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A Hierarchical Machine Learning Solution for the Non-Invasive Diagnostic of Autonomic Dysreflexia

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Abstract: More than half of patients with high spinal cord injury (SCI) suffer from episodes of autonomic dysreflexia (AD), a condition that can lead to lethal situations, such as cerebral haemorrhage, if not treated correctly. Clinicians assess AD using clinical variables obtained from the patient's history and physiological variables obtained invasively and non-invasively. This work aims to design a machine learning-based system to assist in the initial diagnosis of AD. For this purpose, 29 patients with SCI participated in a test at Cruces University Hospital in which data were collected using both invasive and non-invasive methods. The system proposed in this article is based on a two-level hierarchical classification to diagnose AD and only uses 35 features extracted from the non-invasive stages of the experiment (clinical and physiological features). The system achieved a 93.10% accuracy with a zero false negative rate for the class of having the disease, an essential condition for treating patients according to medical criteria.

Keywords: autonomic dysreflexia detection; physiological computing; supervised-learning techniques; eHealth; disease diagnosis

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1. Introduction

Autonomic dysreflexia (AD) is a serious condition common in patients with cervical or upper thoracic (above T6) [1–3] spinal cord injury (SCI) that develops in more than half of all cases [4–6]. When the patient has their spinal cord injured, there is a significant probability that nerve connections between the brain and the peripheral nerve endings become damaged. When this happens, the body is unable to respond adequately to the homeostatic imbalances produced in the areas affected by the nervous system disruption. Accordingly, these physiologically adverse situations gradually become more unbalanced over time. AD is also known as autonomic hyperreflexia, and it is clinically associated with acute hypertension resulting from the hyperactivity of the sympathetic nervous system. Signs and symptoms of AD include sudden increases in blood pressure, anxiety, blurred vision, headache, bradycardia and sweating above the level of the lesion [7,8]. However, the symptoms produced by AD episodes can lead to more serious conditions if they are allowed to develop and not treated quickly, leading to lethal consequences such as myocardial ischaemia or cerebral haemorrhage [9–14]. This is why early diagnosing of the disease and detecting the occurrence of its episodes is of paramount importance to ensure the health of patients suffering from SCI.

AD can develop at any time when a stimulus occurs below the level of the lesion [15]. Among the various AD episode triggering stimuli, the most common are, firstly, bladder distention [16–18], followed by faecal impaction [19]. Controlled bladder-filling is therefore one of the most common diagnostic tests used for determining whether a patient with SCI has AD. During these diagnostic tests, a medical team progressively fills the patient's bladder with a saline solution through a catheter. The saline solution is used for simulating the urine that would concentrate in the bladder in a daily situation and with it, the clinicians intend to induce in the patient a controlled AD attack. If an AD episode arises, then the doctors will know that the result of the diagnostic test is positive and that the patient is susceptible to suffering AD episodes in everyday life. Conversely, the diagnostic test will be negative if the patient's body does not react adversely when the bladder is full (see the symptoms mentioned in the previous paragraph). It is important to note that these tests can only be performed in a controlled clinical environment and that the induction of these AD episodes does not entail a risk for the patient: the medical team can reverse the episodes by emptying the bladder with the same catheter used for filling it.

Concerning the bibliography, most of the papers about AD analyse it from a medical perspective. This way, numerous studies explain what AD is and its potentially lethal consequences. Nevertheless, few are works that study AD from a technological approach to automatically diagnose this condition or detect the onset of its episodes. To the extent of the authors' knowledge, apart from Suresh's and Duerstock's studies [20,21], the literature using machine learning (ML) techniques for detecting AD is practically non-existent. In the case of this work, Suresh and Duerstock present a device that detects the onsets of AD by combining the monitorisation of physiological variables and ML techniques. However, the solution presented in this article is proposed for being used with SCI patients that have previously been diagnosed with the disease and that already have certain experience with this condition.

In this sense, this work takes another path and intends to face the problem of the initial diagnostic instead of trying to detect its onsets in daily situations. The team's objective was to design a ML-based system for diagnosing AD in patients with SCI. Thus, they expanded the previous work of [22] and conducted a pilot experiment with 29 patients with SCI at Cruces University Hospital (CUH, from now on). Some of the data collected in these experiments are of a non-invasive nature: clinical history data, analyses of hormonal variations obtained through blood extraction, monitorisation of physiological variables at rest, etc. On the other hand, the team also collected physiological data using the bladder-filling invasive method within a controlled environment and monitored by a nurse and a doctor. The team selected this method because, as mentioned previously, most of the AD episodes are produced by the stimulus derived from the filling of the bladder. During the total duration of the experiment, the researchers collected the following four physiological signals to extract features usable for diagnosing the infirmity: systolic blood pressure, diastolic blood pressure, heart rate and total peripheral resistance.

Regarding the diagnostic test for this disease, the reader should bear in mind that, due to their injury, the patients taking these tests are highly fragile. For this reason, the objective of this work is to take the diagnostic a step further and minimise the necessity of using invasive methods for detecting the disease. To this end, this work proposes a hierarchical classification system that divides the diagnostic problem into two levels to determine the presence of the disease using only those features that can be extracted non-invasively. The proposal for the first level is to use the information already available from the patient's clinical history. Later, a second level is proposed to diagnose the cases that were not clear in the first level by using the features extracted from the non-invasive stages of the experiment (physiological signal values and blood analysis results). By doing so, the authors intend to minimise the number of cases that require the patients to undergo the bladder-filling test for diagnosing the disease. Besides, the proposed system also considers the costs related to classification errors. Accordingly, it has been tuned so that the false negative (FN) rate

associated with the class of having the disease is zero and avoids the lethal consequences of not diagnosing a patient with AD who does have it.

Thus, to summarise, in this work, the authors pose the hypothesis that states that it is possible to perform the initial diagnosis of the disease by using systems based on ML and features from non-invasive sources. In addition, accordingly, the following two objectives were set for the study: diagnosing the disease using non-invasive features and minimising to zero the rate of FN produced when performing the diagnostic.

The remaining part of this work is organised as follows. Section 2 describes the design of the pilot experiment and the extraction of the features used for automatically detecting the disease. Then, Section 3 describes the steps taken when applying the ML techniques to the diagnostic problem and how the team reached their final proposal of the two-level hierarchical classifier. Finally, in Section 4, this paper comments on the results obtained throughout the study and Section 5 presents the conclusions and future lines derived from this work.

2. Materials and Methods

This section describes the pilot experiment conducted at CUH [23] and the extraction of the features that would be later used for generating the diagnostic system based on ML.

2.1. The Data Collection Experiment

This work continues with the previous study conducted by this team in which they analysed the detection of AD with the data collected from 5 SCI patients [22]. In that work, the classifiers proposed for diagnosing the AD gave promising results and 4 of the 5 patients were classified correctly (2 without AD and 3 with AD). However, the classification error that took place resulted in an FN and, as explained in the introduction, the errors of this type are not acceptable because not diagnosing a patient with the disease may have deadly consequences. For this reason, the researchers teamed with the medical team of CUH and repeated the same experimentation of [22] to expand the sample of the study to 29 SCI patients (20 male and 9 female) ranging between 32 and 85 years old (mean = 52.24 and SD = 12.79 years). In this new sample, 21 of the 29 participants had already been diagnosed with AD and the other 8 were free from the disease. With this expansion of the sample, the researchers intended to obtain a more robust system that diagnoses without producing any FN and that does it, as much as possible, using solely non-invasive features (as it will be explained, taking care of false positive errors, abbreviated as FP from now on, is not that important as their cost is much smaller).

The test took place at CUH's dysautonomia unit under the supervision of a doctor and a nurse. Twenty-four hours before the experiment, the patients signed a consent form and had their bladder emptied. Concerning the process inside the laboratory, the data collection was performed according to the same experimental protocol [22], which received the approval of the Clinical Research Committee of Basque under the PI2013132 validation code. The protocol was divided into the three stages shown in Figure 1, which will be described below.

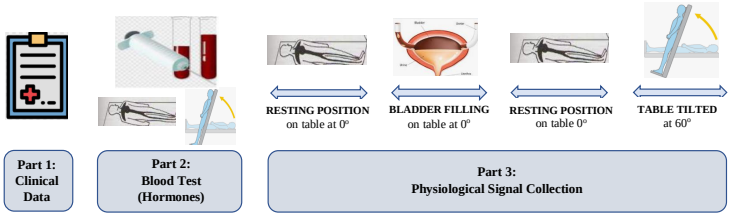

Figure 1. Stages of the experiment.

The first stage of the experiment consisted of collecting the data from the clinical history of the patient, such as the level of the spinal cord at which the SCI took place, the type of injury, the functioning of the sphincters, the previous symptomatology, etc.

The second stage consisted of laying the patient on a tilting table and fastening the chest and lower limbs to the table. Then, the patient was left resting on the table in a supine position (0º) and, after that time, the clinicians extracted a blood sample from the patient's arm. Three minutes later, the clinicians tilted the table to 60º leaving the patient with their head up and took another blood sample. The reason for this second extraction was to compare the hormonal variations between the two blood samples. More precisely, the comparison would be between catecholamine levels (adrenaline, noradrenaline, dopamine and vasopressin). These hormones are also known as amine hormones as they flow within the blood circulation and are subsequently linked to the increases in blood pressure produced by the onsets of AD.

The third and last stage started with fitting the patients with a urinary catheter for the bladder-filling and with the electrodes for monitoring and collecting the physiological signals with a Task Force Monitor device (CNSystems®). As said in the description, four physiological signals were collected during the third part of the experiment: the systolic and diastolic blood pressures, the heart rate and the total peripheral resistance. Then, once both the electrodes and catheter had been placed, the patient's basal physiological values were recorded for 10 min while the patient laid down on the table at 0º. Then, the clinicians proceeded to fill the bladder with a saline solution (0.9% concentration and 37 ºC) aiming to produce the stimulus that could trigger an episode of AD while recording the physiological signals of the patient. This process would last until the bladder was full (the length of the process varied between patients) and, after registering all the physiological signals, the clinicians proceeded to gradually empty the bladder and remove the catheter.

Finally, to finish the third stage of the experiment, the patient laid down in a supine position for 10 min more while the biosignals were being recorded. Later, the table would be tilted back again to 60º and the patient would remain at that position for 10 min. After that time, the clinicians would tilt the table down to 0º degrees and the experiment would conclude by releasing the patient from the table.

This experimental procedure permitted the team to obtain data coming from different sources: clinical history, blood hormonal levels from two positions and physiological signals at rest, during the filling of the bladder and at 60º.

2.2. Feature Extraction

Once all the patients had gone through the data collection experiment of Figure 1, the researchers took all the information and created a new database with different features that would be used later for training a ML system for diagnosing AD. This subsection presents this new database, which consists of 35 features coming from the different non-invasive parts of the experiment.

As mentioned in the introduction, one of the main objectives of this work was to perform the diagnostic of AD in patients suffering from SCI without needing to apply invasive methods such as that of the bladder-filling. These patients are very fragile and so the researchers found it important to organise all the information collected throughout the experiment according to the level of invasiveness. Hence, the extracted features were divided into two main groups.

The first main group embraced the 35 features extracted from the variables collected by non-invasive methods. Depending on the source, these 35 features were also divided into 2 smaller subgroups. On the one side, Table 1 presents the first subgroup, which corresponds to the 5 features belonging to the clinical history of the patient.

On the other side, the second subgroup covered the remaining 30 features shown in Table 2. On the one hand, the first 8 features of Table 2 correspond to the hormonal levels of the 2 blood extractions. On the other hand, the other 22 features of the table were extracted from the 4 physiological signals that were collected while the patients were lying on the tilting table. It is important to note that these 22 features were extracted from the baseline component of the physiological signals, which was obtained using a low-pass filter with a cut-off frequency of 1 Hz. Whereas the first 4 of the 22 were obtained from the part of

the experiment in which the patients were lying at supine position (0º), the last 18 were extracted from the signals recorded with the patient at 60º of inclination.

Table 1. Features extracted from the clinical history of the patients.

Feature Name	Definition
TYPE_INJ	Type of injury.
INJ_LEVEL	Level of the spinal cord injury.
ASIA	Classification according to five grades determined by the absence or preservation of motor and sensory function (ASIA) [24,25].
SPHINCTER	Functioning of the sphincter.
PREV_SYMPT	Previous symptomatology.

Table 2. Features of physiological origin from the non-invasive part of the experiment.

Feature Name	Definition
VASOP_BASAL	Basal vasopressin value at resting position.
AD_BASAL	Basal adrenaline value at resting position.
NA_BASAL	Basal noradrenaline value at resting position.
DOP_BASAL	Basal dopamine value at resting position.
DIV_VASOP_BIPE	Vasopressin at 60º with respect to basal values.
DIV_A_BIPE	Adrenaline at 60º with respect to basal values.
DIV_NA_BIPE	Noradrenaline at 60º with respect to basal values.
DIV_DOP_BIPE	Dopamine at 60º with respect to basal values.
SYS_BASAL	Basal systolic blood pressure value at resting position.
DIA_BASAL	Basal diastolic blood pressure value at resting position.
HR_BASAL	Basal heart-rate value at resting position.
TPR_BASAL	Basal total peripheral resistance value at resting position.
DIV_SYS_TILT_3 min	Systolic blood pressure with respect to basal values 3 min after tilting the table 60º.
DIV_SYS_TILT_10 min	Systolic blood pressure with respect to basal values 10 min after tilting the table 60º.
DIV_SYS_TILT_MIN	Minimum systolic blood pressure with respect to basal values during the 60º table tilt.
TIME_SYS_TILT_MIN	Time to obtain the minimum systolic blood pressure during the 60º table tilt.
DIV_DIA_TILT_3 min	Diastolic blood pressure with respect to basal values 3 min after tilting the table 60º.
DIV_DIA_TILT_10 min	Diastolic blood pressure with respect to basal values 10 min after tilting the table 60º.
DIV_DIA_TILT_MIN	Minimum diastolic blood pressure with respect to basal values during the 60º table tilt.
TIME_DIA_TILT_MIN	Time to obtain the minimum diastolic blood pressure during the 60º table tilt.
DIV_HR_M_3 min	Heart rate with respect to basal values 3 min after tilting the table 60º.
DIV_HR_M_10 min	Heart rate with respect to basal values 10 min after tilting the table 60º.
DIV_HR_M_MAX	Maximum heart rate with respect to basal values during the 60º table tilt.
TIME_HR_M_MAX	Time to obtain the maximum heart rate during the 60º table tilt.
DIV_HR_M_MIN	Minimum heart rate with respect to basal values during 60º table tilt.
TIME_HR_M_MIN	Time to obtain the minimum heart rate during the 60º table tilt.
DIV_TPR_TILT_3 min	Total peripheral resistance with respect to basal values 3 min after tilting the table 60º.
DIV_TPR_TILT_10 min	Total peripheral resistance with respect to basal values 10 min after tilting the table 60º.
DIV_TPR_TILT_MIN	Minimum total peripheral resistance with respect to basal values during the 60º table tilt.
TIME_TPR_TILT_MIN	Time to obtain the minimum total peripheral resistance during the 60º table tilt.

Contrary to the first, the second main group of features is formed by those collected via invasive methods (bladder-filling). The experiment simulated a daily-life situation that could trigger an episode of AD as it can be the filling of the bladder. This simulation was performed using a saline solution that was inserted into the bladder with a urinary catheter while the patient laid down on the table. Thus, this part of the experiment was highly invasive and, accordingly, the features that could be extracted from the four physiological signals recorded during this part of the experiment had to be tagged as invasive. Recalling the objectives of this work, these features did not match the needs of performing the diagnostic in a less invasive manner and their use in the study was subsequently discarded and not included in the database.

Hence, to summarise, the team created a database composed of 35 features of non-invasive origin: 5 from the clinical history and 30 from the blood tests and physiological signals collected through non-invasive methods.

Once the database had been created, the researchers analysed it and observed that, for some patients, certain features coming from the bladder-filling and table-tilting stages had missing values. In this sense, the researchers took into account that the absence of values could be meaningful when performing the classification and decided to normalise the data in the (0.25–1) range and reserve the 0 value for those cases in which it had not been possible to collect the data. To this end, all non-missing values of the data were normalised according to the linear equation of (1), where X_i represents the ith value of the feature vector, X_{norm} for the normalised value and X_{max} and X_{min} stand for the maximum and minimum values of that given feature in the whole register. Then, 1/3 was added to those normalised values and, later, the missing values were replaced by 0 values. Finally, all the values of the feature vectors were divided by the maximum value of the vector. As a result of this process, each feature would be represented with a vector in which the 0 values stand for the data missing cases and all the others would be contained within the (0.25–1) range.

$$X_{norm} = \frac{X_i - X_{min}}{X_{max} - X_{min}} \quad (1)$$

2.3. Experimental Setup

After normalising the database, the data were ready for the ML analysis. Hence, the team explored different types of algorithms and classification structures to build a ML-based AD diagnosing system.

To do so, the team trained 11 supervised learning algorithms in their standard form using the Weka ML software platform [26]. The authors trained the following algorithms: Decision Trees (DT), Random Forests (RF, with 10 trees), AdaBoost (AdaB), Bagging (Bag), Logistic Regression (LR), k-Nearest Neighbours (k-NN, with k = 5), Support Vector Machines (SVM), 1R Rule (1R), Radial-Basis Function (RBF) network, Naïve Bayes (NB) and Multilayer Perceptron (MLP). As it can be seen, these algorithms belong to different types of state-of-the-art paradigms, such as rule or distance-based algorithms, algorithms based on probabilistic methods or ensembles of classifiers, among others.

The results of all the approaches followed until reaching the final solution was obtained using these 11 algorithms and the leave-one-out validation methodology. The reader will find all these results presented in Section 3.

3. Results

This section will present the results of the classification system that was designed to diagnose the presence of AD in patients with SCI. To this end, the researchers used the features that could be extracted from the 29 patients using non-invasive techniques. This section has been split into two subsections. In the first, this paper presents the previous experimentation with which the researchers approached the AD diagnostic classification problem. First, the problem was approached by combining both the clinical and non-invasive physiological features in a single subspace and, after that, exploring the subspaces of those two types of features independently. Then, in the second subsection, the team proposes a two-level hierarchical diagnostic system and will show its results detecting AD in patients with SCI.

3.1. Previous Approaches

3.1.1. The Combined Subspace of Clinical and Non-Invasive Physiological Features

The first attempt of the researchers consisted of seeing whether it was possible to detect AD by applying ML techniques to all the data obtained non-invasively. Hence, in this approach, the researchers used both the features coming from the patients' clinical histories and the ones of physiological nature collected with non-invasive methods. Table 3

presents the results of using the 35 non-invasive features (clinical and physiological) in this initial approach to the problem.

Table 3. Classifier estimation using the combined subspace of the clinical and the non-invasive physiological features (the results of the best algorithm are highlighted in bold).

	1R	DT	k-NN	NB	RBF	SVM	LR	AdaB	Bag	RF	MLP
Accuracy (%)	55.17	68.97	**79.31**	86.21	82.76	82.76	75.86	75.86	75.86	75.86	72.41
Errors class 0 (FP)	6	4	**4**	1	2	2	2	4	4	4	3
Errors class 1 (FN)	7	5	**2**	3	3	3	5	3	3	3	5

Looking at Table 3, the reader could see that the NB algorithm obtained the best accuracy (calculated as the percentage obtained from dividing the correctly classified instances by the total amount of instances), followed by the RBF and SVM. However, all of them produced three FN errors. As mentioned in Section 2.1, if the lethal consequences of AD episodes are taken into account, then this type of error must be avoided by all means as it has a high cost for the patients' health. Thus, when it comes to minimising the amount of FN, the k-NN obtained the best result.

Anyway, none of the algorithms met the objectives defined by the researchers. Consequently, the team decided to explore the features of the clinical history and the non-invasive physiological information in independent subspaces and see if the results could be improved and obtain a null FN rate (Sections 3.1.2 and 3.1.3, respectively).

3.1.2. The Subspace of the Clinical Features

Apart from detecting the AD with a zero FN rate, the other objective of this work is to perform it as least invasively as possible. Therefore, having to choose between exploring the subspace of the features from the clinical history and coming from the physiology, the team decided to first explore the ones of the clinical history as they are completely non-invasive. In this sense, if AD could be detected using only these features, then it would not be necessary to perform any experimentation with the patient to diagnose the disease if the clinicians determined it that way.

Reaching this point, the team tried the same 11 algorithms of the previous attempt with the features coming from the clinical history following the leave-one-out methodology. The results obtained in this second experimentation showed a similar trend to what happened previously. The values shown by Table 4 indicate that k-NN (with k = 5) had again been the one producing less FN.

Table 4. Classifier estimation using the subspace of the features of the clinical history (the results of the best algorithm are highlighted in bold).

	1R	DT	k-NN	NB	RBF	SVM	LR	AdaB	Bag	RF	MLP
Accuracy (%)	79.31	79.31	**86.21**	86.21	82.76	82.76	89.66	79.31	79.31	82.76	89.66
Errors class 0 (FP)	4	4	**3**	1	1	3	1	4	4	3	1
Errors class 1 (FN)	2	2	**1**	3	4	2	2	2	2	2	2

On the other hand, the results of Table 4 also show that it is possible to correctly detect a high number of cases solely using the features coming from the clinical history. Nevertheless, it can also be concluded that some of the information needed to detect the disease is not covered by this subspace as all classifiers made some type of error. That is why the team opted for repeating the experimentation but shifting to the subspace physiological features collected by non-invasive methods.

3.1.3. The Subspace of the Non-Invasive Physiological Features

As explained previously, the team saw the need to eliminate the FN errors produced in the classification. To achieve this, they opted for changing strategy and facing the problem

by analysing the subspace of the 30 features extracted from the physiological data of the non-invasive part of the experiment. Hence, the exploration of this subspace would mean that all patients would have to take some experimentation. Anyway, this experimentation would be minimally invasive and would not differ much from what could be performed in a normal medical check-up.

For the sake of consistency, following with the methodology of the previous subsections, the team used the same 11 supervised learning algorithms to study this third subspace. Accordingly, the results shown below in Table 5 were also validated with the leave-one-out methodology.

Table 5. Classifier estimation using the subspace of the physiological features of non-invasive source (the results of the best algorithm are highlighted in bold).

	1R	**DT**	**k-NN**	**NB**	**RBF**	**SVM**	**LR**	**AdaB**	**Bag**	**RF**	**MLP**
Accuracy (%)	55.17	62.07	79.31	**82.76**	79.31	68.97	62.07	62.07	58.62	58.62	68.97
Errors class 0 (FP)	6	6	2	**2**	3	5	3	5	8	7	3
Errors class 1 (FN)	7	5	4	**3**	3	4	8	6	4	5	6

Looking at the results of Table 5, the reader will see that the results differed slightly from those of the previous two subspaces. On the one hand, the accuracies were generally worse, being that NB was the best scoring algorithm (82.76%). Besides, contrary to what happened before, the NB not only scored the best accuracy but also produced the smallest number of FN (FN = 3). Despite the results of NB not being bad, they were still far from what was desired and so it was clear to the researchers that it is more difficult to diagnose the disease correctly using this subspace.

3.2. The Proposed Hierarchical Classification System

The previous subsection proved that it had been impossible to automatically diagnose the AD by approaching the classification problem in a single level. Therefore, the team proposed a new strategy and suggested the possibility of diagnosing the disease in two different levels. This way, the researchers looked for taking advantage of each subspace's potential and the complementarity between each for performing the classification. The first level was proposed to work with the features of the clinical history to diagnose the AD. This first level was set up very conservatively, i.e., it would only classify the clear cases and it would leave as ambiguous the ones close to the decision boundaries that would not obtain a robust classification. Later, for the unclear cases, the team proposed a second level using the subspace of the non-invasive physiological features to determine the final class of those cases. The reason for exploring the two subspaces in this order is consistent with the objectives of this work: performing it this way minimises the need for taking the patients through experimentation and reduces to the maximum the invasiveness of the diagnostic.

Having posed their strategy, for selecting the best algorithms for each level, the researchers based this on the results of Tables 4 and 5. This way, the first level of the hierarchical classifier would use the k-NN algorithm, and the second would use the NB. However, the previous experimentation proved that it had been impossible to reduce the amount of FN to zero. Therefore, to avoid this problem, the team decided to establish a certainty constraint for the classification of the first level. This way, the classifier would only determine the class of an instance if at least 4 of the 5 neighbour patterns corresponded to a same class. On the contrary, the instance would be left as ambiguous when the certainty of the first classifier was weaker and it would be the second level's classifier who would finally determine, using the non-invasive physiological features, whether the patient is diagnosed with the disease. The conceptual diagram of Figure 2 depicts the functioning scheme of the hierarchical system proposed in this subsection.

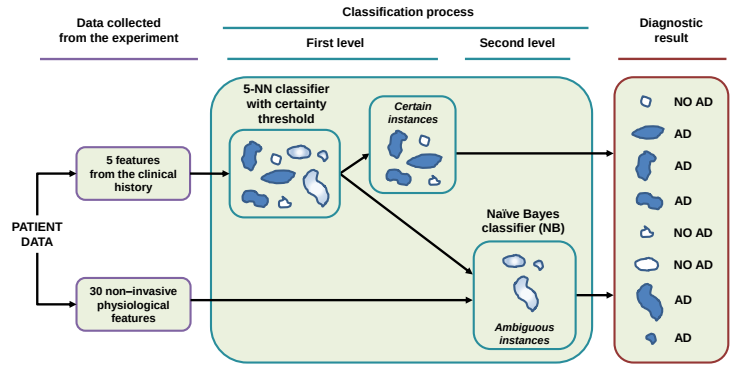

Figure 2. Structure of the proposed hierarchical classification system.

Once the configuration of the system was set, the team tested the system once again using the leave-one-out methodology used throughout the whole study. The results of this experimentation are given in Table 6 where at last it had been possible to perform a classification free of FN errors. This is reflected by the absence of errors for the "AD" class. Besides, Table 6 also shows that the first level's k-NN correctly classified 21 of 29 the cases, missed 1 and considered 7 as ambiguous. Concerning the second level, the reader will observe that the NB algorithm catalogued correctly 6 of the 7 cases that had been marked as ambiguous by the first classifier. This way, the proposed hierarchical system obtained an accuracy of 93.10%.

Table 6. Performance of the two-level hierarchical classifier.

		1st Level: Clinical Feat. 5-NN with 4/5 Pattern Certainty Threshold	2nd Level: Physiological Feat. NB	Total
No AD class: 8 patients	Hit	1	5	6
	Miss	1	1	2
	Ambiguous	6	0	-
AD class: 21 patients	Ambiguous	1	0	-
	Miss	0	0	0
	Hit	20	1	21

For better comprehension, Table 7 shows the results of the hierarchical classification more visually. Marked in green, Table 7 shows the instances that could be correctly classified, either in the first level or the second. Besides, the table also shows which of the cases were left ambiguous by the first level's classifier (in orange). Finally, the system had been unable to classify correctly two of the patients (in red), but these errors belong to the FP class. The consequences of this type of error are not that severe as it would mean that the patient would have to go through the bladder-filling invasive part of the experiment and, accordingly, the clinicians would realise that the patient did not have the disease. As the bladder-filling test does not imply any risk for the patient, the only cost of producing this type of error is that the patient would take a test that could have been avoided.

Table 7. Testing results of the hierarchical classifier using a leave-one-out methodology. Certainties between parentheses are given in the (0–1) range.

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Class: 0-No AD / 1-AD	1	0	1	1	1	1	1	1	1	1	1	0	0	1	0
1st level classification: class (certainty)	0 (1)	1 (0.6)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	0 (0.6)	1 (0.6)	1 (1)	0 (0.6)
2nd level classification: class (certainty)	-	0 (1)	-	-	-	-	-	-	-	-	-	0 (1)	0 (1)	-	0 (1)
Patient	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	
Class: 0-No AD / 1-AD	0	0	1	1	1	1	1	1	0	1	1	0	1	1	
1st level classification: class (certainty)	0 (0.6)	0 (0.8)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	0 (0.6)	1 (1)	1 (1)	1 (1)	1 (1)	0 (0.6)	
2nd level classification: class (certainty)	1 (1)	-	-	-	-	-	-	-	0 (1)	-	-	-	-	1 (1)	

4. Discussion

In this work, the research team has presented an expansion of their previous work [22] that focused on performing the initial diagnostic of AD in patients with SCI using ML algorithms. To the extent of the authors' knowledge, the bibliography that seeks to detect this disease using ML is very scarce [20] and even moreso the one focusing on its initial diagnostic. On the one hand, the team has expanded the sample of study of its previous research from 5 to 29 patients suffering from SCI. On the other hand, the researchers have approached the problem of performing a diagnostic free from FN errors. These types of classification errors represent the diagnostic error of saying that a patient is free from the disease when they have it, and so they may have lethal consequences. Finally, this work also had the objective of performing the diagnostic in the least invasive manner possible, minimising the number of medical tests to be performed and always without using the invasive methods that are common for diagnosing this disease, as is, for example, the bladder-filling test.

Initially, the researchers faced the problem of diagnosing the AD in three different subspaces: the subspace combining features from the clinical history and non-invasive physiological features and the subspaces of analysing them but independently from each other. The best algorithms of these three explorations resulted to be the k-Nearest Neighbours (k-NN, with k = 5 and an accuracy = 79.31%), again the k-NN (k = 5, accuracy = 86.21%) and the Naïve Bayer (NB, with accuracy = 82.76%), respectively. However, even if the accuracy values were relatively high, the classifiers always produced errors of the FN type.

Thus, the team changed strategy and proposed a hierarchical system in which the diagnosis would be performed in two levels: a very conservative first level that would only classify the clearly distinguishable patterns and a second level that would be useful for determining the class of the less clear patterns. The first level would diagnose using k-NN (k = 5) in the subspace of the variables of the clinical history of the patient. Thus, this first level does not require performing any type of medical test on the patient. Besides, to be conservative and not produce FN, a minimum certainty threshold was set for the first level's classifier: an instance would only be classified if 4 of 5 nearest neighbours belonged to the same class. If this constraint was not fulfilled, then the case would be left ambiguous and would be passed onto the second level of the hierarchical system. In the second level, the final diagnostic of the patient would be performed by the NB algorithm using the features extracted from the physiological data collected non-invasively (it requires

performing a medical test). The results of this approach resulted to be satisfactory and detected the disease with an accuracy of 93.10% and achieving FN = 0.

5. Conclusions

According to the results discussed in the previous section, the goodness of the work presented becomes clear: on the one side, the work contributes to an area in which technological approaches are scarce and, on the other, gives support to the clinicians that work in this field. The work presented in this article received the acceptance of Cruces University Hospital's clinicians, proposing a solution to the complex problem of diagnosing AD without producing FN errors [11,12]. Besides, it has minimised the invasiveness and the necessity of performing medical tests thanks to the confluence of different types of information (physiological and from the clinical history).

However, a sample of 29 patients could still be considered small for generalising the results to a wider population. Accordingly, the team poses the future line of expanding the sample of the study even more, even if the access to this type of population is complicated. Apart from that, the proposed hierarchical system has the weakness of not explaining why they chose a class. Because of this reason, the team also proposes the future line of fulfilling the same objectives of this work but only using classifiers with explanatory properties. This way, the classification would not only be robust and non-invasive but would also provide the clinicians with an explanation for taking a diagnostic decision.

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Data Availability Statement: Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

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