Adaptive Bayesian P-splines to estimate Varying Regression Coefficients: Application to Receptor Occupancy Estimation

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Abstract
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. A useful extension of the linear regression models are then varying coefficient models. To link the regression coefficient with the effect modifier, several methods may be considered. Here, we propose to use Bayesian P-splines to relate in a smoothed way the regression coefficient with the effect modifier. We show that this method enables a large level of flexibility: if necessary, adaptive penalties can be introduced in the model (Jullion and Lambert 2007) and linear constraints on the relation between the regression coefficient and the effect modifier may easily be added.

We provide an illustration of the proposed method in a PET study where we want to estimate the relation between the Receptor Occupancy and the drug concentration in the plasma. As we work in a Bayesian setting, credibility sets are easily obtained for receptor occupancy, which take into account the uncertainty appearing at all the different estimation steps.

Key Words: Varying Coefficient Model, Bayesian P-splines, Receptor Occupancy.

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 paper, we propose to use robust Bayesian penalized B-splines as described in Jullion and Lambert (2007) 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).

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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 bounded. 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 paper enables to reflect all the uncertainty in the estimation procedure.

The plan of this paper is as follows. The Bayesian varying coefficient model is first presented in Section 2. 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 paper with a discussion.

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.

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 $\tau_0 > 0$. Ridge regression can be translated in a Bayesian framework by adding a prior on the regression coefficients vector:

$$\alpha \sim \mathcal{N}(0, \tau_0^{-1}I_p)$$
Congdon (2006) suggests either to set a prior on \( \tau_\alpha \) or to assess sensitivity to pre-specified 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:

\[
(\tau|Y, \alpha) \sim \mathcal{G}(n/2, 0.5(Y - X\alpha)'(Y - X\alpha))
\]
\[
(\alpha|Y, \tau) \sim \mathcal{N}((\tau X'X + \tau_\alpha 1_p)^{-1}(\tau X'Y), (\tau X'X + \tau_\alpha 1_p)^{-1})
\]

(see Congdon (2006) for more details).

### 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 robust Bayesian P-splines model presented in Jullion and Lambert (2007) is the following:

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

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 \( b \).

### 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: \( \beta = \beta(E) = B_E\gamma \) 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:

\[
(Y|\alpha, \gamma, \tau) \sim \mathcal{N}(X\alpha + ZB_E\gamma, \tau^{-1}I_n)
\]
\[
p(\tau) \propto \tau^{-1}
\]
\[
(\alpha) \sim \mathcal{N}(0, \tau_\alpha^{-1}1_p)
\]
\[
p(\gamma|\tau_\gamma) \propto \exp(-0.5\tau_\gamma \gamma'D\gamma)
\]
\[
(\tau_\gamma|p) \sim \sum_{m=1}^{M} p_m \mathcal{G}(a, b_m)
\]
\[
p \sim \mathcal{D}(u)
\]
Remembering that $\beta = B E \gamma$, one gets the following conditional posterior distributions:

$$
(\tau | \alpha, \gamma; y) \sim \mathcal{G} \left( n/2, 0.5(y - X \alpha - Z \beta)'(y - X \alpha - Z \beta) \right)
$$
$$
(\alpha | \gamma, \tau, \alpha_0; y) \sim \mathcal{N} \left( (\tau X' X + \alpha_0 1_p)^{-1} \tau X' (y - Z \beta), (\tau X' X + \alpha_0 1_p)^{-1} \right)
$$
$$
(\gamma | \alpha, \tau; y) \sim \mathcal{N} \left( TB' Z' \Sigma \gamma (y - X \alpha), \Sigma \gamma \right)
$$
$$
(\tau | \gamma, \beta; y) \sim \sum_{m=0}^{M} p_m \mathcal{G} \left( a + 0.5 \rho (D' D), b_m + 0.5 \gamma' D' D \gamma \right)
$$
$$
(p | \tau \gamma; y) \propto \sum_{m=1}^{M} \frac{c_m}{\Sigma_{j=1}^{M} e_j} D(u_1, ..., u_m + 1, ..., u_M)
$$

where

$$
c_m = \exp(-\tau \gamma b_m) b_m^a \frac{\sum_{j=1}^{M} u_j}{u_m}
$$
$$
\Sigma^{-1} = \tau \gamma D' D
$$
$$
\Sigma \gamma = (TB' Z' Z B + \Sigma^{-1})^{-1}
$$

These conditional posteriors can be used in the Gibbs sampler (Geman and Geman 1984).

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 : $D_1 \gamma > 0$ where $D_1$ 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.

4. Receptor occupancy estimation

4.1 Context of the study

Interest lies in drugs that bind to some specific receptors in the brain. 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:

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

(1)
For more details, we refer to Ichise et al. (2001). Equation (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:

$$C_{\text{tot}}(t) = \frac{k_1 k_2 k_3}{k_1 k_2 + k_3} \int_0^t C'_2(u)du + \frac{k_1 k_3}{k_1 k_2 + k_3} + \frac{k_2}{k_2 + k_3} C_2(t)$$

(2)

One assumes that $k_1/k_2 = k'_1/k'_2$, common to all reference tissue models. The net uptake rate $K$ is defined as:

$$K = \text{slope} = \frac{k_2 k_3}{k_2 + k_3}$$

The ratio $C_{\text{tot}}(t)/C'_2(t)$ 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 (2) can be rewritten as:

$$\frac{C_{\text{tot}}(t)}{C'_2(t)} = c + K \int_0^t \frac{C'_2(u)du}{C'_2(t)} \forall t \geq t^*$$

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.

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:

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

(3)

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

(4)

Receptor occupancy ($RO$) is defined as:

$$RO = 1 - \frac{K_2}{K_1}$$
Denote by $RO^c$ the complementary value:

$$RO^c = 1 - RO = \frac{K_2}{K_1} \tag{5}$$

By rearranging Equations (3)-(5), one obtains:

$$C_{tot,2}(t) = c_2C_{2,2}(t) + RO^c \left[ C_{tot,1}(t) - c_1C_{2,1}(t) \right] \int_0^t \frac{C_{2,2}(u)du}{\int_0^t C_{2,1}(u)du}$$

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:

$$C_{tot,2}(t) = c_2(k)C_{2,2}(t) + RO^c(k)(C_{tot,1}(t) - c_1(k)C_{2,1}(t)) \int_0^t \frac{C_{2,2}(u)du}{\int_0^t C_{2,1}(u)du} \quad \forall k \in \{1, ..., K\}$$

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

$$y^{(k)}(t) = c_2(k)x_1^{(k)}(t) + RO^c(k)(x_2^{(k)}(t) - c_1(k)x_3^{(k)}(t))$$

$$= c_2(k)x_1^{(k)}(t) + \beta(k)x_4^{(k)}(t)$$

where

$$y^{(k)}(t) = C_{tot,2}^{(k)}(t)$$
$$x_1^{(k)}(t) = C_{2,2}^{(k)}(t)$$
$$x_2^{(k)}(t) = C_{tot,1}^{(k)}(t) \int_0^t \frac{C_{2,2}^{(k)}(u)du}{\int_0^t C_{2,1}^{(k)}(u)du}$$
$$x_3^{(k)}(t) = C_{2,2}^{(k)}(t) \int_0^t \frac{C_{2,1}^{(k)}(u)du}{\int_0^t C_{2,1}^{(k)}(u)du}$$
$$x_4^{(k)}(t) = x_2^{(k)}(t) - c_1(k)x_3^{(k)}(t)$$
$$\beta(k) = RO^c(k)$$

$RO^c(k)$ is expressed as a smoothed function of the drug concentration in the plasma. Details can be found in Appendix 1. The Bayesian model specification is given in Appendix 2. 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 3.

4.2.1 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 1. 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 2 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 (3)-(4) have been estimated by least squares regression. A sensitivity analysis reveals no dependence of the results to this choice. Figure 3 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.

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
Figure 3: Drug concentration-receptor occupancy curve in the case of an irreversible tracer. The stars indicate when the scans occurred.

be written as:

\[
\frac{\int_0^t C_{\text{tot},1}(u)\,du}{C_{\text{tot},1}(t)} = h_1 \frac{\int_0^t C_{\text{2,1}}'(u)\,du}{C_{\text{tot},1}(t)} - h_1 c_1 \frac{C_{\text{2,1}}'(t)}{C_{\text{tot},1}(t)} + b_1 \forall t > t_1^*
\]

\[
\frac{\int_0^t C_{\text{tot},2}(u)\,du}{C_{\text{tot},2}(t)} = h_2 \frac{\int_0^t C_{\text{2,2}}'(u)\,du}{C_{\text{tot},2}(t)} - h_2 c_2 \frac{C_{\text{2,2}}'(t)}{C_{\text{tot},2}(t)} + b_2 \forall t > t_2^*
\]

The binding potentials are:

\[BP_1 = h_1 - 1; BP_2 = h_2 - 1\]

Receptor occupancy is defined from the Binding Potentials as:

\[RO = 1 - \frac{BP_2}{BP_1}; RO^c = \frac{BP_2}{BP_1} = \frac{h_2 - 1}{h_1 - 1}\]

This leads to:

\[
\left( \frac{\int_0^t C_{\text{tot},2}(u)\,du}{C_{\text{tot},2}(t)} - b_2 - \frac{\int_0^t C_{\text{2,2}}'(u)\,du}{C_{\text{tot},2}(t)} + c_2 \frac{C_{\text{2,2}}'(t)}{C_{\text{tot},2}(t)} \left( \frac{\int_0^t C_{\text{2,1}}'(u)\,du}{C_{\text{tot},1}(t)} - c_1 \frac{C_{\text{2,1}}'(t)}{C_{\text{tot},1}(t)} \right) \right) = RO^c \left\{ \left( \frac{\int_0^t C_{\text{2,2}}'(u)\,du}{C_{\text{tot},2}(t)} - c_2 \frac{C_{\text{2,2}}'(t)}{C_{\text{tot},2}(t)} \right) \left( \frac{\int_0^t C_{\text{tot},1}(u)\,du}{C_{\text{tot},1}(t)} - b_1 - \frac{\int_0^t C_{\text{2,1}}'(u)\,du}{C_{\text{tot},1}(t)} + c_1 \frac{C_{\text{2,1}}'(t)}{C_{\text{tot},1}(t)} \right) \right\}
\]

By rearranging terms, one obtains a model similar to the one presented in Section 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 3. Again, the technique proposed in Section 3 is used to impose a monotonic increase of receptor occupancy with drug concentration.

4.3.1 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 4. 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 5 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)-(8) have been estimated by least squares regression. A sensitivity analysis reveals no dependence of the results to this choice. Figure 6 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%.

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 3). We have illustrated the method with data coming from a PET study to estimate receptor occupancy. Estimating the functional relationship between receptor oc-
Figure 5: Time-Activity curves of one patient in the target (circles) and in the reference (stars) regions.

Figure 6: Drug concentration-receptor occupancy for a reversible tracer. The stars indicate when the scans occured.

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, 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 by the first step is ignored. In the one-stage method exposed in this paper, all the uncertainty in the estimation procedure is reflected in the credibility sets obtained for the receptor occupancy.
REFERENCES


Appendix 1: Equations for the irreversible tracer model

The matricial notation of equations (3)-(5) is:

\[ Y = Xc_2 + Z\beta \]

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

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

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

The length of \( Y \) is \( N \).

Appendix 2: Specification for the irreversible tracer model

The Bayesian model is the following:

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

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

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

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

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

\[
(\tau_\gamma|\mathbf{p}) \sim \sum_{m=1}^M p_m \mathcal{G}(a, b_m)
\]

\[
\mathbf{p} \sim \mathcal{D}(\mathbf{u})
\]

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

Appendix 3: Specification for the reversible tracer model

Equations (7)-(9) 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
\[
Y = \frac{\int_0^t C_{tot,2}(u)du}{C_{tot,2}(t)} \int_0^t C'_{2,1}(u)du \frac{\int_0^t C'_{2,2}(u)du}{C_{tot,2}(t)} \frac{\int_0^t C'_{2,1}(u)du}{C_{tot,1}(t)} - \frac{\int_0^t C'_{2,2}(u)du}{C_{tot,2}(t)} \frac{\int_0^t C'_{2,1}(u)du}{C_{tot,1}(t)}
\]
\[
X_1 = \frac{\int_0^t C'_{2,1}(u)du}{C_{tot,1}(t)}
\]
\[
X_2 = \frac{\int_0^t C'_{2,1}(u)du}{C_{tot,1}(t)} \frac{C'_{2,2}(t)}{C_{tot,2}(t)}
\]
\[
X_3 = \frac{\int_0^t C_{tot,2}(u)du}{C_{tot,2}(t)} \frac{C'_{2,1}(t)}{C_{tot,1}(t)}
\]
\[
X_4 = \frac{C'_{2,1}(t)}{C_{tot,1}(t)}
\]
\[
X_5 = \frac{\int_0^t C'_{2,2}(u)du}{C_{tot,1}(t)} \frac{C'_{2,1}(t)}{C_{tot,1}(t)}
\]
\[
X_6 = \frac{C'_{2,2}(t)}{C_{tot,2}(t)} \frac{C_{tot,1}(t)}{C_{tot,1}(t)}
\]
\[
X_7 = \frac{\int_0^t C_{tot,2}(u)du}{C_{tot,2}(t)} \frac{C_{tot,1}(u)}{C_{tot,1}(t)} \frac{\int_0^t C'_{2,2}(u)du}{C_{tot,1}(t)} \frac{\int_0^t C'_{2,1}(u)du}{C_{tot,1}(t)} - \frac{\int_0^t C'_{2,2}(u)du}{C_{tot,2}(t)} \frac{\int_0^t C'_{2,1}(u)du}{C_{tot,1}(t)}
\]
\[
X_8 = \frac{\int_0^t C'_{2,2}(u)du}{C_{tot,2}(t)}
\]
\[
X_9 = \frac{\int_0^t C_{tot,1}(u)du}{C_{tot,2}(t)} \frac{C'_{2,2}(t)}{C_{tot,2}(t)}
\]
\[
X_{10} = \frac{C'_{2,2}(t)}{C_{tot,2}(t)}
\]
\[
\beta = RO^c
\]

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

\[
Y = X\alpha + Z\beta
\]

where

\[
X_k = \begin{bmatrix}
    x^{(k)}_1(1) & x^{(k)}_2(1) & \ldots & x^{(k)}_b(1) \\
    \vdots & \vdots & \ddots & \vdots \\
    x^{(k)}_1(T) & x^{(k)}_2(T) & \ldots & x^{(k)}_b(T)
\end{bmatrix}
\]

and

\[
Z_k = \begin{bmatrix}
    x^{(k)}_7(1) & x^{(k)}_8(1) & \ldots & x^{(k)}_{10}(1) & x^{(k)}_2(1) & x^{(k)}_6(1) & x^{(k)}_5(1) \\
    \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots \\
    x^{(k)}_7(T) & x^{(k)}_8(T) & \ldots & x^{(k)}_{10}(T) & x^{(k)}_2(T) & x^{(k)}_6(T) & x^{(k)}_5(T)
\end{bmatrix}
\]
and

\[ X = \text{diag}([X_1, X_2, \ldots, X_K]) \]
\[ Z = \text{diag}([Z_1 \phi_1, Z_2 \phi_2, \ldots, Z_K \phi_K]) \]
\[ \alpha = [\alpha'_1, \alpha'_2, \ldots, \alpha'_K]' \]
\[ \beta = [\beta_1, \beta_2, \ldots, \beta_K]' \]
\[ \alpha_k = [b_{2k}, c_{2k}, c_{1k}, -b_{2k} c_{1k}, -c_{1k}, c_{1k} c_{2k}]' \]
\[ \phi_k = [1, -b_{1k}, -c_{2k}, b_{1k} c_{2k}, c_{2k} c_{1k}, c_{1k}]' \]

The Bayesian model is:

\[ (Y|b_1, b_2, c_1, c_2, \gamma, \tau) \sim \mathcal{N}(X \alpha + Z \beta \gamma, \tau^{-1}) \]
\[ p(\tau) \propto \tau^{-1} \]
\[ b_1 \sim \mathcal{N}\left(0, \tau_{b_1}^{-1}\right) \]
\[ b_2 \sim \mathcal{N}\left(0, \tau_{b_2}^{-1}\right) \]
\[ c_1 \sim \mathcal{N}\left(0, \tau_{c_1}^{-1}\right) \]
\[ c_2 \sim \mathcal{N}\left(0, \tau_{c_2}^{-1}\right) \]
\[ p(\gamma|\tau) \propto \exp(-0.5 \tau_{\gamma} \gamma' P \gamma) I(D_1 \gamma < 0) \]
\[ (\tau_{\gamma} \mathbf{p}) \sim \sum_{m=1}^{M} p_m G(a, b_m) \]
\[ \mathbf{p} \sim D(\mathbf{u}) \]

where \(\tau_{b_1}, \tau_{b_2}, \tau_{c_1}, \text{ and } \tau_{c_2}\) are constants ensuring a large a priori variance for parameters \(b_1, b_2, c_1\) and \(c_2\) respectively.