Feasibility of an mHealth closed-loop system for the optimization of Parkinson's disease treatment

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***Abstract*—In this work we present the design of a treatment management system for Parkinson's disease (PD). The system is based on patient and device reported outcomes that combined with patient's health record data provide recommendations to treating physicians. The recommendations are based on a two-level system. In the first level patient data are incorporated in a clinical decision support system (CDSS) which provides a number of treatment alternatives based on expert rules and evidence-based guidelines. The second level is based on Pharmacokinetic and Pharmacodynamic (PK/PD) models enabling the evaluation of the expected benefit of each recommendation. The main components and requirements of the specific system are discussed and a real life example supporting its potential is presented.**

***Index Terms*—Parkinson's disease, clinical decision support system, mHealth.**

I. Introduction

Parkinson's disease is a progressive movement disorder. More than 6 million had PD in 2016 with the projections being that more than 12 million will suffer from it within the next 20 years [1]. Especially in low and middle income countries misdiagnosis is a very common issue. The management of Parkinson's is largely based on response to medication as reflected in improved control of symptoms. Patients' and their informal caregivers' feedback, along with the clinical examination during the visits are the main source of information for clinicians which rely on these patients reports to plan and adjust their personalised treatment.

Such personalised approaches are data driven and most effective when they take advantage of modern, widely used mhealth which includes wearable devices, mobile apps and patient portals directly and constantly updating the Electronic Medical Records (EMR) [2] with ecologically valid details about their symptoms. Health literacy and patient activation are promoted by mhealth and are important tools for the self-management of the disease.

CDSS are on the other hand used to augment and support physicians in their complex and difficult decision-making processes [3]. Recommendations and suggestions in CDSS are based on clinical knowledge extracted from clinical practice Guidelines published by Movement Disorders Societies, patient-specific data from EMRs (including medication and comorbidity), patient symptoms (motor also with medical devices, non-motor as reported by patients and relatives), and any other relevant information, e.g regarding adherence to treatment, disease-relates beliefs etc.

The concept of incorporating automated symptoms monitoring and CDSS in PD management was promoted in the PD_Manager EU project [4]. PD_Manager proposed a system architecture for tailoring treatment suggestions to physicians. The provided suggestions were based on an expert-based decision support system that could provide either treatment modifications or dose/timing changes. However, the expected improvement of each intervention using a typical rule-based system cannot be evaluated in advance. To evaluate the expected response to potential treatment changes, information from the patient health record (i.e. medication prescription) objective symptom evaluation and pharmacokinetic/pharmacodynamic models must be combined [5] to produce a model predicting the response in any change. Ursino et al. [6] have presented methods for the estimation of PK/PD models combining PK, Basial Gaglia models and measurements of finger taps as a measure of levodopa effect. Thomas et al. [7] have employed a similar approach for levodopa infusion optimization utilizing Treatment Response Scale [8] instead of finger taps. In this work the PK/PD models presented in [7] are utilized in order to evaluate the feasibility of evaluating oral medication treatment suggestions tailored by the proposed CDSS system. The goal of this manuscript is to: i) present the concept of a closed-loop treatment optimization solution, ii) present the main

PRIME is co-financed by the European Regional Development Fund of the European Union and Greek national funds through the Operational Program Competitiveness, Entrepreneurship and Innovation, under the call RESEARCH – CREATE – INNOVATE (project code: T2EΔK- 05199).

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components and the main requirements and ii) evaluate the feasibility of the solution and its potential for providing reliable estimations of expected improvement in motor symptoms for each treatment suggestion.

II. Materials and Methods

The proposed concept is presented in Figure 1. The requirements of such a system shall include:

- **Demographics and Medical History**. A FHIR (Fast Health Interoperability Resources) compatible EMR is required for the CDSS to evaluate current patient status and provide recommendations. The history should include also structured and standardized medication schedules.
- **Long term Continuous objective home monitoring**. The system shall receive longitudinal home based patient objective measurements of motor symptoms. The objective measurements should provide an estimation of symptom time profile in established scales such as UPDRS, UDysRS or AIMS (Dyskinesia).
- **Patient Reported Outcome (PROMS)**. Any automated medication change system should consider medication adherence as well as patient's perspective on symptom tolerance. In order to evaluate the efficacy of current prescription data related to adherence are required. Medication adherence could be considered for providing confidence intervals in all estimations. Moreover, higher priority should be considered for management of symptoms the patient has reported as most problematic.
- **Integrated in clinical workflows**. In order systems to have success and acceptance by physicians and nurses they should be seamlessly integrated in their daily practice.

The proposed solution that meets the main requirements consists of the following main components:

Home Monitoring Device. Patient telemonitoring has emerged as a necessary and extremely useful tool especially in the era of Covid-19. A number of telemonitoring solutions have demonstrated their efficacy including mobile apps and symptom monitoring devices [9]. The proposed solution requires both objective (device reported) as well as subjective (patient reported) outcomes for the evaluation of the efficacy of the current treatment and the patient satisfaction with that. For the remote objective evaluation of PD motor symptoms a number of medical devices with the specific intended use are available nowadays. Such devices include the PKG [1], Sense4Care [2] and PDMonitor® [3]. In this paper we have adopted the PDMonitor® device since: i) provides an estimation of UPDRS Part III score which is evaluated as a pharmacodynamic parameter and there is evidence regarding the minimum clinically important changes [UPDRS], ii) it is well suited to the proposed closed loop solution since the specific device is intended to be used for continuous

[1] www.pkgcare.com/
[2] www.sense4care.com
[3] www.pdneurotechnology.com

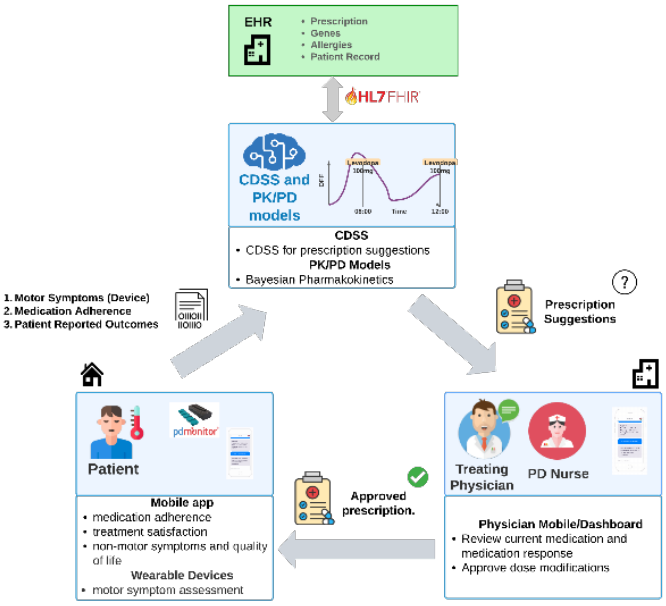

Fig. 1: Flowchart of PD Management suggestions generation.

monitoring as a patient-owned device compared to the rest of the devices which are used as Holter-like devices. The PDMonitor® is used once per month (or more depending on the severity of the disease and the efficacy of the current treatment) and the data are automatically uploaded to the cloud. The feasibility of the use of PDMonitor® device has been evaluated by 133 patients (private sales) and 52 private physicians in Greece. Physicians instructed patients to wear a device for PD motor symptom telemonitoring for one week per month, during their awake hours. For the patients using the device for 12 months, the adherence was above 70% [10]. Therefore, considering also the current population the long-term use of similar devices is feasible.

Patient Reported Outcomes (PROMs). As discussed above, PROMs are required in order to evaluate non-motor symptoms [11] and also the satisfaction with specific medication doses. PDMonitor® provides an integrated way of collecting medication adherence and patient reported symptoms (OFF, Dyskinesia and Tremor). Therefore, the PROMs are also provided by the PDMonitor® Cloud platform. Interestingly, the PDMonitor® medication adherence module is used by more than 70% of the patients when the symptom status in more than 29% [10].

PD Management Platform. It is a SmartOnFhir [12] application which coordinates the data exchange between the different system components. The Management platform may also include a table of patient identifiers on the different subsystems in order to allow the correct data exchange.

CDSS Engine. The CDSS system is based on expert rules like the ones proposed in PD_manager [4]. This was, to the best of our knowledge, the only holistic mHealth CDSS for PD as the other systems target specific symptoms. The validity and feasibility of a manager CDSS system has been evaluated

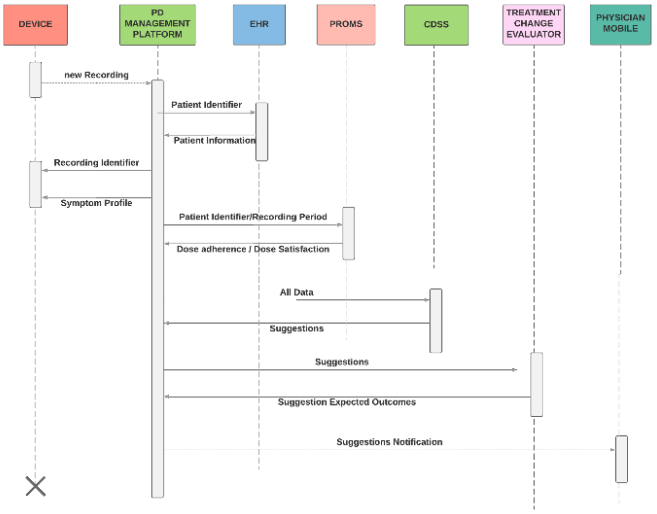

Fig. 2: Proposed closed-loop solution.

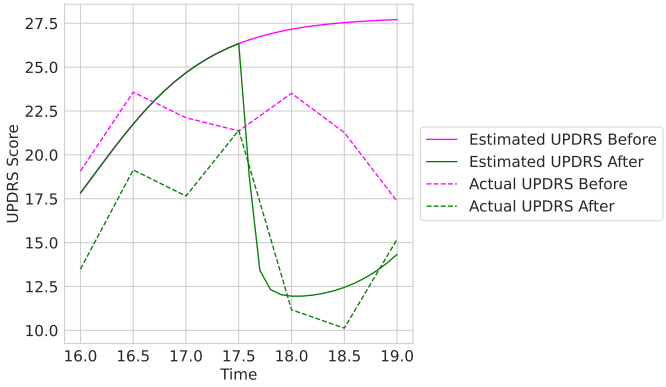

Fig. 3: Estimated and expected UPDRS Part III for the changed dose.

in previous works by Bohanec et al. [13] and Boshkoska et al. [14]. The suggested CDSS takes as input the current medication treatment of the patient (I), present motor (PDMonitor) and non-motor symptoms and epidemiologic factors (I). Then the models determine whether the current medical treatment is effective or not and suggest one or more alternative changes of medications.

Treatment Change Evaluator. This is the module where PK/PD models combined with the patient's treatment outcomes can provide an estimation of the expected response of the patient PK/PD on any new change. Changes that have clinically meaningful changes (OFF time, UPDRS Part III or IV) could be considered as candidate changes. The candidate changes are those recommended to treating physicians for consideration.

Physician App. The specific application can provide the required medical record history, a report of the current patient status and also notifications with treatment recommendations. Recommendations are prioritized based on their estimated benefit and patient reported dissatisfaction.

FHIR compatible EMR. An essential component of the specific system is an interoperable EMR that is able to provide patient record information including current prescription (FHIR MedicationRequest[4]).

In the proposed solution when a recording is performed a new patient treatment evaluation is triggered in the PDManagement Platform as depicted in Figure 2 which describes the data flow between the main system components. The PDManagement platform (SmartOnFhir) collects the required data from all connected systems in order to feed the CDSS. The CDSS system based on the expert rules and patient data provides a number of treatment suggestions. The Treatment Change Evaluator is used to evaluate the expected benefit of those suggestions including a medication change with dose add/remove/increase/decrease. PDManagement is also used as the back-end for the Physician mobile app (or dashboard).

[4]https://www.hl7.org/fhir/medicationrequest.html

III. Results

A. Evaluation of the treatment change evaluator

In this section the feasibility of using PK/PD models and sensor-based outputs for estimating the expected effect of a medication change was evaluated. R and RxODE were used for the estimation of PK/PD parameters. Data from a real-world case were used. In the specific case the physician performed a medication change and the motor symptoms response was measured with the PDMonitor before and after the specific change. Similarly to [7] a two-compartment pharmacokinetic model is considered. The UPDRS Part III outcome was also considered for the pharmacodynamics effect [15]. The differential equations for the PK/PD are the following:

$$\frac{dA_1}{dt} = -A_1 \cdot \text{KA} \tag{1}$$

$$\frac{dA_2}{dt} = \text{KA} \cdot A_1 - K_{11} \cdot A_2 + K_{12} \cdot A_3 \tag{2}$$

$$\frac{dA_3}{dt} = A_2 K_{21} - A_3 \cdot K_{22} \tag{3}$$

$$\frac{dA_4}{dt} = \text{KEO} \cdot \frac{A_2}{V_1} - \text{KEO} \cdot A_4 \tag{4}$$

$$EU = E_0 \cdot \left(1 + \frac{E_{max} \cdot A_4^{\gamma}}{A_4^{\gamma} + EC_{50}^{\gamma}}\right) \tag{5}$$

where $K_{11} = Q/V_1 + \text{CL}/V_1$, $K_{12} = K_{22} = Q/V_2$ and $K_{21} = Q/V_1$. The EU is the estimated UPDRS score. The parameters of the model used are presented in Table I. The medication prescription was also used for the estimation of the parameters. Similarly to [7] the KEO and EC50 parameters were optimized sequentially (Nelder-Mead method). Using the estimated parameters, the expected UPDRS score of the new prescription (a new dose added) was estimated and compared with the actual one measured by the device. The comparison is presented in Figure 2. The model predicted a change of **-5.9** in UPDRS score whereas the actual one was **-6.8**.

TABLE I: PK/PD Parameters

V_1	27
V_2	27
Q	0.58
CL	0.9
γ	2.5
$E_{\max}$	$-\left[\frac{(\max(\text{UPDRS})-\min(\text{UPDRS})}{\max(\text{UPDRS})}\right]$

IV. Discussion

A solution for a closed loop treatment optimization of PD patients is proposed. The system is expected to improve patients' Quality of Life and reduce the physician/PD-nurse burden. The main system components and requirements are presented. Moreover, the feasibility of each component is discussed and the novel Treatment Change Evaluator is evaluated with a specific real-world case. The PK/PD model used in this work can be further improved incorporating information about dyskinesias as additional effect and also by using a Bayesian approach for the estimation of the parameters. The adoption of PDMonitor in real world settings can lead to the streamlined collection of a large dataset with hundreds of cases with medication changes and their actual effect. Future work will include the evaluation of the accuracy of this model, as well as whether this approach can be applied in complex medication prescriptions. Moreover, this model can be used to evaluate the percentage of patients that under current practice could have treatment changes with potential significant improvements. This will have a tremendous impact on the utility of telemonitoring devices for close loop treatment solutions which are currently only encountered in limited clinical scenarios such as glucose meters. However, the success of the specific solution requires the efficient collection of patient medication adherence and satisfaction with current prescription (per dose). Proper strategies for patient empowerment and patient activation are therefore required and mhealth aims also at that. In the same context adoption from physicians and PD-nurses (depending on the health care system) is crucial. Probably the proposed mobile app and/or web-based application is the most straightforward method to integrate such a system in current clinical workflow. Feasibility, usability and user acceptance however needs to be further evaluated to ensure the success of the proposed solution. A longitudinal randomized controlled trial (RCT) study is required in order to evaluate the whole solution compared to the standard of care and provide sound evidence.

V. Conclusions

A closed loop treatment optimization system relying on body worn sensors is proposed and initially seems feasible. The proposed solution is expected to improve patient's quality of life and also reduce physician and healthcare system burden. The essential components and requirements of the system are described and their respective feasibility is evaluated. Finally, the next steps towards the implementation, validation and adoption of the specific system have been discussed.

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