HULAT@IDDP CLEF 2023: Intelligent Prediction of Disease Progression in Multiple Sclerosis Patients

Notebook for the iDPP Lab on Intelligent Disease Progression Prediction at CLEF 2023

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory disease that affects the central nervous system causing neurological damage. This paper describes the participation of HULAT at IDDP CLEF 2023, particularly Task 1 - Predicting Risk of Disease Worsening (Multiple Sclerosis) to compare the performance of different machine learning approaches (Random Survival Forest and Elastic Net Cox) to predict the progression of multiple sclerosis in patients. The patient dataset includes medical history and demographic data. In addition, the dataset integrates records of the EDSS value, which is the degree of disability of the patient, his possible inability to work and to document the follow-up of the evolution of multiple sclerosis, as well as records of the relapses that occurred in his medical study. The results of the models show the ability of the different methods to predict when an event of interest occurs, such as the individual's worsening or the cumulative probability of its occurrence in different time windows.

Keywords

Multiple Sclerosis, Neurological Disease, Disease Progression, Survival Analysis, Disease Progression Prediction, Evaluation Models, Random Survival Forest, Elastic Net Cox

1. Introduction

In medicine, survival analysis task focuses on forecasting relapse or deterioration in Multiple Sclerosis (MS), a chronic condition that affects millions of people worldwide. Certain neurological functions gradually deteriorate because of this condition. Patients with MS alternate long stays in the hospital with intense treatment at home, going unabatedly through the most acute stages of the illness. Hospitals and doctors want systems and tools that can support them throughout the entire therapeutic process, suggesting interventions or advising therapeutic choices for each

Recent advances in Artificial Intelligence (AI) have proven to be optimistic in predicting disease progression and identifying new features for MS. The use of large datasets and different models may be able to identify patterns and relationships that are difficult to detect by human

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experts. This paper describes an approach for the automated prediction of MS progression as part of the iDPP challenge in CLEF 2023.

The main goal is to provide an overview of the current state of AI-based prediction of progression in diseases such as MS and to highlight the potential of these approaches to improve patient outcomes and advance the understanding of this complex neurological disease. Research is being conducted on intelligent prediction of MS worsening. This approach predicts when disease relapse or worsening occurs in a probabilistic and time-dependent manner. However, these techniques continue to present problems and difficulties that are the motivation for conducting cutting-edge studies. The article is organized as follows: Section 2 presents related work; Section 3 describes the methodology employed; Section 4 explains our experimental setup; Section 5 summarizes the results from the evaluation; finally, in Section 6, the conclusions and future work are discussed.

2. Related Work

Patient survival analysis is a statistical technique used to model and analyse the time to the event of interest. Therefore, survival analysis becomes a handy tool to assess when a disease relapse occurs in the patient [1]. Furthermore, the ability to accurately predict disability progression may lead to an improved understanding of MS pathogenesis, facilitate faster treatment development, and inform both patient and physician treatment decisions [2].

Survival analysis aims to establish a relationship between covariates and the time of a given event. Survival analysis was originated in clinical research, where survival prediction is often the main objective. One of the main features of survival analysis is censored data. Censoring is defined as not knowing the exact time of occurrence of the event of interest [3].

The different existing survival analysis methods can be classified into statistical methods or methods based on Machine Learning (ML). Statistical methods focus more on the distributions of event times and the statistical properties related to parameter estimation using the survival technique. In contrast, machine learning-based methods focus on predicting the occurrence of events at specific times by combining the capabilities of traditional survival analysis methods with various ML techniques [4].

ML algorithms are data science approaches to building predictive models that are able to learn patterns and relationships within data while requiring minimal human intervention [2]. ML methods are commonly applied to high-dimensional problems, unlike statistical methods tend to be developed for handling low-dimensional data. In survival analysis, ML methods offer more efficient algorithms by combining statistical and ML techniques. They build on recent advances in ML and optimisation by learning the dependencies between survival times and covariates in various ways.

In this sense, advances in ML models over the last few years have been fundamental in survival analysis, thanks to the ability to model non-linear relationships and make predictions and have led to significant advances in the clinical area [5] [6]. The main challenge of ML methods in survival analysis is the treatment and management of censored data, along with prediction over time of the model. ML methods perform well when the data has a measured number of features. Some models that can be highlighted are Random Survival Forest, Boosting,

Support Vector Machine, and Artificial Neural Networks.

The second edition of IDPPCLEF (Intelligent Disease Progression Prediction CLEF) [7], a challenge that involves different research groups, aims to design and develop an infrastructure to drive the development of AI algorithms capable of describing the characteristics and mechanisms of MS. The goal is to classify patients according to phenotype in the disease period and predict worsening disease progression by measuring time-dependent probability.

Although in a still early stage, it is looking to develop shared perspectives, encourage standard benchmarks, and promote comparability and replicability of experiments. Unlike other IDPPCLEFs, it systematically addresses some issues related to the application of AI in clinical practice in MS and ALS [8]. Therefore, in addition to defining risk scores based on the likelihood of a short- or long-term event occurring, IDPPCLEF also addresses providing information more structured and understandable to clinicians. Once the tasks of this challenge have been completed, a workshop is organised in the form of a conference where the different participants discuss the aspects and questions of the tasks carried out to carry out their research.

In the first edition held, the work described in [9] stands out because he obtained promising results with Gradient-Boosted Survival in the survival analysis by classifying patients according to risk. The authors state that the performance of the proposal could be improved by integrating more training data. In contrast, the hybrid survival-classification/regression approach shows that it is not an appropriate model to use time windows to classify patients according to their risk of worsening.

Another similar work is presented in [10], where a study of MS progression using ML was performed. Different techniques were carried out, obtaining better results with SVM versus KNN-3 and Decision Tree. In this research, the most predictive characteristics are exposed, the Expanded Disability Status Scale (EDSS) variable, functions affected during relapses and age of onset were described as the most predictive characteristics in predicting the patient's risk of worsening.

Typically, four models are explored to the intelligent prediction of MS evolution:

- Random Survival Forest (RSF) [11] is a novel extension of the RF (Random Forest) model for survival environments where time-to-event results are obtained. The method could handle multiple covariates and noise variables and control complex nonlinear relationships between these variables without requiring prior specification. Random survival trees are created by binary partitioning the recursive covariate space to group subjects with similarities according to the survival outcome. The set of RSF predictors is created by integrating the results of multiple survival trees.
- Cox regression is one of the most widely used techniques in survival analysis [12].This regression model can be used to evaluate the relationship between one or more explanatory variables and the time to event occurrence. The ability to consider the observations that undergo censoring differentiates it from linear regression. In the Cox model, the incidence rate is called risk. This model is based on short periods and can contain a single event allowing a constant risk in each small interval and variations in larger gaps. Therefore, the Cox model is used to represent rates that fluctuate rapidly.
- CoxNet is a Cox proportional hazards model based on an elastic net [13] that integrates the Ridge penalty and the LASSO (Least Absolute Shrinkage and Selection Operator)

subset selection, thus achieving a balanced model. The differences between these two penalties are described in the following article [14]. The authors expose that the LASSO penalty selects a few coefficients different from the zero value exclusively. This is obtained by performing a variable selection but producing the presence of correlated predictors and inappropriate behaviour. On the contrary, the Ridge penalty decreases the value of the coefficients approaching zero proportionally without reaching the zero value at any time, thus obtaining superior management of the correlated predictors without including the dispensable variables.

- Survival SVM (Support Vector Machine) [15] is an extension of SVM for time-censored time to-event data. One of its main features is obtaining complex and nonlinear relationships between variables and survival using a kernel. The kernel function maps the input features into high-dimensional feature spaces in which a hyperplane describes the survival. Therefore, SVMs in survival analysis apply to a wide diversity of data. Survival analysis by SVM can be characterized by assigning samples with shorter survival periods to a reduced classification by looking at all pairs of sets in the training data. Conversely, it can be treated as a regression problem where the algorithm directly predicts the logarithm of the survival time.

Considering the works analysed within the state-of-art, this proposal consists of performing a survival analysis on a set of clinical data belonging to different patients to detect when a worsening of the disease may occur. The process includes processing the data sets, analysing and extracting the most relevant features, training the models, and evaluating the results

3. Methodology

This chapter outlines the methodology used in this IDPPCLEF challenge regarding the intelligent prediction of MS progression. It refers to two tasks to be performed. First, task 1 focuses on classifying subjects according to the risk of worsening. Therefore, it is a survival analysis task where risk is predicted by showing how early a patient experiences the worsening event. Following clinical standards, worsening is defined based on the Expanded Disability Status Scale (EDSS). Two different definitions of worsening are considered corresponding to two different subtasks:

- The patient suffers a worsening when he/she crosses the EDSS threshold 2 times in an interval of one year. The EDSS value must be greater than or equal to 3 [16].
- The second definition of worsening is based on the patient's first recorded EDSS value [17].
  - If the first recorded EDSS value is less than or equal to 1, the definition of worsening occurs when an increase of 1.5 points over the EDSS value is observed.
  - If the first recorded EDSS value is greater than or equal to 1 and less than 5.5, the definition of worsening occurs when an increase of 1 point over the EDSS value is observed.
  - If the first recorded EDSS value is greater than or equal to 5.5, the definition of worsening occurs when the 0.5-point increase over the EDSS value is observed.

Secondly, task 2 refines task 1, where the models used must attribute the cumulative probability of worsening in different time windows between years (0, 2, 4, 6, 8 and 10).

The following subsections detail the methodology carried out to address this problem.

3.1. Exploratory Analysis

Fully anonymized actual patient datasets containing 2.5 years of observations are provided for MS tasks 1 and 2. These data come from two clinical institutions (Pavia and Turin). Static patient data and dynamic data constitute the sets, but distinctions must be made for each subtask because the sets have different dimensions. In terms of static data, we have a total of 552 patients for subtask A and 640 patients for subtask B. The datasets were divided into 80% training and 20% test.

The organization provides these datasets, fragmented into different files, and include features concerning tests and analyses performed by the medical staff on the patients. These data integrate static features on the patients and dynamic features concerning relapse in the disease, EDSS scores assessed by the doctors, evoked potentials in the disease (auditory, motor, visual or somatosensory), MRI information, the type of MS observed in the patient (CIS, PP, PR, RR or SP) and, finally, whether the worsening event has occurred along with the time at which it has developed.

Data processing is then performed to prepare and transform the data appropriately before analysis. Data processing involves data cleaning, format transformation, normalization, and removal of outliers. Basic descriptive measures were calculated to understand the distribution of the data. In addition, counts and frequencies of categorical variables were obtained. During the exploratory analysis, it was observed that the dynamic data had numerous missing values omitted, so the authors decided to remove these features. This led to the loss of features that a priori could provide great value in prediction. In future work, it would be good practice to analyze possible ways of extracting information from these features, such as analyzing time windows where these features present more information.

A correlation analysis was performed to assess the relationship between pairs of variables and to obtain information about variable dependencies. In the EDSS assessment observations performed, several additional features were obtained, such as the maximum EDDS assessed in the patient, the first EDSS value estimated, and the number of EDSS assessments performed in the patient to obtain segments and clusters of patients on this assessment because worsening is defined by this feature.

3.2. Model Training

Once the feature extraction is done, the selected models can be trained to perform the tasks of intelligent prediction of MS progression. The models with the best results obtained in the experimentation are Random Survival Forest (RSF) and Elastic Net Cox (ENC). The following subsections describe the most important elements of the two selected models.

3.2.1. Random Survival Forest Training

The RSF model is consistent in showing that the survival function of the set of trees converges uniformly to the survival function of the population of individuals. This is because this survival model performs well when there is right censoring in the data set.

Before starting to detail the RSF setup used in this problem, the key features and details of the algorithm as defined in [14]. RSF is described as $(X, T, \delta), (X_1, T_1, \delta_1), ..., (X_n, T_n, \delta_n)$ independent and identically distributed random variables of random elements such that the feature is a d-dimensional vector taking values in a discrete space. T is the observed survival time $T = min(T^0, C)$ and $\delta = I(T^0 \leq C)$ is the binary censorship value, T^0 is independent of C the censorship time.

An individual i is right-censored if $\delta_i = 0$ otherwise it is equal to 1 and the individual has suffered an event in T_i. Furthermore, (X, T, δ) has a joint distribution and X is independent of δ.

The set of forest trees is created from the learning data $(X_i, T_i, \delta_i)_{1 \leq i \leq n}$. The steps of the RSF algorithm are as follows:

- First, B samples are drawn from $(X_i, T_i, \delta_i)_{1 \leq i \leq n}$ and from each sample the binary tree is recursively grown.
- Once the tree is grown, n candidate variables are randomly selected at each node to split up to $n - 1$. The node splitting is done by maximising the survival difference between the child nodes.
- The optimal tree growth should be as close to the full tree size as possible, the only constraint being that each node must not have less than zero events.
- Finally, the survival function of RSF must be calculated. This function is the KM (Kaplan-Meier) estimator and is calculated for the RSF terminal nodes.

The RSF configuration tested in this problem is detailed below. The configuration has been correctly adjusted following the steps defined in [18]. The survival forest is set with a set of 1000 trees. The survival tree's maximum depth occurs when the nodes are extended until all leaves include the minimum number of samples needed to split the inner node or until all pure leaves are possessed. In the setup, the minimum number of samples to perform the splitting is given as 10. The present problem is a regression problem where the risk of individual worsening is predicted, so the minimum number of samples needed to be in a leaf node is included. Therefore, the splitting is only performed at a depth point if the minimum number of samples in the left and right branches is available to smoothen the regression model. All features included in the training set are considered in the search for the best splitting. It is also indicated that the model starts with randomness when constructing the trees. In addition, it has been indicated in the model that the number of processes executed in parallel is equal to the number of available processes, thus improving the training times of the model.

3.2.2. Elastic Net Cox

Elastic Net Cox is included considering the results obtained during experimentation. Moreover, the Cox proportional hazards model is one of the most common in the medical research field.

The main problem with the standard Cox model is the estimation of the coefficients when the dataset integrates a considerable number of features. The model suffers a collapse when it inverts the matrix obtaining non- singular values due to the relationship between the features. Consequently, a variant such as Elastic Net Cox is used, which includes the Ridge penalty and LASSO subset selection, combining the weighted penalty L1 and L2 of the coefficient vector. L1 results in coefficients that are rigorously 0 and L2 ensures uniform coefficient reduction [19].

Before starting the Elastic Net Cox setup, the model's main features that integrate the Ridge and LASSO techniques are detailed. In [19], the authors define an observation of individuals as $(t_i^l, t_i^u, \delta_i, X_i)$ where t_i^l, t_i^u are the time periods where patient i has an existing relationship between characteristics, where δ_i indicates whether the event has occurred in t_i^u. Finally, (X_i) is the vector of patient covariates. The objective is to treat the different covariates as a function of time using the partial likelihood function of the Cox model.

$$l(\beta) = \sum_{i=1}^{N} \delta_i \left\{ X_i^T \beta - log \left[\sum_{j \in R(t_i)}^{N} exp(X_j^T \beta) \right] \right\} \tag{1}$$

The time function is $X_i = X_i(t)$, and the risk set is $R(t_i)$ when event t_i occurs. Specifically, $R(t_i) = \left\{ j : (t_i^u \geq t_i) \wedge (t_j^l \geq t_i) \right\}$

The condition $(t_i^u \geq t_i)$ expresses that the event occurred on individual j or that the individual suffered censure after t_i. Conversely, condition $(t_l^j \geq t_i)$ indicates that the time of occurrence was before the start of the event.

In data sets with a large volume and difficulties in predicting the event, we can define as a fundamental objective to find a β with the ability to generalise, i.e., to omit the noise that is present in the data set and fit the model using all the features present in the data. An improvement of the generalisation and reduction of the estimation variance of the model is produced by employing the regularisation technique. This technique returns a smaller vector of coefficients. In addition, this technique allows a unique solution to be obtained when the data sets have more features than observations of individuals. Therefore, the Elastic Net Cox model integrates the weighted penalty L1 and the coefficient vector L2. Elastic Net Cox is defined as:

$$\hat{\beta} = \arg\min_{\beta} \sum_{i=1}^{N} \delta_i \left\{ X_i^T \beta - log \left[\sum_{j \in R(t_i)}^{N} exp(X_j^T \beta) \right] \right\} + \lambda(\alpha ||\beta||_1 + 0.5(1-\alpha)||\beta||_2) \tag{2}$$

λ is a hyperparameter that determines the level of regularisation, while α establishes the balance between the LASSO model and the Ridge model approach. If $\alpha = 1$ it is the LASSO model, while $\alpha = 0$ is the Ridge model.

The configuration of the Elastic Net Cox model has been tuned considering the information exposed in [20]. The LASSO model, a tool that helps to select a subset of discriminative features, has been included. This technique presents an issue. It does not allow to select more features than the number of samples. Moreover, in the case of having highly related features, it selects features from that set only. To solve this problem, the authors introduce the relative weight of L1 and penalise L2, i.e., to help stabilise feature selection by adding a weight to improve the

stability of LASSO selection. The parameter l1Ratio is configured by adding a penalty to L1 of 0.9. In addition, a minimum value for α of 0.01 regularisation is included. The minimum value of α is calculated as the division of the maximum α by the data, i.e., the minimum value for which the coefficients are 0. As in this problem, different data sets are used for each task. The estimated coefficients approach does not present correct prediction results because a certain α is needed for each set. Therefore, the use of cross-validation as a solution is chosen. This solution is detailed in [13], showing that the subset and the value of α that generalises best is correctly determined. First, it is necessary to the set of α to be evaluated. Then, the Cox penalty model is fitted to the data set, and the estimated α set is obtained. For this purpose, StandarScaler is used to consider the scale differences between the dataset's characteristics so that a direct comparison of the coefficients can be performed correctly. Once the set of α to be evaluated has been determined, the GridSearchCV technique thoroughly searches the estimator parameters. After choosing the α, the risk or survival predictions relevant to each task are made.

4. Experimental Setup

The experiments were conducted using the data sets distributed by the organisation for task 1 and 2. The experiments were performed with a computer integrating an AMD Ryzen 9 3900X 3.8 GHz CPU and 32 GB of RAM to predict the events. The training process was implemented in Python 3.8, using the scikit-learn and sksurv libraries. The hyperparameters used in the best-performing model are detailed in section 3.2, Model Training.

5. Results

The results obtained in tasks 1 and 2 with the Random Survival Forest and Elastic Net Cox models are presented. The evaluation measures for the models are different in each task. In task 1, the efficiency of the executions is measured by means of Harrell's concordance index (C index). For task 2 on the prediction of the cumulative probability of worsening, the effectiveness of the runs is measured by the area under the receiver operating characteristic curve at each of the time intervals (ROC curve) and the ratio of observed to expected events at each of the time intervals (O/E Ratio).

Table 1
Task 1 metrics, the C-index and the 95% confidence intervals for C-index

Task 1	sub-task a	sub-task a	sub-task b
Metric	RSF	Elastic Net Cox	RSF
C-index	0.766	0.774	0.508
95% CI for C-index	0.863	0.847	0.634

The results of task 1 can be seen in Table 1 where the evaluation metrics are detailed. In subtask A better results are obtained than in subtask B. It would be necessary to test the performance of the Elastic Net Cox model in subtask B. The dataset should also be treated

with a different approach to obtain better results. It should be mentioned that during the experimentation process the results obtained in both subtasks are considerably better. To carry out the experimentation, the training set was randomly divided into 80-20% to verify the models before the organisation provided the test dataset.

The experimental runs achieved a C-index of 0.863 in RSF and 0.872 in Elastic Cox Net. While in subtask B the results were worse, reaching a C-index of 0.811 in RSF. The difference obtained between the experimental phase and the test set is very noticeable.

Table 2
Task 2 metrics, AUROC, O/E Ratio at different time intervals and the 95% confidence intervals for AUROC and O/E Ratio.

Task 2	sub-task a	sub-task a	sub-task b
Metric	RSF	Elastic Net Cox	RSF
95% CI for AUROC 2 years	0.71	0.77	0.329
AUROC 2 years	0.84	0.864	0.56
95% CI for AUROC 2 years	0.969	0.958	0.791
95% CI for AUROC 4 years	0.711	0.812	0.338
AUROC 4 years	0.833	0.898	0.507
95% CI for AUROC 4 years	0.956	0.984	0.675
95% CI for AUROC 6 years	0.667	0.87	0.333
AUROC 6 years	0.809	0.938	0.493
95% CI for AUROC 6 years	0.951	1	0.653
95% CI for AUROC 8 years	0.552	0.735	0.452
AUROC 8 years	0.71	0.859	0.607
95% CI for AUROC 8 years	0.868	0.983	0.761
95% CI for AUROC 10 years	0.567	0.682	0.42
AUROC 10 years	0.741	0.831	0.579
95% CI for AUROC 10 years	0.915	0.98	0.737
95% CI for O/E Ratio 2 years	-0.014	-0.021	0.422
O/E Ratio 2 years	0.451	0.437	1.019
95% CI for O/E Ratio 2 years	0.917	0.895	1.615
95% CI for O/E Ratio 4 years	0.142	0.119	0.375
O/E Ratio 4 years	0.637	0.599	0.784
95% CI for O/E Ratio 4 years	1.132	1.079	1.193
95% CI for O/E Ratio 6 years	0.164	0.133	0.378
O/E Ratio 6 years	0.576	0.529	0.726
95% CI for O/E Ratio 6 years	0.989	0.924	1.074
95% CI for O/E Ratio 8 years	0.244	0.2	0.421
O/E Ratio 8 years	0.653	0.587	0.746
95% CI for O/E Ratio 8 years	1.062	0.975	1.072
95% CI for O/E Ratio10 years	0.239	0.22	0.46
O/E Ratio 10 years	0.61	0.582	0.774
95% CI for O/E Ratio10 years	0.982	0.945	1.089

The results of task 2 can be seen in Table 2 where the evaluation metrics are detailed. As with task 1, subtask B performs worse than subtask A. Therefore, a study on the selection of characteristics for this subtask should be carried out. The results of subtask A depending on the time interval have a better performance. Similarly, in subtask B during the experimental phase better results were obtained.

6. Conclusions and Future Work

The life expectancy of a patient diagnosed with MS is often limited and doctors know this. Diagnosis and treatments focus on delaying infection and keeping the patient from worsening. This is a challenge due to the different manifestations of the disease, the progression, and the quality of life of the patient. Working in this challenge makes it possible to contribute to the field of survival analysis, which focuses on predicting relapse or worsening of MS characterised by progressive deterioration of certain neurological functions. Clinicians need support systems capable of assisting them in all phases of treatment, indicating interventions or recommending therapeutic decisions for each patient. Advances in machine learning have demonstrated their potential in survival analysis, such as in predicting disease progression and identifying new features and patterns in MS.

The results obtained have been considerably better in subtasks 1A and 2A than in subtasks 1B and 2B, so proposing a different approach to solve the results would be correct. Moreover, in subtask B only the Random Survival Forest model was experimented with, so the performance of Elastic Net Cox could be tested. In future work, studying a broader range of methods would be good practice. In addition, it would be interesting to work with a larger dataset to include features eliminated due to missing information. It would also be interesting to study other feature extraction methods when the dataset has many features with missing information, such as in the case of time studies on those features. In addition, stratifications could be performed in the population of individuals with MS to find new patterns to improve the understanding and diagnosis of the disease.

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