23rd ESH Meeting
Milan, May 14-17, 2013

Heterogeneous Machine Learning System For Diagnosing Primary Aldosteronism

N. Lazzarini[1], L. Nanni[1], C. Fantozzi[1], A. Pietracaprina[1], G. Pucci[1], T.M. Seccia[2], and G.P. Rossi[2]

[1]Dept. of Information Engineering, [2]Dept. of Medicine - DIMED,

University of Padova, Italy

Introduction

- Primary Aldosteronism (PA), the most common cause of secondary hypertension, is curable, which makes its early detection desirable.

- However, identification of PA remains challenging since PA can mimic essential hypertension from the clinical and biochemical standpoint.

- Hence, many PA cases go undiagnosed.

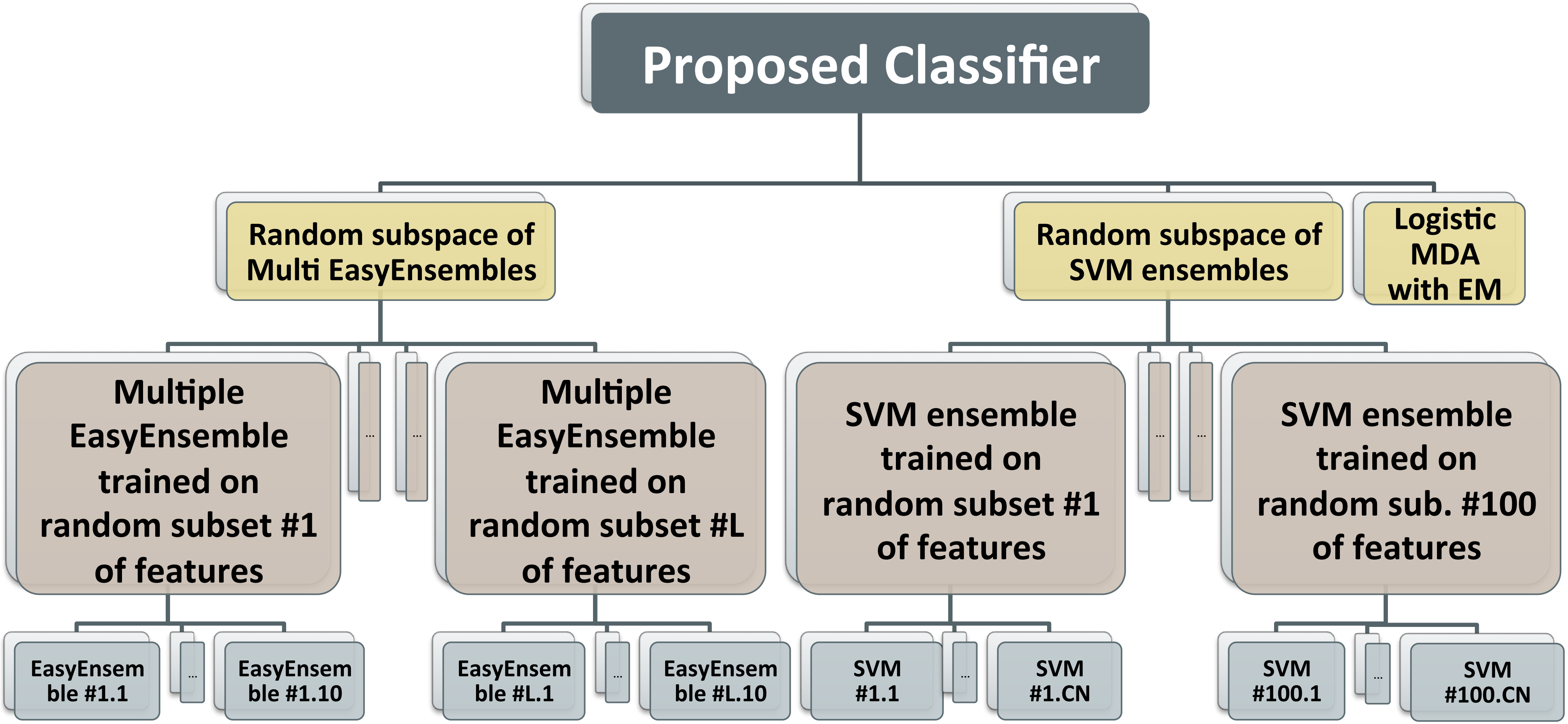
Objective

To develop a machine learning method for the identification of the aldosterone-producing adenoma (APA), the only PA subtype that can be conclusively diagnosed.

Secondary objective

To develop a classifier that handles real-world issues, such as correlation among variables, missing values, and class imbalance.

Design: Ensemble Classifier



The proposed classifier is an ensemble, i.e. the fusion of several base classifiers, some of them being in turn ensembles.

Base Classifiers

Decision Tree

Summarizes possible classification outcomes in a tree-like structure. The tree is built by a greedy algorithm.

Support Vector Machine (SVM)

Finds a linear hyperplane in the feature space that separates 2 classes with maximum distance. The hyperplane is found by solving a suitable minimization problem.

Logistic Multivariate Discriminant Analysis (MDA)

The classification outcome is given by a logistic function that depends on a linear combination of the features. The function is determined by solving a suitable minimization problem.

The Ensemble Classifier

1. An ensemble classifier is an advanced learning system that uses multiple models to yield higher predictive performance.

2. The final output of an ensemble classifier is obtained by fusing the decisions of the composing classifiers with a <u>combination rule</u>. We adopt the <u>*'sum rule'*</u>, *i.e.* an arithmetic mean of all classifiers decisions.

Design: Handling Issues in the Dataset

Correlation among variables:

handled via the use of random subspaces.

Several classifiers are trained on random subsets of features (the random subspaces). This approach reduces the probability of correlation in each training subset.

Class imbalance (i.e., fewer records in the positive class):

handled via a variant of the EasyEnsemble strategy.

Several classifiers are trained on subsets of records where the negative class has been undersampled to reduce its cardinality. This approach eliminates the class imbalance problem in each training subset.

Design: Handling Issues in the Dataset

Missing values:

handled via the expectation-maximization (EM) method.

EM computes maximum likelihood estimates of missing values given the observable values for all the features. The computation is performed with an iterative algorithm.

T.K. Ho, IEEE Trans. Patt. Anal. and Mach. Intell. (1998); 20(8): 832–844.

X.Y. Liu et al., Proc. 6th Intl. Conference on Data Mining (2006); 965-969.

T. Schneider, Journal of Climate (2001); 14: 853–871.

Learning Dataset: the PAPY Study

- The ensemble classifier was trained to identify the APA patients by exploiting the dataset from the PAPY Study (*Rossi G.P. et al, JACC 2006*).
- The dataset includes information on 1,124 consecutive patients referred to 15 specialized centers for hypertension.
- The diagnosis of APA was based on the *'four corner criteria'*:
  1. biochemical diagnosis of PA,
  2. lateralization of aldosterone secretion at bilaterally selective AVS or NP59 scintigraphy,
  3. evidence of adrenocortical nodule at histopathology,
  4. cure or improvement of hypertension, and correction of the biochemical picture of PA at follow-up after adrenalectomy.

Learning Dataset: the PAPY Study

Feature	Feature
Age [years]	SBP after Captopril challenge [mmHg]
Sex [M/F]	DBP after Captopril challenge [mmHg]
Weight [Kg]	MBP after Captopril [mmHg]
Body Mass Index [Kg/m^2]	Heart rate after Captopril challenge [bpm]
Serum K^+ levels [mEq/l]	Plasma Renin Activity (PRA) [ng/ml/h]
Serum Na^+ levels [mEq/l]	PRA after Captopril challenge [ng/ml/h]
Creatinine level [µMol/l]	Basal plasma aldosterone levels (PAC)[pg/ml]
Urine K^+ levels [mEq/24h]	PAC after Captopril [pg/ml]
Urine Na^+ levels [mEq/24h]	Cortisol [ng/ml]
Systolic blood pressure (SBP) [mmHg]	Cortisol after Captopril challenge [ng/ml]
Diastolic blood pressure (DBP) [mmHg]	PAC/PRA ratio (ARR)
BP medium [mmHg]	Therapy followed **(Y/N)**
Heart rate [bpm]	Basal PRA with values <0.2 [ng/ml/h]

Each patient was identified by 26 features.

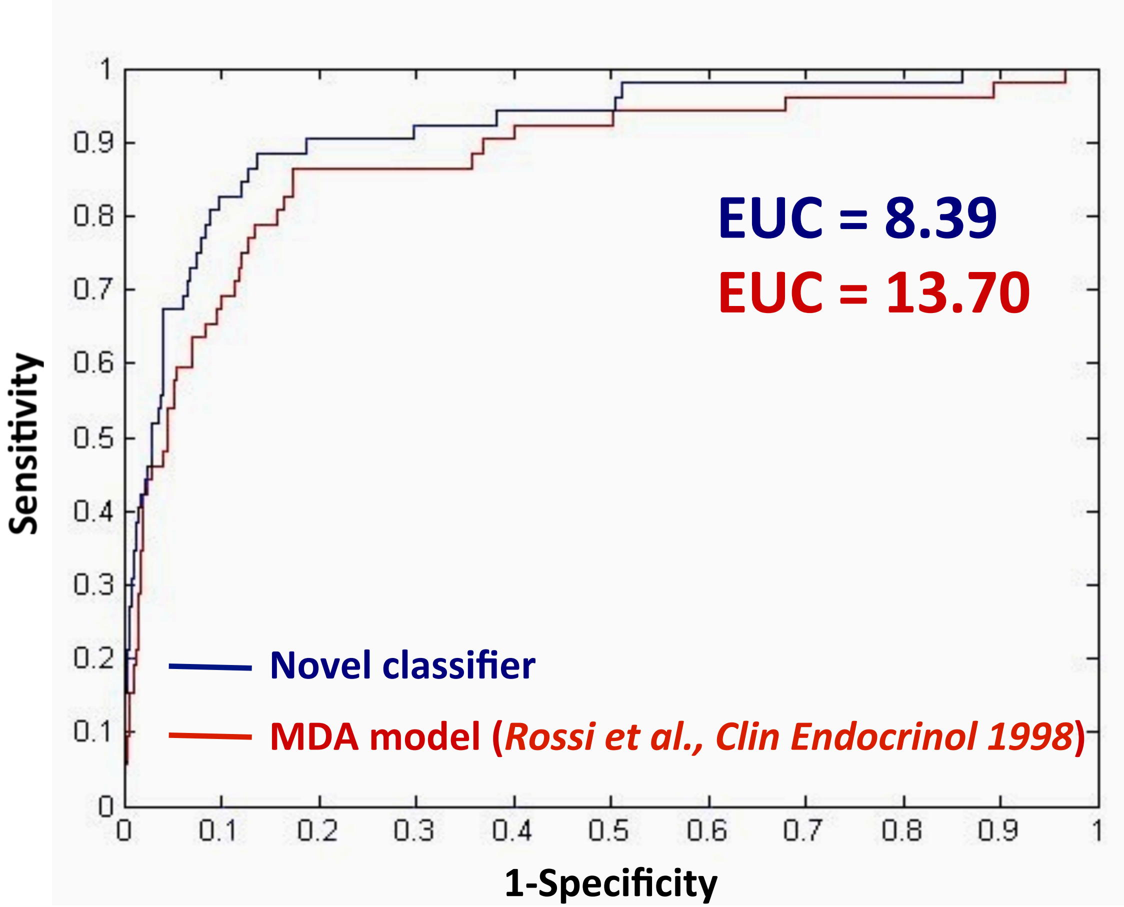
Ensemble Classifier: Performance

The performance was quantitatively evaluated on the PAPY dataset with the following approaches.

- **Validation strategy: "Leave-one-out-clinical" validation.** 15-fold cross-validation: at each step, 14 centers were used for training and 1 was exploited as the test set.
- **Performance metric: Error Under the ROC Curve (EUC).**
- **Test of statistical significance: Wilcoxon signed-rank test.**

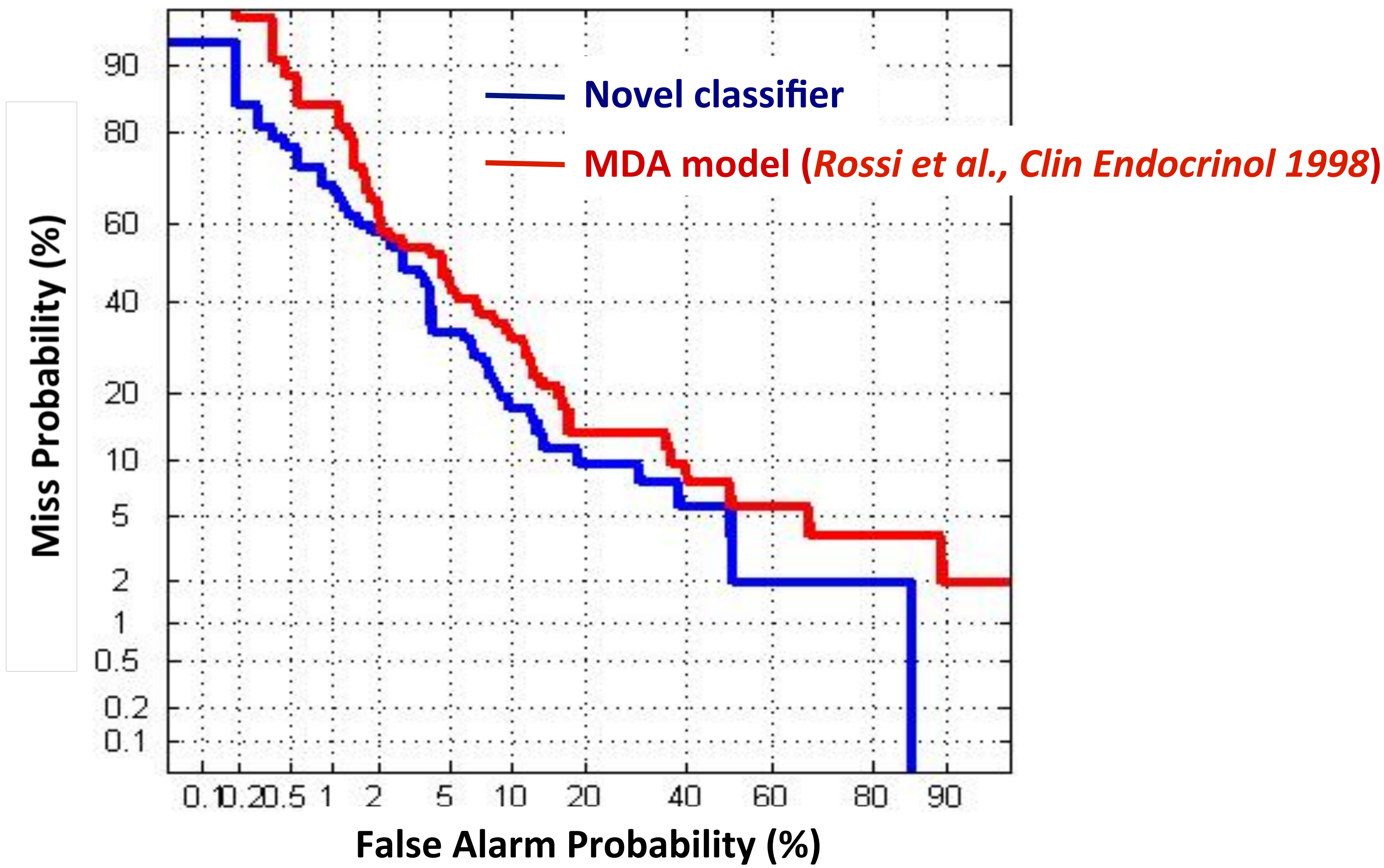
Ensemble Classifier: Performance

Our ensemble classifier considerably outperforms every single base classifier that composes it. Moreover, it outperforms the MDA model proposed in 1998 as a stand-alone classifier for APA.



Detection Error Tradeoff (DET) Curve

The classifier exhibits a False Alarm probability of ~50% (MDA model: ~90%) when a Miss probability as low as ~2% is tolerated.
This corresponds to only 1 PA patient in the PAPY dataset.



Summary of Results

1. The machine learning system created to discriminate APA patients from the other hypertensives and trained on the PAPY Study dataset considerably outperforms any constitutive base classifier.

2. The ensemble method features a statistically significant improvement in performance with respect to the previous classifier developed by our group (*Clin Endocrinol 1998*), as shown by the comparison of EUC.

3. The classifier is robust to common issues, such as collinearity, missing values, and class imbalance.

Conclusions

1. By using an integrated approach that exploits an ensemble classifier and a learning dataset that included patients with an unequivocal diagnosis of APA, we developed a machine learning system to discriminate APA patients from the other hypertensives.
2. The novel classifier provides optimal performance, and robustness to the most common problems that affect real-world data.
3. The machine learning system could be helpful in the diagnostic work-up of the hypertensive patients, thereby avoiding technically demanding and expensive tests in the patients not having high probability of APA.