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A Flexible Semi-Parametric Approach to Estimating a Dose-Response Relationship: the Treatment of Childhood Amblyopia.

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Abstract

In a study of a dose-response relationship, flexibility in modelling is essential to capturing the treatment effect when the mean effect of other covariates is not fully understood, so that observed treatment effect is not due to the imposition of a rigid model for the relationship between response, treatment, and other variables. A semiparametric additive linear mixed (SPALM) model (Ruppert et al. 2003) provides a tractable and flexible approach to modelling the influence of potentially confounding variables. In this paper, we present pure likelihood and Bayesian versions of the SPALM model. Both methods of inference are readily implementable, but the Bayesian approach allows coherent propagation of uncertainty in the model, and, more importantly, allows prediction of future experimental results for as yet untreated individuals, thus allowing an assessment of the merits of different dosing strategies. We motivate the use of the methodology with the Monitored Occlusion Treatment of Amblyopia Study (MOTAS), which investigated the relationship between duration of occlusion and improvement in visual acuity.

1 Introduction

In many study settings, the inter-relationships between an outcome, a predictor of interest such as a treatment, and several other (potentially confounding) covariates are not well understood. Under such situations, it may be neither desirable nor important to explicitly explain the associations between outcome and any covariates other than the pre-specified predictor of interest, and yet we wish to avoid the potential for bias in the estimation of the treatment effect due to rigid assumptions about the relationship between the outcome and other variables.

In this paper, we analyze the data from a recent observational study of the treatment of childhood amblyopia - a common ophthalmological condition, where the visual acuity of one eye is compromised - by occlusion (patching of the fellow eye); in this study, there is clear scope for non-linear relationships, as the amount of occlusion dose received is potentially influenced by continuous child-specific factors such as age (Stewart et al. 2004). We use semiparametric additive linear mixed (SPALM) models as tools for estimating potentially non-linear covariate effects.

1.1 Quantifying dose-response over time: an analysis strategy

Two related models are of interest when analyzing longitudinal data. The first (*absolute-level*) model assumes a repeated measures structure; each participant provides repeated time-varying covariate data over a number of intermediate measurements as well as a final, end-of-study measurement. The second (*interval-level*) model takes as the response the **change** in visual acuity between successive measurements.

In this paper, we mainly focus on the interval-level data: the outcome is taken to be the change in response between successive measurements in a longitudinal study. That is, we set our attention to estimating the short-term effect of occlusion by examining the improvement in visual acuity that may be attributed to the number of hours that an eye patch was worn in the previous two-week interval. It is equally possible to consider change in visual acuity as a function of total (cumulative) dose in the interval-level analysis, or to use SPALM in an absolute-level data context; we also briefly present analyses along these lines. However, it is widely believed in the ophthalmic community that changes to the eye, and therefore improvements in visual acuity, are maintained so that short-term effects are in fact the quantities which are of interest to researchers.

With data in this form, a linear mixed-effects regression model provides a good means of initial analysis, with selection of influential covariates or interactions carried out using the Bayes Information Criterion (BIC) (see, for example, Schwarz (1978) and Kass & Raftery (1995) for definition and discussion). The covariance structure was selected based on exploratory plots of residuals. Potentially confounding relationships between covariates and treatment are then modelled flexibly using semiparametric additive linear mixed (SPALM) models (see, for example, Ruppert et al. (2003)). The analysis methods are demonstrated in the context of the MOTAS data.

1.2 Structure of Paper

The paper is structured as follows: section 2 provides details of our motivating example. Section 3 describes linear and semiparametric mixed models using a frequentist approach, with estimation carried out using maximum likelihood and restricted maximum likelihood methods. A Bayesian version of the SPALM approach is described and implemented in 4. The Bayesian approach necessitates the use of a novel prior structure on the mixed effects components. The Bayesian analysis readily facilitates a study of the impact of different dosing strategies; we present such a study in section 4.5. In section 5, we provide a brief presentation of the absolute-level data. Section 6 concludes.

2 MOTAS: The Monitored Occlusion Treatment of Amblyopia Study

2.1 Amblyopia and its Treatment

Amblyopia is the most common childhood vision disorder, affecting 1-5% of children. The condition is characterized by reduced visual function, and usually affects only one eye. It has been associated with up to a three-fold increased lifetime risk of serious vision loss of the fellow eye (Rahi et al. 2002). Amblyopia can be differentiated into several types, the most common of which are anisometropic, strabismic, and mixed. A standard treatment for the condition is occlusion therapy, that is, patching of the functioning fellow eye. Perhaps surprisingly, the apparent beneficial effect of occlusion therapy has never been well quantified, partly due to difficulty in the accurate measurement of the occlusion dose.

The Monitored Occlusion Treatment of Amblyopia Study (MOTAS) (Stewart et al. 2004) study was carried out between 2001 and 2003, at three hospitals in London, United Kingdom. MOTAS was not the only study to examine the effectiveness of occlusion (see, for example, PEDIG (2003)); however, all previous studies measured compliance by parental report. The MOTAS study was revolutionary as for the first time the amount of occlusion therapy that each child received was accurately recorded using an electronic monitor. This pioneering study offered the possibility of quantification of the magnitude of the dose effect in the improvement in vision.

2.2 Study Design and Implementation

The MOTAS design and a full description of the study base have been published previously (Stewart et al. 2002, Stewart et al. 2004). Prior to study entry, all children had a full ophthalmic assessment. Those who required spectacles entered the refractive adaptation phase; the remainder entered the occlusion phase directly. Children in refraction were prescribed to full-time spectacle use for 18 weeks, and scheduled for vision re-assessment at six week intervals. Children still considered amblyopic began occlusion and were prescribed six hours of occlusion daily. That is, *the same dose* was assigned to all individuals in the occlusion phase of the study.

The study enrolled a total of 116 children aged between 36 and 100 months over a period of two years; of these, 29 did not to meet the study's eligibility criteria or refused any occlusion. Information from these children who refuse all patching is not pertinent to a study of treatment by occlusion; consequently, this attrition is assumed to be non-informative. We analyze the information of 87 children; of these, 18 saw their amblyopia resolved in the refractive adaption phase and did not enter the occlusion phase of the study. The remaining 69 were prescribed occlusion for six hours a day, but received varying occlusion doses because of partial compliance. The duration of follow-up was also variable, as children were considered to have completed the study once visual acuity ceased to improve. The decision to end occlusion was made in a pragmatic fashion, after two inflexions in a plot of acuity against time or after identical acuity measurements were observed on three consecutive visits. All of the 87 children who entered one or both phases of the study and did not refuse occlusion remained in the study until visual acuity stabilized.

Visual acuity was measured on the logarithm of Minimum Angle of Resolution (logMAR) scale; improvement is indicated by a decrease in logMAR. Occlusion doses were recorded to the nearest minute by an *occlusion dose monitor* (ODM) (Fielder et al. 1994). The ODM consists of an eye patch with two small electrodes attached to its under-surface connected to a battery-powered data logger. At each visit, data from the ODM was downloaded to a PC and parents were given the opportunity to review their child's compliance. The ODM records each separate interval during which the child wears the monitor; we restrict attention to simple functions of the total dose (in minutes) and the length (in days) of the interval between clinic visits. Visual function and monitored occlusion dose were recorded at approximately two-week intervals until acuity ceased to improve.

Profile plots of individual visual acuity trajectories over successive visits to the clinician are depicted in Figure 1. These indicate that a piecewise linear model of response is a reasonable foundation for our statistical models.

3 Linear and Semiparametric Mixed Model Analysis

Let the $N = 87$ patients in the study be indexed by i and the n_i post-baseline clinic visits by j; the initial visit will be denoted visit $j = 0$. Then V^a_{ij} is the visual acuity for patient i on visit j on the day denoted t_{ij}. Similarly, let D_{ij} be the (random) occlusion dose (in hours) observed in interval j; $D_{ij} = 0$ for the baseline observation in the occlusion phase. Let A_{ij} be the child's age in months at the start of interval j. Let L_{ij}, P_i, and S_i denote the visual acuity at the start of interval, start of phase and start of study, respectively, and T_i denote the amblyopia type (anisometropic, mixed, strabismic), for patient i. Note that $L_{ij} = V_{ij-1}$. We also considered the covariates Time in Refraction, t_R, and Time in Occlusion, $t_O = \max\{0, t - t_0\}$, where t_0 represents the start of occlusion, for those children who enter occlusion. The response, Y_{ij}, is the change visual acuity between visit $j-1$ and visit j (that is, the change during interval j) for patient i: $Y_{ij} = V^a_{ij} - V^a_{ij-1}$ for $j = 1, ..., n_i$, $i = 1, 2, ..., N$.

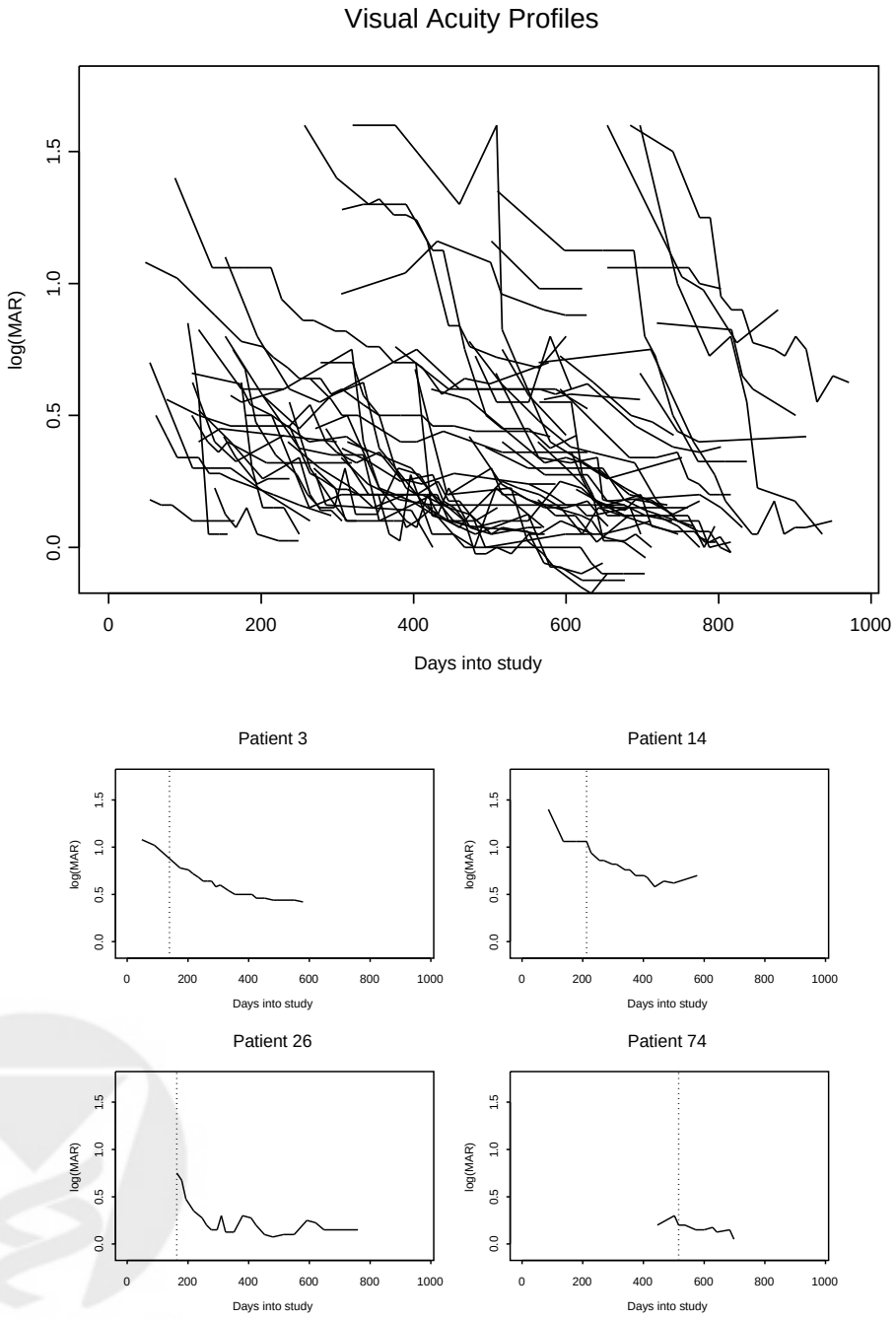

Figure 1: Profile plots for the individuals in the MOTAS study (top) and for four selected patients, with the start of occlusion indicated by the dotted line (bottom).

3.1 Linear Mixed Effects Models Analysis

We begin with the assumption that variation in visual acuity has both a fixed and random component. Specifically, we assume a linear mixed model with an individual-specific random intercept at the first interval. That is

$$Y_{ij} = X_{ij}^{\mathsf{T}}\beta + \eta_i + \epsilon_{ij}, \tag{3.1}$$

where some correlation structure for the residual errors, ϵ_{ij}, of a child is assumed and η_i and X_{ij} are presumed independent. Inference for the linear mixed model in equation (3.1) is achieved using penalized least-squares or likelihood procedures under an assumption of Gaussian residual errors. In particular, we consider mean models that include main effects of each of the aforementioned covariates as well as a small number of first-order interactions. We considered a wide range of covariance structures for the residual errors, including the general positive definite covariance and the unit correlation models; see Pinheiro & Bates (1996) for full details. On the basis of exploratory plots of residuals from a rich mean model, we focused on three models for the variance components; the model with no correlation, an autoregressive (AR(1)) correlation in interval number, and exponential decay in correlation in length (in days) between measurements. Serial correlation appears to account for relatively little of the variability of the data (Figure 2), and that autocorrelation decays to zero by four months.

Linear Mixed Model Results: The model was fit in `R` using the `nlme` library. The BIC was used to select an optimal model. The optimal model for the refraction phase was $L + P + T$, and for the occlusion phase was $D + A + L + P + D.A + D.L + A.L$; residual plots raised no concerns about the fit of the model for the mean. Time on study, t, time in refraction, t_R, and time in occlusion, t_O, added little to the fit of the model.

All models for the refraction and occlusion phases assume random intercepts at the individual level, as in equation (3.1), and for the occlusion phase, the addition of a random slopes model was also considered (see Diggle et al. (2001) for terminology). We retain the model with random intercepts and errors which are AR(1) in interval number: $\text{Corr}[Y_{ij}, Y_{ij'}] = \rho^{|j'-j|}$. Random slopes were not necessary, nor did other correlation structures improve the fit of the model. Table 1 gives parameter estimates for the terms in the final models using REML. The fit of this model yielded estimates of the residual error standard deviation and the correlation of $\hat{\sigma} = 0.0735$ and $\hat{\rho} = -0.1708$.

In the refraction phase, visual acuity measurements suggests that prior to occlusion, the vision of anisometropic children given spectacles decreases on the logMAR scale (i.e. improves) on average by 0.085 (0.023, 0.147) between each visit. Strabismic children exhibit a lesser degree of improvement while children of mixed type do not exhibit significant improvement. Children who were younger, and/or had higher logMAR at the start of occlusion and at the start of an interval all improved further for the same occlusion dose.

Note that age at start of interval, and the interaction between this variable and visual acuity at start of interval appear in the model, the interaction being highly significant. Improvement in vision **not** attributable to the effect of occlusion cannot,

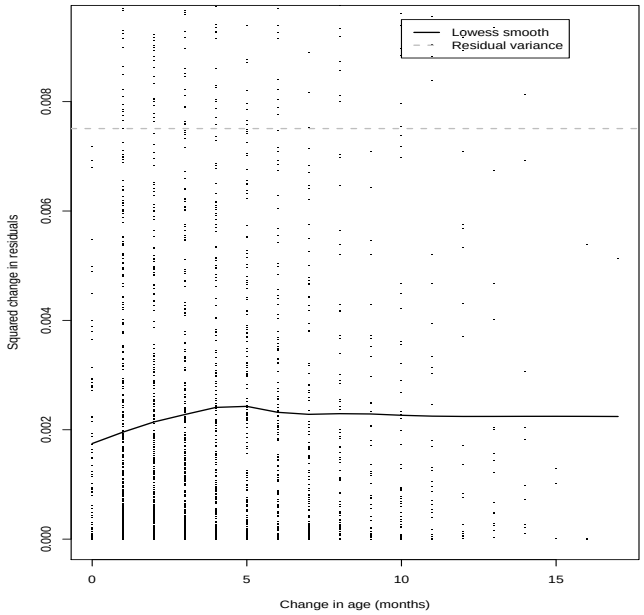

Figure 2: Variogram of change in visual acuity residuals, with individual points, a lowess smooth through these points, and the residual variance.

Table 1: Estimates and standard errors for the parameters from a random intercepts linear mixed effects model with AR correlation.

Phase	Term	Est.	s.e.	t.stat	p
Refraction	Int.	-8.509e-2	3.149e-2	-2.702	0.007
	L	-6.376e-1	4.145e-2	-15.383	0.000
	P	4.839e-1	5.405e-2	8.952	0.000
	T_M	8.313e-2	3.640e-2	2.284	0.023
	T_S	1.682e-2	3.818e-2	0.441	0.660
Occlusion	Int.	-5.728e-3	3.473e-2	-0.165	0.869
	D	-8.645e-4	3.226e-4	-2.680	0.008
	A	-5.738e-4	4.920e-4	-1.166	0.244
	L	-5.113e-1	5.557e-2	-9.237	0.000
	P	1.234e-1	2.144e-2	5.755	0.000
	$D.A$	1.339e-5	5.063e-6	2.645	0.008
	$D.L$	-9.705e-4	2.959e-4	-3.279	0.001
	$A.L$	4.912e-3	9.242e-4	5.315	0.000

by received ophthalmological wisdom, be observed. However, the observed effect is marked, and possible explanations for the presence of these terms include a training effect of repeated visual testing, or the ongoing effect of refractive adaptation.

3.2 Semiparametric Additive Linear Mixed Models Analysis

We now fit a semiparametric additive linear mixed (SPALM) model to attempt to capture potential non-linearity in the covariate effects. We focus on the potential non-linearity in the dose covariate. The model we fit is of the form

$$Y_{ij} = X_{ij}^{\mathsf{T}}\beta + \sum_{k=1}^{K} f_k\left(X_{ij}\right) + \epsilon_{ij}, \tag{3.2}$$

where the f_k, $k = 1, ..., K$, are basis functions of the covariates modelled semiparametrically; see, for example, Ruppert et al. (2003). We use the linear mixed model formulation,

$$Y = X\beta + Zu + \epsilon \tag{3.3}$$

where

$$E\begin{bmatrix} u \\ \epsilon \end{bmatrix} = \mathbf{0} \qquad Var[\theta] = \begin{pmatrix} G & 0 \\ 0 & R \end{pmatrix}$$

and the matrix X contains the fixed effects predictors, Z is the (basis function) design matrix in the semiparametric representation of the function of $f_1, \ldots, f_K$.

3.2.1 The Semiparametric Design: The Truncated Spline Basis

In the semiparametric additive model, the matrix Z contains the truncated spline basis terms, with columns corresponding to knots $\kappa_{k1}, \ldots, \kappa_{kM}$ for $k = 1, \ldots, K$. Typically, the random effects coefficients for function k are assigned a common Gaussian distribution so that the matrix G is diagonal; however this is not necessary.

We use truncated spline basis functions to construct the semiparametric specification. Generically, for scalar x varying across a data-dependent range, we specify fixed (but data-dependent) knot positions $\kappa_{k1}, ..., \kappa_{kM}$, and model function f_k as

$$f_k(x) = \sum_{m=1}^{M} u_{km}(x - \kappa_{km})_+^q \tag{3.4}$$

where $u_{k1}, ..., u_{kM}$ are (random effects) coefficients for function k, and the basis function component $(x - \kappa_{km})_+^q = \max\{0, (x - \kappa_{km})^q\}$, so that a typical row of Z (an $N \times KM$ matrix) in equation (3.3) takes the form

$$\left[(x - \kappa_{11})_+^q \;\; (x - \kappa_{1M})_+^q \;\; \ldots \;\; (x - \kappa_{KM})_+^q\right].$$

We take $q = 1$ and use 10 knots at the covariate quantiles, with a knot also placed at zero, giving $M = 11$. For convenience, we transform (by translation) the covariates so

that they are non-negative. The function f_k in equation (3.4) has vector of coefficients $\mathbf{u}_k$ of length M, which are assumed to be independent random effects with common variance σ_k^2, $k = 1 \ldots, K$. We also assume independence between $\mathbf{u}_1, \ldots, \mathbf{u}_K$, and thus retain a block diagonal structure for the entire random effect matrix.

The semiparametric model can be fit using `lme` in `R` for some choices of the residual error covariance R, and more generally using numerical procedures for general covariance specifications.

3.2.2 Inference for the Semiparametric Linear Mixed Model

Suppose, in conjunction with equation (3.3), $u \sim N(0, G)$ and $\epsilon \sim N(0, R)$ with u and ϵ independent. This model can be interpreted as $Y|\beta, u \sim N(X\beta + Zu, R)$ and $u \sim N(0, G)$, yielding the marginal model $Y|\beta \sim N(X\beta, ZGZ^\mathsf{T} + R)$ (on integrating out u). Let $V = ZGZ^\mathsf{T} + R$. Then estimates can be found using the penalized maximum likelihood or the restricted maximum likelihood (REML), obtained by first integrating out β from the likelihood $Y \sim N(X\beta, V)$.

This model has a (model-based) Bayesian interpretation where the unknown parameters β and u are assigned independent prior distributions, with β having an improper uniform prior on $\mathbb{R}^p$, where $p = \text{ncol}(X)$, and u assigned the Gaussian prior described above. In a fully Bayesian approach, G is set as a fixed hyperparameter, or assigned an informative prior distribution. Here, an empirical Bayes approach is used where G and the parameters in R are estimated using ML/REML. In section 4.3, the fully Bayesian approach is described, and the results of using a diffuse and an informative prior specification for G are compared.

3.2.3 Semiparametric Mixed Model Results for MOTAS

Three semiparametric components were used when considering MOTAS: a component for dose, D, a component for the interaction between D and (translated) Age at Interval, $A - 36$, and a component for the interaction between D and visual acuity at start of interval, $L + 0.175$. We used 10 fixed knots, with positions determined by covariate quantiles, but the results were robust to specifications with up to 50 knots. We retained the covariates suggested by the linear model and examined two covariance structures: an AR(1) model in interval number and an exponential decay-in-time model. There was effectively no difference in the resulting estimates of the semiparametric components.

4 Bayesian Approaches

The results of the likelihood-based analysis above have identified key predictors in the model for changes in visual acuity and quantified the influence of occlusion does on improvement in vision. We now implement a Bayesian analysis. In this analysis, the advantages of the Bayesian framework are twofold. First, realistic prior information can be introduced into the model, and as we demonstrate in section 4.2, this can produce

different inferences compared to the likelihood/empirical Bayes approach that is often used in mixed model settings. Secondly, the Bayesian framework facilitates a prediction study that can predict the improvement in visual acuity of hypothetical future children, thus allowing a comparison of different dosing patterns in terms of ultimate outcome. In this section, we perform inference using Markov chain Monte Carlo (MCMC), as the joint posterior distribution for the parameters in the residual covariance model is not available analytically, and as the prediction of future responses can be achieved in a very straightforward fashion.

4.1 Bayesian Posterior Calculation for Repeated Measures Data

Consider a linear model formulation using the notation introduced earlier, that is where $Y \sim N(X\beta, R)$, where R is a block diagonal error covariance matrix $R = \text{diag}(R_1, \ldots, R_N)$. For example, the components of R can be specified via the exponential decay or AR(1) autocorrelation functions. We focus on the former for illustration.

To complete the specification, we use a diffuse (improper uniform) prior specification for β and an improper Jeffreys-type prior on the positive parameters in the exponential autocovariance function; i.e., take $p(\beta, \lambda, \zeta, \nu) = (\lambda\zeta\nu)^{-1}$ and derive the posterior distribution. The joint posterior factorizes into $p(\beta, \lambda, \zeta, \nu|y) = p(\lambda, \zeta, \nu|y)\, p(\beta|y, \lambda, \zeta, \nu)$ where

$$p(\lambda, \zeta, \nu|y) \propto \frac{|M_3|^{-1/2}}{\prod_{i=1}^{N} |R_i|^{1/2}} \exp\left\{-\frac{1}{2}\left[M_1 - M_2^{\mathsf{T}} M_3^{-1} M_2\right]\right\} \frac{1}{\lambda\zeta\nu} \tag{4.1}$$

with

$$M_1 = \sum_{i=1}^{N} y_i^{\mathsf{T}} R_i^{-1} y_i \qquad M_2 = \sum_{i=1}^{N} X_i^{\mathsf{T}} R_i^{-1} y_i \qquad M_3 = \sum_{i=1}^{N} X_i^{\mathsf{T}} R_i^{-1} X_i$$

and $\beta|y, \lambda, \zeta, \nu \sim N_p(M_3^{-1} M_2, M_3)$. The posterior distribution in equation (4.1) is not available analytically, but inference may be carried out using MCMC on the three parameter joint posterior. We use a Metropolis update on a sweep of the conditionals, reparameterized onto the log scale, and jointly on the block of the three parameters. The conditional posterior for β given (λ, ζ, ν) can be sampled directly.

To extend the mixed model, a further level can be added to the hierarchy in some cases, although this is not sensible for the semiparametric components. For example, fitting a random effects model similar to that in equation (3.1) is straightforward using a Gibbs sampler. Denoting by $\eta = (\eta_1, ..., \eta_N)$ the vector of child-specific random effects (intercepts), the posterior of interest becomes the joint distribution $p\left(\theta, \lambda, \zeta, \nu, \eta, \sigma_\eta^2|y\right)$, where σ_η^2 is the (unknown) random effect error variance, which is included in the MCMC cycle; we might assign an Inverse Gamma prior with parameters 2.5 and 0.25. Then, conditional on η, the posterior for $(\theta, \lambda, \zeta, \nu)$ is updated as in the fixed effect only model, with datum y_{ij} replaced by $y_{ij} - \eta_i$. Conditional on $(\theta, \lambda, \zeta, \nu)$ and σ_η^2, the posterior for η_i is univariate Gaussian. Finally, conditional on all other parameters, the posterior for σ_η^2 is Inverse Gamma.

A fully Bayesian analysis is also possible for the SPALM model. The posterior distribution of the covariance parameters is identical to that in (4.1), but with

$$M_1 = \sum_{i=1}^{N} y_i^{\mathsf{T}} R_i^{-1} y_i \qquad M_2 = \sum_{i=1}^{N} C_i^{\mathsf{T}} R_i^{-1} y_i \qquad M_3 = \sum_{i=1}^{N} C_i^{\mathsf{T}} R_i^{-1} C_i = C^{\mathsf{T}} R^{-1} C.$$

where $R \equiv R(\lambda, \zeta, \nu)$, and the posterior distribution for $\theta = [\beta\, u]^{\mathsf{T}}$ is multivariate Normal (dimension $p + MK$) with mean and variance

$$\mu = (C^{\mathsf{T}} R^{-1} C + B)^{-1} C^{\mathsf{T}} R^{-1} y \qquad \Sigma = (C^{\mathsf{T}} R^{-1} C + B)^{-1}$$

respectively. In addition, rather than using an improper Uniform prior for β, an informative prior can also be specified. In this case, the calculation proceeds as before, with the marginal posterior for (λ, ζ, ν) sampled using Metropolis-Hastings, and the conditional posterior for β (or (β, u)) is multivariate Normal.

4.2 An Informative Prior Specification for the SPALM model

In the SPALM model, the specification of random effects prior matrix G can be engineered to match prior opinion about the nature (that is, smoothness or curvature) of the modelled function. Consider a single semiparametric component $Y = Zu$, where $u \sim N(0, G)$, so that $Y \sim N(0, ZGZ^{\mathsf{T}})$, and we require *a priori* that $Y \sim N(0, V_0)$. Then

$$V_0 = ZGZ^{\mathsf{T}} \Longrightarrow G = (Z^{\mathsf{T}} Z)^{-1} Z^{\mathsf{T}} V_0 Z (Z^{\mathsf{T}} Z)^{-1}$$

and G should adopt a data-dependent form, giving a prior that is similar in structure to the "g-prior" (Zellner 1983). Conditional on knot points $\kappa_1, \ldots, \kappa_M$, we can specify any required prior autocovariance structure. For example, we could specify a prior with high autocorrelation, thereby encouraging smoothness in the semiparametric component. In our analysis, we specify V_0 to be a diagonal matrix such that the prior variation in the semiparametric function is concentrated on the range ±2. This results in a required prior variance for the dose component to be specified by

$$G^{-1} = 10^{-3} \begin{pmatrix} 14 & 13 & 12 & 11 & 11 & 10 & 9 & 8 & 6 & 5 & 2 \\ 13 & 12 & 11 & 11 & 10 & 9 & 8 & 7 & 6 & 4 & 2 \\ 12 & 11 & 11 & 10 & 9 & 9 & 8 & 7 & 6 & 4 & 2 \\ 11 & 11 & 10 & 10 & 9 & 8 & 8 & 7 & 6 & 4 & 2 \\ 11 & 10 & 9 & 9 & 9 & 8 & 7 & 6 & 5 & 4 & 2 \\ 10 & 9 & 9 & 8 & 8 & 7 & 7 & 6 & 5 & 4 & 1 \\ 9 & 8 & 8 & 8 & 7 & 7 & 6 & 5 & 5 & 3 & 1 \\ 8 & 7 & 7 & 7 & 6 & 6 & 5 & 5 & 4 & 3 & 1 \\ 6 & 6 & 6 & 6 & 5 & 5 & 5 & 4 & 4 & 3 & 1 \\ 5 & 4 & 4 & 4 & 4 & 4 & 3 & 3 & 3 & 2 & 1 \\ 2 & 2 & 2 & 2 & 2 & 1 & 1 & 1 & 1 & 1 & 1 \end{pmatrix}$$

This is a much more precise specification than the noninformative prior we selected. However, it is much less precise than the prior deduced using the empirical Bayes procedure based on ML/REML estimation of the components of G; the parameters $(\widehat{\sigma}_1, \widehat{\sigma}_2, \widehat{\sigma}_3)$ that define the diagonal components of G are (7.589e-08, 2.314e-06, 7.430e-04). As the prior is design-dependent, this specification is only strictly appropriate for the fixed-knot case, and will change in a straightforward fashion when the knot positions change.

The results from an analysis using this informative prior are depicted in Figure 3, where results for the non-informative and empirical Bayes priors are also shown for comparison. Overall, results are broadly similar when the two fully Bayesian procedures are used, but the magnitude of the various dose effects are estimated to be much larger than those estimated using the empirical Bayes procedures. We note that the deduced empirical Bayes prior has **extremely** (we argue unreasonably) high precision for several of the components, and prefer the informative specification.

4.3 Bayesian Semiparametric Modelling Analysis and Results

A semiparametric model similar to the one described in section 3.2 can be fitted in the Bayesian framework. Most importantly, the model is fundamentally unchanged from that described in section 3.2; the principal difference in the model specification is the prior used for the random effects coefficients that are used to construct matrix G. In an initial analysis, a non-informative prior specification is used, where the diagonal elements of G are set to be 10^{10}. The results for this prior specification, the empirical Bayes specification implied by the classical analysis, and the analysis based on the informative prior specification of section 4.2 are depicted in Figure 3. Qualitatively, the differences between the prior specifications, and the interaction between dose and the other predictors are evident. It is clear, for example, that the empirical Bayes prior appears to shrink the magnitude of effect more towards zero relative to the informative prior.

4.4 Relaxing the assumption of fixed knot positions

As a final check of the reported effect magnitude, we relax the assumption that knot positions in the truncated basis spline SPALM analysis of previous sections are fixed. We treat the knot positions as further unknown parameters to be estimated, and assign a prior distribution that states that the knot positions are the order statistics from a Uniform sample on the range of the variable concerned. Incorporating this into the MCMC scheme is straightforward; we augment the algorithm described in section 4.1 with a further Metropolis-Hastings step that selects a knot at random, samples a candidate new knot position from its conditional prior distribution, and performs the usual accept/reject step.

The results from the MCMC analysis comparing fixed and movable knots (using the informative prior from 4.2 and an AR(1) residual error structure) are nearly identical to those using fixed knots, however 95% pointwise credible intervals are slightly wider for

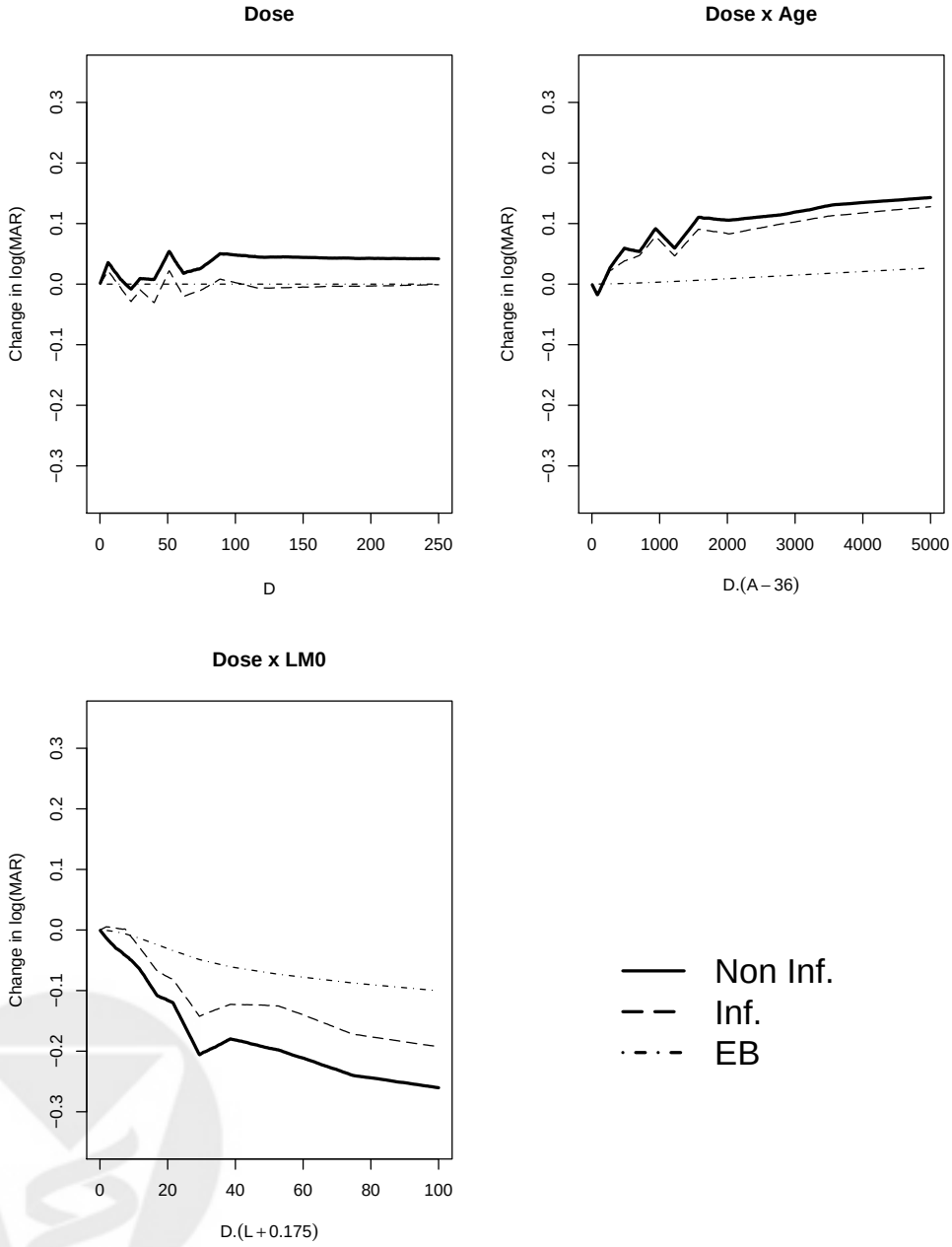

Figure 3: Estimated semiparametric functions for dose and interactions. Bayesian median estimates under the three prior structures: non-informative, informative and empirical Bayes for the SPALM analysis, assuming an AR(1) residual errors structure for the interval-level data.

the movable knots analysis. That is, allowing movable knots provides a more honest reflection of the uncertainty in the model.

4.5 Bayesian Prediction: The Impact of Different Dosing Strategies

The Bayesian analysis is useful as it readily facilitates a study of the impact of different dosing strategies. Once a large sample from the posterior distribution has been obtained, a sample from the posterior predictive distribution can be obtained for fixed values of the covariates by sampling from the likelihood part of the model, given on each posterior sample in turn.

We examine the impact of different dosing strategies on two hypothetical children, one aged 42 months at the start of study, the other aged 60 months. Each child will enter the occlusion phase of the study with a visual acuity of 0.8 logMAR, and be diagnosed as of anisometropic type. They could receive 0, 2, 6, and 9 hours of occlusion per day, over a 12 month period, when the study will end.

The impact of the different dosing strategies for the two children, respectively, is depicted in the four panels of Figures 4 and 5, where boxplots of samples from the posterior predictive profiles are plotted; the posterior samples were generated in the Bayesian linear mixed model analysis of the interval-level data in section 4.1. The difference between the response profiles under different strategies is evident (the expected profile under a zero dose strategy is included for comparison). Also, comparing the results for the two children, the impact of age is striking, with the younger child improving to a greater degree than the older child under each strategy. Note that even under a zero dose, there is gradual improvement through the occlusion phase, and this can be attributed to ongoing time on study/time in occlusion, both of which are apparently influential predictors in the model. This analysis is illustrative; the impact for children with varying characteristics can readily be studied in the same way.

5 Analysis of the Absolute-level Data

Had it been scientifically of interest to do so, the data could have analyzed longitudinally by considering the absolute-level data. We briefly describe such an analysis here. For such an analysis, we take the response to be visual acuity, V^a_{ij}, and denote the total cumulative dose by the end of interval j for child i by D^c_{ij}, so that $D^c_{ij} = \sum_{l=0}^{j} D_{il}$.

5.1 A SPALM Analysis of the Absolute-level Data

As in the interval-level analysis, we performed preliminary model-selection using a standard Gaussian linear model to the set of 684 observations, without any by-individual grouping. The BIC suggested that the model for the refraction phase was should include $t_R + T + S$, and for the occlusion phase was $t_O + S + A + D^c + D^c.A + D^c.t_O + t_O.S$. The estimated coefficients in the model confirm conventional ophthalmological wisdom; for cumulative dose, D^c, the interaction between dose and age at interval, $D^c.A$, and the interaction between dose and time in occlusion, $D^c.t_O$, the estimates

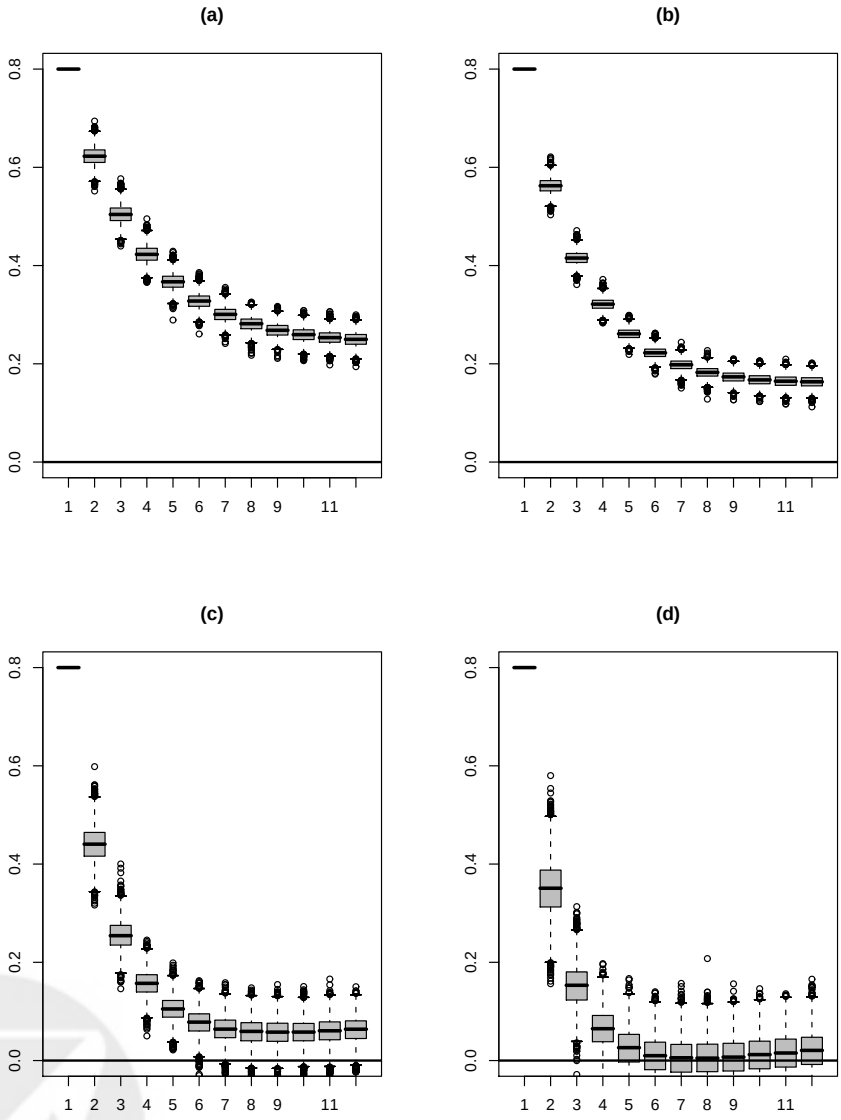

Figure 4: Predicted response for different occlusion dosing strategies from the Bayes analysis in a linear model for interval-level data. Boxplots of 5000 samples of the posterior predictive profiles for anisometropic children aged 42 months, with initial visual acuity 0.8. Plots are for 0, 2, 6, and 9 hours of occlusion per day, respectively, in (a), (b), (c), and (d).

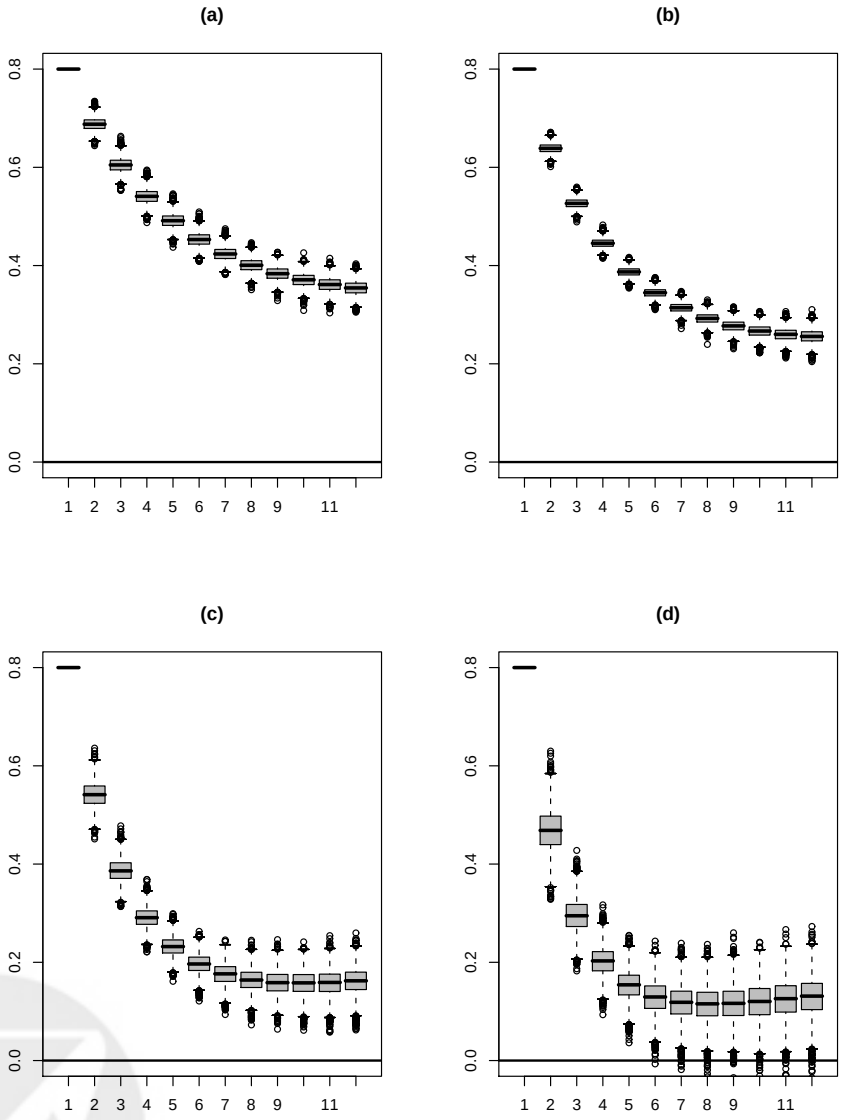

Figure 5: Predicted response for different occlusion dosing strategies from the Bayes analysis in a linear model for interval-level data. Boxplots of 5000 samples of the posterior predictive profiles for anisometropic children aged 60 months, with initial visual acuity 0.8. Plots are for 0, 2, 6, and 9 hours of occlusion per day, respectively, in (a), (b), (c), and (d).

(standard errors) are -9.975e-4 (1.756e-4), 1.121e-5 (2.648e-6) and 1.517e-6 (3.351e-7) respectively. Thus it appears that visual acuity improves with increasing cumulative dose, although this improvement is moderated by the age of the child and the time spent in occlusion.

In principal, many parts of the models of earlier sections can be replaced by semiparametric components. In this analysis of the absolute-level data, we fit $K = 3$ semiparametric components for the terms involving dose in the final Gaussian model selected, namely cumulative dose, D^c, and the interactions between D^c and age at interval, A, and D^c and time in occlusion t_O. We transform A by subtracting the minimum observed age, 36 months.

Figure 6 clearly shows the effect of cumulative dose, and the interaction between cumulative dose and age at interval, and the non-linear nature of these functions. Note that the empirical Bayes prior produces markedly different posterior inference from the non-informative and informative priors constructed similarly to those described in section 4.3.

5.2 Bayesian SPALM for Absolute-Level Data

A semiparametric model similar to the one described in the previous subsection section can be fitted in the Bayesian framework. Most importantly, the model is fundamentally unchanged from that described in section 4.1 and equation (4.1). The principal difference in the model specification is the prior used for the random effects coefficients that are used to construct matrix G. In an initial analysis, a non-informative prior specification is used, where the diagonal elements of G are set to be 10^{10}. The results for this prior specification, the empirical Bayes specification implied by the classical analysis, and the analysis based on an informative prior specification are depicted in Figure 6. For brevity, we have omitted details of the posterior summaries and focus only on the semiparametric components.

6 Discussion

The MOTAS study has facilitated, for the first time, the efficacy of occlusion therapy in the treatment of amblyopia to be quantified. In this paper, we quantified the improvement in visual acuity of amblyopic children in refractive adaption, as well as the dose-response relationship between improvement in vision and occlusion. We studied the interval-level data. Key determinants of the change in visual acuity amongst the measured variables were identified. It was evident that occlusion dose was an influential factor and, using a semiparametric mixed effect model, we were able to identify and quantify the marginal dose-response impact of dose on visual acuity. The impact of different levels of occlusion dose per interval was studied.

Our analysis demonstrates that the relationship between dosing and age is complex. However the pattern of results from both the linear and the semi-parametric analyses of MOTAS are in line with ophthalmological opinion and practice: higher doses give greater improvement in vision and the impact is greater in children with inferior vision,

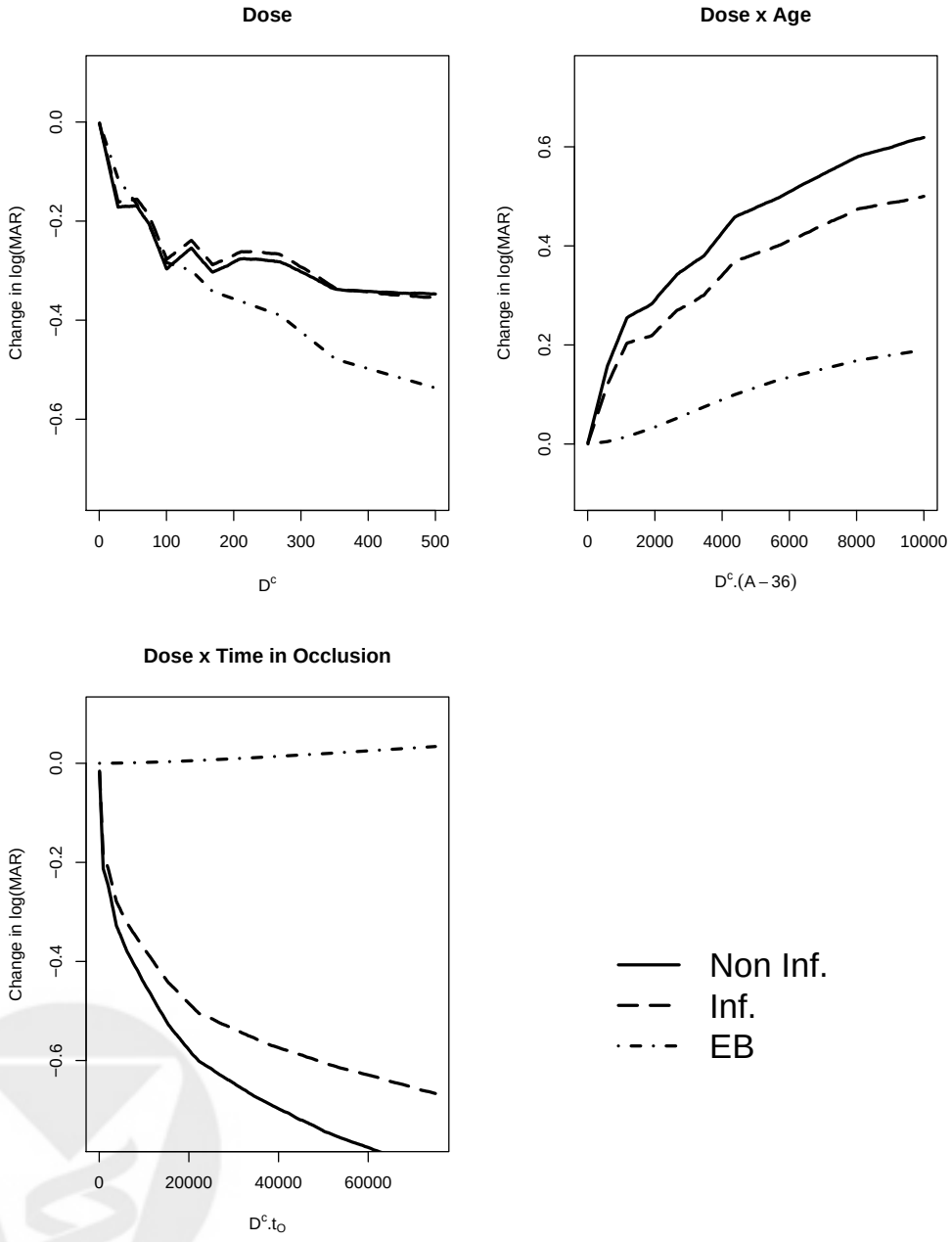

Figure 6: Estimated semiparametric functions for cumulative dose and interactions. Estimates from SPALM analyses of the absolute-level data: for cumulative dose D^c, the interaction $D^c.A - 36$, and for the interaction $D^c \cdot t_O$. Estimates are from the fully Bayesian model using non-informative, informative and empirical Bayes priors on the random effects.

but the effect is moderated by increasing age of the child. The Bayesian predictive analysis makes clear the importance of treating occlusion early, as older children require far greater doses of occlusion to improve or resolve their amblyopia. MOTAS is just one example where the relationships between dosing and covariates are complex and not well-approximated with linear forms.

When looking for a dose-response effect, the associations between outcome and individual characteristics or treatment and these characteristics are not of interest in themselves. To estimate the dose-response relationship with confidence, modelling potentially confounding relationships flexibly is key. Semiparametric additive linear mixed (SPALM) models are of practical value: they are tractable and flexible, particularly when implemented in a Bayesian framework. The splines used in SPALM models offer a much higher degree of adaptability to the data than linear models, and perhaps provide better control of confounding effects. The Bayesian implementation of the SPALM model was readily implementable and allowed for cohesive propagation of the uncertainty in the model.

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