varbvs: Fast Variable Selection for Large-scale Regression

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Abstract

We introduce varbvs, a suite of functions written in R and MATLAB for regression analysis of large-scale data sets using Bayesian variable selection methods. We have developed numerical optimization algorithms based on variational approximation methods that make it feasible to apply Bayesian variable selection to very large data sets. With a focus on examples from genome-wide association studies, we demonstrate that varbvs scales well to data sets with hundreds of thousands of variables and thousands of samples, and has features that facilitate rapid data analyses. Moreover, varbvs allows for extensive model customization, which can be used to incorporate external information into the analysis. We expect that the combination of an easy-to-use interface and robust, scalable algorithms for posterior computation will encourage broader use of Bayesian variable selection in areas of applied statistics and computational biology. The most recent R and MATLAB source code is available for download at Github (https://github.com/pcarbo/varbvs), and the R package can be installed from CRAN (https://cran.r-project.org/package=varbvs).

Keywords: Bayesian variable selection, linear regression, logistic regression, approximate posterior computation, variational inference, Bayes factors, genome-wide association studies, quantitative trait locus mapping, R, MATLAB.

1. Introduction

Bayesian variable selection (BVS) models, and extensions to these models, have recently been shown to provide attractive solutions to a number of important problems in genome-wide association studies (e.g., Carbonetto and Stephens 2012, 2013; Guan and Stephens 2011; Lee et al. 2008; Hoggart et al. 2008; Logsdon et al. 2010; Meuwissen et al. 2001; Moser et al. 2015; Wallace et al. 2015; Zhou et al. 2013). Despite this progress, BVS methods have not been widely adopted for genome-wide association studies (GWAS) and other areas where large-
scale regression is applied. One limiting factor is that computing exact posterior probabilities, which reduces to a high-dimensional integration problem, is intractable except in very small data sets, and standard approaches for approximating these high-dimensional integrals using Monte Carlo techniques scale poorly to large data sets (Bottolo and Richardson 2010; Clyde et al. 2011; Dellaportas et al. 2002; Erbe et al. 2012; Guan and Stephens 2011; Perez and de los Campos 2014; Wallace et al. 2015; Zhou et al. 2013). A second barrier is that the choice of priors requires considerable expertise in Bayesian data analysis. We aim to address these limitations and make BVS methods more accessible.

Here, we present a software toolkit for fitting variable selection models to large-scale data sets. We call our software \texttt{varbvs}—short for “variational Bayesian variable selection”—as it builds on Bayesian models for variable selection in regression (George and McCulloch 1993; Mitchell and Beauchamp 1988; O’Hara and Sillanpää 2009) and variational approximation techniques for fast posterior computation (Blei et al. 2016; Jordan et al. 1999; Logsdon et al. 2010; Ormerod and Wand 2010; Wainwright and Jordan 2008). We have developed efficient implementations for both R (R Core Team 2016) and MATLAB (The MathWorks, Inc. 2016), which we have applied to data sets containing hundreds of thousands of variables and thousands of samples. \texttt{varbvs} also provides default priors that are suitable for many problem areas, while allowing for extensive customization. While our initial motivation was to facilitate use of multiple regression models for genome-wide association studies (Carbonetto and Stephens 2012; Guan and Stephens 2011), Bayesian variable selection methods are general and widely applicable, and we expect that \texttt{varbvs} will be useful in many other areas of applied statistics and computational biology.

Our second aim is to provide an alternative to commonly used toolkits for penalized regression. \texttt{varbvs} is comparable to the popular R package \texttt{glmnet} (Friedman et al. 2010), which combines penalized sparse regression—specifically, the Lasso (Tibshirani 1994) and the Elastic Net (Zou and Hastie 2005)—with advanced optimization techniques (Friedman et al. 2007). The \texttt{varbvs} interface is designed to be similar to \texttt{glmnet} so that researchers already familiar with these methods can easily explore the benefits of the BVS approach. In our first example (Sec. 2), we illustrate the shared features and differences of \texttt{glmnet} and \texttt{varbvs}.

An important advantage of BVS over penalized regression is that it provides a measure of uncertainty in the parameter estimates. For example, \texttt{varbvs} computes, for each candidate variable, the probability that the variable is included in the regression model—what we call the “posterior inclusion probability” (PIP). A second advantage of BVS over penalized regression is that it allows for the possibility of model comparison through approximate computation of Bayes factors (Kass and Raftery 1995). We demonstrate both advantages in the examples below.

The structure of the paper is as follows. In Sec. 2, we given an extended example that illustrates the key features of \texttt{varbvs}, comparing it to \texttt{glmnet}. Section 3 briefly reviews Bayesian variable selection in regression, and explains how it is implemented in \texttt{varbvs}. Sections 4 and 5 give more advanced examples illustrating the application of \texttt{varbvs} to large data sets with tens or hundreds of thousands of variables. In Section 7, we end with additional discussion and recommendations on applying \texttt{varbvs} to small and large data sets.

Although this paper focuses on the R package, we note that a MATLAB interface is also available. The MATLAB implementation can be substantially faster for large data sets thanks to MATLAB’s state-of-the-art numerical computing platform. For this reason, we use the
MATLAB interface for the large data analyses in Sections 4 and 5.

2. Example illustrating features of glmnet and varbvs

We illustrate glmnet and varbvs on a smaller data set that has been used in previous papers to compare methods for penalized regression (e.g., Brehezy and Huang 2011; Friedman et al. 2010; Tibshirani et al. 2005; Zou and Hastie 2005). Our example is meant to demonstrate the varbvs R interface, and to provide some intuition for the different properties of BVS and penalized regression as implemented by varbvs and glmnet, respectively. The “leukemia” vignette in the R package reproduces the results and figures in this section.

The data consist of expression levels recorded for 3,571 genes in 72 patients with leukemia (Golub et al. 1999). The genes are the candidate variables. The binary outcome, modeled using a logistic regression, encodes the disease subtype: acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). We use the preprocessed data of Dettling (2004) retrieved from the supplementary materials accompanying Friedman et al. (2010). The data are represented as a 72 × 3571 matrix X of gene expression levels, and a vector y of 72 binary disease outcomes. We fit logistic models to these data using glmnet and varbvs, and explore properties of the fitted models.

We begin with glmnet. For each setting of the penalty strength parameter λ, glmnet fits a logistic regression by solving this convex optimization problem:

\[
\minimize_{\beta_0 \in \mathbb{R}, \beta \in \mathbb{R}^p} - \frac{1}{n} \sum_{i=1}^{n} \Pr(y_i | x_i, \beta_0, \beta) + \frac{\lambda}{2} (1 - \alpha) \| \beta \|^2_2 + \lambda \alpha \| \beta \|_1,
\]

where \( x_i \) is the vector of expression levels recorded in patient \( i \), \( y_i \) is the disease outcome, \( n = 72 \) is the number of samples, \( p = 3571 \) is the number of candidate variables, \( \beta \) is the vector of logistic regression coefficients, \( \beta_0 \) is the intercept, \( \| \cdot \|_1 \) is the \( \ell_1 \)-norm, \( \| \cdot \|_2 \) is the Euclidean (\( \ell_2 \)) norm, \( \Pr(y_i | x_i, \beta_0, \beta) \) is the logistic regression likelihood (see Equation 4 below). Following Friedman et al. (2010), \( \lambda \) determines the overall penalty strength, and \( \alpha \) balances the \( \ell_1 \) and \( \ell_2 \) penalty terms (here, we set \( \alpha = 0.95 \)).

This model fitting is accomplished with a single call to the glmnet function:

```R
R> data(leukemia, package = "varbvs")
R> library(glmnet)
R> X <- leukemia$x
R> y <- leukemia$y
R> fit.glmnet <- glmnet(X, y, family = "binomial", alpha = 0.95,
+ lambda = 10^seq(0, -2, -0.05))
```

(Note that we overrode the default lambda to make the plots below easier to follow—it yields a similar result to the default setting.) As part of the glmnet model fitting, the intercept and regression coefficients are estimated for each entry of lambda, and these are represented as a 3572 × 42 matrix coef(fit.glmnet).

The right-hand plot in Fig. 1 shows the characteristic shrinkage pattern of sparse regression methods such as the Lasso and the Elastic Net; as \( \lambda \) becomes larger, the \( \ell_1 \)-penalty term...
becomes more prominent, thereby encouraging more shrinkage of the regression coefficients. The bottom-left plot shows the total number of variables with non-zero coefficients at each \( \lambda \), and is another way visualizing this shrinkage pattern.

The top-left plot in Fig. 1 shows the evolution of the cross-validation classification error at the same settings of \( \lambda \). Small values of \( \lambda \) allow for more complex models, and therefore offer a better fit to the data. To guard against overly complex models that “overfit” to the data, \texttt{glmnet} uses cross-validation:

\[
R> \text{out.cv.glmnet <- cv.glmnet}(X, y, \text{family} = \text{"binomial"}, \text{type.measure} = \text{"class"}, + \lambda = 10^{-2}, 0.05)), \text{alpha} = 0.95, \text{n.folds} = 20) \\
R> \text{print(out.cv.glmnet$lambda.1se)}
\]

[1] 0.2239

The penalty strength selected by 20-fold cross-validation, \texttt{lambda.1se}, is depicted in the figure by the dotted vertical red lines. At this penalization level, \texttt{glmnet} yields a very sparse regression model—only 7 out of the 3,571 gene expression features are included in the model (Fig. 1, right-hand panel)—yet these 7 features are sufficient to correctly predict the leukemia outcome in 68 of the 72 training examples:

\[
R> \text{y.glmnet <- c(predict(fit.glmnet, X, s = out.cv.glmnet$lambda.1se, + type = \text{"class"}) )} \\
R> \text{print(table(true = factor(y), pred = factor(y.glmnet))} \\
\]

| pred | true |
|------|------|
|      | 0 47 |
|      | 1 21 |

The entire \texttt{glmnet} analysis, including cross-validation, is very fast; it took less than 3 seconds to run on a computer with a 1.86 GHz Intel Core 2 Duo processor.

Next, we compare this \texttt{glmnet} analysis against an analysis of the same data using \texttt{varbvs}. As before, we use logistic regression to model the outcome given the regression coefficients. However, rather than optimize the coefficients subject to a penalty, we introduce an exchangeable “spike-and-slab” prior \( \text{(Mitchell and Beauchamp 1988; George and McCulloch 1993)} \) on the coefficients \( \beta \),

\[
\Pr(\beta_i | \pi, \sigma^2_a) = (1 - \pi)\delta_0 + \pi N(0, \sigma^2_a), \tag{2}
\]

and we compute approximate posterior probabilities with respect to this prior. Additionally, instead of a two-step analysis—modeling fitting and cross-validation—the \texttt{varbvs} analysis is accomplished in a single function call:

\[
R> \text{library(varbvs)} \\
R> \text{fit.varbvs <- varbvs}(X = X, y = y, Z = NULL, \text{family} = \text{"binomial"})
\]
This command took about 30 seconds to run on the same computer.

The complexity of the regression model is controlled by the prior, which is determined by two parameters: the prior probability $\pi$ that a variable is included in the regression model, and $\sigma_a^2$, the prior variance of the non-zero regression coefficients. Similar to \texttt{glmnet}, \texttt{varbvs} fits a model separately for each setting of $\pi$. The default is a grid with 20 settings of $\pi$. Parameter $\sigma_a^2$ is estimated separately for each setting of $\pi$. This is only the default behaviour—it is also possible to define a grid over $\pi$ and $\sigma_a^2$ and fit models across all grid points.

To illustrate the effect that $\pi$ has on model complexity, we compute the classification error at each setting of $\pi$, stored as the prior log-odds, $\log_{10}(\frac{\pi}{1-\pi})$, in \texttt{fit.varbvs$logodds$}:

```r
R> m <- length(fit.varbvs$logodds)
R> err <- rep(0, m)
R> for (i in 1:m) {
```
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The classification error is shown in the top-left panel of Fig. 2. Like **glmnet**, the **varbvs** model predictions improve as the variable selection prior allows for more complex models. However, in contrast to **glmnet**, cross-validation is not needed to select an appropriate level of regularization—the Bayesian inference approach automatically weighs the accuracy of the model predictions against the model complexity (Jefferys and Berger 1992; MacKay 1992). In this example, more complex models—i.e., more variables included in the model—offer only a marginally better fit to the data, so the posterior distribution is most concentrated on less complex models (Fig. 2, top-right). In fact, the posterior is most concentrated on models in which the variance in the leukemia outcome is largely explained by a single feature (Fig. 2, bottom-left).

Like **glmnet**, the **varbvs** model also predicts the regression outcomes with good accuracy:

```r
R> y.varbvs <- predict(fit.varbvs, X)
R> print(table(true = factor(y), pred = factor(y.varbvs)))
```

Figure 2: **varbvs** analysis of leukemia data. *Top-left panel:* Prior inclusion probability $\pi$ against proportion of samples that are misclassified by the **varbvs** model. This should be compared against the wider orange line in the top-left panel of Fig. 1. *Bottom-left panel:* For each $\pi$ setting, expected number of variables (variables with non-zero coefficients) that are included in the model. *Top-right panel:* Estimated posterior distribution of $\pi$. 

```r
+ r <- subset(fit.varbvs, logodds == fit.varbvs$logodds[i])
+ ypred <- predict(r, X)
+ err[i] <- mean(y != ypred)
+ }
```
The accuracy of \texttt{varbvs} is statistically indistinguishable from \texttt{glmnet} in this case (6 errors compared to 4 errors in the \texttt{glmnet} analysis) and this accuracy is achieved by concentrating the posterior distribution on much simpler models than \texttt{glmnet} in which the variance in the leukemia outcome is mostly explained by a single predictor. This is possible in \texttt{varbvs} because the shrinkage behaviour is quite different from \texttt{glmnet}; as $\pi$ is decreased, the model becomes sparser (fewer included variables), but the most strongly included variable is hardly shrunk at all. That is, \texttt{varbvs} can achieve strong shrinkage of effects near zero without correspondingly strong shrinkage of the important predictors. This is a highly desirable feature that convex penalization methods such as the Lasso and Elastic Net struggle to achieve.

By default, \texttt{varbvs} yields \textit{averaged} predictions—that is, the model predictions are collected from all hyperparameter settings, and the final prediction $y_{varbvs}$ is computed as a weighted average of the individual predictions, with weights given by posterior probabilities of the hyperparameter settings (Fig. 2, right-hand side). Model averaging in BVS is typically computationally prohibitive in large-scale data sets, but the variational approximation yields a simple and efficient approach to account for uncertainty.

Finally, we note that parameter estimation in \texttt{varbvs} is a nonconvex optimization problem (as we explain below), so it can be sensitive to variable ordering and initialization of the fitting procedure. By contrast, \texttt{glmnet} will always produce the same model fit for the same data because the parameter estimation reduces to a convex optimization problem. For example, if we reorder the columns of $X$ before fitting the \texttt{varbvs} model,

\begin{verbatim}
R> fit.varbvs.alt <- varbvs(X = X[, sample(3571)], y = y, Z = NULL,
+    family = "binomial")
\end{verbatim}

then the variance in the leukemia outcome is again mostly explained by two different variables:

\begin{verbatim}
R> print(summary(fit.varbvs, nv = 3)$top.vars)

   index variable  prob PVE  coef Pr(coef.>0.95)
X3441  3441 X3441 0.999949 NA -4.2957 [-5.072, -3.527]
X1608  1608 X1608 0.001876 NA -0.8076 [-1.430, -0.214]
X2529  2529 X2529 0.001291 NA  0.7560 [+0.165, +1.350]
\end{verbatim}

\begin{verbatim}
R> print(summary(fit.varbvs.alt, nv = 3)$top.vars)

   index variable  prob PVE  coef Pr(coef.>0.95)
X1182  1336 X1182 0.989419 NA  2.9051 [+2.145, +3.651]
X2507    46 X2507 0.989007 NA  2.3199 [+1.289, +3.011]
X2888  1104 X2888 0.001825 NA  0.6126 [+0.055, +1.124]
\end{verbatim}
As expected, the top two variables in the second \texttt{varbvs} analysis are strongly correlated with the top variable from the first analysis:

\begin{verbatim}
R> print(cor(X[, "X3441"], X[, c("X1182", "X2507")]))

X1182  X2507
[1,] -0.7717 -0.6737
\end{verbatim}

More generally, when multiple variables are strongly correlated with each other, the parameter estimation can be sensitive to the variable ordering and initialization of optimization procedure. To ensure that a \texttt{varbvs} analysis is reproducible, we recommend using \texttt{set.seed} to fix the sequence of pseudorandom numbers, and checking that different seeds and/or variable orderings yield reasonably consistent estimates (see “Summary and discussion”).

3. Bayesian variable selection, and the \texttt{varbvs} \texttt{R} interface

In this section, we define the general analysis setup: the regression model (Sec. 3.1), the variable selection priors (Sec. 3.2), and the approach taken to efficiently compute posterior quantities (Sections 3.3 and Sec. 3.4). As we walk through the setup, we connect aspects of the analysis to the \texttt{varbvs} interface, then we review the interface in Sec. 3.5. For background on Bayesian approaches to variable selection, see George (2000) and O’Hara and Sillanpää (2009).

3.1. Regression model

The data consist of an $n \times p$ matrix $X$ containing observations $x_{ij}$ of the candidate variables, an $n \times m$ matrix $Z$ containing measurements $z_{ij}$ of the covariates, and a vector $y = (y_1, \ldots, y_n)^T$ containing observations of the regression outcome. These data are provided to function \texttt{varbvs} through arguments $X$, $Z$ and $y$.

The \texttt{varbvs} package implements methods for both linear regression (\texttt{family = "gaussian"}) and logistic regression (\texttt{family = "binomial"}). For linear regression, the outcome $Y$ is modeled as a linear combination of the candidate predictors, covariates and residuals $\epsilon \sim N(0, \sigma^2)$:

\begin{equation}
Y = \sum_{i=1}^{m} Z_i u_i + \sum_{i=1}^{p} X_i \beta_i + \epsilon. \tag{3}
\end{equation}

For logistic regression, we model the log-odds of $Y = 1$ as a linear combination of the predictors and covariates:

\begin{equation}
\log \left\{ \frac{\Pr(Y = 1)}{\Pr(Y = 0)} \right\} = \sum_{i=1}^{m} Z_i u_i + \sum_{i=1}^{p} X_i \beta_i. \tag{4}
\end{equation}

(Since $\sigma^2$ is not needed for logistic regression, in the definitions below we set $\sigma^2 = 1$ in this case.) At least one covariate, the intercept, must always be included in the model.

3.2. Variable selection prior
We use the one of the most successful Bayesian approaches to variable selection, based on the “spike-and-slab” prior (Equation 2). Small values of \( \pi \) encourage sparse regression models, in which only a small proportion of the candidate variables \( X_i \) help predict the outcome \( Y \). The rationale for this prior has been given in previous papers (e.g., Carbonetto and Stephens (2012); Guan and Stephens (2011); Servin and Stephens (2007); Zhou et al. (2013)), and we do not repeat this discussion here.

The grid of hyperparameter settings \((\sigma^2, \sigma_a^2, \pi)\) is defined by three inputs to \texttt{varbvs}: \texttt{sigma}, the residual variance for linear regression (for logistic regression, we set \( \sigma^2 = 1 \)); \texttt{sa}, the prior variance of the regression coefficients; and \texttt{logodds}, the prior inclusion probability \( \pi \) defined on the log-odds scale, \( \log_{10}\left\{\frac{\pi}{1-\pi}\right\} \). A plausible range of prior log-odds are generated automatically if they are not supplied by input \texttt{logodds}. When inputs \texttt{sigma} and \texttt{sa} are not provided, the default behaviour is to estimate these parameters separately for each setting of \( \pi \).

This standard variable selection prior (Equation 2) treats all candidate variables \( X_i \) equally. However, in some settings we may have additional information that suggests the importance of some variables more than others. \texttt{varbvs} can encode these preferences with a non-exchangeable prior \( \pi = (\pi_1, \ldots, \pi_p) \), which is specified by setting input \texttt{logodds} to a matrix with rows corresponding to variables and columns corresponding to hyperparameter settings. We demonstrate a non-exchangeable prior in one of the examples below.

An alternative to specifying a grid of hyperparameter settings is to estimate one or more of the hyperparameters. This option is activated by setting \texttt{update.sigma = TRUE} and/or \texttt{update.sa = TRUE} in \texttt{varbvs}, and it is activated by default when \texttt{sigma} or \texttt{sa} are not specified. For estimating one or more of the hyperparameters, we implemented a fast approximate expectation maximization (EM) approach (Heskes et al. 2004; Neal et al. 1998) in which the E-step is approximated using the variational techniques described below.

The \( Z_i \)'s are additional predictors that are always included in the model. Note that an intercept \((Z_i = 1)\) is always included so the user should never provide and intercept as one of the covariates. The \( Z_i \)'s are assigned an improper, uniform prior (i.e., a normal prior with large variance). This prior is convenient because the covariates are easily integrated out from the linear model (Chipman et al. 2001), as well as the logistic regression model after introducing an additional variational approximation (see the Appendix). We caution that improper priors can result in improper posteriors and Bayes factors (O’Brien and Dunson 2004).

### 3.3. Fast posterior computation via variational approximation

We use an alternative to MCMC (George and McCulloch 1993) based on variational methods (Blei et al. 2016; Jordan et al. 1999; Ormerod and Wand 2010; Wainwright and Jordan 2008) that yields fast computation of posterior probabilities at the cost of sometimes requiring a more careful interpretation due to the approximations made. The basic idea is to recast the problem of computing posterior probabilities—which is inherently an intractable, high-dimensional integration problem—as an optimization problem. This is achieved by introducing a class of approximating distributions, then optimizing a criterion (the Kullback-Leibler divergence) to find the distribution within this class that best matches the posterior. To make this approach viable for large problems, we enforce a simple conditional independence approximation (Carbonetto and Stephens 2012; Logsdon et al. 2010): conditioned on the
hyperparameters \( \theta \equiv \{ \sigma^2, \sigma_a^2, \pi \} \), each regression coefficient \( \beta_i \) is independent of the other regression coefficients \textit{a posteriori}. We then search for a distribution with this conditional independence property that best “fits” the posterior. This conditional independence assumption was initially motivated from the GWAS setting in which the variables are genetic markers. For more details, see Carbonetto and Stephens (2012).

The algorithm for fitting the variational approximation consists of an inner loop and an outer loop. The outer loop iterates over the hyperparameter grid points, and is described in the next section (Sec. 3.4). The inner loop, given a setting of the hyperparameters, cycles through co-ordinate ascent updates that try to minimize the Kullback-Leibler divergence between the approximate posterior and exact posterior. The inner loop co-ordinate ascent updates terminate when either the maximum number of inner loop iterations is reached, as specified by input \texttt{maxiter}, or the maximum difference between the estimated posterior inclusion probabilities is less than \texttt{tol}. The computational complexity of the co-ordinate ascent updates scales linearly with the number of variables and the number of samples. The number of co-ordinate ascent updates required to reach convergence depends on the covariance structure of the candidate variables; fastest convergence occurs when the variables are uncorrelated or weakly correlated.

Function \texttt{varbvs} outputs three posterior quantities for each variable \( X_i \) and for each hyperparameter setting \( \theta^{(j)} \):

\[
\alpha_{ij} \approx \Pr(\beta_i \neq 0 \mid X, Z, \theta = \theta^{(j)}) \quad (5)
\]
\[
\mu_{ij} \approx \mathbb{E}[\beta_i \mid X, Z, \theta = \theta^{(j)}, \beta_i \neq 0] \quad (6)
\]
\[
s_{ij}^2 \approx \text{Var}[\beta_i \mid X, Z, \theta = \theta^{(j)}, \beta_i \neq 0]. \quad (7)
\]

Each of these outputs is represented as a \( p \times n_s \) matrix, where \( p \) is the number of variables and \( n_s \) is the number of hyperparameter grid points. For the \( i \)th variable and \( j \)th hyperparameter setting, \( \texttt{alpha}[i,j] \) is the variational estimate of the PIP (Equation 5), \( \texttt{mu}[i,j] \) is the variational estimate of the posterior mean coefficient given that it is included in the regression model (Equation 6), and \( \texttt{s}[i,j] \) is the estimated posterior variance (Equation 7). Many other posterior statistics can be easily derived from these outputs. For example, \( \texttt{alpha} * \texttt{mu} \) gives the marginal posterior mean estimates of the regression coefficients.

These posterior statistics are also the free parameters of the approximating distribution; that is, they are the parameters that are optimized as part of the “inner loop.” An additional set of free parameters is needed for the logistic regression model, and the fitted values for these parameters are returned as \( n \times n_s \) matrix \( \texttt{eta} \). When a good guess of the variational parameters are available in advance, they can be used to initialize the co-ordinate ascent algorithm by specifying inputs \( \texttt{alpha}, \texttt{mu}, \texttt{s} \) and \( \texttt{eta} \) to function \texttt{varbvs}.

### 3.4. Averaging over the hyperparameters

In the simplest case, the hyperparameter vector \( \theta = (\sigma^2, \sigma_a^2, \pi) \) is known, or fixed, and \texttt{varbvs} can fit the model and compute approximate posteriors \( \Pr(\beta \mid X, Z, y, \theta) \). The variational method also yields an approximation (actually, a lower bound) to the marginal likelihood \( \Pr(y \mid X, Z, \theta) \) integrating over the coefficients \( \beta \). We denote this lower bound by \( \text{LB}(\theta) \). This scheme is conceptually simple, but the results may be sensitive to choice of the hyperparameters \( \theta \). It is analogous to fixing \( \lambda \) in \texttt{glmnet} rather than estimating it by cross-validation.
A natural alternative is to estimate $\theta$. The simplest way to do this is to treat $LB(\theta)$ as if it were the likelihood and maximize $LB(\theta)$ over $\theta$; that is, compute $\hat{\theta} = \arg\max_{\theta} LB(\theta)$ and report approximate posteriors $Pr(\beta | X, Z, y, \hat{\theta})$. This is analogous to estimating $\lambda$ in glmnet by cross-validation. This is usually preferable to fixing $\theta$ by hand, and it has the practical advantage of having little computational overhead and does not require the user to specify a prior. But it does not take account of uncertainty in the hyperparameters, nor does it allow for incorporation of prior information about the hyperparameters.

To address these limitations, we can introduce a prior on the hyperparameters. The varbvs package allows any discrete uniform prior on $\theta$: just specify a grid of values $\theta_1, \ldots, \theta_{ns}$ and it will treat the prior on the hyperparameters as uniform on that grid. It will use the lower bound to the likelihood to approximate the posterior on $\theta$, so $Pr(\theta = \theta(j) | X, Z, y)$ is approximated by $w(j) = LB(\theta(j))/\sum_{j'=1}^{ns} LB(\theta(j'))$. Further, it implements the Bayesian model averaging (Hoeting et al. 1999), computing approximate posteriors on $\beta$ by averaging over this approximate posterior; i.e., $Pr(\beta | X, Z, y) \approx \sum_{j=1}^{ns} w(j) Pr(\beta | X, Z, y, \theta(j))$. This has the advantage of incorporating prior information and taking account of uncertainty along with a manageable increase in computational cost. We have made the model averaging approach the recommended option in varbvs, although it does require the user to specify the prior, which may be off-putting to some people. (To make this less painful, we provide guidelines in the package documentation. For example, we recommend setting the prior on $\sigma^2_a$ indirectly through the proportion of variance in $y$ explained by $X$; see Guan and Stephens (2011); Zhou and Stephens (2012).)

We have also implemented a hybrid approach, which allows the user to specify a prior on some of the hyperparameters while maximizing the others. In fact, the default in varbvs is to estimate $\sigma^2$ and $\sigma^2_a$, and assign an exchangeable prior for $\pi$ that is uniform on the log-odds scale. This was the approach used in the leukemia example above, in which posterior probabilities were approximated at 20 grid points of $\pi$ ranging from $10^{-3.5}$ to $10^{-1.0}$ (Fig. 2, right-hand plot). Importantly, this hybrid approach provides flexibility for tackling large data sets, and it is used in most of the larger-scale examples below.

One practical issue with the variational computation strategy is that the variational approximation can be sensitive to the choice of starting point $\theta^{(\text{init})}$. To provide a more accurate variational approximation of the posterior distribution, the optimization procedure is run in two stages by default. In the first stage, the entire procedure is run to completion, then the fitted variational parameters (stored in outputs alpha, mu, s, eta) corresponding to the maximum marginal likelihood are used to initialize the co-ordinate ascent updates in the second stage. The final posterior estimates tend to be more accurate using this two-stage optimization approach (Carbonetto and Stephens 2012). Set initialize.params = FALSE in varbvs to skip over the initialization phase.

3.5. The varbvs function

We end this section with an overview of the core package function for all BVS posterior computation and model fitting procedures in the R package. To provide a familiar interface, we have modeled it after glmnet. The inputs to varbvs are grouped by their function:

varbvs(X, Z, y, family, # Data.
sigma, sa, logodds, # Hyperparameter grid.
alpha, mu, eta, # Variational parameters.)
The first four input arguments are for the data: the $n \times p$ input matrix $X$ and the $n \times m$ input matrix $Z$, where $n$ is the number of data examples, $p$ is the number of candidate variables and $m$ is the number of covariates (not including the intercept); the $n$ observations of the regression outcome, $y$; and the option to specify a linear regression model (family = "gaussian", the default) or logistic regression when all entries of $y$ are 0 or 1 (family = "binomial").

The next three input arguments, sigma, sa and logodds, are optional, and specify the grid of hyperparameter settings. Each of these inputs must be a single value, or have the same number of entries $n_s$, except in the special case when the prior inclusion probability is specified separately for each variable, in which case logodds is a $p \times n_s$ matrix. If inputs sigma or sa are missing, they are automatically fitted to the data by computing approximate maximum-likelihood or maximum a posteriori estimates.

When good initial estimates of the variational parameters are available, they can be provided to varbvs through input arguments alpha, mu and s. Each of these inputs must be an $p \times n_s$ matrix, or a $p \times 1$ matrix when all variational approximations are provided the same initial parameter estimate. Input eta is an additional set of free parameters for the variational approximation to the logistic regression model. It is either an $n \times n_s$ matrix or an $n \times 1$ matrix. The remaining input arguments control various aspects of the model fitting and optimization procedures, and are detailed in the varbvs help page.

The varbvs function returns an S3 object of class "varbvs". The main components of interest are:

- logw—Array in which logw[i] is the variational approximation to the marginal log-likelihood for the $i$th hyperparameter grid point.
- w—Approximate posterior probabilities, or “weights,” $w^{(j)}$ computed from logw.
- alpha—Variational estimates of posterior inclusion probabilities, $a_{ij}$, for each variable $X_i$ and hyperparameter setting $\theta^{(j)}$.
- mu—Variational estimates of posterior mean coefficients, $\mu_{ij}$, for each variable $X_i$ and hyperparameter setting $\theta^{(j)}$.
- s—Variational estimates of posterior variances, $s_{ij}$, for each variable $X_i$ and hyperparameter setting $\theta^{(j)}$.
- pip—The “averaged” posterior inclusion probabilities computed as a weighted sum of the individual PIPs (alpha), with weights given by w.
- mu.cov—Posterior mean regression coefficients $\text{mu.cov}[i,j]$ for each covariate $Z_i$ (including the intercept) for each hyperparameter setting $\theta^{(j)}$.
- eta—Additional variational parameters for family = "binomial" only.
- pve—For each hyperparameter setting $\theta^{(j)}$, and for each variable $X_i$, $\text{pve}[i,j]$ is the mean estimate of the proportion of variance in the outcome $Y$ explained by $X_i$, conditioned on $X_i$ being included in the model. This is computed for family = "gaussian" only.
- **model.pve**—Samples drawn from the posterior distribution giving estimates of the proportion of variance in the outcome $Y$ explained by the fitted variable selection model. For example, `mean(fit.varbvs$model.pve)` yields the posterior mean of the proportion of variance explained, where `fit.varbvs` is the `varbvs` return value. This is provided for `family = "gaussian"` only.

The components $\alpha$, $\mu$, $s$ and $w$ are basic posterior quantities that can be used to quickly calculate many other posterior statistics of interest. For example, the probability that at least 1 variable is included in the regression model is computed as

```r
R> p0 <- apply(1 - fit$alpha, 2, prod)
R> sum(fit$w * (1 - p0))
```

The `varbvs` R package also provides standard supporting functions for the "varbvs" class, including `summary`, `predict` and `plot`.

### 4. Example: mapping a complex trait in outbred mice

In our second example, we illustrate the features of `varbvs` for genome-wide mapping of a complex trait. The data, downloaded from Zenodo (Carbonetto 2017), are body and testis weight measurements recorded for 993 outbred mice, and genotypes at 79,748 single nucleotide polymorphisms (SNPs) for the same mice (Parker et al. 2016). Our main aim is to identify genetic variants contributing to variation in testis weight. The genotype data are represented in R as a 993 x 79,748 matrix, `geno`. The phenotype data—body and testis weight, in grams—are stored in the "sacwt" and "testis" columns of the `pheno` matrix:

```r
R> head(pheno[, c("sacwt", "testis")])

    sacwt  testis
26305 46.6 0.1396
26306 35.7 0.1692
26307 34.1 0.1878
26308 41.8 0.2002
26309 39.5 0.1875
26310 36.0 0.1826
```

The “cfw” vignette in the R package reproduces all the results of this analysis except for Fig. 4, which can be reproduced by running script `cfw.cv.R` accompanying this paper.

The standard approach in genome-wide mapping is to quantify support for a quantitative trait locus (QTL) separately at each SNP. For example, this was the approach taken in Parker et al. (2016). Here, we implement this univariate regression (“single-marker”) mapping approach using the `-lm 2` option in GEMMA version 0.96 (Zhou and Stephens 2012), which returns a likelihood-ratio test $p$ value for each SNP. We compare this single-marker analysis against a `varbvs` multiple regression (“multi-marker”) analysis of the same data.

In the `varbvs` analysis, the quantitative trait (testis weight) is modeled as a linear combination of the covariate (body weight) and the candidate variables (the 79,748 SNPs). As before, the model fitting is accomplished with a single function call:
This call is completed in less than 4 minutes on a MacBook Air with a 1.86 GHz Intel CPU, 4 GB of memory and R 3.3.3. Note that, to simplify this example, we have fixed \( sa \) to 0.05, a choice informed by our power calculations. In this application, it would be preferable to average over a range of settings to avoid sensitivity to prior choice.

Once the model fitting is completed, we quickly generate a summary of the results using the `summary` function:

\[
R> \text{print(summary(fit))}
\]

Summary of fitted Bayesian variable selection model:

- **family**: gaussian
- **num. hyperparameter settings**: 9
- **samples**: 993
- **iid variable selection prior**: yes
- **variables**: 79748
- **fit prior var. of coefs (sa)**: no
- **covariates**: 2
- **fit residual var. (sigma)**: yes
- **maximum log-likelihood lower bound**: 2428.7093
- **proportion of variance explained**: 0.149 [0.090, 0.200]

### Hyperparameters:

- **estimate**
  - \( \sigma \): 0.000389 [0.000379, 0.000404]
  - \( sa \): NA
  - \( \text{logodds} \): -3.78 [-4.25, -3.50]

- **Pr>0.95**
  - \( \sigma \): NA
  - \( sa \): 0.05--0.05
  - \( \text{logodds} \): (-5.00)--(-3.00)

Selected variables by probability cutoff:

- >0.10: 3
- >0.25: 3
- >0.50: 3
- >0.75: 2
- >0.90: 2
- >0.95: 1

Top 5 variables by inclusion probability:

| index | variable      | prob | PVE  | coef   | Pr(coef.>0.95) |
|-------|---------------|------|------|--------|---------------|
| 59249 | rs6279141     | 1.0000 | 0.0631 | -0.00806 | [-0.010, -0.007] |
| 24952 | rs33217671    | 0.9351 | 0.0220 | 0.00509  | [+0.003, +0.007] |
| 9203  | rs33199318    | 0.6869 | 0.0170 | 0.00666  | [+0.004, +0.009] |
| 67415 | rs52004293    | 0.0739 | 0.0136 | 0.00347  | [+0.002, +0.005] |
| 44315 | rs25372277    | 0.0707 | 0.0133 | -0.00369 | [-0.005, -0.002] |

This summary tells us that only 3 out of the 79,748 SNPs are included in the model with posterior probability greater than 0.5, and that the included SNPs explain 15% of the variance of testis weight. (Precisely, this is the variance explained in testis weight residuals after controlling for body weight.) Further, a single SNP (rs6279141) accounts for over 6% of variance in testis weight. This SNP is located on chromosome 13 approximately 1 Mb from *Inhba*, a gene that has been previously shown to affect testis morphogenesis (Mendis et al. 2011; Mithraprabhu et al. 2010; Tomaszewski et al. 2007).

We can also quickly create a visual summary of the results using the `plot` function:

\[
R> \text{print(plot(fit, vars = c("rs33199318", "rs33217671", "rs6279141"), groups = map$chr, gap = 1500))}
\]
Figure 3: QTL mapping of a complex trait in outbred mice. (a) Posterior inclusion probabilities for all 79,748 candidate SNPs on chromosomes 1–19 computed using varbvs. SNPs with PIPs greater than 0.5 are highlighted. (b) p values for the same candidate SNPs computed using GEMMA. threshold determined via permutation analysis, at p value = $2 \times 10^{-6}$ (Parker et al. 2016). (c) Posterior probabilities computed using the BVSR method in GEMMA version 0.96 (Zhou et al. 2013). In BVSR, since multiple correlated SNPs at a single QTL are expected to be included in the model with lower probability, plotting individual PIPs does not highlight the QTLs. Therefore, the results are summarized by dividing each chromosome into contiguous segments containing 100 SNPs, in which consecutive segments overlap by 50 SNPs, and computing the posterior probability that at least 1 SNP is included within each of these segments.

The output is shown in Fig. 3a. Note that the plot function has a "group" argument, which allows us to arrange the variable selection results by chromosome.

It is informative to compare these probabilities against the “single-marker” p values that ignore correlations between SNPs (Fig. 3b). Reassuringly, the loci with the strongest support for association in the single-marker analysis (Fig. 3b) also exhibit the strongest support for association in the multi-marker analysis (Fig. 3a). Further, SNPs included with the highest posterior probabilities are among the SNPs with the smallest p values. One QTL on chromosome 2 is not significant in the single-marker analysis (p value = $5.2 \times 10^{-6}$), yet shows moderate probability of association in the multi-marker analysis. The multi-marker associa-
Figure 4: Scatterplot comparing accuracy of \texttt{varbvs} and BVSR predictions. To assess prediction accuracy, we perform a simple cross-validation experiment in which the mouse data are split evenly into 10 test data sets: in each of the 10 rounds of cross-validation, the \texttt{varbvs} and BVSR models are fit to the remaining training samples, then the predictions are evaluated in the test set. The $x$ and $y$ axes in the plot show differences between predicted and observed phenotype (testis weight controlling for body weight) in the left-out test samples. These differences are normalized by the standard deviation of the phenotype computed from the full sample. The adjoining script \texttt{cfw.cv.R} reproduces the results of the cross-validation experiment, as well as this figure. The BVSR method is implemented in GEMMA version 0.96.

In Fig. 3b, we observe that many SNPs have low $p$ values at each of the identified testis weight loci. This illustrates the common situation in GWAS in which many SNPs at a single locus are associated with the trait. In general, when multiple variables are strongly correlated with each other, the fully-factorized variational approximation in \texttt{varbvs} tends to concentrate the posterior mass on a single variable.

We also assessed the accuracy of the variational approximation by comparing the \texttt{varbvs} results (Fig. 3a) against another method, BVSR (Zhou et al. 2013), that uses a very similar model. The BVSR method implemented in GEMMA uses MCMC to estimate posterior probabilities. Comparing panels a and c in Fig. 3, BVSR yields a more complex model in which hundreds of SNPs are included in the model with low probability—yet the loci with the strongest support in the \texttt{varbvs} and BVSR analyses closely agree. The simpler \texttt{varbvs} model also achieves similar prediction accuracy to the BVSR model; in a simple cross-validation
experiment in which 10% of the samples in each round are used to test the model, the prediction errors of the varbvs and BVSR methods are 97% correlated (Fig. 4).

5. Example: mapping Crohn’s disease risk loci

Our third example again illustrates varbvs’s ability to tackle large data sets for mapping genetic loci contributing to a complex trait. The data set in this example contains 4,686 samples (1,748 Crohn’s disease cases, 2,938 controls) and 442,001 SNPs (Wellcome Trust Case Control Consortium 2007). The genotypes are stored in a $4,686 \times 442,001$ matrix $X$, and the binary outcome is disease status ($0 =$ control, $1 =$ case):

```r
> print(summary(factor(y)))

  0 1  
2938 1748
```

We model Crohn’s disease disease status using logistic regression, with the 442,001 SNPs as candidate variables, and no additional covariates. On a machine with a 2.5 GHz Intel Xeon CPU, fitting the BVS model to the data took 39 hours to complete:

```r
R> fit <- varbvs(X, NULL, y, family = "binomial", 
                 logodds = seq(-6,-3,0.25), n0 = 0)
```

The “cd” vignette reproduces all the results and plots shown here. Since the data needed to run the script cannot be made publicly available due to data sharing restrictions, those wishing to reproduce this analysis must apply for data access by contacting the Wellcome Trust Case Control Consortium.

Similar to the previous examples, the fitted regression model is very sparse; only 8 out of the 442,001 candidate variables are included in the model with probability at least 0.5:

```r
R> print(summary(fit, nv = 9))
```

Summary of fitted Bayesian variable selection model:

- family: binomial
- num. hyperparameter settings: 13
- samples: 4686
- iid variable selection prior: yes
- variables: 442001
- fit prior var. of coefs (sa): yes
- fit approx. factors (eta): yes
- maximum log-likelihood lower bound: -3043.2388

Hyperparameters:

| estimate | Pr>0.95 | candidate values |
|----------|---------|------------------|
| sa       | 0.032   | [0.0201,0.04]    |
| logodds  | -4.06   | [-4.25,-3.75]    |

Selected variables by probability cutoff:

|   | >0.10 | >0.25 | >0.50 | >0.75 | >0.90 | >0.95 |
|---|-------|-------|-------|-------|-------|-------|
| n | 13     | 10    | 8     | 7     | 7     | 7     |

Top 9 variables by inclusion probability:
### Table 1: Variable Selection Results

| Index | Variable  | Prob PVE | Coef* | Pr(coef. > 0.95) |
|-------|-----------|----------|-------|-----------------|
| 1     | rs10210302| 1.000    | -0.313| [−0.397, −0.236]|
| 2     | rs1805303| 1.000    | 0.291 | [+0.207, +0.377]|
| 3     | rs17234657| 1.000   | 0.370 | [+0.255, +0.484]|
| 4     | rs17221417| 1.000   | 0.279 | [+0.192, +0.371]|
| 5     | rs2542151 | 0.992    | 0.370 | [+0.255, +0.484]|
| 6     | rs10995271| 0.987    | 0.236 | [+0.151, +0.323]|
| 7     | rs7095491  | 0.969    | 0.222 | [+0.141, +0.303]|
| 8     | rs9469220  | 0.586    | -0.194| [-0.269, -0.118]|
| 9     | rs12035082 | 0.485    | 0.195 | [+0.111, +0.277]|

*See help(varbvs) about interpreting coefficients in logistic regression.

The **varbvs** results, summarized in Fig. 5a, provide strong support for nearly the same reported *p* values at the previously used “whole-genome” significance threshold, $5 \times 10^{-7}$; in particular, the 7 SNPs included in the regression model with probability greater than 0.9 correspond to the smallest trend *p* values, between $7.1 \times 10^{-14}$ and $2.68 \times 10^{-7}$ (Wellcome Trust Case Control Consortium 2007). Additionally, the SNP highest posterior probability is most cases the exact same SNP with the smallest trend *p* value. (See Carbonetto and Stephens 2013 for an extended comparison of the *p* values and PIPs.) Only one disease locus, near gene IRGM on chromosome 5, has substantially stronger support in the single-marker analysis; the originally reported *p* value is $5.1 \times 10^{-8}$, whereas the **varbvs** analysis yields a largest posterior probability of 0.05 at this locus.

To further validate the **varbvs** analysis of the Crohn’s disease data, we compared the **varbvs** results against posterior probabilities computed using the BVSR method. As before, we obtain similar variable selection results; the loci with the strongest support in the **varbvs** analysis (Fig. 5a) are the same loci identified by the BVSR method (Fig. 5b) aside from a few loci with moderate support in the BVSR analysis near genes TNFSF18, MST1 and IRGM.

### 6. Example: gene set enrichment analysis in Crohn’s disease

In this section, we revisit the Crohn’s disease data set to demonstrate the use of **varbvs** for model comparison. This analysis is implemented in the “cytokine” vignette.

Here, we incorporate additional information about the 442,001 candidate variables, stored in a vector, `cytokine`:

```r
R> data(cytokine)
R> print(summary(factor(cytokine)))
```

```
0 1 435290 6711
```

An entry of 1 means that the SNP is located within 100 kb of a gene in the “Cytokine signaling in immune system” gene set. This gene set was previously identified in an interrogation of 3,158 gene sets from 8 publicly available biological pathway databases (Carbonetto and Stephens 2013).
Figure 5: `varbvs` and BVSR analysis of Crohn’s disease data. (a) Posterior inclusion probabilities for all 442,001 candidate SNPs on chromosomes 1–22. SNPs with PIP greater than 0.5 are highlighted. Human Genome Assembly hg17 (NCBI release 35). (b) Posterior probabilities estimated in BVSR (Zhou et al. 2013). Similar to the mouse data, each chromosome is divided into overlapping 50-SNP segments, and the plot shows the posterior probability that at least 1 SNP is included within each segment. Three points are highlighted in light green; these are segments with posterior probability greater than 0.5 in the BVSR analysis that do not contain a SNP with PIP greater than 0.5 in the `varbvs` analysis. (c) PIPs for all SNPs conditioned on enrichment of cytokine signaling genes. Two SNPs are highlighted in yellow; they are the two SNPs with a PIP greater than 0.5 only after prioritizing SNPs near cytokine signaling genes.

To assess relevance of cytokine signaling genes to Crohn’s disease risk, we modify the prior so that SNPs near cytokine signaling genes are included in the model with higher probability (i.e., cytokine signaling genes are “enriched” for Crohn’s disease risk loci). To simplify this example, the default prior log-odds is set to -4, which is the maximum-likelihood value from the above analysis. We evaluate 13 settings of the modified prior, ranging from -4 (1 out of 10,000 SNPs is included in the model) to -1 (approximately 1 out of 10 SNPs is included):

```r
R> logodds <- matrix(-4,442001,13)
R> logodds[cytokine == 1,] <- matrix(seq(0,3,0.25) - 4,6711,13,byrow = TRUE)
```

We then fit the BVS model to the data using this modified prior:

```r
R> fit.cytokine <- varbvs(X, NULL, y, family = "binomial",
                       logodds = logodds, n0 = 0)
```
The new variable selection results are summarized in Fig. 5c. The SNPs identified in the previous analysis are retained under the new prior. Further, 2 new SNPs, near genes *IRF1* and *STAT3*, show strong support for association only after allowing for enrichment of associations near cytokine signaling genes.

To assess support for this model, we compute a Bayes factor (Kass and Raftery 1995) that compares against the “null” model in which all SNPs are equally likely to be included *a priori* (i.e., an exchangeable prior):

```r
R> fit.null <- varbvs(X, NULL, y, "binomial", logodds = -4, n0 = 0)
R> BF <- varbvsbf(fit.null, fit.cytokine)
R> print(format(BF, scientific = TRUE))
[1] "9.355e+05"
```

This Bayes factor is strong evidence that Crohn’s disease risk loci are found with greater frequency near cytokine signaling genes.

### 7. Summary and discussion

In this paper, we illustrated the benefits of Bayesian variable selection techniques for regression analysis, and showed that *varbvs* provides a user-friendly interface for applying BVS to large data sets. Mathematical details and derivations of the algorithms are found in the Appendix and in Carbonetto and Stephens (2012). In the remainder, we provide some additional background and guidance.

As our examples illustrate, one benefit of BVS is that it provides a measure of uncertainty in the parameter estimates. Assessing uncertainty is often not done in practice because it requires careful selection of priors. Therefore, we have provided default priors that are suitable in many settings. This allows the practitioner to expedite the analysis, and perhaps revisit the prior choices at a later date. The default priors are based on detailed discussions from our earlier work (Guan and Stephens 2011; Servin and Stephens 2007; Zhou et al. 2013). As an alternative, *varbvs* also allows for computation of hyperparameter point estimates.

Fast computation of posterior probabilities is made possible by the formulation of a variational approximation derived from a simple conditional independence assumption. Even when many of the variables are strongly correlated, this approximation can often yield accurate inferences so long as individual posterior statistics are interpreted carefully. The computational complexity of the co-ordinate ascent algorithm for fitting the variational approximation is linear in the number of samples and in the number of variables so long as the correlations between variables are mostly small. This makes the algorithm suitable for many genetic data sets since correlations are limited by recombination. However, for data sets with widespread correlations between variables, convergence of the algorithm can be slow. We are currently investigating faster alternatives using quasi-Newton methods and acceleration schemes such as SQUAREM (Varadhan and Roland 2008; Varadhan 2016).

In practice, final estimates can be sensitive to initialization of the variational parameters. We have reduced this sensitivity by including an additional optimization step that first identifies a good initialization of the variational parameters (Sec. 3.4). However, it is good practice
Figure 6: Convergence of varbvs model fitting algorithm with less numerically stable (\texttt{xdx1}) and more numerically stable (\texttt{xdx2}) updates. The vertical axes show the variational lower bound to the marginal log-likelihood, which is also the objective function being maximized; the co-ordinate ascent updates terminate when they no longer increase the lower bound. The right-hand plot is a magnified version of the left-hand plot.

to verify that different random initializations of these parameters do not yield substantially different conclusions. The documentation for function \texttt{varbvs} gives further guidance on this, as well as guidelines for correctly interpreting variational estimates of the posterior statistics. Finally, we would like to remark on an often overlooked aspect of statistical analyses—numerical stability. In the logistic regression model, part of the variational optimization algorithm involves computing the diagonal entries of the matrix product $X^T \hat{D} X$, in which $\hat{D}$ is an $n \times n$ diagonal matrix (see the Appendix). In the \texttt{MATLAB} implementation, the following two lines of code are mathematically equivalent,

\begin{align*}
\texttt{xdx1} & = \text{diag}(X^T \hat{D} X) - (X^T \hat{D} X) \cdot \text{sum}(d) \\
\texttt{xdx2} & = \text{diag}(X^T \hat{D} X) - (X^T (d / \text{sqrt(sum(d))})) \cdot \text{sum}(d)
\end{align*}

where $d = \text{diag}(D)$. Yet, in floating-point arithmetic, the order of operations affects the numerical precision of the final result, which can in turn affect the stability of the co-ordinate ascent updates. To illustrate this, we applied \texttt{varbvs}, using the two different updates (\texttt{xdx1} and \texttt{xdx2}), to a data set with simulated variables and a binary outcome. In Fig. 6, we see that the second update (\texttt{xdx2}), corresponding to the solid blue line in the plots, produced iterates that progressed more smoothly to a stationary point of the objective function, whereas the first update (\texttt{xdx1}) terminated prematurely because it produced a large decrease in the objective. This illustrates the more general point that numerical stability of operations can impact the quality of the final solution, particularly for large data sets.

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A. About this document

This manuscript was prepared using the Sweave function from the weaver package (Falcon 2017). The code chunk below records the version of R and the packages that were used to generate the results contained in this manuscript.

```R
R> sessionInfo()
```
B. Additional derivations for linear regression model

Most of the derivations for the linear regression model are given in Carbonetto and Stephens (2012). Here, we extend the variational approximation to allow for additional variables \((Z_1, \ldots, Z_m)^T\) that are included in the model with probability 1, and a non-exchangeable prior on the regression coefficients \(\beta_i\). Additionally, we derive an approximate EM algorithm for the residual variance \(\sigma^2\) and prior variance \(\sigma^2_a\).

First, we analytically integrate out the regression coefficients \(u = (u_1, \ldots, u_m)^T\) by making use of the following result:

\[
|\Sigma_0|^{1/2} \Pr(y \mid X, Z, \beta, \sigma^2) = |Z^T Z|^{-1/2} \Pr(\hat{y} \mid \hat{X}, \beta, \sigma^2),
\]

in which \(\Pr(y \mid X, Z, \beta, \sigma^2)\) is the multivariate normal likelihood defined by the linear regression model (Equation 3). \(\Pr(\hat{y} \mid \hat{X}, \beta, \sigma^2)\) is the likelihood given by linear regression \(\hat{y} = \hat{X} \beta + \sigma^2\), \(\hat{u}\) is assigned a multivariate normal prior with zero mean and covariance \(\Sigma_0\) such that \(|\Sigma_0^{-1}|\) is close to zero (yielding a “flat” prior density on \(u\)), and we define \(\hat{X} = X - Z(Z^T Z)^{-1} Z^T X\) and \(\hat{y} = y - Z(Z^T Z)^{-1} Z^T y\). Therefore, we can easily account for the linear effects of covariates \(Z\) by replacing all instances of \(X\) with \(\hat{X}\) and all instances of \(y\) with \(\hat{y}\), and by multiplying the likelihood by \(|Z^T Z|^{-1/2}\). Therefore, in the derivations below we assume the simpler linear regression \(y = X \beta + \sigma^2\), replace \(X\) with \(\hat{X}\) and \(y\) with \(\hat{y}\), and multiply by \(|Z^T Z|^{-1/2}\) to obtain the final solution.
The basic idea behind the variational approximation is to formulate a lower bound to the marginal likelihood, \( \Pr(y \mid X, \theta) \geq \text{LB}(\theta) \equiv e^{f(X, y, \theta, \phi)} \), then to adjust the free parameters, which we denote here by \( \phi \equiv \{\alpha, \mu, s\} \), so that this bound is as tight as possible. This lower bound is formulated by introducing a probability distribution \( q(\beta; \phi) \) that approximates the posterior of \( \beta \) given \( \theta \). Maximizing the lower bound corresponds to finding the approximating distribution that best matches the posterior; more precisely, it amounts to searching for the free parameters \( \phi \) that minimize the Kullback-Leibler divergence between \( q(\beta; \phi) \) and the posterior of \( \beta \) given \( \theta \) (Jordan et al. 1999).

The "fully-factorized" class of approximating distributions yields the following analytical expression for the variational lower bound:

\[
\begin{align*}
\ell(X, y, \theta, \phi) &= -\frac{n}{2} \log(2\pi \sigma^2) - \frac{\|y - X\|_2^2}{2\sigma^2} - \frac{1}{2\sigma^2} \sum_{i=1}^{p} (X^T X)_{ii} \text{Var}[\beta_i] \\
&\quad - \sum_{i=1}^{p} \alpha_i \log \left( \frac{\alpha_i}{\pi_i} \right) - \sum_{i=1}^{p} (1 - \alpha_i) \log \left( \frac{1 - \alpha_i}{1 - \pi_i} \right) \\
&\quad + \sum_{i=1}^{p} \frac{\alpha_i}{2} \left[ 1 + \log \left( \frac{s_i^2}{\sigma_a \sigma^2} \right) - s_i^2 + \frac{\mu_i^2}{\sigma_a^2} \right], \quad (9)
\end{align*}
\]

where \( \| \cdot \|_2 \) is the Euclidean norm, \( r_i = \alpha_i \mu_i \), and \( \text{Var}[\beta_i] = \alpha_i (s_i^2 + \mu_i^2) - (\alpha_i \mu_i)^2 \) is the variance of \( i \)th coefficient under the approximating distribution. As in Carbonetto and Stephens (2012), the co-ordinate updates for the free parameters conditioned on a hyperparameter setting \( \theta \) are obtained by taking partial derivatives of the lower bound (Equation 9), setting these partial derivatives to zero, and solving for the free parameters. This yields the following expressions:

\[
\begin{align*}
\mu_i &= \frac{s_i^2}{\sigma_a} (X^T y)_i - \sum_{j \neq i} (X^T X)_{ij} \alpha_j \mu_j \quad (10) \\
\sigma_i^2 &= \sigma^2 / (X^T X)_{ii} + 1/\sigma_a^2 \quad (11) \\
\alpha_i &= \frac{\pi_i}{1 - \pi_i} \times \frac{s_i}{\sigma_a \sigma^2} \times e^{(\mu_i^2)/2\sigma_a^2}. \quad (12)
\end{align*}
\]

The E and M steps in the EM algorithm can be viewed as both minimizing the Kullback-Leibler divergence (Neal et al. 1998) or, equivalently in this case, maximizing the lower bound (Equation 9). Therefore, we obtain an “approximate” EM algorithm (e.g., Heskes et al. 2004) by computing posterior expectations in the E-step under the assumption that the true posterior is “fully-factorized.” We derive the M-step updates for \( \sigma^2 \) and \( \sigma_a^2 \) in the standard way by solving for roots \( \sigma^2 \) and \( \sigma_a^2 \) of the gradient, yielding

\[
\begin{align*}
\sigma^2 &= \frac{\|y - Xr\|_2^2 + \sum_{i=1}^{p} (X^T X)_{ii} \text{Var}[\beta_i]}{n + \sum_{i=1}^{p} \alpha_i} + \sum_{i=1}^{p} \alpha_i (s_i^2 + \mu_i^2)/\sigma_a^2 \quad (13) \\
\sigma_a^2 &= \frac{\sum_{i=1}^{p} \alpha_i (s_i^2 + \mu_i^2)}{\sigma^2 \sum_{i=1}^{p} \alpha_i}. \quad (14)
\end{align*}
\]

C. Additional derivations for logistic regression model
In the Appendix of Carbonetto and Stephens (2012), we described an extension to the fully-factorized variational approximation for Bayesian variable selection with a logistic regression model and an intercept. Here, we extend these derivations to allow for for additional variables $Z = (Z_1, \ldots, Z_m)^T$ that are not subject to the spike-and-slab priors.

We split the derivation into four parts: in the first part, we derive a linear approximation to the non-linear likelihood; in the second part, we analytically integrate out the coefficients $u$ from the linearized likelihood; in the third part, we introduce the fully-factorized variational approximation, and derive the co-ordinate ascent updates for maximizing the variational lower bound; finally, in the fourth part, we derive “M-step” updates for the additional free parameters $\eta$ that were introduced to approximate the logistic regression likelihood.

Taking care of the nonlinear factors in the likelihood. For the moment, we assume the simpler logistic regression with no additional variables $Z$; it is easy to introduce these variables into the expressions later on by substituting $\beta$ with $(u \beta)$ and $X$ with $(Z X)$. The expression for the log-likelihood given the simpler logistic regression can be written as

$$\log \Pr(y \mid X, \beta) = (y - 1)^T X \beta + \sum_{i=1}^{n} \log p_i,$$

in which we define $p_i \equiv \Pr(y_i = 1 \mid x_{i1}, \ldots, x_{ip}, \beta) = \sigma(\sum_{j=1}^{p} x_{ij} \beta_j)$, and $\sigma(x) = 1/(1 + e^{-x})$ is the sigmoid function (or inverse of logit function). Written in this way, the linear components are contained exclusively in the first term of Equation 15.

The basic idea behind the variational approximation is to formulate a lower bound to the logarithm of the sigmoid function. Skipping the technical details (Jaakkola and Jordan 2000), we obtain the following lower bound:

$$\log \sigma(x) \geq \log \sigma(\eta) + \frac{1}{2} (x - \eta)^2 - \frac{d}{2} (x^2 - \eta^2),$$

in which we define $d = \frac{1}{\eta} (\sigma(\eta) - \frac{1}{2})$. Notice that this expression introduces an additional parameter, $\eta$. This identity holds for any choice of $\eta$, and this is the free parameter that we will adjust to tighten the fit of the lower bound as best as possible. We will have one free parameter $\eta_i$ for every factor in the likelihood. Also notice that all terms involving $x$—later replaced by linear combinations of $\beta$—are linear or quadratic in $x$.

Inserting this lower bound into the expression for the log-likelihood, we obtain a lower bound to the log-likelihood, denoted by $g(\beta; \eta)$:

$$g(\beta; \eta) = \sum_{i=1}^{n} \log \sigma(\eta_i) + \frac{1}{2} d_i (\eta_i - 1) + (y - \frac{1}{2})^T X \beta - \frac{1}{2} \beta^T X^T D X \beta,$$

where $D$ is the $n \times n$ matrix with diagonal entries $d_i$. By extension, we have a lower bound on the marginal likelihood:

$$\Pr(y \mid X) = \int \Pr(y \mid X, \beta) \Pr(\beta) d\beta \geq \int e^{g(\beta; \eta)} \Pr(\beta) d\beta.$$
in which we substitute $\beta$ with $\left(\beta_i\right)$, and we substitute $X$ with $(Z X)$. This yields the following expression for the lower bound:

$$|\Sigma_0|^{1/2} \Pr(y \mid X, Z) \geq |\hat{\Sigma}|^{1/2} \int e^{g(\beta ; \eta)} \Pr(\beta) \, d\beta,$$

in which we define

$$g^*(\beta ; \eta) = \sum_{i=1}^{n} \log \sigma(\eta_i) + \frac{n}{2}(d_i \eta_i - 1) + \hat{y}^T X \beta - \frac{1}{2} \beta^T X^T \hat{D} X \beta + \frac{1}{2} \hat{u} \hat{\Sigma}^{-1} \hat{u},$$

and we introduce the following notation:

$$\hat{\Sigma} = (\Sigma_0^{-1} + Z^T D Z)^{-1}$$
$$\hat{u} = Z^T (y - \frac{1}{2})$$
$$\hat{D} = D - D Z \hat{\Sigma} Z^T D$$
$$\hat{y} = (I - D Z \hat{\Sigma} Z^T) (y - \frac{1}{2}).$$

**Introducing the fully-factorized variational approximation.** Similar to the linear regression case, the fully-factorized approximating distribution yields an analytic expression for the lower bound to the marginal log-likelihood:

$$\frac{1}{2} \log |\Sigma_0| + \log \Pr(y \mid X, Z, \theta)$$

$$\geq \frac{1}{2} \log |\hat{\Sigma}| + \frac{1}{2} \hat{u}^T \hat{\Sigma}^{-1} \hat{u} + \sum_{i=1}^{n} \log \sigma(\eta_i) + \frac{n}{2}(d_i \eta_i - 1) + \hat{y}^T X r - \frac{1}{2} r^T X^T \hat{D} X r$$

$$- \frac{1}{2} \sum_{i=1}^{p} (X^T \hat{D} X)_{ii} \text{Var}[\beta_i] + \sum_{i=1}^{p} \alpha_i \left[ 1 + \log \left( \frac{s_i^2}{\sigma_a^2} \right) - \frac{s_i^2 + \mu_i^2}{\sigma_a^2} \right]$$

$$- \sum_{i=1}^{p} \alpha_i \log \left( \frac{\alpha_i}{\pi_i} \right) - \sum_{i=1}^{p} (1 - \alpha_i) \log \left( \frac{1 - \alpha_i}{1 - \pi_i} \right).$$

As before, $\text{Var}[\beta_i]$ is the variance of $\beta_i$ with respect to the approximating distribution, and $r$ is a column vector with entries $r_i = \alpha_i \mu_i$. Finding the best fully-factorized distribution amounts to adjusting the free parameters $\theta$ to make the lower bound as tight as possible. The co-ordinate ascent updates for the free parameters are derived by taking partial derivatives of the lower bound, setting these partial derivatives to zero, and solving for $\theta$. This yields the following updates:

$$\mu_i = s_i^2 \left( (X^T \hat{y})_i - \sum_{j \neq i} (X^T \hat{D} X)_{ij} \alpha_j \mu_j \right)$$

$$s_i^2 = \left( (X^T \hat{D} X)_{ii} + 1/\sigma_a^2 \right)^{-1}$$

$$\frac{\alpha_i}{1 - \alpha_i} = \frac{\pi_i}{1 - \pi_i} \times \frac{s_i}{\sigma_a} \times e^{\mu_i^2/(2s_i^2)}.$$  

The co-ordinate ascent algorithm consists of repeatedly applying these updates until a stationary point is reached.

As in the linear regression case, we derive an approximate EM algorithm to fit the prior variance parameter $\sigma_a^2$. (Recall, $\sigma^2$ is not needed for logistic regression.) The M-step update for $\sigma_a^2$ is identical to Equation 14 after setting $\sigma^2 = 1$. 


Adjusting the linear approximation to the logistic regression likelihood. In the fourth and final part, we explain how we adjust the parameters $\eta = (\eta_1, \ldots, \eta_n)$ so that the lower bound on the marginal likelihood is as tight as possible. The algorithm is derived interpreting the situation within an EM framework: in the E-step, we compute expectations (the mean and covariance of $\beta$); and in the M-step, we maximize the expected value of the lower bound to the log-likelihood.

We begin by considering the simpler case when we have a single set of variables $X$. Afterward, we substitute to introduce the additional variables $Z$. Taking partial derivatives of $E[g(\beta; \eta)]$ with respect to the variational parameters, we obtain

$$\frac{\partial E[f(\beta; \theta)]}{\partial \eta_i} = \frac{d_i}{2}(\eta_i^2 - (x_i^T \mu)^2 - x_i^T \Sigma x_i),$$

where $x_i$ is the $i$th row of $X$, and $\mu$ and $\Sigma$ here are posterior mean and covariance of $\beta$ computed in the E-step. The typical approach is to set the partial derivatives to zero and solve for $\eta$. At first glance, this does not appear to be possible. But a couple of observations will yield a closed-form solution: first, the slope $d$ is symmetric in $\eta$, so we only need to worry about the positive quadrant; second, for $\eta > 0$, $d$ is strictly monotonic as a function of $\eta$, so $d'$ is never zero. Therefore, we can solve for the fixed point:

$$\eta_i^2 = (x_i^T \mu)^2 + x_i^T \Sigma x_i. \quad (23)$$

To derive the M-step update for the fully-factorized variational approximation, after analytically integrating out the coefficients $u$, we need to replace $\mu$ and $\Sigma$ by the correct mean and covariance of $(\beta)$ under the variational approximation. The means and variances of the coefficients $\beta$ are easily obtained from the variational approximation. The remaining means and covariances in Equation 23 are

$$E[u] = \hat{\Sigma}Z^T(y - \frac{1}{2} - DXr)$$
$$\text{Cov}[u] = \hat{\Sigma} + \hat{\Sigma}Z^TDX\text{Cov}[\beta]X^TDZ\hat{\Sigma}$$
$$\text{Cov}[u, \beta] = -\hat{\Sigma}Z^TDX\text{Cov}[\beta].$$

Therefore, the final M-step update for $\eta$ is

$$\eta_i^2 = (z_i^T E[u] + \sum_{j=1}^p x_{ij} E[\beta_j])^2 + z_i^T \text{Cov}[u]z_i + \sum_{j=1}^p x_{ij}^2 \text{Var}[\beta_j] + 2z_i^T \text{Cov}[u, \beta]x_i, \quad (24)$$

in which $z_i$ is the $i$th row of $Z$. 

**varbvs:** Fast Variable Selection for Large-Scale Regression
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