PPSNV:A novel predictor for pathogenicity of SNV based on ensemble learning

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1. Introduction

With the next-generation sequencing(NGS) technologies developing, situations become routinely common that doctors conduct genetic variant detection for patients in clinical diagnosis. Providing helpful insight into individual heredity and human diversity, genetic testing is vital for personalized medicine and targeted therapy. Among numerous output of genome sequencing, nonsynonymous single nucleotide variant(SNV) is a common type of genetic variants which probably cause disease, which means aligning SNVs with phenotypes and diseases accurately are necessary. However, identifying the pathogenicity of SNVs by experiment is costly and infeasible and calling for computational methods of pathogenicity prediction of SNVs is always urgent. Concurrently, actual consequence of genetic variants in vivo veils behind complicated biological mechanisms through many pathways. Hench, discriminating SNVs between benign and pathogenic variants with high confidence remains challenging.

Based on different roadmaps of genetic central dogma, many tools are developed to predict the pathogenicity of genetic variants. Some tools utilizes the conservation of amino acid or nucleotide to assess the damage when the reference allele is substituted, and several predictive tools focus on the alteration of molecular mechanisms, such as the structure or functional change of protein. Trained with different algorithms and individually collected data, different tools may provide different results for the same genetic variant. However, most tools are still handy references for the assessment of genetic variants. Extra information of SNVs that may represent deep predictive features in machine learning are refined during the prediction of developed tools in silicon, which probably facilitates related research.

As a strategy of machine learning, ensemble learning is proved to acquire advantages from its base learners. Through the combination of various existing predictors, better prediction results are obtained without additional primary features. Inspired by it and integrating several existing predictors, we propose PPSNV, a novel predictor for pathogenicity of SNV based on ensemble learning in this study. We implement PPSNV by Gradient Boosting Decision Tree(GBDT), a machine learning algorithm that perform well in classification and regression task. With fine parameter tuning, we achieve our predictive model and test it with two independent datasets and compare it with four ensemble predictors, PPSNV outperforms all compared predictors overall.

1. METHODS
   1. Gradient Boosting Decision Tree(GBDT)

Utilizing a boosting strategy, Gradient Boosting Decision Tree(GBDT) is a method which outstands among other machine learning methods in the tasks of classification and regression. Previous research works have used GBDT to perform prediction in biological problem and achieved best performance. Give its superior classification performance, we build our pathogenic predictors based on GBDT. Especially, we use LightGBM, an implementation of GBDT to optimize our model which is friendly to categorical features and dense numerical features of SNVs.

* 1. Datasets

We use the dataset provided by a previous work, containing 5 subsets and 88,332 variants which are collected from publicly available and commonly used benchmark datasets. After removing overlapping variants between five subsets, *HumVar, VariBenchSelected, predictSNPSelected* are merged into a new dataset which we use to train our model. The merged dataset, consisting of 66577 SNVs, is split into split into a training set and a validation set in an 7:3 ratio.

As for *ExoVar and SwissVarSelected,* we leave them as two independent test datasets based on which we compare our proposed predictors with others. Annovar is used to annotate all variants in our datasets, by which we obtained input features of our model and output of the comparators. Especially, we removed a variant in the test datasets if its output of the comparators is missing.

The details of our datasets are listed in Table 1.

Table . The Datasets used in this study

| Dataset | Benign(B) | Pathogenic(P) | Total |
| --- | --- | --- | --- |
| Training | 21,740 | 24,863 | 46,603 |
| Vaildation | 9,455 | 10,519 | 19,974 |
| ExoVar | 568 | 4,984 | 5,552 |
| SwissVarSelected | 5,004 | 4,356 | 9,360 |

* 1. Training

We used GridSearch provided by Scikit-learn to tune the parameters. The main parameters, such as learning rate, max depth of the decision trees and number of stacked estimators, were tuned. We trained our model by maximizing the area under the ROC curve(AUC) for binary pathogenicity classification. The initial outcome of a SNV is a probability score ranging between 0 and 1 which indicates the pathogenicity. We used the threshold of 0.5 to classify the SNV into a benign or pathogenic variant(pathogenic if the score > 0.5).

* 1. Features

We include 15 features in total to train PPSNV which can be divided into two parts. One part is four primary features of SNV(chromosome, location, reference amino acid, alternate amino acid) and the other part is ten pathogenicity predictions scores(SIFT, Polyphen2\_HDIV, Polyphen2\_HVAR, LRT, MutationTaster, MutationAssessor, FATHMM, RadialSVM, VEST3, CADD) from existing tools. Except for two primary features(chromosome, location), features are obtained by annotation using Annovar. Missing features are not imputed as decision trees are robustly designed to handle some missing values in input features. Besides, tolerating missing input is suitable for practical prediction because many SNVs are annotated by existing prediction tools but some tools do not return valid result.

* 1. Testing
  2. Comparators

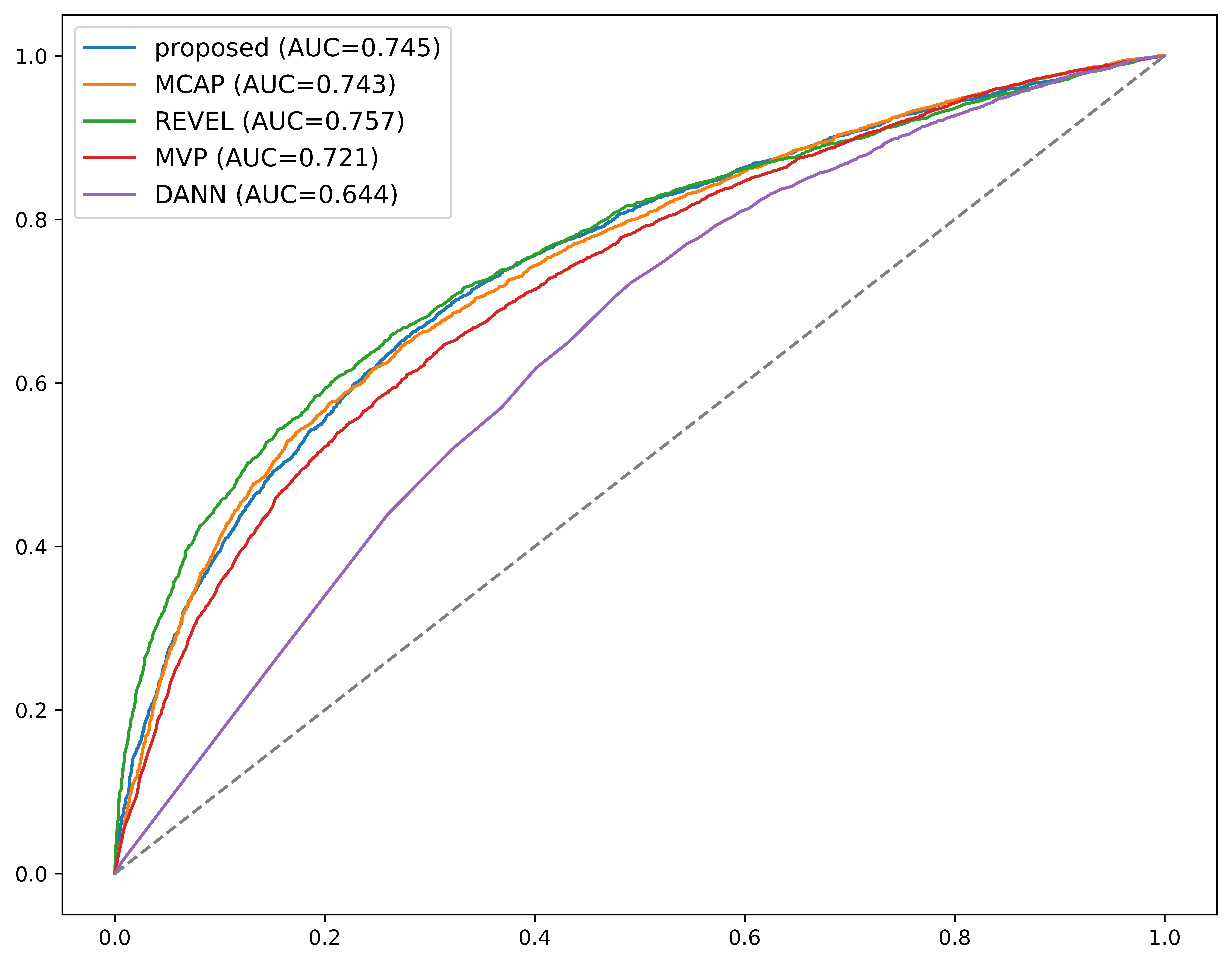
PPSNV are compared with four predictions tools that are commonly used and readily implemented：M-CAP, REVEL, MVP, DANN which are all ensemble prediction tools. The results of these tools are obtained by Annovar and the SNVSs in our test dataset with missing values are removed. Considering that several compared tools return pathogenic scores instead of binary classification results and the thresholds recommended to decide a SNV pathogenic or not may be not optimal in our research, we apply receiver operating characteristic(ROC) curves, the area under the ROC curve(AUC) and precision-recall (PR) curve to assess the overall performance of six predictors including the proposed accurately.

1. RESULT
   1. Characterization of Features

The PPSNV ensemble the pathogenic predictions of 10 individual tools as features besides 6 basic properties of SNV. The importance of a feature in PPSNP reflects how the feature contributes to the final prediction result. The top five important features in our model are VEST3, FATHMM, CADD, MutationAssessor, RadialSVM. Compared with the basic features, features from ensemble tools earn much higher importance which indicates the prediction scores of existing tools represents more intrinsic information.

* 1. Performance of PPSNV compared with other methods

The PPSNV performs well in the test with an AUC of 0.745, which surpasses M-CAP, MVP and DANN. However, its performance is slightly worse than the performance of REVEL. Considering that REVEL ensembles 18 individual pathogenicity prediction score, PPSNV is a lightweight model.



1. DISCUSSION

Aiming to predict the pathogenicity of genetic variants accurately, there are many methods which base on different biological mechanism.

1. Citing Related Work

This section cites a variety of journal [5, 15], conference [1, 6, 8, 12, 13], and magazine [3] articles to illustrate how they appear in the references section. It also cites books [9, 10], a technical report [7], a PhD dissertation [4], an online reference [14], a software artifact [11], and a dataset [2].

ACKNOWLEDGMENTS

Acknowledgments are placed before the references. Add information about grants, awards, or other types of funding that you have received to support your research. Author can capture the **grant sponsor information**, by selecting the grant sponsor text and apply style ‘GrantSponsor’. After this, select grant no and apply ‘GrantNumber’ from style panel. Example of Grant sponsor: Competitive Research Programme and example of Grant no: CRP 10-2012-03.

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