Machine Learning for Personalized Medicine: Predicting Primary Myocardial Infarction from Electronic Health Records

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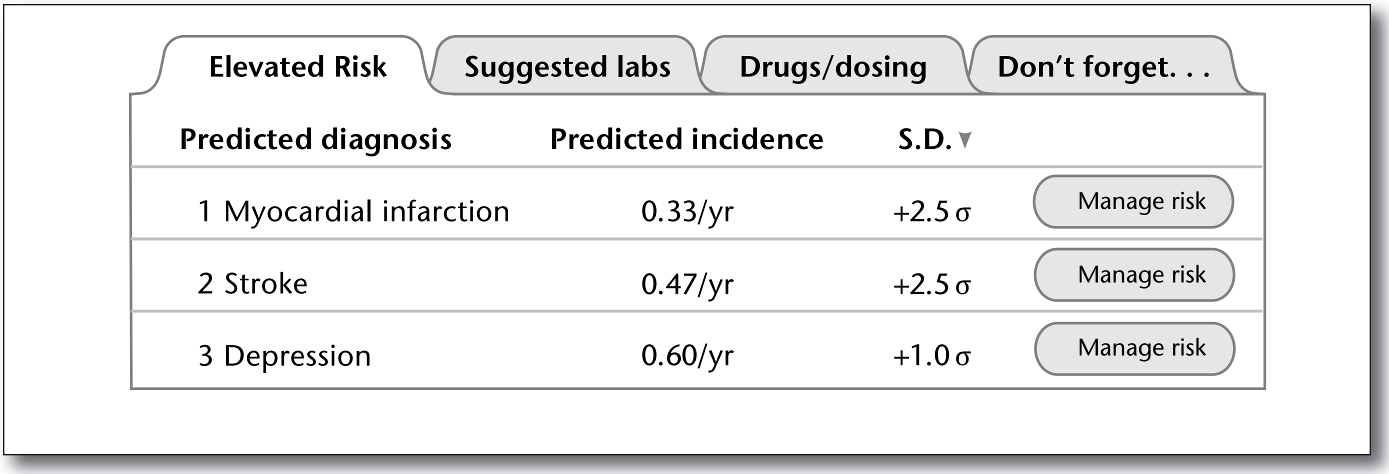
■ *Electronic health records (EHRs) are an emerging relational domain with large potential to improve clinical outcomes. We apply two statistical relational learning (SRL) algorithms to the task of predicting primary myocardial infarction. We show that one SRL algorithm, relational functional gradient boosting, outperforms propositional learners particularly in the medically relevant high-recall region. We observe that both SRL algorithms predict outcomes better than their propositional analogs and suggest how our methods can augment current epidemiological practices.*

One of the most studied pathways in medicine is the health trajectory leading to heart attacks, known clinically as myocardial infarctions (MIs). MIs are common and deadly, causing one in six deaths overall in the United States totaling 400,000 per year (Roger et al. 2011). Because of its medical significance, MI has been studied in depth, mostly in the fields of epidemiology and biostatistics, yet rarely in machine learning. So far, it has been established that prediction of future MI is a challenging task. Risk stratification has been the predictive tool of choice (Group 2002, Wilson et al. 1998), but these methods have produced strata where the baseline risk is nonnegligible; that is, everyone is still at risk. A much richer area of study is the identification of risk factors for MI. Common risk factors have been identified such as age, gender, blood pressure, low-density lipoprotein (LDL) cholesterol, diabetes, obesity, inactivity, alcohol, and smoking. Studies have also identified less common risk factors as well as subgroups with particular risk profiles (Greenland et al. 2010, Antonopoulos 2002).



Predicted diagnosis	Predicted incidence	S.D.▼	
1 Myocardial infarction	0.33/yr	+2.5 σ	Manage risk
2 Stroke	0.47/yr	+2.5 σ	Manage risk
3 Depression	0.60/yr	+1.0 σ	Manage risk

Figure 1. A Possible Future EHR Interface for the Physician That Includes Machine-Learning Predictions for the Current Patient.

The diagram shows model results suggesting that the patient is at elevated risk for specific diagnoses. It depicts a tabbed environment, where the machine-learning system also provides optimal drug regimens, recommends the collection of additional health information such as laboratory assays, and reminds physicians of steps involved in providing continuing care.

The canonical method of study in this field is the identification or quantification of the risk attributable to a variable in isolation using case-control studies, cohort studies, and randomized controlled trials. Case-control or cross-sectional studies identify odds ratios for the variable (or exposure) while controlling for confounders to estimate the relative risk. Cohort studies measure variables of interest at some early time point and follow the subjects to observe who develops the disease. Randomized controlled trials are the gold standard for determining relative risks of single interventions on single outcomes. Each of these methods is highly focused, centered on the goal of providing the best risk assessment for one particular variable. One natural question to ask is: by using machine learning, can we conduct fewer studies by analyzing the effects of many variables instead?

A different and crucial limitation of the longitudinal methods is that they make measurements at fixed points in time. Typically in these studies, data are collected at the study onset t_0 to serve as the baseline variables, whose values are the ones used to determine risk. To illustrate this, consider the Skaraborg cohort study (Bg-Hansen et al. 2007) for the identification of acute MI mortality risk factors. The study measured established risk factors for MI at t_0, and then the subjects participated in annual checkups to assess patient health and determine whether an MI event had occurred. It is important to note that, in line with current practice, the subjects who did not possess risk factors at time t_0 but developed them at some later time were considered as not possessing them in the analysis. If we knew that these developments had occurred, say from an electronic health record (EHR), would it be possible to estimate the attributable risk more precisely? In the extreme, can we estimate the risk factors and make reliable predictions without the annual checkups and the baseline t_0 measurements?

More generally, can we bring a machine-learning perspective to this task that provides new insights to the study of MI prediction and risk-factor identification? The answer is yes, and we present here a glimpse of the potential machine learning has to bring to this field (for example, see figure 1). We suggest that the emergence of the EHR as the new data source for population health analyses may be able to answer these clinical questions more efficiently, effectively adding another method of study to the standard three, as shown in figure 2. We argue that, using clinical events from EHRs as a supplement to clinical study data collection, we can improve risk-stratification and risk-attribution methods because EHRs provide richer and temporally precise data. For the prediction task, we emphasize the evaluation of methods on statistics that are clinically relevant, specifically on class separability (for risk stratification) and precision at high recalls (for use as a screening tool). Class separability, which can be directly assessed using ROC curves, is a well-established tool for risk stratification (Group 2002). Evaluating precision at high recalls assesses an algorithm's ability to predict while disallowing many false negatives, which is the critical component to a good screening tool. For predicting MI, a false negative means categorizing a patient as "low-risk" who goes on to have a heart attack, a costly outcome we wish to avoid.

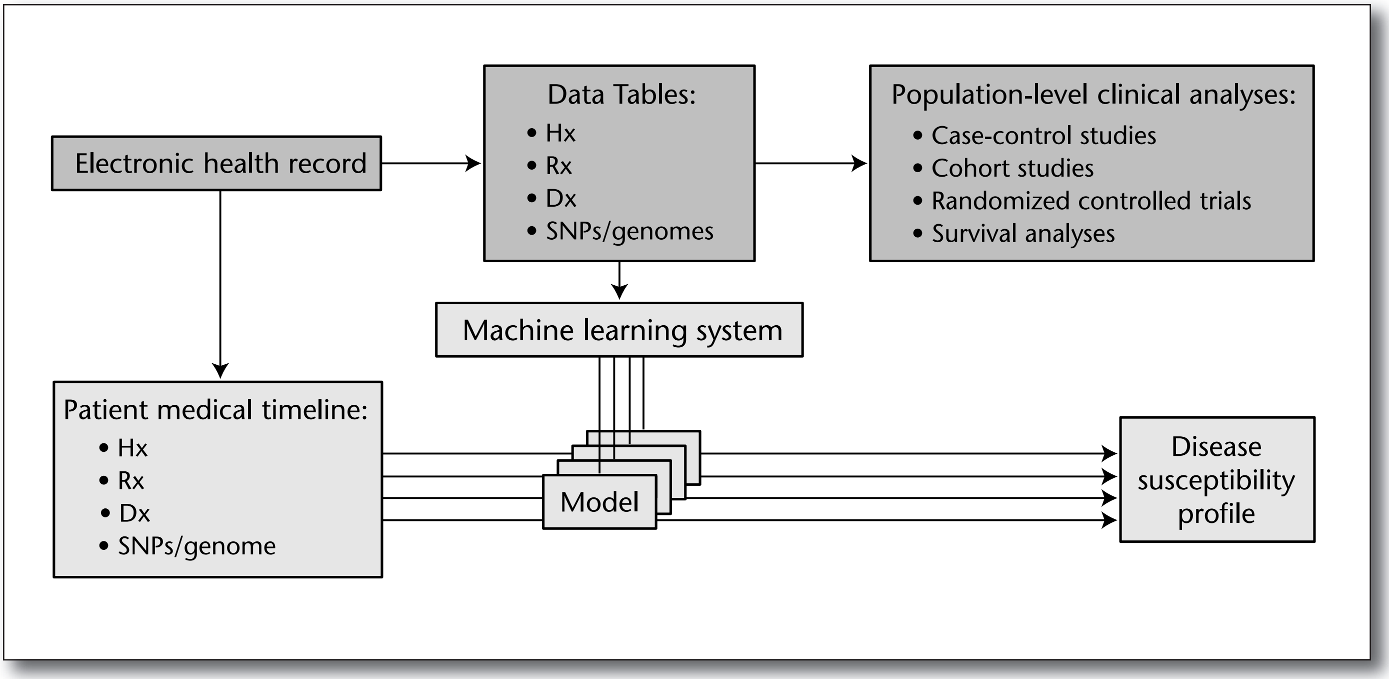


Figure 2. Machine-Learning Systems Can Augment Current Clinical Analyses by Producing Personalized Health Profiles Given Medical Timelines of Incoming Patients.

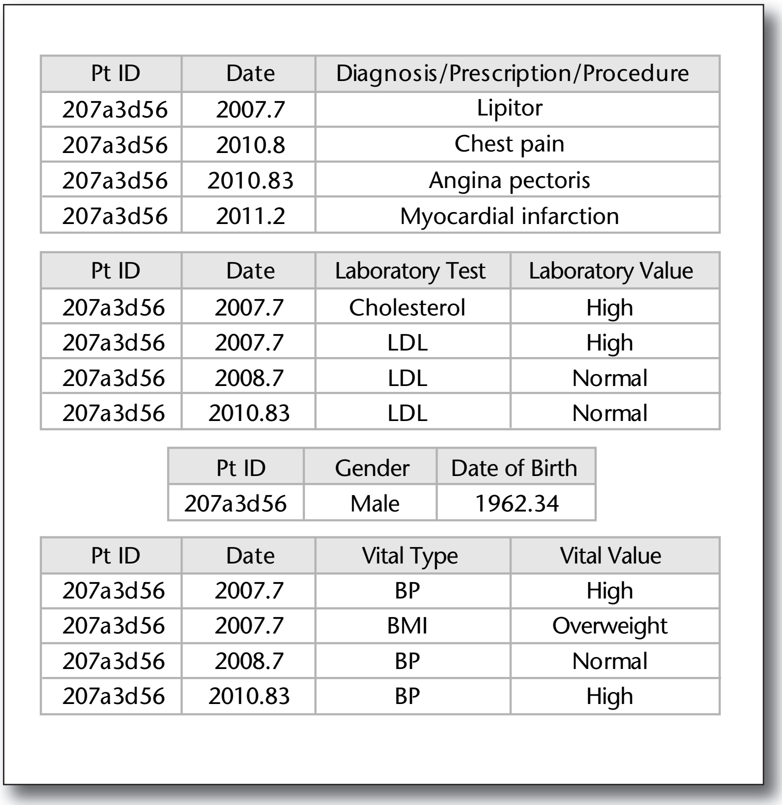
The clinical analyses typically identify and quantify risk factors that lead to disease; machine-learning models integrate such risk factors into comprehensive predictive models. Medical history (Hx), drugs prescribed (Rx), and diagnoses (Dx) are abbreviated. Machine-learning systems are shown in light gray. Current clinical analyses are shown in dark gray.

We also focus our methodology on algorithms with good interpretability, as this is critical for using the models for risk-factor identification. In this work we survey a host of established machine-learning algorithms for their performance on this task and select the most promising algorithm for further analysis. We attempt to answer some of these questions by providing an EHR-based framework for prediction and risk-factor identification.

EHRs are an emerging data source of great potential use in disease prevention. An EHR effectively tracks the health trajectories of its patients through time for cohorts with stable populations (figure 3). But as of yet they have been used primarily as a data warehouse for health queries, rather than as a source for population-level risk assessment and prevention. This trend is changing, however, as exemplified by the ongoing Heritage Health Prize contest, which uses medical claims data to predict future hospitalization.

Analogously, we can use EHR data to predict future disease onset and produce personalized risk scores, with direct potential applications to improving health care, as described in figure 1. Risk-stratification models do exist, but they typically require additional medical intervention, for example, running laboratory tests required to quantify risk. Thus, one advantage of risk modeling from EHRs is that many of the interventions required for standard risk stratification are rendered superfluous. While interventions provide up-to-date information and could improve risk stratification, a risk profile without them based on EHR data would be available regardless. As an example, the Framingham risk score (FRS) assessment of 10-year coronary heart disease (CHD) risk requires two lipoprotein laboratory assays, blood pressure measurements, and basic demographic information (Antonopoulos 2002). The FRS is a well-established, robust test for evaluating CHD risk, but a similar risk could be established with information from the EHR, which might include overlapping clinical information, without the additional intervention. Furthermore, the ability to account for disease occurrences across time instead of the disease state at an initial time could help modify risk status. Finally, for less high impact diseases than MI, the medical field has focused largely on identifying individual risk factors for disease. Relational models using EHRs could then easily produce aggregate risk models analogous to the FRS. Figure 4 compares the FRS framework with one based on EHR data.

Accurate predictive models of MI or other major health events have many more potential applications. First, such models can be incorporated into the EHR to provide prompts to clinicians such as, “your patient is at high risk for an MI and is not cur-



Pt ID	Date	Diagnosis/Prescription/Procedure
207a3d56	2007.7	Lipitor
207a3d56	2010.8	Chest pain
207a3d56	2010.83	Angina pectoris
207a3d56	2011.2	Myocardial infarction

Pt ID	Date	Laboratory Test	Laboratory Value
207a3d56	2007.7	Cholesterol	High
207a3d56	2007.7	LDL	High
207a3d56	2008.7	LDL	Normal
207a3d56	2010.83	LDL	Normal

Pt ID	Gender	Date of Birth
207a3d56	Male	1962.34

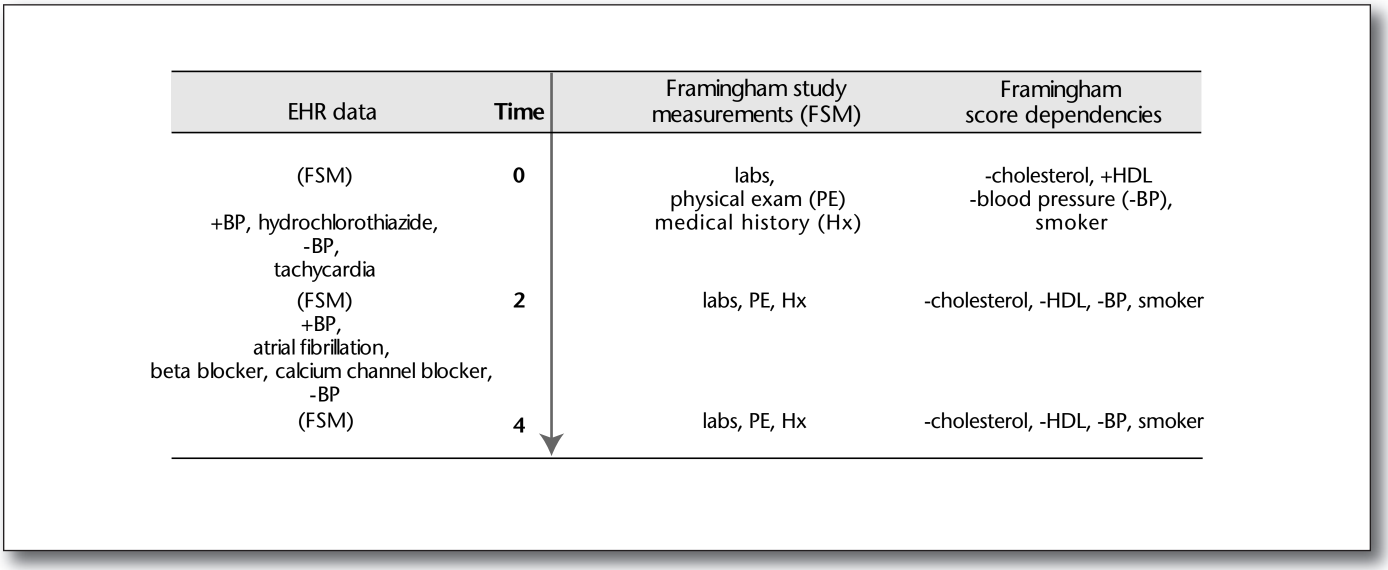
Pt ID	Date	Vital Type	Vital Value
207a3d56	2007.7	BP	High
207a3d56	2007.7	BMI	Overweight
207a3d56	2008.7	BP	Normal
207a3d56	2010.83	BP	High

Figure 3. Example of an EHR.

The EHR database consists of tables including patient information such as diagnoses, drugs, labs, and genetic information.

rently on an aspirin regimen." Second, the models themselves can be inspected in order to identify surprising connections, such as a correlation between the outcome and the use of certain drugs, which might in turn provide important clinical insights. Third, these models can be used in research to identify potential subjects for research studies. For example, if we want to test a new therapy for its ability to prevent an event such as MI, it would be most instructive to test it in a population of high-risk subjects, which a predictive model can accurately identify. Other works have focused on similar prediction tasks, for example, prediction of CHD, MI risk factor and biomarker identification, and prediction of MI in subgroups. The prediction of CHD includes the FRS and other works, for example, the numerous machine-learning models tested on the UCI heart disease data set (Detrano and Janosi 1989). Risk factors specifically for MI continue to be identified, for example, the characterization of circulating endotheial cells (Damani et al. 2012). The use of additional biomarkers in subgroups also helps predict future MI, as shown in studies involving postacute coronary syndrome (Syed et al. 2011), postangioplasty (Resnic, Popma, and Ohno-Machado 2000), and COX-2 inhibitors (Davis et al. 2008). However, we do not know of any work that predicts MI from EHR data. This framework, which can encapsulate the aforementioned studies, provides benefits described previously as well as new challenges, which directs us in our choice of models.

The primary approach we use draws from rela-



EHR data	Time	Framingham study measurements (FSM)	Framingham score dependencies
(FSM)	0	labs, physical exam (PE) medical history (Hx)	-cholesterol, +HDL -blood pressure (-BP), smoker
+BP, hydrochlorothiazide, -BP, tachycardia			
(FSM)	2	labs, PE, Hx	-cholesterol, -HDL, -BP, smoker
+BP, atrial fibrillation, beta blocker, calcium channel blocker, -BP			
(FSM)	4	labs, PE, Hx	-cholesterol, -HDL, -BP, smoker

Figure 4. Comparison of EHR and Framingham Heart Study Data.

This diagram compares EHR data extracted to timelines (left) and Framingham Heart Study (FHS) data collection as a time series (right). The Framingham health cohort requires clinic visits every other year to perform laboratory assays (for example, cholesterol levels), conduct physical exams (for example blood pressure [BP] measurements), and document medical history (for example, smoking status). The EHR contains FHS data and additional medical information with accurate time stamps, shown on the left. The FRS is recalculated every two years, whereas one based on the EHR would be updated as new clinical events occur.

tional probabilistic models, also known as statistical relational learning (SRL) (Getoor and Taskar 2007). Their primary advantage is their ability to work with the structure and relations in data; that is, information about one object helps the learning algorithms to reach conclusions about other objects. Unfortunately, most SRL algorithms have difficulty scaling to large data sets. One efficient approach that yields good results from large data sets is the relational probability tree (Neville et al. 2003). The performance increase observed moving from propositional decision trees to forests is also seen in the relational domain (Anderson and Pfahringer 2009, Natarajan et al. 2011b). One method called functional gradient boosting (FGB) has achieved good performance in the propositional domain (Friedman 2001). We apply it to the relational domain for our task: the prediction and risk stratification of MI from EHRs.

EHR data present significant challenges to current machine-learning methodology. If we hope to augment traditional clinical study analyses, we must be able to effectively address these challenges. A few of them are size, time-stamped data, relational data, and definition shifts over time. We use relational functional gradient boosting (RFGB) because it addresses all but the last challenge, which is difficult for any algorithm to capture. Notably, it is one of the few relational methods capable of learning from large data sets. Moreover, RFGB can efficiently incorporate time by introducing temporal predicates like *before*(*A, B*):- *A* < *B*. Also, unlike most other state-of-the-art SRL algorithms, RFGB allows us to learn structure and parameters simultaneously and grows the number of models as needed. Hence, we apply RFGB (Natarajan et al. 2011b) and relational probability trees (RPTs) (Neville et al. 2003) to the task of predicting primary MI. Our goal is to establish that, even for large-scale domains such as EHRs, relational methods and in particular RFBG and RPTs can scale and outperform propositional variants.

This article makes a few key contributions: First, we address the challenging problem of predicting MI in real patients and identify ways in which machine learning can augment current methodologies in clinical studies. Second, we address this problem using recently developed SRL techniques, adapt these algorithms to predicting MI, and present the algorithms from the perspective of this task. Third, the task of MI prediction is introduced to the SRL community. To our knowledge, this is the first work to use SRL methods to predict MI in real patients. Fourth, we focus our analysis on interpretable RPT models, making it easy to discern the relationship between different risk factors and MI. Finally, this article serves as a first step to bridge the gap between SRL techniques and important, real-world medical problems.

Learning Algorithms: Relational Probability Trees and Relational Functional Gradient Boosting

RPTs (Neville et al. 2003) were introduced for capturing conditional distributions in relational domains. These trees upgrade decision trees to the relational setting and have been demonstrated to build significantly smaller trees than other conditional models and obtain comparable performance. We use a version of RPTs that employs the TILDE relational regression (RRT) learner (Blockeel and Raedt 1998) where we learn a regression tree to predict positive examples (in this case, patients with MI) and turn the regression values in the leaves into probabilities by exponentiating the regression value and normalizing them. Hence, the leaves of the RPTs hold the predicted probability that a person has an MI given the other attributes. We use weighted variance as the criterion to split on in the inner nodes. In RRTs, the inner nodes (that is, test nodes) are conjunctions of literals, and each RRT can be viewed as defining several new feature combinations, one corresponding to each path from the root to a leaf. The resulting potential functions from all these different RRTs still have the form of a linear combination of features but the features are complex (Gutmann and Kersting 2006).

An example of such a tree is presented in figure 5 (left). The leaves of the learned tree indicate the probability of the target, in this case coronary artery calcification (Natarajan et al. 2012), being greater than 0. The first argument *A* of every predicate (inner node of the tree) is the subject's ID and the last argument of every predicate (except sex) indicates the year of measurement (year 0 indicates base measurements). The left branch out of every node is the true branch, the right branch the false branch. We use *_bw* in predicates to indicate that the value of a certain variable is between two values. For instance, *ldl_bw(A, B,* 0, 100, 10) indicates that the LDL level of subject *A* is *B* and is between 0 and 100 in year 10. So the leftmost path indicates that if the person is a male and his age is between 35 and 45 in year 7 of the study and if LDL level is greater than 90 in year 0 of the study, then the probability of his having a coronary artery calcification (CAC) level greater than 0 is 0.79.

For relational functional gradient boosting, assume that the training examples are of the form $(\mathbf{x}_i, y_i)$ for $\boldsymbol{i} = 1, \ldots, N$ and $y_i \in \{0, 1\}$ where $y_i = 1$ indicates *MI* and $\mathbf{x}$ represents the set of all observations about the current patient $\boldsymbol{i}$. The goal is to fit a model $P(y|\mathbf{x}_i) \propto e^{\psi(y,\mathbf{x})}$. The standard method of supervised learning is based on gradient descent directly on the parameters where the learning algorithm starts with initial parameters $_0$ and computes the gradient of the likelihood function. A more general approach is to train the potential functions

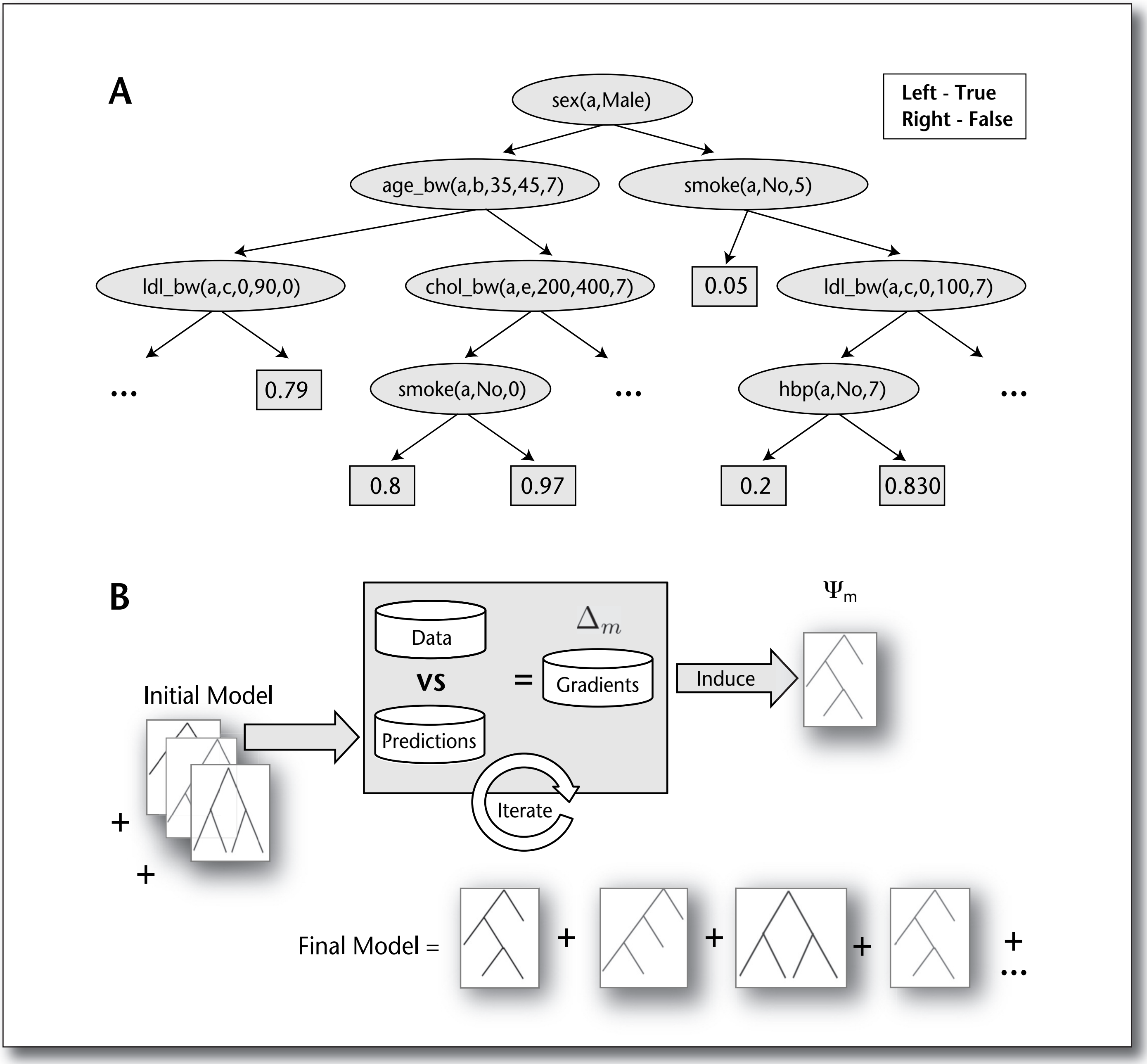


Figure 5. An Example of a Relational Proability Tree.

The leaves indicate *P* (target) > 0. The left branch at any test corresponds to the test returning true while the right branch corresponds to false. This tree was learned in a related project (Natarajan et al. 2012) where the goal was to predict the CAC levels from longitudinal data. A relational functional gradient boosting schematic is shown (right). Like standard FGB, RFGB induces trees in stagewise manner. In RFGB the trees are relational regression trees.

based on Friedman's gradient tree boosting algorithm where the potential functions are represented by sums of regression trees that are grown stagewise (Friedman 2001). The key difference from the standard method is that the gradients are computed directly on the functions instead of the parameters. Thus while the final potential is itself the linear sum of the gradients, each gradient could be nonlinear, leading to a more expressive model.

More formally, functional gradient ascent starts with an initial potential ψ_0 and iteratively adds gradients Δ_i. Thus, after m iterations, the potential is given by $\psi_m = \psi_0 + \Delta_1 + \ldots + \Delta_m$. Here, Δ_m is the functional gradient at episode m and is

$$\Delta_m = \eta_m \times E_{x,y}[\partial / \partial \psi_{m-1} log\, P(y \mid x; \psi_{m-1})] \qquad (1)$$

where η_m is the learning rate. Note that in the functional gradient, the expectation $E_{x,y}$ [..] cannot be computed as the joint distribution $P(\mathbf{x}, \mathbf{y})$ is unknown. Functional gradient boosting methods treat the data as a surrogate for the joint distribution. Instead of computing the functional gradients over the potential function, they are instead computed for each training example *i* given as ($\mathbf{x}_i$, y_i). Now this set of local gradients forms a set of training examples for the gradient at stage *m*.

Dietterich, Ashenfelter, and Bulatov (2004) suggested fitting a regression tree to these derived examples, that is, fit a regression tree h_m on the training examples $[(x_i, y_i), \Delta_m (y_i ; x_i)]$. They point out that although the fitted function h_m is not exactly the same as the desired Δ_m, it will point in the same direction, assuming that there are enough training examples. So ascent in the direction of h_m will approximate the true functional gradient. The same idea has later been used to learn several relational models and policies (Natarajan et al. 2011b, Sutton et al. 2000, Kersting and Driessens 2008, Natarajan et al. 2011a, Gutmann and Kersting 2006). The functional gradient with respect to $\psi(y_i = 1; \mathbf{x}_i)$ of the likelihood for each example $(\mathbf{x}_i, y_i)$ can be shown to be:

$$\frac{\partial \log P(y_i; \mathbf{x}_\mathbf{i})}{\partial \psi(y_i = 1; \mathbf{x}_\mathbf{i})} = I(y_i = 1; \mathbf{x}_\mathbf{i}) - P(y_i = 1; \mathbf{x}_\mathbf{i}),$$

where *I* is the indicator function, that is, 1 if $y_i = 1$ and 0 otherwise. This expression is fairly intuitive. Consider for example a subject who had an MI and hence is a positive example. If the current model predicts that he or she is likely to have MI with probability 0.6, his/her weight is 1 – 0.6 = 0.4 which means that the next model should push the example toward 1. On the other hand, if the subject is a negative example and the current model predicts his/her probability of having an MI as 0.3, then his/her weight is –0.3, indicating that the next model should push this example toward 0. We fit RRTs at each step instead of a regression tree as is traditionally done in FGB.

This idea is illustrated in figure 5 (right). As can be seen, first a tree is learned from the training examples and this tree is used to determine the weights of the examples for the next iteration (which in this case is the difference between the true probability of being true and the predicted probability). Once the examples are weighted, a new tree is induced from the examples. The trees are then considered together and the regression values are added when weighing the examples and the process is repeated. The key idea underlying the present work is to represent the distribution over MI as a set of RRTs on the features.

Experimental Methods

Figure 6 shows an outline of the experimental setup. We analyzed 31 years of deidentified EHR data on 18,386 subjects enrolled in the Personalized Medicine Research Project (PMRP) at Marshfield Clinic (McCarty et al. 2005; 2008). The PMRP cohort is one of the largest population-based biobanks in the United States and consists of individuals who are 18 years of age or older, who have consented to the study, and who have provided DNA, plasma, and serum samples along with access to their health information in the EHR. Most of the subjects in this cohort received most, if not all, of their medical care through the Marshfield Clinic integrated health-care system.

Within the PMRP cohort, 1153 cases were selected using the first International Classification of Diseases, Ninth Revision (ICD9) code of 410.0 through 410.1. Cases were excluded if the incident diagnosis indicated treatment for sequelae of MI or "MI with subsequent care." The age of the first case diagnosis was recorded and used to right-censor EHR data from both the case and the matching control one month prior to the case event. In other words, all facts linked to the case and the matched controls after the case age — one month prior to case diagnosis — were removed so that recent and future events could not be used in MI prediction.

To achieve a 1-1 ratio of cases to controls (that is, positive and negative examples), cases were matched with controls based on the last age recorded in the EHR. For many matches, this corresponds to a case who is alive being matched to a control of the same age. For others it means matching someone who died from a heart attack to someone who died from other causes or was lost to followup. Matching on last reported age was chosen to control for differences in health trajectories across age groups.

As CHD, of which MI is a primary component, is the leading cause of mortality in the United States, risk factors are well studied (Antonopoulos 2002, Greenland et al. 2010, Manson et al. 1992, Wilson et al. 1998), and those represented in the EHR were included in our experiments. We included major risk factors such as cholesterol levels (total, LDL, and HDL in particular), gender, smoking status, and systolic blood pressure, as well as less common risk factors such as history of alcoholism and procedures for echocardiograms and valve replacements. Drugs known to have cardiac effects were included, notably the coxibs and tricyclic antidepressants. As EHR literals are coded in hierarchies, we chose to use the most specific level of information, which often split established risk factors into multiple subcategories. The risk factors were chosen a priori as opposed to employing algorithmic feature selection (for example, the feature

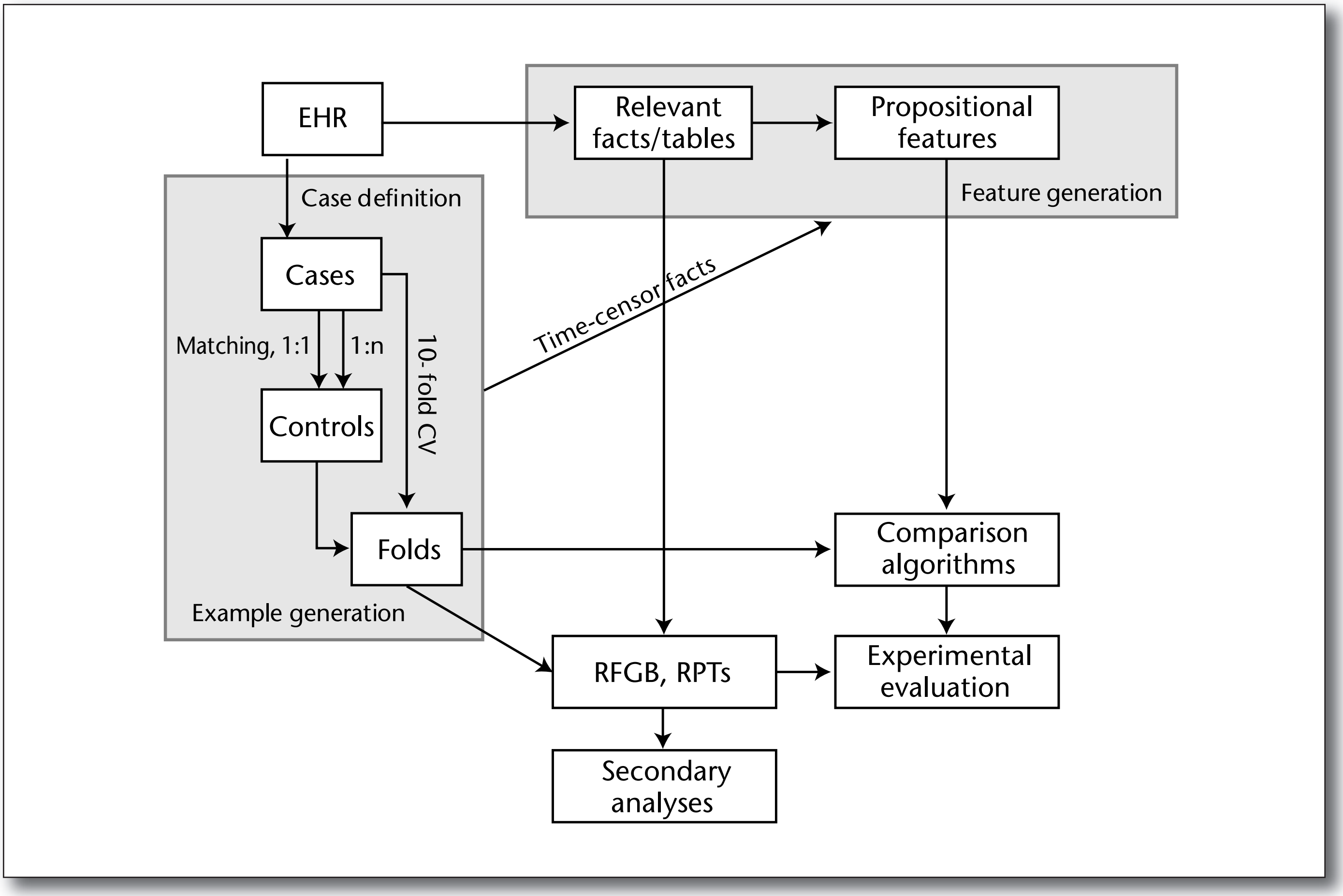


Figure 6. Flow Chart Depicting Experimental Setup.

selection inherent in decision trees) to shrink the feature size from hundreds of thousands (excluding genetic data) to thousands for computational reasons and so that algorithms without inherent feature selection would perform comparably. The feature values came from relational tables for diagnoses, medications, labs, procedures, vitals, and demographics.

Patient relations were extracted to temporally defined features in the form of "patient ever had $x \in X$" or "patient had $x \in X$ within the last year." For laboratory values and vitals, both of which require an additional literal for the result of the test, the result was binned into established value categories (for example, for blood pressure, we created five binary features by mapping the real value to {critically high, high, normal, low, and critically low}). This resulted in a total of 1528 binary features.

The cases and controls were split into tenfolds for cross-validation in a ninefold train set to one-fold test set. Although we did choose a one-to-one ratio of cases to controls, in general this would not be the case, so we chose to assess the performance of the algorithms with the area under the ROC curve (AUC-ROC), accuracy, and by visualizing the results with a precision-recall plot. Also, precision at high recalls {0.95, 0.99, 0.995} were calculated to assess a model's usefulness as a screening tool. The *p*-values were calculated comparing the RFGB model with the comparison methods using a two-sided paired *t*-test on the tenfold test sets, testing for significant differences in accuracy and precision at a recall of 0.99.

The key question is whether the relational algorithms consistently produced better predictions than their corresponding propositional variant. Thus we compared RFGB models to boosted decision trees (AdaBoostM1 (Ada); default parameters) and RPTs with decision tree learners (J48; $C = 0.25$, $M = 2$). We also included other common models: Naive Bayes (NB; default parameters), tree-augmented naive Bayes (TAN; SimpleEstimator), support vector machines (SVMs; linear kernel, C 1.0; radial basis function kernel, C 250007, G 0.01), and random forests (RF; 10 trees, default parameters). All propositional learners were run using Weka software (Hall et al. 2009). In our secondary analysis, we varied both the experimental setup and the RFGB parameters to investigate the effect on their predictive ability. First, we altered the case-control ratio {1:1, 1:2, 1:3}, holding the number of cases fixed. Second, we altered the maximum number of clauses (for internal node splits) allowed per tree {3, 10 (default), 20, 30}. Third, we altered the maximum depth of the tree {1 (stump), 5}. Finally, we altered the number of trees {3, 10 (default), 20, 30}. We also compared the results among these analyses if they contained the same maximum number of parameters (for example, 30 parameters: 3 trees × 10 clauses, 10 trees × 3 clauses).

Results

The best cross-validated predictor of primary MI according to AUC-ROC was the RFGB model as shown in table 1. RFGB outperformed the other tree learners, forest learners, and SVMs. The RPT model did not score as well, ranking in the middle of the propositional learners. It is of note that the RFGB and RPT models significantly outperformed their direct propositional analogs (Boosted Tree and Tree models, respectively). The Bayesian model (NB; TAN) scores may be somewhat inflated because only features known to be CHD risk factors were specifically chosen for this analysis. They may be more prone to irrelevant feature noise, as those models include all features into their final models.

The precision-recall curves for the algorithms are shown in figure 7 (SVMs are omitted as their outputs do not admit a ranking over examples). Medically, the most important area is the region of high recall (that is, sensitivity) because typically the cost of leaving a condition undiagnosed is high. In other words, the expected cost of a false positive is much smaller than a false negative because a false positive incurs the costs of additional interventions, while a false negative incurs costs of untreated human morbidity, and usually expensive, delayed treatments. Given that we cannot accept models with many false negatives (that is, low recall), we look to the high-recall region for the best performing algorithm, and RFGB gives the highest precision as shown in table 1.

In our secondary analysis, when changing the case-control ratio we observed an increase in the AUC-ROC as well as the expected increase in accuracy and decrease in precision shown in table 2. We suspect the improvement in AUC-ROC may be attributed to the larger population size, as for example CC 1:3 has twice as many examples as CC 1:1. RFGB performance improved with increases with forest size, with the greatest gains coming between using 3 and 10 trees, and no overfitting was observed using our largest 50-tree forest.[1] Varying the number of clauses or tree depth made no visible difference in RFGB performance, at least when holding the number of trees fixed at 10. Per parameter, we found that increasing forest size improved prediction more than increasing individual tree sizes, as we see by comparing equal-parameter rows in table 2.

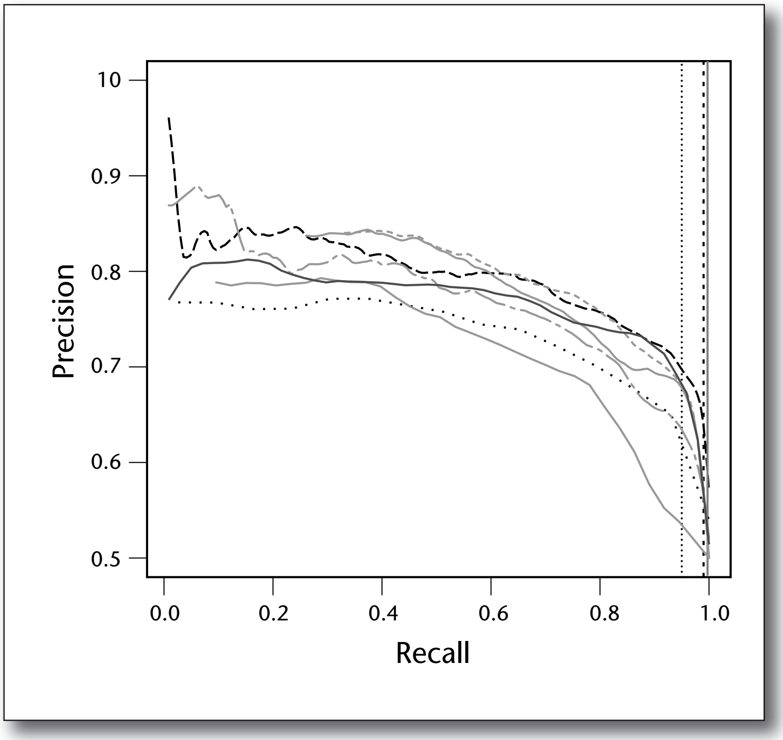


Figure 7. Precision-Recall Curves.

Vertical lines denote the recall thresholds {0.95, 0.99, 0.995}. RFGB (dashed) and RPT (dotted) are bolded. RFGB outperforms all other algorithms in the medically relevant region (high recall). At recall = 0.9, the ordering of algorithms (best to worst) is: RFGB, Random Forests, TAN, NB, RPT, Boosted Trees, J48.

Figure 8 shows an example tree produced in the RFGB forest. Direct interpretation of the tree can lead to useful insights. In the example above, the tree indicates that patients are more likely to have a future MI event if they have had a normal non-HDL cholesterol level reading in the last year compared to patients who have had normal cholesterol readings not in the last year. Now, since it is implausible that the measurement itself is causing MI, it could be considered a proxy for another "risk factor," which in this case could be physician concern, as frequent lipoprotein measurements may display a concern for atherosclerosis-related illness. The set of trees can also be converted into a list of weighted rules to make them more interpretable (Craven and Shavlik 1996).

The density plot in figure 9 shows the ability of RFGB and RPT models to separate the MI class from the controls. It is clear from the far left region of the RFGB graph that we can accurately identify

	AUC-ROC	Accuracy	p	P@R=0.95	P@R=0.99	P@R=0.995	p(P@R=0.99)
Tree J48	0.744	0.716	4e-5	0.500	0.500	0.500	6e-7
Boosted Trees	0.807	0.753	1e-4	0.634	0.572	0.532	4e-4
Random Forests	0.826	0.785	4e-1	0.669	0.593	0.525	2e-3
NB	0.840	0.788	8e-1	0.680	0.513	0.500	1e-4
TAN	0.830	0.768	6e-3	0.662	0.518	0.500	2e-4
SVM (linear)	0.704	0.704	5e-6	--	--	--	--
SVM (rbf)	0.761	0.761	1e-2	--	--	--	--
RFGB	0.845	0.791	--	0.688	0.655	0.625	--
RPT	0.792	0.738	4e-6	0.622	0.595	0.578	4e-5

Table 1. RFGB Gives the Highest Precision.

Area under the ROC curve, accuracy and corresponding p-value(RFGB versus all), precision at recalls (P@R), and p-value(RFGB versus all, P@R = 0.99). Bold indicates best performance.

	AUC-ROC	Accuracy	P@R=0.99
CC 1:1;1:2;1:3	.84; .87; .88	.79; .80; .82	.66; .51; .43
Trees 3;20;30	.80; .85; .85	.74; .80; .80	.61; .67; .66
Clauses 3;20;30	.85; .85; .85	.79; .79; .79	.66; .66; .66
Tree depth 1;5	.85; .85	.79; .79	.66; .66

Table 2. Secondary Analyses.

RFGB performance as case-control (CC) ratio, number of clauses, trees, and tree depth are modified. Default number of clauses = 10 and trees = 10.

a substantial fraction of controls with few cases by thresholding around 0.25, or more stringently at 0.05. This region captures an algorithm's utility as a screening tool, where we see that RFGB significantly outperforms the others.

Discussion and Conclusion

In our work, we presented the challenging and high-impact problem of primary MI from an EHR database using a subset of known risk factors. We adapted two SRL algorithms in this prediction problem and compared them with standard machine-learning techniques. We demonstrated that RFGB is as good as or better than propositional learners at the task of predicting primary MI from EHR data. Each relational learner does better than its corresponding propositional variant, and in the medically relevant, high-recall region of the precision-recall curve, RFGB outperforms all the other methods that were considered.

One additional layer of complexity not addressed in this experiment is the use of other relational information such as hierarchies. EHRs have hierarchies for diagnoses, drugs, and laboratory values, and it is important to be able to capture detail at each level. For example, characteristic disease progression pathways stem from infarctions of different heart walls, but at a high level, the presence of any MI leads to standard sequelae. Relational domains can easily incorporate this knowledge into hierarchical "is a" relations, whereas propositional learners must create new features for every level. The challenge for relational tree-based learners is that the search algorithm is greedy; identifying high-level relations requires traversing several "is a" relationships first, and thus they might not be found in a greedy search. Expanding internal nodes to longer clauses has been implemented with some success (Natarajan et al. 2011b, Anderson and Pfahringer 2009), although this does have the effect of rapidly increasing the number of features to consider during branching. The use of SRL algorithms could also allow the use of relations like patient physicians and providers, which form complex relations

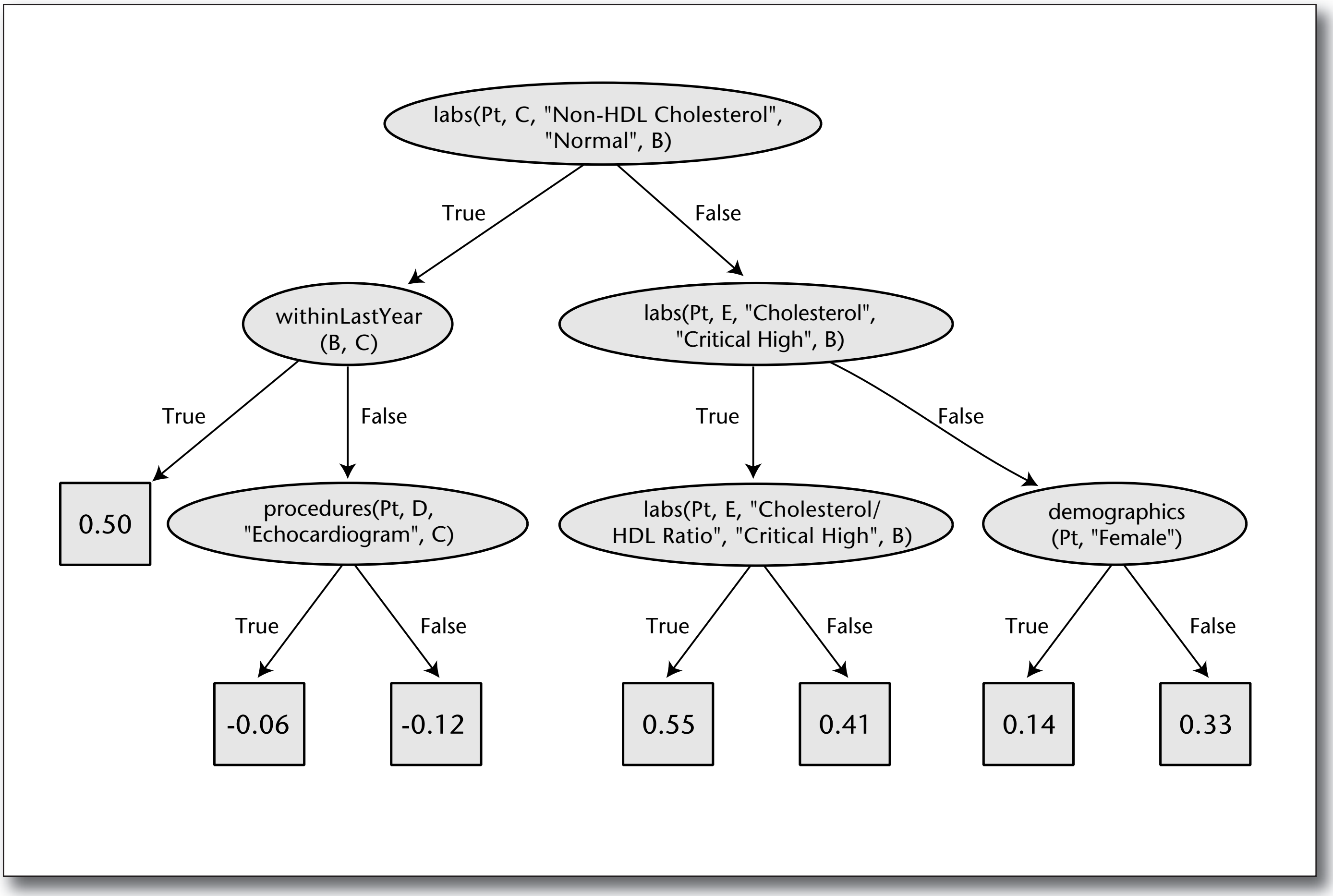

labs(Pt, C, "Non-HDL Cholesterol", "Normal", B)
True
False
withinLastYear (B, C)
labs(Pt, E, "Cholesterol", "Critical High", B)
True
False
True
False
0.50
procedures(Pt, D, "Echocardiogram", C)
labs(Pt, E, "Cholesterol/ HDL Ratio", "Critical High", B)
demographics (Pt, "Female")
True
False
True
False
True
False
-0.06
-0.12
0.55
0.41
0.14
0.33

Figure 8. The First Learned Tree in the RFGB Forest.

Given a patient A and his or her censor age B (that is, for cases, one month before the patient's first MI; for controls, the censor age of the corresponding case), if A had a normal non-HDL cholesterol measurement at time C, take the left branch, otherwise take the right branch. Assuming we take the left branch, if the measurement C was within one year of the censor age, take the left branch again. The leaf regression value is the best estimate of the residual of the probability of the covered examples given the model at that iteration. The whole RFGB forest is available at our website.[2]

less "patient-disease" oriented but ones that still may be central to patient care. Questions regarding disease heritability could also be addressed through relational family-based analyses.

The design of analyses using predictive models and EHR data also warrants some discussion. Naturally, some patients will not seek frequent care, so the information recorded in the EHR about them will be sparse. This could potentially include the lack of a reported MI when one actually occurred. If we had not chosen to conduct a case-control type of analysis, we would likely have increased the bias of our findings toward patients with rich clinical history being more likely to have a recorded MI, simply because they have more medical encounters documented in the EHR. However, by adopting this design, we may have decreased our performance due to class imbalance and subsampling the negative class. Also, this design required us to select a future time at which MIs occur in cases. We chose to predict MIs one month in advance, and other durations could have been chosen instead.

Given our initial success, we plan to extend our work by including more potential risk factors for learning (that is, include all the measurements on all the patients). This will be challenging as the number and frequencies of the measurements will differ greatly across patients. In our current model, we used time as the last argument of our predicates. While there is a vast body of work in learning and reasoning with temporal models in propositional domains, the situation is not the same for relational models. We plan to investigate a principled approach to learning and reasoning with relational dynamic models that will allow physicians to monitor the cardiovascular risk levels of patients over time and develop personalized treatment plans. Finally, we plan to build a complete

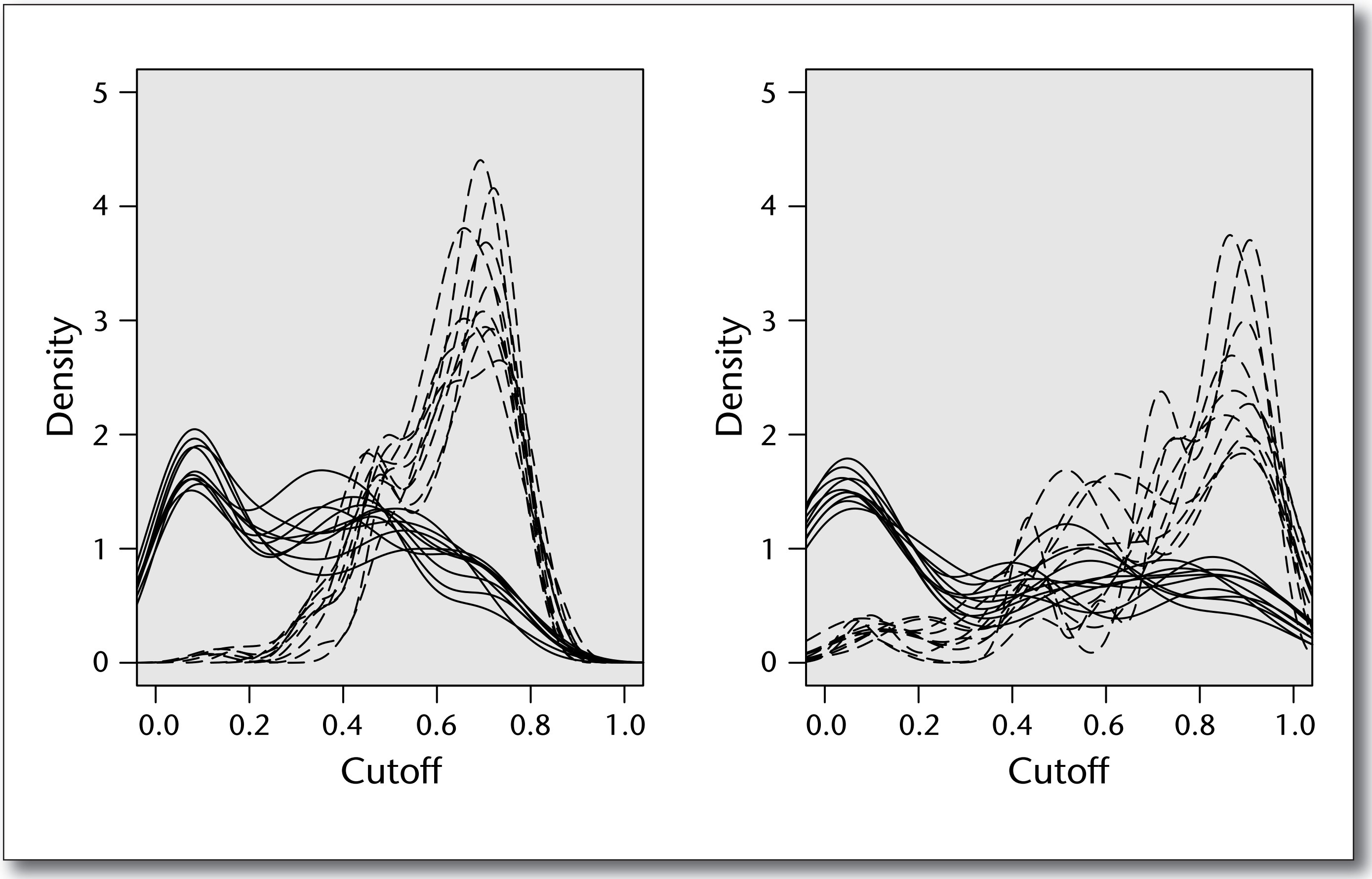


Figure 9. Density Plot.

Density of cases (dashed) and controls (solid) by {RFGB (left), RPT (right)} prediction, one line per fold. Taking the integral from 0 to cutoff *c*, for example, at *c* = 0.05 or *c* = 0.25 shows that the RFGB model identifies many controls at low risk of developing MI while maintaining a very low false negative rate.

machine-learning system for identifying risk factors across many diseases given the longitudinal data available in the EHR and plan to deploy it in a real clinical setting to identify its ability to improve patient outcomes.

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Notes

1. See our website: cs.wisc.edu/˜jcweiss/iaai2012.

2. cs.wisc.edu/˜jcweiss/iaai2012.

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