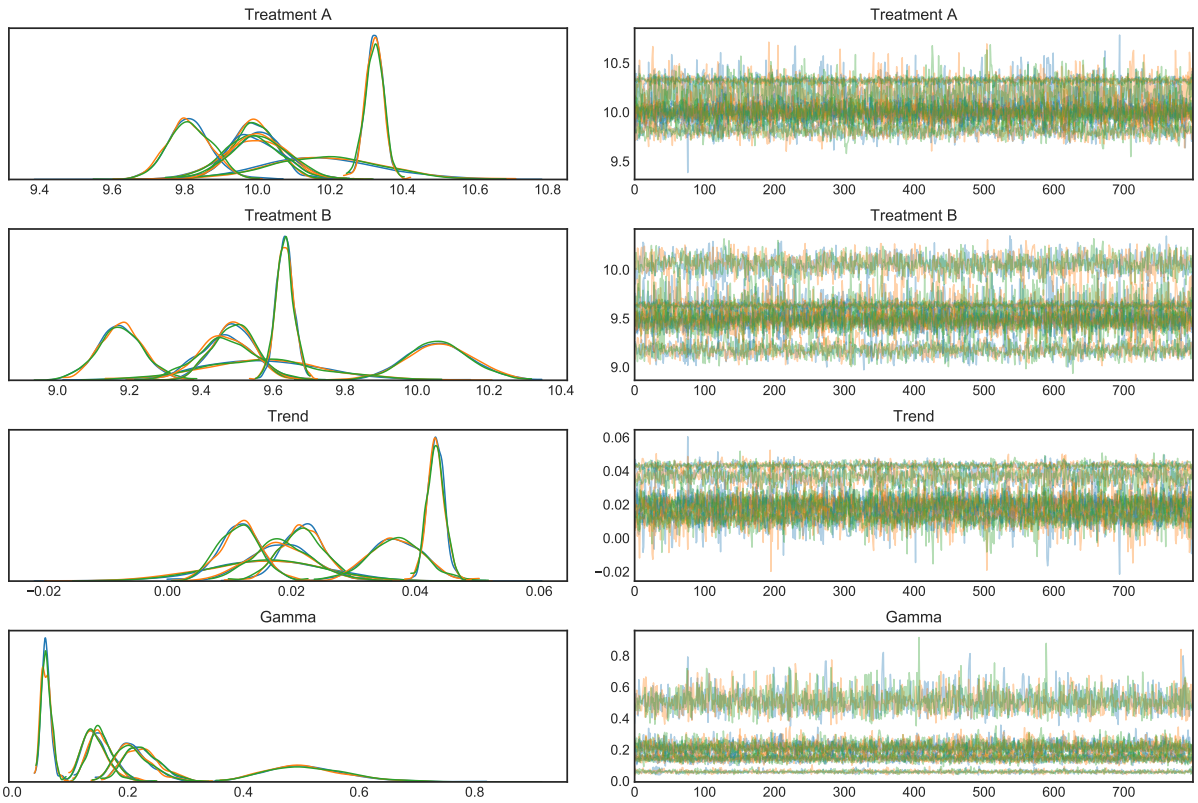
When checking algorithm diagnostic the amount of parameters is now so big that it makes sense to separate the traceplots into multiple chunks. We start with the population traceplots as these look the same as with patient level traceplots in the single patient model. In figure 5.9 we can see traceplots for each of the 7 population level parameters. Once again, we hope to see that the timeseries looks like noise and that the posterior distributions of the chains align nicely. Everything seems to be in order.

Figure 5.9: Hierarchical Model Population Level Traceplots



Next we check the traceplots of the patient level parameters (figure 5.10). These look bit different now as the patient level parameters are multidimensional as every patient has their own parameter. This make the right side of the plot hard to interpret, but left side is still intelligible and see wee that the posteriors of the three chain align. It is possible to plot the traceplots for single patients by passing the indices of parameters to be plotted in a Python dictionary to "coords" parameter in the traceplot function. This is more work, but is worth it if the right side of the plot would show some problems. In this case everything looks okay, so we skip this.

Figure 5.10: Hierarchical Model Patient Level Traceplots



Even if the graphs look good, it always a good idea to also check the diagnostic metrics 5.11. These also look good.

Figure 5.11: Hierarchical Model Diagnostic Metrics

	mcse_mean	mcse_sd	ess_mean	ess_sd	ess_bulk	es
Population Treatment A Mean	0.003	0.002	1426.0	1426.0	1806.0	
Population Treatment B Mean	0.005	0.004	1522.0	1522.0	1857.0	
Population Trend Mean	0.000	0.000	2045.0	2045.0	2168.0	
Treatment A[0]	0.001	0.001	1773.0	1769.0	1861.0	
Treatment A[1]	0.003	0.002	2567.0	2558.0	2640.0	
Treatment A[2]	0.002	0.001	1990.0	1990.0	1995.0	
Treatment A[3]	0.001	0.001	1850.0	1847.0	1891.0	
Treatment A[4]	0.002	0.001	2256.0	2255.0	2257.0	
Treatment A[5]	0.001	0.000	2148.0	2148.0	2160.0	
Treatment B[0]	0.001	0.001	2096.0	2092.0	2103.0	
Treatment B[1]	0.003	0.002	2594.0	2589.0	2608.0	
Treatment B[2]	0.002	0.002	1844.0	1844.0	1933.0	
Treatment B[3]	0.001	0.001	1739.0	1736.0	1793.0	
Treatment B[4]	0.002	0.001	2286.0	2284.0	2293.0	
Treatment B[5]	0.001	0.000	2300.0	2300.0	2308.0	
Trend[0]	0.000	0.000	1837.0	1837.0	1888.0	
Trend[1]	0.000	0.000	2134.0	2134.0	2206.0	
Trend[2]	0.000	0.000	2175.0	2044.0	2183.0	
Trend[3]	0.000	0.000	1734.0	1734.0	1761.0	
Trend[4]	0.000	0.000	1709.0	1709.0	1715.0	
Trend[5]	0.000	0.000	2162.0	2152.0	2184.0	
Population Treatment A Sd	0.004	0.003	1126.0	1025.0	1602.0	
Population Treatment B Sd	0.006	0.004	1397.0	1397.0	1996.0	
Population Trend SD	0.000	0.000	1436.0	1290.0	1826.0	
Population Gamma	0.003	0.003	2488.0	1342.0	4643.0	
Gamma[0]	0.000	0.000	2411.0	2282.0	2538.0	
Gamma[1]	0.001	0.001	2772.0	2594.0	2960.0	
Gamma[2]	0.001	0.000	2717.0	2532.0	2967.0	
Gamma[3]	0.000	0.000	2746.0	2503.0	3140.0	
Gamma[4]	0.001	0.000	2547.0	2379.0	2713.0	
Gamma[5]	0.000	0.000	2793.0	2498.0	3108.0	
Population Treatment Difference (A-B)	0.006	0.005	1616.0	1255.0	1838.0	
Treatment Difference (A-B)[0]	0.001	0.001	3200.0	3180.0	3217.0	
Treatment Difference (A-B)[1]	0.003	0.002	3290.0	3174.0	3263.0	
Treatment Difference (A-B)[2]	0.002	0.001	2654.0	1707.0	2684.0	
Treatment Difference (A-B)[3]	0.001	0.001	2882.0	2795.0	2901.0	
Treatment Difference (A-B)[4]	0.001	0.001	3658.0	3597.0	3636.0	
Treatment Difference (A-B)[5]	0.000	0.000	3124.0	3108.0	3121.0	

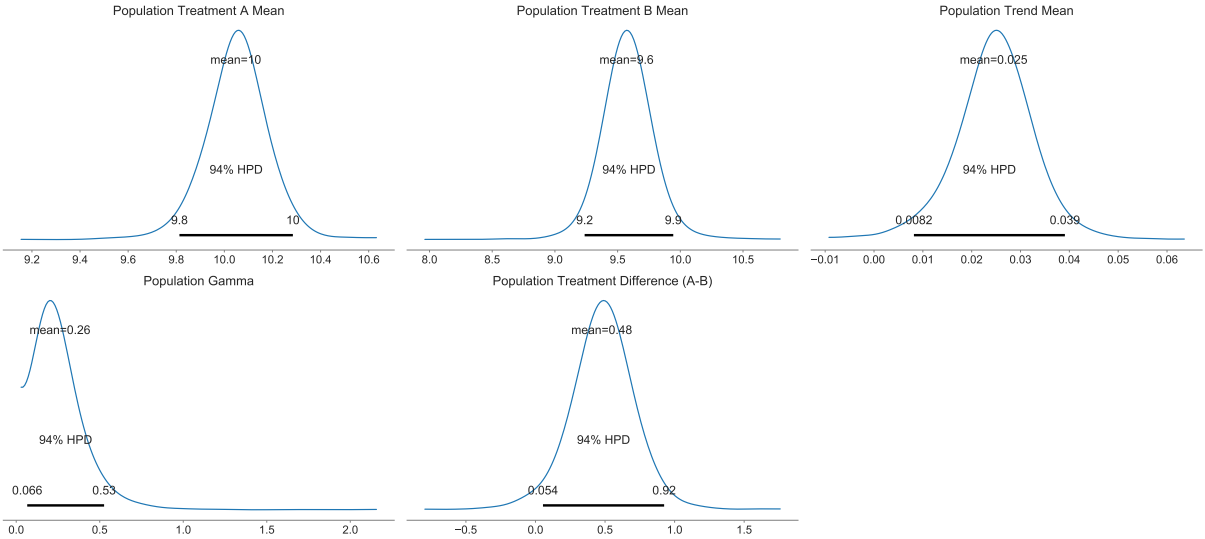
Checking the Posterior

```
pm.plot_posterior(
    trace,
    [
        "Population Treatment A Mean",
        "Population Treatment B Mean",
        "Population Trend Mean",
        "Population Gamma",
        "Population Treatment Difference (A-B)",
    ],
)
plt.show()
pm.plot_posterior(
    trace, ["Treatment A", "Treatment B", "Trend", "Treatment Difference (A-B)"]
)
pm.plot_posterior(trace)
plt.show()
```

After checking the diagnostics, now its the time to see our results. As the there are now so many parameters we will only focus on the interesting ones. It is always of course advisable to check every parameter to make sure that the results seem realistic, but we skip this here for sake of brevity and clarity.

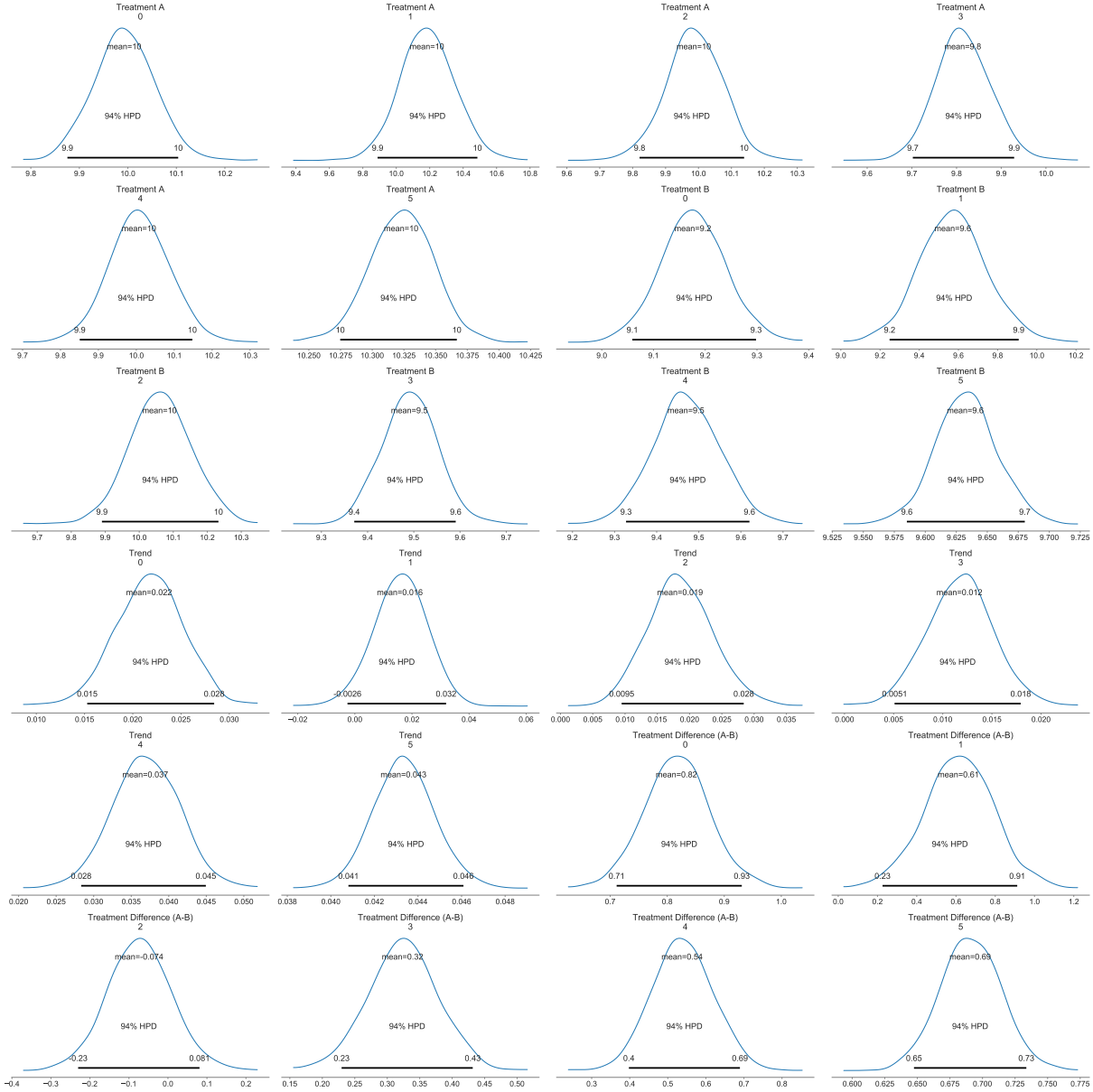
We start with the population level

Figure 5.12: Hierarchical Model Population-level Posterior Distributions



Next the patient level

Figure 5.13: Hierarchical Model Patient-level Posterior Distributions



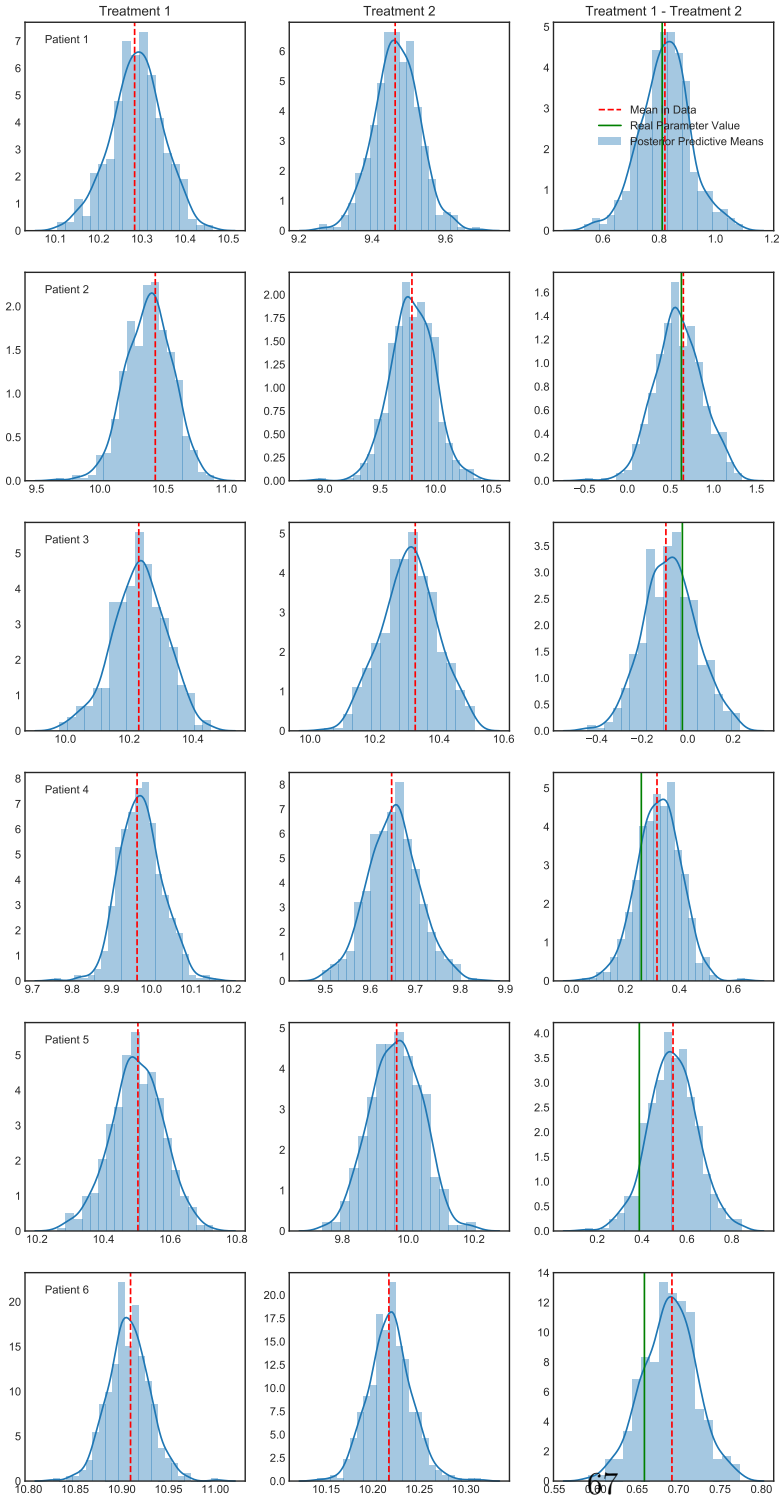
Checking Model Fit with Posterior Sampling

```
with hierarchical_model as model:
    post_pred = pm.sample_posterior_predictive(trace, samples=500)
    predictions = post_pred["y"]

draw_posterior_checks(
    predictions=predictions,
    measurements_df=measurements_df,
    parameters_df=parameters_df,
    plot_name="hierarchical_model_posterior_sampling",
)
```

Checking the posterior sampling 5.14.

Figure 5.14: Hierarchical Model Posterior Sample



5.4.3 Final Results

Lets compare the results that we got with the hierarchical model with the results we got from the single patient model for patient 1.

Chapter 6

Conclusion

We did not go over all the usual steps when building the models.

No model testing and now trial and error with the amount of steps.

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