

# Discussion of “Multivariate Bayesian Logistic Regression for Analysis of Clinical Trial Safety Issues” by W. DuMouchel

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We would like to comment on this article by William DuMouchel, as it gives an interesting application of logistic regression to clinical safety data. Not to underscore the scope of the multivariate Bayesian logistic regression (MBLR) model, but the use of numerical integration is arguably its most important feature. Avoiding Markov chain Monte Carlo (MCMC) sampling techniques for other data-mining tools, such as the Multiple-item Gamma Poisson Shrinker (DuMouchel, 1999), has proven successful for Dr. DuMouchel in their acceptance among nonstatisticians. With MBLR this should not be an exception.

As most statisticians lack the clinical insight required to specify the appropriate MBLR model inputs, it makes MBLR an ideal tool for use by the clinicians. However, targeted users may not appreciate some subtleties of MBLR, which we present below. We also present findings from our empirical evaluation of the MBLR algorithm. This commentary provides some perspective that we have gained through multiple interactions with Dr. DuMouchel and from our reviews of different versions of MBLR formulation at FDA since 2009.

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## 1. MBLR AND META-ANALYSIS

In order to fully appreciate the MBLR methodology, one has to contrast it with a more traditional meta-analytical formulation when data from multiple trials are investigated. Dr. DuMouchel is correct in pointing out that the MBLR methodology is in the spirit of a full-data meta-analysis and does not consider it a meta-analytic model. The current MBLR model formulation does not render the flexibility of separating out patient- and trial-level variations in the model. Consequently, MBLR is very different from a multi-level/meta-analysis model that would consist of a patient-level model and a trial-level model, each with independent sources of variation. This makes MBLR effectively a patient-level model; the inclusion of trial-level variables (e.g., study identifiers) into equation (2) results in the variance components in equations (3)–(6) being influenced by both patient and trial heterogeneity.

This distinction between the MBLR and its meta-analytic formulation is critically important. The main advantage of a meta-analytic formulation is that it preserves the trial-specific randomized comparison between the treatment and control groups, thereby avoiding confounded estimates. With the MBLR formulation this is not necessarily the case, as Dr. DuMouchel aptly notes for the Pollakiuria example that the trial-specific estimates do not preserve the between-trial differences. Additionally, shrinkage estimates used to identify vulnerable patient subgroups depend on factors which are typically considered unrelated of patient characteristics.

The practical concern of applying a methodology that does not ensure the randomized comparison is preserved is that it may lead to a possible signal being missed or hidden. A recent high-profile example of

this concern was the meta-analysis of the diabetes drug rosiglitazone (Rucker and Schumacher, 2008). When safety data collected from the randomized controlled trials were pooled by trial arm, it resulted in Simpson’s paradox.

It is, therefore, important to understand the subtle distinction of how MBLR differs from the more traditional meta-analytic models, and the potential consequences that may arise from the use of MBLR. Unfortunately, the MBLR tool/program in its current capacity does not have the capability to evaluate the potential implications discussed in the aforementioned paragraphs. This necessitates the use of other statistical methodologies to fully evaluate the results from MBLR software, which, paradoxically, is the situation that Dr. DuMouchel initially set out to avoid. That said, it would be a nice extension if the MBLR methodology was expanded, incorporating the suggestions outlined above, thereby increasing the general utility of the tool. Next, we present an attempt toward this extension.

**2. META-ANALYTIC MBLR FORMULATION**

We present a modified MBLR model motivated from a meta-analytic perspective, which we shall, henceforth, refer to as meta-analytic MBLR (MA-MBLR). Using the notation from the paper, let the  $J$  covariates correspond only to patient-level characteristics and assume that there are a total of  $L$  trials. Then, the MA-MBLR patient-level model for trial  $l, l = 1, \dots, L$ , and issue  $k$  is given by

$$\text{logit}(p_{ikl}) = \alpha_{0kl} + \sum_g X_{igl} \alpha_{gk} + T_{il} \left( \beta_{0kl} + \sum_g X_{igl} \beta_{gk} \right).$$

Unlike the MBLR formulation, the MA-MBLR would assume the trial-specific intercept  $\alpha_{0kl}$  and treatment effect  $\beta_{0kl}$  have distinct variance components, thereby separating patient and trial variability. This can be formally achieved by assigning the trial-specific intercept and treatment effect of the following hierarchical prior:  $\alpha_{0kl} \sim N(\alpha_{0k}, \sigma_{A,k}^2)$  and  $\beta_{0kl} \sim N(\beta_{0k}, \sigma_{0,k}^2)$ , for  $k = 1, \dots, K$  and  $l = 1, \dots, L$ . The MA-MBLR model is fully specified by equations (3)–(6), as well as by the hyperpriors for the model’s hyperparameters, and has the  $(2K + 4)$  standard deviations,  $(\sigma_{A,1}, \dots, \sigma_{A,K}, \sigma_{0,1}, \dots, \sigma_{0,K}, \sigma_A, \sigma_0, \sigma_B, \tau)$ , that have independent uniform distribution on the interval 0 to  $d$ , as specified in the paper.

We investigated for the data-example in the paper whether the MBLR and MA-MBLR formulations make a substantive impact on the risk assessment for the five most frequent issues. Both the MBLR and MA-MBLR models were fit using OpenBUGS (Lunn et al., 2009), and thus are fully Bayesian MBLR and MA-MBLR. The fully Bayesian models differed from the MBLR model described in the paper in three ways, namely, (i) it assumes diffused normal priors for the location parameters rather than uniform noninformative priors, (ii) it constrains the hyperpriors  $A_g$  such that the  $g_j$ th level of covariate  $j$  is equal to the negative sum of the remaining  $g_j - 1$  levels, and (iii) the support of the prior for the standard deviation  $d$  was increased to 3.

Figure 1 shows the relationship for some of the estimated parameters. The issue specific treatment effect  $\beta_{0k}$  did not differ too much between models. However, the interaction term between treatment and the patient-level covariates tended to be closer to the null value for MA-MBLR, while the MA-MBLR trial-specific treatment effect tended to be further away from the null value than MBLR. Although there were no surprising differences noted between the MBLR and MA-MBLR coefficients for this example, the two different formulations can possibly result in different substantive conclusions.

**3. BORROWING INFORMATION ACROSS ISSUES**

It is important to note that MBLR borrows information across issues by positing a hierarchical distribution to parameters from parallel logistic regression models, and *does not* model the joint distribution of the endpoints. An example of the latter approach is given by Bayesian multivariate logistic regression (O’Brien and Dunson, 2004). More importantly, there needs to be recognition among its users that an analysis that borrows information across issues is not inherently better than the one that does not.

To illustrate a possible peril of borrowing information across issues, suppose the issues selected are medically related, but they vary in their severity; in particular, assume there is one severe issue that occurs infrequently and the remaining issues are less severe but occur more frequently. Because the amount of information borrowed across issues from MBLR is related to the precision of the estimate (which is a function of the issue frequency), the effect for the less frequent issues would be sensitive to the effects for the more frequent issues. It is important that users of the tool are mindful of such considerations.

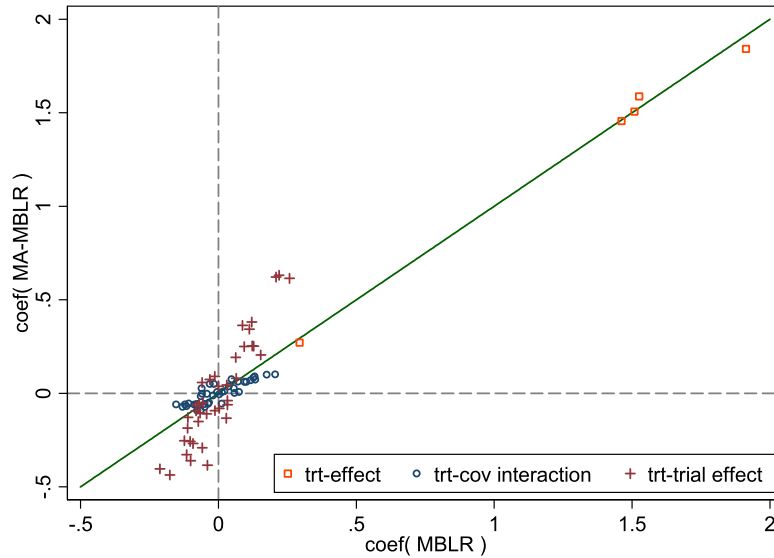


FIG. 1. Relationship between MA-MBLR and MBLR for selected model parameters.

#### 4. MBLR ESTIMATION ALGORITHM

As stated previously, we believe the advantage of the MBLR methodology is in obtaining posterior inferences that do not rely on computationally time-consuming estimation methods (such as MCMC methods). However, the timeliness of the analysis has to be balanced by the well-known limitations of the Laplace approximation of the integral of the posterior density (Carlin and Louis, 2009), which are applicable to MBLR.

As part of the software review at FDA, we evaluated the adequacy of MBLR’s estimation algorithm by contrasting results obtained from the fully Bayesian

MBLR using OpenBUGS; the comparison was based on the data described in the paper. The fully Bayesian MBLR differed from the MBLR by points (i) and (ii) listed above. The two estimation approaches yielded similar estimates for the variance components  $\varphi = (\sigma_A, \sigma_0, \sigma_B, \tau)$  and the parameter estimates had almost perfect correlation ( $\rho = 0.9998$ ). However, the relationship based on  $z$ -scores (=estimate/standard error), presented in Figure 2, suggests that MBLR has smaller standard errors than the full Bayesian analysis. This observation is also supported by the simulation results, where MBLR tended to have a type-I error rate that slightly exceeded the nominal 10% level.

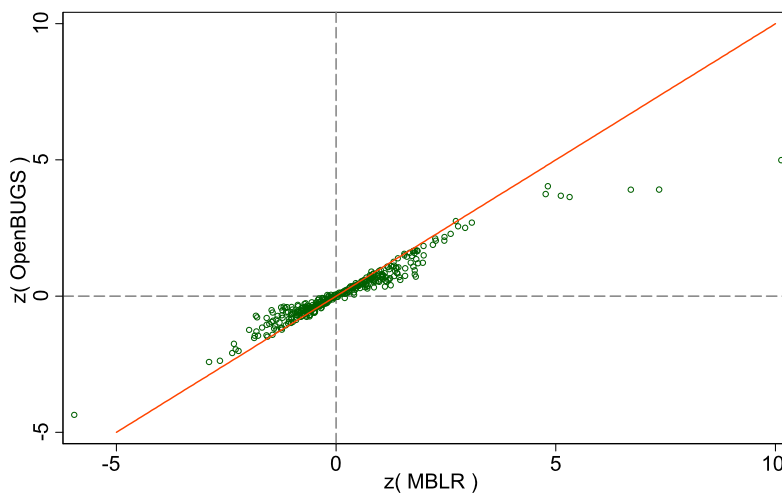


FIG. 2. Relationship of  $z$ -scores from fully Bayesian model fit using OpenBUGS compared to MBLR.

## 5. CONCLUSION

The MBLR model will have a profound impact as it is rolled-out being used for clinical safety data analysis. However, in order to realize MBLR's potential strengths and pitfalls, it will require collaboration between its different user-constituents, those being statisticians and subject-matter experts.

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