GIMO-PD: Towards a Health Technology Proposal for Improving the Personalized Treatment of Parkinson's Disease Patients

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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease and its pharmacological treatment usually has unwanted side effects (motor fluctuations, dyskinesias and other motor alterations). These effects vary from patient to patient, resulting in the use of «trial and error» manual methods by healthcare professionals to optimize treatment. The GIMO-PD project (Mobile health solution based on Genetic profile, Image analysis and the permanent Monitoring of symptoms for the personalized management of Parkinson's Disease patients) aims to present a technological solution for improving clinical decision-making on the allocation of appropriate personalized treatments according to the characteristics of each PD patient. This clinical decision support system integrates and combines patient biomarkers (such as genetic and neurological markers), motor markers (based on the computerised monitoring of activity and movement) and the digitization of clinical practice guidelines to optimise the diagnosis and treatment processes of patients with PD and to improve their quality of life.

1 INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease (Dorsey *et al.*, 2007). One of the limitations of its treatment is the appearance of unwanted effects like motor fluctuations, dyskinesias and other motor disorders. Furthermore, the way in which patients respond to treatment is not always the same, resulting in a great disparity of responses and a high degree of variability in clinical progression (Jankovic, 2005).

In medical practice, clinicians often still use a «trial and error» approach to optimizing their patients' treatments (e.g., increasing or reducing doses, deciding whether to change one drug or combine it with another). This approach typically involves high socio-economic and clinical expenses (Olesen *et al*., 2012), a problem compounded by the increase in the prevalence of PD as the population ages. There is therefore an urgent need to develop new paradigms in the PD patient care model.

Another constraint of current clinical practice is the limited monitoring of patients with PD. Clinical examinations and follow-ups are limited to short visits excessively spaced in time. The adoption of new activity and movement monitoring methodologies, and the use of new computing, storage, and data analysis techniques would allow continuous monitoring and make it possible to detect symptoms of great value for optimising PD treatments.

There are also other limitations that currently make such systems difficult to implement, such as the lack of digitization of Clinical Practice Guidelines for treating Parkinson's disease and for integrating those guidelines with other sources of clinical information (Espay *et al*., 2016).

Over the last ten years, basic clinical research has contributed a considerable amount of Clinical Knowledge based on highly effective biological markers capable of accurately predicting the evolution of PD and patients' response to treatment (Poewe *et al*., 2017). However, these markers are applied manually by healthcare professionals, causing variability in clinical practice.

This paper presents the objectives of the GIMO-PD project (Mobile health solution based on Genetic profile, Image analysis and permanent Monitoring of symptoms for the personalized management of Parkinson's Disease patients). GIMO-PD will propose a technological solution for improving clinical decision-making on the allocation of

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appropriate, personalized treatments adapted to the characteristics of each PD patient. This clinical decision support system will integrate and combine:

1. Patient biomarkers. A personalized medicine model is applied to PD, proposing the integration of information from different biological biomarkers, both genetic (drug-gene interaction and genetic risk factors) and neuroimaging (SPECT with the [123I] FP-CIT technique).
2. Motor markers based on the computerised monitoring of activity and movement. The GIMO-PD platform will include technologies based on wearable devices for detecting symptoms and motor disorders.
3. Digitization of Clinical Practice Guidelines (CPGs)[1] associated with the treatment of PD. For this purpose, our objective is to apply the Model-Driven Engineering (MDE) paradigm (Schmidt, 2006) to systematize and automate the management, definition, and execution of clinical guidelines.

The integration of these technologies for monitoring, diagnosing, and treating patients with Parkinson's disease will make it possible to optimise their diagnostic and treatment processes and thus improve their quality of life.
In this regard, GIMO-PD presents a technological proposal for integrating clinical information obtained from multiple sources (such as genetic analysis, molecular markers, neuroimaging, motor monitoring and clinical practice recommendations).

GIMO-PD also aims to further existing knowledge about the etiology of PD and introduce standard mechanisms (supported by Information and Communications Technologies) to diagnose and treat patients with this disease. These mechanisms can help define digitized clinical practice processes to establish personalized medical treatments for each patient. Another objective of GIMO-PD is to reduce the costs incurred through the ineffective use of drugs and hospital visits, expenditure which has a great sanitary and socio-economic impact. From a technological point of view, the project's application of the MDE paradigm to the healthcare context is an important innovation in terms of its potential results (reduction of errors and costs, increase in quality, etc.).

This paper is organized as follows. Section 2 presents some related works on the digitization of Clinical Practice Guidelines. To describe the background, we divided Section 3 into two sub-sections: Section 3.1 details the model driven engineering paradigm, and Section 3.2 briefly describes the project's genetic background. Section 4 explains the GIMO-PD platform, including its 5 functional modules: the clinical guide management module (Section 4.1); the decision-making module (Section 4.2); the motor control module (Section 4.3); the neuroimaging module (Section 4.4); and the genetic analysis module (Section 4.5). Finally, Section 5 presents the main conclusions and sets out some strategic considerations regarding future lines of research.

2 RELATED WORKS

This section describes some works related to the digitization of Clinical Practice Guidelines to improve the treatment of patients with specific diseases. No proposals specifically designed to improve the treatment of patients with PD could be found, but the works described here are nevertheless interesting as they provide an idea of the current state of the art in the digitization of Clinical Practice Guidelines in general.

Laleci *et al.* (Laleci Erturkmen *et al.,* 2019) presented and implemented a semi-automatic care plan management tool integrated with clinical decision support services. The tool seamlessly accessed and assessed patients' Electronic Health Records (EHRs) to suggest personalised recommendations for individually customized care plans.

Jimenez-Molina *et al.* (Jimenez-Molina *et al.*, 2018) proposed a framework for the development of chronic disease support systems and applications as a solution to shortcomings in the integration of applications and existing healthcare systems, the reusability of technical knowledge in the creation of new systems and the use of gathered data in the generation of new knowledge.

El-Sappagh *et al.* (El-Sappagh *et al*., 2018) proposed a semantically fuzzy, rule-based system framework for diabetes diagnosis using multiple aspects of knowledge—fuzzy inference, an ontological reasoning process, and a fuzzy analytical hierarchy process—to provide a more intuitive, dynamic, accurate design.

Aborokabah *et al.* (Aborokbah *et al.,* 2018) proposed a context-aware clinical decision support model for heart failure risk prediction. The proposed

[1] CPGs are sets of systematic statements which provide health professionals and patients with a basis on which to take decisions about the healthcare responses most appropriate in specific clinical circumstances (Field & Lohr, 1990).

model was evaluated using a dataset of potential heart failure patients with metrics including prediction accuracy, sensitivity, specificity and receiving operating characteristic.

Afzal *et al.* (Afzal *et al.*, 2017) proposed an automated knowledge acquisition methodology with a comprehensible knowledge model for cancer treatment based directly on information in existing cancer treatment documents. This methodology is supported by software tools and is helpful in finding hidden knowledge in clinical documents. It is also generalizable to other domains as a means of assisting clinicians in decision making and education.

Pombo *et al.* (Pombo *et al.*, 2016) presented a Clinical Decision Support System (CDSS) based on data imputation principles for pain evaluation. The system produced tailored alarms, reports and clinical guidance based on collected patient-reported data.

After analyzing previous related works, we can identify some specific contributions of our paper: (1) The application and validation of the technological solution in a poorly treated disease through the digitization of clinical guidelines (that is, PD); (2) Previous works are focused on the follow-up of patients and their treatments, while GIMO-PD integrates the use of neuroimaging techniques, mobile technologies for the detection of motor symptoms, genetic and pharmacological information; (3) The use of MDE-based mechanisms to systematize the technological development of the platform.

3 BACKGROUNDS

3.1 Model Driven Paradigm

In the context of GIMO-PD, the objective of the model-driven engineering (MDE) paradigm was to improve the automation and digitization of the clinical practice guidelines associated with the treatment of Parkinson's disease.

The MDE paradigm (Schmidt, 2006) emerged in response to the complexity of software systems, making it possible to express the concepts of the problem domain in an effective manner. The paradigm defines models and establishes transformation rules based on those models to generate new, more technologically oriented models. These mechanisms are intended to increase automation during the software development life cycle.

To implement this new paradigm in real projects, standardization was necessary. OMG standardized the use of the MDE paradigm using Model Driven Architecture (MDA, 2003). MDA defines transformation rules between models until source code or another model with the characteristics of a particular technology are obtained. It is based on the following four types of levels or models as shown in Figure 1:

- ICM (Independent Computing Model). This is considered the highest and the most abstract level of business model.
- PIM (Platform Independent Model). This represents the business process and system structure model. These models are not related to any one specific technology.
- PSM (Platform Specific Model). This is specifically related to the platform where the system is to be implemented: for example, operating systems, programming languages or middleware platforms.
- Source code. This refers to the appropriate coding and implementation of the system.

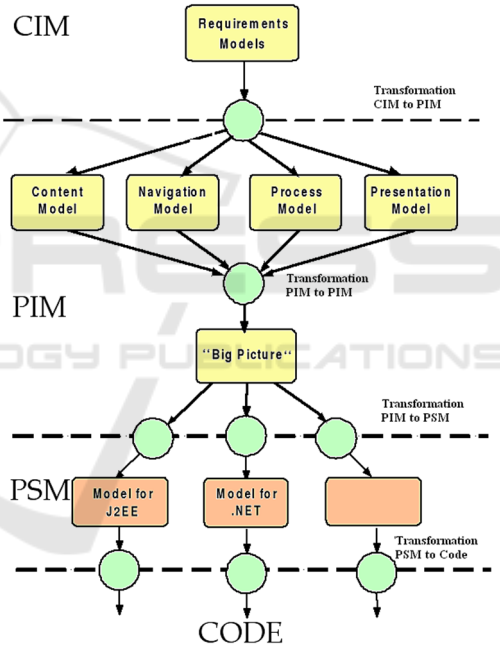

Figure 1: Model-Driven Engineering.

MDE has big advantages for software development. It provides specific, relevant results in software projects. The systematic generation of models based on previous models assures traceability through levels and can potentially cut down development time. If suitable tools were defined, this process could also even be automatic.

3.2 Genetic Background

GIMO-PD proposes the joint integration of information from different biological biomarkers

(genetic and neuroimaging) with movement analysis and the digitalization of clinical guidelines, making it possible to apply personalized medicine models to PD patients.

Genetics can impact patient profiles through drug-gene factors and genetic risk factors:

1) Drug-gene factors. Genes can modulate a person's response to drugs, and the study of this interaction is called pharmacogenomics (Grant, 2001). Studies have been carried out in recent years into the benefits of certain drugs in the treatment of PD. Some, for example, focussed on correlating the clinical responses of patients who had received different doses of the drug levodopa with their activity (Bialecka et al., 2008; Cheshire et al., 2013). These studies also identified a relationship between clinical responses and the SLC6A3 gene that encodes the dopamine transporter. That same gene is related to levadopa absorption. A comprehensive review of pharmacogenetics pertaining to PD can be found in the literature (Kurzawski et al., 2015; Politi et al., 2018).
2) Genetic risk factors. Genes can also predispose patients to certain motor and non-motor symptoms. To adapt the patient's treatment and improve her quality of life, these genetic factors must therefore be taken into account. The genetic risk factors associated with symptoms of Parkinson's disease have been identified in different research papers. They include increased risk of cognitive impairment (Foltynie et al., 2009), risk of visual hallucinations (Redenšek et al., 2019), and risk of severe movement control disorders (Napier et al., 2015; Redenšek et al., 2019).

4 GIMO-PD ARCHITECTURE

The GIMO-PD platform will have five functional modules with which to achieve its objectives (see Section 1):

1. Clinical Practice Guidelines management model. This covers the definition, execution and monitoring of clinical guidelines, and their integration with external systems.
2. Decision-making module. This module considers combination of the information collected from the neuroimaging, genetic analysis, and motor control modules to establish a clinical recommendation.
3. Motor control module. This includes technologies based on wearable devices for detecting symptoms and motor disorders.
4. Neuroimaging module. This analyses DAT-SPECT images and provides quantitative, objective information about the patient's condition.
5. Genetic analysis module. This proposes the integration of information from different biological biomarkers.

The above modules will be integrated into a software platform based on Cloud-computing to host, exchange and process all genetic, neuroimaging and motor monitoring information. Figure 2 shows the architecture of the GIMO-PD platform.

The core of this platform is the clinical guidelines management module, which will provide recommendations to be followed by health professionals. These recommendations will be established after analysing the genetic, neurological, and motor variables of the patient. The analysis will be carried out in conjunction with the Clinical Decision Support System (CDSS). It will include machine learning algorithms trained with experimental clinical data.

The project's genetic and neurological analysis will include a chemical component to determine which genetic variants described in the literature influence the evolution and treatment of the disease. The genetic variables identified are then included in the CDSS. The patient's pathological situation will also be evaluated by neuroimage analysis.

With regard to the management of motor and non-motor markers, the GIMO-PD platform will include mechanisms to monitor these aspects. On the one hand, it will include the design and development of a wearable bracelet with sensors to monitor the patient's motor function and detect motor complications. On the other, non-motor markers will be periodically checked with short scales and validated using the patient's smartphone.

The objective of each module is explained in detail below.

4.1 Clinical Practice Guidelines Management Model

This GIMO-PD module will run the CPG management life cycle. This includes the definition, execution and monitoring of clinical guidelines, and their integration with external systems. To achieve these goals, the module has three main sub-modules:

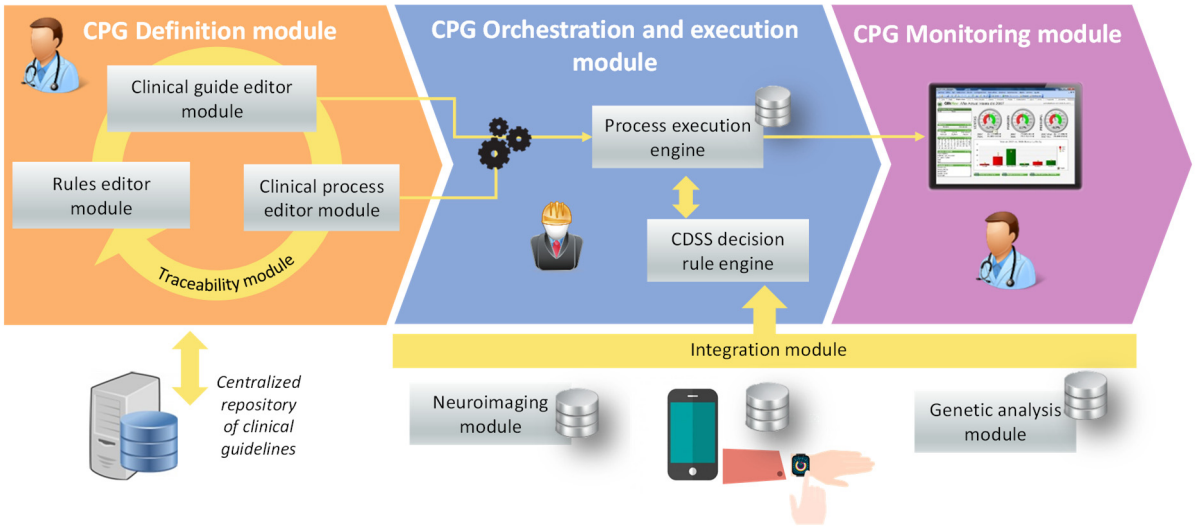

Figure 2: GIMO-PD: towards to model-driven software architecture.

1. Definition sub-module. This will contain model-driven mechanisms (based on MDE principles; see Section 3.1) for defining static CPG models. For this purpose, a set of domain-specific metamodels and languages will have been designed to describe activity flows, clinical recommendations, clinical variables, decision rules, etc. All these aspects are essential to define any clinical guideline. This sub-module will also include a set of transformation rules to obtain an executable version from a previously defined static model. The executable version can then be deployed in the execution sub-module.
2. Execution and integration sub-module. This sub-module will comprise a process engine for executing the static CPD models defined in the previous sub-module. It could be considered the core of GIMO-PD because it will be responsible for orchestrating communications with the other modules on the GIMO-PD platform. It will also provide the user entry point to the platform.
3. Monitoring sub-module. This sub-module will monitor the healthcare professional's performance and task flow. For this purpose, the platform will define key performance indicators related to running instances, average running time, etc.

4.2 Decision-Making Module (CDSS Decision Rule Engine)

Clinical practice guidelines provide protocols for establishing quality diagnoses and treatments. Although these guidelines are usually quite broad, however, they are descriptions that do not fully cover all the casuistry associated with evaluating clinical variables to make an optimal decision. This module will complement the clinical guideline execution module by providing additional functions for improving evaluation and decision-making.

In this module, the GIMO-PD platform will include a Clinical Decision Support System (CDSS). CDSSs are decision systems that provide specific recommendations based on the knowledge model that feeds them (Liu et al., 2006).

The CDSS collects information from the neuroimaging, genetic analysis, and motor control modules. Once the combination of this information has been considered, a clinical recommendation can be established.

GIMO-PD's clinical decision module will be designed and developed considering two design techniques: (1) Rule Based Reasoning (RBR) (Shoaip et al., 2019), which establishes a set of clinical rules considering specific clinical criteria and recommendations previously defined in CPGs ; and (2) Case Based Reasoning (CBR) (Li *et al.,* 2018), which will be capable of automatically generating clinical rules after analysing prior knowledge stored, for example, in knowledge bases.

The module's hybrid design is due to the intrinsic characteristics of the GIMO-PD project, in which most of the on-park data comes from previously diagnosed and treated cases. Diagnosis and treatment of Parkinson's disease requires the analysis both of patient information and of historical information (based on previously populated knowledge bases). In this regard, the application of CBR techniques makes

it possible to automatically generate rules, thus complementing the rules defined by the clinical practice guide using RBR techniques.

4.3 Motor Control Module

Tremor is a primary symptom and one of the most disabling general symptoms of Parkinson's disease (Ruonala *et al.*, 2013). In fact, it is one of the aspects most evaluated by health professionals to determine the progression of the disease. The monitoring and evaluation of motor symptoms in PD is mainly based on historical information and neurological examinations (usually biannual). These methods have many drawbacks: (1) the data may be subjective, because it depends on the patient's memory and perception of his own symptoms (and his ability to identify symptoms and medical terminology); and (2) the data are highly dependent on the experience of the healthcare professional.

Many research articles have analysed parkinsonian gait to try to detect movement disorders (Cifuentes et al., 2010). However, there is a significant handicap. These movements are disturbed by other factors (lack of balance, trunk bent forward, stiffness, tremor, etc.) which are not isolated and usually cause a high rate of false positives and negatives. This makes it difficult to determine exactly what movement the patient is making at any given moment. It is also important to mention that these motor symptoms depend on each patient and their degree of illness. The study of a PD patient's gait is therefore a field that still requires protracted research if useful results are to be obtained.

In this context, GIMO-PD presents a technological proposal for identifying motor disorders in patients with Parkinson's disease. The platform will include technologies based on wearable devices for the detection of symptoms and motor disorders. The wearable nature of these devices facilitates their continuous, non-invasive use to capture kinematic information through inertial sensors, and also through lifelong learning techniques.

4.4 Neuroimaging Module

Image quantification techniques are common in medical research, but their complexity has historically prevented their effective use in clinical practice.

As a solution to this problem, GIMO-PD proposes integrating neuroimage analysis and clinical practice. For this purpose, this module will include functionalities and machine learning algorithms for analysing SPECT (single photon emission computed tomography) images with the [123I] FP-CIT[2] technique. This technique makes it possible to visualize DAT[3] (Dopamine Active Transporter) activity and detect presynaptic dopaminergic deficit. This is useful in the early diagnosis of Parkinson's disease and also in differentiating the disease from other nondegenerative parkinsonian disorders.

DAT-SPECT image analysis provides quantitative, objective information on the patient's condition, which can then easily be compared with historical patient data and clinical knowledge bases. By comparing data in this way, the clinical specialist can specify the patient's situation more accurately.

4.5 Genetic Analysis Module

In GIMO-PD, a personalized medicine model will be applied to PD, proposing the integration of information from different biological biomarkers, both genetic and neuroimaging. As explained earlier in Section 3.2, genetics play a key role in defining patient profiles in two areas: drug-gene interaction and genetic risk factors.

GIMO-PD will offer a catalogue of genetic biomarkers identified in the literature as being relevant to patients' responses to treatment (pharmacogenetic interaction), the evolution of Parkinson's disease, and the appearance of certain symptoms (genetic risk factors). These biomarkers are useful for prognosis and as predictors of response to treatment.

5 CONCLUSIONS AND FUTURE RESEARCH

Parkinson's disease is the second most common neurodegenerative disease, and its pharmacological

[2] Single-photon emission computed tomography with ioflupane (123I), also known as 123I-FP-CIT SPECT, is the most widely used complementary test in this type of diagnosis. (Olivares Romero & Arjona Padillo, 2013).

[3] The dopamine transporter (DAT) is responsible for clearing dopamine from the synaptic cleft after its release. Imaging DAT availability measures dopamine terminal functionality and provides a method for detecting states of striatal dopamine deficiency in idiopathic Parkinson's disease and atypical neurodegenerative parkinsonian disorders such as multiple system atrophy and progressive supranuclear palsy (Brooks, 2010).

treatment usually has undesired effects (motor fluctuations, dyskinesias and other motor alterations).

This paper details a software platform for improving clinical decision-making and providing individual Parkinson's disease patients with the treatment most appropriate to their own personal characteristics. This platform is going to be named GIMO-PD: a project for applying a personalized medicine model to Parkinson's disease. To achieve this objective, GIMO-PD will integrate information from different data sources: biological biomarkers (both genetic and image), analysis of movement disorders observed while monitoring patients in real time, and clinical information from clinical practice guidelines for the treatment of Parkinson's disease.

Regarding future lines of work, this project can be expanded in several ways. One area of study would be to look at new functionalities of the GIMO-PD platform and the monitoring of more parameters when analysing patient movement disorders. The project might also be extended to address other diseases, taking into account i) different parameters when monitoring patients and ii) the recommendations of different clinical guidelines specific to other diseases.

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