VARIANT RELEVANCE PREDICTION
IN EXTREMELY IMBALANCED TRAINING SETS

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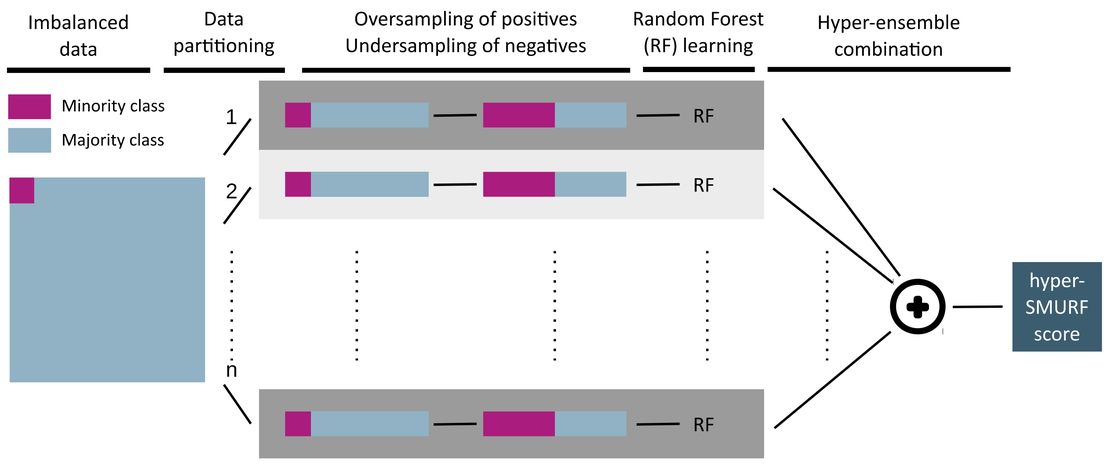
MOTIVATION

The imbalance between the small set of available disease-associated variants and the large set of benign genomic variants is intrinsic to genetic variant data, especially in non-coding regulatory regions of the human genome [1].

In this context machine learning (ML) for variant relevance prediction is like a chicken and egg problem – they cannot be easily found without ML, but ML cannot be applied effectively until a sufficient number of instances has been found. Unfortunately, most common ML-based methods [2,3,4] do not adopt specific imbalance-aware learning techniques to deal with imbalanced data, resulting in a poor performance with reduced sensitivity and precision [5].

HYPERSMURF



Outline of hyperSMURF

We designed the ML method *hyper SMOTE Undersampling with Random Forests (hyperSMURF)* for extremely imbalanced datasets. HyperSMURF adopts over- and undersampling techniques [6,7] to increase the count of the minority class and reduce the cardinality of the majority class. The resulting training sets are relatively small and balanced, thus avoiding a bias of learning algorithms towards the majority class and reducing runtime.

Data partitioning: The training set is partitioned into *n* partitions using all minority class instances (magenta) in every partition and an equal split of the majority class instances (blue).

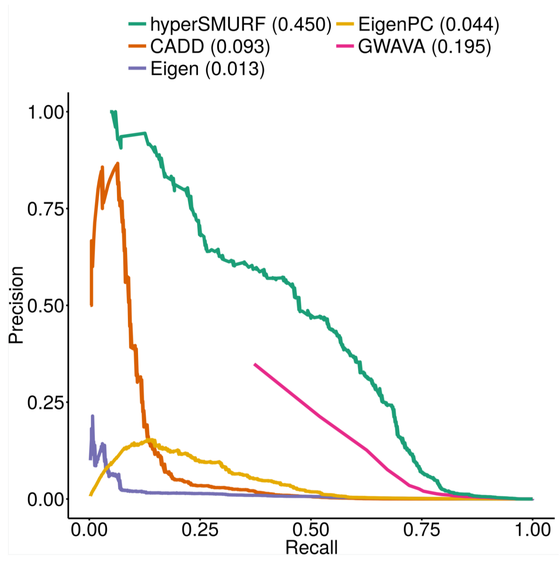
Over- and Undersampling: In every partition the minority instances are oversampled using the synthetic minority over-sampling technique (SMOTE) [6] and the majority instances are subsampled to an appropriate size. This results in balanced datasets per partition and a comprehensive coverage of the input data.

RF learning: For each partition a random forest (RF) is trained.

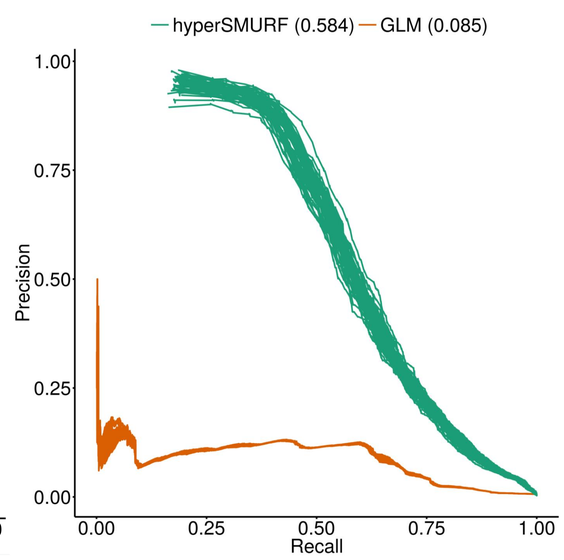
Hyper-ensemble combination: A new variant will be classified by an average vote of the resulting *n* RFs.

PERFORMANCE TESTING

	Regulatory Mendelian mutations [1]	miRNA-eQTL SNPs [8]
Positives	406	4785
Imbalance	1:36,000	1:400
Features	26 genomic attributes (e.g. conservation scores, and chromatin states)	18 genomic features (e.g. transcription factors, chromatin states, miRNA promoters)
Cross-validation (CV)	Cytoband-aware 10-fold CV [1]	50-times repeated sampling using random splits (75%/25%)
Comparison to retrained base-learners	SVM/CADD, Eigen, EigenPC and modified RF/GWAVA [2, 3, 4]	Logistic regression model (GLM) [8]



Regulatory Mendelian mutations



miRNA-eQTL SNPs

The hyperSMURF precision-recall curve (green) lies significantly above the other methods (Wilcoxon rank sum test, p-value < 10^{-9}) showing that our imbalance-aware procedure outperforms competing learning strategies on the same data set in prioritizing pathogenic variants at any given level of sensitivity.

CONCLUSION

These results strongly suggest that imbalance-aware learning strategies, like hyperSMURF, are essential for relevance prediction of disease associated non-coding variants in the human genome and we recommend their use to deal with imbalanced genomic data. HyperSMURF is implemented and freely available in R and Java. For more information see *https://hypersmurf.readthedocs.io* and *Schubach et al [9]*.

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