2023 45th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC) | 979-8-3503-2447-1/23/$31.00 ©2023 IEEE | DOI: 10.1109/EMBC40787.2023.10340618

Monitoring medication optimization in patients with Parkinson's disease

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***Abstract*— Medication optimization is a common component of the treatment strategy in patients with Parkinson's disease. As the disease progresses, it is essential to compensate for the movement deterioration in patients. Conventionally, examining motor deterioration and prescribing medication requires the patient's onsite presence in hospitals or practices. Home-monitoring technologies can remotely deliver essential information to physicians and help them devise a treatment decision according to the patient's need. Additionally, they help to observe the patient's response to these changes. In this regard, we conducted a longitudinal study to collect gait data of patients with Parkinson's disease while they received medication changes. Using logistic regression classifier, we could detect the annotated motor deterioration during medication optimization with an accuracy of 92%. Moreover, an in-depth examination of the best features illustrated a decline in gait speed and swing phase duration in the deterioration phases due to suboptimal medication.**

***Clinical relevance*— Our proposed gait analysis method in this study provides objective, detailed, and punctual information to physicians. Revealing clinically relevant time points related to the patient's need for medical adaption alleviates therapy optimization for physicians and reduces the duration of suboptimal treatment for patients. As the home-monitoring system acts remotely, embedding it in the medical care pathways could improve patients' quality of life.**

I. INTRODUCTION

Parkinson's disease (PD) emerges with motor symptoms influencing the patient's gait with short strides and shuffling patterns [1]. The severity of the symptoms increases with the disease progression as the dopaminergic nigrostriatal pathways degenerate over time [2]. The disease advancement aggravates the gait of PD patients, increasing instability in mobility and the risk of falls [3].

Dopaminergic therapy is the dominant source of treatment to reduce the effects of motor symptoms by addressing the reduction of dopamine levels in PD patients [4]. However, chronic Dopaminergic therapy will result in symptom fluctuations and a shorter response to medication in the later stages of the disease [5, 6]. Furthermore, a high dosage of dopamine in the brain leads to an overactivation of the receptors in the striatum and the emergence of dyskinesia over time [7].

Thus, identifying the precise amount of medication that retains the patient in the symptom-free zone and avoids potential side effects is crucial and requires long-term and integrative considerations [8, 9]. Moreover, the subjectivity and short duration of the visiting time add to the complexity of drug management [10].

Home-monitoring systems using wearables and particularly inertial measurement units (IMUs) provide an objective solution with the ability of long-term observations, in contrast to the conventional methods [3].

Previous studies have investigated the differences in the spatiotemporal gait parameters among various disease stages [3] or degrees of motor impairment such as wearing-off episodes [11]. However, to our knowledge, monitoring patients' responses to medication change have yet to be investigated thoroughly.

This research examines the potential of foot-worn IMUs in monitoring the gait of PD patients while experiencing medication changes during their therapy. We contribute to improving home-monitoring systems by observing the patient's response to these changes and delivering detailed gait characteristics to clinicians for a more informed decision on managing prescriptions.

II. METHOD

A. Data Acquisition

The dataset used in this study consists of the longitudinal gait data of nine PD patients during a minimum period of sixty days. It was acquired during the "Digital Gait Care" study registered at the U.S. National Library of Medicine (ID: NCT04931303) as part of the DiGaitAppPD (digital gait analysis as a health application for therapy monitoring in Parkinson's patients) project.

The selection criteria were: patients older than 18, diagnosed with an idiopathic PD syndrome with a disease severity between one to four according to Hoehn and Yahr (H&Y) scale, able to perform the four times ten meter (4x10m) test without rest and assistance, and able to read and comprehend the instructions for using the IMUs at home. The local ethics committee (Friedrich-Alexander-University Erlangen-Nuremberg, Germany) approved the study with reference number 131_21 B. All patients gave written, informed consent before the data collection.

*This work was supported by the Bavarian Ministry for Economy, Regional Development and Energy via the project DiGaitAppPD - Digital gait analysis as a health application for therapy monitoring in Parkinson's patients (grand No. LSM-1910-0011/0012/0013/0014)

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Initially, patients visited the Movement Disorders Outpatient Clinic of the Department of Molecular Neurology at the University Hospital Erlangen. During their visit, we recorded the score of the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) [12] and gait parameters of the 4x10m test using two IMUs attached to their shoe insteps. We provided the patients with two IMUs to attach at the same positions while performing a similar test at home. They recorded the data using a mobile application designed by Systemhaus Ulm GmbH, Senden, Germany. For further gait-related analysis, the data were transferred to Portabiles HealthCare Technologies GmbH, Erlangen, Germany.

The patients performed the tests daily for a week after their first visit to the hospital. Subsequently, they conducted the tests weekly if they remained on the same medication and experienced no deterioration or side effects (figure 1). Upon receiving a change in their medication, they executed the walk tests three times a day until they acquired the best medication plan and had no deterioration (medication change in figure 1a).

Among nine patients in this study, five experienced an increase in the dopamine dosage due to bradykinesia (group 1, table I), and four had no change in their medication plan (group 2, table I).

TABLE I: Patients demographics in two groups of changed medication and unchanged medication

	Med Increase (group 1)	No Change (group 2)
count	4 male/ 1 female	4 male
Age	57 ± 5.72	69.75 ± 3.77
Disease Duration	2±0	9.5 ± 9.74
Height	172.8±8.40	176±7.78

B. Parameter Calculation

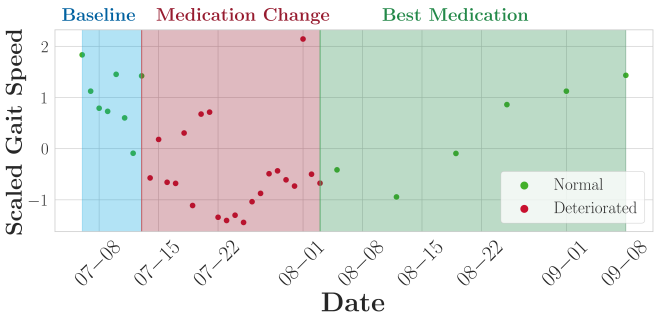
From the unsupervised recorded walk tests, we calculated a list of gait parameters consisting of stride length (cm), stride length (norm), stride time (s), gait speed (m/s), swing percentage (%), stance time (s), maximum of foot clearance (cm), heel strike angle (deg), toe off angle (deg). Since the main focus of this study is to observe the longitudinal data during the therapy, we computed the mean, standard deviation, coefficient variable, maximum, and minimum of the nine gait parameters mentioned above per day. Therefore, the feature map of each walking test consisted of 45 statistical gait-related parameters.

Every day with at least one performed walk test represents a data point during the therapy, with the gait parameters as the features of those data points. To also have a comparable stride length parameter, we computed the norm stride length by dividing the stride length by the height of the patients. Moreover, the swing percentage defines the duration of the swing phase to the relative stride duration.

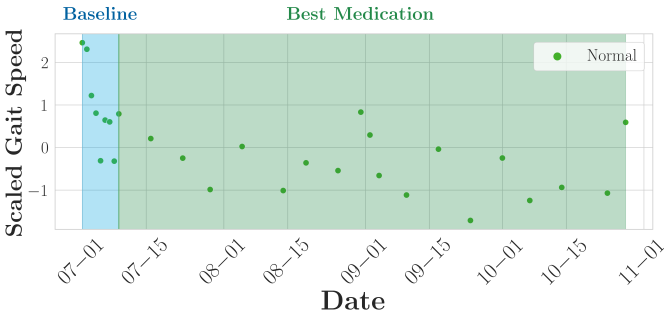
C. Labeling

We labeled the data points according to the patient's status. The period in which patients have excessive bradykinesia, more than usual, and were under medication adjustment, took the "Deteriorated" gait label. The "Normal" label was assigned to the data points after the medication adjustment completion and during the patient's optimal state (figure 1a). We repeated this procedure for the five patients who received medication adjustments due to bradykinesia (group 1 in table I).

As the patients in group 2 (table I) did not experience any changes in their plan, they received the "Normal" label for all data points (figure 1b).



(a) Patient with medication adjustment



(b) Patient with sustained medication

Fig. 1: The longitudinally recorded data of two patients. The gait data were recorded daily during the baseline and weekly in the best medication mode. The data were averaged over the three times daily recordings during the medication adjustment.

D. Classification

To assess the dissimilarities between the two labels, we approached the problem in two sections by developing different classifiers.

1) Group-1 Model: Initially, we focused on the five patients in group 1 (table I) who had a medication change. We scaled the data points of each patient individually. The patient-specific scaling represents the highest and lowest amount of every feature according to the individual characteristics of the patients. It also makes the data of different patients comparable. Due to the lack of "Normal" data points in one patient, we eliminated that patient from the further steps of this part of the method.

We appointed logistic regression for classification and determined the impactful features combined with the optimal hyper-parameters by looping through the K-best features and performing a grid search cross-validation. To measure

the classifier's performance, we applied leave-one-out cross-validation over the four patients. We also compared the mean and standard deviation of the obtained scores according to the number of features.

2) General Model: Additionally, we investigated the distinctions between the two designated labels among all patients (groups 1 and 2 together). In this approach, we scaled each feature independently over all data points since patients in group 2 did not have a deterioration phase. We then split the data into 20% for testing and 80% for training. Similar to the previous section, we selected a logistic regression model with tuned hyper-parameters using the cross-validation grid search technique. The recursive feature elimination (RFE) delivered the effective parameters separating the two groups.

III. RESULTS

A. Group-1 model

Based on our method, the mean of the scores over all four patients with the lowest standard deviation represents the best-tuned hyperparameters accompanied by the number of features selected. Our analysis illustrates that the model performs best using only the following five features: mean swing percentage, mean of maximum foot clearance, maximum gait speed, minimum stride time, and minimum stance time. Moreover, The increase in the number of features results in a decrease in the mean scores and a rise in the standard deviations (figure 2).

Further investigation of the high-weighted features shows significant differences in the gait parameters (figure 3a). The gait speed, foot clearance, and swing time significantly decline as the minimum stride time and stance time significantly increase.

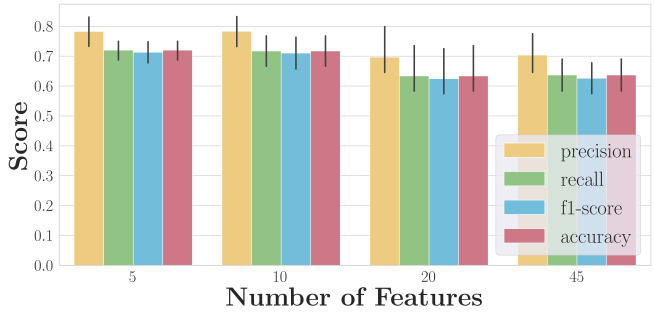


Fig. 2: The scores of the group 1 model with different numbers of features.

B. General model

TABLE II: Metrics of the general model (groups 1 and 2)

	Mean Precision	Mean Recall	Mean F1-score
Macro Average	94 %	90%	92%
Weighted Average	93%	92%	92%
Mean Accuracy: 92%			

We acquired a mean accuracy of 92% in the general model (table II). The RFE identified the mean gait speed, mean swing percentage, and CV stride length as the three most impactful features in the general model. Comparing the two labels illustrates a significant decrease in gait speed and swing percentage. Furthermore, a significant increase is visible in the CV of the stride length in the deterioration episodes (figure 3b).

IV. DISCUSSION AND CONCLUSION

Medication optimization in PD patients is a crucial matter, and the well-being of the patients is highly dependent on it during the treatment. We investigated the capabilities and potentials of home-monitoring systems to observe PD patients' responses during the optimization process. We examined the prime gait differences between the motor-related deterioration periods due to medication change and the best treatment condition. The analysis was executed initially by solely including patients who underwent medication adjustment. Later, we compared patients who had medication optimization with those who remained on the same treatment throughout the study.

In our investigations, we obtained an accuracy of 72% in classifying deterioration gait sequences from the normal gait among those with a treatment alteration (group 1 table I). While testing the model on individual patients, We observed changes in the outcome of the classifier based on the number and set of features. This shows that the changes in most gait parameters are specific to each individual. Personalized models might provide more detailed and explicit information, which requires further investigation. Nonetheless, the five most influential parameters show a clear change trend (figures 2 & 3a).

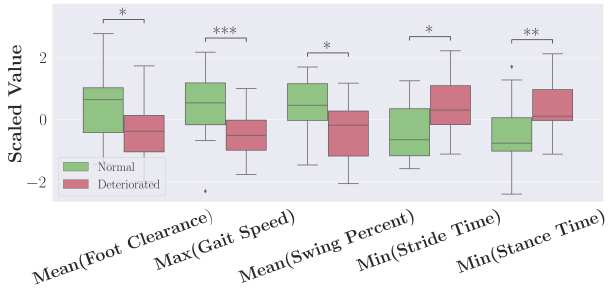
Patients prominently have a lower foot clearance, less gait speed, and less swing phase duration in the deterioration periods compared to their best treatment periods. The differences show a vivid decline in the gait quality within group 1 patients. During the deterioration phase, the gait gets slower with more foot-dragging and shuffling patterns, similar to the results of the related studies [3, 11, 13].

Our general model over the entire dataset could identify the deteriorated gait data with an accuracy of 92%. The high score exhibits a clear contrast between the two labeled events. The following two-fold reasoning can explain the higher score of the general model compared to the group 1 model.

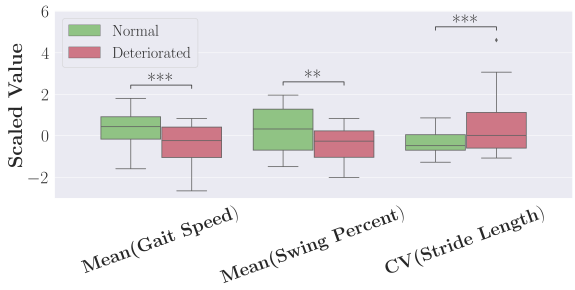
1) Higher number of training data points in the general model.
2) The decline in gait quality appears over time, which prevents a clear labeling line between the two phases.

Although longitudinal data represents a decline in gait parameters, the deterioration appears seamlessly in the data. Considering lengthier periods of stability may be a solution to this issue which needs further analysis.

The parameter analysis shows that PD patients have a slower gait cadence during the medication adjustment phase, similar to the earlier result. The lower gait speed and swing time during these periods can be representative of patients' compensation for the gait aggravation by taking



(a) Important features in group-1 model



(b) Important features in general model

Fig. 3: Significant differences between the deteriorated and normal gait parameters using paired t-tests with: *: p <= 5.00e-02, **: p <= 1.00e-02, ***: p <= 1.00e-03.

shorter strides. Moreover, the stride length parameter has a significantly higher variation during a bout and is less consistent while patients are under medication optimization (figure 3b).

The obtained results in this study depict the potential of the introduced methods in the home-monitoring paradigm in deriving meaningful information about the disease state and well-being of patients with PD. This information would assist physicians in decision-making about modifying the medication, alongside the patient's response to those alterations. The longitudinal gait data provides in-depth information on the patient's deviation from their prime state of the medication. Furthermore, the proposed system in this study can serve as a detective model in identifying responder and non-responder patients to an altered treatment. A Predictive model in identifying responders and non-responders would considerably impact the home-monitoring systems, which requires further experimentation.

ACKNOWLEDGMENT

Bjoern M. Eskofier gratefully acknowledges the support of the German Research Foundation (DFG) within the framework of the Heisenberg professorship program (grant number ES 434/8-1). The authors would like to thank PD Dr. med. Zacharias Kohl (Universitätsklinikum Regensburg), PD Dr. med. Martin Winterholler (Sana Klinik Rummelsberg), PD Dr. med. David Pedrosa (Universitätsklinikum Marburg) and Dr. med. Daniela Rau (Neuropraxis Ulm) for their contributions to this project. The authors also thank the institutes, companies, patients, and individuals involved in this project for their time and efforts.

REFERENCES

[1] Pablo Martinez-Martin et al. "Parkinson symptoms and health related quality of life as predictors of costs: a longitudinal observational study with linear mixed model analysis". In: *PLoS One* 10.12 (2015).

[2] A. H. Evans et al. "Factors influencing susceptibility to compulsive dopaminergic drug use in Parkinson disease". In: 65.10 (2005), pp. 1570–1574.

[3] Johannes CM Schlachetzki et al. "Wearable sensors objectively measure gait parameters in Parkinson's disease". In: *PloS one* 12.10 (2017), e0183989.

[4] Delphine Charvin et al. "Therapeutic strategies for Parkinson disease: beyond dopaminergic drugs". In: *Nature Reviews Drug Discovery* 17.11 (2018).

[5] Peter A. LeWitt. "Levodopa therapy for Parkinson's disease: Pharmacokinetics and pharmacodynamics". In: *Movement Disorders* 30.1 (2015), pp. 64–72.

[6] Stanley Fahn. "The history of dopamine and levodopa in the treatment of Parkinson's disease". In: *Movement Disorders* 23.S3 (2008), S497–S508.

[7] Stanley Fahn. "The spectrum of levodopa-induced dyskinesias." In: *Annals of neurology* (2000).

[8] Biljana Mileva Boshkoska et al. "Decision Support for Medication Change of Parkinson's Disease Patients". In: *Computer Methods and Programs in Biomedicine* 196 (2020), p. 105552. ISSN: 0169-2607.

[9] Fabrizio Stocchi. "The levodopa wearing-off phenomenon in Parkinson's disease: pharmacokinetic considerations". In: *Expert Opinion on Pharmacotherapy* 7.10 (2006), pp. 1399–1407.

[10] John Prince, Fernando Andreotti, and Maarten De Vos. "Multi-Source Ensemble Learning for the Remote Prediction of Parkinson's Disease in the Presence of Source-Wise Missing Data". In: *IEEE Transactions on Biomedical Engineering* 66.5 (2019), pp. 1402–1411.

[11] Hamid Moradi et al. "Detection of distorted gait and wearing-off phenomenon in Parkinson's disease patients during Levodopa therapy". In: *2022 IEEE-EMBS International Conference on Biomedical and Health Informatics (BHI)*. IEEE. 2022, pp. 01–04.

[12] Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. "The unified Parkinson's disease rating scale (UPDRS): status and recommendations". In: *Movement Disorders* 18.7 (2003).

[13] Franz Marxreiter et al. "Sensor-based gait analysis of individualized improvement during apomorphine titration in Parkinson's disease". In: *Journal of neurology* 265.11 (2018), pp. 2656–2665.