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TremorSoft: An decision support application for differential diagnosis between Parkinson's disease and essential tremor

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ABSTRACT

A cost-effective, non-invasive, and easy-to-use tool is presented that uses the 6-axis inertial sensor of the smartphone or a specific wearable sensor, boosted by machine learning, to support early differential diagnosis of Parkinson's disease and Essential Tremor. A dedicated web server helps extract the kinematic indexes from the recorded signals, implement the machine learning models and return the resulting classification to the App. Thus, clinicians can use this App as a support tool in the clinic, contributing to performing motor evaluations in the uncertain and undecided stages of the diseases and promoting appropriate, fast, and timely therapeutic responses.

Code metadata

Current code version	v1.0
Permanent link to this code version	https://github.com/ElsevierSoftwareX/SOFTX-D-22-00185
Legal Code License	Safe creative, ID: 2206021281741
Code versioning system used	Git
Software code languages, tools, and services used	Kotlin, Android SDK, IntelliJ IDEA
Compilation requirements, operating environments & dependencies	IntelliJ IDEA or Android Studio, Android SDK,
If available link to developer documentation/manual	None
Support email for questions	julian.david.loaiza@upc.edu

Software metadata

Current software version	v1.0
Permanent link to executables of this version	
Legal Software License	Safe Creative, ID: 2206021281741
Computing platform/Operating System	Android
Installation requirements & dependencies	Android 8.0 or higher
User manual	In the appendix
Support email for questions	julian.david.loaiza@upc.edu

1. Motivation and significance

Essential Tremor (ET) is a neurological disorder characterized by the manifestation of involuntary and rhythmic tremors in different parts of the body and is considered to be the most common tremor disorder worldwide [1,2], primarily affecting older adults. In some cases, ET is confused with Parkinson's Disease (PD) [3], a progressive neurodegenerative disease that, among

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its clinical manifestations, and as in ET, affects movement. The difference between these conditions has both therapeutic and prognostic implications. Therefore, the early and correct differential diagnosis of PD and ET is crucial to ensure adequate and timely treatments to control the evolution of the disease and also, to prevent the patient from suffering adverse effects when receiving medication prescribed due to an erroneous diagnosis [4]. The confusion in diagnosis is caused mainly by the fact that, although these are two distinct diseases, there are similarities in physiological and psychological symptoms between PD and ET. This is why differentiation of the two nervous system disorders remains a challenging task even for movement disorder specialists [5]. Neuroimaging by single-photon emission computed tomography (SPECT) has been considered a potential diagnostic option to differentiate PD from ET [6]. However, it is a high-cost test that limits its use in developed countries and involves long waiting periods in countries where the test is available. In addition, the procedure is invasive and requires patient compatibility with the radiopharmaceutical tracer used for this test, which may limit its applicability [7]. Therefore, a medical evaluation by a neurologist remains the gold standard for diagnosing both diseases.

To date, there are no low-cost, easy-to-use confirmatory or diagnostic tests or tools that ensure accurate, safe and reproducible differentiation between the two diseases [8]. However, with the progressive development of smartphone technologies and functionalities in recent years, mobile applications have been created for the medical sector, some of them aimed at supporting the diagnosis, assessment, analysis and monitoring of some movement disorders [9,10]. However, the applications developed as a diagnostic support tool mainly focus on differentiating a pathological tremor from a physiological one, mainly for PD. The above has motivated researchers to be interested in developing new support systems for the differential diagnosis of different movement disorders, particularly differentiating PD from ET. Numerous methods using various approaches have been developed over the past two decades [11]. However, only a few systems have been implemented as ready-to-use applications until now. In one of our previous works, hand tremor recordings from subjects with a confirmed diagnosis of PD and ET were analyzed from a protocol described in [12] to analyze the recorded signals and extract biomarkers that could be used in the context of routine clinical care to support the differential diagnosis of these tremor disorders. The proposed protocol consists of an easy, quick test that requires no specialized equipment other than a smartphone and/or a specific wearable inertial sensor. To perform it, either of these two devices was placed on the dorsum of the hand to record the tremor in two arm positions (resting and posture) at a defined frequency rate for 30 s. The recorded data were analyzed using statistical methods, and it was found that some biomarkers in the frequency spectrum can contribute to differentiating physiological and pathological tremors and, in turn, differentiate PD from ET. The results allowed us to use these biomarkers, also called kinematic features, to train Machine Learning (ML) models to classify hand tremors accurately. Thus, a methodology was initially developed to train ML models in Matlab using the kinematic features of the linear acceleration [13] and angular velocity [14] signals of the hand tremor of 51 subjects previously recorded at the Hospital Clìnic de Barcelona with an iPhone 5 at a sampling frequency of 100 Hz [12]. For this work, the same methodology was implemented in Python and the Scikit-Learn machine learning library to train and test new ML models using the data from the 51 subjects and new data from 25 subjects recorded at the Centro de Trastornos del Movimiento (CETRAM) in Chile between November 2021 and January 2022. The new data were recorded at a sampling rate of 120 Hz using a wireless inertial sensor, Xsens DOT. The new data were sub-sampled at 100 Hz to homogenize the dataset due to the difference in the sampling frequency used for the two devices. The biomechanical analysis was performed in the frequency domain in the range of 3 to 10 Hz to calculate the kinematic features, as described in [13] and [14]. Finally, the sample was split in a 70–30 ratio; 70% for training and 30% for testing. The ML models implemented in the App showed an accuracy of 96.77% for differentiating between physiological tremors and 94.73% for differentiating pathological tremors (PD and ET). Finally, as a result of these three works, it was proposed to develop TremorSoft. This Android-based mobile application uses the built-in inertial sensors of the smartphone or the external wirelessly connected inertial sensor (Xsens DOT) to serve as a tool to support the differential diagnosis of PD and ET during routine clinical practice.

TremorSoft is a novel e-health application in the field of movement disorders research, whose main contribution lies in implementing ML algorithms that have a high efficiency to easily and quickly classify PD and ET. It is expected that this application can be used as an additional tool in the medical evaluation of patients with high suspicion of PD or ET that, through an alternative and non-invasive test procedure, allows the physician to have timely and reliable information to make a correct diagnosis of the patient. Especially for developing countries, where hospitals often have only simple tools and techniques at their disposal, a standardized, convenient and accurate low-cost tool to differentiate PD from ET would be of considerable help.

2. Software description

2.1. Software architecture

TremorSoft implements the 6-axis inertial sensor from the smartphone or a wearable sensor connected via Bluetooth to record and analyze hand tremor data, classifying them accordingly. The tool consists of two parts: (1) a smartphone application to record the demographic, clinical, and kinematic data of the subject to be evaluated, and (2) a web server where the recorded kinematic data are processed to classify them deferentially, accordingly, between HS, ET and PD by applying ML models to the features extracted from these data. The mobile application is built on the Android operating system and represents the front-end of the tool, written in Kotlin using the Android SDK and the Xsens DOT SDK. The target version of the operating system is Android 8.0 Oreo or higher. All processes running on the web server, the back-end, are hosted on the Heroku platform, written in Python. The Retrofit network library is implemented as a REST client to load and retrieve data from the back-end. Regarding the Authentication services, the Firebase platform is used. Fig. 1 shows the general architecture of the developed software.

2.2. Software functionality

2.2.1. Front-end

The Front-end consists of an Android application in which users, physicians, and movement disorder specialists can record information about patients with suspected or diagnosed PD or ET. The information that can be recorded corresponds to primary clinical data, hand tremor signals, and, in the case of diagnosed patients, information related to their diagnosis and the treatment received. The mobile app guides the user to record hand tremor signals using the built-in inertial sensors (gyroscope and accelerometer) of the smartphone or an external inertial sensor (Xsens DOT) connected to it wirelessly. The recorded signals correspond to two positions, rest and posture, which are stored separately in two ArrayList class variables, *restData* and *postureData*. When the external sensor is used to record hand tremor

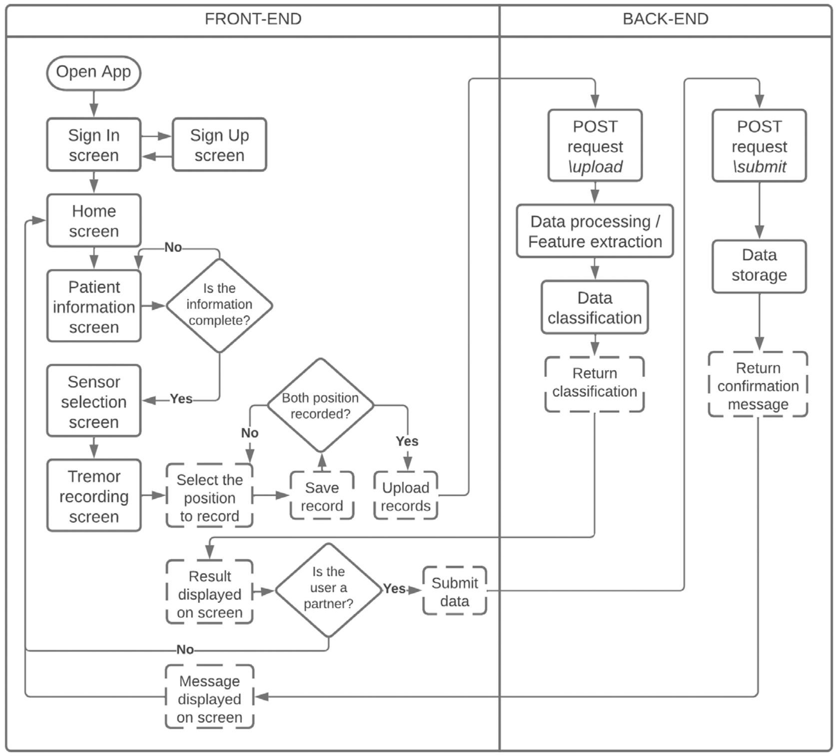


Fig. 1. TremorSoft flowchart.

signals, these are stored in the internal device memory, so they must first be exported to the application and then assigned to *restData* and *postureData* as appropriate. Once both positions are recorded and saved, the two lists are combined into a single list called *tremorData*. Then, a new variable of type JSONArray, called *dataArray*, is created from the latter list. This JSONArray is the one that is sent to the server hosted on the Heroku platform, where the signals are processed, analyzed, and classified. The application then receives and displays a message corresponding to the result returned by the server. The three possible messages the application can display according to the classification obtained are: (1) A pathological tremor has been identified. It has been classified as PD; (2) A pathological tremor has been identified. It has been classified as ET, or (3) The recorded tremor has been classified as a physiological tremor.

If the user who enters the application is an associated user, i.e., a user accredited as a TremorSoft collaborator, the application enables the *SEND* button. The user confirms the classification received by pressing this button and authorizes the submission and storage of the recorded data in the webserver database. When this process is initiated, the application takes each of the collected clinical and diagnostic data and stores them in a new JSONObject, called *patientDataJSON*, which is subsequently added to the JSONArray called *tremorsoftData*, a copy of *dataArray* which contains the recorded signals at rest and posture. Then, *tremorsofData* is sent via a POST request under the path */submit*. Finally, the server returns a confirmation message displayed on the application screen upon completing this task. Here the user can decide whether to restart the classification process on the same patient (*RESET* button) or perform a new test on a different patient (*NEW* button). Fig. 2 shows the user interface of the software.

2.2.2. Back-end

The back-end was developed as a RESTful API using Python and Flask and is deployed on the Heroku platform. The back-end has hosted all the functions and elements essential for processing, analyzing, and classifying the hand tremor records and storing these records and other patient data in the SQL database. The three main components of the TremorSoft web server are described below:

1. **Data preprocessing and extraction of kinematic features:** The server receives the JSONArray via the */upload* path from the mobile application and transforms it into a Pandas Dataframe for further processing. The signals are initially filtered during preprocessing to reduce sensor drifts and distortions due to various physical phenomena. Next, the Power Spectral Density (PSD) of each accelerometer and gyroscope axes is calculated. From the PSD of the components, kinematic features are extracted and then evaluated by ML models.
2. **Classification of hand tremor using ML:** The server hosts the classification models developed based on the methodology and results obtained in previous studies [12–14]. The Classification function uses a model and specific kinematic features, previously extracted with the Preprocessing function, to initially classify the recorded tremor as physiological or pathological. If the tremor is classified as pathological by the first model, a second model is used to classify the tremor of the subject as PD or ET. Although many kinematic features have been extracted in previous works, the classification models only use a small number of these, i.e., only those that, together with the model, provide high predictive power.
3. **Storing patient data with a confirmed diagnosis:** An SQL database was linked to the server using the Heroku Postgres service for data upload and storage. Subject data is uploaded to the web server in a POST request via the */upload* path once it is verified that all required information has been supplied. As shown in Figs. 3 and 4, the data set that is stored for each patient contains 25

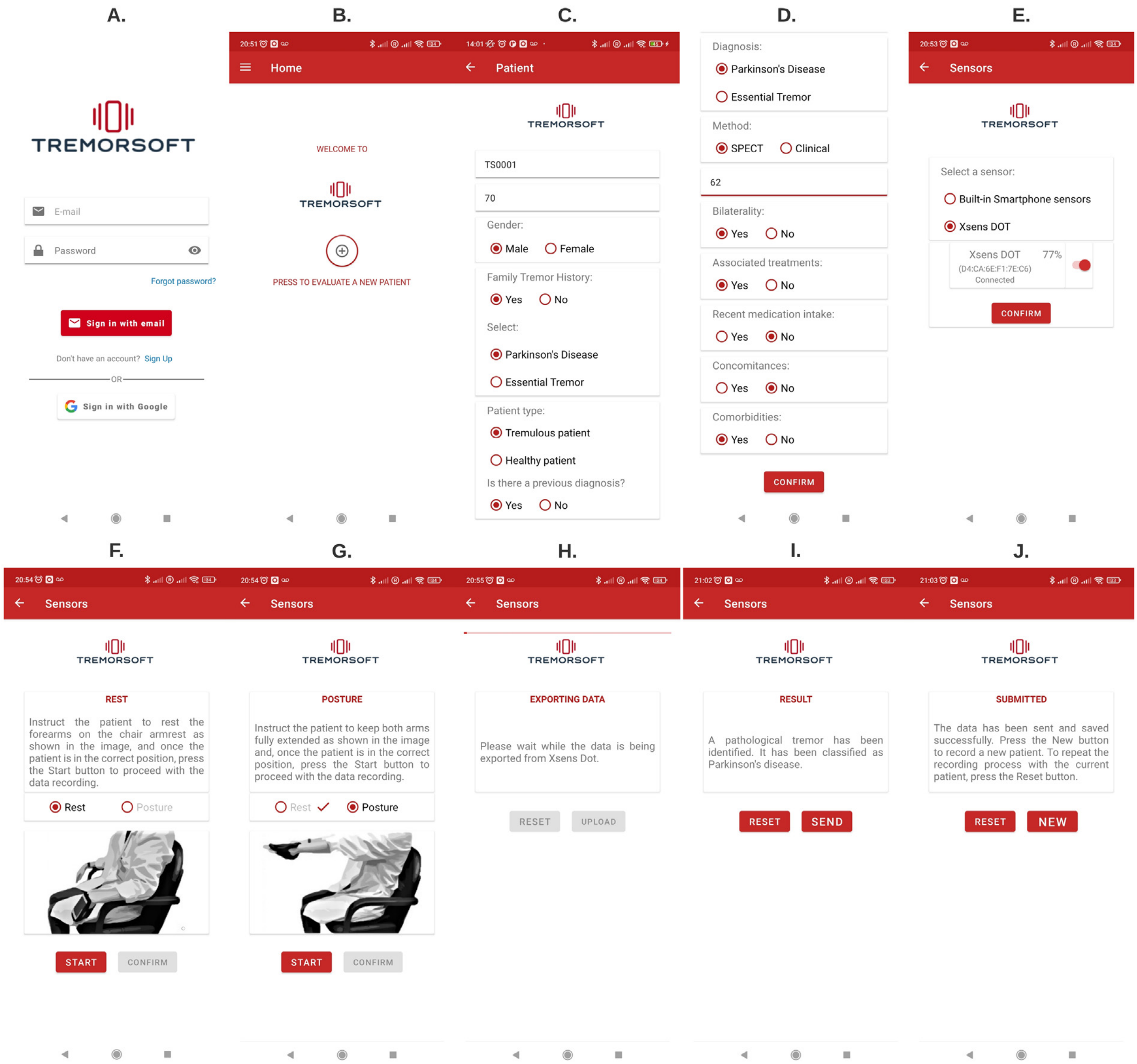


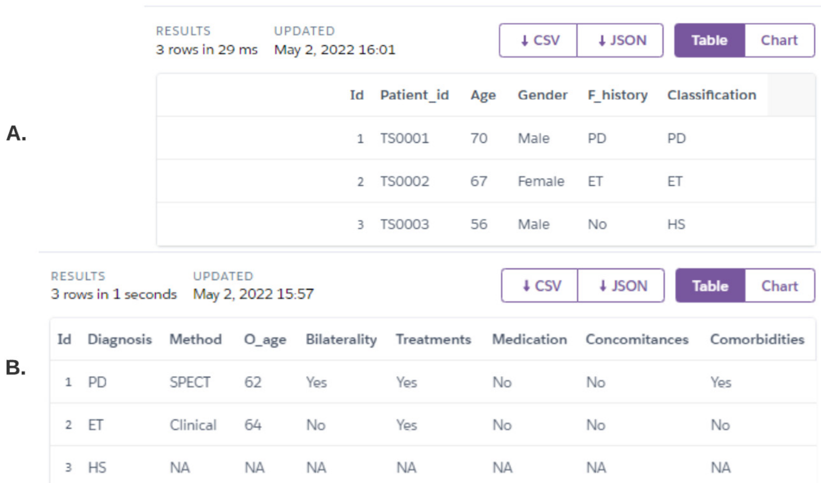
Fig. 2. Overview of the TremorSoft user interface dialog screens: (A) Login screen; (B) Home screen; (C) Basic patient data; (D) Patient diagnostic data; (E) Sensor selection for recording hand tremor; (F) Recording hand tremor in resting position; (G) Recording hand tremor in postural position; (H) Export of records when using Xsens DOT; (I) Tremor classification result returned by the web server; (J) Confirmation of data submission and saving to the web server.

columns: Patient identification (Patient_id), Age, Gender, Family history of tremor (F_history), Classification received by ML models (Classification), Previous diagnosis of the patient (Diagnosis), Method of diagnosis (Method), Age of onset or diagnosis of the disease (O_age), Bilaterality, Treatments received (Treatments), Medication intake prior to registration (Medication), Concomitances, Comorbidities, Accelerometer signals at Rest (AccX_r, AccY_r, AccZ_r), Accelerometer signals at Posture (AccX_p, AccY_p, AccZ_p), Gyroscope signals at Rest (GyrX_r, GyrY_r, GyrZ_r) and Gyroscope signals at Posture (GyrX_p, GyrY_p, GyrZ_p).

3. Impact

The medical relevance of this e-Health App is framed in the achievement of new advances and knowledge beyond the state of the art of movement disorder testing methods, as this tool will serve as an additional evaluation technique to help differentiate pathological tremors that, in some cases, mainly in the early stages of diseases, are not easy to identify. Furthermore, compared to the one obtained with SPECT, the level of reliability that this app will achieve will be high enough to help neurologists correctly evaluate and identify movement disorders and, in turn, measure their severity. Likewise, the knowledge generated from this tool will represent a significant scientific contribution to improving the differential diagnosis of different movement disorders.

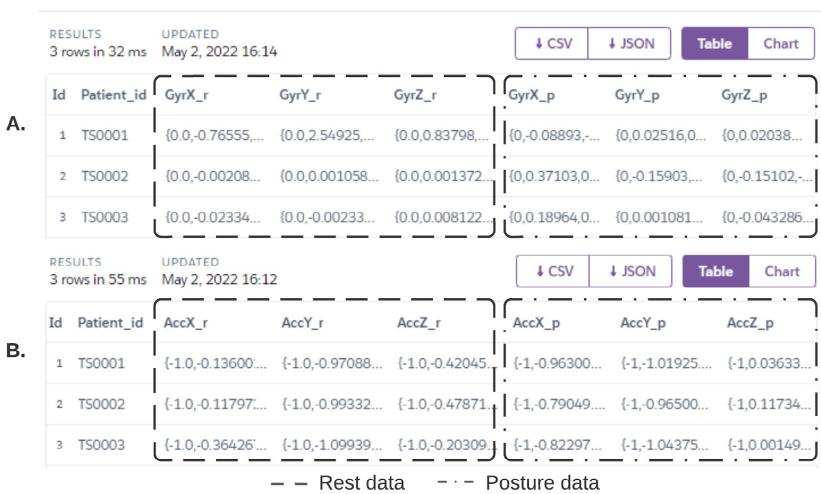
This application aims to provide more objective information to facilitate decision-making and, above all, reduce waiting times before receiving a final diagnosis, making it possible for patients to access appropriate treatment promptly. Three stakeholders will benefit from the success of the application. First, the attending physician can use the app to support the initial evaluation of the disease, especially in undiagnosed, early, or complicated cases. For the patient, correct and early treatment can positively affect the health condition, helping reduce complications and prolong the quality of life. Finally, for healthcare systems, the impact is mainly financial where. For example, in Spain, medical costs per patient with PD can amount to 17,000 € per year [15].



Id	Patient_id	Age	Gender	F_history	Classification
1	TS0001	70	Male	PD	PD
2	TS0002	67	Female	ET	ET
3	TS0003	56	Male	No	HS

Id	Diagnosis	Method	O_age	Bilaterality	Treatments	Medication	Concomitances	Comorbidities
1	PD	SPECT	62	Yes	Yes	No	No	Yes
2	ET	Clinical	64	No	Yes	No	No	No
3	HS	NA	NA	NA	NA	NA	NA	NA

Fig. 3. Patient data stored in the SQL database hosted on the Heroku server: A. Basic patient data and tremor classification; B. Diagnosis-related data.



Id	Patient_id	GyrX_r	GyrY_r	GyrZ_r	GyrX_p	GyrY_p	GyrZ_p
1	TS0001	{0.0,-0.76555,...	{0.0,2.54925,...	{0.0,0.83798,...	{0,-0.08893,-...	{0,0.02516,0...	{0,0.02038...
2	TS0002	{0.0,-0.00208...	{0.0,0.001058...	{0.0,0.001372...	{0,0.37103,0...	{0,-0.15903,...	{0,-0.15102,-...
3	TS0003	{0.0,-0.02334...	{0.0,-0.00233...	{0.0,0.008122...	{0,0.18964,0...	{0,0.001081...	{0,-0.043286...

Id	Patient_id	AccX_r	AccY_r	AccZ_r	AccX_p	AccY_p	AccZ_p
1	TS0001	{-1.0,-0.13600...	{-1.0,-0.97088...	{-1.0,-0.42045...	{-1,-0.96300...	{-1,-1.01925....	{-1,0.03633...
2	TS0002	{-1.0,-0.11797...	{-1.0,-0.99332...	{-1.0,-0.47871...	{-1,-0.79049....	{-1,-0.96500...	{-1,0.11734...
3	TS0003	{-1.0,-0.36426...	{-1.0,-1.09939...	{-1.0,-0.20309...	{-1,-0.82297...	{-1,-1.04375...	{-1,0.00149...

Fig. 4. Data from the resting and postural tremor records stored in the SQL database hosted on the Heroku server: (A) Records of angular velocities from the gyroscope; (B) Records of linear accelerations from the accelerometer.

The use of this tool could contribute to the reduction of expenses incurred on erroneous or ineffective treatments and even avoid the need to use expensive techniques or technologies. It is important to highlight that the classification given by the App cannot be considered as a definitive diagnosis, it would serve as an added value in the decision-making of physicians and movement disorder specialists. They are the ones who would execute these assessments and not the patients, taking into account other clinical criteria of the patient besides the hand tremor. Likewise, given the short time it takes to register and classify the patient, the treating physician can repeat the test if it is considered that a false positive or false negative has occurred due to an error at the time of registering the patient.

In future work, we intend to seek the collaboration of different movement disorders centers to expand the database with records of patients with confirmed diagnoses in order to perform constant improvement and maintenance of the implemented models and, thus, to have a higher degree of reliability in the classification made by the models. Taking into account the nature of the data that may be collected from both the user (Name, email, profile picture, etc.) and the patients (Age, gender, diagnosis, etc.), we will ensure that the final version of TremorSoft complies with all standards and measures imposed by the General Data Protection Regulation (GDPR) by performing the encryption of personal data, preventing unauthorized access to this data and constantly evaluating the security measures implemented. Finally, we also plan to add a new function in the mobile application that will allow sending reports to the email of physicians and specialists who use the application in their clinical routine.

4. Conclusions

This work provides a quantitative, easy-to-use, non-invasive, and cost-effective method that can be used as a supportive tool in diagnosing PD and ET based on recording the hand tremor. The tremor classification result is available in a short time during the medical evaluation by the physician, either in person or remotely. The combination of clinical information with kinematic feature information for ML model training is the key to the functionality of this tool, providing the application with increased classification accuracy. Typically, the classification of these motor disorders focuses on obtaining one or more kinematic biomarkers; however, the heterogeneity of both diseases makes this approach difficult, and we believe that complementing clinical data with kinematic biomarkers is more efficient.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Antonio J. Sánchez Egea reports financial support was provided by Polytechnic University of Catalonia. Antonio J. Sánchez Egea reports a relationship with Polytechnic University of Catalonia that includes: employment. Julián D. Loaiza Duque, Antonio J. Sánchez Egea and Hernán A. Gónzalez Rojas have patent #2206021281741 licensed to Safe Creative.

Data availability

No data was used for the research described in the article

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.softx.2023.101393.

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