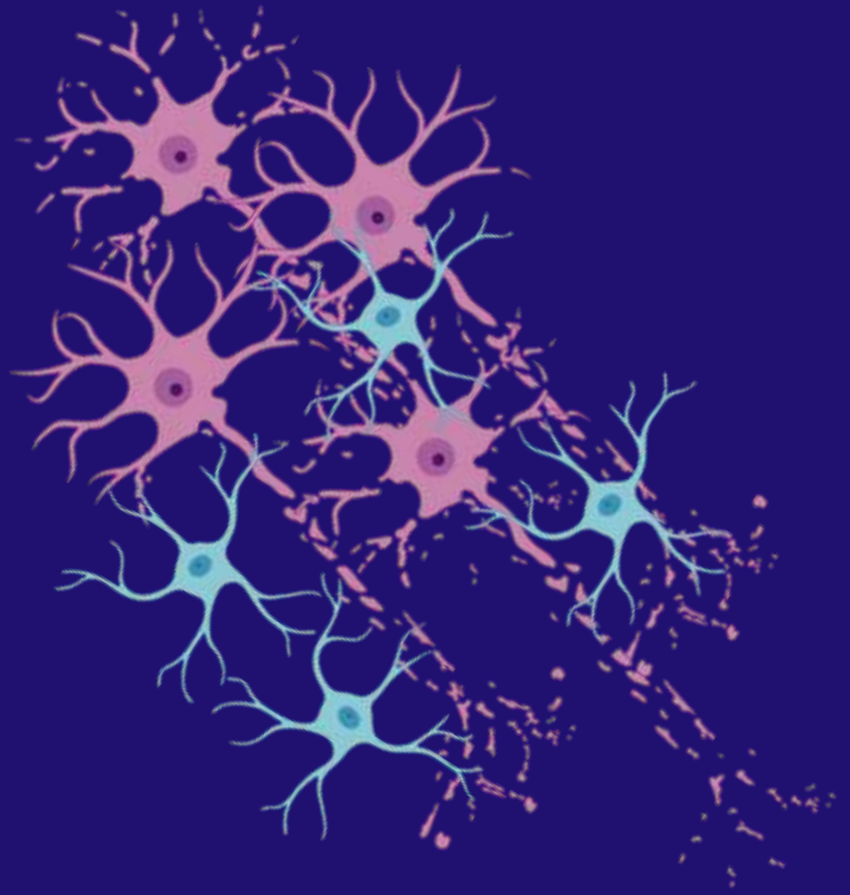
University of Pisa
Department of Information Engineering
Artificial Intelligence and Data Engineering



CogniPredictAD

Francesco Panattoni

Project for Data Mining and Machine Learning

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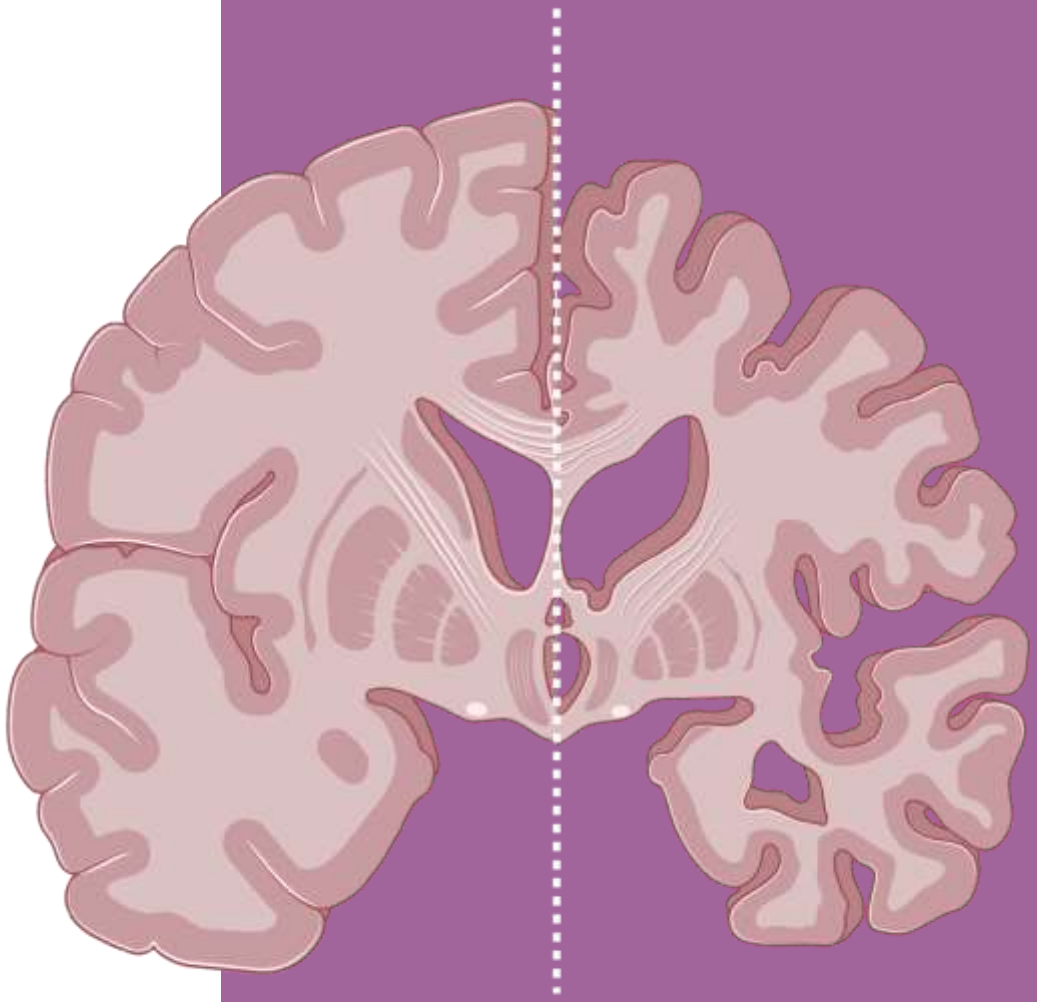
Motivations and Clinical Background

Alzheimer’s Disease

- **Alzheimer’s Disease** is a progressive neurodegenerative disease that affects memory, cognitive function, and daily living skills. It is the most common form of dementia and has no definitive cure.

- It primarily affects the **elderly** and its incidence is increasing as the population ages. It has a **significant social, family, and economic impact**, requiring **long-term care**.

- **Early diagnosis is difficult but crucial** for slowing the progression of the disease and improving quality of life.

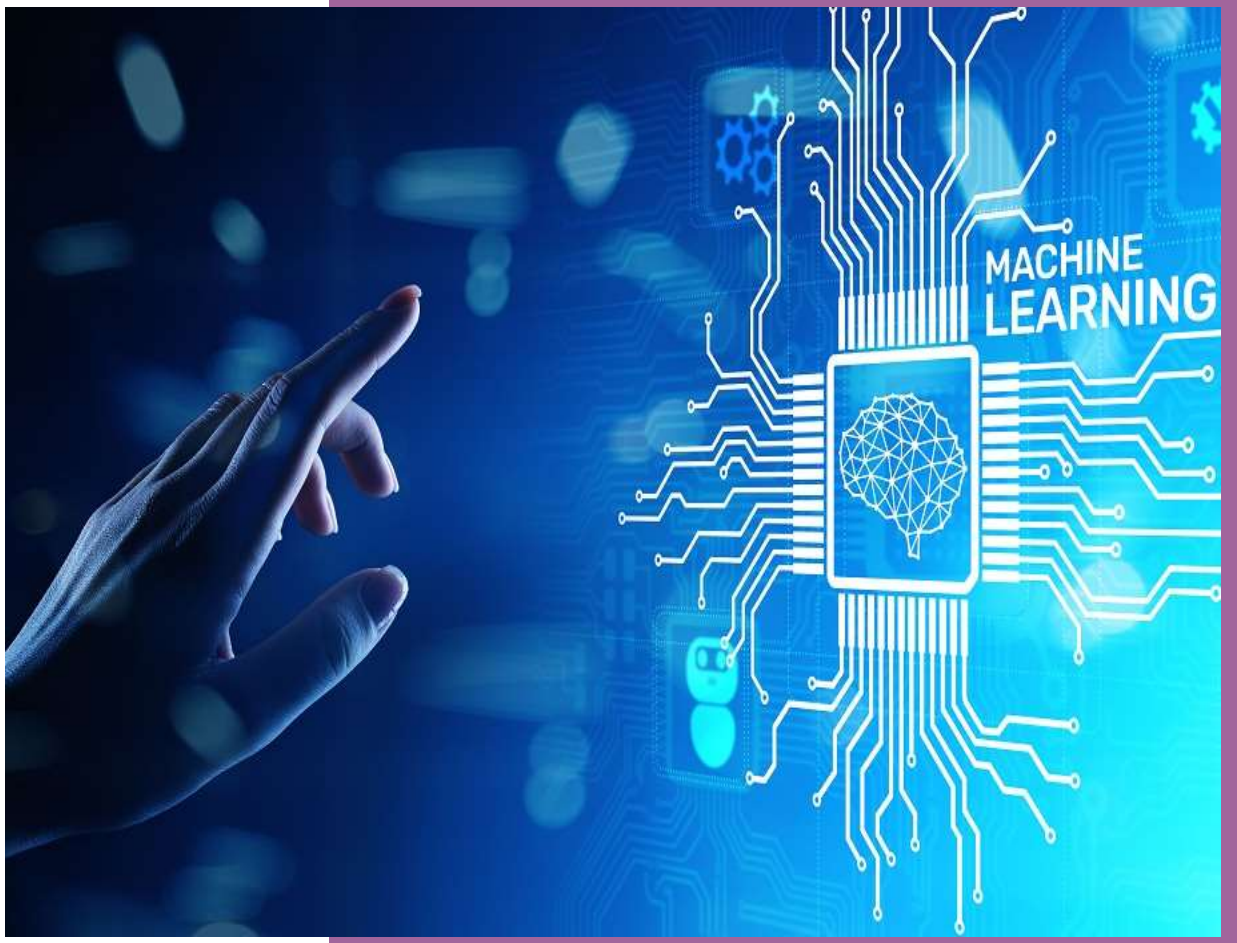


So why Machine Learning?

- **Machine Learning models** could support doctors in diagnosis by **analyzing large amounts of data**, **identifying hidden patterns**, and **improving accuracy and speed**.

- Alzheimer's disease is **multifactorial**. Machine Learning helps integrate **complex and nonlinear information**.

- They help **personalize clinical pathways** and **identify at-risk patients** before the most serious symptoms appear.



Dataset ADNI

ADNIMERGE.csv

- The **Alzheimer's Disease Neuroimaging Initiative (ADNI)** is a longitudinal, multicenter, observational study involving over 60 clinical sites in the United States and Canada.
- Launched in **2004** and divided into the following phases: **ADNI1** (2004–2009), **ADNIGO** (2009–2010), **ADNI2** (2011–2016), and **ADNI3** (2016–2022).
- **ADNI4**, the most recent phase of the study, was initiated in **2022.**
- **16,421 rows x 116 columns.** The columns are divided into current visit columns and baseline visit columns (with the "_bl" suffix) to aid quick comparison.
- Obtained from the **fusion of clinical data** collected during phases ADNI1, ADNIGO, ADNI2 and ADNI3. Unfortunately, the ADNI4 data has not yet been merged.
- The dataset contains **numerous visits** from different patients, with **associated diagnoses**.

Features of ADNIMERGE.csv

- **Diagnosis (target)**: DX, DX_bl
- **Administrative**: RID, COLPROT, ORIGPROT, PTID, SITE, VISCODE, update_stamp
- **Timestamps**: EXAMDATE
- **Demographics**: AGE, PTGENDER, PTEDUCAT, PTETHCAT, PTRACCAT, PTMARRY, APOE4
- **PET Imaging**: FDG, PIB, AV45, FBB
- **CSF Biomarkers**: ABETA, TAU, PTAU
- **Clinical Scores**: CDRSB, ADAS11, ADAS13, ADASQ4, MMSE, RAVLT_immediate, RAVLT_learning, RAVLT_forgetting, RAVLT_perc_forgetting, LDELTOTAL, DIGITSCOR, TRABSCOR, FAQ, MOCA
- **ECog (self-report)**: EcogPtMem, EcogPtLang, EcogPtVisspat, EcogPtPlan, EcogPtOrgan, EcogPtDivatt, EcogPtTotal
- **ECog (informant-report)**: EcogSPMem, EcogSPLang, EcogSPVisspat, EcogSPPlan, EcogSPOrgan, EcogSPDivatt, EcogSPTotal
- **MRI Imaging**: FLDSTRENG, FSVERSION, IMAGEUID, Ventricles, Hippocampus, WholeBrain, Entorhinal, Fusiform, MidTemp, ICV
- **Composite Scores**: mPACCdigit, mPACCtrailsB
- **Baseline Values**: all variables with the suffix _bl
- **Time Measures**: Years_bl, Month_bl, Month, M

Strengths and Weaknesses of ADNIMERGE.csv

Strengths

- It groups demographic, cognitive, imaging (MRI, PET) and CSF biomarker data into a **single large dataset**, **useful for integrated analyses**.
- **Rigorous post-data acquisition** correction procedures, which reduce technical variability and increase the statistical reliability of the features;
- One of the most **widely used datasets** in Alzheimer's disease research, with well-documented protocols and support for harmonization and comparative studies.

Weaknesses

- Many variables have **numerous missing values**, and the missingness varies depending on the diagnosis or phase of the visit, so it is **not Missing Completely at Random**.
- Participants are predominantly **white**, **highly educated**, **motivated**, and **married**, **reducing their representativeness** of the general population.
- Many features are **highly correlated or duplicated**, increasing computational complexity and the risk of **overfitting** in ML models.

Data Preparation

The **Data Preparation** involves building the **learning set** from the original ADNIMERGE table file. This phase concentrates on converting the visit-centric csv file into a single-row-per-subject, analysis-ready baseline cohort and on producing compact, multimodal feature tables for modelling.

Data Preparation

1

Selection of baseline visits only

Only baseline visits were considered (VISCODE == 'bl'), so as to predict the diagnosis based on the information from the first visit.

2

SMC diagnosis management

SMC (Subjective Memory Concern) subjects were realigned with DX and finally reclassified as CN, ensuring consistency with objectively defined diagnostic categories.

3

Consolidating baseline columns

Clean up duplicates and merge ”baseline” values into visit columns.

4

Text Category Cleaning

Features representing ethnicity and social status have been standardized for better readability and to avoid inconsistencies.

5

Encoding of categorical variables

One-hot encoding (PTMARRY), binary mapping (PTGENDER: Male=1, Female=0) and ordinal encoding for DX (CN=0, EMCI=1, LMCI=2, AD=3).

6

Preliminary Feature Reduction

Removal of columns not relevant to the diagnosis.

7

Error Correction

Clinically implausible values are detected using IQR Method and either clamped, nullified, or set aside for model-aware imputation rather than being arbitrarily corrected.

8

Holdout Method

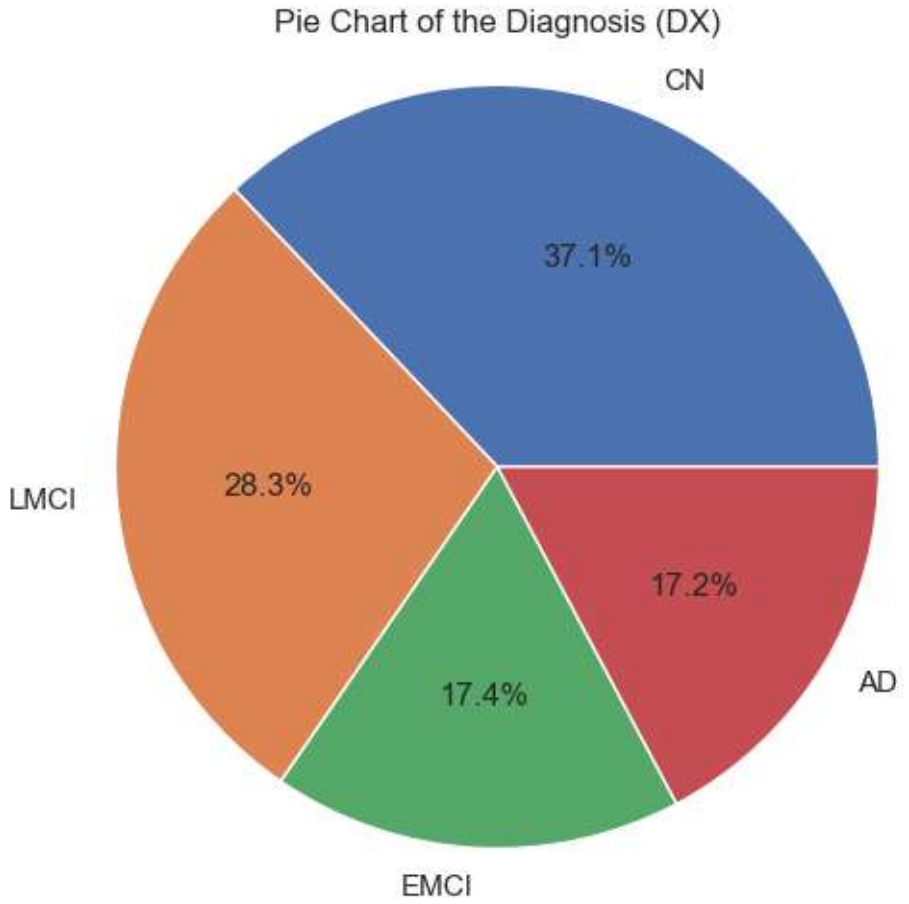
Separation of the learning set into training and test datasets while avoiding leakage.

Multiclass Problem: DX and DX_bl

- DX_bl has 5 possible values:
  - CN: Cognitively Normal
  - SMC: Subjective Memory Concern
  - EMCI: Early Mild Cognitive Impairment
  - LMCI: Late Mild Cognitive Impairment
  - AD: Alzheimer's Disease

- DX has 3 possible values:
  - CN: Cognitively Normal
  - MCI: Mild Cognitive Impairment
  - Dementia: Alzheimer's Disease

- **We create a new DX as our target with this 4 classes:**
  - CN: Cognitively Normal
  - EMCI: Early Mild Cognitive Impairment
  - LMCI: Late Mild Cognitive Impairment
  - AD: Alzheimer's Disease



Preprocessing

Data Preprocessing

This *phase* involves *transforming* the *dataset* to make it *suitable* for *Machine Learning*. These operations would risk *data leakage* if evaluated on the entire dataset. Therefore, they are performed on the *train set*, and the *test set* is modified accordingly to make it consistent, before evaluating the models built on the train. It is divided into *Data Cleaning*, *Data Transformation, Data Reduction and eventually Hybrid Sampling*.

Data Cleaning

- **Handling missing values:** Identifying percentages of missing values and using KNN Imputer for continuous variables.
- **Numeric Value Conversion:** Converted nearly all cognitive scales and age from float to int, correcting approximations to imputation or format errors.

Data Transformation

- **Creation of new CSF metrics:** TAU/ABETA and PTAU/ABETA ratios more predictive than single measures according to the literature.
- **MRI normalization to ICV:** Necessary to correct for differences due to gender and cranial size.

Data Reduction

- **Removal of redundant features:** *ADAS11*, *ADASQ4*, *EcogPtTotal*, *EcogSPTotal*, *mPACCtrailsB*, and *TAU* were removed because they had a high correlation with other features and their informative value was low.

- **Outcome of reduction:** The resulting dataset is a compact multiclass baseline table containing only the most informative demographic, cognitive, CSF and MRI/ICV features, reducing noise and redundancy and forming a robust foundation for the modelling phase.

Hybrid Sampling

To overcome class imbalance, we used a combination of:

- **Random Under-Sampling** (RUS) to reduce the number of instances in the majority classes (CN and LMCI), preventing the dataset from becoming excessively biased toward synthetic examples;

- **Synthetic Minority Over-Sampling Technique for Nominal and Continuous features** (SMOTENC) to generate new synthetic examples of the minority classes (EMCI and AD).

We use another pipeline to evaluate performance on the dataset with and without sampling.

Classification & Results

Model Selection

We selected the following classification models:

- **Decision Tree**
- **Random Forest**
- **Extra Trees**
- **AdaBoost**
- **Multinomial Logistic Regression**

Model Construction

1

Hyperparameter Tuning

To optimize the performance of the classifiers, a Grid Search procedure with 5-fold-cross validation was adopted.

2

Model Building

We built the models on the *training set* and evaluate with *5-fold-cross validation* and *Wilcoxon test*.

3

Explainability

We used *SHAP Summary Plots* on all models to identify which features were most important overall and by class. Built *trees* and *rules* for Decision Trees.

4

Models Final Evaluation

We evaluated the models on the *train dataset*, using *5-fold cross-validation*, and on the *test dataset*, as well as using the explainability results. *The evaluations primarily considered the statistics on the test dataset.*

Results

Model	F1 Score (macro)	Accuracy	Balanced Accuracy	Precision (weighted)	Recall (weighted)	F1 Score (weighted)	ROC AUC (macro)
Extra_Trees	0.9376	0.9442	0.9408	0.9448	0.9442	0.9443	0.9867
Extra_Trees_Sampled	0.9359	0.9421	0.9411	0.9435	0.9421	0.9425	0.9890
Random_Forest	0.9301	0.9380	0.9341	0.9387	0.9380	0.9381	0.9886
Adaptive_Boosting	0.9285	0.9360	0.9347	0.9378	0.9360	0.9363	0.9878
Random_Forest_Sampled	0.9271	0.9339	0.9358	0.9367	0.9339	0.9344	0.9863
Adaptive_Boosting_Sampled	0.9262	0.9339	0.9329	0.9361	0.9339	0.9343	0.9890
Decision_Tree_Sampled	0.9131	0.9236	0.9178	0.9244	0.9236	0.9235	0.9804
Decision_Tree	0.8934	0.9050	0.9026	0.9096	0.9050	0.9057	0.9824
Multinomial_Logistic_Regression	0.8700	0.8843	0.8816	0.8893	0.8843	0.8843	0.9825
Multinomial_Logistic_Regression_Sampled	0.8677	0.8822	0.8754	0.8851	0.8822	0.8826	0.9827

The problem with CDRSB, LDELTOTAL, and mPACCdigit

- The **CDRSB**, **LDELTOTAL**, and **mPACCdigit** cognitive scores show significantly higher predictive power than other variables.
- This **can improve model accuracy**, but creates the **risk of feature dominance**, where a few variables excessively influence predictions.
- This imbalance can cause **local overfitting**: excellent performance on ADNI but possible loss of accuracy on external or more heterogeneous populations.
- It is not possible to definitively determine whether these variables **are simply very strong predictors of Alzheimer's disease diagnosis**.
- We divided the pipeline into datasets **with** CDRSB, LDELTOTAL and mPACCdigit and **without** CDRSB, LDELTOTAL and mPACCdigit.

Without CDRSB, LDELTOTAL and mPACCdigit

Model	F1 Score (macro)	Accuracy	Balanced Accuracy	Precision (weighted)	Recall (weighted)	F1 Score (weighted)	ROC AUC (macro)
Adaptive_Boosting	0.7303	0.7459	0.7327	0.7456	0.7459	0.7437	0.9037
Adaptive_Boosting_Sampled	0.7112	0.7293	0.7157	0.7316	0.7293	0.7277	0.9001
Random_Forest	0.7061	0.7252	0.7052	0.7256	0.7252	0.7245	0.9022
Random_Forest_Sampled	0.7035	0.7190	0.7050	0.7251	0.7190	0.7208	0.9041
Extra_Trees_Sampled	0.7011	0.7211	0.7075	0.7258	0.7211	0.7202	0.9003
Extra_Trees	0.6998	0.7293	0.6952	0.7215	0.7293	0.7238	0.9105
Multinomial_Logistic_Regression _Sampled	0.6829	0.7066	0.6933	0.7135	0.7066	0.7063	0.8921
Multinomial_Logistic_Regression	0.6768	0.7004	0.6882	0.7055	0.7004	0.6996	0.8952
Decision_Tree	0.6603	0.6632	0.6622	0.6960	0.6632	0.6736	0.8467
Decision_Tree_Sampled	0.6482	0.6508	0.6543	0.6990	0.6508	0.6626	0.8445

Model Choosing

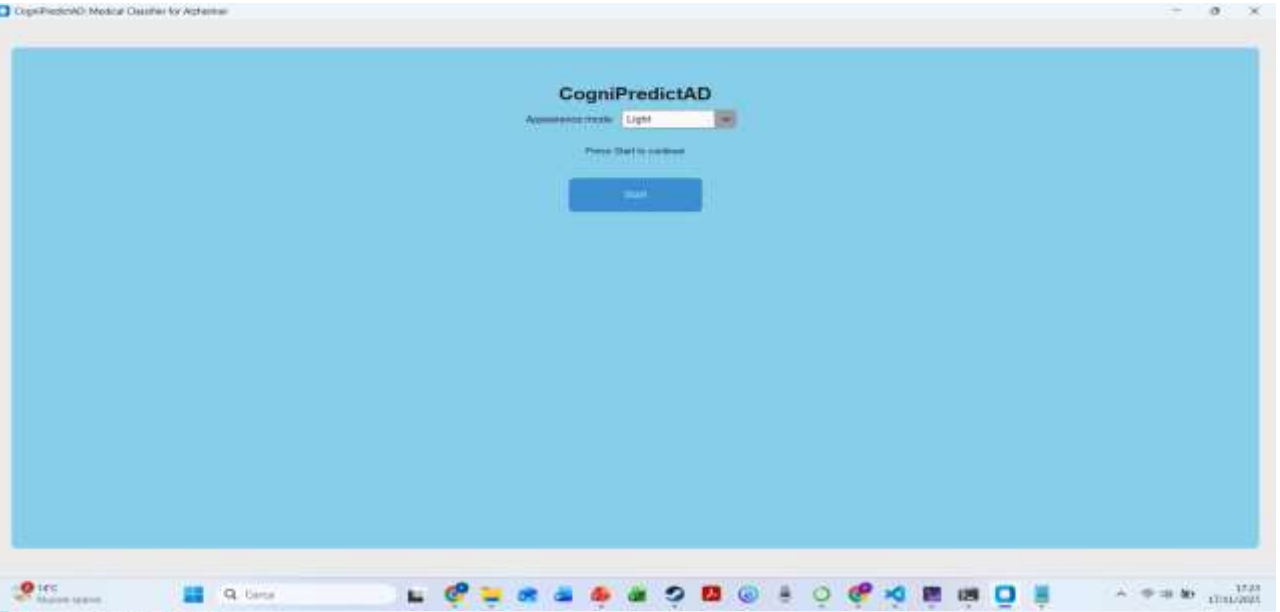
- **With CDRSB, LDELTOTAL, and mPACCdigit: (DS1, DS2)** Extra_Trees was chosen as the main model and Decision_Tree_Sampled as the XAI model, due to the best metrics (Balanced Accuracy, F1, ROC-AUC).

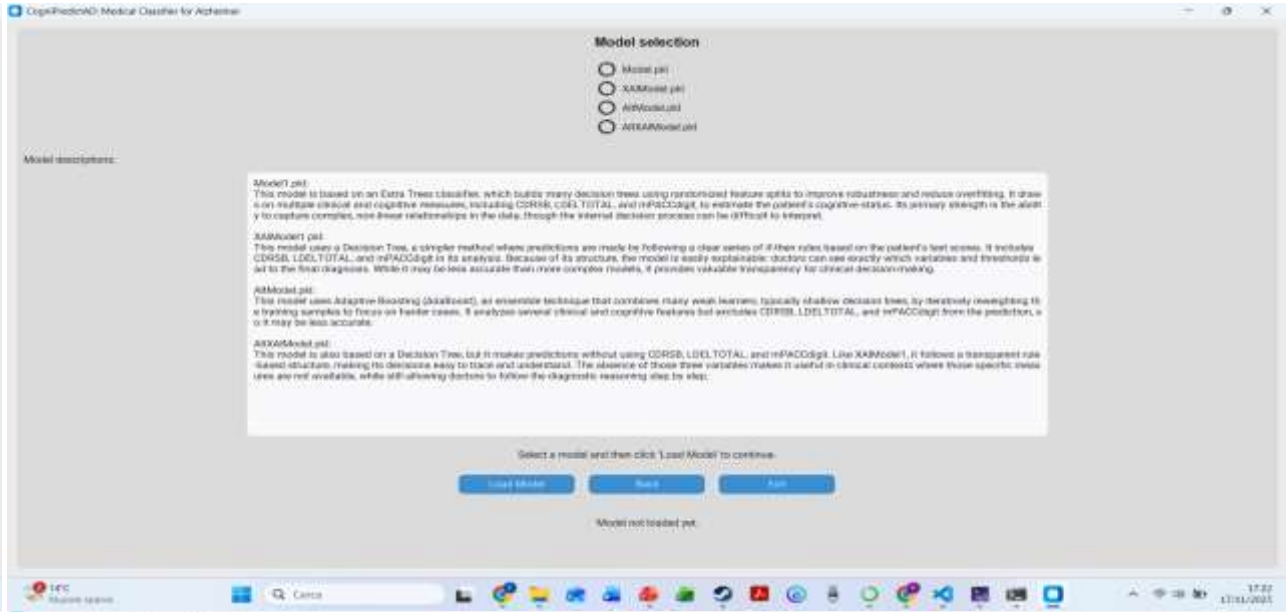
- **Without CDRSB, LDELTOTAL, and mPACCdigit: (DS3, DS4)** Adaptive_Boosting was chosen as the main model and Decision_Tree as the XAI, based on testing performance.

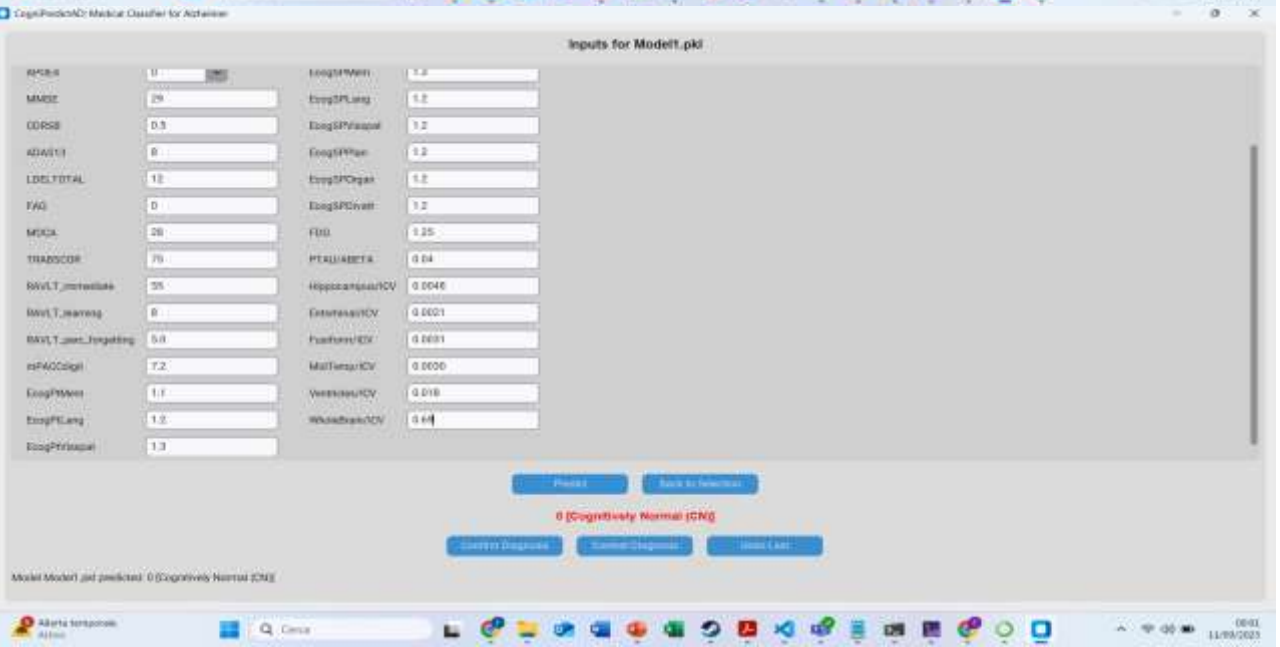
- The saved models are **Model.pkl** (Extra_Trees), **XAIModel.pkl** (Decision_Tree_Sampled), **AltModel.pkl** (alternative/Adaptive_Boosting), and **AltXAIModel.pkl** (alternative/Decision_Tree).

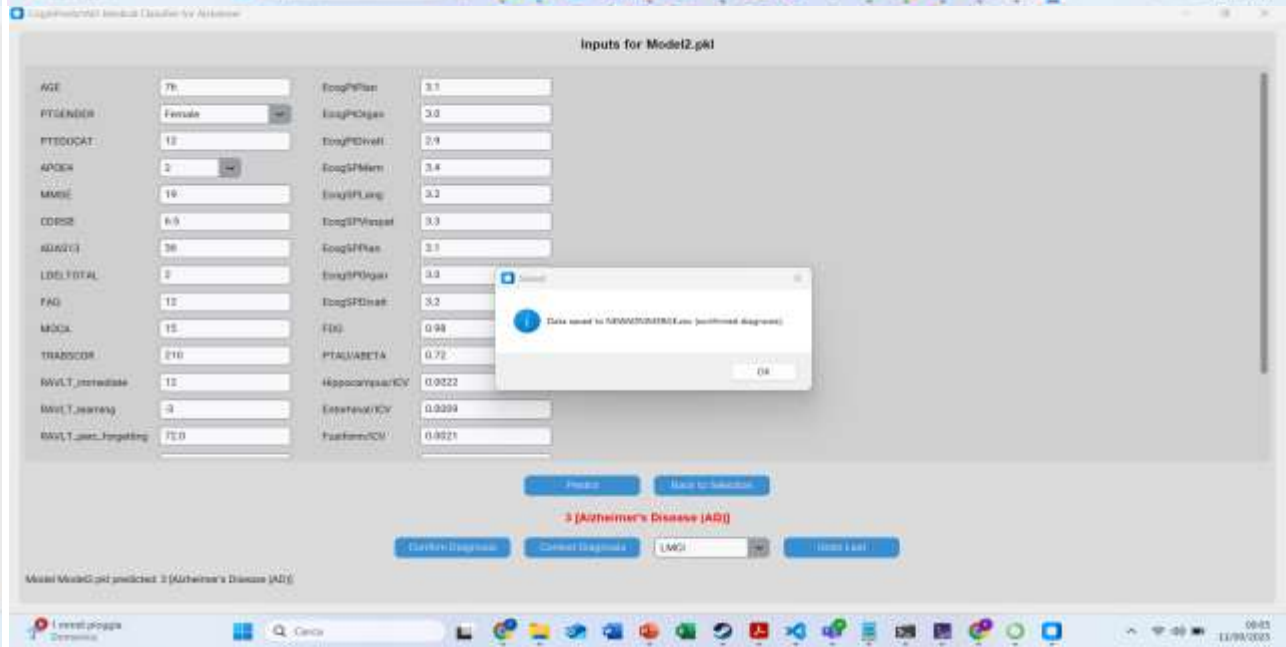
Applications & Conclusions

APP


CogniPredictAD
Start


Model selection
Model descriptions:
Select a model and then click 'Load Model' to continue.
Load Model
Back
Exit
Model not loaded yet.


Inputs for Model1.pkl
Predict
Back to Selection
0 (Cognitively Normal (CN))
Confirm Diagnosis
Correct Diagnosis
Undo Last


Inputs for Model2.pkl
Predict
Back to Selection
3 (Alzheimer's Disease (AD))
Confirm Diagnosis
Correct Diagnosis
Undo Last

Conclusions

- **Dataset limitations:** only 2,429 patients, many missing values (CSF, PET), strong dependence on three cognitive scores. Risk of local overfitting, dataset bias, and imputations increasing noise. External validation required.
- **Model Performance:** The models perform well overall, especially *Model.pkl*. Furthermore, *XAIModel.pkl* and *AltXAIModel.pkl* are easily interpretable. If the three features prove unpredictable in external validation, *AltModel.pkl* and *AltXAIModel.pkl* can be used instead.
- **State of the Art:** Although it was not possible to make a precise state of the art due to the lack of similar studies, the statistics make it a solid project.
- **Application value:** Useful as a support (screening, risk stratification), but obviously does not replace clinical evaluation.
- **Future developments:** Expand cohorts (ADNI4, external), integrate with similar datasets, and include geographic area as a feature.

Thanks for your attention!

Brain
(sagittal cut)

Brain
(coronal cut)

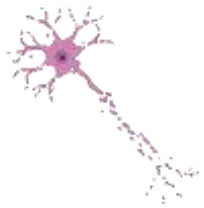
Brain
(lateral)

Brain with
Alzheimer's

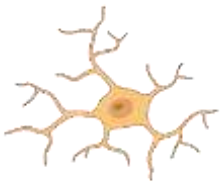
Brain with regions
(coronal cut)

Amyloid-beta plaque

Myelinated
motor neuron



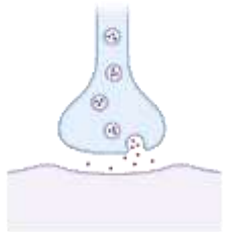
Degenerating
motor neuron



Microglia

Astrocyte

Dynamic line
neurons



Synaptic cleft