Bayesian ensemble methods for survival prediction in gene expression data
Vinicius Bonato¹, Veerabhadran Baladandayuthapani²,*, Bradley M. Brooᵐ³, Erik P. Sulman⁴, Kenneth D. Aldape⁵ and Kim-Anh Do²
¹Pfizer Inc., Groton, CT 06340, ²Department of Biostatistics, ³Department of Bioinformatics and Computational Biology, ⁴Department of Radiation Oncology and ⁵Department of Pathology, The University of Texas, M. D. Anderson Cancer Center, Houston, TX 77030, USA
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ABSTRACT
Motivation: We propose a Bayesian ensemble method for survival prediction in high-dimensional gene expression data. We specify a fully Bayesian hierarchical approach based on an ensemble ‘sum-of-trees’ model and illustrate our method using three popular survival models. Our non-parametric method incorporates both additive and interaction effects between genes, which results in high predictive accuracy compared with other methods. In addition, our method provides model-free variable selection of important prognostic markers based on controlling the false discovery rates; thus providing a unified procedure to select relevant genes and predict survival functions.
Results: We assess the performance of our method several simulated and real microarray datasets. We show that our method selects genes potentially related to the development of the disease as well as yields predictive performance that is very competitive to many other existing methods.
Availability: http://works.bepress.com/veera/1/
Contact: veera@mdanderson.org

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1 INTRODUCTION
Gene expression profiling using DNA microarray technology has successfully identified molecular classes of cancer and revealed gene expression patterns that are associated with disease recurrence or prognosis of patient survival (Berchuck et al., 2005). Survival prediction is often formulated in terms of categorical outcomes (e.g. ‘poor’ versus ‘good’ prognosis), which may be useful for guiding decisions about cancer management and treatment (Ross, 2009). However, due to a large degree of heterogeneity observed within prognostic classes, prediction of time to a clinical event/occurrence may not be successful. Improved accuracy of survival prediction can be attained by relating time-to-event measures directly with gene expression profiles, which requires specific survival analysis methods that account for the presence of right censored outcomes, such as the (multivariable) Cox proportional hazards (CPH) model (Cox, 1972) and the accelerated failure time model (AFT; Klein and Moeschberger, 1997). In our context, we define the (uncensored) survival time as the dependent variable of interest representing the time to an event (such as death or recurrence), and a right censored observation is an observation that is lost to follow-up after the period of study.

In spite of their widespread use in other settings, these standard multivariable survival methods cannot be directly applied to clinical outcome prediction using gene expression data because the number of covariates (genes) under investigation is considerably larger than the number of samples (patients) — the ‘large’ p, small n problem’ (West, 2003). Many different strategies have been employed to solve this high dimensionality problem. For example, clustering techniques have been applied to group-correlated sets of genes, (D’haeseleer, 2005), linear combinations of covariates obtained by the partial least squares method (Nguyen and Rocke, 2002; Park et al., 2002) or the principal components of the design matrix (Li and Gui, 2004) have been used as explanatory variables in survival regression models. In addition, some authors have proposed the use of penalized versions of the CPH model, L1-penalized (Lasso regression) and L2-penalized (ridge regression) versions, for estimating parameters while simultaneously performing variable selection (Gu and Li, 2005; Park et al., 2002; Tibshirani, 1997). Similarly, Datta et al. (2007) developed penalized variants of the AFT model for fitting high-dimensional datasets. Bayesian techniques for variable selection have also been developed for Weibull and CPH models (Lee and Mallick, 2004) as well as for the AFT model (Sha et al., 2006).

Although these strategies address the high-dimensionality problem with some degree of success, they fail to incorporate complex interactions between genes because they model genes in an additive and linear manner. Ensemble methods such as bagging (Breiman, 1996), boosting (Friedman, 2001) and random forests (Breiman, 2001) are flexible alternatives for accommodating variable interactions that are more stable in high-dimensional settings (Breiman, 2001). Because ensemble methods use a linear combination of trees to fit data variations such that each tree fits part of the data, these methods have been shown to have high predictive accuracy (Lee et al., 2005). The ensemble methods were originally developed for modeling binary or continuous responses. Extensions for modeling survival data, often called survival ensembles (Hothorn et al., 2006), address the censoring problem by growing relative risk forests (Ishwaran et al., 2004), by

*To whom correspondence should be addressed.
We denote the observed data for the covariate effects. For computational convenience, the covariates are determined by Schmid and Hothorn (2008) estimates the predictor function of the AFT model simultaneously with the estimation of the scale parameter, so that the boosting algorithm can be applied to minimize a predefined loss function. Bayesian estimation has been shown to improve the predictive performance of tree models with nominal or continuous responses (Chipman et al., 1998; Denison et al., 1998; Pitman et al., 2004). The application of Bayesian survival ensembles has been limited to a study by Clarke and West (2008), in which they proposed using a tree-based Weibull model to predict the outcome of advanced stage ovarian cancer.

In this article, we propose a Bayesian ensemble method for survival prediction that is appropriate for high-dimensional data such as gene expression data (Section 2). Our approach is based on the ensemble ‘sum-of-trees’ model (Chipman et al., 2010) and is defined by a likelihood and a prior. We specify a fully Bayesian hierarchical approach with uncertainty in estimation being captured at each stage of the hierarchy to make predictions. We illustrate our methodology using three popular survival models: the CPH (Section 2.1), Weibull (Section 2.2) and AFT models (Section 2.3). Our approach is unique as we overcome the lack of conjugacy by using a latent variable formulation to model the covariate effects, which not only allows stochastic deviations from the parametric model but also results in efficient and computationally less expensive model fitting. Our approach is non-parametric and incorporates additive and interaction effects between genes, which results in high predictive accuracy as compared with other methods. In addition, our method provides model-free variable selection of important predictive prognostic markers that is based on controlling the false discovery rates (Section 2.5). We compare the predictive accuracy of our method with baseline reference survival methods that were reviewed by van Wieringen et al. (2009) using a benchmark breast cancer dataset (Section 3.1). We also apply our methodology to a brain tumor dataset (Section 4) and conclude with a brief discussion (Section 5). Additional technical and computational details as well as simulation results are available via Supplementary Materials.

2 METHODS

We denote the observed data for the $i$-th patient ($i = 1, ..., n$) as $(t_i, X_i)$, the survival time, along with $δ_i$, the event indicator function, where $δ_i = 0$ if the data are right-censored and $δ_i = 1$ if they are not. In addition to the survival response, the $p$-dimensional vector of the covariates (genes/probes) potentially associated with the $i$-th patient survival time, $X_i$, is also available. Let $f(t_i|x_i)$ denote the vector of the survival times and let $X_{seq}$ denote the matrix of the gene expression data. In the following sections, we develop the survival distribution, which aids to predict the survival time of a new patient with covariates $X_{new}$.

Modeling the survival data usually proceeds in two steps: (i) specification of a sampling distribution $p(y|X)$, conditional on a function of the covariates $f(X)$, such as modeling either the hazard function (as in CPH models) or directly modeling the survival time (as in Weibull and AFT models) and (ii) specification of the regression function $f(X)$, which models the covariate effects. For computational convenience, the covariates are usually assumed to be linear and independently related to survival, such that $f(X) = Xβ$ where $β$ is a vector of $p$ unknown regression coefficients that captures the covariate effects on the survival time or hazard. There are two drawbacks to this approach. First, the linear and independent assumption is a restrictive one. Second, and more importantly, in high-throughput studies such as those based on gene expression data, the problem becomes much more complex when $p$, the dimension of $X$, is very large, possibly larger than the sample size $n$. This makes the estimation of $β$ unstable and exacerbates the high dimensionality problem if interactions between covariates are considered. Dimension reduction approaches such as feature selection or partial least squares methods alleviate this problem to a certain degree. However, these methods are based on a linear relationship between the response and the covariate, which may not be very realistic. If the actual $f$ is non-linear, these models may fail to produce a reasonable prediction due to a lack of flexibility. We propose to model $f(X)$ in a flexible manner using ensemble methods that not only accommodate non-linear effects but which also incorporate the interactions of the covariates to estimate the effects on survival time. The non-parametric representation of $f(X)$ is introduced in the context of three alternative established survival time models in the following.

2.1 Ensemble-based proportional hazards regression

The Cox proportional hazards model (CPH, Cox, 1972), one of the most popular survival models in the statistical literature, does not model the time-to-event measures directly, rather, it models the hazard function $h(t)$, at any time $t$ as

$$h(t) = h_0(t)\exp(\beta'x),$$

where $h_0(t)$ is the baseline hazard function and $x$ is an unknown function modeling the associated latent covariate effect. The joint conditional survival function of $t$ in the CPH model can then be written as

$$S(t|x) = \exp\left(-\sum_{i=1}^{n} A(t)_i \exp(\alpha_i)\right),$$

where $A$ represents the cumulative hazard function. The associated complicated form of the likelihood makes it impossible to express conditional distributions of the parameters ($\alpha, A$) in closed forms (Ibrahim et al., 2001). As a result, the drawing of posterior distributions requires the sampling of all model parameters using complex Markov chain Monte Carlo (MCMC) procedures at each iteration, which makes the process computationally intensive and potentially leads to poor mixing, especially in high-dimensional settings.

We simplify the joint likelihood in two ways. First, for the cumulative hazard function, we follow the approach of Kalbfleisch (1978) by specifying a Gamma process prior for $\Lambda^t\delta_i$, such that

$$\Lambda^t\sim GP(\Lambda^\alpha, \alpha),$$

where $\Lambda^\alpha$ is the mean process and $\alpha$ is a weight parameter about the mean with $A(t)\sim G(\alpha A^\alpha(t), a)$. The use of the Gamma process prior allows us to analytically integrate out the $A$ vector, such that the marginal likelihood, conditional on $\alpha$, can be written as

$$L(\alpha) = \exp\left(-\sum_{i=1}^{n} A^\alpha(t)_i \right) \left(\sum_{i=1}^{n} \exp(\alpha_i)\right)^K,$$

where $K$ is the number of individuals at risk at time $t_i$, and $\Lambda(t)$ is the set of individuals at risk at time $t_i$. We modify the model by treating the $\alpha_i$’s as random latent variables, conditional on the $t$’s being independent of the $X_i$’s by the following factorization: $p(T|\alpha, p(0|X))$. This latent variable construction has the following advantages: (i) allows deviations from the fixed parameterized survival models by including a latent error term ($\delta$) and (ii) preserves the conjugacy of the ensemble structure which enables us to employ efficient MCMC algorithms such as Gibbs sampler that greatly aids computations for such large datasets. Specifically, we assume a Gaussian process on $p(\delta|X)$, such that $\delta = \delta(X) + e$, where $\delta(X)$ is the regression function and $e$ is residual random effects assumed to be distributed $\text{Normal}(0, \sigma^2)$. 

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The residual random effects, \( \epsilon_i \), account for the unexplained sources of variation in the data, most probably due to explanatory variables (genes) not included in the study (Lee and Mallick, 2004).

We approximate \( f(\cdot) \) using a tree-based ensemble method in order to model the non-linearity effects of the genes and also to account for the high dimensionality of the data. We use the ‘sum-of-trees’ approach of Chipman, George and McCulloch (2010; hereafter referred to as CGM), which they called the Bayesian additive regression trees (BARTs) model, as our candidate choice due to its excellent predictive performance on a variety of datasets. Compared with other ensemble methods, BART is preferable because it is explicitly defined in terms of a full probability model, i.e. with likelihoods and priors, and, therefore, can be used to implement a full Bayesian hierarchical approach for the estimation of all relevant uncertainties. BART as developed by CGM only considered continuous and categorical outcome variables, and in the following we extend it to survival models in the presence of censoring in high-dimensional settings using a fully Bayesian hierarchical framework. We present a brief review of BART; see CGM for more details.

Let \( T \) represent a single-decision tree containing both internal and terminal nodes. Internal nodes of the tree are grown through recursive partitions of the data using splitting rules. Splitting rules produce binary splits of the data and are defined in terms of splitting variables and cut-off values. Dropping an individual with covariates \( x_i \) down the tree assigns it to a terminal node according to the tree splitting rules. Let each tree be indexed by \( B \) terminal nodes and define \( \mu = (\mu_1, \ldots, \mu_B) \) as the vector of averages \( \mu_b \) of individuals assigned to the same node \( b \), where \( b = 1, \ldots, B \). Thus, each observation can be mapped by a function \( f_i \) such that \( f_i(x_i) = \mu_b \). Since BART is a ‘sum-of-trees’ model, \( f \) can be approximated by

\[
f(X) = \sum_{b=1}^{B} f_b(X; \tau_b, \omega_b),
\]

where \( B \) is the total number of trees. Compared to single tree models, BART is more flexible since several trees incorporate the additive effects and, consequently, improve estimation. However, a large number of trees can increase the computation time. We discuss the computational trade-offs related to the size of \( B \) in later sections.

To complete the full Bayesian hierarchical formulation of our ensemble-based proportional hazards regression model, we need to specify the following priors: \( p(\mu_1, \ldots, \mu_B) \) and \( p(f(\cdot)) \) for \( \Phi = (\tau, \omega, \mu) \) represents the tree-specific parameters. Our prior for \( p(f) \) is of the form

\[
p(f) \propto \prod_{b=1}^{B} p(f_b) \prod_{i=1}^{n} p(\mu_i | f_b(x_i)),
\]

where the second equality is obtained by recursively conditioning on the terminal nodes.

We follow CGM and define \( p(T_b) \) by three factors: (i) the distribution on the splitting variable assignments at each interior node is a uniform prior over all available variables; (ii) the distribution on the splitting rule assignment in each interior node, conditional on the splitting variable, is a uniform distribution over the set of available splitting values; and (iii) the probability that a node at depth \( d \) is non-terminal is given by \((1-\delta)^d\), where \( c \) is the number of variables, and \( \delta \) is a fixed parameter controlling the size of the tree. Following CGM, we set \( c=0.95 \) and \( \delta=2 \) to give prior probabilities of \(0.05, 0.55, 0.25, 0.09 \) and \( 0.03\) for trees to have \(1, 2, 3, 4, \geq 5\) terminal nodes, respectively. As in CGM, we assume independent conjugate normal priors for \( \mu_b | T_b \). Assigning prior distributions for the set of tree parameters \( T \) and \( \mu \) constrains the size of the trees, which avoids having the model populated by noninformative covariates. This imposed variation in the tree size grants BART the flexibility to accommodate the main effects as well as the interactions of different orders (more than one splitting rule). This results in a better predictive performance from BART compared with competing methods such as random forest and boosting algorithms. To complete the prior formulations, we assume a conjugate inverse chi-squared distribution on \( \sigma^2 \) as \( \sigma^2 \sim \text{IG}(v/2, v/2) \), where \( v \) is a data-determined fixed hyperparameter. The full conditional posterior distributions for sampling can be accessed via the Supplementary Material.

The complete hierarchical Bayesian model for the ensemble-based CPH model can be concisely written as

\[
\begin{aligned}
&\{\mu\} \sim L_0(\mu_0), \\
&\{\omega\} \sim \text{Normal}(\mu_0, \sigma^2), \\
&f(X) \sim \text{Tree}(\Phi), \\
&\sigma^2 \sim \chi^2_2,
\end{aligned}
\]

where \( T \) encompasses all the priors and distributional assumptions detailed in the above paragraph.

### 2.2 Ensemble-based Weibull regression

The Weibull model is parametric and used extensively to describe lifetimes, and can be reparameterized as both a CPH and an AFT model (Klein and Moeschberger, 1997). The Weibull distribution is indexed by a shape parameter \( \tau \) and scale parameter \( \omega \), and models the probability of survival at time \( t \), for patient \( i \) as

\[
f(t_i | \tau, \omega) = \tau \omega t_i^{\tau-1} \exp(-\omega t_i^\tau),
\]

where \( \tau > 0 \) and the survival function as \( S(t_i | \tau, \omega) = \exp(-\omega t_i^\tau) \). Letting \( \lambda = \sum_b \) represent the number of censored observations, the joint likelihood function for the parameter \( \tau \) and the vector of parameters \( \omega = (\omega_1, \ldots, \omega_B) \) becomes

\[
L(t_i | \tau, \omega) = \prod_{i=1}^{n} \left[ (1 - \delta_i)^{\lambda} \left( \exp(-\omega_0 t_i^\tau) \right) \right] - \sum_{i=1}^{n} \exp(-\omega i^\tau).
\]

As in the previous section, we model the covariate effects using a latent variable formulation, as \( \omega_0 \sim \text{Normal}(\mu_0, \sigma_0^2) \), and use BART to model \( f \). We complete our hierarchical model by assigning a conjugate gamma prior on \( \tau \) as \( \Gamma(\nu, \mu_0) \) with fixed but vague hyperparameters. Thus, our ensemble-based Weibull regression model can be concisely written (following the above notations) as

\[
\begin{aligned}
&\{\tau_{i,0}\} \sim \text{Weibull}(\tau_{0,0}), \\
&\{\tau\} \sim \Gamma(\nu, \mu_0), \\
&\{\omega_i\} \sim \text{Normal}(\mu_0, \sigma_0^2), \\
&f(X) \sim \text{Tree}(\Phi), \\
&\mu_i \sim \chi^2_2,
\end{aligned}
\]

### 2.3 Ensemble-based accelerated failure time model

The AFT model is a parametric survival model that assumes that the individual survival time \( t \) depends on the multiplicative effect of an unknown function of covariates \( f(X) \) over a baseline survival time \( \omega \). The AFT model (on log scale) can be written as,

\[
\log(t_i) = \omega + f(X) + \epsilon_i, \quad i = 1, \ldots, n
\]

where \( f \) captures the covariate effects affecting the \( \log \) survival time directly.

We assume that the random errors, \( \epsilon_i \), are normally distributed; however, we can easily adopt other distributions such as an extreme value or \( \tau \) distribution (Klein and Moeschberger, 1997). Note that under an extreme value distribution, the AFT model is equivalent to the Weibull model described previously.

As before, let \( \omega_0 \) be a latent variable such that \( \omega_0 \sim f(X) + \epsilon_i \), where the \( \epsilon_i \)'s are i.i.d Normal \( (0, \sigma^2) \). The AFT model can then be expressed using
We use MCMC (Gilks, 1996) for the CPH model uses a Gibbs sampler to estimate the set of parameters. The specific drawing scheme is as follows:

(i) updating \( \Phi \) by using a Gibbs sampler;
(ii) updating \( \alpha, \phi, \tau, \sigma^2 \) using a Metropolis–Hastings procedure.

The posterior distributions of the Weibull model parameters are obtained in a similar manner:

(i) updating \( \Phi \) by using a Gibbs sampler;
(ii) updating \( \alpha, \phi, \tau, \sigma^2 \) componentwise, where \( i = 1, \ldots, n \) for each \( \alpha \) a similar Metropolis–Hastings procedure with the probability of accepting the change given by:

\[
\pi_{\alpha} = \min \left( 1, \frac{p(h_{\alpha}^{\alpha_{i-1}} | X, \delta, \tau, \sigma^2)}{p(h_{\alpha}^{\alpha_{i}} | X, \delta, \tau, \sigma^2)} \right)
\]

The drawing scheme for the AFT model parameters follows the steps:

(i) updating \( \Phi \) using a Bayesian backfitting MCMC algorithm described in CGM;
(ii) updating \( \alpha, \phi, \tau, \sigma^2 \) using a Metropolis–Hastings procedure with the acceptance probability given by:

\[
\pi_{\alpha} = \min \left( 1, \frac{p(h_{\alpha}^{\alpha_{i-1}} | \Phi, \tau, \sigma^2)}{p(h_{\alpha}^{\alpha_{i}} | \Phi, \tau, \sigma^2)} \right)
\]

The Bayesian FDR of \( \phi_\alpha \) is estimated using cross-validation, for example, the Brier score (BS), the coefficient of determination (\( R^2 \)), and the concordance index (CI). Studies have shown that these metrics are good descriptors of predictive performance.
Around 73% of these observations are right censored. Patient age
The close the CI is to 1, the better is the fit.
We compared the performance of our method with other survival
We discuss each of these measures in detail. The BS is a specialized
and employ it to obtain the survival distribution
BS is given by
\[ \text{BS} = \frac{1}{n} \sum_{i=1}^{n} \left( \frac{S(t_i | X_i) \delta_i}{\tilde{S}(t_i)} \right) \]
where \( \delta_i \) is the Kaplan–Meier estimate of the survival distribution
for the observations \( (t_1, \ldots, t_n) \) and \( I \) denotes an indicator function.
For the BS, we utilize the training data \( t \) and \( X \) to fit a model \( p(t|X) \),
and employ it to obtain the survival distribution \( \hat{S}(t_i | X_i) \) for a
future patient with covariate \( X_i \). The BS ranges from 0 to 1; the
smaller the score, the better the fit.
The \( R^2 \) measure is the usual coefficient of determination of the
fitted model and quantifies the proportion of variability observed in
the test set that can be explained by the predictor. \( R^2 \) is estimated as
\[ R^2 = 1 - \frac{\text{SS}_{\text{res}}}{\text{SS}_{\text{tot}}} \]
where \( \text{SS}_{\text{res}} \) denotes the log-likelihood function evaluated at a
particular value. In order to obtain the \( R^2 \), we use the median of
the posterior distribution to estimate \( \hat{\omega} \), the vector of the latent
covariate effects and then we use it as a predictor in the univariable
version of the specific underlying model. For example, the vector \( \hat{\omega} \)
estimated from the ensemble version of the AFT model is used as
the predictor vector in a univariable AFT. \( R^2 \) also ranges from 0 to 1
and a predictor that explains a high proportion of variability in the
survival data will have \( R^2 \) values close to 1.
The CI can be expressed in the form
\[ CI = \frac{\hat{\omega}_i - \omega_i}{\hat{\omega}_i + \omega_i} \]
where \( \hat{\omega}_i, \omega \) is 1 if \( \hat{\omega}_i > \omega_i \) or 0 if otherwise, is based on pairwise
comparisons between the prognostic scores \( \hat{\omega}_i \) and \( \omega \) for patients
\( i \) and \( j \), respectively. \( \Omega \) consists of all the pairs of patients \( [i,j] \).
The close the CI is to 1, the better is the fit.

3.1 Breast cancer data
We compared the performance of our method with other survival
prediction methods tailored for gene expression data as recently
reviewed by van Wieringen et al. (2009) and other popular survival
methods. We used the breast cancer dataset of Van Veer et al. (2002; http://www.rri.com/publications/2002/vantveer.html), which
contains gene expression profiles for 295 breast cancer patients and
5057 gene expression values, along with patient survival outcomes.
Around 73% of these observations are right censored. Patient age
ranges from 26 to 53 years and the percentage of patients with tumor
grade I is 34%, grade II is 40% and grade III is 26%. We replicated the
‘best’ methods found by van Wieringen et al. (2009): multivariable
linear CPH model (CPH), L1-regularized Cox regression (CPH-L1)
of Tibshirani (1997) and the L2-regularized Cox regression (CPH-
L2) of Gu and Li (2005). We replicate the same setup used by
van Wieringen et al. (2009) to allow comparisons across studies, i.e. we use the multivariable linear CPH model, in which the top 10
genes were obtained using a univariable Cox regression. In addition, we
run a multivariable linear Weibull model, in which the top 10 most
significant genes were obtained using univariable Weibull models.
We also used a multivariable linear AFT model, in which the top
10 genes were pre-selected by using a univariable AFT analysis.

We also included conditional inference tree ensemble methods as
Bagging, Random Forest (Hothorn et al., 2006) and Random
Survival Forests (ntree = 2000; Ishwaran et al., 2008) as well as
CoxBoost (Binder & Schumacher, 2009). Bagging and Random
Forest models were also studied by van Wieringen et al. (2009).
Similarly to van Wieringen et al. (2009), we used the top-200 most
significant genes obtained by the underlying univariable model to
run our ensemble versions of the accelerated failure time model
(AFT-TREE), the Weibull model (WEI-TREE) and the CPH model
(CPH-TREE). We used a long single chain of \( K = 10000 \) iterations
for each survival model with a burn-in of the first 5000 samples. In
addition, we ran several chains with different initial values and found
that our results are robust to these convergence checks. We repeated
the cross-validation procedure 50 times with the data randomly split
into training and test sets in a 2:1 ratio and with the number of
censored observations kept balanced between training and test sets.
We used the training set to build the predictor and then used the test
set to assess the performance of the competing methods.
Based on the BS, our proposed ensemble-based methods outperformed most of the competing methods. The median BS for
the ensemble method is roughly 10% smaller than those for the
CPH-L1 and CPH-L2 methods, which were reported to be the
best performing methods by van Wieringen et al. (2009). The best
median BS is for the AFT-TREE model (0.158), followed by WEI-
TREE (0.160). The median BS for CPH-TREE (0.164) model is
also small and close to the medians of CoxBoost (0.162) and Bagging
(0.165) methods. In terms of \( R^2 \), the AFT-TREE (0.141) model
seems to have performance equivalent to CoxBoost (0.145) and RSF
(0.146) methods while CPH- and Weibull-TREE methods did not
perform as well. For the CI, all methods seem to have equivalent
performance leaded by AFT (0.603) and CoxBoost (0.600) methods.
The performance of some or all proposed tree-based models
(0.582–0.598) is better than the performance of RSF (0.571), CPH-
L1 (0.582) and RF (0.583) (see Supplementary Material for
detailed information). Based on these three evaluation measures,
our proposed method improves survival prediction accuracy in some
cases or is, at least, equivalent in performance to competing methods.
We believe that this improvement may be attributable to added
flexibility when accounting for additive and non-linear effects.
We use a Bayesian FDR cutoff of 0.1 to select significant
covariates for survival prediction (explained in Section 2.5) and,
as a result, we found that a total of 9 variables were significant in
the CPH-TREE, 7 in the WEI-TREE and 12 in the AFT-TREE. One
gene (BCL2) was simultaneously listed for the AFT-TREE and the
WEI-TREE. Genes identified by the models represent promising
targets for further biological investigation as, for example, BCL2
gene which is one of the strongest predictors of shorter survival
among breast cancer patients and was also reported by Van’t Veer
et al. (2002) or STK12 gene which is located in a region frequently
deleted in tumors, which contains tumor-related genes such as p53
(Tatsuoka et al., 1998). More details and results are presented in the
Supplementary Material.

4 APPLICATION TO BRAIN TUMOR DATA
We applied the proposed method to a dataset containing gene
expression profiles of brain tumors in order to identify molecular
and genetic signatures that could be of prognostic value. The dataset
contains gene expression measurements and survival information for
shown in Table 1. There is a significant overlap in the metagenes.

In practice, we are often interested in clusters containing correlated genes with very similar measurements in all samples. One use of these clusters is to infer the relatedness of individual genes from their membership in a common cluster. A second use is to suggest possible functions for individual genes of interest, based on the functions of other variables in the cluster, and to suggest additional related genes that might also be of interest. A third use is to calculate a cluster metagene for each sample by averaging the individual genes in the cluster. The cluster metagenes might yield more robust measurements and tests of sample characteristics than the individual variables. Converting the individual genes into metagenes also reduces the number of variables, and makes searching high dimensional spaces for interaction effects more tractable. Since our main interest is in finding prognostic groups of correlated genes, we focus our analysis on a set of metagenes that we obtained by applying an unsupervised clustering algorithm, gene shaving (Hastie et al., 2000). Gene shaving is an established method for generating such clusters. Gene shaving identifies the largest principal component, clusters the genes highly correlated with it and shaves out the less correlated genes. After finding the largest principal component, the procedure repeats until it has obtained a maximum number of clusters chosen a priori. The median BS calculated for the proposed tree-based models are similar to the median BS for other models, all of them around 0.11, which indicates a good model fit. In terms of medians of $R^2$, the tree-based method CPH-TREE (0.218) and CoxBoost (0.218) figure as the best models followed by RF (0.214) and AFT-TREE and SRF (both with median 0.212). For the CI, all methods seem to have equivalent performance leaded by AFT-TREE (0.618). In general, the performance of the proposed tree-based models (0.608–0.618) is better than the performance of other tree-based methods as SRF (0.609), RF (0.614) and Bagging (0.601) (see Supplementary Material for detailed information).

The posterior probabilities of the covariates used by our models are shown in Figure 1 along with the BFDR cut-off at $\alpha = 0.1$. The significant covariates for what are above this cut-off are shown in Table 1. There is a significant overlap in the metagenes and clinical covariates found by all three methods. In addition, the top five covariates mostly used by the AFT-TREE and WEI-TREE models are the same (although in different order). Tumor grade, one of the most important clinical factors for predicting survival of patients with brain tumors (The Cancer Genome Atlas Network, 2008), was confirmed in our results as one of the covariates more frequently used by all the models. Patient age, another important clinical covariate (The Cancer Genome Atlas Network, 2008), is also among the top covariates for the AFT-TREE and WEI-TREE models. In all the models, we found metagenes 52 and 99 had the highest posterior probabilities of inclusion. A search of the OMIM database (http://www.ncbi.nlm.nih.gov/omim/) revealed that these metagenes include genes known to be associated with the development and progression of tumors, including many associated with brain tissue. For example, metagene 52 includes four genes that are associated with glioma phenotypes: PHLP, GRIPE, PIK3R1 and BAI3. PHLP is known for its capacity to dephosphorylate Akt, triggering apoptosis and suppressing tumor growth via the p53 and RTK mitogenic pathways. GRIPE induces neuronal differentiation (Heng and Tan, 2002) and, therefore, prevents cells going through migration or invasion processes, resulting in good prognosis gliomas. Further, alterations of the PIK3R1 signaling pathway are present in close to 90% of glioblastomas (Cancer and Genome Atlas Network, 2008). Likewise, BAI3 is an inhibitor of
of angiogeneses and its downregulation is linked to an increasing
of tumor vascularization, a marked characteristic of high-grade
gliomas as Glioblastoma Multiforme (Shiratsuchi et al., 1997). In
addition, metagene 82 includes the gene MXI1, which negatively
regulates the MYC oncprotein, an important glioblastoma tumor
inductor (Albarosa et al., 1995). The downregulation of MXI1
covers the overexpression of MYC that activates cell proliferation,
deactivates apoptosis (controls the death receptor Bcl-2) and triggers
the mesenchymal phenotype in high-grade gliomas (Albarosa et al.,
1995). In addition, metagene 70 includes the EGFR gene, which
is one of the most important genes related to the development
of gliomas (The Cancer Genome Atlas Network, 2008) and its
downregulation is linked to an increasing
survival time in weeks, draw a vertical line from the ‘Total Points’
spot on the linear predictor scale.

To evaluate the predictive accuracy of our methods, we used
the same setup designed for the breast cancer data, i.e. we performed
a cross-validation procedure with the data randomly split 50 times into
testing and training sets at a 2:1 ratio. First, we built the predictor using
the training set. Then, we assessed and compared the performance of
different methods using evaluation measures calculated for the test
set. To evaluate the predictive ability of the proposed models, we
conducted a time-dependent area under the curve (AUC) analysis
(Fig. 3) that compares the prognostic capacity of the survival
models across different binary splits of the survival response. The
clinical literature reports frequent use of the time-dependent AUC
analysis (Cerhan et al., 2007) to help physicians better categorize
patients in terms of survival classes. In our study, the proposed
tree-ensemble methods performed better than the competing methods
and demonstrated higher sensitivity.

In conclusion, our results show that the clinical covariates and the
expression values of few (meta)genes impact the overall survival
of patients with brain tumors. We believe that these genes might
be worthy of further scientific investigation, especially as potential
therapeutic targets.

5 DISCUSSION

We propose Bayesian ensemble methods for survival prediction for
high-throughput data such as gene expression data. Using a powerful
predictive tool, BART, we model the covariate effects via a latent
variable scheme, that not only allows stochastic deviations from
the parametric model but also greatly reduces the computational
complexity. We chose BART because it has the flexibility to
accommodate a high number of covariates and their interactions.
In addition, our primary reason of working under a Bayesian paradigm
is that the uncertainty in estimation is propagated at each stage of
the hierarchy, thus the credible intervals on all our model parameters
are in some sense exact by conditioning on all sources of variation.
Thus, using the selected gene expression profile one can estimate
the median survival time and credibility intervals for a given patient
using the posterior distributions of the process parameters obtained
with the AFT-TREE model or, alternatively, survival curves along
with confidence bounds for the population using the WEI-TREE and
CPH-TREE methods. Although our method is based on the BART

Fig. 2. Marginal effects of significant covariates. Left panel: partial
dependence function plots for metagene 82 with y-axis in weeks. Right
panel: nomogram of the most important variables in the AFT-TREE model.
High-resolution version of this figure can be viewed in the supplementary
materials.

Fig. 3. Time-dependent AUC analysis. The plots compare the performance
of the proposed tree-ensemble methods with their multivariable linear
versions, as applied to the brain tumor data. Dots represent the medians across
splits of training/test sets; lines depict the interquartile limits. Left plot: CPH
dashed lines) and CPH-TREE (solid lines); center plot: Weibull (dashed)
and WEI-TREE (solid); right plot: AFT (dashed) and AFT-TREE (solid).
High-resolution version of this figure can be viewed in the supplementary
materials.
formulation, our framework can be extended to allow for the use of any other ensemble method.

Our primary motivation of using gene sets for the brain tumor dataset was that we were more interested in groups of common genes that predict survival rather than individual genes. These gene sets can be derived in various ways either using prior pathway knowledge [e.g. gene ontology (GO) or Kyoto Encyclopedia of Genes and Genomes (KEGG) databases] or using data-driven methods for finding clusters of correlated genes with very similar measurements in all samples, such as gene sharing. Although our methods can accommodate both scenarios, we choose the latter since it allows to infer the relatedness of individual genes from their membership in a common cluster as well as to suggest possible functions for individual genes of interest, based on the functions of other variables in the cluster, and to suggest additional related genes that might also be of interest.

The screening ability of the BART identifies important predictors across trees and training test splits of data, which allowed the model to reveal the impact of many important genes and clinical covariates on the survival of cancer patients. The application of our method to two different datasets showed that the prediction accuracy of our model outperforms that of many available models. In addition, the variable selection procedure, partial dependence functions and nomogram techniques imbue the final model with a high level of interpretability. We have a highly efficient R package available at http://works.bepress.com/vmeer1/1. A limitation of our proposed method is the lack of interpretability as compared to simpler regression models which is, at least, counterbalanced by gains in prediction accuracy and the ability to incorporate complex interaction effects among the covariates.

We note that the number of regression trees M set for the tree-ensemble methods dictates how often a covariate will be selected to be part of the model. Chipman et al. (2010) showed that setting a relatively small number of trees benefits the variable selection procedure since variables compete with each other to improve fit and therefore, relevant predictors should appear more frequently in the tree model. Because we were interested in exploring the BART variable selection feature, we set the number of trees in the tree model. Because we were interested in exploring the BART variable selection feature, we set the number of trees in the tree model. Because we were interested in exploring the BART variable selection feature, we set the number of trees in


denotes in the Supplementary Material. Although motivated by a gene expression dataset, our methodology can be applied to other genomic data as well such as array-based comparative genomic hybridization and SNP data. This is so, since we do not assume any structure on the covariate space—via a ensemble formulation that accommodates complex combination of continuous and categorical predictors. We leave this task for future consideration.

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REFERENCES


Ensemble methods for survival prediction


