An integrated ontology-based model for the early diagnosis of Parkinson's disease

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Abstract. In our days there is no single test or biomarker that can predict whether a particular person will develop Parkinson Disease and a definitive diagnosis is only possible after death, with postmortem analysis. Recent discoveries have highlighted that defects in mitochondrial dynamics are associated with neurodegenerative disease. In this paper the general architecture of an integrated multi-scale ontology-based modeling technology for early diagnosis of PD and for progress monitoring is proposed. The proposed model will be used to identify physics and biology-based biomarkers of processes occurring at radically different scales, from cell to whole body.

Keywords: Parkinson Disease, ontology-based modeling, mitochondrial dynamics, neurodegenerative disease, biomarkers

1 Introduction

The Parkinson's disease (PD) is just one of the several neurologic movement disorders that produce similar symptoms. It affects about 2% of the population at some time in life [1]. In certain cases patients rapidly become totally disabled; in others, the disease progresses extremely slowly; and in yet others, illness is chronic and may have more severe symptoms as time goes on. Due to the fact that the physical properties, or evolution, of these diseases varies greatly, proper diagnosis is crucial.

Today there is no single test or biomarker that can predict whether a particular person will develop PD and a definitive diagnosis is only possible after death - with post-mortem analysis [2]. The brain changes that create neurodegenerative diseases such as PD are microscopic, on a chemical level and are not revealed by the following scans:

- Laboratory testing of the blood of patients with the symptoms typical of Parkinson's only rarely uncovers any abnormality.
- Electroencephalograms (EEGs) record some aspects of brain electrical activity, but they are not effective in spotting Parkinson's.
- The MRI and CAT scans of the brain produce remarkable and exquisite anatomic pictures.

- The MRI and CAT scans of the brain of people with Parkinson's disease appear normal. The brain of people with Parkinson's disease appears normal.

With no specific diagnostic tools, physicians must prove their scientific diagnosis for PD based on the physical examination of the patient and some general symptoms. Physicians are intimately familiar with the characteristic history and the signs and symptoms found when examining a person with Parkinson's. Then, they have to judge how closely the history of symptoms and the neurologic findings of any specific person match those of typical Parkinson disease. Non blood or lab tests can definitively diagnose PD, while the pathological causes of the disease have not been specified yet.

PD pathology is now known to start in the lower brain stem and ascend rostrally to the dopaminergic pathways of the midbrain and beyond to the neocortex, in a predictable, temporospatial pattern. This process may occur at different rates in different patients with PD, but takes essential the same route, providing an attractive explanation for symptoms that precede motor dysfunction. Research has failed to determine why these brain cells begin to die or why they continue to die.

The molecular pathogenesis of PD is still not understood, while at least two forms of PD exist: idiopathic (sporadic) and heritable (familial) [3]. The majority of PD cases are sporadic with unclear aetiology [1]. However 10% of PD cases are inherited and linkage analysis has identified a number of PD-associated genes, as well as disruption of mitochondrial dynamics [4-7]. Additionally, after years of intense studies, a considerable number of scientific researches demonstrated the important role of mitochondrial dysfunction and oxidative stress to development of the more common neurogenerative diseases, like Alzheimer’s disease, Parkinson’s disease and Huntington’s disease [8].

Recent discoveries have highlighted that neurons are reliant particularly on the dynamic properties of mitochondria. In addition, mitochondria are actively recruited to sub cellular sites, such as the axonal and dendritic processes of neurons. Defects in mitochondrial dynamics are associated with neurodegenerative disease [6].

Two genes identified in hereditary PD are Pink1 and Parkin, both of which have been shown to be important for mitochondrial integrity [7]. In the same research [7] has been proved that Parkin is specifically recruited to mitochondria with low membrane potential and these targeted mitochondria are then destroyed through the autophagosome. The mitochondrial accumulation of Parkin is voltage dependent, and does not depend on changes in pH or ATP levels. These experiments suggest that Parkin may act as a sensor for mitochondrial integrity and trigger mitophagy upon dysfunction. It is unclear whether Pink1 is involved in this pathway. Recent genetic studies in flies suggest that Pink1 and Parkin act to promote mitochondrial fission or inhibit fusion [9]. Concluding, this short review in PD studies, interpretation of the functions of Pink1 and Parkin have been complicated by the discrepancies in mitochondrial morphology defects, found among various mammalian cell lines and between the fly and mammalian model systems. Such complexity is also apparent in studies of Alzheimer’s disease (AD) and Huntington’s disease (HD) [6].

Furthermore, PD is no longer considered only as a movement disorder; it is a neurophysiological and neuropsychiatric disorder with many non-motor symptoms

that can be as or more debilitating than the motor symptoms [10]. Developing in parallel with this broadening view of the disease is the recognition that we need to widen our therapeutic arsenal by not only focusing on medical treatment of motor symptoms, but also including non-medical therapies. Exercise is one of the most useful non-medical therapies for patients with PD. Exercise can improve strength and balance, help with weight management, alleviate depression and improve quality of life [11].

Aspects of the patient history that suggest PD include gradual onset and steady progression. The United Kingdom Parkinson Disease Society (UKPDS) Brain Bank (BB) has published Diagnostic Criteria that are widely accepted and used for diagnosing PD in clinical practice and for research purposes. According to the UKPDS BB criteria for PD, signs must include bradykinesia and at least one of the following: muscular rigidity, rest tremor or postural instability.
In addition, patients should not have any atypical features, such as early memory loss, early hallucinations, severe dysautonomia, cerebellar signs, or supranuclear gaze palsy. Finally, a list of supportive criteria that increase the probability of idiopathic PD is included, such as asymmetric onset, maintained asymmetry over time and response to levodopa [12].

Considering the above, we present the general architecture of an integrative multi-scale ontology-based modelling technology in a more theoretical base which manages to identify physics and biology-based predictive models of processes occurring at radically different scales, from cell to whole body. The initial clinical data of the proposed model include neuropsychological test scores, brain tissue samples, genetic material (DNA and RNA) and their mutations, molecular data (metabolomics and proteomics), imaging data (MRI imaging, PET (FDG/PIB) imaging), electrophysiological data (TMS/EEG), biomarkers detected from blood (metabolomic, proteomic), patient's history data and demographic data (i.e. age, sex). The proposed model also take as input measurement data of mitochondrial dysfunctions (such as mitochondrial DNA, four mitochondrial complexes, pH and ATP levels and energy potential in the inner mitochondrial membrane) in order to define novel biomarkers. Until now, although the role of mitochondrial dysfunctions in PD have been identified [4-6], it is not clear how and why these dysfunctions cause PD symptoms.

The proposed approach is based on the complete model that has been proposed in [4] for the description of dysfunctions in the mitochondrial membrane and it's denoted as the phenomenon of 'electric thromboses'. According to this phenomenon, electric complexes result higher concentration of protons H+, leading to the interruption of the normal flow of electrons, resulting the inadequate production of ATP. This phenomenon affects the energy requirements of the cell and the required electrical capacity of mitochondrial membranes.

2 The general structure of the proposed model

The general structure of the proposed model is described below (Figure 1):

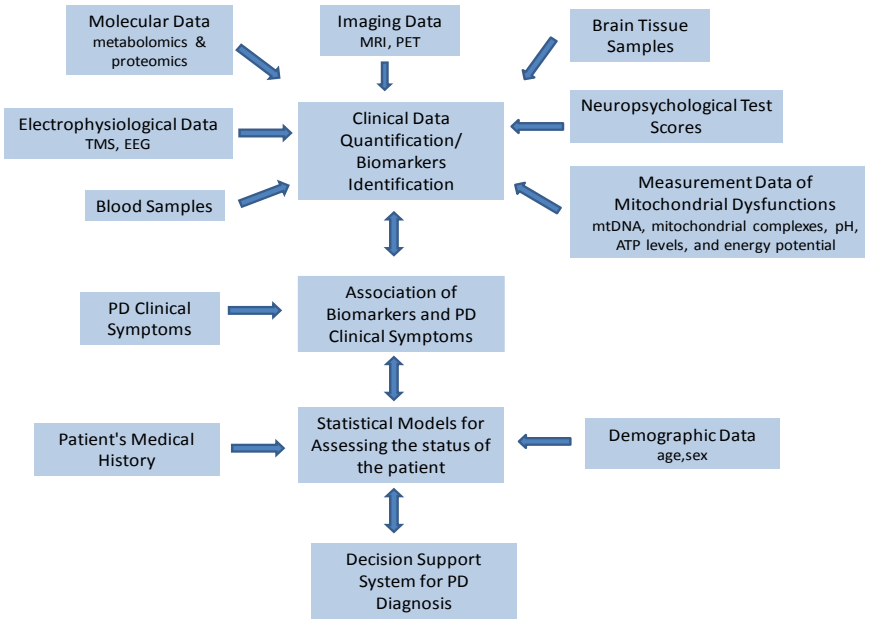

Figure 1: The general structure of the proposed model

1. At the first level, the unit models represent the association of already mentioned heterogeneous patient clinical data. Artificial Intelligent techniques can be developed and applied for extracting various biomarkers from these data, and combining this biomarker information.
2. At the second level, new models integrate the above models, associating the identified from the above level biomarkers with PD symptoms. PD should be regarded as a multi-regional, multi-system neurodegenerative disorder in which the pathology appears in a regionally specific sequence [11]. The classic motor features of PD typically start insidiously and emerge slowly over weeks or months, with tremor being the most common initial symptom [13]. The three cardinal signs of PD are resting tremor, rigidity, and bradykinesia. Postural instability (balance impairment) is sometimes listed as the fourth cardinal feature. However, balance impairment in PD is a late phenomenon and in fact, prominent balance impairment in the first few years suggests that PD is not the correct diagnosis. Nonmotor symptoms can be categorized as autonomic, cognitive/psychiatric and sensory [14] and may include depression, dementia, hallucinations, rapid eye movement (REM), sleep behaviour disorder (RMD), orthostatic hypotension, and constipation. Nonmotor symptoms can also fluctuate, especially depression, pain, numbness, paresthesia/dysesthesia, akathisia and restless-legs syndrome. Recognition of nonmotor symptoms of Parkinson disease is essential for appropriate management [14].
3. At the third level statistical models for assessing the status of the patient will be developed. Thorough statistical analysis of combined biomarkers

will be used to define the relevance and efficiency of sets of biomarkers. These models will take as input the output of the above models and for the producing of the final decision will take into consideration other factors such as patient's medical history, the age and gender of the patient during the analysis.

4. Finally, a decision support system will be developed, predicting if the patient has the PD and if yes, the current status of the patient. Depending on the stage of disease (early or advanced), the system will also propose the corresponding treatments. The goal of medical management of PD is to provide control of signs and symptoms for as long as possible while minimizing of adverse effects is occurred. Latest studies demonstrate that a patient's quality of life deteriorates quickly if treatment is not instituted at or shortly after diagnosis [15]. The main criterion for the evaluation is the diagnostic accuracy. In addition, the cost-effectiveness of various combinations of biomarkers in PD diagnostics should be studied. This information will be used to optimize diagnostic protocols.

For the validation of the proposed model researchers can use retrospective patient data and can also create patient groups consisted of patients with PD in different stages of the disease.

3 Ontology-based modeling and XML standards for early diagnosis of PD

A critical challenge in neuroscience is the accessibility, organization and management of the tremendous quantity of neuro-scientific knowledge. In the case of question, in order to combine or import the already mentioned separately models into an integrated model we have to uniquely identify the terms that each model uses. In order to achieve this, we figured a controlled vocabulary of terms for describing gene product characteristics and gene product annotation, as well as tools to access and process this data by using ontology-based modeling, which combine structured vocabularies with a small set of relationships between their components. In the literature a few ontology-based models have been proposed for modeling PD. More specific, Rubin et al. [16] proposed an ontology-based model of neuroanatomy to enable symbolic lookup, logical inference and mathematical modeling of neural systems. The authors applied this model in the case of PD based on the fact that in this disease there is degeneration of neural elements, leading to a decrease in the activity of the direct basal ganglia pathway relative to the indirect pathway activity. Well-known examples of biological ontologies also include the Gene Ontology project (www.geneontology.org) and BioPAX (www.biopax.org). Such ontologies can be used to provide unique biological identification for each component in the proposed PD model.

Open source ontology editors and knowledge-based frameworks for pathological alterations of neural circuits in PD can be also used, such us the Protégé platform (http://protege.stanford.edu/) that provides a growing user community with a suite of

tools to construct domain models and knowledge-based applications with ontologies. At its core, Protégé implements a rich set of knowledge-modeling structures and actions that support the creation, visualization, and manipulation of ontologies in various representation formats. Protégé can be customized to provide domain-friendly support for creating knowledge models and entering data. Furthermore, we will use the ontology-based model of neuroanatomy proposed by Rubin et al. [16] to enable symbolic lookup, logical inference and mathematical modelling of the PD neural systems.

In order to store the already mentioned computer-based biological models and exchange them with others, an XML markup language standard which will be compatible with others standards has to be developed, such as the CellML (http://www.cellml.org/) and FieldML (http://models.fieldml.org/fieldml). This standard will allow scientists to share models even if they are using different model-building software. It also enables them to reuse components from one model in another, thus accelerating model building. Combined, these languages will provide a complete vocabulary for describing biological information at a range of resolutions from the subcellular to organism level.

4 The proposed system functionality and core components

The layout of the proposed overall system is presented among with the main entities in the following figure (Figure 2):

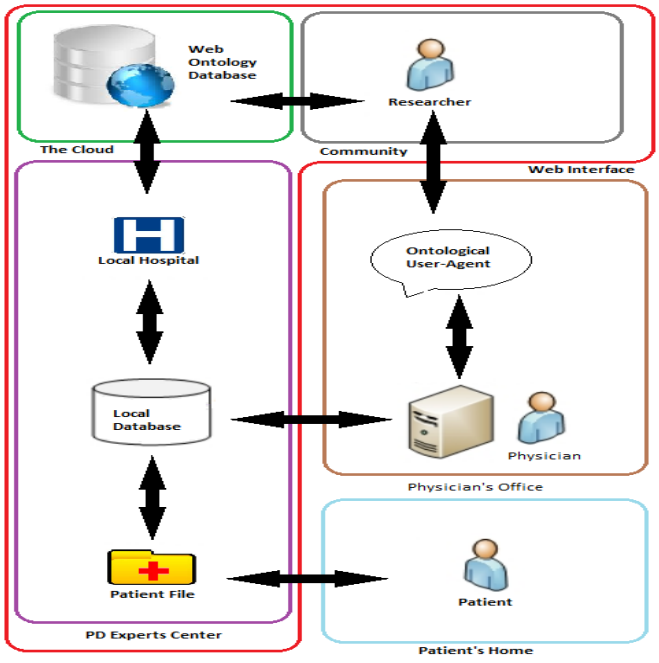

Figure 2 The proposed system

Specifically, the main components of the proposed system are:

1. The web ontology database: Central role in our system plays the web ontology database containing the semantically organized knowledge-base which the user-agent will use in order to produce responsible decision support to the medical personnel. Situated on the cloud, it relies on the user community for maintenance.
2. The user-agent: It is the application used by the medical personnel that provides the access point to the knowledge base. Hosted either along with the database (as a web service) or installed in the physician's computer, it implements the ontological modeling scheme that we are planning to develop. The user-agent provided by the necessary clinical data and history of a patient (patient's file) will query the web ontology database and produce decision support for the medical personnel to use. A second procedure supported by the user-agent is feedback. After the decision support, a physician can validate the application's correct results and report the wrong ones. This feedback will be sent to the community to improve the model. Also for the sake of further improving the model, the patient's health and treatment are monitored and recorded.
3. The PD expert center: It is responsible for all the clinical trials and tests and keeps all results in electronic form in the local database; therefore user-agents will have the most updated personalized information regarding the patient's status and health. Furthermore, if a patient followed by the program, is hospitalized, their clinical data are constantly monitored and the same decision support is provided, along with summarized, visualized information to the hospital's medical personnel. Finally the hospital may also post feedback to the community for review.
4. The patient: They can be part of the system, in case that intensive home care is needed. In this occasion a medical network of several sensors and automations are integrated within the patient's environment to provide a continuous stream of on-line data as if the patient was in the hospital.
5. The scientific community: Their operation is to curate and maintain the web ontology database as well as to manage and evaluate the feedback from various user-agents and hospitals. This way the system will continue to improve by adding to the knowledge base. A robust community dynamic may well be able to widen the scope of the system, depending on the acceptance from physicians and researchers alike.

5 Conclusions

PD is recognized as one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years. Estimates indicate that 4 to 6 million people have been diagnosed with PD. Parkinson disease is a clinical diagnosis. No specific blood tests or diagnostic studies are currently available to make the diagnosis [2]. In addition, no laboratory biomarkers exist for the condition, and

findings on routine magnetic resonance imaging (MRI) and computed tomography (CT) scan are unremarkable. In the general community, there is also a high diagnosis error rate between Parkinson disease and essential tremor.

Considering the above, it is obvious that future treatments are born of today's unmet needs. In this paper the general architecture of a software tool for early diagnosis of PD and for progress monitoring is proposed in a more theoretical base. The backbone of the tool is the statistical integrated ontology-based model including information about numerous biomarkers measured from a high number of data. The proposed system will generate new knowledge of biomarkers characteristic to PD. To achieve these goals, a combined effort incorporating information from genetic/clinical data, development of innovative integrated systems that combine multi-parametric data and application of complex algorithms is required.

The proposed model will help physicians to decide more easily and faster what treatment to give to patients with PD, providing different treatment options in individual patients. An early diagnosis may enable physicians to provide medical care at an earlier stage, at a time when clinical diagnosis using only signs and symptoms of disease is challenging. Early diagnosis combined with future drugs and prevention strategies will also delay or stop the onset or the progress of PD. This can be shifted directly to reduced costs of PD prevention and treatment.

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