# Ensemble classification of heterogeneous biomarkers in the diagnosis of Parkinsonism

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## Introduction

Parkinson's Disease (PD) is characterized by a marked reduction of dopaminergic neurons in the striatal region that affects the motor system.

**Known fact**: In last years, several approaches to develop an effective Computer-Aided-Diagnosis (CAD) system for PD have been proposed [1]. Most of these methods have focused almost exclusively on brain images through the use of Machine-Learning to characterize structural or functional patterns.

**Hypothesis**: As these patterns could not provide enough information about the status and/or the progression at early stages of PD, the finding of new biomarkers (not only imaging) has strengthened during the last years.

We have proposed an **ensemble classification model which combines multiple heterogeneous data sources** and weights those more discriminative for PD study.

## Materials & Methods

### 1. Dataset

Data used in the preparation of this work was obtained from use the **Parkison's Progression Markers Initiative (PPMI)** dataset available at www.ppmi-info.org. It includes 194 healthy control subjects (HC), 168 patients with PD and 26 subjects labelled as SWEDD (PD subjects whose scans had no evidence of dopaminergic deficit).

### 2. Image preprocessing

All DaTSCAN images have been spatially registered using the SPM (Statistical Parametric Mapping) tool SPM12. After being co-registered and averaged, each cerebral image was reoriented into a standard image grid. Obtained images had a dimension of 79x95x78 voxels and a voxel size of 2x2x2 mm. In a second phase, an intensity normalization procedure based on the use of α-Stable distributions as described in [2] was performed.

In order to reduce computational costs, we have selected only voxels in the *striatum* region.

### 3. Ensemble classification

Ensemble classification refers to the process of combining classifiers in order to provide a single and unified classification to an unseen instance [3].

Assuming a fusion approach for ensemble, the output of each classifier i is a k-long vector $p_{i,1},\ldots,p_{i,k}$, where the term $p_{i,j}$ represents the support that instance x belongs to class j according to the classifier i. As we are considering a weighting method with coefficients ($w_i$) proportional to the accuracy of each classifier ($\alpha_i$) as described in (2). Once the weights for each classifier are computed, classes with the highest score are selected by means of expression (3), where $y_k(x)$ represents the classification of the $k^{th}$ classifier and g(y,c) is an indicator function defined as (4).

$$w_i = \frac{\alpha_i}{\sum_{j=1}^{T} \alpha_j} \qquad (2)$$

$$\text{Class}(\mathbf{x}) = \underset{c_i \in dom(y)}{\arg\max} \left( \sum_k w_i g(y_k(\mathbf{x}), c_i) \right) \qquad (3)$$

$$g(y,c) = \begin{cases} 1 & y = c \\ 0 & y \neq c \end{cases} \qquad (4)$$

As several classifiers may present low accuracies, we have opted for a windowing technique consisting in maximizing the contribution of classifiers with high accuracy rates (5).

$$\mathbf{w}(w_i) = \begin{cases} f(\alpha_i) & \alpha_i \geq 0.5 \\ 0 & \alpha_i < 0.5 \end{cases} \qquad f(\alpha_i) = \alpha_i^2 + 0.5\,\alpha_i - 0.5 \qquad (5)$$

Our final ensemble classifier based on [4] is depicted in Figure 1. This flowchart consists in the use of two classification loops. A nested loop is used to get the accuracies of several linear SVM classifiers by means of the training set. Once those accuracies are obtained, they are used in the model of an ensemble classifier (main loop).

## Results

We have defined 7 experiments corresponding to different combinations of biomedical tests (CSF, RNA and Serum) apart from VAF and Morp features. Once data sources have been preprocessed, we have classified (diagnosed) subjects through the ensemble classification model proposed making use of linear SVM classifiers and leave-one-out validation strategies. Results are summarized as follows:

| Exp | VAF | Morp | CSF | RNA | Serum | Ensemble |
|---|---|---|---|---|---|---|
| **1** | 82.93% | 88.32% | 52.99% | - | - | 88.32% |
| **2** | 96.00% | 90.67% | 56.67% | 58.67% | - | 94.67% |
| **3** | 96.73% | 91.50% | 53.27% | - | 51.96% | 96.08% |
| **4** | 96.62% | 89.86% | 55.41% | 48.65% | 52.03% | 95.27% |
| **5** | 96.00% | 91.33% | - | 48.00% | - | 96.00% |
| **6** | 95.95% | 90.54% | - | 52.03% | 52.70% | 95.27% |
| **7** | 96.45% | 92.26% | - | - | 52.58% | 94.27% |

To highlight differences between experiments; a further comparison was performed by means of the Receiver Operating Characteristic (ROC) curves as shown in Figure 2.

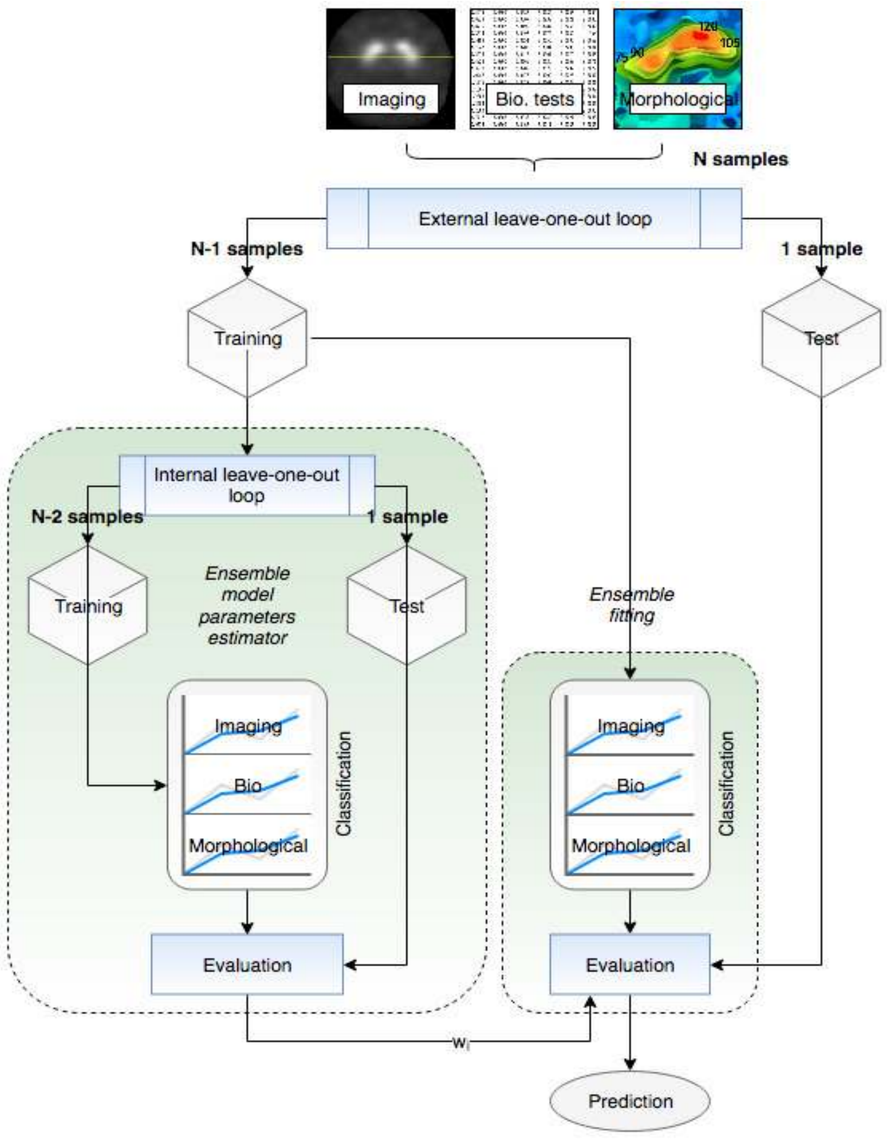


**Figure 1** - Ensemble classification flowchart for an experiment with N subjects.

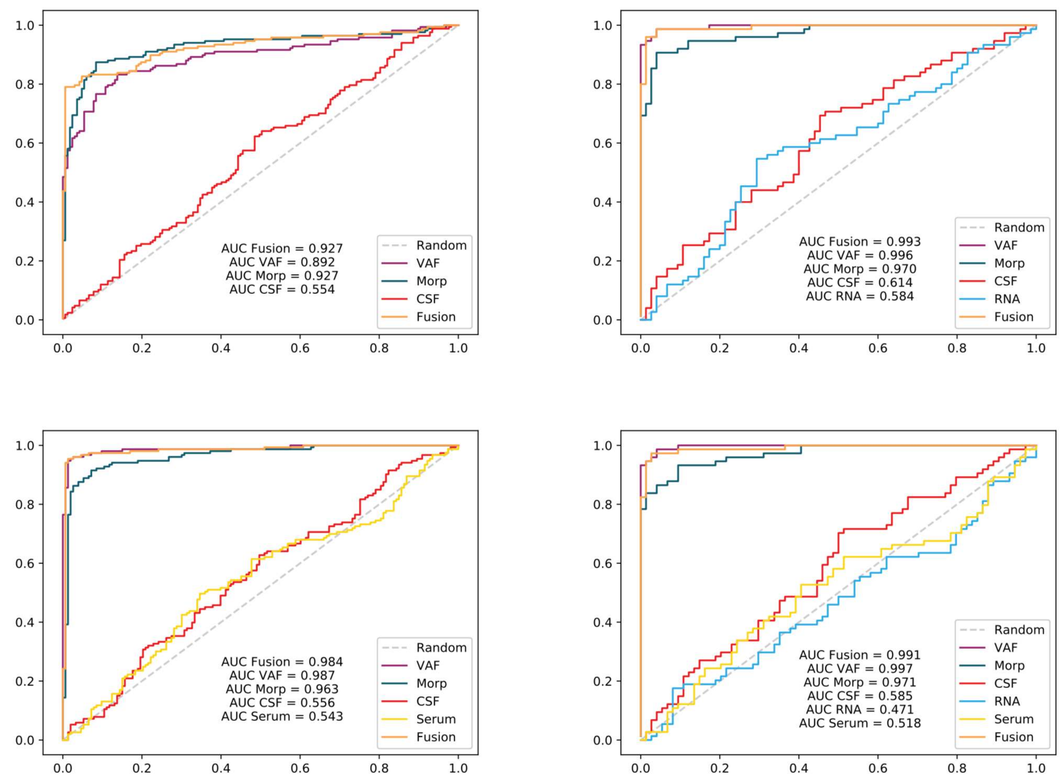


**Figure 2** - ROC curves and Area Under the Curve (AUC) parameters obtained (CSF experiments).

## Conclusions

**Known fact**: It is expected that combination of different data sources will give us the keys to determine the origins and predictive factors of PD.

**Strengths**: The work represents a multimodal and robust CAD system that selects the most reliable characteristics from input sources to reach the highest classification rates.

**Conclusions**: If we compare this ensemble proposal with its commonly used equivalent based on Majority Voting (MV), we obtain an averaged improvement of 7.43%. These results are expected to increase the interest in finding new biomarkers (imaging + biomedical tests) in the diagnosis of not only Parkinsonism but also different neurological disorders like Alzheimer's.

## References

[1] F. Segovia, et. al., "Multivariate Analysis of 18F-DMFP PET Data to Assist the Diagnosis of Parkinsonism", Frontiers in Neuroinformatics, vol. 11, pp. 23, 2017.

[2] D. Salas-Gonzalez, et. al., "Linear intensity normalization of FP-CIT SPECT brain images using the α-stable distribution", NeuroImage, vol. 65, no. C, pp. 449-455, 2013.

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[4] Z. Dai, et. al., "Discriminative analysis of early Alzheimer's disease using multi-modal imaging and multi-level characterization with multi-classifier (M3)", NeuroImage, vol. 59, no. 3, pp. 2187-2195, 2012.

Informed consents to clinical testing and neuroimaging prior to participation of the PPMI cohort were obtained, approved by the institutional review boards (IRB) of all participating institutions. More info, visit: www.ppmi-info.org/data.