Statistical analysis of precapillary sphincter data

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This analysis aims to model measurements of vessel diameter, pressure and pulsatility in the brain blood vessels of mice that were subjected to an experimental protocol designed to elicit vascular stress responses. The results will be used to assess differences in these responses between old and adult mice, between mice in general and between different types of brain blood vessels.

Whisker stimulation data

In order to measure how the vascular responsiveness changed during our experimental protocol, the diameters of different vessel types was recorded before and during whisker stimulation, at baseline, post-hypertension and post-ablation stages. The ratio of the peak compared with the pre-stimulation level for each mouse at each stage, on natural logarithmic scale, also known as the 'log change', was standardised by subtracting the overall mean and dividing by the standard deviation, then treated as a single measurement.

This way of the measurements was chosen to facilitate modelling, as log change is a symmetric and additive measure of relative change (see Tornqvist, Vartia, and Vartia (1985)). Note that when the difference between the two values $v1$ and $v2$ is far less than 1, the log change $\ln \frac{v2}{v1}$is approximately the same as the classical relative difference $\frac{v2-v1}{v1}$.

We were interested in two specific questions pertaining to whisker stimulation:

1a) Is there a difference between old and adult mice in the diameter log change for different vessels?

1b) Does sphincter ablation affect diameter log change to a different extent for adult and old mice?

To answer these questions, we fit a Bayesian multilevel regression model.

Missing data

[DESCRIBE MISSING DATA]

We assume that all missing measurements were caused by factors that were unrelated to our main target process (equivalently that the absent measurements were "missing at random"). We therefore did not attempt to model the measurement removal process explicitly.

Implementation

We implemented our model in Stan (Carpenter et al. 2017) and interfaced with data via the Python library cmdstanpy (Stan Development Team 2022). Posterior analysis was facilitated by the library arviz (Kumar et al. 2019). The analysis was orchestrated using the template package bibat (Groves 2023).

All the code implementing the analysis, as well as instructions for reproduction, can be found at https://github/teddygroves/sphincter.

Statistical Model

The final model is shown below:

$$
\begin{aligned}
y_{vtm} &\sim ST(\nu, \hat{y}_{vtm}, \sigma) \qquad (1)\\
\hat{y}_{vtm} &= \mu + \alpha_t^{treatment} + \alpha_v^{vessel} + \alpha_{vt}^{protocol} + \beta_{vt}^{age} \cdot old(m) + \alpha_{vtm}^{mouse}\\
\alpha_t^{treatment} &\sim N(0, \tau^{treatment})\\
\alpha_v^{vessel} &\sim N(0, \tau^{vessel})\\
\alpha_{vt}^{protocol} &\sim N(0, \tau^{protocol})\\
\alpha_{vtm}^{mouse} &\sim N(0, \tau_t^{mouse})\\
\beta_{vt}^{age} &\sim N(0, \tau^{age})\\
\nu &\sim Gamma(2, 0.1)\\
\sigma &\sim HN(0, 0.5)\\
\mu &\sim N(0, 0.7)\\
\tau^{treatment} &\sim HN(0, 0.7)\\
\tau^{vessel} &\sim HN(0, 0.7)\\
\tau^{protocol} &\sim HN(0, 0.7)
\end{aligned}
$$

In equation (1), the term ST indicates the student t distribution, *old* is an indicator function with value $old(m) = 1$ if mouse m is old, and zero otherwise, N indicates the normal distribution, $Gamma$ the gamma distribution and HN the 'half-normal' distribution, i.e. the normal distribution with support only for non-negative numbers.

This model was the end result of fitting a series of Bayesian multilevel models, following the strategy outlined in Gelman et al. (2020). The prior standard deviation 0.7 was chosen because it led to what we judged to be a reasonable allocation of prior probability mass over possible data realisations. The prior for the student t degrees of freedom parameter ν was set following the recommendation in Juárez and Steel (2010).

This model is flexible enough to allow age effects that vary depending on treatment and vessel type, but also allows these parameters to be shrunk towards zero if the data suggests that there is little difference between these categories. Our questions

can be answered by inspecting the parameters β^{age}. If, for a particular vessel type, our model allocates low probability mass to small values of this parameter, this indicates a difference between old and adult mice with respect to this vessel type. In particular, if the values for the sphincter vessel type tend to be far from zero, that would show an age difference for this vessel type.

Results

Figure 1 shows the observed log change measurements with colours illustrating the various categorical information. Note that there is more variation in the baseline log change values than in the values after either treatment.

Figure 1: Raw measurements

Figure 2 compares the measurements with our model's posterior predictive distribution. This shows that our model achieved a reasonable fit to the observed data. There is a pattern in the model's bad predictions, in that these tend to be for higher baseline measurements. However, we judged that this pattern was small enough that for our purposes we could disregard it.

Figure 3 answers our questions 1a) and 1b): we found no significant age effects for any vessel or treatment.

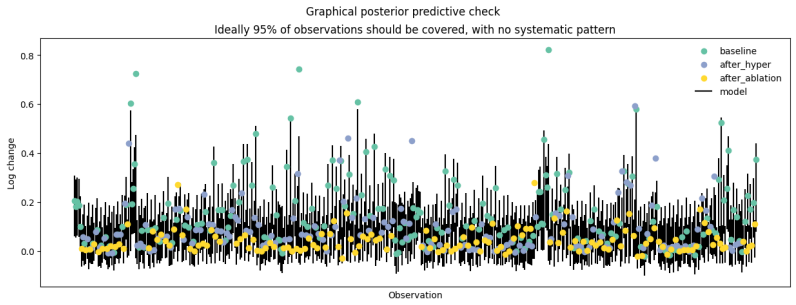

Figure 2: Graphical posterior predictive check

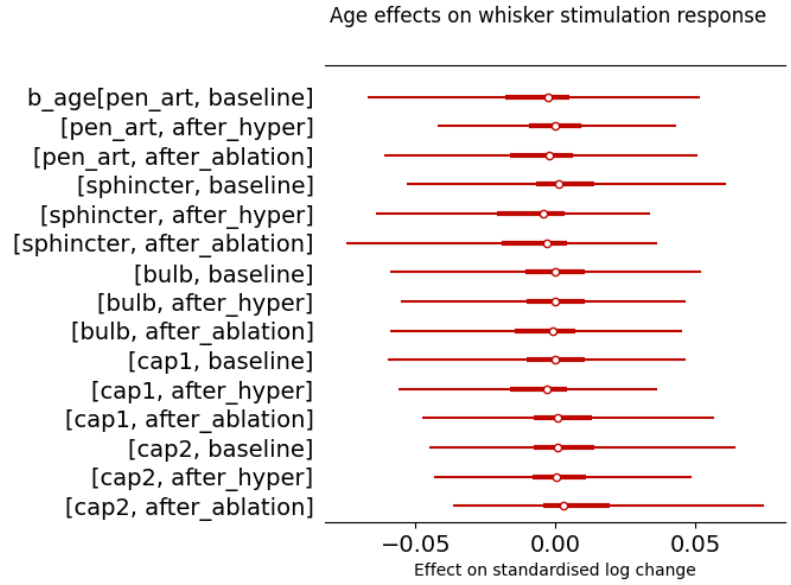

Figure 3: Marginal 2.5%-97.5% posterior intervals for age effects

This does not mean that there were no significant treatment effects, but just that these effects did not depend on age or vessel type. Figure 4 shows the marginal posterior distributions for hypertension and ablation effects relative to the baseline, showing a clear effect in both cases.

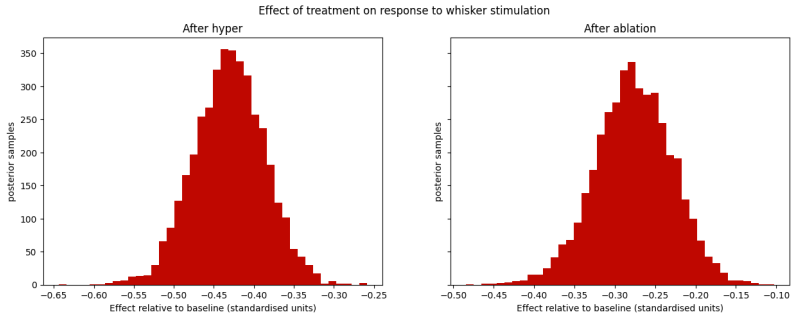

Figure 4: Marginal posterior intervals for treatment effects, relative to the baseline treatment.

These effects were the same for all vessel types, as can be seen from Figure 5, which shows that these were largely irrelevant.

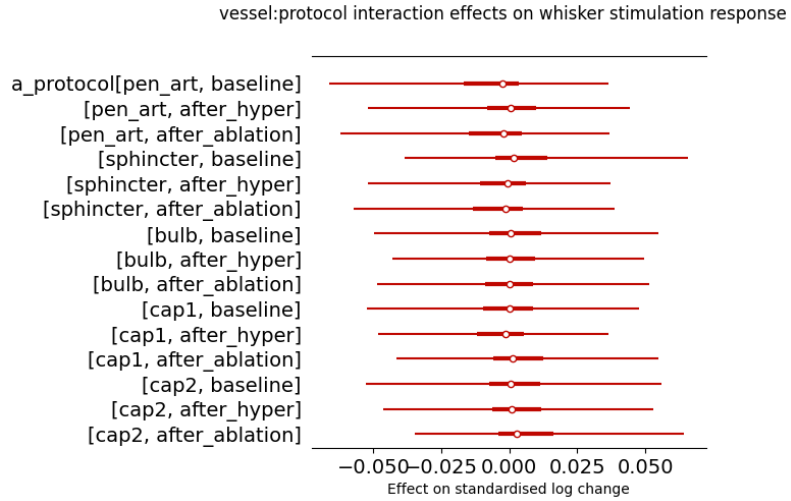

Figure 5: Marginal 2.5%-97.5% posterior intervals for protocol effects

There was also a significant distributional effect of treatment. This is captured by Figure 6, which shows marginal posterior

distributions for the parameters τ^{mouse}. It was higher for the baseline treatment than for either of the interventions, reflecting the pattern noted above in the raw data.

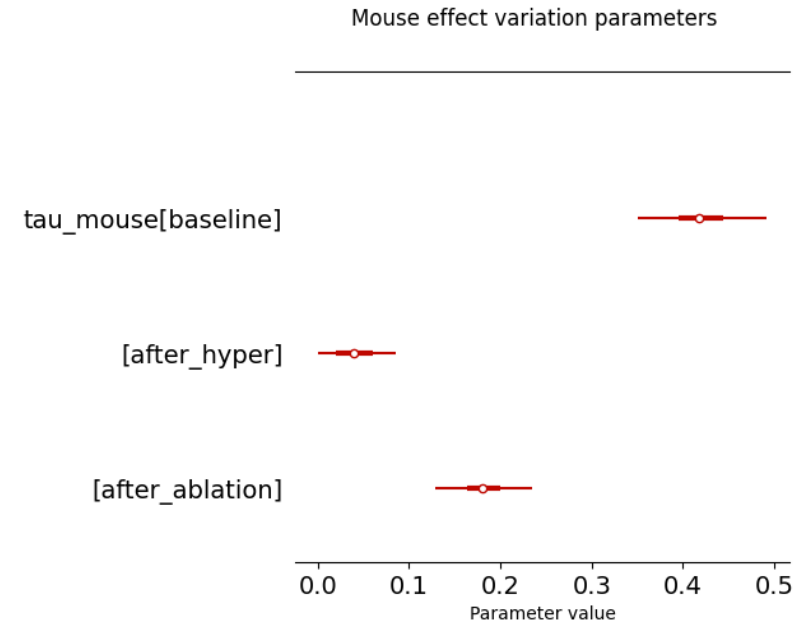

Figure 6: Marginal 2.5%-97.5% posterior intervals for τ^{mouse} parameters.

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