

Order-Constrained Reference Priors with Implications for Analysis of Variance/Covariance Models

ABSTRACT

Under the framework provided by Berger and Bernardo (1992), we proposed theorems of deriving reference priors for Analysis of Variance (ANOVA) and Analysis of Covariance models (ANCOVA) with a categorical variable under common ordering constraints. The reference priors were further investigated by simulation studies, with comparison to Jeffreys' prior and Least Squares Estimation. Following that, we analyzed two data sets: diabetes data in which the relationship between the type 2 diabetes risk (through Hemoglobin A1c) and different smoking levels is studied and the rats data where the effect of d-amphetamine sulfate on the behavior of rats was discussed. In both simulation studies and real data set modeling, the reference priors incorporating the internal order information showed good performances and were suggested to use as default priors.

Keywords: Reference priors, ANOVA/ANCOVA models, Ordering constraint.

1. INTRODUCTION

The prior distribution plays a central role in Bayesian analysis and statisticians spend a considerable amount of time looking for *a priori* that suits their needs (subjective, objective, or other). In real data analysis, a common situation is that the data analyst has some known *a priori* information about the parameters. For example, in many applications inequality constraints among parameters θ_i , $i = 1, 2, \dots, k$, may be adopted. Some common ordering restrictions of interest are:

Simple order

$$\theta_1 < \theta_2 < \dots < \theta_k$$

Simple tree order

$$\theta_1 < \theta_i, \quad i = 2, \dots, k$$

Umbrella order(with peak at i)

$$\theta_1 < \theta_2 < \dots < \theta_i > \theta_{i+1} \dots > \theta_k$$

One example, explored by Morrisette and McDermott (2013), concerns patient outcomes and drug dosages. It may be known that the effect of the placebo is lower than any effects corresponding to dosage amounts of a drug (simple tree order). Another reasonable assumption is that higher dosages correspond to a larger effect (simple order). Incorporating this information into a prior distribution is extremely attractive as it can produce better inferences for the parameters, especially when the sample size is small and variability of the data is large.

When posed with this information, the statistician must somehow incorporate it into a functional form of a prior. One option is to pick a subjective prior (perhaps conjugate to ease the derivation) and simply add the ordering restrictions. However, unless care is taken in the subjective prior elicitation that resulting prior may be much more influential than originally envisioned. A similar problem can occur when the constraints are naively applied to a standard non-informative prior. In this work we utilize the reference prior framework of Berger and Bernardo (1992) to construct reference priors conditional on these orderings. The derivation of the reference priors involves the typical sequential maximization of the Kullback-Leibler divergence between the prior and the posterior, which utilizes an iterative algorithm and requires model parameters to be grouped and ordered by inferential importance. A reference prior is then derived for the given likelihood, conditional on the specified grouping and ordering.

Under the constraints in (1), (2) and (3), we derived the general forms of the reference priors for any ordering and grouping. This result can be used whenever the likelihood is regular and there are additional conditions on the Fisher information matrix. With those reference priors, the resulting models are a compromise between using the subjective information and letting the data drive the inferences.

The rest of the paper is organized as follows. In Section 2, we derive and evaluate the performance of reference priors in a simulation study, with comparisons to Jeffreys' prior and Least Squares Estimation. In Section 3, with our reference priors, we fit a Bayesian ANCOVA model for the diabetes data and an ANOVA model for the rats data. In Section 4, we provide the final conclusions.

2. REFERENCE PRIORS SUBJECT TO ORDER RESTRICTIONS

2.1 Prior Derivation

Let us assume we have a model $Y_{ij} = \theta_i + \varepsilon_{ij}$ with $\varepsilon_{ij} \stackrel{iid}{\sim} N(0, 1)$ for $i = 1, 2, \dots, k$ and $j = 1, \dots, n_i$. Let $\boldsymbol{\theta} = \{\theta_1, \theta_2, \dots, \theta_k\}$ with $\boldsymbol{\theta} \in \Theta$ and the θ 's follow a certain order. Setting the variance equal to 1 does not lose generality for this problem.

To derive reference priors for this model, we rely on the sequential algorithm of Berger and Bernardo (1992). Since Θ is noncompact, a compact subset Θ^l is

needed, where l is any real number that denotes the boundary of the compact subset. The elements of $\boldsymbol{\theta}$ are first partitioned into m groups and ordered by relative inferential importance, which gives $\boldsymbol{\theta} = (\boldsymbol{\theta}_{(1)}, \boldsymbol{\theta}_{(2)}, \dots, \boldsymbol{\theta}_{(m)})$. Suppose that group j contains m_j elements, that is, $\boldsymbol{\theta}_{(j)} = (\theta_{j_1}, \theta_{j_2}, \dots, \theta_{j_{m_j}})$. Actually, the user is totally in control of the specific ordering and grouping, which may have a noticeable influence on the resulting prior distribution.

Paralleling the grouping and ordering that we have above, the Fisher information matrix for this Gaussian likelihood can be written as

$$I(\boldsymbol{\theta}) = \text{diag}[h_1(\boldsymbol{\theta}), h_2(\boldsymbol{\theta}), \dots, h_m(\boldsymbol{\theta})].$$

with $h_j(\boldsymbol{\theta}) = \text{diag}[n, n, \dots, n]_{m_j \times m_j}$. Let us define $\boldsymbol{\theta}_{(1:j)} = (\boldsymbol{\theta}_{(1)}, \boldsymbol{\theta}_{(2)}, \dots, \boldsymbol{\theta}_{(j)})$. Because our model is regular and the determinant of $h_j(\boldsymbol{\theta})$, $|h_j(\boldsymbol{\theta})| = n^{m_j}$, we can use the simplified expression for the reference prior that is given in Lemma 1 of Berger and Bernardo (1992) and obtain

$$\pi^l(\boldsymbol{\theta}) = \frac{\prod_{j=1}^m |h_j(\boldsymbol{\theta})|^{1/2}}{\prod_{j=1}^m \int_{\Theta^l \cap [\Theta_j | \Theta_{(1:(j-1))}] } |h_j(\boldsymbol{\theta})|^{1/2} d\boldsymbol{\theta}_{(j)}} I_{\Theta^l}(\boldsymbol{\theta}), \quad (1)$$

where $[\Theta_j | \Theta_{(1:(j-1))}]$ is the parameter space of $\boldsymbol{\theta}_{(j)}$ given $\boldsymbol{\theta}_{(1:(j-1))}$.

To derive a general expression for the reference prior, we need to determine the integrals in the denominator of Equation (1). We define $\boldsymbol{\theta}_{(1:j), k}$ to be the k^{th} element of the vector $\boldsymbol{\theta}_{(1:j)}$. The term $|h_j(\boldsymbol{\theta})|^{1/2}$ can be canceled out from Equation (1) because it is only a function of n . Under regularity conditions, if the Fisher information matrix of the model satisfies Lemma 1 in Berger and Bernardo (1992), careful calculation can prove the following innovative theorems:

Theorem 1 For a simple order, $\theta_1 < \theta_2 < \dots < \theta_k$,

$$\pi^l(\boldsymbol{\theta}) \propto \frac{1}{\prod_{j=2}^m (\gamma_j - \eta_j)^{m_j}} I_{\Theta^l}(\boldsymbol{\theta})$$

with

$$\gamma_{j+1} = \begin{cases} \min_k \{\boldsymbol{\theta}_{(1:j), k} : \boldsymbol{\theta}_{(1:j), k} > \max[\boldsymbol{\theta}_{(j+1)}]\} & , \text{ if } \max[\boldsymbol{\theta}_{(1:j)}] > \max[\boldsymbol{\theta}_{(j+1)}] \\ l & , \text{ if } \max[\boldsymbol{\theta}_{(1:j)}] < \max[\boldsymbol{\theta}_{(j+1)}] \end{cases}$$

and

$$\eta_{j+1} = \begin{cases} \max_k \{\boldsymbol{\theta}_{(1:j), k} : \boldsymbol{\theta}_{(1:j), k} < \min[\boldsymbol{\theta}_{(j+1)}]\} & , \text{ if } \min[\boldsymbol{\theta}_{(1:j)}] < \min[\boldsymbol{\theta}_{(j+1)}] \\ -l & , \text{ if } \min[\boldsymbol{\theta}_{(1:j)}] > \min[\boldsymbol{\theta}_{(j+1)}]. \end{cases}$$

Theorem 2 For a simple tree order, $\theta_1 < \theta_i$, $i = 2, \dots, k$,

$$\pi(\boldsymbol{\theta}) \propto I_{(\theta_1 < \theta_i)}.$$

Theorem 3 For an umbrella order, $\theta_1 < \theta_2 < \dots < \theta_i > \theta_{i+1} > \dots > \theta_k$, parameters in group j can be separately treated as (1) with increasing order and (2) with decreasing order, then,

$$\pi^l(\boldsymbol{\theta}) \propto \frac{1}{\prod_{j=2}^m (\gamma_{j1} - \eta_{j1})^{m_{j1}} (\gamma_{j2} - \eta_{j2})^{m_{j2}}} I_{\Theta^l}(\boldsymbol{\theta}).$$

γ_{j1} , η_{j1} , γ_{j2} and η_{j2} can be determined by the definitions in Theorem (1) with $m_{j1} + m_{j2} = m_j$. The final reference priors in the true parameter space in Theorems (1) and (3) can be obtained by making $l \rightarrow \infty$.

Detailed proofs can be found in the appendix.

These three theorems are extension of the results in Sonksen and Peruggia (2012). The theorems provide the general expressions that can be used to determine the reference priors of any grouping and ordering. In addition, if the variance σ^2 is introduced in the model, it can be grouped by itself and considered as the first grouping. Then the theorems derived above can be adopted without any adjustment.

Further more, in more complicated models, such as a regression model with a grouping variable of interest and other predictors, with the same assumption that $\varepsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2)$, one can show that the general expressions of the reference priors, given the mean responses of the grouping variable follow a common order, share the same forms as we showed in Theorem (1), Theorem (2) and Theorem (3).

2.2 Simulation Study

In this simulation study, we focus on a one-way ANOVA model with group means following a simple order, i.e., $\mu_1 < \mu_2 < \dots < \mu_k$. To derive the reference priors for this model, the user has to specify the ordering and grouping of the parameters. Berger and Bernardo (1992) suggest to completely separate the parameters with groups of one element each. On the other hand, Sonksen and Peruggia (2012) follow the Nicholls and Jones (2001) approach and suggest that the primary attention should be given to the extreme parameters, i.e., μ_1 and μ_k . Based on the general expression derived in Theorem 1, we consider these two ways of grouping and ordering and label them as $\pi(\boldsymbol{\theta})_{uni}$ and $\pi(\boldsymbol{\theta})_{u1k}$, respectively. The resulting prior distributions are listed in Table 1.

TABLE 1. Reference priors for one-way ANOVA model with a simple order

Label	Parameter Grouping and Ordering	Reference Prior
$\pi(\boldsymbol{\theta})_{uni}$	$(\{\sigma^2\}, \{\mu_1\}, \dots, \{\mu_k\})$	$\frac{1}{\sigma^2} \times I_{\Theta}(\boldsymbol{\theta})$
$\pi(\boldsymbol{\theta})_{u1k}$	$(\{\sigma^2\}, \{\mu_1, \mu_k\}, \{\mu_2, \dots, \mu_{k-1}\})$	$\frac{1}{\sigma^2} \times \frac{1}{(\mu_k - \mu_1)^{k-2}} \times I_{\Theta}(\boldsymbol{\theta})$

Note: $\boldsymbol{\theta} = \{\boldsymbol{\beta}, \sigma^2\} = \{\mu_1, \dots, \mu_k, \sigma^2\}$. $\Theta = \{(\boldsymbol{\beta}, \sigma^2) : -\infty < \mu_1 < \dots < \mu_k < +\infty \text{ and } 0 < \sigma^2 < +\infty\}$.

The total number of simulated studies is 1000. Each study is analyzed by obtaining 11000 MCMC iterations and the first 1000 iterations are treated as burn-in. With an acceptance rate around 0.4, the posterior medians are used as the Bayesian estimates.

For each setting, the 95% credible or confidence intervals are determined and the true parameter values are checked to see if covered by the 95% intervals for each method. The empirical coverages of the intervals are then computed based on these 1000 simulations. The root mean square error (RMSE) for each parameter between estimates and real parameter value is also calculated. The average DIC from simulations is determined for each prior as an important tool for Bayesian model comparison and selection. The detailed settings and results are shown in the following figures and later discussed in detail.

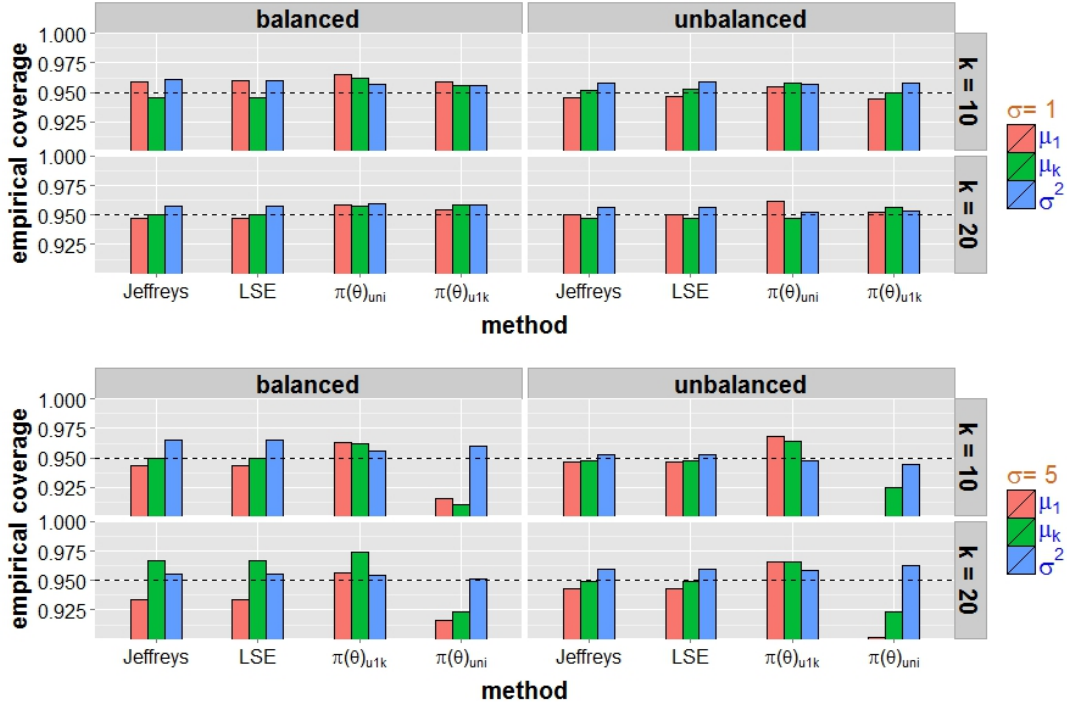


FIG. 1. Empirical coverage of 95% CI under different settings and methods.

All the simulation results from 8 different settings are summarized in Figures 1-3 for $k = 10$ or 20 , $\sigma = 1, 5$ and $n = 40, 80$. Figure 1 shows the empirical coverages of 95% confidence or credible intervals. All these coverages look close to 0.95 except when $\sigma = 5$, the coverage of $\pi(\theta)_{uni}$ is relatively low especially for unbalanced design. This is in accordance with the fact that when the variance is large, the estimates from $\pi(\theta)_{uni}$ are somewhat off the true values for μ_1 and μ_k .

Figure 2 shows the RMSEs of μ_1 , μ_k and σ^2 under different settings. The reference prior $\pi(\theta)_{u1k}$ always gives the smallest RMSE when estimating σ^2 , although the RMSEs from these four methods are actually close. When estimating

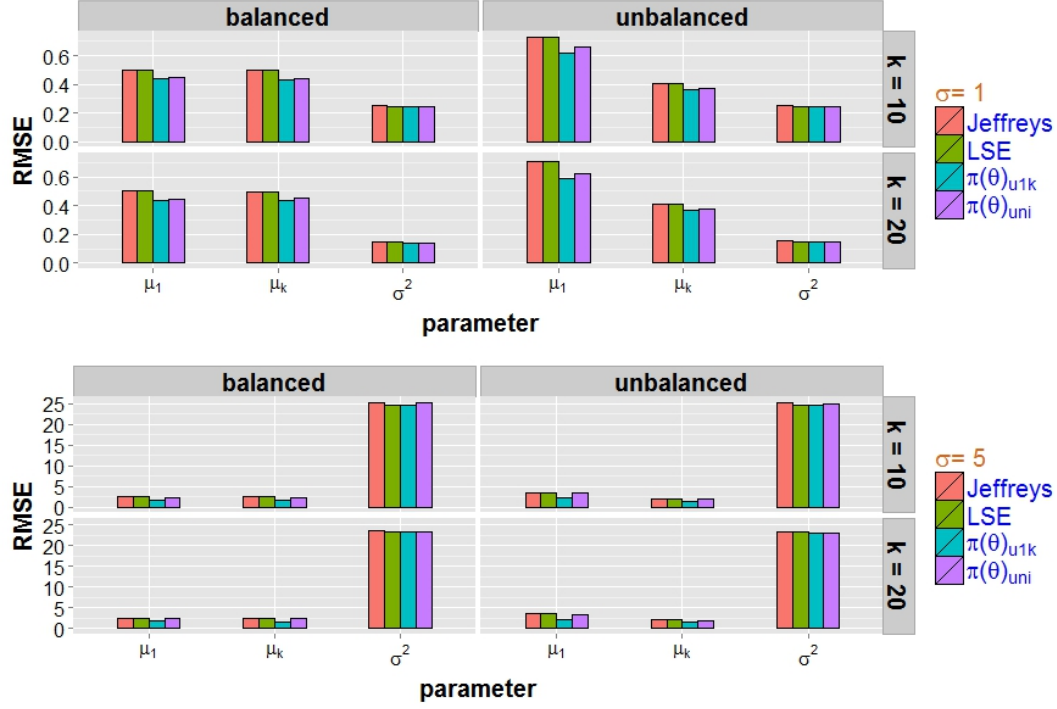


FIG. 2. RMSE comparisons of μ_1 , μ_k and σ^2 under different settings and methods.

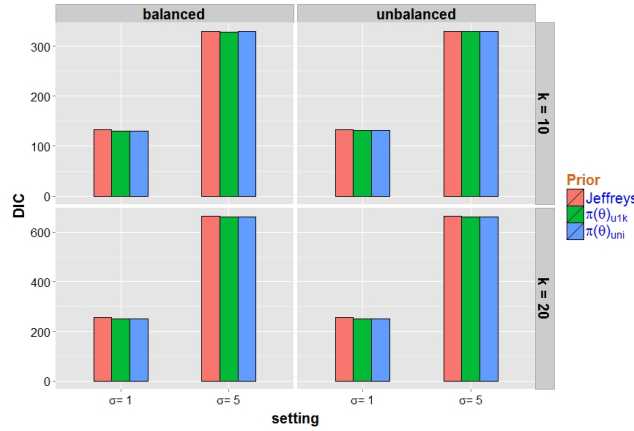


FIG. 3. Average DIC comparisons of three Bayesian methods.

μ_1 and μ_k , the reference prior $\pi(\theta)_{u1k}$ tends to give the smallest RMSE under all settings. The reference prior $\pi(\theta)_{uni}$ also gives pretty small RMSEs when $\sigma = 1$, however, this is not obvious when $\sigma = 5$.

Figure 3 shows simulation averages for DIC under the three Bayesian priors. The resulting values are close and the reference prior $\pi(\theta)_{u1k}$ always gives the smallest average DIC value while Jeffreys' prior seems the worst.

Based on all our simulation results, we can conclude the reference priors that consider the internal order information are good choices when dealing with isotonic models, especially when the number of parameters is large. Under this situation the internal ordering information is important and the reference priors that incorporate this information stand out and work really well when looking for default priors.

3. APPLICATION OF REFERENCE PRIORS

Smoking and Type 2 Diabetes

In 2013, Dr. Mark Burge at UNM Health Science Center started a study with regard to type 2 diabetes. In this study, 218 adults in New Mexico at risk for type 2 diabetes were screened to determine their glucose homeostasis status. Hemoglobin A1c (HbA1c), a common variable used to measure diabetes status, was measured for each patient along with other variables, such as the participant's high-density lipoprotein (HDL), body mass index (BMI) and age etc.

Among these potential covariates the smoking levels become interesting in that:

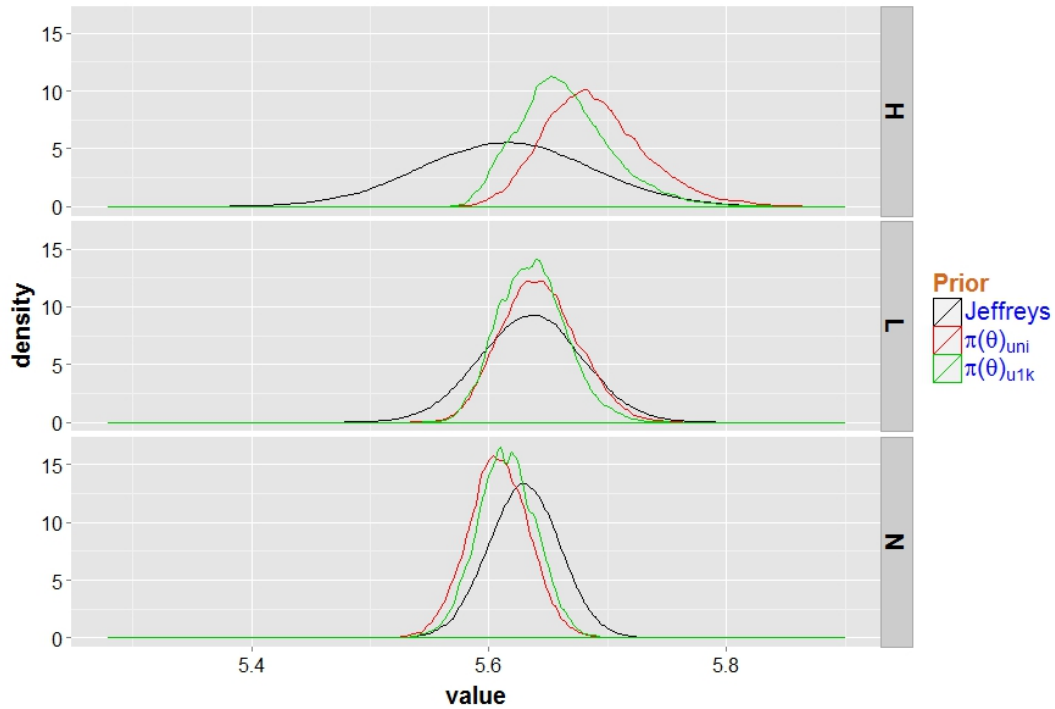


FIG. 4. Marginal posterior distributions for different smoking levels under three priors

Smoking tends to induce high risk of having type 2 diabetes (Xie et al., 2009). At the same time, people with diabetes who smoke are more likely than nonsmokers to have trouble with insulin dosing. However, this relationship sometimes is masked by the variability in observational data. That is, smoking may show

a non-significant effect, which will certainly hamper the interpretation of the model. In this section, we assume internal order information and that there is a simple order for the mean responses of smoking levels. Then, we construct an ANCOVA model to investigate the relationship of type 2 diabetes and smoking along with several other covariates. We adopt the reference priors derived in previous sections and perform an analysis under a Bayesian framework. For comparisons, we also consider Jeffreys' prior and LSE approaches. We use three classifications for smoker status: High-level smokers (more than 10 pack-years), Low-level smokers (between 0 and 10 pack years) and non-smokers (0 pack years), or H, L, N. Variable selection is done by classical regression and LDL, BMI and ages of the participants seem important for the model. After centering these variables, we add the smoking effect, which contains three levels: High, Low and None.

TABLE 2. Bayesian analysis for diabetes data with reference priors and Jeffreys' prior

Smoking level	$\pi(\boldsymbol{\theta})_{u1k}$			$\pi(\boldsymbol{\theta})_{uni}$			Jeffreys		
	2.5%	mean	97.5%	2.5%	mean	97.5%	2.5%	mean	97.5%
N	5.557	5.609	5.658	5.556	5.608	5.661	5.574	5.630	5.692
L	5.588	5.645	5.708	5.584	5.643	5.710	5.552	5.636	5.718
H	5.619	5.692	5.785	5.619	5.692	5.787	5.473	5.618	5.771
DIC	1513			1532			1542		

A Bayesian analysis with a prior distribution that considers a simple order for the smoking effects can be performed, where heavier smokers induce higher risk of type 2 diabetes. Two reference priors, $\pi(\boldsymbol{\theta})_{uni}$ and $\pi(\boldsymbol{\theta})_{u1k}$ are considered. Fitted models can be compared with Jeffreys' prior $\pi(\boldsymbol{\theta})_J \propto \frac{1}{\sigma^2}$. Figure 4 shows the marginal posterior distributions of the mean responses of different smoking levels under the different priors. Posterior distributions from two reference priors show similar patterns, which is not surprising since the sample size is fairly large. The results from Jeffreys' prior are close to LSE, where the estimates for the three smoking levels tend to be mixed up. Compared with the reference priors, the marginal posterior from Jeffreys' prior seems to have heavier tail when estimating the mean responses for different smoking levels (Figure 4), while they behave similarly when estimating other parameters.

The MCMC results based on different priors is summarized in Table 2. Although Jeffreys' prior gives similar results as classical regression, its DIC is the largest. The one with the reference prior $\pi(\boldsymbol{\theta})_{u1k}$ gives the smallest DIC, which turns to be the evidence of better fitting and less complexity of the model. If we consider the differences between different smoking levels, the reference priors incorporating the simple order show there is a significant difference between high level smokers and non-smokers, while the results from Jeffreys' prior cannot show this relationship.

Rats and d-Amphetamine Sulfate

In Heffner et al. (1974), the effect of d-amphetamine sulfate on the behavior of rats was discussed, where the lever press rate at which a rat deprived of water pressed a lever to get water was considered. The rate was defined as the total number of lever presses divided by the elapsed time (in seconds) during a session for a given dosage of amphetamine. The resulting data show that the dose-response relationship has a downturn at high dosages. Other studies, such as Dews (1958), where the relationship between amphetamine and key pecking by pigeons was studied, also show a similar pattern. It is reasonable to anticipate the effect of d-amphetamine sulfate on a rat's rate of lever pressing follows an umbrella order. That is, the initial rate increases as the drug dosage increases and decreases at high dosages. As shown in Table 3, we adopt this data as another

TABLE 3. d-Amphetamine sulfate dosage and rats

Rats	Dosage (mg/kg)				
	0.0	0.5	1.0	1.5	2.0
1	0.60	0.80	0.82	0.81	0.50
2	0.51	0.61	0.79	0.78	0.77
3	0.62	0.82	0.83	0.80	0.52
4	0.60	0.95	0.91	0.95	0.70
5	0.92	0.82	1.04	1.13	1.03
6	0.63	0.93	1.02	0.96	0.63
7	0.84	0.74	0.98	0.98	1.00
8	0.96	1.24	1.27	1.20	1.06
9	1.01	1.23	1.30	1.25	1.24
10	0.95	1.20	1.18	1.23	1.05

example for our reference priors. In this data, ten male albino rats of the same strain and of approximately the same weight were included. The study contains five dosage levels of the drug, including a zero level of a saline solution. Each rat received all five dosage levels randomly. One hour after a drug injection, an experimental session started during which the rat received water each time after a second lever was pressed. If each rat is treated as a block and the focus of the analysis is on the treatments, i.e., different dosage levels, then a randomized block design ANOVA model can be set up as:

$$\mathbf{y} = X\boldsymbol{\theta} + \boldsymbol{\varepsilon}, \boldsymbol{\varepsilon} \sim N(\mathbf{0}, \sigma^2 I),$$

, where $\boldsymbol{\theta} = (\tau_1, \dots, \tau_5, \beta_2, \dots, \beta_{10})'$. τ stands for treatment effect and β stands for block effect. Based on Mack and Wolfe (1981) and Lim and Wolfe (1997), we can estimate the peak of treatment effect at $\hat{p}=3$, 1.0 mg/kg dosage. One way to group and order the parameters is: $(\{\sigma^2\}, \{\tau_1, \tau_3\}, \{\tau_4, \tau_5\}, \{\tau_2\}, \{\beta\})$.

Based on theorem 3, we can derive the corresponding reference prior, which is $\frac{1}{\sigma^2} \times \frac{1}{\tau_3 - \tau_5} \times \frac{1}{\tau_3 - \tau_1} \times I_{\Theta}(\boldsymbol{\theta})$.

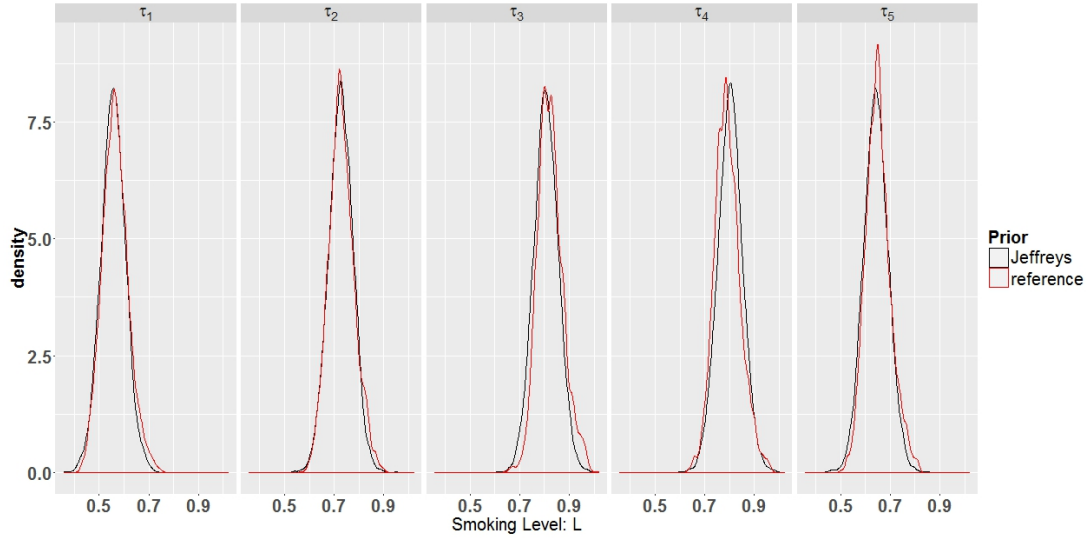


FIG. 5. Marginal posterior distributions for treatment effects under different dosage levels

We fit the above ANOVA model with this reference prior and Jeffreys' prior. The marginal posterior distributions for 5 treatment effects are shown in Figure 5 and the major results are summarized in Table 4. As shown in the figure and table, although the model fittings from the two priors are very similar, the model with the reference prior where the umbrella order is considered provides a more reasonable inference. It highlights the peak in the treatments groups, which can be very important especially when this relationship is masked by the variability of the data.

TABLE 4. Bayesian analysis for rats data with reference priors and Jeffreys' prior

Dosage level	reference			Jeffreys		
	2.5%	mean	97.5%	2.5%	mean	97.5%
τ_1	0.466	0.564	0.677	0.457	0.556	0.656
τ_2	0.632	0.729	0.838	0.629	0.727	0.821
τ_3	0.733	0.823	0.942	0.708	0.806	0.903
τ_4	0.694	0.791	0.904	0.701	0.802	0.901
τ_5	0.560	0.651	0.765	0.545	0.643	0.742
DIC	8173			8217		

4. CONCLUSIONS

Under the frame-work by Berger and Bernardo (1992), we provide the general formulas of the reference priors for ANOVA and ANCOVA models with a categor-

ical variable under common ordering constraints. The derivation is a compromise of subjective information and “let the data talk itself”. Both simulation studies and data analysis suggests incorporating the ordering information can improve goodness-of-fit, which can be adopted as typical priors when handling similar questions.

The three common ordering restrictions summarized at the beginning cover the most common types of multiple comparisons for dose-finding studies. The proposing method could be broadly used in modeling dose-response relationship, for both monotonous relationship and “inverted U-shape” pattern. They can be treated as candidate models in Multiple Comparison Procedures - Modelling (MCP-Mod) methodology, where a “best” model can be selected through optimal model contrasts while controlling the family-wise error rate by the use of multiple comparison procedures. An optimal dose can then be determined afterwards.

APPENDIX

Proof of Theorem 1

Above it was shown that $|h_j(\boldsymbol{\theta})| = n^{m_j}$ thus the numerator of Equation (1) is a constant. Careful bookkeeping is needed to evaluate the integrals in the denominator of Equation (1). Without loss of generality, assume that the elements of each $\boldsymbol{\theta}_{(j)} = (\theta_{(j),1}, \theta_{(j),2}, \dots, \theta_{(j),m_j})$ are ordered. Note the following simple integrals for a parameter $l < \theta < u$.

$$\begin{aligned}\int_l^u d\theta &= u - l \\ \int_l^u (\theta - l)^m d\theta &= (u - l)^{m+1} \\ \int_l^u (u - \theta)^m d\theta &= (u - l)^{m+1}\end{aligned}$$

The joint integral over $\Theta^l \cap [\Theta_j | \Theta_{(1:(j-1))}]$ can be broken down to one of these 3 simple integrals at each step, only the range (greatest lower bound and least upper bound) for each $\theta_{(j),i}$ needs to be determined. Namely, if either the extreme bounds ($-l$ or l), a parameter in the integral ($\theta_{(i)}$) or a parameter in $\boldsymbol{\theta}_{(1)}, \dots, \boldsymbol{\theta}_{(j-1)}$. There are m_j total integrals with the joint integral of the following form

$$\int_{\Theta^l \cap [\Theta_j | \Theta_{(1:(j-1))}]} |h_j(\boldsymbol{\theta})|^{1/2} d\boldsymbol{\Theta}_{(j)} = (\gamma_j - \eta_j)^{m_j}.$$

Where γ_j is the smallest element of $\Theta_{(1:(j-1))}$ larger than the largest value of $\Theta_{(j)}$ or l if no such element exists. Similarly, η_j is the largest element of $\Theta_{(1:(j-1))}$ smaller than the smallest value of $\Theta_{(j)}$ or $-l$ if no such element exists.

Repeating the above for $j = 1, \dots, m$ and collecting the results yields Equation (1)

Proof of Theorem 2

Proof of Theorem 3

Works Cited

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