DISCOVERING INTERACTIONS USING COVARIATE
INFORMED RANDOM PARTITION MODELS

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Combination chemotherapy treatment regimens created for pa-
tients diagnosed with childhood acute lymphoblastic leukemia have
had great success in improving cure rates. Unfortunately, patients
prescribed these types of treatment regimens have displayed suscep-
tibility to the onset of osteonecrosis. Some have suggested that this is
due to pharmacokinetic interaction between two agents in the treat-
ment regimen (asparaginase and dexamethasone) and other physio-
logical variables. Determining which physiological variables to con-
sider when searching for interactions in scenarios like these, minus
a priori guidance, has proved to be a challenging problem, particu-
larly if interactions influence the response distribution in ways beyond
shifts in expectation or dispersion only. In this paper we propose an
exploratory technique that is able to discover associations between
covariates and responses in a general way. The procedure connects
covariates to responses flexibly through dependent random partition
distributions, and then employs machine learning techniques to high-
light potential associations found in each cluster. We provide a simu-
lation study to show utility and apply the method to data produced
from a study dedicated to learning which physiological predictors in-
fluence severity of osteonecrosis multiplicatively.

1. Introduction. In studies that collect covariate measurements on
subjects/experimental units in addition to a response, determining which
covariates influence the response and in what way are of principal inter-
est. This seemingly benign statistical problem has been seriously considered
for many years with methods ranging from exploratory techniques to more
model based procedures. Perhaps the reason why research dedicated to this
problem persists is that in practice building a statistical model is as much an
art as a science. This is a consequence of important or “significant” associa-
tions depending completely on the factors included in the model. Therefore,

* Keywords and phrases: multiplicative associations, dependent random partition mod-
els, nonparametric Bayes, exploratory data analysis
knowing which effects to include in a model is crucial, but this information is rarely known \textit{a priori}. Since this information is rarely known, an approach that is commonly used in practice proposes fitting a saturated model (a model containing all possible covariates or predictors) and then employing some type of multiplicity test correction, model selection criteria, shrinkage method, or stochastic search to locate “significant” factors (see, e.g., Tibshirani, 1996; Smith and Kohn, 1996; George and McCulloch, 1997; Ishwaran and Rao, 2005; Chung and Dunson, 2009; Scott and Berger, 2010; Mitra, Müller and Ji, 2017). These methods have been shown to work well in many instances (Barrera-Gómez et al. 2017). However, when multiplicative effects and/or nonlinear associations are present and are of interest, a fairly common scenario (see, e.g. Hu, Joshi and Johnson, 2009; Lim and Hastie, 2015a), the process of identifying associations becomes much more problematic as the saturated model can quickly become unwieldy. This happens to be the case in the study under consideration, where we examine which factors affect the severity of osteonecrosis in children treated for acute lymphoblastic leukemia (ALL). Interest lies in learning how time-varying physiological and other baseline covariates such as gender, triglycerides, and body mass index (BMI) influence disease severity in an additive or multiplicative fashion. Employing the saturated model approach here with all possible two-way and/or three-way interactions becomes computationally expensive and inferentially difficult, so knowing which covariates to consider is important.

Adding to the complexity of the scenario just described, methods used to identify associations (either additive or multiplicative) are geared towards discovering covariates that only influence the mean of the response distribution. It is completely plausible that interactions also influence the variance or even the shape of the response distribution, and most methods are not equipped to detect these types of associations. Regression methods that allow covariates to influence the entire response (or error) distribution have been developed and are commonly known as density regression (see Fan, Yao and Tong, 1996; Dunson, Pillai and Park, 2007). There has been work in density regression that simultaneously carries out variable selection (Tokdar, Zhu and Ghosh 2010; Shen and Ghosal 2016), but they require that all effects of interest be included in a model. Though it may be possible to extend work done in density regression to incorporate multiplicative effects, \textit{a priori} information would be necessary to guide which of these effects to consider. In light of this, an exploratory procedure that is able to discover possible associations in a general way, prior to model fitting, would be appealing.

There is a growing literature dedicated to methods developed with the
main purpose of explicitly identifying interactions without restricting themselves to variable selection. Reich et al. (2012) develop a statistical emulator and devise a procedure that allows them to learn how the inputs of a stochastic computer model influence the output (which is a distribution). Bien, Taylor and Tibshirani (2013) use the Lasso and Lim and Hastie (2015b) the group Lasso to detect interactions from hierarchically coherent models (i.e., two-way interactions are present only if both main effects are present). Kapelner and Bleich 2016 employ Bayesian additive regression trees (BART) to identify interactions while Du and Linero (2018) develop methods based on Bayesian decision tree ensembles that incorporate an additive component, something we are not limited to. XGBoost (Chen and Guestrin, 2016) is a scalable machine learning system for tree boosting, that has also been employed to discover interactions. In more recent work Ferrari and Dunson (2019) use a factor model to induce models that include interactions and Agrawal et al. (2019) search for interactions in high dimensions.

The methods just cited are developed for a specific scenarios while what we propose is more general and can be employed with any data model, making the procedure essentially “model free”. This is important for our application as the response is ordinal rendering many of the works just cited unavailable. Thus, the exploratory procedure we propose discovers associations where anything is fair game in the sense that associations could be additive and/or multiplicative and could influence any aspect of the response density (i.e., mean, spread, shape, etc.) regardless of the data model that will eventually be employed. Our goal is ambitious and admittedly being able to discover all possible interactions in the general way we are proposing is presumably not possible. Thus, we do not claim that the exploratory approach detailed in the sequel discovers all “significant” interactions, rather it provides guidance to practitioners by highlighting possible interactions with very little overhead.

We finish our literature review noting that there is a growing literature dedicated to so called subgroup analysis, i.e., the study of heterogeneous treatment effects among subgroups of a study population. Subgroups are typically identified or defined based on specific values in the covariate space. Since subpopulation treatment effects are of principal interest, focus is placed on studying the interaction between a covariate and a treatment (see e.g., Simon 2002; Berger, Wang and Shen 2014; Varadhan and Wang 2014; Schnell et al. 2016; Liu et al. 2017; Su et al. 2018; Henderson et al. 2020). Our approach is more general in nature, but can be used as an exploratory tool to help discover which covariates interact with the treatment and provide guidance by spotting subpopulations of potential interest.
As a point of terminology, in what follows we use the term “interaction” to denote something more general than what is referred to in a linear model setting. Here, an interaction exists if the response distribution is in some way influenced by specific combinations of covariate values. This general conception includes the special case where all the influence is carried by only one of the covariates. Our general recommendation is then to carefully assess any influences that may be detected using the proposed procedure to gain insight on the source(s) of the detected difference(s). This highlights the exploratory nature of our proposal.

The remainder of the article is organized as follows. In Section 2 we detail the data collected from the study that motivated this work. Section 3 provides an overview of our approach some background on dependent random partition distributions and association rules. Section 4 provides more details of our approach and Section 5 details two simulation simulation studies. In Section 6 we apply the procedure to the osteonecrosis data and Section 7 contains a brief discussion.

2. Osteonecrosis Study. The study we consider was designed to learn more about factors affecting risk for osteonecrosis in children suffering from acute lymphoblastic leukemia (ALL). With combination chemotherapeutic regimens, five-year survival is around 85% overall for childhood ALL, with some subgroups’ rates well above 90% (American Cancer Society 2018). These regimens include the drug asparaginase and the steroid dexamethasone. Some have suggested that there is a pharmacokinetic interaction between these two agents, leading to greater inter-patient variability and severe adverse events (Kawedia et al. 2011). The principal aim of the motivating study was to learn about relationships between physiological characteristics and treatment characteristics and how these relationships influence susceptibility to osteonecrosis as a result of therapy. The analysis considers a number of physiological covariates measured on each patient, including low-density lipoprotein (LDL), high-density lipoprotein (HDL) levels, body mass index (BMI), and others. In addition to these covariates, the data include plasma levels of dexamethasone, cortisol, and asparaginase at various times during each patient’s course of treatment (baseline, week 7, week 8) to explore how the pharmacokinetics (PK) of these substances influenced the risk and severity of osteonecrosis and whether other factors interact with the drugs’ PK. Finally, demographic variables include age at diagnosis, gender, and race. In total 23 predictors where considered with numerical summaries provided in Tables 1 and 2. Out of the 400 patients in the study, we have complete data vectors for 234, and we focus on these.
Table 1 displays the gender-by-race distribution with each gender being equally represented. A third binary covariate (called LowRisk) which indicates the prognosis of the patient’s leukemia (low or high risk of relapse) is also included. This variable should be highly influential because exact treatment regimens are based on patients’ risk factors relating to prognosis of their leukemia. Of the 234 subjects, 109 were in the low risk group while 125 were in the high risk. From Table 2 it is clear that a few continuous covariates are highly right skewed. Empirical correlations between time varying covariates suggest that temporal dependence is present. This dependence can be accommodated in our approach and is formally considered in the model developed by Barcella et al. (2018). We briefly comment that week 12 measurements were also collected, but very irregularly. This resulted in many incomplete covariate vectors, and for this reason we only consider measurements taken up to week 8.

The response measured in this study reflects the severity of osteonecrosis ranging on an ordinal scale from 0 for none up to 4 for high grade. Table 3 contains the number of patients by grade of osteonecrosis. We expect, but do not force, the covariates’ influences on osteonecrosis grade to be multiplicative, but it is not clear which covariates to pair together when exploring multiplicative effects. This is something we hope to discover.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Asian</th>
<th>Black</th>
<th>Hispanic</th>
<th>Other</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1</td>
<td>21</td>
<td>8</td>
<td>7</td>
<td>96</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>19</td>
<td>8</td>
<td>3</td>
<td>69</td>
</tr>
</tbody>
</table>

3. Background and Preliminaries. The exploratory procedure we develop consists of three stages. In this section we introduce each one and then provide notation and background information necessary to make ideas concrete.

The first step consists of connecting covariates to the response by way of a dependent random partition model. These types of models create partitions of the data taking into account homogeneity among covariates, and in particular, some of these models, such as the PPMx by Müller, Quintana and Rosner (2011), aim specifically at constructing priors for which two individuals with similar covariate values are more likely to cocluster. The resulting partition is, *a posteriori*, weighted by the corresponding cluster sizes, the likelihood component and the similarity of covariates that belong to a clus-
### Table 2

*Five number summary of the continuous covariates.*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Min.</th>
<th>Q1</th>
<th>Q2</th>
<th>Mean</th>
<th>Q3</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AgeAtDiagnosis</td>
<td>1.02</td>
<td>3.20</td>
<td>5.23</td>
<td>6.77</td>
<td>9.68</td>
<td>18.84</td>
</tr>
<tr>
<td>DexClWk07</td>
<td>1.99</td>
<td>9.03</td>
<td>14.69</td>
<td>21.83</td>
<td>25.03</td>
<td>458.07</td>
</tr>
<tr>
<td>DexClWk08</td>
<td>1.62</td>
<td>8.09</td>
<td>11.67</td>
<td>14.07</td>
<td>16.62</td>
<td>61.71</td>
</tr>
<tr>
<td>CortisolBaseline</td>
<td>0.25</td>
<td>4.07</td>
<td>5.67</td>
<td>7.46</td>
<td>8.22</td>
<td>59.41</td>
</tr>
<tr>
<td>CortisolWk07</td>
<td>0.11</td>
<td>4.93</td>
<td>7.12</td>
<td>9.00</td>
<td>10.34</td>
<td>55.16</td>
</tr>
<tr>
<td>CortisolWk08</td>
<td>0.00</td>
<td>0.32</td>
<td>0.58</td>
<td>1.11</td>
<td>1.01</td>
<td>30.27</td>
</tr>
<tr>
<td>HDLBaseline</td>
<td>11.30</td>
<td>39.05</td>
<td>48.60</td>
<td>56.28</td>
<td>59.25</td>
<td>271.00</td>
</tr>
<tr>
<td>HDLWk07</td>
<td>10.70</td>
<td>41.92</td>
<td>52.50</td>
<td>59.10</td>
<td>67.20</td>
<td>198.00</td>
</tr>
<tr>
<td>HDLWk08</td>
<td>1.90</td>
<td>29.45</td>
<td>44.00</td>
<td>50.31</td>
<td>61.50</td>
<td>238.00</td>
</tr>
<tr>
<td>LDLBaseline</td>
<td>13.00</td>
<td>62.00</td>
<td>82.00</td>
<td>83.95</td>
<td>104.75</td>
<td>195.00</td>
</tr>
<tr>
<td>LDLWk07</td>
<td>15.00</td>
<td>57.25</td>
<td>80.00</td>
<td>82.04</td>
<td>100.38</td>
<td>218.00</td>
</tr>
<tr>
<td>LDLWk08</td>
<td>5.00</td>
<td>50.25</td>
<td>68.00</td>
<td>73.44</td>
<td>91.50</td>
<td>179.00</td>
</tr>
<tr>
<td>TriglyceridesBaseline</td>
<td>20.00</td>
<td>58.62</td>
<td>87.50</td>
<td>104.60</td>
<td>124.75</td>
<td>472.00</td>
</tr>
<tr>
<td>TriglyceridesWk07</td>
<td>20.00</td>
<td>55.02</td>
<td>74.50</td>
<td>114.79</td>
<td>132.50</td>
<td>885.00</td>
</tr>
<tr>
<td>TriglyceridesWk08</td>
<td>15.90</td>
<td>75.25</td>
<td>122.50</td>
<td>220.75</td>
<td>286.00</td>
<td>1029.50</td>
</tr>
<tr>
<td>AlbuminBaseline</td>
<td>3.30</td>
<td>4.00</td>
<td>4.20</td>
<td>4.17</td>
<td>4.40</td>
<td>5.10</td>
</tr>
<tr>
<td>AlbuminWk07</td>
<td>2.10</td>
<td>3.20</td>
<td>3.90</td>
<td>3.75</td>
<td>4.30</td>
<td>4.80</td>
</tr>
<tr>
<td>AlbuminWk08</td>
<td>2.20</td>
<td>3.10</td>
<td>3.60</td>
<td>3.56</td>
<td>4.00</td>
<td>4.80</td>
</tr>
<tr>
<td>BMIBaseline</td>
<td>12.19</td>
<td>15.68</td>
<td>16.77</td>
<td>18.05</td>
<td>19.23</td>
<td>38.48</td>
</tr>
<tr>
<td>AsparaginaseAntibodyAUC</td>
<td>0.42</td>
<td>1.07</td>
<td>3.54</td>
<td>14.20</td>
<td>24.83</td>
<td>93.85</td>
</tr>
</tbody>
</table>

### Table 3

*Grade of osteonecrosis and the number of patients diagnosed for each one.*

<table>
<thead>
<tr>
<th>Osteonecrosis Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>73</td>
<td>115</td>
<td>27</td>
<td>17</td>
<td>2</td>
</tr>
</tbody>
</table>
This feature has proven to be quite useful in capturing many types of nonlinearities present in the data, including combined changes in shape, location and scale of the predictive distribution as the predictors change. Since these types of models are closely related to discrete random probability models of the type used in Bayesian nonparametrics, which are well known for their flexibility (see, e.g., Müller et al., 2015), in theory any statistical model that produces (explicitly or implicitly) a covariate dependent partition may be employed. This includes the dependent Dirichlet process mixture (DDP) model of MacEachern (2000) and its variants (e.g., ANOVA DDP of De Iorio et al. 2004). As explained below, we adopt here the PPMx model.

In the second step the estimated partition from step 1 is used to identify potentially interesting interactions. One possible way of employing the partition to pinpoint potential interactions is to identify covariates that seem to influence cluster formation. This would imply that an association exists among the influential covariates and the response (a necessity for an interaction to exist). Identifying influential covariates can be done by determining which covariates have the same (or similar) values for many individuals in a cluster. An unsupervised learning technique developed to carry out this type of search establishes so called association rules (Han, Kamber and Pei, 2012, Chapter 6). There is precedence to using association rules as a tool to identify interactions (see Heba et al. 2014), but we use them to rank potential interactions based on their “importance.” Ranking interactions based on their “importance” is, implicitly, something all procedures described in Section 1 do. Many of the procedures, however, provide very little guidance or criteria on how to determine which interactions are simply noise. This motivates the inclusion of a third step to our exploratory approach.

In the third step of our procedure we verify that a detected interaction indeed affects the response distribution. This is done by comparing posterior predictive densities that are based on specific values from covariates that were identified by an association rule. If the posterior predictive densities do not change as a function of the covariates found in the association rule, then their association with the response is weak at best. (As a side note, Gabry et al. (2019) advocate using a posterior predictive distribution as an exploratory or confirmatory tool.) We now provide more pertinent background information for dependent random partition models and association rules.

3.1. Dependent Random Partition Models. We begin by introducing some notation. Let \( i = 1, \ldots, m \) index the \( m \) experimental units in a designed
experiment or $m$ subjects in an observational study. Further, let $\rho_m = \{S_1, \ldots, S_{k_m}\}$ denote a partitioning (or clustering) of the $m$ units into $k_m$ subsets such that $i \in S_j$ implies that unit $i$ belongs to cluster $j$. A common alternative notation that specifies a partitioning of the $m$ units into $k_m$ clusters is to introduce $m$ cluster labels $s_1, \ldots, s_m$ such that $s_i = j$ implies $i \in S_j$. We will use $Y_i$ to denote the $i$th subject’s response variable with $Y = (Y_1, \ldots, Y_m)$ denoting an $m$ dimensional response vector and $Y^*_j = \{Y_i : i \in S_j\}$ the $j$th cluster’s response vector. Similarly, let $X = (X_1, \ldots, X_m)$ denote a covariate vector and $X^*_j = \{X_i : i \in S_j\}$ a partitioned covariate vector. When $p$ covariates are measured on each individual, both continuous and qualitative, then $X_i = (X_{i1}, \ldots, X_{ip})$ will denote the $i$th individual’s $p$-dimensional covariate vector and with a slight abuse of notation set $X^*_j = (X^*_j, \ldots, X^*_jp)$ where $X^*_mh = \{X_{ih} : i \in S_j\}$ for $h = 1, \ldots, p$. Thus depending on context, $X^*_j$ could possibly be a super vector of stacked patients’ covariate vectors.

We now introduce notation associated with the model that will be employed to connect $X$ to $Y$ through $\rho_m$. A dependent random partition prior distribution is assigned to $\rho_m$. This prior distribution parametrized by $\eta$, will be denoted using $RPM_X(\eta)$. Once a prior for $\rho_m$ is specified, we will make use of $f(Y|\rho) = \prod_{j=1}^{k_m} f_j(Y^*_j)$ as a data model where $f_j(Y^*_j) = \int \prod_{i \in S_j} f_j(Y_i|\theta^*_s) dG_0(\theta^*_j)$, $f(\cdot|\theta^*_j)$ denotes the likelihood for $Y$, and $G_0$ a prior for cluster specific parameters $\theta^*_j$. Note that unit-specific parameters can be connected to their cluster-specific counterpart via $\theta_i = \theta^*_{s_i}$. Alternatively, the data model can be written hierarchically using the cluster labels $s_1, \ldots, s_n$ in the following way

$$Y_i \mid \theta^*, s_i \overset{\text{ind}}{\sim} f(\theta^*_{s_i}), \text{ for } i = 1, \ldots, m$$

$$\theta^*_\ell \overset{iid}{\sim} G_0, \text{ for } \ell = 1, \ldots, k_m,$$

$$\rho_m \mid X \sim RPM_X(\eta).$$

Notice that covariates do not appear in the data model so that neither pre-specified associations nor their forms are required. As a result, $Y$ is only connected to $X$ through the posterior distribution of $\rho_m$ (denoted by $\pi(\rho_m|Y, X)$) which will facilitate our interaction search. There are a number of computational techniques that have been developed to fit model (3.1). Most are some variant of MCMC that depends on the exact specification of $RPM_X(\eta)$. We opt to employ algorithm 8 of Neal (2000) when fitting model (3.1), since it is a general algorithm that can be used in a variety settings.

As already discussed, there are many possibilities for $RPM_X(\eta)$. In what follows we employ the covariate dependent random partition model (PPMx)
described in Müller, Quintana and Rosner (2011) (and further explored in Page and Quintana 2018) because of its flexibility in being able to easily incorporate all types of covariates. The exact form of $RPM_X(\eta)$ when adopting the PPMx is

$$RPM_X(\eta) \propto \prod_{j=1}^{km} c(S_j)g(X^*_j|\eta),$$

where $c(S)$ is a set function that measures the chance elements in $S$ co-cluster a priori, and $g(X^*|\eta) = \int \prod_{i \in S_j} g(X_i|\xi^*) q(\xi^*|\eta) d\xi^*$ is a similarity function that produces higher values for $X^*$’s that contain covariate values that are more similar. Here, $g(\cdot|\cdot)$ denotes an auxiliary probability model (likelihood and prior) that has no effect in the data model and is used only to introduce the desired effect in the similarity function. When multiple covariates of different types are available Müller, Quintana and Rosner (2011) suggest using the following multiplicative form

$$g(X^*_j|\eta) = \prod_{\ell=1}^{p} g(X^*_{j\ell}|\eta)$$

3.2. Association Rules. Association rules are used to discover patterns or relations among a large collection of variables. They are typically denoted using $\{A\} \Rightarrow \{B\}$ where $A$ and $B$ define a subset of the covariate space that does not share any variables. Connecting the idea to the osteonecrosis study, a possible association rule is $\{A = \text{AgeAtDiagnosis} \in [3, 5]\} \Rightarrow \{B = \text{DexClWk07} \in [9, 12]\}$ which would indicate that if $\text{AgeAtDiagnosis}$ is between 3 and 5, then $\text{DexClWk07}$ is between 9 and 12.

There are two criteria to evaluate the importance of $\{A\} \Rightarrow \{B\}$. The first, called support, is the proportion of patients whose covariate vector contains both $A$ and $B$. The second criterion, called confidence, is the fraction of patients that display $B$ among those that display $A$. Our criteria to determine which covariate pairs to consider when looking for interactions will be those with large support and confidence. For a more detailed overview of association rules we refer interested readers to Hastie, Tibshirani and Friedman (2009, chapter 14) or Han, Kamber and Pei (2012, chapter 6).

The typical notation used for association rules highlights the fact that they are by nature directional. However, our only purpose in using association rules is to identify pairs of covariates that are associated with each other and possibly influence the distribution of $Y$ in a non-additive way. Because of this, we will use $X_1 \leftrightarrow X_2$ to denote that at least one association rule contained the pair $X_1, X_2$ in some fashion as the direction of the association is immaterial for our purposes.
4. Interaction Discovery Procedure. In this section we provide more details of our three-step interaction discovery procedure, after which we provide two simulation studies. In what follows we will refer to the three step procedure as the Random partition, Association rule, Interaction Discovery procedure (or the RAID procedure).

A natural way of employing $\pi(\rho_m|Y, X)$ in the second stage of the exploratory procedure is to produce a point estimate of $\rho_m$ using methods found in Dahl (2020) (or some other alternative) and then apply association rules to each of the resulting $X_j^*$s. However, as noted by Wade and Ghahramani (2018), there might be substantial variability associated with the partition point estimate. Therefore, we instead apply association rules to the resulting $X_j^*$s for each (or a subset) of the MCMC draws collected. This approach provides a means of propagating uncertainty associated with $\rho_m$ through the exploratory procedure. Since the interactions identified will be based on specific clusters they are local in the same way that treatment effects are local in subset analysis. That is, the interaction may not remain consistent across the entire population. (We explore this in the simulation study of Section 5.2.) We briefly note that applying association rules to each of the $X_j^*$ is crucial to finding interactions as they are connected to $Y$ through $\pi(\rho_m|Y, X)$. Applying association rules directly to $X$ would make interaction detection impossible as there is no connection to $Y$.

As stated previously, the third step consists of using posterior predictive densities to confirm interactions. To make this step concrete, consider an example with three binary covariates. Let $f_{ijk}(Y_0|Y, X)$ denote the posterior predictive density for $X_1 = i, X_2 = j,$ and $X_3 = k$ with $i, j, k \in \{0, 1\}$ and assume that within a cluster, the association rule with highest total support and confidence is $X_1 \Leftrightarrow X_2$. To verify that there does indeed exist what we call an interaction between $(X_1, X_2)$, we test the following hypothesis (after fixing $X_3 = k$ to its empirical median)

$$H_0 : f_{00k}(Y_0|Y) = f_{01k}(Y_0|Y) = f_{10k}(Y_0|Y) = f_{11k}(Y_0|Y).$$

(4.1)

If the hypothesis is rejected, then we conclude that $X_1$ and $X_2$ interact. That is, the predictive distribution of $Y$ is in some way influenced by $X_1$ and/or $X_2$, and the specific way in which this occurs can be later explored separately. A similar approach would be employed if association rules highlighted any of the other possible two-way interactions (i.e., $X_1 \Leftrightarrow X_3$, $X_2 \Leftrightarrow X_3$). We also consider the possibility of a three-way interaction in Section 6.

There are a number of procedures that might be selected to test the hypothesis found in (4.1). The Pólya tree procedure outlined in Chen and Hanson (2014) is quite flexible and powerful, and thus we opt to use it in
what follows. However, any other procedure that is able to formally test
the hypothesis in (4.1) is completely valid. Just as with Chen and Hanson’s
(2014) method, most methods employed to test (4.1) will produce a “p-
value”. We use the “p-values” as a validation tool and thus, there is no
guarantee that Type 1 error rates are preserved. That said, the simulation
in the Section 5.2 suggests that error rates are not far from the size of the
test.

5. Simulation Studies. In this section we detail two simulation stud-
ies carried out to explore the RAID procedure’s ability to detecting interac-
tions. The first is based on a toy example that is included to provide insight
into each of the three steps of our approach. The second is a more realistic
setting that is based on the covariate structure found in the osteonecrosis
data set. In both simulation studies a continuous response variable is used
even though the response in the osteonecrosis study is ordinal. This was
done so that we could compare our approach to other procedures found in
the literature. As far as we are aware, no other procedure is able to accom-
mmodate an ordinal response. This highlights the “model free” property of
our approach.

In order to connect \( Y \) to \( X \) through \( \pi(\rho_m|Y, X) \), we fit the following
particular case of model (3.1) to each generated synthetic data set in both
simulation studies

\[
Y_i \mid \mu^*, \sigma^*, s_i \overset{\text{iid}}{\sim} N(\mu^*_i, \sigma^*_i), \text{ for } i = 1, \ldots, m \\
(\mu^*_i, \sigma^*_i) \overset{\text{iid}}{\sim} N(\mu_0, \sigma_0^2) \times Unif(0, A), \text{ for } \ell = 1, \ldots, k_m,
\]

\[\rho_m | X \sim RPM_X(\eta),\]

with \( \mu_0 \sim N(0, 10^2), \sigma_0 \sim Unif(0, 10), \) and \( A = 1 \). For the \( RPM_X(\eta) \)
we used the PPMx with cohesion \( c(S) = M \times (|S| - 1)! \) connecting the
partition model to that induced by a Dirichlet process (DP) mixture and the
“rich get richer” property (i.e., a model that favors a small number of large
clusters). \( M \) has connections with the DP dispersion parameter and we used
\( M = 1 \). For the similarity we employed the auxiliary similarity function (see
Müller, Quintana and Rosner 2011; Page and Quintana 2018). As a result,
for qualitative variables, \( q(\cdot|\xi^*) \) and \( q(\xi^*|\eta) \) correspond to Multinominal and
Dirichlet density functions, respectively and for continuous variables they
take on a Gaussian and Gaussian-Inverse-Gamma density functions. Thus,
for qualitative covariates \( \eta \) is a vector of Dirichlet shape parameters that
we set to 0.1 and for continuous covariates, \( \eta \) corresponds to the \( m_0 = \) center,
\( k_0 = \) scale, \( \nu_0 = \) shape, and \( \kappa_0 = \) rate parameters of Gaussian-
Inverse-Gamma distribution. After standardizing continuous covariates, we
employed $m_0 = 0$, $k_0 = 0.5$, $\nu_0 = 1$, $\kappa_0 = 2$. In this model, the prior parameters that seem to have the most influence over $\pi(\rho_m|Y, X)$ are $A$ and $k_0$. These parameters determine how much weight is placed on $Y$ or $X$ when forming clusters. We explore sensitivity to the specification of these prior parameters in Section 6.1.

5.1. Simulation Study: Toy Example. In this simulation, data sets consisting of three binary covariates are generated (i.e., $X_i \in \{0, 1\}$, for $i = 1, 2, 3$). The response distribution $f(Y|X_1, X_2, X_3)$ is made to explicitly depend on $X = (X_1, X_2, X_3)$ in the three ways that are listed in Table 4. Each row of the table represents a possible covariate combination and the columns correspond to a particular response distribution. Note first that only $X_1$ and $X_2$ influence the distribution of $Y$ and they do so multiplicatively (i.e., they interact in the linear model sense). As a control, we consider the case where the distribution of $Y$ does not depend on $X$ in any way, which is denoted by $f_0(Y|X)$. From Table 4 note that $f_0(Y|X)$ corresponds to a standard normal regardless of the values of $X$. For $f_1(Y|X)$ the variance and shape remain the same regardless of the value of $X$, but the mean changes based on the values of $X_1$ and $X_2$. For $f_2(Y|X)$, the mean and shape remain the same, but the variance changes depending on the values of $X_1$ and $X_2$. Lastly, for $f_3(Y|X)$ the mean and variance do not change but the values $X_1$ and $X_2$ influence the shape. The scenario under $f_1(Y|X)$ follows the traditional definition of an interaction and thus can be detected using any number of procedures. The other two scenarios would not be detected even if an interaction between $X_1$ and $X_2$ is explicitly included in a linear model.

| $X_1$ | $X_2$ | $X_3$ | $f_0(Y|X)$ | $f_1(Y|X)$ | $f_2(Y|X)$ | $f_3(Y|X)$ |
|-------|-------|-------|------------|------------|------------|------------|
| 1     | 1     | 1     | $N(0, 1)$  | $N(0, 1)$  | $N(0, 1)$  | $N(0, 1)$  |
| 1     | 1     | 0     | $N(0, 1)$  | $N(0, 1)$  | $N(0, 1)$  | $N(0, 1)$  |
| 1     | 0     | 1     | $N(0, 1)$  | $N(2, 1)$  | $N(0, 3)$  | $SN(a, b, c)$ |
| 1     | 0     | 0     | $N(0, 1)$  | $N(2, 1)$  | $N(0, 3)$  | $SN(a, b, c)$ |
| 0     | 1     | 1     | $N(0, 1)$  | $N(0, 1)$  | $N(0, 1)$  | $N(0, 1)$  |
| 0     | 1     | 0     | $N(0, 1)$  | $N(0, 1)$  | $N(0, 1)$  | $N(0, 1)$  |
| 0     | 0     | 1     | $N(0, 1)$  | $N(4, 1)$  | $N(0, 6)$  | $\sum_{j=1}^2 p_j N(m_j, s_j^2)$ |
| 0     | 0     | 0     | $N(0, 1)$  | $N(4, 1)$  | $N(0, 6)$  | $\sum_{j=1}^2 p_j N(m_j, s_j^2)$ |
For each scenario we generated 1000 data sets each with 500 observations and model (5.1) was fit. At each MCMC iterate of $\rho_m$, cluster-specific association rules were gathered using the \texttt{apriori} function found in the \texttt{arules} package (Hahsler et al. 2015) of the statistical software \texttt{R} (R Core Team 2017). This function is based on the \texttt{apriori} algorithm of Agrawal et al. 1996. We considered association rules from clusters that contained at least 10 subjects/experimental units. After association rules were gathered using a lower bound support of 0.25 and confidence of 0.5, we identified the covariate tandem that had the highest total support and confidence. If this resulted in a tie, then both covariate tandems were considered. Then for each association rule, the Pólya tree-based testing procedure of Chen and Hanson (2014) was used to test the hypothesis in (4.1). The $X$ variable absent from the association rule was fixed to its empirical median value. The $p$-values from this testing procedure are derived from permutation tests and values in Table 5 are based on 500 permutations.

Lastly, since the number of posterior predictive draws collected to test (4.1) can be selected somewhat arbitrarily, the adage “statistical vs practical significance” is important here as it would be undesirable to reject (4.1) for differences among predictive densities that are inconsequential. Thus, when carrying out the test of Chen and Hanson (2014), we considered $N \in \{50, 100, 250\}$ posterior predictive draws.

| Table 5 |

$p$-values averaged over 1000 synthetic datasets from testing hypothesis (4.1) using the Pólya tree method of Chen and Hanson (2014).

<table>
<thead>
<tr>
<th>arules</th>
<th>$N = 50$</th>
<th>$N = 100$</th>
<th>$N = 250$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$f_0$</td>
<td>$f_1$</td>
<td>$f_2$</td>
</tr>
<tr>
<td>$X_1 \leftrightarrow X_2$</td>
<td>0.53</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>$X_1 \leftrightarrow X_3$</td>
<td>0.47</td>
<td>0.54</td>
<td>0.50</td>
</tr>
<tr>
<td>$X_2 \leftrightarrow X_3$</td>
<td>0.49</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

In the online supplementary material, we provide a more detailed description of the simulation study results for each of the 24 possible association rules, but here we focus on results for testing (4.1) which are found in Table 5. Each column of the table contains the $p$-values produced by the Chen and Hanson (2014)’s Pólya tree method averaged across the 1000 data sets. The Monte Carlo errors associated with entries found in Table 5 are all small with the largest being 0.01. From Table 5 it seems that for this data generating mechanism, it is sufficient to only consider 50 posterior predictive draws when testing the hypothesis for all three interaction types.

From Table 5 it also seems that under $f_0$ the average $p$-value is large
Fig 1. Posterior predictive densities for the six combinations of $X_1$, $X_2$, and $X_3$ based on a synthetic data set used in the simulation study.
in all cases indicating that the posterior predictive densities in (4.1) are essentially the same regardless of the number of posterior predictive draws and association rule. This was expected. Similarly, $X_1 \leftrightarrow X_3$ under $f_1$, $f_2$, and $f_3$ and $X_2 \leftrightarrow X_3$ under $f_3$ produced large $p$-values which was also expected. Since there is an interaction between $X_1$ and $X_2$, the small $p$-values associated with $X_1 \leftrightarrow X_2$ under $f_1$, $f_2$, and $f_3$ were expected. However, notice that under $f_1$ and $f_2$ the association rule that includes $X_2$ and $X_3$ also produced small $p$-values for (4.1). This was unexpected. Since $X_2$ and $X_3$ do not interact, fixing $X_1$ makes it so that (4.1) amounts to testing for the “marginal effect” of $X_2$. Thus, small $p$-values associated with hypothesis (4.1) can indicate an interaction or a marginal effect. To correctly determine which, further testing can be carried out, or the posterior predictive densities being compared in (4.1) should be carefully examined. Here, we carried out the later by providing posterior predictive densities in Figure 1. Estimated densities in the figure correspond to the first synthetic data set generated based on $f_1$. The first row of the figure corresponds to densities when $X_3$ is fixed, the second row when $X_2$ is fixed, and the third when $X_1$ is fixed. Notice that the densities in the first row are noticeably different and clearly depend on the levels of $X_1$ and $X_2$ (i.e., there is an interaction between $X_1$ and $X_2$). Close inspection of rows 2 and 3 of the figure shows that differences seen in the posterior predictive densities are not due to $X_3$ at all, but entirely to $X_1$ for the second row and $X_2$ for the third. Thus, graphs like Figure 1 are able to help determine if interactions correspond to “main effects” or “interaction effects” as they are typically defined in a linear model setting. Ultimately, the take home message of Table 5 and Figure 1 is that the exploratory procedure is able to identify that $X_1$ and $X_2$ interact regardless of the influence that they have on the distribution of $Y$.

Next we compared the performance of our method to five other approaches to detect an interaction between $X_1$ and $X_2$. To this end, to each generated data set, we applied the following procedures:

1. linear model with all main effects and two-way interactions;
2. spike & slab model of Ishwaran and Rao (2005) with all main effects and two-way interactions;
3. the hierarchical group-Lasso (hgLASSO) procedure in Lim and Hastie (2015a);
4. the BART procedure detailed in Kapelner and Bleich (2016);
5. procedure based on XGBoost (Karbowiak and Biecek 2019).

Each of the listed methods were fit in R using the following: `lm` function for linear model, the `spikeslab` package (Ishwaran, Rao and Kogalur 2013) for
spike & slab, the glinternet package (Lim and Hastie 2019) for hgLASSO, the bartMachine package (Kapelner and Bleich 2016) for BART, and the xgboost package (Chen et al. 2019) coupled with the EIX package (Karbowiak and Biecek 2019) for XGBoost. To apply the procedures just listed, some-type of user input was required to confirm an interaction was detected. For sake of conciseness, we provide specific details of how procedures were implemented in the online supplementary material.

To study the impact that the RPM prior might have on results, we also used the RAID procedure coupled with the induced random partition distribution from the ANOVA DDP. The particular ANOVA DDP we employed is that for which the atoms were made to depend on group membership (as defined by the three categorical covariates), but weights did not. Lastly, we checked the sensitivity of results to posterior convergence by identifying interactions based on an MCMC chain that was run for only 500 iterations.

The values listed in Table 6 are the proportion of data sets for which the interaction between $X_1$ and $X_2$ was correctly identified. The Monte Carlo standard errors associated with proportions in Table 6 were all very small with 0.09 (associated with “RAID with ANOVA DDP, N = 100”) being the largest. Notice that when no interaction was present all procedures performed similarly except for XGBoost and RAID with ANOVA DDP. These two procedures seemed to be more liberal in their interaction detection. When the interaction was based on the expectation of the response distribution (column $f_1$), all procedures detected the interaction except for XGBoost. However, if the interaction was based on the variance or shape of the response distribution, the RAID procedure with PPMx was the only one that consistently detected it. Lastly, the RAID procedure still performed surprisingly well even when the number of collected MCMC iterates was small.

5.2. Simulation Study: Osteonecrosis Study Covariate Structure. We now describe a simulation study where the number of covariates in each synthetic data set is similar to that found in the osteonecrosis study. More specifically, each synthetic data set contained 21 covariates, 19 of which were continuous and 2 binary. The binary covariate values were generated using a Bernoulli distribution with probability of success equal to 0.5. The continuous covariates were generated using a continuous uniform distribution with support $(-1, 1)$. We created interactions that impact the mean, spread, and shape of the response distribution in two ways. The first employed the setup established in Table 4 except that instead of one noise covariate that was categorical, there were 19 continuous noise covariates.
Table 6: Percent of datasets in the simulation study for which the interaction between $X_1$ and $X_2$ was correctly identified.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>$f_0$</th>
<th>$f_1$</th>
<th>$f_2$</th>
<th>$f_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear Model</td>
<td>0.04</td>
<td>1.00</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Spike &amp; Slab</td>
<td>0.08</td>
<td>1.00</td>
<td>0.05</td>
<td>0.09</td>
</tr>
<tr>
<td>hgLASSO</td>
<td>0.09</td>
<td>1.00</td>
<td>0.12</td>
<td>0.10</td>
</tr>
<tr>
<td>BART</td>
<td>0.00</td>
<td>0.99</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>XGBoost</td>
<td>0.27</td>
<td>0.54</td>
<td>0.37</td>
<td>0.40</td>
</tr>
<tr>
<td>RAID with ANOVA DDP, $N = 50$</td>
<td>0.19</td>
<td>1.00</td>
<td>1.00</td>
<td>0.23</td>
</tr>
<tr>
<td>RAID with ANOVA DDP, $N = 100$</td>
<td>0.44</td>
<td>1.00</td>
<td>1.00</td>
<td>0.47</td>
</tr>
<tr>
<td>RAID with ANOVA DDP, $N = 250$</td>
<td>0.61</td>
<td>1.00</td>
<td>1.00</td>
<td>0.87</td>
</tr>
<tr>
<td>RAID with PPMx, $N = 50$</td>
<td>0.06</td>
<td>1.00</td>
<td>1.00</td>
<td>0.96</td>
</tr>
<tr>
<td>RAID with PPMx, $N = 100$</td>
<td>0.04</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>RAID with PPMx, $N = 250$</td>
<td>0.08</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Results with only 500 MCMC iterates

<table>
<thead>
<tr>
<th>Procedure</th>
<th>$f_0$</th>
<th>$f_1$</th>
<th>$f_2$</th>
<th>$f_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAID with PPMx, $N = 50$</td>
<td>0.10</td>
<td>1.00</td>
<td>1.00</td>
<td>0.23</td>
</tr>
<tr>
<td>RAID with PPMx, $N = 100$</td>
<td>0.28</td>
<td>1.00</td>
<td>1.00</td>
<td>0.73</td>
</tr>
<tr>
<td>RAID with PPMx, $N = 250$</td>
<td>0.13</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

The second method of generating data sets was based on interactions that depend on continuous covariates. This was done by using the following data generating mechanisms to generate response values:

- $Y \sim N(5X_1X_2, \sigma)$ (interaction affecting mean);
- $Y \sim N(0, \exp\{5X_1X_2\}\sigma)$ (interaction affecting spread);
- $Y \sim \pi(X_1, X_2)N(0, \sigma) + (1 - \pi(X_1, X_2)) \left[0.5N(-0.5, \sigma) + 0.5N(0.5, \sigma)\right]$ where $\pi(X_1, X_2) = 1/(1 + \exp\{200X_1X_2\})$ (interaction affecting shape).

For this setting $X_1$ and $X_2$ were continuous covariates generated using a uniform distribution with support $(-1, 1)$. Similar to what was done before, 19 “noise” covariates were also included 17 of which were continuous (coming from a uniform distribution with support $(-1, 1)$) and two binary (coming from a Bernoulli distribution with probability of success equal to 0.5).

We explored how the ratio of signal to noise affected the ability to detect interactions by considering $\sigma \in \{10^{-3}, 10^{-2}, 10^{-1}, 10^0\}$. Finally, we also considered the case when only 60% and 25% of observations exhibited the interaction. This was done by using a $N(0, 1)$ distribution to generate response values for 40% (or 75%) of the units.

To each synthetic data set, the RAID PPMx procedure was fit along with the six competitors introduced in the previous section. For each procedure we recorded if the interaction was detected (True Positive) and also enu-
merated the number of falsely detected interactions (False Positives). We briefly note that since association rules require discrete variables, before employing association rules for each cluster, the continuous covariates were dichotomized such that an equal number of observations belonged to each interval.

Here we only present results for when the interaction was present in 100% of the population and include results when the interaction was present in only 60% or 25% of the population in the online supplementary material (see figures S.1-S.4). Trends were similar in all scenarios except that it became more challenging to detect interactions as the percent of population that exhibits interaction decreased with the RAID method being the least impacted when the interaction only applies to a subset of the population.

In Figure 2, notice that except for XGBoost all methods did reasonably well in recovering the interaction that affects the mean between two categorical covariates, with the RAID and LM methods decaying more when the signal-to-noise ratio decreased. When interactions based on continuous covariates affected mean, the RAID method did the worst (only detecting the interaction in about 50% of the synthetic datasets). However, when interactions affected spread or shape, the RAID procedure is the only method that was able to detect the interaction with any type regularity. The BART method won when interaction between continuous covariates affected the spread and the XGBoost method tended to perform the worst.

Figure 3 displays the false positives. It seems that the spike & slab and RAID procedures tended to produce the most amount of false positives while the LASSO and BART method did reasonably well in avoiding this. Upon further investigation, many of the false positives detected by the RAID procedure included one of $X_1$ or $X_2$ (covariates that participated in the interaction). In fact, if interactions that included either $X_1$ or $X_2$ were not classified as false positives, then the number of false positives detected by the RAID procedure averaged over all data generating scenarios was only 1.01. Thus, as discussed in the previous section, the RAID procedure detects any combination of covariates that affect the response distribution in some way.

6. Interactions in the Osteonecrosis Study. We now turn our attention to the osteonecrosis study. Since the response is an ordinal variable it is natural to consider latent variable ordinal data models as those described in Bao and Hanson (2015) and in Kottas, Müller and Quintana (2005). These types of models are clearly more complex than that in (3.1), but they permit demonstrating the flexibility of the exploratory procedure
Fig 2. Results from the second simulation study. The percentage of synthetic datasets for which the interaction was detected. In each figure, the top row corresponds to an interaction that is based on categorical covariates and the bottom row to continuous covariates.
Fig 3. Results from the second simulation study. The average number of falsely detected interactions are provided. In each figure, the top row corresponds to an interaction that is based on categorical covariates and the bottom row to continuous covariates.
as any data model can be employed so long as the response is connected to the covariates through a dependent random partition model (or analogous predictor dependent clustering procedures).

For the sake of completeness we detail the ordinal model in its entirety. Let \( Y_i \in \{0, 1, 2, 3, 4\} \) be the ordinal response measured on the \( i \)th patient \( i = 1, \ldots, 234 \). Further, let \( X_i = (X_{i1}, \ldots, X_{i22}) \) denote subject \( i \)'s 22-dimensional covariate vector. As is done in Bao and Hanson (2015), real-valued latent scores \( Z_1, \ldots, Z_n \) are introduced such that for \( -\infty = \gamma_0 < \gamma_1 < \ldots \gamma_4 < \gamma_5 = \infty \),

\[
Y_i = \ell \Leftrightarrow \gamma_\ell < Z_i \leq \gamma_{\ell+1} \text{ for } \ell = 0, \ldots, 4.
\]

The appeal of employing the methods described in Bao and Hanson (2015) and Kottas, Müller and Quintana (2005) is that the values selected for \( \gamma \) are immaterial, so long as the model is flexible enough to assign sufficient probability mass to each \( (\gamma_\ell, \gamma_{\ell+1}] \) interval. Since assigning a PPMx prior to \( \rho_m \) results in modeling the latent ordinal scores with a mixture (which is essentially the same data model arising from marginalizing the random measure in the approach by Bao and Hanson 2015), we conclude that the model we specify affords sufficient flexibility and, therefore, the \( \gamma \)'s can be selected arbitrarily. In light of this we set \( \gamma_1 = 0, \gamma_2 = 1/3, \gamma_3 = 2/3, \gamma_4 = 3/3 \). The remainder of the model is expressed hierarchically after introducing latent cluster labels \( s_1, \ldots, s_n \)

\[
Z_i | \mu^*, \sigma^{2*}, s_i \sim N(\mu^*_s, \sigma^{2*}_s),
\]

\[
(\mu^*_j, \sigma^{*}_j) \sim N(\mu_0, \sigma^2_0) \times \text{Unif}(0, A),
\]

\[
Pr(\rho | X) \propto \prod_{j=1}^k c(S_j) g(X^*_j),
\]

where \( c(S_j) \) and \( g(X^*_j) \) are set to functions detailed in Section 3.1. Further, we assume \( \mu_0 \sim N(0, 10^2), \sigma_0 \sim \text{Unif}(0, 10) \), and set \( A = 0.1 \).

This model was fit to the osteonecrosis data by collecting 1000 MCMC iterates after discarding the first 10,000 as burn-in and thinning by 15. Afterwards, we identified association rules for each MCMC iterate of \( \rho_m \). Covariate values for those variables not identified in the association rule are set to the overall median. Testing (4.1) was done by using Chen and Hanson (2014)'s method based on 500 permutations and 100 posterior predictive draws. This testing procedure was replicated five times with a unique set of 100 random posterior predictive draws and the average \( p \)-value is reported. (We stress again that \( p \)-values are used only as a validation summary and no
notion of Type I error is implied.) As in the simulation study, each continuous covariate was dichotomized such that an equal number of observations belonged to each interval when employing association rules. Also, we explored the impact that trichotomizing continuous covariates might have on the RAID exploratory procedure. Results are provided in the online supplementary material.

Since the study was conducted specifically to explore if dexamethasone clearance (DexCl) and/or asparaginase (AsparaginaseAntibodyAUC) interact with other physiological measurements, we restrict attention to those association rules that contain at least one of these two covariates. Results for interactions that appeared in at least 50% of the MCMC iterates are provided in Table 7. The column “Pr” corresponds to the percent of MCMC iterates that identified the particular association rule, “Supp.” is the support, “Conf.” the confidence, $|S|$ corresponds to average cluster size from which association rule was identified and “p-value” indicates the result of testing (4.1). Details associated with the “#Prior” column are provided in Section 6.1. Notice that DexClWk07 interacts with LowRisk and AlbuminWk07 while DexClWk08 interacts with HDLWk08. On the other hand, Asparaginase seems to interact with AlbuminWk07, HDLWk07, and LDLWk08. Figure 4 contains the posterior predictive densities corresponding to the first four association rules in Table 7 that do not contain LowRisk. Interestingly, we can also note that the interaction between AlbuminWk07 and AsparaginaseAntibodyAUC influences the shape of the predictive densities verifying that there is indeed an interaction between them and the interaction seems to impact the shape of the response distribution (as evidenced by changes in shape of the predictive distributions).

| Association Rule | Pr   | Supp. | Conf. | $|S|$ | p-value | #Prior |
|------------------|------|-------|-------|-----|---------|--------|
| DexClWk07 ⇔ LowRisk | 1.00 | 0.62  | 0.91  | 43.44 | 0.00    | 16     |
| DexClWk07 ⇔ AlbuminWk07 | 0.99 | 0.58  | 0.85  | 39.65 | 0.01    | 15     |
| AsparaginaseAntibodyAUC ⇔ AlbuminWk07 | 0.93 | 0.84  | 0.95  | 39.35 | 0.00    | 14     |
| AsparaginaseAntibodyAUC ⇔ HDLWk07 | 0.81 | 0.72  | 1.00  | 10.40 | 0.01    | 7      |
| AsparaginaseAntibodyAUC ⇔ LowRisk | 0.81 | 0.87  | 0.98  | 40.55 | 0.18    | 17     |
| AsparaginaseAntibodyAUC ⇔ LDLWk08 | 0.55 | 0.53  | 0.88  | 15.71 | 0.00    | 6      |
| DexClWk08 ⇔ HDLWk08 | 0.53 | 0.51  | 0.88  | 16.36 | 0.00    | 8      |
| DexClWk08 ⇔ AlbuminWk08 | 0.50 | 0.83  | 0.98  | 10.66 | 0.85    | 3      |

Being able to interpret results at the latent level is not always straightforward. Thus it would be appealing to determine how interactions influence
the risk of osteonecrosis. Table 8 contains predictive probabilities associated with each osteonecrosis grade for specific levels of covariates found in interactions displayed Figure 4 that contain DexCl. It appears that low level of DexCl results in higher risk of grade 2 or higher osteonecrosis, but the exact risk depends on the levels of the other covariates (AlbuminWk07 and HDLWk08). The combination of low DexClWk07 and high AlbuminWk07 results in the highest risk of osteonecrosis. This leads one to hypothesize that a three-way interaction between Albumin, HDL, and DexCl may be present. We explored this by testing a version of (4.1) that includes posterior predictive densities for all possible combinations of the three covariates (eight in total). Doing this resulted in rejecting the null (with a $p$-value of 0) that all densities are equal and hence we conclude that a three-way interaction exists. More details are provided in the online supplementary material.

The online supplementary material also provides details on how the RAID procedure can accommodate the temporal structure that exists among the covariates through the PPMx prior. This is done by considering a multivariate similarity. As is seen in the supplementary material, including temporal dependence in the partition prior affects partition configuration and as a result interactions that are identified by the RAID procedure.

Table 8

<table>
<thead>
<tr>
<th>Covariates</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlbuminWk07 - L, DexClWk07 - L</td>
<td>0.124</td>
<td>0.818</td>
<td>0.058</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>AlbuminWk07 - L, DexClWk07 - H</td>
<td>0.193</td>
<td>0.805</td>
<td>0.002</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>AlbuminWk07 - H, DexClWk07 - L</td>
<td>0.282</td>
<td>0.643</td>
<td>0.061</td>
<td>0.014</td>
<td>0.000</td>
</tr>
<tr>
<td>AlbuminWk07 - H, DexClWk07 - H</td>
<td>0.414</td>
<td>0.569</td>
<td>0.017</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>DexClWk08 - L, HDLWk08 - L</td>
<td>0.200</td>
<td>0.799</td>
<td>0.001</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>DexClWk08 - L, HDLWk08 - H</td>
<td>0.195</td>
<td>0.805</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>DexClWk08 - H, HDLWk08 - L</td>
<td>0.287</td>
<td>0.682</td>
<td>0.030</td>
<td>0.001</td>
<td>0.000</td>
</tr>
<tr>
<td>DexClWk08 - H, HDLWk08 - H</td>
<td>0.330</td>
<td>0.667</td>
<td>0.003</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

6.1. Sensitivity to Prior Specification. Even though we developed the RAID procedure to be as automatized as possible (after standardizing covariates and possibly the response), there still are “tuning” parameters that can affect the list of possible interactions. Those that are most influential are prior parameter specifications that have direct impact on $\pi(\rho_m|Y, X)$. In Section 5 we mentioned that for model 5.1 these are $A$ and $k_0$ as they
Fig 4. Posterior predictive densities for the latent variable $z$ and used in hypothesis test (4.1) for the first four association rules in Table 7 that do not include LowRisk. The vertical lines correspond to $\gamma_1, \ldots, \gamma_4$. 

\[ p\text{valueBNP} = 0.0052 \]

\begin{align*}
\text{Density} & \quad z \\
\text{AlbuminWk07} = L, \text{DexClWk07} = L & \quad \text{Density} \\
\text{AlbuminWk07} = H, \text{DexClWk07} = L & \quad \text{Density} \\
\text{AlbuminWk07} = L, \text{DexClWk07} = H & \quad \text{Density} \\
\text{AlbuminWk07} = H, \text{DexClWk07} = H & \quad \text{Density}
\end{align*}

\[ p\text{valueBNP} = 0 \]

\begin{align*}
\text{Density} & \quad z \\
\text{AlbuminWk07} = L, \text{AsparaginaseAntibodyAUC} = L & \quad \text{Density} \\
\text{AlbuminWk07} = H, \text{AsparaginaseAntibodyAUC} = L & \quad \text{Density} \\
\text{AlbuminWk07} = L, \text{AsparaginaseAntibodyAUC} = H & \quad \text{Density} \\
\text{AlbuminWk07} = H, \text{AsparaginaseAntibodyAUC} = H & \quad \text{Density}
\end{align*}

\[ p\text{valueBNP} = 0.0088 \]

\begin{align*}
\text{Density} & \quad z \\
\text{AsparaginaseAntibodyAUC} = L, \text{HDLWk07} = L & \quad \text{Density} \\
\text{AsparaginaseAntibodyAUC} = H, \text{HDLWk07} = L & \quad \text{Density} \\
\text{AsparaginaseAntibodyAUC} = L, \text{HDLWk07} = H & \quad \text{Density} \\
\text{AsparaginaseAntibodyAUC} = H, \text{HDLWk07} = H & \quad \text{Density}
\end{align*}

\[ p\text{valueBNP} = 0 \]

\begin{align*}
\text{Density} & \quad z \\
\text{DexClWk08} = L, \text{HDLWk08} = L & \quad \text{Density} \\
\text{DexClWk08} = H, \text{HDLWk08} = L & \quad \text{Density} \\
\text{DexClWk08} = L, \text{HDLWk08} = H & \quad \text{Density} \\
\text{DexClWk08} = H, \text{HDLWk08} = H & \quad \text{Density}
\end{align*}
regulate the influence that \( Y \) and \( X \) have on cluster formation. Note that as \( A \to 0 \), clusters become more heterogeneous with respect to \( Y \) while as \( k_0 \to 0 \) clusters become more heterogeneous with respect to \( X \). To explore sensitivity to these three prior specifications, we ran the RAID procedure for the osteonecrosis data based on \( A \in \{0.1, 1, 10\} \) and \( k_0 \in \{0.1, 1, 10\} \). Since the cohesion function also has an effect on \( \pi(\rho_m|Y, X) \), we ran the RAID procedure using \( c(S_j) = 1 \) (a uniform type cohesion function) in addition to \( c(S_j) = M \times (|S| - 1)! \). This resulted in 18 runs of the RAID procedure which on average took about 15 minutes for each to run. Tables that list the potential interactions for each of the 18 runs are provided in the online supplementary material. Here we briefly summarize the results.

The prior specification that had the least impact on the list of interactions was the cohesion function \( c(\cdot) \). Overall, 23 unique interactions were detected in at least one of the 18 prior configurations. All the interactions found in Table 7 were part of the list of 23. The column labeled “#Prior” in Table 7 is the number of prior configurations in which the interaction was detected. There seems to be a general agreement among the prior specifications making the results fairly robust.

Lastly, as a type of follow-up analysis, using the \texttt{polr} function found in the \texttt{MASS} R-package (Venables and Ripley 2002), we fit a ordered logistic regression model that included all eight two-way interactions listed in Table 7 and their corresponding main effects along with the three-way interaction detailed in the online supplementary material. (We remark that fitting a saturated ordered logistic regression model with all two-way interactions for these data is not possible.) This model did provide some evidence to suggest that an interaction between \texttt{DexClWk08} and \texttt{HDLWk08} along with \texttt{AsparaginaseAntibodyAUC} and \texttt{HDLWk07} was present in addition to the three-way interaction, but failed to identify any of the other interactions. This suggests that the added flexibility of our exploratory approach can be useful to detect interactions that would not be possible under more restricted alternatives.

\textbf{7. Conclusions.} We have detailed an exploratory procedure that in a general way is able to identify interactions. The definition of interaction that we espouse is more general than that typically associated with linear models. Here we conceptualize an interaction as influencing any aspect of the response distribution rather than focusing solely on the first moment. Further, the procedure is able to identify interactions without \textit{a priori} information regarding which (multiplicative) effects to include in a data model. This was seen when applying the procedure to the osteonecrosis data set.
In the application, relationships that were known to exist (e.g., Low DexCl and higher risk of osteonecrosis) were identified without considering them explicitly in the procedure. In addition, a three-way interaction, also not explicitly included in the data model, was highlighted (see supplementary material). This interaction was not previously known by the investigators, and its scientific relevance has yet to be determined.

We also demonstrated that the procedure can be easily employed regardless of the type of response being measured. Indeed, the procedure is essentially “data model free” as it can be employed regardless of the data model so long as some type of random partition model is employed. Note however, that our exploratory procedure only identifies potential interactions. That is, it does not estimate their effect. If this is desired, then any number of statistical procedures that include the specific covariates identified by our procedure can be employed (i.e., some form of regression).

One limitation of the RAID procedure (which is more a MCMC limitation) is that computation associated with the PPMx does not tend to scale well as \( p \) and/or \( n \) grows. Future research will be dedicated to implementing methods in the RAID procedure that permits it to scale well.

Finally, we provide some general recommendations when employing the RAID procedure. For the first step we recommend using the PPMx as the RPM. To automate the prior specification of model 5.1, we suggest standardizing the response and covariates and setting \( A = 0.5 \) and \( k_0 = 0.5 \). This essentially puts equal weight on \( Y \) and \( X \) when forming clusters. Decisions associated with step two determine how big a “net” one wants to cast when searching for interactions with the understanding that a larger “net” could result in more false positives. Decreasing support and confidence will cast a larger “net” as will decreasing the number of MCMC iterates in which an association must appear. Informal explorations led us to set support to 0.25, confidence of 0.5 and that a particular association rule should appear in 50% of MCMC iterates before being formally considered. For step three we suggest using 100 posterior predictive draws when comparing predictive densities and a cut-off of 0.01 for “\( p \)-values” if the Chen and Hanson (2014) method is used. This is somewhat arbitrary but worked to identify interactions well in the simulations. Lastly, we recommend using posterior predictive densities to visualize the interactions. Doing so will highlight how the interaction is affecting the response distribution be it a shift in expectation as in Figure 1 or a change in shape as in Figure 4. If it is determined that the interaction affects the expectation of the response distribution, then a follow-up analysis to quantify interaction effects can be carried out using generalized linear models. If the interaction affects the response dis-
tribution in some other way, then formal additional analysis is not available and quantifying the interaction effects will requiring other (perhaps ad-hoc) approaches similar to our approach with the osteonecrosis data set.

Acknowledgements. We thank all the reviewers for comments and suggestions that helped us to greatly improve this manuscript. We thank Drs. Yuhui Chen and Timothy Hanson for kindly sharing code that carries out the Pólya Tree permutation test. Garritt L. Page was partially supported by the Basque Government through the BERC 2018-2021 program, by the Spanish Ministry of Science, Innovation and Universities through BCAM Severo Ochoa accreditation SEV-2017-0718. Fernando A. Quintana was supported by grant FONDECYT 1180034 and by Millennium Science Initiative of the Ministry of Economy, Development, and Tourism, grant “Millenium Nucleus Center for the Discovery of Structures in Complex Data”. Gary L. Rosner was partially funded by grants GM092666 and P30CA006973.

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