Supplementary Materials

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**Supplementary Materials S1 : Prior Specification**

We made use of a multifactor model (Betancourt, 2021), with a global mean, together with partially pooled deviations from the global mean for each region across all individuals, and for each individual across all regions. We also added a final partially pooled parameter to accommodate any residual differences at the level of individual TACs after accounting for average regional and individual effects. We therefore anticipate that most of the variation in the pharmacokinetic parameters will be accounted for by individual differences and regional differences, and that TAC-level will be much smaller. For this reason, we defined wider zero-centred priors over the standard deviation across individuals and regions, but more constrained priors over the standard deviation across TACs.

For the simulations, we did not include any covariates (other than region where we used unpooled effects for BP_{ND} and K_1) for any parameters besides BP_{ND}, which was compared between the two groups.

**Global Intercepts**

Below are the priors defined for the global intercepts. Note that all priors are defined over the natural logarithms of the parameters.

\[
\alpha_{K_1} \sim \text{Normal}(-2.5, 0.25) \\
\alpha_{v_{ND}} \sim \text{Normal}(-1.0, 0.25) \\
\alpha_{BP_{ND}} \sim \text{Normal}(2.0, 0.25) \\
\alpha_{K_4} \sim \text{Normal}(-4.0, 0.25) \\
\alpha_{v_B} \sim \text{Normal}(-4.0, 0.50) \\
\alpha_{\sigma} \sim \text{Normal}(-5.0, 1.00)
\]

**Individual effects**

Differences between individuals were defined by specifying the primary pharmacokinetic parameters in one variance-covariance matrix, and v_B and \( \sigma \) on their own.
\[
\begin{bmatrix}
\tau_{K_1} \\
\tau_{V_{ND}} \\
\tau_{BP_{ND}} \\
\tau_k
\end{bmatrix}
\sim MVNormal
\begin{pmatrix}
0 \\
0 \\
0 \\
0
\end{pmatrix}, 
\Sigma_{\text{Subject}}
\]

\[
\Sigma_{\text{Subject}} = \begin{bmatrix}
\sigma_{K_1} & 0 & 0 \\
0 & \ddots & 0 \\
0 & 0 & \sigma_{k_4}
\end{bmatrix}
\]

\[
R_{\text{Subject}} \sim LKJ(1)
\]

\[
\tau_v \sim \text{Normal}(0, \sigma_{\text{Subject}, v}^2)
\]

\[
\tau_\sigma \sim \text{Normal}(0, \sigma_{\text{Subject}, \sigma}^2)
\]

\[
\sigma_{K_1} \sim \text{Half-Normal}(0, 0.3)
\]

\[
\sigma_{V_{ND}} \sim \text{Half-Normal}(0, 0.3)
\]

\[
\sigma_{BP_{ND}} \sim \text{Half-Normal}(0, 0.3)
\]

\[
\sigma_{k_4} \sim \text{Half-Normal}(0, 0.3)
\]

Regional effects

For logBP_{ND} and logK_1, regional differences were defined as unpooled effects using a dummy (indicator) variable defined with reference to the dorsolateral prefrontal cortex as covariates. For simplicity, all regional differences were defined as zero-centred regularising priors with the same SD.

\[
\beta_{K_1|k-1} \sim \text{Normal}(0, 0.3)
\]

\[
\beta_{BP_{ND}|k-1} \sim \text{Normal}(0, 0.3)
\]

For the remaining parameters, regional differences were defined as pooled variables, arising from a common distribution.
\[
\begin{bmatrix}
\nu_{V_{ND}} \\
\nu_{k_4}
\end{bmatrix}
\sim \text{MVNormal}\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \Sigma_{\text{Region}}\right)
\]
\[
\Sigma_{\text{Region}} = \begin{bmatrix}
\sigma_{V_{ND}} & 0 \\
0 & \sigma_{k_4}
\end{bmatrix} \cdot R_{\text{Region}} \cdot \begin{bmatrix}
\sigma_{V_{ND}} & 0 \\
0 & \sigma_{k_4}
\end{bmatrix}
\]
\[
\nu_{v_B} \sim \text{Normal}(0, \sigma_{\text{Region, } v_B}^2)
\]
\[
\nu_\sigma \sim \text{Normal}(0, \sigma_{\text{Region, } \sigma}^2)
\]
\[
\sigma_{V_{ND}} \sim \text{Half-Normal}(0, 0.1)
\]
\[
\sigma_{V_{ND}} \sim \text{Half-Normal}(0, 0.1)
\]
\[
R_{\text{Region}} \sim \text{LKJ}(2)
\]
\[
\sigma_{\text{Region, } v_B} \sim \text{Half-Normal}(0, 0.1)
\]
\[
\sigma_{\text{Region, } \sigma} \sim \text{Half-Normal}(0, 0.5)
\]

**TAC effects**

Residual TAC effects were defined for the major four pharmacokinetic parameters, but were not included for \(v_B\) or \(\sigma\) as these were not considered to be of central importance.

\[
\begin{bmatrix}
\phi_{K_1} \\
\phi_{V_{ND}} \\
\phi_{BP_{\text{ND}}} \\
\phi_{k_4}
\end{bmatrix}
\sim \text{MVNormal}\left(\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \Sigma_{\text{TAC}}\right)
\]
\[
\Sigma_{\text{TAC}} = \begin{bmatrix}
\sigma_{K_1} & 0 & 0 & 0 \\
0 & \ddots & 0 & 0 \\
0 & 0 & \sigma_{k_4} & 0 \\
0 & 0 & 0 & \sigma_{k_4}
\end{bmatrix}
\cdot R_{\text{TAC}} \cdot \begin{bmatrix}
\sigma_{K_1} & 0 & 0 & 0 \\
0 & \ddots & 0 & 0 \\
0 & 0 & \sigma_{k_4} & 0 \\
0 & 0 & 0 & \sigma_{k_4}
\end{bmatrix}
\]
\[
\sigma_{K_1} \sim \text{Half-Normal}(0, 0.025)
\]
\[
\sigma_{V_{ND}} \sim \text{Half-Normal}(0, 0.025)
\]
\[
\sigma_{BP_{\text{ND}}} \sim \text{Half-Normal}(0, 0.025)
\]
\[
\sigma_{k_4} \sim \text{Half-Normal}(0, 0.025)
\]
\[
R_{\text{TAC}} \sim \text{LKJ}(2)
\]

**Smooth sigma function**

The smooth basis function makes use of a penalised regression spline. The \(\sigma_{\text{spline-coefficients}}\) term refers to the standard deviation of the spline coefficients, which penalises the wiggliness of the spline. The \(\alpha_{\text{spline-coefficients}}\) term refers to the fixed effects term, which describes the magnitude of the influence of the smooth term around the estimated mean value.
\[ \sigma_{\text{spline-coefficients}} \sim \text{Half-Student-t}(3, 0, 2.5) \]
\[ \alpha_{\text{spline-coefficients}} \sim \text{Half-Student-t}(3, 0, 4.0) \]

**Covariates**

For the simulations, there was only one additional covariate for group effects on BP\(_{\text{ND}}\). For this, we used a zero-centred regularising prior. This prior conservatively assumes that no difference is most likely, and assigns 95\% of its probability between differences of -48\% and 48\% differences between groups.

\[ \beta_{\text{Group}, BP_{\text{ND}}} \sim \text{Normal}(0, 0.2) \]

**Analysis data**

For the analysis, we included more covariates due to variation in the data.

**Covariates**

We included effects of age and sex covariates for the estimation of \(K_1\), \(V_{\text{ND}}\) and \(BP_{\text{ND}}\). For age, we divided ages by 10, so that it was not defined by years, but by decades. This makes it easier to specify priors, and is expected to improve efficiency of estimation by estimating parameters in a similar order of magnitude.

\[ \beta_{\text{Age}, K_1} \sim \text{Normal}(0, 0.1) \]
\[ \beta_{\text{Age}, BP_{\text{ND}}} \sim \text{Normal}(0, 0.1) \]
\[ \beta_{\text{Age}, V_{\text{ND}}} \sim \text{Normal}(0, 0.1) \]

\[ \beta_{\text{Sex}, K_1} \sim \text{Normal}(0, 0.05) \]
\[ \beta_{\text{Sex}, BP_{\text{ND}}} \sim \text{Normal}(0, 0.05) \]
\[ \beta_{\text{Sex}, V_{\text{ND}}} \sim \text{Normal}(0, 0.05) \]

Covariates for the measurement error included the centred natural logarithm of the average region size, as well as the centred natural logarithm of the injected radioactivity.

\[ \beta_{\text{RegionSize}, \sigma} \sim \text{Normal}(0, 0.3) \]
\[ \beta_{\text{InjectedRadioactivity}, \sigma} \sim \text{Normal}(0, 0.5) \]

Because so much of the variation in the measurement error between regions would be explained by region size, we reduced the variance of the prior for the partial pooling of measurement error across regions.

\[ \sigma_{\text{Region}, \sigma} \sim \text{Half-Normal}(0, 0.1) \]
Supplementary Materials S2 : Simulated parameters

Global Intercepts

| Parameter   | Mean    |
|-------------|---------|
| log($K_1$)  | -2.33   |
| log($BP_{ND}$) | 1.75   |
| log($V_{ND}$) | -0.62  |
| log($k_4$)  | -3.84   |
| log($v_B$)  | -3.63   |
| log($\sigma$) | -4.12  |

Individual effects

Standard deviations

| Parameter | SD    |
|-----------|-------|
| log($K_1$) | 0.27  |
| log($BP_{ND}$) | 0.33  |
| log($V_{ND}$) | 0.39  |
| log($k_4$)  | 0.12   |
| log($v_B$)  | 0.67   |
| log($\sigma$) | 0.42  |

Correlation Matrix

| Parameter   | log($K_1$) | log($BP_{ND}$) | log($V_{ND}$) | log($k_4$) |
|-------------|------------|----------------|---------------|------------|
| log($K_1$)  | 1.00       | 0.16           | 0.60          | -0.25      |
| log($BP_{ND}$) | 0.16   | 1.00           | -0.56         | -0.32      |
| log($V_{ND}$) | 0.60   | -0.56          | 1.00          | 0.02       |
| log($k_4$)  | -0.25      | -0.32          | 0.02          | 1.00       |

Regional effects

Mean values

Here are the regional means. For simplicity of interpretation, I have added the global mean value to all of the deviations from the mean so that they are displayed as the values themselves.

| Region     | log($K_1$) | log($BP_{ND}$) | log($V_{ND}$) | log($k_4$) | log($v_B$) | log($\sigma$) |
|------------|------------|----------------|---------------|------------|------------|---------------|
| ACC        | -2.37      | 1.90           | -0.67         | -3.75      | -3.48      | -4.23         |
| Amygdala   | -2.66      | 1.85           | -0.62         | -3.92      | -3.63      | -4.00         |
| PCC        | -2.35      | 1.75           | -0.72         | -3.72      | -3.50      | -4.13         |
| DLPFC      | -2.33      | 1.75           | -0.72         | -3.67      | -3.70      | -4.42         |
| Hippocampus| -2.55      | 1.93           | -0.33         | -4.06      | -3.70      | -4.12         |
| Insula     | -2.37      | 2.11           | -0.61         | -3.83      | -3.46      | -4.18         |
Region log($K_1$) log($BP_{ND}$) log($V_{ND}$) log($k_4$) log($v_B$) log($\sigma$)
MPFC -2.34 1.78 -0.68 -3.70 -3.58 -4.35
Parahippocampus -2.60 1.76 -0.26 -3.75 -3.61 -4.22
DRN -2.63 1.72 -0.93 -4.14 -4.03 -3.43

**TAC effects**

**Standard deviations**

| Parameter | SD |
|-----------|----|
| log($K_1$) | 0.053 |
| log($BP_{ND}$) | 0.037 |
| log($V_{ND}$) | 0.054 |
| log($k_4$) | 0.015 |

**Correlation Matrix**

| Parameter | log($K_1$) | log($BP_{ND}$) | log($V_{ND}$) | log($k_4$) |
|-----------|------------|----------------|---------------|-------------|
| log($K_1$) | 1.00       | -0.21          | 0.66          | -0.35       |
| log($BP_{ND}$) | -0.21     | 1.00           | 0.40          | 0.71        |
| log($V_{ND}$) | 0.66       | 0.40           | 1.00          | 0.28        |
| log($k_4$) | -0.35      | 0.71           | 0.28          | 1.00        |

**Smooth sigma function**

The smooth sigma function across time is depicted below.
Supplementary Materials S3: Comparisons between power estimation approaches

In Figures 1 and 2, we compare the outcomes estimated using the following datasets:

1. **Large Empirical**: 1000 simulated studies, with power and false positive rate calculated empirically. These datasets were only used with NLS estimation.
2. **Small Empirical**: 50 simulated studies, with power and false positive rate calculated empirically.
3. **Small Modelled**: 50 simulated studies, with power and false positive rate calculated using logspline functions applied to the confidence or credible intervals.

Figure 1: Power estimated using the same and different datasets between methods, with power calculated with different methods. All methods produce similar results. Error bars are not included for NLS: t-test figures for clarity.

In Figure 3 are the fits of the logspline function to the SiMBA 95% credible intervals for the calculation of the small empirical power and false positive rates.
Figure 2: False positive rate estimated using the same and different datasets between methods, with the rate calculated with different methods. All methods produce similar results. Error bars are not included for NLS: t-test figures for clarity.
Figure 3: Fitted logspline density plots, from which power and false positive rates were calculated. Blue histograms represent the lower bound of the credible interval (i.e. the 2.5% quantile of the samples) and the red histograms represent the upper bound of the credible intervals (i.e. the 97.5% quantile of the samples).
Supplementary Materials S4: Group difference properties in the same data

Calculated in the same set of 50 datasets for each condition, we examined the mean of the 50 estimated differences, the standard deviation of the means across these datasets, the mean standard error of these estimated means across the datasets, and the (modelled) power and false positive rates. In the Figures 4 and 5, we show plots in the style of the power and false positive plots of the standard deviation and standard error of these methods in the same datasets.

![Figure 4: Standard deviation of estimated group differences across simulated datasets.](image)

The following table includes all the data together.
Figure 5: Mean standard error of estimated group differences across simulated datasets.

| n  | Outcome | NLS: LME Mean | SD  | SE  | Power | SiMBA Mean | SD  | SE  | Power |
|----|---------|---------------|-----|----|-------|------------|-----|----|-------|
|    |         | n             |     |    |       |             |     |    |       |
|    |         | False Positives |     |    |       |             |     |    |       |
|    |         | 10 BPND       | -0.006 | 0.196 | 0.180 | 0.079 | -0.014 | 0.076 | 0.085 | 0.047 |
|    |         | 10 BPP        | 0.004  | 0.183 | 0.163 | 0.091 | -0.014 | 0.076 | 0.085 | 0.047 |
|    |         | 10 VT         | 0.002  | 0.173 | 0.153 | 0.087 | -0.012 | 0.065 | 0.072 | 0.052 |
|    |         | 20 BPND       | 0.002  | 0.114 | 0.126 | 0.058 | -0.005 | 0.052 | 0.061 | 0.037 |
|    |         | 20 BPP        | 0.011  | 0.107 | 0.113 | 0.053 | -0.005 | 0.052 | 0.061 | 0.037 |
|    |         | 20 VT         | 0.012  | 0.102 | 0.105 | 0.079 | -0.004 | 0.045 | 0.052 | 0.052 |
|    |         | 50 BPND       | 0.008  | 0.074 | 0.079 | 0.049 | -0.008 | 0.035 | 0.038 | 0.069 |
|    |         | 50 BPP        | 0.008  | 0.072 | 0.073 | 0.061 | -0.008 | 0.035 | 0.038 | 0.069 |
|    |         | 50 VT         | 0.006  | 0.068 | 0.068 | 0.052 | -0.007 | 0.030 | 0.032 | 0.069 |
|    |         | Power         | 10 BPND | 0.156 | 0.192 | 0.182 | 0.166 | 0.142 | 0.075 | 0.086 | 0.334 |
|    |         |               | 10 BPP  | 0.215 | 0.145 | 0.153 | 0.275 | 0.142 | 0.075 | 0.086 | 0.334 |
|    |         |               | 10 VT   | 0.191 | 0.133 | 0.144 | 0.268 | 0.124 | 0.065 | 0.075 | 0.305 |
|    |         |               | 20 BPND | 0.170 | 0.120 | 0.129 | 0.229 | 0.161 | 0.059 | 0.061 | 0.760 |
|    |         |               | 20 BPP  | 0.190 | 0.121 | 0.115 | 0.352 | 0.161 | 0.059 | 0.061 | 0.760 |
|    |         |               | 20 VT   | 0.167 | 0.113 | 0.107 | 0.317 | 0.139 | 0.051 | 0.053 | 0.760 |
|    |         |               | 50 BPND | 0.181 | 0.094 | 0.079 | 0.634 | 0.170 | 0.036 | 0.038 | 0.970 |
|    |         |               | 50 BPP  | 0.183 | 0.060 | 0.071 | 0.764 | 0.170 | 0.036 | 0.038 | 0.970 |
|    |         |               | 50 VT   | 0.157 | 0.055 | 0.067 | 0.676 | 0.147 | 0.031 | 0.033 | 0.970 |
Supplementary Materials S5: SD of estimated mean differences by method

Figure 6: The standard deviation of estimated mean group differences for different sample sizes as a measure of consistency. With larger samples, the standard deviation of the estimates is decreased, indicating greater consistency of estimates. Linear mixed effects (LME) modelling of binding outcomes show less variation than t-tests, and the Bayesian hierarchical pharmacokinetic modelling of TACs has greatly reduced variation compared to both LME modelling and t-tests.
Supplementary Materials S6: Sensitivity to measurement error

In Figure 7, we show the power (estimated using logsplines and bootstrapped 95% confidence intervals), the mean posterior estimates of $\alpha$, the standard deviation (SD) of the mean posterior estimates of the group differences (with 95% confidence intervals estimated using a case resampling bootstrap procedure), and the mean standard error (SE) of the differences from within each simulated study (with 95% quantiles). All values are calculated for BP\textsubscript{ND} and BP\textsubscript{P} (as these two are the same due to not estimating different $V_{ND}$ values between groups).

![Figure 7](image-url)

Figure 7: The SiMBA model is sensitive to measurement error, but even with the standard deviation of the measurement error equal to 20% of the mean TAC value, the power with n=10 is still over 20%.
Supplementary Materials S7: Application to data with no parameter intercorrelations

Data were simulated with the originally estimated parameter intercorrelations, as well as following sampling from univariate distributions, thereby removing the correlations between parameters. We examined the distribution of the estimated parameter intercorrelations in the original, and in the uncorrelated data. Comparisons between correlated and uncorrelated data are shown in figures 8 and 9.

Also displayed are the estimated correlations in the original data for different sample sizes in figures 10 and 11.

In all cases, the measurement error of the simulated data is 10%, which is more than twice that of the original dataset.

Figure 8: Estimated correlations comparing correlated and uncorrelated data in the presence of no group difference. True values are represented using black circles.
Figure 9: Estimated correlations comparing correlated and uncorrelated data in the presence of a group difference. True values are represented using black circles.

Figure 10: Estimated correlations for correlated data with different sample sizes in the presence of a group difference.
Correlation Estimates: 20% Group Difference

Estimates for correlated parameter values for simulations with measurement error = 10%.

Figure 11: Estimated correlations for correlated data with different sample sizes in the presence of a group difference.