"Adaptive Bayesian P-splines models for fitting time-activity curves and estimating associated clinical parameters in Positron Emission Tomography and Pharmacokinetic study"

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ABSTRACT

In clinical experiments, the evolution of a product concentration in tissue over time is often under study. Different products and tissues may be considered. For instance, one could analyse the evolution of drug concentration in plasma over time, by performing successive blood sampling from the subjects participating to the clinical study. One could also observe the evolution of radioactivity uptakes in different regions of the brain during a PET scan (Positron Emission Tomography). The global objective of this thesis is the modelling of such evolutions, which will be called, generically, pharmacokinetic curves (PK curves). Some clinical measures of interest are derived from PK curves. For instance, when analysing the evolution of drug concentration in plasma, PK parameters such as the area under the curve (AUC), the maximal concentration (Cmax) and the time at which it occurs (tmax) are usually reported. In a PET study, one could measure Receptor Occupancy (RO) in some regions of the brain, i.e. the percentage of specific receptors to which the drug is bound. Such clinical measures may be badly estimated if the PK curves are noisy. Our objective is to provide statistical tools to get better estimations of the clinical measures of interest from appropriately smoothed PK curves. Plenty of literature addresses the problem of PK curves fitting using parametric models. It usually relies on a compartmental approach to describe the kinetic of the product under study. The use of parametric models to fit PK curves can lead to problems in some specific cases. Firstly, the estimat...
Chapter 7

Estimation of receptor occupancy using varying coefficients models

We have the project to submit this chapter to Pharmaceutical Statistics.

7.1 Introduction

Linear regression models are widely used in practice. Usually, the regression coefficients are fixed. However, one can find useful to have regression coefficients varying as smoothed functions of another covariate named "effect modifier" (Hastie and Tibshirani 1993). Typically, one assumes that the coefficients vary with time to express the temporal evolution of the effect of the variable on the response.

Several authors have studied the varying-coefficients models either in a frequentist framework (Hastie and Tibshirani 1993; Eubank et al. 2004) or in a Bayesian setting. For instance, Lambert and Eilers (2005) use time-varying regression coefficients in the context of proportional hazards models. Biller and Fahrmeir (2001) have proposed to work with a fully Bayesian B-spline basis function approach with adaptive knots selection.

In this chapter, we propose to use robust Bayesian penalized B-splines as described in Chapter 1 to link in a smooth way the regression coefficients with the effect modifier. This offers a highly flexible tool to model the change of the regression coefficients with the effect modifier.

Some linear constraints can be enforced to describe that relationship. For instance, one could assume that the relationship is monotonically increasing (decreasing) or concave (convex). Constrained Monte Carlo simulations from the joint posterior can be set up (Geweke 1991).

The method will be used in the context of a Positron Emission Tomography (PET) study to estimate receptor occupancy. Receptor occupancy ($RO$) is an important concept in drug
screening, quantifying the amount of specific receptors to which the drug is bound. The estimate of the function relating receptor occupancy to the drug concentration in plasma will be helpful to assess whether the drug binds to the target receptors and, hence, in the selection of the efficacy dose.

Credibility sets are easily obtained for receptor occupancy, from the generated Markov chains Monte Carlo. They offer the advantage to take into account the uncertainty appearing at all the different estimation steps. In a traditional two-stage method, the first step consists in receptor occupancy estimation for different levels of drug concentrations in plasma. In a second step, the relation between receptor occupancy and drug concentration is estimated, conditionally on the first step results. With this process, the uncertainty involved by the first step is ignored. The one-stage method proposed in this chapter enables to reflect all the uncertainty in the estimation procedure.

The plan of this chapter is as follows. The Bayesian varying coefficient model is first presented. In Section 3, the technique of Geweke (1991) to add linear constraints into the model is described. Receptor occupancy estimation using the Bayesian varying coefficient model is presented in Section 4. Section 5 concludes the chapter with a discussion.

### 7.2 Bayesian varying coefficient model

In this section, a brief description of the basic Bayesian linear regression model is first given. Then, the robust Bayesian P-splines model is defined. Finally, the Bayesian varying coefficient model is presented.

#### 7.2.1 Bayesian linear regression model

Consider first the Bayesian linear regression model with fixed regression coefficients. Denote by $Y$ the $n$-vector of responses, by $X$ the $n \times p$ design matrix and by $\alpha$ the corresponding vector of regression coefficients. The regression model can be specified as follows (Box and Tiao 1992):

$$(Y|\alpha, \tau) \sim \mathcal{N}(X\alpha, \tau^{-1}I_n)$$

with non-informative priors:

$$p(\tau) \propto \tau^{-1}$$
$$p(\alpha) \propto 1$$
This model is suited when there is no multicollinearity problem. However, in the coming illustrations, problem of interrelationships among the independent variables will arise. In such circumstances, regression parameters will tend to exhibit large posterior variances. One solution to multicollinearity includes ridge regression (Marquardt and Snee 1975), in which the regression parameters depend on a shrinkage parameter \( \tau_\alpha > 0 \). Ridge regression can be translated in a Bayesian framework by adding a prior on the regression coefficients vector:

\[
\alpha \sim N\left(0, \tau_\alpha^{-1}I_p\right)
\]

Congdon (2006) suggests either to set a prior on \( \tau_\alpha \) or to assess sensitivity to prespecified fixed values. In this latter case, estimates for \( \tau_\alpha \) can be based on the least squares regression coefficients of \( Y \) on \( X \).

Using a prespecified fixed value for \( \tau_\alpha \), the conditional posterior distributions of the Bayesian ridge regression model can easily be derived:

\[
\begin{align*}
(\tau|Y, \alpha) & \sim G\left(n/2, 0.5(Y - X\alpha)'(Y - X\alpha)\right) \\
(\alpha|Y, \tau) & \sim N\left((\tau X'X + \tau_\alpha I_p)^{-1}(\tau X'Y), \left(\tau X'X + \tau_\alpha I_p\right)^{-1}\right)
\end{align*}
\]

(see Congdon (2006) for more details).

### 7.2.2 Bayesian P-splines

The regression coefficients can be forced to vary in a smooth way with an effect modifier by using Bayesian P-splines. The Bayesian P-splines model presented in Chapter 1 is the following:

\[
\begin{align*}
(Y|\theta, \tau) & \sim N\left(B\theta, \tau^{-1}\right) \\
p(\tau) & \propto \tau^{-1} \\
p(\theta|\tau_\lambda) & \propto \exp\left[-0.5 \tau_\lambda \theta'P\theta\right] \\
(\tau_\lambda|p) & \sim \sum_{m=1}^M p_m G(a, b_m) \\
p & \sim \mathcal{D}(u)
\end{align*}
\]

where \( \mathcal{D} \) stands for the Dirichlet distribution and \( u' = \{u_1, ..., u_M\} \) is a set of (small and equal) hyperprior parameters expressing our likely prior ignorance for the optimal choice for \( b \).
7.2.3 Bayesian varying coefficient model

Assume that a subset of the explanatory variables require varying regression coefficients. Let \( X \) be the design matrix of the variables for which the regression coefficients \( \alpha \) are fixed. Let \( Z \) be the design matrix corresponding to the variables for which the regression coefficients \( \beta \) vary (smoothly) with an effect modifier \( E \). Parameter \( \beta \) is expressed as a smoothed function of \( E \) using P-splines: 
\[
\beta(E) = B_E \gamma
\]
where \( B_E \) is the matrix of the B-splines basis evaluated at the observed values of the effect modifier \( E \) and \( \gamma \) is the corresponding vector of splines coefficients. Denote by \( \tau_{\gamma} \) the associated roughness penalty parameter.

The specification of the varying coefficient model is then:
\[
(Y|\alpha, \gamma, \tau) \sim N(X\alpha + ZB_E \gamma, \tau^{-1}I_n)
\]
\[
p(\tau) \propto \tau^{-1}
\]
\[
\alpha \sim N(0, \tau^{-1}_\alpha I_p)
\]
\[
p(\gamma|\tau_\gamma) \propto \exp(-0.5\tau_\gamma \gamma' D'D\gamma)
\]
\[
(\tau_\gamma | p) \sim \sum_{m=1}^{M} p_m G(a, b_m)
\]
\[
p \sim D(u)
\]
Remembering that \( \beta = B_E \gamma \), one gets the following conditional posterior distributions:
\[
(\tau|\alpha, \gamma; y) \sim G\left(\frac{n}{2}, 0.5(y - X\alpha - Z\beta)'(y - X\alpha - Z\beta)\right)
\]
\[
(\alpha|\gamma, \tau; y) \sim N\left((\tau X'X + \tau_\alpha I_p)^{-1}\tau X'(y - Z\beta), (\tau X'X + \tau_\alpha I_p)^{-1}\right)
\]
\[
(\gamma|\alpha, \tau; y) \sim N(\tau B_E'Z'\Sigma_\gamma(y - X\alpha), \Sigma_\gamma)
\]
\[
(\tau_\gamma | p; y) \sim \sum_{m=0}^{M} p_m G(a + 0.5\rho(D'D), b_m + 0.5\gamma'D'D\gamma)
\]
\[
(p|\tau_\gamma; y) \propto \sum_{m=1}^{M} \frac{c_m}{\sum_{j=1}^{M} c_j} D(u_1, ..., u_m + 1, ..., u_M)
\]

where
\[
c_m = \exp(-\tau_\gamma b_m)\sum_{j=1}^{M} u_j
\]
\[
\Sigma^{-1} = \tau_\gamma D'D
\]
\[
\Sigma_\gamma = (\tau B_E'Z'ZB_E + \Sigma^{-1})^{-1}
\]

These conditional posteriors can be used in the Gibbs sampler (see Appendix A.3.3).
7.3 Inclusion of a linear constraint

Suppose that one wants to impose a constraint (such as monotonicity) to the relationship between the regression coefficient and the effect modifier. This constraint is translated on the splines coefficients vector by imposing the positivity of the differences between two successive splines coefficients: $\gamma_1 > 0$ where $\gamma_1$ is the first order difference matrix (Kaishev et al. 2006).

Such a constraint can be introduced at the simulation stage, using the technique proposed by Geweke (1991) which allows the construction of samples from an $m$-variate normal distribution subject to linear inequality restrictions. The main points of this technique are given in Appendix 7.1.

7.4 Receptor occupancy estimation

7.4.1 Context of the study

Interest lies in drugs that bind to some specific receptors in the brain. As defined in Chapter 5, receptor occupancy is the proportion of specific receptors to which a drug is bound. Therefore studying the relation between receptor occupancy and the drug concentration in plasma is an important issue. To estimate this curve, a varying coefficient model where receptor occupancy appears as a regression coefficient varying with drug concentration will be set up.

Two illustrations will be provided, considering reversible and irreversible binding tracer. The reference region method proposed by Ichise et al. (2001) will be used when binding is reversible. It relies on the following equation:

$$\int_0^t C_{\text{tot}}(u) du = \frac{a}{a'} \int_0^t C_2'(u) du + \left( -\frac{ab'}{a'} \right) C_1(t) + b \quad \forall t \geq t^*$$

(see chapter 5 for the notation). For more details, we refer to Ichise et al. (2001). Equation (7.1) is multilinear beyond time $t^*$. From this equation, the binding potential, $BP$, is equal to $(a/a' - 1)$. An estimate for that quantity can be obtained by plugging in the regression coefficients estimates.

In the case of an irreversible tracer, the method of Patlak and Blasberg (1985) yields the following equation:

$$\frac{C_{\text{tot}}(t)}{C_2(t)} = \frac{k_1 \eta_2 k_3 \int_0^t C_2'(u) du}{k_1 \eta_2 + k_3} + \frac{k_1 k_3}{k_1 \eta_2 + k_3} + \frac{k_2}{k_2 + k_3} C_2(t)$$

(7.2)
One assumes that \( \frac{k_1}{k_2} = \frac{k'_1}{k'_2} \), common to all reference tissue models. The net uptake rate \( K \) is defined as:

\[
K = \text{slope} = \frac{k_3 k_5}{k_2 + k_3}
\]

The ratio \( \frac{C_{\text{tot}}(t)}{C'_{2}(t)} \) becomes linear after some \( t \geq t^* \), when the concentrations of free tracer in the target region, \( C_2(t) \), and in the reference region, \( C'_2(t) \), follow the plasma concentration and their ratio is constant (Logan 2000). Under the last assumption, and when \( t \geq t^* \), Equation (7.2) can be rewritten as:

\[
\frac{C_{\text{tot}}(t)}{C'_{2}(t)} = c + K \int_0^t \frac{C'_{2}(u) du}{C'_{2}(t)} \quad \forall t \geq t^*
\]

An example of a Gjedde-Patlak plot is given in Figure 7.1 where \( x = \frac{\int_0^t C'_{2}(u) du}{C'_{2}(t)} \) and \( y = \frac{C_{\text{tot}}(t)}{C'_{2}(t)} \). Receptor occupancy is then computed as

\[
RO = 1 - \frac{K_2}{K_1}
\]

where \( K_1 \) is the slope obtained for the drug-free condition and \( K_2 \) after drug administration.

### 7.4.2 Bayesian model for an irreversible tracer

An illustration of the method with irreversible tracers is first presented. The Bayesian varying coefficients model will be applied in a PET study where the objective is to use a one-stage method to estimate receptor occupancy as a function of the drug concentration in plasma, starting from the equations of the Gjedde-Patlak model. Therefore, the effect modifier in this context is the drug concentration in the plasma.

Indexes 1 and 2 refer to the concentrations observed before and after treatment respectively. The equations of the Gjedde-Patlak model become:

\[
\frac{C_{\text{tot},1}(t)}{C'_{2,1}(t)} = c_1 + K_1 \int_0^t \frac{C'_{2,1}(u) du}{C'_{2,1}(t)} \quad \forall t \geq t^*_1
\]

\[
\frac{C_{\text{tot},2}(t)}{C'_{2,2}(t)} = c_2 + K_2 \int_0^t \frac{C'_{2,2}(u) du}{C'_{2,2}(t)} \quad \forall t \geq t^*_2
\]

Receptor occupancy \((RO)\) is defined as:

\[
RO = 1 - \frac{K_2}{K_1}
\]
7.4 Receptor occupancy estimation

Figure 7.1: Example of a Gjedde-Patlak graph with $x = \frac{\int_0^t C'_{22}(u)du}{C_{2}(t)}$ and $y = \frac{C_{\text{tot}}(t)}{C_{2}(t)}$

Denote by $RO^c$ the complementary value:

$$RO^c = 1 - RO = \frac{K_2}{K_1} \quad (7.5)$$

By rearranging Equations (7.3)-(7.5), one obtains:

$$C_{\text{tot},2}(t) = c_2 C'_{2,2}(t) + RO^c \left[ C_{\text{tot},1}(t) - c_1 C'_{2,1}(t) \right] \frac{\int_0^t C'_{2,2}(u)du}{\int_0^t C'_{2,1}(u)du}$$

This is the equation for one subject. Consider a study with $K$ subjects for whom the drug concentration in the plasma has been measured at several occasions. One has:

$$C_{\text{tot},2}^k(t) = c_2(k)C'_{2,2}^k(t) + RO^c(k)(C_{\text{tot},1}(t) - c_1(k)C'_{2,1}^k(t)) \frac{\int_0^t C'_{2,2}^k(u)du}{\int_0^t C'_{2,1}^k(u)du} \quad \forall k \in \{1, ..., K\}$$

where subscript "$k$" refers to subject $k$. Notations can be simplified to:

$$y^{(k)}(t) = c_2(k)x^{k}_1(t) + RO^c(k)(x^{k}_1(t) - c_1(k)x^{k}_3(t))$$
$$= c_2(k)x^{k}_1(t) + \beta(k)x^{k}_4(t)$$
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where

\[ \begin{align*}
    y^k(t) &= C_{tot,2}^k(t) \\
    x_1^k(t) &= C_{2,2}^k(t) \\
    x_2^k(t) &= C_{tot,1}^k(t) \int_0^t \frac{C_{2,2}^k(u) du}{\int_0^t C_{2,1}^k(u) du} \\
    x_3^k(t) &= C_{2,1}^k(t) \int_0^t \frac{C_{2,2}^k(u) du}{\int_0^t C_{2,1}^k(u) du} \\
    x_4^k(t) &= x_3^k(t) - c_1(k) x_3^k(t) \\
    \beta(k) &= RO^c(k)
\end{align*} \]

\( RO^c(k) \) is expressed as a smoothed function of the drug concentration in the plasma. Details can be found in Appendix 7.2. The Bayesian model specification and the conditional posterior distributions are given in Appendix 7.3.

It is known that receptor occupancy has to increase monotonically with drug concentration. This can be translated into a linear constraint on spline coefficients, see Section 7.3.

Illustration on real data

In a real experiment involving an irreversible tracer, 6 patients have been scanned once before treatment, once after treatment with a first dose and a third time after treatment with a second dose. The drug concentrations in plasma are presented in Figure 7.2. At each scan, the radioactivity uptake has been measured in two regions of the brain (a reference and a target one) during the time-length of the scan. Figure 7.3 shows the Time-Activity-Curves of one patient. Circles (stars) are the radioactivity uptakes observed in the target (reference) region.

The time \( t^* \), after which linearity is observed, must be determined to use the Gjedde-Patlak technique. From a Graphical analysis of the Gjedde-Patlak plots, one could decide to fix the value of \( t^* \) to 6. If necessary, a formal analysis (Thornby 1972) can be realized to estimate the time at which the graph becomes linear.

An estimate for the ridge penalties (fixed to 0.1) has been derived from a preliminary analysis where the unknown coefficients of Equations (7.3)-(7.4) have been estimated by least squares regression. A sensitivity analysis reveals no dependence of the results to this choice.

Figure 7.4 presents the estimated drug concentration-receptor occupancy curve with 95% credibility set for it. One can conclude that receptor occupancy is at least 70% for patients presenting a drug concentration in plasma larger than 25 ng/ml.
7.4 Receptor occupancy estimation

7.4.3 Bayesian model for the reversible tracer case

The same analysis as in previous section is performed from the equations of Ichise et al. (2001). These equations before (indice 1) and after (indice 2) treatment can be written as:

$$\int_0^t C_{tot,1}(t) dt = h_1 \int_0^t \frac{C'_{2,1}(t)dt}{C_{tot,1}(t)} - h_1 c_1 \frac{C_{2,1}(t)}{C_{tot,1}(t)} + b_1 \quad \forall t > t_1^* \quad (7.6)$$

$$\int_0^t C_{tot,2}(t) dt = h_2 \int_0^t \frac{C'_{2,2}(t)dt}{C_{tot,2}(t)} - h_2 c_2 \frac{C_{2,2}(t)}{C_{tot,2}(t)} + b_2 \quad \forall t > t_2^* \quad (7.7)$$

The binding potentials are:

$$BP_1 = h_1 - 1; \quad BP_2 = h_2 - 1$$

Receptor occupancy is defined from the Binding Potentials as:

$$RO = 1 - \frac{BP_2}{BP_1}; \quad RO^c = \frac{BP_2}{BP_1} = \frac{h_2 - 1}{h_1 - 1} \quad (7.8)$$

This leads to:
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Figure 7.3: Time-Activity Curves of one patient in the target (circles) and in the reference (stars) regions.

\[
RO_c = \left\{ \frac{\int_0^t C_{tot,2}(u)du}{C_{tot,2}(t)} \right\} \left\{ \frac{\int_0^t C_{tot,1}(u)du}{C_{tot,1}(t)} \right\}
\]

By rearranging terms, one obtains a model similar to the one presented in Section 7.4.2 where receptor occupancy appears as a regression coefficient that varies with the drug concentration in plasma. The Bayesian model is given in Appendix 7.4 with the conditional posterior distributions. Again, the technique proposed in Section 7.3 is used to impose a monotonic increase of receptor occupancy with drug concentration.

Illustration on real data

This model is applied in a real study involving a reversible tracer. In this study, 12 patients have received a single dose of drug of 30, 80, 120 or 160 mg. These patients have been
scanned once before treatment and 2, 7 and 24 hours after treatment, see Figure 7.5. At each scan, the radioactivity uptake has been measured in two regions of the brain (a reference and a target one) during the time-length of the scan. Figure 7.6 shows the Time-Activity-Curves of one patient. Circles (stars) are the radioactivity uptakes observed in the target (reference) region.

The Ichise method requires the determination of $t^*$. We fix it to 0. More details on this choice can be found in Ichise et al. (2001).

An estimate for the ridge penalties (finally fixed to 0.1) has been derived from a preliminary analysis where the unknown coefficients of Equations (7.6)-(7.7) have been estimated by least squares regression. A sensitivity analysis reveals no dependence of the results to this choice.

Figure 7.7 presents the relation between drug concentration and receptor occupancy with 95% credibility sets for it. Patients receiving a dose of 120 or 160 mg show a plasma concentration after 2 hours of at least 360 ng/ml minimum. Then, receptor occupancy is estimated to be at least 50%.

### 7.5 Discussion

In many applications of linear regression models, the regression coefficients are not regarded as fixed but as varying with another covariate named the effect modifier. Then, varying
Coefficient models provide a potentially useful extension of the linear regression model. Bayesian P-splines is a flexible tool to link in a smoothed way the regression coefficient with the effect modifier. If necessary, more flexibility can be introduced by using the two extensions provided by Jullion and Lambert (2007).

We have also shown how to translate linear constraints on the relation between the regression coefficient and the effect modifier in the MCMC sampler (see Section 7.3). We have illustrated the method with data coming from a PET study to estimate receptor occupancy. Estimating the functional relationship between receptor occupancy and the drug concentration in the plasma is important in a PET study since it allows to evaluate whether the drug reaches its target site and also to select the efficacy dose. Estimation was performed using a nonparametric method based on P-splines. A monotonic functional can be forced if necessary (using e.g. an Emax model).

Credibility sets are obtained for receptor occupancy which take into account the uncertainty appearing at all the different estimation steps. In a traditional two-stage method,
Figure 7.6: Time-Activity curves of one patient in the target (circles) and in the reference (stars) regions.

receptor occupancy is first estimated for different levels of drug concentrations in the plasma, on the basis of the Ichise or Patlak equations for instance. In a second step, the relation between receptor occupancy and the drug concentration is estimated conditionally on the first step results. With this process, the uncertainty involved in the first step is ignored. In the one-stage method exposed in this chapter, all the uncertainty in the estimation procedure is reflected in the credibility sets obtained for the receptor occupancy.
Appendix 7.1: Linear constraints when sampling from a normal (Geweke 1991)

Let’s assume that we want to generate $x$ from: $x \sim N(\mu, \Sigma)$, subject to the constraints $a \leq Qx \leq b$ where $x$ is of length $m$, $Q$ is a full-rank $m \times m$ matrix and $a, b$ are possibly infinite in order to accommodate for fewer than $2m$ linearly independent restrictions. This problem is equivalent to the construction of samples from the $m$-variate normal distribution subject to linear restrictions:

$$z \sim N(0, \Sigma_Q), \quad \alpha \leq z \leq \beta \quad (7.9)$$

where $\Sigma_Q = Q\Sigma Q'$, $\alpha = a - Q\mu$, $\beta = b - Q\mu$. We take then $x = \mu + Q^{-1}z$. The idea is to use the fact that the distribution of each element of $z$, conditional on all the other elements of $z$ is truncated normal. Let’s assume that in the nontruncated distribution $N(0, \Sigma_Q)$,

$$E(z_i|z_{-i}) = \sum_{j \neq i} c_{ij} z_j$$
Then, in the truncated normal distribution of (7.9), the distribution of $z_i$, conditional on $z_{-i}$ has the construction:

$$z_i = \sum_{j \neq i} c_{ij} z_j + h_i \epsilon_i$$

$$\epsilon_i \sim TN((\alpha_i - \sum_{j \neq i} c_{ij} z_j)/h_i, (\beta_i - \sum_{j \neq i} c_{ij} z_j)/h_i)$$

where $TN(a, b)$ is the univariate normal restricted to $(a, b)$: its density is $(\Phi^{-1}(b) - \Phi^{-1}(a))^{-1}\phi(.)$ with $\phi(.)$ the univariate normal density function and $\Phi$ the corresponding cumulative distribution function. The vector $c^i = (c_{i1}, ..., c_{i,i-1}, c_{i,i+1}, ..., c_{in})'$, $i = 1, ..., n$ is defined as:

$$c^i = -({\Sigma}_{Q}^{ii})^{-1}{\Sigma}_{Q}^{i,<i}$$

and we have:

$$h_i^2 = ({\Sigma}_{Q}^{ii})^{-1}$$

where $\Sigma_{Q}^{ii}$ is the element in row $i$ and column $i$ of $\Sigma_{Q}^{-1}$, and $\Sigma_{Q}^{i,<i}$ is row $i$ of $\Sigma_{Q}^{-1}$ with $\Sigma_{Q}^{ii}$ deleted. Sampling from the univariate truncated normal can be made using the normal rejection sampling or the uniform rejection sampling.

**Appendix 7.2: Equations for the irreversible tracer model**

The matricial notation of equations (7.3)-(7.5) is:

$$Y = Xc + Z\beta$$

where

$$X = \begin{bmatrix}
  x_1^{(1)}(1) & 0 & \ldots & 0 \\
  \vdots & \vdots & \ddots & \vdots \\
  x_1^{(1)}(T) & 0 & \ldots & 0 \\
  0 & x_1^{(2)}(1) & \ldots & 0 \\
  \vdots & \vdots & \ddots & \vdots \\
  0 & x_1^{(2)}(T) & \ldots & 0 \\
  0 & 0 & \ldots & x_1^{(K)}(1) \\
  \vdots & \vdots & \ddots & \vdots \\
  0 & 0 & \ldots & x_1^{(K)}(T)
\end{bmatrix}$$

and

$$Z = \begin{bmatrix}
  x_4^{(1)}(1) & 0 & \ldots & 0 \\
  \vdots & \vdots & \ddots & \vdots \\
  x_4^{(1)}(T) & 0 & \ldots & 0 \\
  0 & x_4^{(2)}(1) & \ldots & 0 \\
  \vdots & \vdots & \ddots & \vdots \\
  0 & x_4^{(2)}(T) & \ldots & 0 \\
  0 & 0 & \ldots & x_4^{(K)}(1) \\
  \vdots & \vdots & \ddots & \vdots \\
  0 & 0 & \ldots & x_4^{(K)}(T)
\end{bmatrix}$$

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\[ c_2 = (c_{2,1}, c_{2,2}, ..., c_{2,K})', \beta = (\beta_1, \beta_2, ..., \beta_K)' \] and \[ Y = (y_{11}, ..., y_{1T}, ..., y_{K1}, ... y_{KT})'. \] The length of \( Y \) is \( N \).

**Appendix 7.3: Specification and conditional posterior distributions for the irreversible tracer model**

The Bayesian model is the following:

\[
(Y|c_2, c_1, \gamma, \tau) \sim \mathcal{N}(Xc_2 + ZB_E\gamma, \tau^{-1}I_n)
\]

\[ p(\tau) \propto \tau^{-1} \]

\[ c_2 \sim \mathcal{N}(0, \tau_c^{-1})I_{[0, +\infty]}(c_2) \]

\[ c_1 \sim \mathcal{N}(0, \tau_c^{-1})I_{[0, +\infty]}(c_1) \]

\[ p(\gamma|\tau) \propto \exp(-0.5\tau_\gamma\gamma'D'\tau_\gamma)I(D_1\gamma < 0) \]

\[ (\tau, \gamma) \sim \mathcal{M}\sum_{m=1}^{M} p_m G(a + 0.5 \text{ rank}(P), b_m + 0.5\gamma'P\gamma) \]

where \( c_1 = (c_{1,1}, c_{1,2}, ..., c_{1,K})' \)

The conditional posterior distributions are the following:

\[ (\tau|c_2, \gamma; y) \sim \mathcal{G}(n/2, 0.5(Y - Xc_2 - ZB_E\gamma)'(Y - Xc_2 - ZB_E\gamma)) \]

\[ (c_2|\gamma, \tau; y) \sim \mathcal{N}((\tau X'X + \tau_c 1K)^{-1}(\tau Y'X - \tau\beta'Z'X), (\tau X'X + \tau_c 1K)^{-1}) \]

\[ (c_1|\gamma, \tau; y) \sim \mathcal{N}((\tau Z'_2Z_2 + \tau_c 1K)^{-1}(\tau V'Z_2), (\tau Z'_2Z_2 + \tau_c 1K)^{-1}) \]

\[ (\gamma|c_2, \tau, \gamma; y) \sim \mathcal{N}(\tau B'_EZ'\Sigma\gamma(Y - Xc_2), (\tau B'_EZ'ZB_E + \Sigma^{-1})^{-1})I(D_1\gamma < 0) \]

\[ (\tau, \gamma; P; y) \sim \mathcal{M}\sum_{m=1}^{M} p_m G(a + 0.5 \text{ rank}(P), b_m + 0.5\gamma'P\gamma) \]

\[ (P|\tau, \gamma; y) \propto \mathcal{M}\sum_{m=1}^{M} \frac{c_m}{\sum_{j=1}^{M} c_j} D(u_1, ..., u_m + 1, ... u_M) \]
where

\[ c_m = \exp(-\tau \gamma b_m) b_m^\gamma \sum_{j=1}^M u_j \]

\[ \Sigma^{-1} = \tau P \]

\[ V = Y - X\alpha - Z_1\beta \]

\[ \beta = B_E\gamma \]

and

\[
Z_1 = \begin{bmatrix}
  x_2^{(1)}(1) & 0 & \ldots & 0 \\
  \vdots & \vdots & \ddots & \vdots \\
  0 & x_2^{(2)}(1) & \ldots & 0 \\
  \vdots & \vdots & \ddots & \vdots \\
  0 & 0 & \ldots & x_2^{(K)}(1) \\
  \vdots & \vdots & \ddots & \vdots \\
  0 & 0 & \ldots & x_2^{(K)}(T) \\
\end{bmatrix}
\]

\[
Z_2 = \begin{bmatrix}
  -x_3^{(1)}(1)\beta_1 & 0 & \ldots & 0 \\
  \vdots & \vdots & \ddots & \vdots \\
  -x_3^{(1)}(T)\beta_1 & 0 & \ldots & 0 \\
  0 & -x_3^{(2)}(1)\beta_2 & \ldots & 0 \\
  \vdots & \vdots & \ddots & \vdots \\
  0 & -x_3^{(2)}(T)\beta_2 & \ldots & 0 \\
  0 & 0 & \ldots & -x_3^{(K)}(1)\beta_K \\
  \vdots & \vdots & \ddots & \vdots \\
  0 & 0 & \ldots & -x_3^{(K)}(T)\beta_K \\
\end{bmatrix}
\]

Appendix 7.4: Specification and conditional posterior distributions for the reversible tracer model

Equations (7.6)-(7.8) can be rearranged such that:

\[
Y = b_2X_1 - c_2X_2 + c_1X_3 - c_1b_2X_4 - c_1X_5 + c_1c_2X_6 + \beta(X_7 - b_1X_8 + c_1X_5 - c_2X_9 + b_1c_2X_{10} + c_2X_2 - c_1c_2X_6)
\]
with

\[ Y = \frac{\int_0^t C_{tot,2}(u) du }{C_{tot,1}(t)} \frac{\int_0^t C_{2,1}^2(u) du}{C_{tot,1}(t)} - \frac{\int_0^t C_{2,2}^2(u) du}{C_{tot,2}(t)} \frac{\int_0^t C_{2,2,1}(u) du}{C_{tot,1}(t)} \]

\[ X_1 = \frac{\int_0^t C_{2,1}'(u) du}{C_{tot,1}(t)} \]

\[ X_2 = \frac{\int_0^t C_{2,1}'(u) du}{C_{tot,2}(t)} \frac{C_{2,2}^2(t)}{C_{tot,1}(t)} \]

\[ X_3 = \frac{\int_0^t C_{tot,2}(u) du}{C_{tot,2}(t)} \frac{C_{2,1}'(t)}{C_{tot,1}(t)} \]

\[ X_4 = \frac{C_{2,1}'(t)}{C_{tot,1}(t)} \]

\[ X_5 = \frac{\int_0^t C_{2,2}'(u) du}{C_{tot,2}(t)} \frac{C_{2,1}'(t)}{C_{tot,1}(t)} \]

\[ X_6 = \frac{C_{2,2}^2(t)}{C_{tot,2}(t)} \frac{C_{2,1}^2(t)}{C_{tot,1}(t)} \]

\[ X_7 = \frac{\int_0^t C_{2,2}'(u) du}{C_{tot,2}(t)} \frac{\int_0^t C_{tot,1}(u) du}{C_{tot,1}(t)} - \frac{\int_0^t C_{2,2}'(u) du}{C_{tot,2}(t)} \frac{\int_0^t C_{2,2,1}(u) du}{C_{tot,1}(t)} \]

\[ X_8 = \frac{\int_0^t C_{2,2}'(u) du}{C_{tot,2}(t)} \]

\[ X_9 = \frac{\int_0^t C_{tot,1}(u) du}{C_{tot,2}(t)} \frac{C_{2,2}^2(t)}{C_{tot,1}(t)} \]

\[ X_{10} = \frac{C_{2,2}^2(t)}{C_{tot,2}(t)} \]

\[ \beta = RO^\circ \]

Denote by \( K \) the number of subjects. In matricial terms, one has:

\[ Y = X_\alpha + Z_\beta \]

where

\[ X_k = \begin{bmatrix} x_1^{(k)}(1) & x_2^{(k)}(1) & \cdots & x_6^{(k)}(1) \\ \vdots & \vdots & \vdots & \vdots \\ x_1^{(k)}(T) & x_2^{(k)}(T) & \cdots & x_6^{(k)}(T) \end{bmatrix} \]
The Bayesian model is:

\[
\begin{align*}
Y & \sim N(X(\alpha + Z\beta), \tau^{-1}) \\
(Z|Y, \alpha, \beta, \tau, \gamma) & \sim N((WV + \tau P)^{-1}WV, (WV + \tau P)^{-1}) \text{I}(D(1, \alpha) > 0)
\end{align*}
\]

where \(\gamma, \tau, \beta, \alpha, c, b, \text{ and } \phi\) are constants ensuring a large a priori variance for parameters \(b, c, \text{ and } \phi\) respectively.

and

\[
Z = \text{diag}(x_1, x_2, \ldots, x_K)
\]

The Bayesian model is:

\[
Y = (Y_1, Y_2, \ldots, Y_N) \sim N(X(\alpha + Z\beta), \tau^{-1})
\]

where \(\gamma, \tau, \beta, \alpha, c, b, \text{ and } \phi\) are constants ensuring a large a priori variance for parameters \(b, c, \text{ and } \phi\) respectively.

and

\[
Z = \text{diag}(x_1, x_2, \ldots, x_K)
\]

The Bayesian model is:

\[
Y = (Y_1, Y_2, \ldots, Y_N) \sim N(X(\alpha + Z\beta), \tau^{-1})
\]
Conditional Posterior of $\tau$:

$$(\tau | \alpha, \beta; y) \sim G \left( n/2, 0.5(Y - X\alpha - Z\beta)'(Y - X\alpha - Z\beta) \right)$$

Conditional Posterior of $\tau_{\gamma}$:

$$(\tau_{\gamma} | \gamma, p; y) \sim \sum_{m=1}^{M} p_m G \left( a + 0.5 \text{rank}(P), b_m + 0.5 \gamma' P \gamma \right)$$

$$(p | \tau_{\gamma}; y) \propto \sum_{m=1}^{M} \frac{c_m}{\sum_{j=1}^{M} c_j} D(u_1, ..., u_m + 1, ... u_M)$$

where

$$c_m = \exp(-\tau_{\gamma} b_m) b_m^0 \frac{\sum_{j=1}^{M} u_j}{u_m}$$

Conditional Posterior of $b_1$:

$$(b_1 | \tau, \beta, \tau_{b_1}; y) \sim N \left( \Sigma_{b_1} \tau U' \Xi, \Sigma_{b_1} \right)$$

where

$$\Sigma_{b_1} = (\tau \Xi' \Xi + (\tau_{b_1} 1_K))^{-1}$$

$$\Xi = V \beta$$

$$V = c_2 X_{10} - X_8$$

$$U = W - R\beta$$

$$R = X_7 + c_1 X_5 - c_2 X_9 + c_2 X_2 - c_1 c_2 X_6$$

$$W = Y - b_2 X_1 + c_2 X_2 - c_1 X_3 + b_2 c_1 X_4 + c_1 X_5 - c_1 c_2 X_6$$

Conditional Posterior of $b_2$:

$$(b_2 | \tau, \beta, \tau_{b_2}; y) \sim N \left( \Sigma_{b_2} \tau V' U, \Sigma_{b_2} \right)$$

where

$$\Sigma_{b_2} = (\tau U' U + (\tau_{b_2} 1_K))^{-1}$$

$$U = X_1 - c_1 X_4$$

$$V = W - R\beta$$

$$R = X_7 - b_1 X_8 + c_1 X_5 - c_2 X_9 + b_1 c_2 X_1 + c_2 X_2 + c_1 c_2 X_6$$

$$W = Y + c_2 X_2 - c_1 X_3 + c_1 X_5 - c_1 c_2 X_6$$
Conditional Posterior of $c_1$:

$$(c_1|\tau_{c_1}, \beta, \tau; y) \sim \mathcal{N}(\Sigma_{c_1}^{-1} \Phi \Xi, \Sigma_{c_1})$$

where

$$\Sigma_{c_1} = (\tau \Xi \Xi + (\tau_{c_1} 1_K))^{-1}$$
$$\Xi = V + U\beta$$
$$V = X_3 - b_2 X_4 - X_5 + c_2 X_6$$
$$U = X_5 - c_2 X_6$$
$$\Phi = W - R\beta$$
$$R = X_7 - b_1 X_8 - c_2 X_9 + b_1 c_2 X_{10} + c_2 X_2$$
$$W = Y - b_2 X_1 + c_2 X_2$$

Conditional Posterior of $c_2$:

$$(c_2|\tau_{c_2}, \beta; y) \sim \mathcal{N}(\Sigma_{c_2}^{-1} \Phi \Xi, \Sigma_{c_2})$$

where

$$\Sigma_{c_2} = (\tau (\Phi \Phi) + (\tau_{c_2} 1_K))^{-1}$$
$$\Phi = U + \beta V$$
$$V = b_1 X_{10} - X_9 + X_2 - c_1 X_6$$
$$U = -X_2 + c_1 X_6$$
$$\Xi = W - \beta R$$
$$W = Y - b_2 X_1 - c_1 X_3 + b_2 c_1 X_4 + c_1 X_5$$
$$R = X_7 - b_1 X_8 + c_1 X_5$$