A Study On Home Based Parkinson’s Disease Monitoring and Evaluation:

Design, Development, and Evaluation

by

Di Pan

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Graduate Supervisory Committee:

Diana Petitti, Chair
Robert Greenes
William Johnson
Rohit Dhall

ARIZONA STATE UNIVERSITY

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ABSTRACT

Parkinson’s disease, the most prevalent movement disorder of the central nervous system, is a chronic condition that affects more than 1000,000 U.S. residents and about 3% of the population over the age of 65. The characteristic symptoms include tremors, bradykinesia, rigidity and impaired postural stability. Current therapy based on augmentation or replacement of dopamine is designed to improve patients’ motor performance but often leads to levodopa-induced complications, such as dyskinesia and motor fluctuation. With the disease progress, clinicians must closely monitor patients’ progress in order to identify any complications or decline in motor function as soon as possible in PD management. Unfortunately, current clinical assessment for Parkinson’s is subjective and mostly influenced by brief observations during patient visits. Thus improvement or decline in patients’ motor function in between visits is extremely difficult to assess. This may hamper clinicians while making informed decisions about the course of therapy for Parkinson’s patients and could negatively impact clinical care.

In this study we explored new approaches for PD assessment that aim to provide home-based PD assessment and monitoring. By extending the disease assessment to home, the healthcare burden on patients and their family can be reduced, and the disease progress can be more closely monitored by physicians. To achieve these aims, two novel approaches have been designed, developed and validated. The first approach is a questionnaire based self-evaluation metric, which estimate the PD severity through using self-evaluation score on pre-designed questions. Based on the results of the first approach, a smart phone based approach was invented. The approach takes advantage of the mobile computing technology and clinical decision support approach to evaluate the motor
performance of patient daily activity and provide the longitudinal disease assessment and monitoring. Both approaches have been validated on recruited PD patients at the movement disorder program of Barrow Neurological Clinic (BNC) at St Joseph’s Hospital and Medical Center. The results of validation tests showed favorable accuracy on detecting and assessing critical symptoms of PD, and shed light on promising future of implementing mobile platform based PD evaluation and monitoring tools to facilitate PD management.
DEDICATION

I dedicate this work to my advisors, Dr. Diana Petitti, my mom Xia Tian and my dad Zian Pan, and all my friends who supported me in any respect during the completion of this work.
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CHAPTER 1
INTRODUCTION AND BACKGROUND

Parkinson’s Disease (PD) is a progressive neurodegenerative disorder, which influences 0.3 percent of the U.S population, and up to 3 percent of population over 65 ages in the world (1, 2). As the most common movement disorder, PD can cause significant disability and decreased quality of life(3). The course of the disease is chronic and progressive, and may be complicated by a wide range of motor and non-motor features(4). When PD becomes clinically overt, tremor, rigidity, bradykinesia, and postural instability become the cardinal signs of the disease(5). Although PD remains an incurable progressive disease, modern treatment can substantially improves quality of life and functional capability. Current therapy based on augmentation or replacement of dopamine is successful in improving patients’ motor performance in early stages of disease(6). However, the management of advanced PD becomes more complex. For PD patients who receive levodopa treatment for more than 5 years, the vast majority of them experience motor complications in the form of motor fluctuation and dyskinesia. These levodopa-induced complications constitute a substantial problem in the long-term management of PD. Current medical approaches to manage the motor complications include manipulation of the medication dosage and frequency, according to the assessment of disease status change and progress of symptoms. However, since PD evaluation is mostly conducted in clinical setting during patients’ visits, the decline and improvement of symptoms between the clinic visits can only be tracked through subjective reporting by patients to physicians. This methodological weakness, to some extent, prohibits physicians to make more informed decisions from a closer monitoring...
on disease progress, and limits the information for predicting long-term disease progression from research perspective. Moreover, frequent clinic visits also increase the clinical burden of PD management, as well as the physical and economic burden for PD patients’ family. To fill the information gap between two clinic visits and to reduce the patients’ physical burden as well as the care of burden, we conducted an initiative study to explore a tentative home based PD assessment and monitoring approach, by taking advantage of mobile computing, machine learning and advanced sensor technologies. This approach aims to provide a quantitative and objective evaluation approach to measure Parkinson’s disease status in home based environment, which could be used as an extension to current clinical setting based evaluation in long term PD management. In this study, two approaches have been explored, including initial methodology design, development, validation, clinical test results, and feasibility discussion. The first approach, which is based on patient self evaluation questionnaires, is described in CHAPTER 2. With the preliminary results of the self evaluation questionnaires, we further designed a smart phone based PD evaluation approach in CHAPTER 3, which takes advantage of the 3D accelerometer integrated in smart phone to provide Parkinson’s disease motoring and evaluation.
1. Parkinson’s Disease

1.1. Epidemiology

1.1.1. Prevalence and Incidence

Parkinson’s disease (PD) is the most common movement disorder besides essential tremor, and the second most common neurodegenerative disease(3). Early onset of sporadic PD is rare, with about 4% of patients developing clinical signs of the disease before an age of 50 years(7). The incidence of the disease rises steeply with age, from 17.4 in 100,000 persons between 50 and 59 years old to 93.1 in 100,000 persons between 70 and 79 years old, and increase to 3% ~ 5% in people 85 years older, while a lifetime risk of developing the disease is 1.5% (8-10). The median age of onset is 60 years and the mean duration of the disease from starting diagnosis to death is 15 years, with a mortality ratio of 2 to 1(11). Although PD has been found in all ethnic groups, it has geographical difference. It is found more common in developed countries.

1.1.2. Risk factors

Although etiology of PD still remains unclear, current studies suggest that a combination of age, genetic and non-genetic factors are involved together in PD etiology(12). Similar to other neurodegenerative diseases, aging is the major risk factor. Although 10% of people with PD are younger than 45 years of age, the PD incidence rate in subjects more than 85 years old was about 14 times that observed in subjects aged 56 to 65 years(13). Evidence from prospective long term studies also suggests that higher age at motor onset is the major denominator of more rapid motor progression in PD (14, 15). Other than age, gender has also been found a risk of developing PD. It has been reported males, particularly in the older age groups, have a higher incidence rate, around
1.5 times more likely than women to develop Parkinson’s disease (16). However, in younger PD patients less than 60 years at onset, several studies found no differences in incidence of PD between men and women (17). The environmental factors and living style have also been reported to be related to PD development. It has been found that smoking cigarette, drinking coffee and tea can lower the risk of incidence of PD, but consistently exposure to pesticides increases the risk (18, 19). Although smoking, tea and coffee have been shown to influence the onset of PD, they appear not to impact the rate of motor progression in overt PD (20-22).

Family history is also an important risk factor that closely associated with the risk of PD. The patients who have family members affected by PD are at 3 to 4 fold increased risk to develop the disease comparing to others in general population (11, 23). Due to this aggregation of PD within families and pedigrees, a genetic cause of the disease has been hypothesized for several decades. From the genetic studies in the recent decades, several gene loci have been found to be associated with the Parkinsonism. Some of them were found to be associated with autosomal-dominantly (24-27) or recessively (28-30) inherited parkinsonism, while others such as the most recently identified leucine-ripcle repeat kinase 2 (LRRK2) mutations appear to cause parkinsonism resembling sporadic PD with respect to both clinical and demographical features (31). The discovery of these genetic mutations and the increased understanding of dysfunction of their aberrantly encoded proteins have provided important and novel insights into the molecular pathogenesis of the disease. There is now compelling evidence that impairment of the ubiquitine-proteasome system, mitochondrial dysfunction and decreased oxidative stress tolerance are key pathological mechanisms in PD pathogenesis (32, 33). However, the exact
mechanisms are not completely understood, and monogenetic causes only account for a small proportion (<10%) of all PD cases, while the vast majority of PD cases appear to be sporadic. In these sporadic PD cases, occupational, lifestyle and environmental factors, possibly interacting with each other and with susceptibility genes, may play a part.

1.2. Clinical Features and Symptoms

The initial presentation of PD is with onset of a rest tremor, impairment of dexterity or, less commonly, with a slight dragging of one foot. The onset is gradual and the earliest symptoms might be unnoticed or misinterpreted. When PD becomes clinically overt, tremor, rigidity, bradykinesia, and postural instability are considered to be the cardinal signs of the disease (5). The course of the disease is chronic and progressive, and may be complicated by a wide range of motor and non-motor features.

1.2.1 Cardinal Signs

Rest tremor (4 ~ 6 Hz frequency) is the most common cardinal sign at motor onset. Roughly around 30% of individuals do not have rest tremor at onset, (34), and 25% of patients with PD never develop tremor. Rest tremor usually appears maximal when the limb is at rest and disappears with voluntary movement and sleep, and is worsened by excitement, anxiety, or apprehension. It affects to a greater extent the most distal part of the limb and at onset typically appears in only a single arm or leg, and then becomes bilateral later. The rest tremor is usually a pronation-supination tremor that is described as "pill-rolling"; a term used to describe a circular movement of the tips of the thumb and the index finger when brought together. Such term was given due to the similarity of the movement in PD patients with the former pharmaceutical technique of manually making
pills(35). As opposed to essential tremor, rest tremor in PD is not improved with alcohol intake(34).

Rigidity is characterized by increased resistance to passive stretch of skeletal muscles, and is frequently seen with PD. Rigidity may be associated with joint pain; such pain being a frequent initial manifestation of the disease(34). When PD patients’ limbs are passively moved by others, a "cogwheel rigidity" is commonly observed(34). Cogwheel-like refers to the ratcheting jerks by which the articulation is moved as opposed to the normal fluid movement: when a muscle is externally tried to be moved, it get resist at first but with enough force it is partially moved until it get resist again, and only with further force it will be moved(34, 36). The combination of tremor and increased muscle tone is considered to be at the origin of cogwheel rigidity.

Bradykinesia, referring to slowness of movements with difficulties in initiating and maintaining motions, is the most characteristic clinical feature of PD, and is associated with difficulties along the whole course of the movement process, from planning, initiating to finally executing of a movement(34). The performance of sequential and simultaneous movements is also hindered(34). Bradykinesia is the most disabling symptom in the early stages of the disease(36). Initial manifestations of bradykinesia are problems when performing daily life tasks requiring fine motor control such as writing, sewing or getting dressed(34). Clinical evaluation is based on similar tasks such as alternating movements between both hands or feet(36). Bradykinesia is not equal for all movements or times. It is modified by the activity or emotional state of the subject to the point that some patients barely able to walk may be capable of riding a
bicycle(34). Generally patients have less difficulty when external cues are provided (34, 37).

Postural instability, although is not typical at disease onset, becomes a common complication of advanced PD in late disease stage. Postural instability usually causes impaired balance and frequent falls, and also leads to bone fractures(34). Instability is often absent in the initial stages, especially for younger people(36). Up to 40% of the patients may experience falls and around 10% may have falls weekly, with number of falls being related to the severity of PD. It is produced by a failure of postural reflexes, along with other disease related factors such as orthostatic hypotension or cognitive and sensory changes(34).

1.2.2. Motor Symptoms

Besides the four cardinal signs of PD, the individuals with PD also show one or more other motor symptoms in the course of PD. The motor symptoms can be generally grouped to gait and posture disturbance and speech and swallowing related disturbance. Shuffling of gait, freezing of gait, dystonia and festination are usually the typical gait and posture disturbance appearing in PD patients (38). Among these gait and posture symptoms, the freezing of gait (FOG) is one common symptom affecting advanced PD patients in their daily livings. FOG describes patients’ difficulty moving their feet and may become apparent as start hesitation, turn hesitation, destination hesitation, or halting when walking (39). FOG often occurs suddenly, and the frequency and severity of FOG increases with the progression of PD. Dystonia is a disorder occasionally found in Parkinson’s disease, which causes uncontrollable and painful spasms in parts of body. Dystonia is very uncommon in untreated patients and is more frequently seen as a
complication of PD treatments(12). Festinating gait (FSG) is a unique disturbance of locomotion associated with Parkinsonism. FSG is observed in PD as rapid and small steps, done in an attempt to keep the center of gravity in between the feet while the trunk leans forward involuntarily and shift the center of gravity forward(20). Other than gait and posture disturbance, the speech and swallowing disturbances include voice disorders and mask-like face expression (14).

In the very majority of patients with PD, the initial motor symptoms are localized to the upper extremities(40), then spread to the other ipsilateral limb within one to three years, and affect the contralateral limbs in three to eight years(41). The asymmetrical pattern, however, usually persists during the course of the disease, even in advanced stages(42). Severity of bradykinesia, rigidity, and gait and balance progress similarly, while tremor severity appears to be rather stable over time, possibly indicating different underlying pathophysiological processes.

1.2.3. Non-motor Symptoms

Although the symptoms of PD are typically observed as motor disturbance, the vast majority of PD patients also experience non-motor problems during the course of their disease. In a cross-sectional clinic-based study of 99 PD patients, only 12% of them have not experienced any non-motor problems after seven years of disease duration(43). The non-motor symptoms usually include sleep disturbances, autonomic dysfunction, olfactory deficits, sensory complaints, and in particular a wide range of neuropsychiatric problems including cognitive impairment and dementia. These non-motor symptoms may also lead to substantially decreased functioning and quality of life of patients(44).
The cognitive impairment and dementia are two major non-motor symptoms that attract much more attention in PD management. Cognitive impairment can occur in the initial stages of the disease and sometimes even prior to diagnosis, and is progressive with duration of the disease (8, 34). Patients with cognitive impairment usually find that they have difficulties in planning and carrying through tasks, paying attention, word-finding, learning and memorizing information(45). The severe cognitive impairment can lead to dementia, which is a more severe decline in multiple mental abilities, including but not limited to memory. The dementia can interfere with daily living and lead to trouble at home or at work, or in social situations, and results in the patient’s inability to live independently in severe condition (46).

1.2.4. Motor Complications

The course of PD is frequently complicated by variations in motor response. Motor complications comprise dyskinesia, which are episodes of abnormal involuntary movements involving head, trunk, limbs, and motor fluctuations, describing a transient decline in motor performance(47). The presence and development of dyskinesia and motor fluctuations are associated with each other and both features increase in frequency and severity with the duration of disease(31, 48). Around 1/3rd of patients develop motor complications within four to six years after disease onset(49), and dyskinesia and “end of dose failure” is experienced by almost all patients past 15 years of disease duration(15).

Motor fluctuations in PD are induced by taking levodopa, which is an effective medication in controlling PD symptoms and used by almost all patients with Parkinson’s disease. The motor fluctuation mainly represents in two patterns: “Wearing-off” fluctuations and “On-off” fluctuations. Patients with “Wearing-off” pattern develop a
predictable worsening at the end of the current dose because of the short-duration benefit after a given dose of levodopa. “On-off” fluctuations are characterized by sudden and unpredictable shifts between on and off states. This produces off states in a random fashion such that patients cannot predict when the next will occur. These episodes vary in time, are unrelated to medication dose, and occur suddenly. Most patients with “On-off” pattern also experience “Wearing-off”.

1.3. Diagnosis

There are two approaches usually used to diagnose Parkinson’s disease in clinical practice: 1) functional neuroimaging and 2) clinical criteria. Although functional neuroimaging is useful in the differential diagnosis of PD and more or less frequently used in everyday practice, the common diagnosis of PD is still conducted at the clinic visits by using clinical criteria to provide a diagnosis of probable PD. A diagnosis of PD requires the presence of at least two of the following cardinal signs: rest tremor, rigidity, bradykinesia, asymmetrical onset, and the absence of atypical features such as severe postural instability, frequent falls, autonomic, pyramidal or cerebellar features, eye movement disorders, or lack of response to dopaminergic treatments (50).

Parkinson’s disease is by far the most common cause of bradykinesia (51). Among the four cardinal signs, the bradykinesia is the most important diagnostic criteria, without which the diagnosis of Parkinson’s disease cannot be made (38). Although individuals with monosymptomatic rest tremor who have abnormalities of striatal dopamine on functional imaging exist. Bradykinesia can display in rigid facial expression, as well as the slow ability to express emotions. Speaking might also be slow, quiet, and lack in rhythm and melody. The rapid repetitive finger tapping of the index finger on the thumb
for about 20s on each hand is a commonly used clinical test. Bradykinesia of the lower limbs can be assessed by fast foot tapping and walking.

The rest tremor (within 4~6 Hz), which might be the only evident when the part of body is truly at rest, is another important characteristic associated with Parkinson’s disease diagnosis. Young patients (<40 years of age) frequently present with tremor, which is more severe on legs and noted when lying or sitting, whereas older patients (>70 years of age) might have tremor on jaw, chin, lips, and tongue (38). Although the presence of rest tremor is helpful for the diagnosis of Parkinson’s disease, a similar tremor can occur in some cases of dystonic and atypical tremor syndromes (52). Besides rest tremor, essential re-emergent postural tremor as well as an action tremor can also be seen in Parkinson’s disease (53).

Flexion of the limbs and trunk is also a characteristic of Parkinson’s disease. The flexion of limbs and trunk can represent in a variety of ways on different individuals. Some patients have transient fixed hand posturing after completing a motor task. Some patients have motor impatience with a difficulty finding a comfortable position to rest their limbs, and few have striking mirror movements. Absent arm swing, a mild flexion of arm at elbow, can be one of the earliest clues to diagnosis.

Besides the above clinical signs of PD, other well-known signs of PD include late-onset postural instability, decreased olfaction, and micrographia. In diagnosis of PD, patients must also respond to an adequate therapeutic challenge of levodopa or a dopamine agonist. For detail description of symptoms and signs associated with Parkinson’s disease, please refer to results of related studies (51, 54).
1.4. Treatment

Although Parkinson’s disease is still an incurable progressive disease, treatments can substantially improve the quality of life and motor function of capacity. Treatments of PD mainly focus on symptom management, and include motor symptom and non-motor symptom management. Symptomatic therapy for Parkinson’s disease should be initiated at the onset of functional impairment. In early-stage disease management, the treatment with monoamine oxidase-B (MAO-B) inhibitors, amantadine, or anticholinergics may modestly improve mild symptoms. However, most patients need levodopa or a dopamine agonist when there is functional impairment. Levodopa is the most effective pharmacologic agent for Parkinson’s disease and remains the primary treatment for symptomatic patients (6, 9). Levodopa is particularly effective at controlling bradykinesia and rigidity(6); However, speech, postural reflex, and gait disturbance are less likely to respond. In general, for early-stage PD, a dopamine agonist is initiated for patients with mild disease with onset at a younger age, whereas levodopa is initiated for older patients with severe motor symptoms.

The late-stage Parkinson’s disease includes patients already received carbidopa/levodopa treatments who have developed motor complications. After five years of treatments with levodopa, about 40% patients develop to motor fluctuation(1). Patients may experience a “wearing-off” and “on-off” effects in motor complications. These motor complications can be treated by adding a dopamine agonist, MAO-B inhibitor, or catechol O-methyltransferase (COMT) inhibitor (9, 55). Dopamine agonists have demonstrated the function to significantly reduce “off” time, improve motor impairment and disability, and reduce the need for levodopa(32). The COMT inhibitors
also show the ability to decrease the degradation of levodopa and extend its half-life, thus relieve the end-of-dose wearing-off effect and reducing “off” time(56).

However, with the progress of PD to late-stage, the pharmacologic intervention may hard to effectively improve motor function and reduce motor fluctuations. When PD develops into this stage, surgical treatment becomes the last therapeutic option to improve the motor functions. Deep brain stimulation (DBS) of the subthalamic nucleus has demonstrated the effect to improve motor function and reduces motor fluctuations, dyskinesia, and antiparkinsonian medication use. Unilateral pallidotomy is another surgery treatment for PD, which is an effective symptomatic adjunct to levodopa and can treat motor complications. However, the unilateral pallidotomy is used less often because it causes destructive lesions(57).

2. Current PD management strategies

As described in Parkinson’s disease treatment part, the primary disease management on PD is through the pharmaceutical therapy to control the symptoms and improve the motor function. Current therapy based on augmentation or replacement of dopamine is successful in improving patients’ motor performance in early stage disease. However, the management of advanced PD is complex. For PD patients who receive levodopa treatment for more than 5 years, the vast majority of them experience motor complications in the form of motor fluctuation and dyskinesia. These levodopa-induced complications constitute a substantial problem in the long-term management of PD. Current medical approaches to these motor complications include manipulation of the medication dosage and frequency, according to assessment of disease status change and progress of symptoms. Therefore, in order to optimize the outcome of PD management
and make informed decision on medication plan, physicians need to accurately assess the
PD status from the represented symptoms and also estimate the disease progress.

2.1. Disease Assessment Tools

Due to lack of in vivo biomarkers and the current limitations of functional
neuroimaging methods as surrogate markers of disease progression in PD(33), clinical
assessment using established clinical rating scale remains the gold standard in charting
the course of the disease. Because the manifestations of PD are complicated, and include
motor symptoms to non-motor symptoms, and the influence of PD is diverse and
different for each individual, various clinical assessment tools have been used for
evaluating various aspects of Parkinson’s disease, including motor and non-motor
severity and disability in patients with PD. Although many of them have not been
sufficiently evaluated for reliability, some of them have been validated and used widely
in clinical practice by clinical professionals, such as UPDRS (Unified Parkinson’s disease
Rating Scale)(58) and Hoehn and Yahr scale(59). Other than the disease severity
assessment, some other evaluation scales are primarily used as patient self-reporting from
the influence of PD on quality of life and social-economic perspectives, including PDQ39
scale and MCSI scale (60, 61). To provide a through coverage on influence of PD in
patients’ quality of life, the UPDRS scale is usually accompanied by additional measures
focusing on other aspects of Parkinson’s disease and their influence on patients’ life, such
as the Beck Depression Inventory (BDI), Fatigue Severity scale, Care Burden scale,
Sleep scale, Cognitive scale, and etc(21, 61-63).
2.1.1. UPDRS

In current Parkinson’s disease assessment, the Unified Parkinson’s Disease Rating Scale (UPDRS) is the most widely used primary clinical rating scales for PD evaluation, which was introduced in 1987 by an international group of movement disorders specialists (64). The UPDRS was designed to follow the longitudinal course of the disease and has been shown to be both reliable and valid to provide a comprehensive but efficient and flexible measurement to evaluate PD-related disability and impairment (24). The maximum total score of UPDRS is 132 points. These 132 points are composed of 4 parts, each of which focuses on one dimension of PD evaluation (Part I, Mentation, Behavior and Mood; Part II, Activities of Daily Living; Part III, Motor; Part IV, Complications). Despite its strengths, the UPDRS was revised to adapt to recent scientific advances, particularly to better capture the wide spectrum of non-motor problems experience by patients with PD. In these four parts, Part I and Part II of UPDRS can be answered by patients via self-evaluation. However, Part III Motor and Part IV Complications, the substantial two parts to evaluate PD symptoms severity and patients’ disability, can only be rated by a clinician professional in a clinic setting. In addition, the rating of the UPDRS heavily relies on raters’ subjective assessment, and has limited sensitivity to detect small change in disease progression. The rating of Part III and Part IV have become a regular routine in PD patients’ visits, and charted as a standard evaluation part in movement disorder program, to provide longitudinal information on the disease progress. In this study, we also used UPDRS scale as gold standard to evaluate PD severity, which was rated by movement disorder experts.
2.1.2. Hoehn & Yahr

The Hoehn & Yahr scale was devised in 1967 and is another main scale used in PD (59). It measures the stage of the disease by including both impairment and disability of movements, balance, and gait. The scale was initially allocating 6 stages from 0 (no signs of disease) to 5 (wheelchair bound or bedridden unless assisted), and later stages 1.5 and 2.5 have been added (65). In stage 1 the disease is confined to one side of the body (unilateral). In stage 2, the disease is bilateral but there is no problem with balance. In stage 3, postural instability becomes an issue. In stage 4 there is severe disability but the patient is still able to walk or stand. In stage 5, the patient is wheelchair bound or bedridden unless aided. However, non-motor features are not captured by this scale.

2.1.3. PDQ39

Other than the PD assessment scales rated by clinicians, another noteworthy scale, the Parkinson Disease Questionnaire (PDQ39), is a self-evaluation scale commonly used for PD patients’ self assessment. PDQ39 is composed of 39 questions from 8 dimensions (Mobility, Activities of daily living, Emotional well being, Stigma, Social support, Cognitive impairment, Communication, Bodily discomfort), which could provide general information about patients’ feeling and disease impact on their lives (60). Although PDQ39 has shown its value for measuring quality of life of Parkinson’s disease patients, it is limited in providing diagnostic information for physicians’ clinical decision making (66, 67).

2.2. Socioeconomic effect

Since PD is chronic and progressive, and is currently still an incurable disease, this disease places a substantial burden on patients, their families and carers, as well as on
society as a whole. PD can severely affect the health-related quality of life (HR-QOL) of both patients and their carers, and also induce high economic cost.

Over the course of the disease, the HR-QOL of patients is affected by factors such as depression, motor complications, education and surgery, with the change of PD progress. The motor complications, including motor fluctuation and dyskinesia, are the primary factor to result in deterioration of quality of life. Several studies have found that the motor fluctuations and levodopa-induced dyskinesia can significantly worsen patient HR-QOL\(^{(54, 68, 69)}\). The depression is another major detrimental factor on HR-QOL, associated with sleep disturbance, cognitive decline, occurrence of falls\(^{(70)}\), and is one of the most common psychiatric disorders in PD\(^{(52)}\).

The economic outcomes associated with PD are of particular importance not only to patients, but also to their families and the society\(^{(11)}\). The economic costs of PD are mainly contributed by cost of care burden, which are particularly high for patients in advanced stages of the disease and those with motor complications\(^{(71)}\). The economic and health burden of PD also result in increasing healthcare costs and major reduction in the HR-QOL of both patients and their families. The total annual cost of the PD was estimated to be 13,800 Euros per individual \(^{(72)}\). Due to the progressive nature of PD, costs increase with disease severity. The economic costs of PD are significant associated with PD severity, with costs increasing as the disease progresses and doubling from Hoehn and Yahr (H&Y) stage I to V\(^{(19)}\). In H&Y stage of V, the direct annual costs were estimated to be nearly 30,000 Euros\(^{(19)}\). The direct costs include medical (drugs, physician visits etc) and non-medical services (special care, transport, equipment). The direct costs of PD account for the major part of economic burden of the disease,
particularly in early stages of PD, and increase substantially with clinical progression of symptoms(73). The indirect costs can include changes in worker productivity, absence from work and decreased earning ability. They also include certain intangible costs, such as pain, suffering and reduced HR-QOL. The largest components of indirect costs are the hours required for informal caring and the earnings lost by both patients and their families. With more advanced stage of the disease, the fraction of indirect costs increase, approximately 25% after 5 years and 80% after 9 years, because many patients become unable to work(25). For patients with motor fluctuations, the mean costs are three times higher than those without motor fluctuation, and cost doubling with each H&Y stage(11).

2.3. Challenges

Although life expectancy and control of motor symptoms and tremor have improved with new treatments for Parkinson’s disease, motor complications and cognitive impairment in advanced disease still face important unmet therapeutic needs. The challenges can be divided from disease assessment and therapeutic treatment challenges. In terms of therapeutic challenge, the control of cognitive impairment and postural instability, are still important unmet therapeutic needs. Furthermore, no neuroprotective treatment can arrest the underlying disease progress, and dopaminergic therapy is far from perfect in controlling motor disability (38). Since the goal and application of this study mainly aim to resolve the disease assessment challenges, we will mainly focus on these challenges in this part.

As the disease progresses, motor disability and non motor problems have to be managed efficiently. To manage motor complications, the physician is required to modify the medication plan according to disease progression and appearance of new symptoms.
Although the current most widely used PD state assessment method, UPDRS, has been approved its validity and reliability in assessing PD progress, it can only be applied in a clinic setting under the supervision of a trained clinical observer(24). Therefore, in order to capture disease status change, PD patients have to repeatedly visit a clinic in person during long-term PD management, which is time consuming, economically burdensome, and brings extra care burden for patients with motor disability(34). In addition, current PD assessment is mostly conducted via brief observation by a clinical professional during a patient visit. The assessment is based on the patient’s performance at a specific time during the visit, not on a comprehensive assessment based on the comparative performance of a patient over an interval of time. In long term management, most clinical trials assesses the UPDRS scores at baseline and at 3 months interval, precluding detection of change on a weekly or monthly basis(62). Thus, the improvement or decline of disease status is hard to capture by clinicians during the period between two visits. This prevents clinicians from making the most informed decision about the course of therapy for Parkinson’s patients and could negatively impact clinical care.

Another deficiency in current PD management is that PD disease assessment in a clinic setting is not able to effectively track and evaluate motor fluctuation, which requires continuous assessment of PD motor-related symptoms over a period of time. Motor fluctuation is one significant medical therapy-induced complication, which is marked by On-Off status. For patients using levodopa, a widely used medication to control Parkinson’s disease symptoms, the time efficacy of the medication (On-time) gradually decreases, as a result of which the PD symptoms come back earlier (Off time). To overcome the decrease of On-time while using this medication, increased levodopa
dosage is one solution used in early PD disease management. However, the increase of levodopa dosage also induces peak-dose dyskinesia, which appears as restless movement of a patient. Once motor fluctuations appear, therapeutic treatment should be individualized to retain optimal control of the symptoms based on accurate assessment of each patient’s levodopa cycle and responses to drugs. Because the on-off-on cycle refers to the several hour period after taking the medication, the change of motor performance with medication effect declining and peak-dose dyskinesia are hard to observe on an outpatient basis. In current PD management, due to lack of effective monitoring and evaluation tools that could track motor performance change over time, clinicians can only roughly estimate patient motor fluctuation by asking patients when they took their medication. This difficulty prevents clinicians from making an optimal medication plan based on patient motor fluctuation.

3. Prospective Home-based PD Assessment

Considering the limitation of current PD assessment approaches, the home-based PD assessment is a potential solution to fill the information gap by extending the clinical based PD evaluation to patients’ daily livings. Although many self-evaluation scales for PD exist in current PD management, such as PDQ 39, most of them aim to provide information about quality of living and are not related to clinical assessment. So it is hardly to use current available approaches to assess PD severity and progress for physicians’ decision making and longitudinal disease tracking. In this study we will explore the new approaches for PD assessment in home-based environment. Two novel approaches have been designed and developed in this study, and the preliminary testing and validation have been performed on PD patients. The first approach is a self-
evaluation scale based approach, which estimates the PD severity by using the patients’ self-evaluation answers on pre-designed questions. Based on the result of the first approach, the second approach is more advanced, which takes advantage of the mobile computing technology and clinical decision support approach to collect the PD related patients’ motion data in their daily life and provide the disease assessment and monitoring for physicians in long term disease management. Both approaches have been validated on recruited patients with diagnosed Parkinson’s disease at the movement disorder program of Barrow Neurological Clinic (BNC) at St Joseph’s Hospital and Medical Center. Based on the initial result and validation tests, the feasibility of applying these approaches in future PD management has been also analyzed and discussed in this study.
CHAPTER 2

HOME BASED PD SELF EVALUATION METRIC APPROACH

1. Introduction

As discussed in Disease Assessment Tools section in INTRODUCTION and BACKGROUND part, the current PD evaluation methods are either clinical setting based rating scales, such as UPDRS, which requires subjective rating from clinical professionals, or self-evaluation scales, such as PDQ39, which mainly focuses on quality of life but not too much on disease assessment. Neither of these two kinds of scales is suitable for home based patient self-evaluation on PD. To resolve the above limitations of current PD assessment approaches and thus extend the PD evaluation to home based setting, the first part of this study developed a simple PD self-evaluation metric, which is designed to provide quantitative and objective evaluation for patients based on their motor performance in daily activities. With this self-evaluation metric, the association between the rating score of this metric and the disease status was then studied in order to build the predicative models to identify critical PD features and estimate severity of PD.

Considering that the UPDRS is the standard clinical evaluation measurement in clinical practice, this metric was validated by comparing with UPDRS rating on the same patients. The accuracies of these predictive models were further verified in cross-validation, to compare with ground truth, the experts’ opinion. The validation results proved that this self-evaluation metric could effectively differentiate the performance of patients with different motor symptoms. The validation and the accuracy of predictive models demonstrated that this metric can provide objective, quantitative, and meaningful information for clinical assessment of PD motor related disability, and can be easily
implemented in a home-based computer monitoring system and e-health applications for PD assessment.

2. Method

2.1. Development of Self-evaluation scale

In collaboration with Muhammad Ali Parkinson Center (MAPC) at St Joseph’s Hospital and Medical Center, the initial PD self-evaluation scale was drafted based on Dr Lieberman’s long term clinical practice and study. Based on his practice in evaluating Parkinson’s disease patients’ motor related problems, several particular observations which are not typically adopted widely in PD evaluation are included in Dr Lieberman’s evaluation protocol. These particular observations include standing on one foot, tandem walking, and turning 360 degree. Based on these observations from Dr Lieberman’s experience, plus two quantitative measurements walking speed and stride length, this PD self-evaluation metric is composed of five evaluation questions. Because this self-evaluation metric aims to be applied in a non-clinical environment by patients themselves or care givers, who do not have professional training and knowledge in PD. Therefore, the answer for each evaluation question is designed to be as objective as possible. So that the rater can easily select which category the patient should fall in based on the objective observation, without involving subjective decision making. Similar as part III (Motor examination) of UPDRS scale, the rating score for each evaluation question is from 0 to 4 points. The metric includes total 5 questions, each of which require patients to complete a simple motor task to evaluate the motor related performance on either stability or walking. Different from UPDRS scale, which assesses the PD from patients’ social, cognitive and motor abilities, this self-evaluation metric only focus on assessing the motor ability of PD,
and the rating of each evaluation question is designed to be more quantitative and objective than UPDRS. This metric aims to provide approach for patient to easily compete the rating only with simple counting and calculation, and without any PD professional knowledge and training. The detail definition of the scale is listed in Table 1.
Table 1

The self-evaluation scale for home-based PD evaluation

<table>
<thead>
<tr>
<th>Scale item</th>
<th>Description</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standing on one leg</td>
<td>Evaluation for standing on right and left leg separately. For each leg, the score is from 0~4.</td>
<td>Integer points: 0, 1, 2, 3, 4</td>
</tr>
<tr>
<td></td>
<td>0: Can stand stably on one leg without assistance;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1: Can stand on one leg without assistance, but with a little bit shaking;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2: Need one hand assistance to stand on one leg;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3: Need two hands assistance to stand on one leg;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4: Cannot stand on one leg even with assistance;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The total score for two legs are from 0~8.</td>
<td></td>
</tr>
<tr>
<td>Turning 360 degrees</td>
<td>Evaluation for turning from left to right, and right to left separately.</td>
<td>Integer points: 0, 1, 2, 3, 4</td>
</tr>
<tr>
<td></td>
<td>0: Need less than 4 steps to turn 360 degrees;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1: Need 4~8 steps to turn 360 degrees;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2: Need more than 8 steps to turn 360 degrees;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3: Need assistance to complete the turning;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4: Cannot complete the turning even with assistance;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The total score for two directions turning are from 0~8.</td>
<td></td>
</tr>
<tr>
<td>Tandem walking</td>
<td>Evaluation for tandem walking.</td>
<td>Integer points: 0, 1, 2, 3, 4</td>
</tr>
<tr>
<td></td>
<td>0: Can walk with tandem step stably without any assistance;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1: Can walk with tandem step without any assistance, but with a little bit shaking;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2: Need one hand assistance to walk with tandem step;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3: Need two hands assistance to walk with tandem step;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4: Cannot walk with tandem step even with assistance.</td>
<td></td>
</tr>
<tr>
<td>Step length</td>
<td>The average length (feet/step) of each step, calculated from number of steps taken to walk 25 feet.</td>
<td>Decimal: Feet</td>
</tr>
<tr>
<td>Stride velocity</td>
<td>The average walking speed (feet/second), calculated from time taken to walk 25 feet.</td>
<td>Decimal: Feet /s</td>
</tr>
</tbody>
</table>
2.2. Experiments Design and Data Collection

To validate the scale and build the predicative models to estimate PD status, 204 patients diagnosed with PD were recruited to participate in this study. The participants were selected from regular outpatients at movement disorder program at Barrow Neurological Clinic (BNC). The outpatients who received PD assessment using UPDRS scale in their regular clinic visits were invited in this study. The participants were first given introduction of this metric before their clinic visit appointments. The self evaluation using this metric were completed by patient themselves or care givers at any time before their visits, and the rating result were collected during the visits. Then in their regular clinic visits, their disease statuses were evaluated by movement disorder experts at MAPC using the UPDRS scale. The UPDRS scores rated by clinical experts were used to validate this proposed metric and served as ground truth in building predictive models. Since this self-evaluation metric mainly focuses on assessing the stability and walking disabilities, therefore, not the full set of UPDRS scores, but only part of UPDRS scores, which are related to stability and working, were collected in this study. The collected UPDRS scores in this study are listed in Table 2. The participants’ self evaluation results and their UPDRS based clinical assessment were associated together for validating and building predicative models. Because the disease progress and status of PD are closely associated with the patient’s age and disease duration, the age and disease duration were also collected in this study for including patient demographic and general disease characteristics information.
Table 2

Subset of UPDRS score collected in this study

<table>
<thead>
<tr>
<th>Data field</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midline motor activity score.</td>
<td>From 0~24. The summary score of 6 questions related to motor impairment from subset of UPDRS part III.</td>
</tr>
<tr>
<td>Balance difficulty</td>
<td>As reported on UPDRS part II. 0: no difficulty with balance. 1: difficulty with balance.</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>As reported on UPDRS part IV. 0: no dyskinesia. 1: dyskinesia.</td>
</tr>
<tr>
<td>Freezing of gait (FOG)</td>
<td>Freezing when walking. UPDRS Score from 0<del>4 points. 0,1: no FOG. 2</del>4: FOG</td>
</tr>
<tr>
<td>Gait difficulty</td>
<td>Gait difficulty. UPDRS Score from 0<del>4 points. 0, 1: no gait difficulty. 2</del>4: gait difficulty</td>
</tr>
<tr>
<td>Postural stability</td>
<td>Response to sudden, strong posterior displacement produced by pull on shoulders, while patient erect with eyes open and feet slightly apart. Patient is prepared. Score from 0~4 points.</td>
</tr>
</tbody>
</table>

2.3. Validation

With the collected patient self-evaluation rating and physicians’ assessments using UPDRS score, the proposed self-evaluation metric was validated in t-test to compare the ratings of the self-evaluation scale between patients with and without specific motor disabilities. Four motor disabilities, including gait difficulty, freezing of gait, dyskinesia and postural instability, are used to divide the 204 participants into four pair of comparing groups, as described in Table 3. The self evaluation scores were then compared between the patients who have and do not have the specific disability in each pair of comparison group through the student T-test, using SAS® 9.1 software package.
Table 3

Comparing groups of patients, divided based on motor disabilities.

<table>
<thead>
<tr>
<th>Group</th>
<th>Disability</th>
<th># Patients Having</th>
<th># Patients Not having</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Gait difficulty</td>
<td>74</td>
<td>130</td>
<td>204</td>
</tr>
<tr>
<td>G2</td>
<td>Freezing of gait</td>
<td>28</td>
<td>176</td>
<td>204</td>
</tr>
<tr>
<td>G3</td>
<td>Postural stability</td>
<td>122</td>
<td>82</td>
<td>204</td>
</tr>
<tr>
<td>G4</td>
<td>Dyskinesia</td>
<td>84</td>
<td>120</td>
<td>204</td>
</tr>
</tbody>
</table>

2.4. Predictive Model Construction

The self-evaluation metric provides an objective evaluation on motor related performance. However, this objective evaluation’s results are hardly useful for either patients or physicians, unless the self-evaluation metric can be associated with clinical assessment measurements. In order to build up this association, we attempted to construct a couple of predicative models to identify motor disabilities and estimate motor related UPDRS scores. To identify the four critical PD features, dyskinesia, gait difficulty, freezing of gait, and postural stability, we constructed four binary classification models using Support Vector Machine (SVM)(61). The ground truths of these four features are the UPDRS score rated from movement disorder experts at BNC’s movement disorder program. To train these classification models, we chose the all five items in the proposed self-evaluation metric plus patients’ age and disease duration to construct the input feature vector. The training process is done using the polynomial kernel in SVM(61) and 10 folds cross validation(74). All the 204 data records were equally divided into training set and test set. The 102 records were used to train the four classification models and the left 102 records were used in model validation and verification.
The midline motor activity score in UPDRS, ranging from 0 ~ 24, was estimated in a linear regression model. We used the same input feature vector, as well as training and testing procedure explained above. To avoid the collinearity between input features, the stepwise forward selection approach was applied in feature selection to build the linear regression model on midline motor score estimation (69).

3. Result

3.1. Patient general characteristics

Table 4 presents the general patient characteristics of all 204 patients in this study. The average age is 68.3 years old, and average disease duration is 6.3 years. The average stage of Parkinson’s disease is 2.6 in term of Hoehn and Yahr stage, ranging from 0 to 5. The disease severity is measured using UPDRS. The average UPDRS motor score is 19.8, and the midline motor activity score is 5.6. Among the 204 patients, 41.2% (84) have dyskinesia, 13.7% (28) have freezing of gait, 36.3% (74) have gait difficulty, and 60.7% (124) have shown postural stability. 160 patients in this study were using levodopa in their disease management plan.
Table 4

Patients general characteristics and UPDRS scores (N = 204)

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Median (Q1-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td>68.3(9.2)</td>
<td>40-89</td>
<td>69(62-75)</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td></td>
<td>6.3(4.7)</td>
<td>1-30</td>
<td>5(3-8)</td>
</tr>
<tr>
<td>Using levodopa (number of Yes/No)</td>
<td>160/44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoehn and Yahr stage</td>
<td></td>
<td>2.6(0.7)</td>
<td>0-4</td>
<td>2.5(2-3)</td>
</tr>
<tr>
<td>UPDRS motor score</td>
<td></td>
<td>19.8(9.4)</td>
<td>1-55</td>
<td>18(14-25)</td>
</tr>
<tr>
<td>UPDRS midline motor activity score</td>
<td>5.6(3.5)</td>
<td></td>
<td>0-16</td>
<td>5(3-8)</td>
</tr>
<tr>
<td>Presence of motor related disabilities:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dyskinesia (Yes/No)</td>
<td>84/120</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>freezing of gait (Yes/No)</td>
<td>28/176</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gait difficulty (Yes/No)</td>
<td>74/130</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>postural stability problem</td>
<td>124/80</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2. Validation

This self-evaluation metric was validated by comparing the rating of each item of this metric between patient groups who have and do not have a specific motor related disability, listed in Table 3. The difference is compared in student T-test, at critical level of α=0.05. The null hypothesis H₀ is that there is significant difference of self-evaluation rating between the patients with and without presence of a specific motor disability. The result is listed in Table 5.

In Table 5, we can observe that in terms of balance difficulty, the self evaluation scores of standing on one leg, turning, tandem walking demonstrate significant increase of values from asymptomatic patients to symptomatic patients, and decrease of values of step length and step velocity. The same comparing differences exist in gait difficulty, freezing of gait, and postural stability. However, the differences on step length and step velocity between patients have or do not have dyskinesia are insignificant. The higher
scores of standing on one leg, turning, and tandem walking, meaning the poor performance in movement, the lower values of step length and walking velocity imply less motor ability.

In gait difficulty comparison groups, ratings on standing on one leg, turning, and tandem walking show significant larger value in patients having gait difficulty than patients without the difficulty. The larger values in rating of standing on one leg, turning, and tandem walking indicate that the patient needs more help to finish the motor task, which suggests a more severe disease condition. The stride length and step velocity also show the consistent difference according to disease condition. For gait difficulty, the patients having gait difficulty exhibit shorter stride length and slower step velocity than the patients without the difficulty, and the differences are significant at p value < 0.05. Same as the comparison of gait difficulty, the similar comparison differences also exist in freezing of gait, postural difficulty, and dyskinesia. All these differences are significant at the p value < 0.05. From t-test results, the self-evaluation metric shows a strong ability to differentiate the motor related performance of PD patients. The differences not only keep consistent with the condition of a disability, but also show strong significance in all the four types of motor disabilities. These comparison results serve as the validation evidence for the proposed self-evaluation metric to prove the consistency and reliability of using this metric in PD self-evaluation. After validation, the association between the self-evaluation metric and motor disabilities was investigated by building the predicative models. The performances and accuracy of the predicative models are discussed in the following session.
Table 5

T-test result of each term in our proposed scale compared between patients whether having or not having balance difficulty, gait difficulty, freezing of gait, postural stability and dyskinesia.

<table>
<thead>
<tr>
<th></th>
<th>gait difficulty</th>
<th>freezing of gait</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Stand on one leg</td>
<td>2.0±1.7</td>
<td>4.4±1.7</td>
</tr>
<tr>
<td>Turning</td>
<td>1.9±1.4</td>
<td>4.2±1.9</td>
</tr>
<tr>
<td>Tandem walking</td>
<td>0.9±0.9</td>
<td>2.5±1.2</td>
</tr>
<tr>
<td>Stride length</td>
<td>2.0±0.3</td>
<td>1.4±0.4</td>
</tr>
<tr>
<td>Step velocity</td>
<td>3.6±0.8</td>
<td>2.4±0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>postural difficulty</th>
<th>dyskinesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Stand on one leg</td>
<td>1.8±1.8</td>
<td>3.5±1.9</td>
</tr>
<tr>
<td>Turning</td>
<td>1.9±1.5</td>
<td>3.3±2.0</td>
</tr>
<tr>
<td>Tandem walking</td>
<td>0.8±0.8</td>
<td>1.9±1.3</td>
</tr>
<tr>
<td>Stride length</td>
<td>2.0±0.3</td>
<td>1.6±0.4</td>
</tr>
<tr>
<td>Step velocity</td>
<td>3.5±0.8</td>
<td>2.8±0.9</td>
</tr>
</tbody>
</table>

3.3. Predicative Model

With the validated consistency and reliability of the metric, we further moved on to build the predicative models to identify critical motor disabilities and estimate disease severity. These predicative models play an important role in determining the competency and usability of this self-evaluation metric in home-based PD assessment and monitoring.

3.3.1. Detect motor disability

As described in Predictive models construction section, four classification models for identifying whether a patient has gait difficulty, postural stability, freezing of gait, and dyskinesia have been constructed using the Support Vector Machine (SVM) approach. Each model was trained and tested separately. The precision and recall are calculated for each model to show the accuracy of using the self-evaluation metric to identify whether a
patient suffering a motor disability, in Table 6. The classification model on gait difficulty identification shows the accuracy, 82.4% in recall, 82.7% in precision, and 82.3% in F measure. The accuracy of freezing of gait classification follows the gait difficulty. The recall, precision and F measure for freezing of gait are 76.5%, 74.9%, and 75.6% respectively. For postural stability and dyskinesia identification, the recall, precision, and F measure are all above seventy percent, and the classification models for these two disability identification show the similar accuracy.

Table 6

<table>
<thead>
<tr>
<th></th>
<th>Gait difficulty</th>
<th>freezing of gait</th>
<th>postural stability</th>
<th>dyskinesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recall</td>
<td>82.4%</td>
<td>76.5%</td>
<td>71.6%</td>
<td>70.6%</td>
</tr>
<tr>
<td>Precision</td>
<td>82.7%</td>
<td>74.9%</td>
<td>72.6%</td>
<td>72.1%</td>
</tr>
<tr>
<td>F Measure</td>
<td>82.3%</td>
<td>75.6%</td>
<td>72.0%</td>
<td>69.9%</td>
</tr>
<tr>
<td>ROC Area</td>
<td>0.906</td>
<td>0.728</td>
<td>0.724</td>
<td>0.75</td>
</tr>
</tbody>
</table>

The ROC curves of these four models are compared in Figure 1. The ROC curve is a graphic plot usually used to illustrate the performance of a binary classification model. The ROC area, which is under the ROC curve, is for measuring the predictive ability of a classification model. The value of ROC area is from 0 to 1. Ideally, the perfect classification model has a ROC area of 1. Generally, the larger the ROC area is, the better performance of the classification model is. In Figure 1, the ROC area of classification model for gait difficulty, which is 0.906, is obviously larger than other three models. This large ROC area close to 1 indicates the strong ability of the model to identify the gait difficulty, using the self-evaluation metric. For freezing of gait, postural
stability, and dyskinesia, the ROC areas are 0.728, 0.724, and 0.75 respectively. In each of the four classification models, it can be observed that the recall and precision value of the model are very close, which suggests that the model has the same power in identifying a motor disability as excluding the possibility of disability. Because dyskinesia is most commonly related to the movement disability of upper body, especially hand, limp and face, it was assumed that this proposed metric may have very poor performance in identifying the upper body motor impairment, such as hand tremor and rigid face. However, the performance for classification dyskinesia shows acceptable accuracy, recall 70.6, precision 72.1, and ROC area 0.75. But for identifying the lower body related movement disability, especially for gait difficulty, our proposed metric indicates high accuracy. These four classification models will play the role in bridging the self-evaluation of patients with to the PD disease status, to identify several critical motor disabilities in home based PD assessment and monitoring.
3.3.2. Hoehn & Yahr stage estimation

The Parkinson’s disease stage, Hoehn & Yahr score, is estimated using the patient’s self-evaluation information through regression model. The predicated variable, Hoehn & Yahr stage, ranges from 0 to 5. The predictor vector is composed of age, disease duration, standing on one foot, turning, tandem walking, stride length and walking velocity. By optimizing the model through the backward stepwise selection, the correlation coefficient of the final optimized regression model is $r = 0.85$, and the root mean squared error is $\text{RMSE} = 0.4$.

3.3.3. UPDRS score predication

The classification models developed in this study provide an approach to detect critical motor related symptoms through the patient evaluation. However, in regular PD evaluation, the motor part of UPDRS score is a major indicator on severity of the disease.
In order to provide more quantitative information for physicians to capture the disease progress and severity of PD patients based on patients’ self-evaluation, we further attempted to predicate the UPDRS score using patients’ self rating. Since this proposed self-evaluation metric is for motor related evaluation, and more focus on assessing the motor ability of lower body, therefore, we chose the midline motor activity score in UPDRS to predicate. The midline motor activity score is calculated by summing the value of a subset of part III (motor examination) of UPDRS, including leg agility, arising from chair, posture, gait, postural stability, and body bradykinesia and hypokinesia(6, 58). Not like identifying the motor disability, which is binary result, the midline activity score is interval variable. To predicate this score, we applied the stepwise forward selection approach to construct a linear regression model(75). The input predicator vector started from containing only step length, which yields a model with correlation coefficient $r = 0.62$ and root of mean squared error $\text{RMSE} = 2.6$. By adding other independent variables to the predicator vector, the correlation coefficient was improved to $r = 0.84$ and $\text{RMSE} = 1.81$. The final regression model is composed by five predicators, which include standing on one leg, turning, tandem walking and step length. Figure 2 shows the linear regression model on the test dataset ($N = 102$). The result of this regression model exhibits a strong correlation between the self-evaluation metric and the midline motor activity score. The regression model performs a good interpolation on the test dataset. Figure 3 shows the residue plot of the predicted value of midline motor activity score. The residue plot shows that 70.5% of the residues fall into the (-1, 1) region, and 95.1% of the residues fall into the (-2, 2) region. The $R^2 = 0.84$ and residue plot figure demonstrate that this regression model has a favorable accuracy in estimating UPDRS midline activity score.
This model is promising to be implemented in home-based PD evaluation system to estimate the PD disease progress on axial motor performance evaluation.

Figure 2

The scatter plot on predicated vs. actual midline motor activity score of test data set, in the final regression model with correlated efficient $r=0.84$. 

![Scatter plot with regression line and $R^2=0.84$]
4. Discussion

To explore a novel approach for home-based Parkinson’s disease, this initiative study proposed a simple Parkinson’s disease self-evaluation metric for PD patient self-evaluation. The preliminary validation and analysis have been investigated. The analyses on the self-evaluation data of 204 participants in this study prove that the metric can effective evaluate the PD patient performance on motor related symptoms, and provide clinical meaningful information for disease status estimation. The validation result shows that this self-evaluation metric can effectively differentiate the different motor performance between patients having or not having specific motor disability. With the validated metric, four classification models and one linear regression model have been constructed to associate the patients’ self-evaluation rating with critical PD symptoms.
and disease severity. The performances of these models were evaluated through the preliminary analyses. The results indicate acceptable accuracies of using this metric to identify critical PD motor disabilities, including gait difficulty, postural stability, freezing of gait, and dyskinesia. The estimation on midline motor activity score has also been investigated and the result shows a high correlated coefficient $R^2=0.84$, which suggests a high accuracy to estimate axial motor performance.

The validation on these metric and preliminary results of using this metric for basic disease status estimation show the usability of applying this metric in home-based PD assessment. This self-evaluation metric fills the gap between PD self evaluation scale and clinical used evaluation, so that the clinician can track the disease progress easily and more frequently through the patients’ self evaluation. However, the current version of this metric mainly focus on the evaluation on motor performance of lower body, and has limited power to assess the upper body performance, including hand tremor, face rigidity, and speech. The other limitation is the subjective bias of the patients incurred in self-evaluation, which can lower the effectiveness of using this self-evaluation metric in PD disease monitoring and management. Therefore, to resolve these limitations, we further explored other approach to provide more objective and efficient PD evaluation by using motion sensor technology and mobile information technology, which is discussed in CHAPTER 3 in this thesis.
CHAPTER 3

SMARTPHONE BASED PD ASSESSMENT AND MONITORING APPROACH

In CHAPTER 2, an initial attempt to design a home-based PD evaluation approach was discussed, and the results show acceptable accuracy and promising feasibility to implement this approach in PD management. However, using this self-evaluation metric still requires patients’ subjective rating. Therefore, this approach is still subject to perceptual bias and is less consistent and reliable. Moreover, the rating result of this self-evaluation approach contains only descriptive information about patients’ motor performance and but less quantitative motion feature information, which is important for more accurate PD assessment, predication of disease progress and cross patients’ comparison. At last, the limitation of this approach, which inhibits developing a system to monitor patients with PD, is that it is difficult to integrate the patients’ self-reported rating, the analytical algorithms and data transmission to estimate disease severity, to effectively monitor disease progress and to provide decision support in disease management. Moreover, there is no way to avoid manual input of the self-rating in real use case scenario, even when the analytics and data transmission framework is given. Therefore, these disadvantages largely limit the usability and clinical value of this approach and lower the feasibility of implementing this approach into a remote Parkinson’s disease monitoring system. To resolve these limitations, we further took advantage of the sensor technology, mobile computing technology and client/server architecture to develop a smart phone based e-health monitoring system on Parkinson’s disease management. The system design, development, and initial test and validation
were discussed in this chapter. This proposed system aims to provide an integrated home-based PD assessment solution, which is convenient to use and reduce the subjective bias.

1. Introduction

Long-term clinical management of Parkinson’s disease requires extensive monitoring of a PD patient’s status and suitable medication plan according to the disease progress. The intermittent hospital assessment, which only provides a brief window to a person’s health, might miss trends that can lead to early detection of a problem (76). Home-based monitoring of PD is an ideal approach that has potential to fill the disease information gap of hospital monitoring, to reduce the necessity to attend frequent consultations with specialist personnel and to offer more precise and continuous monitoring paradigms to extensively assess PD progression and medication effects (77).

With current and on-going advances in wearable sensor technology, wireless network and information platform, it becomes more feasible to monitor the physiological parameters remotely on a continuous basis in people’s daily activities. Such monitoring systems sensing PD related bio-parameters are promising tools that enable long-term PD monitoring at home basis.

1.1. Home-based health monitoring system

With the advance in sensor technology and the development of internet technology, the home-based monitoring system has drawn a lot of attention and efforts from both research and industrial communities to develop such kind of system to provide real-time health status information in managing chronic diseases and postoperative rehabilitation patients (78, 79). Several research prototype systems have been developed to monitor health status, using commercial products or custom hardware-based system.
The LiveNet, designed in the Media Laboratory of MIT, is a custom built system to monitor integrated physiological signal, including electrocardiogram (ECG), electromyogram (EMG) and blood pressure (BP, and posture position\(^{80}\)). AMON, an advanced care and alert portable telemedical monitor system, has been reported to provide real time measurement of blood pressure, skin temperature, blood oxygen saturation and basic ECG monitoring \(^{81}\). Lin et al. described the development of a real-time wireless physiological monitoring system (RTWPMS), which is based on a cordless phone and a custom made medical examination module to measure blood pressure, heart rate and temperature\(^{82}\). Researchers in Harvard University have developed CodeBlue, a medical sensor network platform for multi-patient monitoring environment, using wearable wireless body area network (WWBAN)\(^{83}\). As multi-functionality and computing power of cell phone advances, attempts to use cell phone as data transmission and user interface control module have been reported in several health monitoring applications\(^{84}\). HeartToGo is a cell phone based wearable platform, which is capable of continuously monitoring ECG signal via a wireless ECG sensor, to analyze the electrocardiogram in real time and possibly to detect any abnormal patterns pertaining to cardiovascular disease\(^{85}\). These initial studies in health monitoring system have already the remote real time monitoring on vital signs, and many of them have been implemented in various use case scenarios, such as soldier health monitoring, space and terrestrial applications \(80, 86\). Due to the complicity of motoring features of PD and lack of automatic analytical and monitoring algorithm, there is few integrated monitoring system targeting on PD assessment.
1.2. Parkinson’s disease monitoring

Given the characteristics of Parkinson’s disease and its challenges on disease management, designing ambulatory equipments for remote-monitoring PD patients has also attracted a lot of attentions recently, as can be observed in recent conferences (87-89) and study reports (90, 91). As tremor is one of the most significant motor disability symptoms of PD patients, several previous studies have reported prototype systems for tremor monitoring. Eskov et al described a research system for human micro movements that can be used to measure tremor using eddy-current detector (92). Hoff et al used a commercial portable multichannel recorder for quantitative continuous 24-hour monitoring of tremor while the patient is at home (93). Yang et al presented a portable device for long-term measurement and recording of tremor, using a compact flash memory card for storage (94). Besides tremor, gait is another critical PD feature that attracts a lot of research attentions to design ambulatory monitoring system and analytical algorithms. The primary measurement of gait mainly go into three avenues: i) force based measurement, ii) angular rate measurement and iii) accelerometer measurement (95).

Several accelerometer based measurement systems for ambulatory monitoring gait related symptoms in PD have been reported in freezing of gait detection, posture and walking speed estimation (96-98). More recently, Salarian et al and Patel et al, in Harvard medical school, used wearable accelerometers to evaluate motor complications on persons with PD, and attempt to predicate the clinicians’ estimates of disease symptoms severity (99-101). Moreover, the ambulatory assessment on bradykinesia has also been investigated by using off-the-shelf accelerometer sensors by Cancela et al (88, 102).

Except patients’ motor data, other information has also been studied for the use of PD
remote-monitoring. Little et al. assessed the practical value of discriminating healthy people by detecting dysphonia (103). Tsanas et al. proposed the use of speaking tests in the evaluation of PD progression (104). Goetz et al. tested the feasibility of using a telemonitoring testing device in early-stage, unmedicated PD patients (105).

1.3. Limitations and Challenges

Despite recent advanced researches and studies in ambulatory monitoring of Parkinson’s disease and many attempts to develop a home-based monitoring system for PD management, most approaches are based on using separate sensor network and control module. By this way, the sensed data need to be transmitted to control and storage module through wireless network, and the system needs extra power supply for sensor and storage module and control module. These detached components increase complicity and decrease the system reliability (106, 107). Another big limitation of previous work on developing systems to monitor patients with Parkinson’s disease is the lack of integration between monitored data and analytical algorithms for providing integrated service for disease severity assessment and disease progress estimation. At last, such home-based disease monitoring system needs to be affordable and easy to be used by patients or caregivers in the daily living environment, in order to ensure wide adoption and implementation in PD management. Therefore the current wearable sensor based monitoring system can hardly satisfy economic and usability requirements, due to hardware resource limitations and strict medical criteria.

Portable electronic monitoring equipment has been used in assisting home monitoring of blood glucose, congestive heart failure, cardiovascular function and risk of falling down. Due to dramatic progress and rapid growth of smart phone applications,
especially the current tendency in mobile computing technology, more and more individuals have gained efficient access to information and communication solutions through smart phone platform(108). Current mainstream smart phone manufactories, such as Samsung, HTC and Apple, have already integrated the 3D accelerometer and gyroscope as a standard module to provide wide applications, such as orientation sensing and motion control. Since the major Parkinsonian symptoms are motor related disabilities, such as tremor, freezing of gait and walking difficulty, the accelerometer in smart phone may serve as a sensor component for motor exam in PD evaluation. With the high computing performance and powerful mobile operating system, data transmission, user interaction and storage can be seamlessly integrated to provide efficient PD monitoring. Moreover, with the ubiquitous 3G or wireless network, the smart phone can also serve as client terminal to communicate with the server-side analytics for disease monitoring and even medication consulting. An initial attempt to use iphone to assess tremor and gait difficulty of Parkinson’s disease patients were discussed in Lemoyne’s recent papers (109, 110). The results showed it is promising to use the built-in 3D accelerometers to capture tremor and gait features of individuals with Parkinson’s disease. However, their study is very preliminary and did not discuss how to use the iphone sensed data to provide disease severity assessment and how to extend the iphone application to a monitoring system in PD management. In this chapter, we described a pilot PD home-based monitoring prototype system using smart phone device, web analytics and decision-supported technologies. The preliminary test of the system on PD patients was performed, and the test results will serve as feasibility evidence for future development or implementation.
2. Method

2.1. System Design and Development

2.1.1. System Architecture

To provide ambulatory Parkinson’s disease monitoring and assessment through smart phone based mobile technology, this proposed system adopts three layers of architecture shown in Figure 4. These three layers are composed of: 1) the mobile unit, which is a smart phone with installed home-developed app to acquire patient’s motion data and to transmit data with server side; 2) the hospital server unit, which contains the analytics, and enables the medical staff remotely monitor the patient’s condition and send medical recommendations; 3) patient data warehouse, which is a patient centric relational database to store raw motion data and analysis results.

In real use case scenario, patients use a specific app installed in the smart phone to log into the system and perform motor tasks for disease assessment. The real time motion data is sensed and acquired when patients performing a predefined motor task. After each motor task is done, the raw motion data and related test meta-data are stored on smart phone and then sent to hospital server unit when network is available. At the server’s side, received raw motion data are directly persisted into the patient data warehouse. While in a separate route, raw motion data goes through a series of pre-processing steps to remove noise and extract motion features and patterns. The extracted motion features are inputted into decision support modules for PD symptoms detection and disease severity estimation. Once some abnormal situations are observed or disease status declines, recommendation messages will be sent to physicians to require further review or follow up. Physicians can also send recommendation to patients through the system. Bidirectional transmission of
The data between mobile unit and hospital server unit is implemented by the TCP/IP architecture using SOAP protocol.

**Figure 4**

System architecture diagram.

2.1.2. Requirement Analysis

In designing this system, function specification and requirement analysis were conducted before choosing test device. The requirements analysis to determine choosing which smart phone in this study was considered based on three factors: 1) device capability to effectively capture motion features related to Parkinson’s disease; 2) Communication and storage capacity; 3) Cost and device quality. The first factor is the major factor in determining which device was selected.

The device capability for sensing and collecting motion features were analyzed based on the characteristics of PD motion data. In this study, hand resting tremor, walking, turning, and finger tapping data are four types motion data to be collected. It
was reported that hand tremor motion acceleration is along three directions, composed of low frequency components, less than 20 Hz, and the acceleration rate is less than 2g (111, 112). Walking and turning acceleration signal is between 2 and 5 Hz (97). In order to extract gait features, including stride length, walking speed, and turning speed, both linear acceleration along x, y, z direction, and angular acceleration along pitch, yaw, and roll directions are required. Therefore, based on the above motion signal characteristics, the candidate device needs to have a 3D accelerometer and gyroscope sensors, and the 3D accelerometer should have at least ±2g amplitude range.

Furthermore, because the precision of collected motion acceleration signal is determined by sampling rate of sensor, the sampling rate is another factor that determines device selection. Based on the Nyquist-Shannon sampling theorem (113), the minimal sampling frequency should be at least 2 times of the highest frequency components. Therefore, the sampling rate of a qualified smart phone needs to support at least 40 Hz sampling rate, which is two times of the potential upper bound of hand tremor frequency component.

In order to store collected motion data and related patient information, the selected smart phone should have at least 500MB storage space, and support basic database system and wireless or 3G internet communication. The cost of a candidate smart phone device should be in the middle class in current smart phone market and is mainstream brand. The over high end device will limit the future adoption of using this system, and over low end device will have high risk that influences the system stability and reliability.
2.1.3. Hardware

Based on the above requirement analysis, we chose a Samsung Galaxy Epic smart phone, running on Android 2.1 Eclair operating system, as the mobile unit in this prototype system. We chose this device in this study considering the balance between required tech specs and economic cost. This device is mid-end product in smart phone market, and has standard tech specs and functional module compared with mainstream smart phones. Therefore, using this device is appropriate for test purpose to validate our system, and minimize variation of system performance resulting from device characteristics. Because this prototype system is developed for android system, so in real case implementation this proposed system can be extent to any android smart phones as long as they have built-in 3D accelerometer. This test device has 1GHz Gortex-A8 CPU and 512 MB internal memory, and can support Wi-Fi 802.11 b/g/n, Bluetooth, and USB 2.0 data transmission protocol. The display of the device is 4.0 inches touch screen with resolution of 480 x 800 and supports multi-touch. The device is 124 × 65 × 14mm and its total weight is 155g. The power supply of the device is a standard Li-lon battery 1500mAh, which can support stand-by time up to 300h and talk time up to 5h 30 min. The sensor module is composed of a tri-axial accelerometer, a proximity and a compass. Tri-axial accelerometer is capable of measuring up to +/- 8g and sampling frequency can be up to 1 KHz. This tri-axial accelerometer is used as the primary motion sensor module, which functions in the principle of differential capacitance in response to motion and constant gravity to measure both acceleration and inclination.

The server side unit is a workstation constituted by an Intel Core 2 Duo 2.2 GHz computer with 4 GB of RAM, a hard disk of 250 GB and Microsoft Windows XP
operating system. The server is configured as a web server and data server, running Apache 5.5 and MySql 5.1. The workstation server is located in the restricted area and with password protection, and connected to the hospital network. In the prototype system, considering the limited volume of data load and scalability in test phase, we did not use a high performance workstation as dedicated server. In real implementation of the system, separated web server and data base server are highly desired.

2.1.4. Software

The software part in this system was developed in three parts: 1) smart phone application, using Android 2.1 SDK, 2) server side analytics running on Apache 5.5, and 3) relational database MySQL 5.1. All these programs running on smart phone and on server were developed using Java programming language.

2.1.3.1. Application on smart phone

On the smart phone, we developed an application, named PD ODLs, for users to perform PD evaluation. The app was developed using the Android Software Development Kit (SDK), which provides the programming interface for sensor control, data storage and transmission. This SDK supports the custom setting on sampling rate of the accelerometer. We used the highest sampling rate supported by android platform in this study, which was tested up to 100Hz. On the smart phone side, an internal relational database, Sqlite, was also used in this system for temporary local data storage and user information management. In case neither wireless network nor cell phone network is available, acquired motion data can be temporarily stored in the internal database and then sent to server side when network is available.
In order to make the application easier for patients to use, dedicated user-friendly user interface was developed. These interfaces are shown in Figure 5, and the workflow and information flow are shown in Figure 6. The software is composed of four main modules. The first module performs user account verification for data security and privacy protection (Figure 5A). The account authorization is required each time using the system. The second module acquires motion signals when patients completing motor tasks. Measurement of acceleration signals is collected simultaneously, at a sampling frequency of 100 Hz, when patients conducted the test. The sensed motion data are displayed on the smart phone screen when patient performing the task and are saved for further analysis. Totally four motor exams were designed for assessing different PD features (Figure 5B). After patient select one motor task, detailed instruction is displayed on screen to direct users how to perform task step by step. The third module is a
communication module based on SMS and email, which allows users to send questions and receive medical recommendations from the hospital server (Figure 5C). This could provide significant benefits for patients, allowing fast and easy adjustment of medical treatments. The fourth module enables users to review their test history and analysis result. This module also includes the function to send completed motor test data from smart phone to hospital server Figure 5(D).

Figure 6

State diagram of the application on smart phone for Parkinson’s disease evaluation
2.1.3.2. Hospital server side analytics

On the hospital server side, all the analytical modules were developed under Spring Framework, using Service Oriented Programming (SOP) paradigm. Each module provides a single self-contained service, and all these modules are connected together using Spring Dependency Injection (DI). The framework of the server side modules is shown in Figure 7. The collected motor test data by smart phone are received in XML format at the server side. This XML file is first unmarshaled by the data preprocessing module to extract raw motion signal and test meta data, which includes sampling rate, time duration, date, type of motor test and user ID. The extracted data is then persisted to database, and also inputted into the signal processing module. In the signal processing module, the noise and Parkinson’s disease unrelated motion signal is filtered out, followed by calibrating signal to baseline. The filtered signal then goes into motion feature extraction module to extract PD related motion patterns and features according to each type of motor task. The motion features are categorized to two types: 1) time domain features and 2) frequency features. For different type of motor test, different motion features are extracted through specific analysis algorithm. The extracted features contain the input feature vector for the decision support module. The decision support module is composed of several individual predication models for detecting symptom and estimating disease progress. The output of the decision support module is estimated UPDRS (Unified Parkinson’s Disease Rating Scale) score for evaluating the disease status and tracking disease progress.
2.1.3.3. Data warehouse

The back end patient relational database serves as the primary repository to store patients’ Parkinson’s disease motor test data and evaluation results. This database uses a patient-centric structure and uses MySQL 5.1 as the database server. The raw motion data and estimated disease severity score of each disease assessment are persisted into this database. Figure 8 shows the ER diagram of the database structure. Beside the test data and disease assessment results, user account information is also managed in the database and all operations on the database are logged using Apache log4j. One point that needs to be pointed out is that considering future potential needs to integrate this proposed system...
with other research or clinical information system, this database structure reserves the interface for future extension.

Figure 8

ER diagram of the database system on hospital server side

2.1.3.4. Data transmission

The motion data collected by the motion sensors of smart phone is just a series of numeric numbers, which are not very meaningful for physicians and patients to understand. Therefore, the raw motion data must be processed and analyze through signal processing step to transfer to clinical meaningful information. In this data processing and analysis module, the input is raw motion data, and output is the estimated UPDRS scale (Unified Parkinson’s Disease Rating Scale). Because each PD related motion, including hand tremor, gait and finger tapping, has different spectrum characteristics and distinct
motion pattern, so each type of PD related motion data goes through a specific designed data processing and analysis path respectively. The general path of data processing and analysis of motion data is shown in Figure 7, and explained in detail in the following three sections, data processing, feature extraction and disease severity estimation model.

2.2. Parkinson’s disease motor assessment

2.2.1. Motor tasks design

In order to assess the major features of Parkinson’s disease through the smartphone, we designed four motor tasks to assess Parkinson’s disease severity in different dimensions. These four motor tasks are included in our designed monitoring system as regular routines to be performed in home-based PD evaluation. The rationale of the designing is based on our study result in CHAPTER 2 of this thesis. In CHAPTER 2, it has been found that the critical Parkinson’s lower body motor disabilities are associated with turning and walking performances. Many studies have proven that the finger tapping test is closely associated with bradykinesia, and using finger tapping test for quantification of bradykinesia has been attempted in many studies (114, 115). In addition, the hand resting tremor is a typical symptoms existing in most of the early stage PD patients (5). Therefore, we chose the turning, walking, hand resting tremor and finger tapping as the motor task set in this study. The detail descriptions for designed motor tasks are explained in Table 7, and the mount positions of the smartphone in hand resting tremor, walking and turning tasks are shown in Figure 9.
Table 7

Designed motor tasks for Parkinson’s disease evaluation.

<table>
<thead>
<tr>
<th>Task</th>
<th>Task Description</th>
<th>Data Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand Tremor</td>
<td>Patient attaches the smart phone to the dorsum of each hand and keeps the hand hanging for 20 seconds.</td>
<td>Translational acceleration rate at X, Y, Z directions and angular acceleration rate at pitch, roll, and yaw directions.</td>
</tr>
<tr>
<td>Walking</td>
<td>Patient attaches the cell phone to the ankle of one leg and walking 25 feet.</td>
<td>Translational acceleration rate at X, Y, and Z directions and rotation matrix of cell phone with time change.</td>
</tr>
<tr>
<td>Turning</td>
<td>Patient attaches the cell phone to the pivot leg in turning 360°.</td>
<td>Angular acceleration rate at pitch, roll, and yaw directions with time change.</td>
</tr>
<tr>
<td>Finger tapping</td>
<td>Patient tries to continuously tap the screen as soon as possible using index finger in 10s.</td>
<td>The timestamp when patient tap the target.</td>
</tr>
</tbody>
</table>

Figure 9

Smart phone and motor test application in hand tremor task (A) and Walking & Turning task (B).

2.2.2. Motion data analysis

The collected motion signal goes through the signal processing and analysis steps before disease severity is estimated. Because in each motor task as described in Table 7,
motion signal has different characteristic and is featured with distinct patterns, so each type of motion signal goes through different signal processing path and is analyzed with specifically designed feature extraction algorithm. The following parts describe the processing flow and algorithm for each type of motion data.

2.2.2.1. Hand resting tremor

The raw acceleration signals along the three axes of the accelerometer were considered for the hand resting tremor analysis. Accelerometer signal consists of two different components, a acceleration component of motion and a gravity component related to the position of the accelerometer relative to gravity. In hand resting tremor, the change of hand position should not be considered as tremor related acceleration change. So a high pass filter (HPF) with 3-dB cut-off frequency at 0.3 Hz was first applied to removing gravity component of acceleration and slow displacement of hand. Because the hand tremor signals are at low frequency, usually 7~12 Hz for physiological tremor and 4~6 for parkinsonian tremor, therefore a low pass filter with 3-dB cut-off frequency at 20 Hz was then applied to remove the non-tremor related components. Fourier analysis was then applied on this filtered signal to calculate the frequency spectrum. Because a parkinsonian resting tremor has a typical frequency between 4 and 6 Hz but an action or postural tremor could also be present at higher frequencies (111, 116), so the characteristic of signal between 4~6 Hz and its ratio to other signal components were calculated to construct hand resting tremor feature set, shown in Table 8.
Table 8

The extracted motion features of hand resting tremor evaluation.

<table>
<thead>
<tr>
<th>Tremor Features</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF4_6</td>
<td>The power of the motion data between 4 and 6 Hz.</td>
</tr>
<tr>
<td>%PF4_6</td>
<td>Fraction of power of motion data between 4 and 6 Hz.</td>
</tr>
<tr>
<td>PR</td>
<td>Power ratio of the motion data in 3.5 ~15 Hz to 0.15 ~ 3.5 Hz frequency components</td>
</tr>
<tr>
<td>PF0_20</td>
<td>The total power of motion data from 0 ~ 20 Hz</td>
</tr>
<tr>
<td>PEAK_POWER</td>
<td>The peak power value of hand resting tremor motion data.</td>
</tr>
<tr>
<td>AVG_ACC</td>
<td>The average acceleration of motion of hand resting tremor.</td>
</tr>
</tbody>
</table>

The power of signal is calculated using equation (1), where $f(t)$ is the signal in time domain.

$$P = \frac{1}{T} \int_{t_0}^{t_0+T} f(t) \cdot \tilde{f}(t)dt$$

(1)

2.2.2.2. Gait

The walking and turning task is for assessing the gait performance of individuals with Parkinson’s disease. From motion data collected in these two tasks, the primary aim is to extract the gait feature of the subjects to detect gait difficulty and freezing of gait.

The extracted gait features are listed in Table 9. Gait is a periodic movement, which can be decomposed into a series of single gait cycles. Each gait cycle consists of stance and swing phase(117). Stance phase is approximately 60% of the gait cycle and begins at the end of the contact (EC) of foot on ground, goes through the loading phase, mid stance and ends at the initial contact (IC) of foot on ground. Therefore, to effectively extract the gait features, the major problem is to detect the swing and stance phase in each gait cycle, through detecting the IC and EC time stamp. After each IC and EC timestamps in gait
cycle are detected, the walking speed and stride length can be easily estimated by integrating the acceleration rate within the swing phase.
Table 9

The extracted gait features from walking and turning motion data.

<table>
<thead>
<tr>
<th>Gait Features</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking Straight Task</td>
<td></td>
</tr>
<tr>
<td>CT(s)</td>
<td>Average gait cycle time.</td>
</tr>
<tr>
<td>SL(m)</td>
<td>Average stride length.</td>
</tr>
<tr>
<td>SP(m/s)</td>
<td>Average walking speed.</td>
</tr>
<tr>
<td>AVG_ACC(m/s^2)</td>
<td>Average acceleration during walking.</td>
</tr>
<tr>
<td>Turning Task</td>
<td></td>
</tr>
<tr>
<td>NUM_TURN</td>
<td>The number of step used to finish turning 360°</td>
</tr>
<tr>
<td>TURN_SP</td>
<td>The speed of turning 360°, calculated by 360°/time</td>
</tr>
</tbody>
</table>

To detect the gait cycle and extract gait features from the acceleration signal collected by the smart phone, the acceleration along the x, y and z direction were used in gait analysis, as shown in
Figure 10. The acceleration waveform of gait cycle was shown in Figure 11.

Normally, acceleration signal of a single cycle gait shows characteristic peaks. In the $x$-axis, there is a smooth positive peak in swing phase and a sharp positive peak next to EC. In the $y$-axis, there are a smooth positive peak in swing phase and some positive peaks near EC event. However, abnormal gait sometimes shows peaks with different characteristics. Due to slow movement of Parkinson’s disease patients, the positive peak during the IC–loading phase in the $x$-axis is usually weak when distinguishing the IC peak from the next positive peak. In the $y$-axis, the amplitude during swing phase is similar to the amplitude of other peaks; therefore, it is difficult to exactly discern the swing phase.
Figure 10

The attaching position of the smart phone in walking task. The $x$, $y$ and $z$ are three axes of sensors and equivalent to horizontal, vertical and transverse direction respectively.
Figure 11

Acceleration waveform of gait cycle. The dotted lines are marked ECs, ICs, swing (SW) phase, and stance (ST) phase.
According to the characteristics of gait, the anterior–posterior acceleration \( a_x \) and proximal–distal acceleration \( a_y \) signals were processed sequentially to find the EC and IC peaks. The lateral acceleration \( a_z \) was highly dependent upon the individual, and therefore, was only used for non-walking period removal. The algorithm consists of seven steps as illustrated in Figure 12. Each step is described below in detail.

- **Step 1: Bias removal**

  The original acceleration signal at three directions, \( a_x, a_y, \) and \( a_z \) contains the gravitational acceleration, which is changed with slow transition movement. To remove the gravitational component, a second order low pass Butterworth filter (LPF) with 3-db cut-off frequency at 0.5 Hz was applied to the original acceleration signals.
to extract gravitational component (118). By subtracting the gravitational component from the original signal, the bias-removed signals \([a_{x0}, a_{y0}, a_{z0}]\) were obtained.

- Step 2: Non-walking period removal

  In order to assess the dynamics of activities, magnitude of the ankle’s acceleration \(||a||, a = [a_{x0}, a_{y0}, a_{z0}]\) was calculated. Periods of dynamic activity were searched using a simple threshold method just as Veltink et al. used (119). At first, \(||a||\) was filtered with the 0.1 Hz low pass filter, LPF\(||a||\). If a point in the filtered signal was above 1/10 of the value of gravity, that point was assigned to a dynamic point, Figure 13(a). In this study, we considered an isolated gait as a non-walking period. Therefore, when dynamic samples were connected for \(> 2\) s, those periods were grouped into candidates of walking periods. Other periods were grouped as non-walking periods.

- Step 3: Stance and swing phase discrimination:

  During candidates of walking periods, stance phases were detected. A stance phase is the phase when foot is in total contact with the ground. At this phase, the dynamics of activity is at the lowest point in the walking cycle. In order to determine the stance phase, \(||a||\) was compared with a threshold value LPF\(||a||\), where LPF\(||a||\) was obtained from 0.1 Hz low pass filtered \(||a||\). The gait signal at vertical direction \(a_{y0}\), was divided into sub-segments by 0.1 seconds. If more than two consecutive sub-segments had lower value than LPF\(||a||\), those were determined as stance phase. The other subsegments were determined as swing phase. The time stamp at beginning of a swing phase was extracted as end of contact (EC) time, and the time at end of a swing phase was extracted as initial of contact (IC) time.
Figure 13

Comparison between $\|a\|$ and $LPF\|a\|$ for a non-walking period removal.

- **Step 4: Peak detection:**
  
  Simple peak detection method was used in the detected swing phase (120).
  
  Among many detected peaks, peaks shown in vertical and horizontal acceleration signal simultaneously were selected.

- **Step 5: Removal of non-gait peak:**
  
  In the selected peaks, if the amplitude of a peak is lower than threshold value, which is set to $1/5$ of $LPF\|a\|$, or the shapes of $x$ and $y$ accelerations near a peak are different, those peaks are removed. In the remained peaks, if the interval of two consecutive peaks is less than 0.5 second, one of two peaks is removed selectively. At last, the remained peaks not removed by the above rules are determined to be the gait
peaks. The positive peaks and negative peaks are saved in each swing phase. The first positive peak in each swing phase is the acceleration of initial of a step (ACC_INI) and the last negative peak is the end of a step (ACC_END).

After these five steps were completed, the EC, IC, positive peaks and negative peaks were detected per swing phase. With these detected features, the following two steps were applied on \([a_x, a_y, a_z]\) to estimate stride length and walking speed.

- **Step7: Walking speed estimation:**

  With the detected swing phase in each gait cycle, walking speed is calculated. Walking speed is contributed by two directions of acceleration, \(x'\) and \(y'\) in world coordinate system, Figure 14(b). The \(x'\) direction is tangential to the ground at the device’s current location and roughly points east, and \(y'\) is tangential to the ground at the device’s current location and point’s towards the magnetic north pole. To compute the displacements along \(x'\) and \(y'\) axes, we first applied a low pass Butterworth filter with 2.5 cutoff frequency to \([a_x, a_y, a_z]\) to remove noise and walking unrelated signal. This filtered signal is denoted as\([a_{x1}, a_{y1}, a_{z1}]\)s. Because the acceleration signal\([a_{x1}, a_{y1}, a_{z1}]\) is measured by accelerometer in reference coordinate system of cell phone, shown in Figure 14(a), and because the position of cell phone changes with body movement, thus the coordinate system of cell phone is not constant and cannot be used as reference coordinate system for measuring either displacement or velocity. As the real world coordinate system is usually seemed as a constant system, the estimation of velocity and displacement needs to use real world coordinate as reference. Therefore, the acceleration signals measured in cell phone
coordinate system need to be transformed to real world coordinate system first. The acceleration signal in cell phone system, \([a'_{x1}, a'_{x1}, a'_{x1}]\), is transformed into signal real word coordinate system \([a'_{x1}, a'_{x1}, a'_{x1}]\) by:

\[
[a'_{x1}, a'_{x1}, a'_{x1}] = R \cdot \begin{bmatrix}
a_{x1} \\
a_{y1} \\
a_{z1}
\end{bmatrix}
\]

Where R is the rotation matrix, which is a 3 x 3 matrix saved with acceleration signal together in data collection by android system.

With transformed acceleration signal in real world coordinate system, we computed the associated velocities \(v_x(t)\) and \(v_y(t)\),

\[
v_x(t) = \int_0^t a'_{x1}(\tau) \, d\tau + v_x(0)
\]

\[
v_y(t) = \int_0^t a'_{y1}(\tau) \, d\tau + v_y(0)
\]

Where \(v_x(0)\) and \(v_y(0)\) are the initial horizontal and vertical velocity at the beginning of a swing phase, and \(t\) is the time offset from the beginning of a swing phase. The \(v_x(t)\) and \(v_y(t)\) were combined together for final walking speed in a swing phase \(v(t) = \sqrt{v_x^2(t) + v_y^2(t)}\).
Step 8: Stride length estimation:

After obtaining the velocities $v_x(t)$ and $v_y(t)$, horizontal displacement $s_x(t)$ and vertical displacement, $s_y(t)$, were obtained by integration,

$$s_x(t) = \int_0^t v_x(\tau) d\tau + s_x(0)$$

$$s_y(t) = \int_0^t v_y(\tau) d\tau + s_y(0)$$

Where $s_x(t)$ and $s_y(t)$ are the initial horizontal and vertical positions before the start of a swing phase. The continuous walking motion was segmented into a series of swing phase. In each swing phase, initial conditions for integration were assumed to be $v_x(0) = 0$, $v_y(0) = 0$, $s_x(0) = 0$, and $s_y(0) = 0$. The final stride
length was calculated by \( s(t) = \sqrt{s_x^2(t) + s_y^2(t)} \), where \( t \) is the duration of each swing phase.

The extracted swing phase duration, speed, stride length, acceleration at initial and end of a step were averaged of all swing phases to get the averaged value listed in Table 8.

In turning task, the sensed acceleration data at \( y \) direction \( a_y \) was used to identify each turning step. The 1\(^{st}\) to 4\(^{th}\) steps of the algorithm shown in Figure 12 were applied to \( a_y \) to detect the number of steps, NUM_TURN were detected for completing turning 360 degree, and the average turning speed TURN_SP divided the 360 degree to get time used.

2.2.2.3. Finger tapping

In finger tapping test, individuals in tests were requested to use their index finger to tap a target appearing on the center of smart phone screen. The timestamp of each attempt tapping the target was saved and marked with whether success or failure of hitting the target. The number of tapping (NUM_TAP) within 10 seconds, the average interval (INTVL_TAP) between two taps and the tapping frequency (FREQ_TAP) were calculated as finger tapping features, shown in Table 10.

Table 10

The extracted features from finger tapping test.

<table>
<thead>
<tr>
<th>Finger tapping Features</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUM_TAP</td>
<td>The number of tapping on screen in 10 seconds.</td>
</tr>
<tr>
<td>FREQ_TAP</td>
<td>The average finger tapping frequency.</td>
</tr>
<tr>
<td>INTVL_TAP</td>
<td>The average interval between two attempts to tap the screen.</td>
</tr>
</tbody>
</table>
2.2.3. Decision support

The decision support module provides critical symptom detection and disease severity estimation in this system. Here we utilized a subset of data mining techniques that are suitable for assessing whether different disease status are marked by specific patterns or disease progress trends from the extracted motion features. We used supervised learning method Support Vector Machine (SVM) to detect critical symptoms, including bradykinesia, fall, gait difficulty, freezing of gait, postural stability, and hand tremor, and use regression model to estimate the Parkinson’s disease stage in term of Hoehn & Yahr score and motor disabilities severity on UPDRS scale. All constructed decision support models for PD assessment in this study are listed in Table 11.
Table 11

Decision support models in smart-phone based PD monitoring and evaluation system.

The predictors (features), predicated value, and type of model are listed per model. (The descriptions of referenced predictors are listed in Table 8, Table 9, and Table 10)

<table>
<thead>
<tr>
<th>Model ID</th>
<th>Predictors</th>
<th>Predicated Value</th>
<th>Predicated Value Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVM_1</td>
<td>Age, Disease duration, CT, SL, SP, AVG_ACC, NUM_TURN, TURN_SP, NUM_TAP, TAP_FREQ, INTVL_TAP</td>
<td>Bradykinesia</td>
<td>Binary classification</td>
</tr>
<tr>
<td>SVM_2</td>
<td>Age, Disease duration, CT, SL, SP, ACC_AVG, NUM_TURN, TURN_SP</td>
<td>Fall</td>
<td>Binary classification</td>
</tr>
<tr>
<td>SVM_3</td>
<td>same as SVM_2</td>
<td>Gait difficulty</td>
<td>Binary classification</td>
</tr>
<tr>
<td>SVM_4</td>
<td>same as SVM_2</td>
<td>Freezing of gait</td>
<td>Binary classification</td>
</tr>
<tr>
<td>SVM_5</td>
<td>same as SVM_2</td>
<td>Postural stability</td>
<td>Binary classification</td>
</tr>
<tr>
<td>SVM_6</td>
<td>Age, Disease duration, NUM_TAP, LAG, INTVL_TAP, PF4_6, %PF4_6, PR, PF0_20, PEAK_POWER, AVG_ACC</td>
<td>Hand tremor</td>
<td>Binary classification</td>
</tr>
<tr>
<td>REG_1</td>
<td>Age, Disease duration, CT, SL, SP, AVG_ACC, NUM_TURN, TURN_SP, NUM_TAP, FREQ_TAP, INTVL_TAP, PF4_6, %PF4_6, PR, PF0_20, PEAK_POWER, AVG_ACC</td>
<td>Hoehn&amp;Yahr Stage</td>
<td>Numeric: 0, 1, 1.5, 2, 2.5, 3, 4, 5.</td>
</tr>
<tr>
<td>REG_2</td>
<td>same as SVM_6</td>
<td>UPDRS: Tremor at rest</td>
<td>Numeric: 0, 1, 2, 3, 4</td>
</tr>
<tr>
<td>REG_3</td>
<td>same as SVM_3</td>
<td>UPDRS: Gait difficulty</td>
<td>Numeric: 0, 1, 2, 3, 4</td>
</tr>
<tr>
<td>REG_4</td>
<td>same as SVM_5</td>
<td>UPDRS: Posture stability</td>
<td>Numeric: 0, 1, 2, 3, 4</td>
</tr>
</tbody>
</table>

2.2.3.1. Predictive variable selection

As described in 2.2.2 Motion data analysis section, specific motion features were extracted from the designed motion tasks in this study. These motion features were used...
as predictors in constructing predictive models for PD symptom detection and disease severity detection. Because each PD symptom impairs different aspects of patients’ motor ability, we selected different motion features to compose base predictor set for each predictive model specifically. With a base predictor set, an original regression model was constructed and then stepwise backward selection steps were applied to reduce the dimension of predictors.

In hand resting tremor detection, the predictors were chosen from the motion features extracted from hand resting tremor task. Based on the frequency characteristics of hand resting tremor motion signal, the acceleration signal between 4~6 Hz range is an important indicator of hand resting tremor (111, 116). Several studies have reported using power spectrum analysis for detecting hand resting tremor, and discussed the feature selection results(121). Based on these existing results and heuristic selection, the power of motion data between 4 ~ 6 Hz (PF4_6), fraction of power of motion data between 4 ~ 6 Hz (%PF4_6), power ratio of the motion data in 3.5~ 15Hz to 0.15 ~ 3.5 Hz frequency components (PR), total power of motion data from 0 ~ 20 Hz( PF0_20), the peak power value of hand resting tremor acceleration (PEAK_POWER), and average acceleration of hand resting tremor (AVG_ACC) were selected as the base predictor set for hand resting tremor predictive models. Besides these selected features, patient age and disease duration were added into the predictor set, considering the association of these two factors with PD progress.

In detecting and estimating lower body motor disabilities, including fall, gait difficulty, freezing of gait and postural stability, we composed the base predictor set from walking and turning tasks. In the result of PART 2, the step length, walking speed, and
the number of steps used for completing turning 360 degrees, have shown strong
association with balance difficulty, freezing of gait (FOG), gait difficulty, and postural
stability. Therefore, the average gait cycle time (CT), average stride length (SL), average
working speed (SP), average acceleration during walking (AVG_ACC), number of step
used to finish turning 360° (NUM_TURN), and turning speed (TURN_SP) were selected
to compose the base predictor set for lower body disability assessment.

One study using finger tapping test for detecting bradykinesia reported strong
association between the speed of finger tapping and bradykinesia(115). Therefore, for
bradykinesia detection, the speed of finger tapping was measured using the number of
tapping in 10 seconds (NUM_TAP), average finger tapping frequency (FREQ_TAP), and
average interval between two taps (INTVL_TAP). These three variables were chosen as
base predictor set for bradykinesia detection.

In stepwise backward feature reduction step, the F test criteria at significance
level at $\alpha = 0.1$ was used. We eliminated the predictor with the lowest F value for the test
of significance of the predictor, conditioned on the F-value being smaller than the criteria
value, $F_0$. The criteria $F_0$ value was pre-defined at significance level of $\alpha = 0.1$, which is
$F_0 = 3.14$. Next, we fitted the reduced model (having removed the predictor from the
original model), and remove from the reduced model the predictor with the lowest F-
value for the test of significance of that predictor. And so on. The backward stepwise
selection procedure ends when no more predictor can be removed from the model at
significance level $\alpha = 0.1$. 
2.2.3.2. Support Vector Machine (SVM) classification

SVM is a type of supervised machine learning technique that can automatically adjust its capacity according to the scale of a specific problem by maximizing the width of classification margin (122, 123). One of the benefits is its ability to explore more information from the given data by using a nonlinear function to map the original features into a high-dimensional space as shown in the following description.

Let the training set $D$ be $\{(x_i, y_i)\}_{i=1}^l$, with each input $x_i$ as one motion feature, and the output label as $y_i \in \pm 1$. With the nonlinear function $\Phi$, input vector $x$ is mapped to $\Phi(x)$. The optimal classifier is obtained by solving a quadratic optimization problem:

$$W(\alpha) = \sum_{i=1}^l \alpha_i - \frac{1}{2} \sum_{i,j=1}^l [\alpha_i \alpha_j y_i y_j \cdot \Phi(x_i) \cdot \Phi(x_j)]$$

With $0 \leq \alpha_i \leq C$, $i = 1, \ldots, l$, in which $C$ is the regularization parameter that controls the trade-off between model complexity and error. According to the Kuhn–Tucker theorem, samples that have $\alpha_i > 0$ must lie along with the margins of the decision boundary, which are called support vectors. To avoid computation of the inner product $\langle \Phi(x_i), \Phi(x_j) \rangle$ in a high-dimensional space, only those functions that can satisfy Mercer’s condition, $K(x_i, x_j) = \langle \Phi(x_i), \Phi(x_j) \rangle$, are considered to be the kernel. With the derived support vectors, the decision function for a new sample $x$ is expressed as

$$f(x) = \text{sgn} \left( \sum_{\text{support vectors}} y_i \alpha_i K(x_i \cdot x) \right)$$

In SVM, the kernel function plays as an important role in determining the final classification accuracy. Typical kernel functions include linear, polynomial and radial
basis function (RBF). Previous studies have reported the performance of different kernel functions in detection on motor disabilities. Kamruzzaman et al. compared different kernel functions for the diagnosis of cerebral palsy gait and reported that RBF and polynomial kernel function obtained good overall accuracy (124, 125). In Patel et al.’s study, it was reported that the polynomial kernel has a better performance than RBF kernel in bradykinesia classification (100). Since there are no analytical results about which kernel function is optimal in Parkinson’s disease status classification, we tested both polynomial and RBF kernel to determine the final SVM model.

The polynomial kernel is used for creating nonlinear classifier to maximum-margin hyperplanes. This kernel function allows the classifier to fit the maximum-margin hyperplane in a transformed hyperplane in the high-dimensional feature space. The polynomial kernel function is:

$$K(x_i, x_j) = (x_i \cdot x_j)^d$$

Where $d$ is the degree of the kernel function, which is determined by testing the performance of the SVM model through bootstrapping $d$ at different value [2, 3, 4, 5].

The kernel function of RBF is:

$$K(x_i, x_j) = \exp \left( -\frac{\|x_i - x_j\|^2}{2\sigma^2} \right)$$

Where $\sigma$ controls the width of the radius in RBF kernel and needs to be determined in training SVM model. In this study, the width of radius is optimized by grid-search and cross-validation procedures. The parameters are firstly digitized through a number of grids, and for each grid, performance of the SVM classifier is evaluated by
the 10 fold cross-validation(74). The optimal values can be found by exhaustively searching in all of the parametric grids.

2.2.3.3. Regression

To estimate general PD disease stage and each specific motor disability severity, the regression analysis approach was applied to predicate Hoehn & Yahr scale, and UPDRS motor scores, including tremor at rest, posture, gait, postural stability and bradykinesia. Considering the limited number of training data and the redundancy of motion feature, the Lasso regression was applied to eliminate the irrelevant or redundant predictors and diminish the effect of over-fitting(126). Lasso regression is a regularized version of least square approach for estimating regression model, by adding a regularization constraint into the loss function. The loss function of Lasso regression is defined as:

\[ L = \sum_{i} \left( y_{i} - \sum_{p} \beta_{p} x_{ip} \right)^{2} + \lambda \sum_{p} \| \beta_{p} \|_{1} \]

Where \( x_{ip} \) denotes the \( p \)th predictor (feature) in the \( i \)th record, \( y_{i} \) denotes the value of the response in \( i \)th data record, and \( \beta_{p} \) denotes the regression coefficient of the \( p \)th predictor. The norm-1 regularizer \( \sum_{p} \| \beta_{p} \|_{1} \) in Lasso regression typically leads to a sparse solution in the feature space, which means that the regression coefficients for most irrelevant or redundant features are shrunk to zero. The \( \lambda \) controls the model complexity. The regression coefficients are estimated by minimizing the value of loss function:

\[ \hat{\beta} = \arg\min_{\beta} \left\{ \sum_{i} \left( y_{i} - \sum_{p} \beta_{p} x_{ip} \right)^{2} + \lambda \sum_{p} \| \beta_{p} \|_{1} \right\} \]
2.3. Recruiting and Data Collection

To test this smart phone based Parkinson’s disease evaluation and monitoring system, an evaluation study on this system was tested in clinical setting at Muhammad Ali Parkinson Center (MAPC) at St Joseph’s Hospital and medical center (SJHMC). This evaluation study has been approved by IRB at St Joseph’s Hospital and Medical Center (IRB#:12BN033) and Arizona State University’s IRB (IRB#:1208008142). The collected data were analyzed to investigate using motion data for Parkinson’s disease evaluation, and validated the accuracy of using this system to detect critical Parkinson’s symptoms and to estimate disease severity.

- Recruiting

We recruited 40 out-patients, who have been diagnosed having Parkinson’s disease and have shown motor related symptoms, from the Muhammad Ali Parkinson Center (MAPC) at St Joseph’s Hospital and medical center (SJHMC). No pregnant women, children under 18 years of age, mentally incompetent individuals, and individuals with conditions that increase their vulnerability, were recruited. Patients who receive UPDRS (Unified Parkinson’s Disease Rating Scale) based evaluations as part of their regular clinic visits were invited to participate in this study. The study instructions and consent forms were given to patients and explained by the principal Investigator. If patients agree to participate in this study, they signed the consent forms, which were collected by the principal investigator. The participation is voluntary, and patients can withdraw from participation at any time during the study.

- Data Collection
Data collection was conducted at MAPC during patients’ regular clinical visit. Only one SAMSUNG Galaxy Epic smart phone was used in this study. To protect the privacy and identification of participants, once the patient agrees to participate in this study, a study ID was assigned to this patient for identification purpose. The study ID is a unique numeric number, and doesn’t include any information that could be potentially related to Protected Health Information, such as DOB, medical record ID, or SSN. This study ID is the only identification information that was stored with collected data, and was used to differentiate the data related to different patients. After the consent forms were collected, the test procedure was explained to participant during their regular visits. The principal investigator directed and assisted the participants to complete the full set of 3 tests.

- Hand resting tremor test: the principal investigator will assist patient to wear a wrist band on one hand, and attach the test device to the wrist band. Then the patient will keep one hand hanging for 20 seconds for data collecting. After the recording of one hand is done, the wrist band is taken off. Repeat the same procedure on the other hand.

- Gait difficulty test: physician will assist patient to attach the test device on one of their ankle using an ankle band. Then the patient will be asked to walk straight 25 feet, and then turn 360 degrees. The motion data during the patient’s walking and turning will be recorded. After the recording of one leg is done, the ankle band is removed. Repeat the same procedure on the other leg.

- Finger tapping test: the patient in the finger tapping test will be asked to use the index finger to hit the target alternative appearing on the across corner of cell
phone screen as fast as possible in 15 seconds. Then switch to the other hand to repeat
the same procedure.

All these three tests together take approximately 5 minutes for each participant to
complete. After test procedure was completed, participant’s disease status was evaluated
using UPDRS (Unified Parkinson’s Rating Scale) scale. The collected motion data and
UPDRS scores rated by physician were analyzed to validate the accuracy and provide
feasibility evidence of this smart-phone based approach.

3. Results

To evaluate the performance of this smart-phone based PD monitoring and
evaluation tool in detecting critical PD symptoms and to estimate motor disability
severity, 40 subjects were recruited for the clinical laboratory-based tests. The
recruitment and data collection procedure followed the protocol described in Recruiting
and Data Collection section. The motion features of PD patients at different disease
severity stages were extracted and compared first, and the accuracy of the predicative
models for PD symptom detection and motor disability severity estimation were analyzed
and discussed in this section.

3.1. General patient description

Table 12 shows the general characteristics of all 40 participants recruited in this
study. Among these 40 patients, 5 were female and 35 were male. Ages of the
participants ranged from 44 to 84, and the average age was 68.5 years old. The disease
duration distributes from 0 to 19 years, and the median disease duration was 6 years and
average disease duration was 6.6 years. Among all subjects, 16 of them were in early
disease stage (disease duration less than 6 years), and 24 subjects were in late disease
stage (disease duration more than 6 years). The average Hoehn & Yahr stage was 2.4. There were six subjects at stage 1, 13 subjects at stage 2, 12 subjects at 3, and three subjects at stage 4. No subjects at the stage 5 were recruited in this study. The severities of motor disabilities were evaluated by two movement disorder experts using UPDRS scale. If their evaluations differ, the third rater was invited. The detail scores for each UPDRS item, rated by experts, were shown in Table 12. In these 40 subjects, 10 of them had bradykinesia, 9 subjects had freezing of gait, 11 subjects had gait difficulty, 15 subjects had postural stability problems, and 5 subjects reported having falls on weekly basis. Because most of the recruited patients were from follow up clinic visits, not new diagnosed patients, therefore most of them, 32 subjects, were using levodopa when they participated in this study.
Table 12

Patients general characteristics and UPDRS scores (N = 40)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Median (Q1-Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>68.5±9.5</td>
<td>44-84</td>
<td>70(63-74)</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>6.6±4.0</td>
<td>0-19</td>
<td>6(4-8)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr stage</td>
<td>2.4±0.8</td>
<td>1-4</td>
<td>2(2-3)</td>
</tr>
<tr>
<td>UPDRS arising from chair score</td>
<td>0.5±0.8</td>
<td>0-3</td>
<td>0(0-1)</td>
</tr>
<tr>
<td>UPDRS posture score</td>
<td>1.0±1.1</td>
<td>0-4</td>
<td>1(0-2)</td>
</tr>
<tr>
<td>UPDRS hand resting tremor score</td>
<td>1.7±0.7</td>
<td>0-4</td>
<td>1(0-3)</td>
</tr>
<tr>
<td>UPDRS gait score</td>
<td>1.1±1.0</td>
<td>0-4</td>
<td>1(0-2)</td>
</tr>
<tr>
<td>UPDRS freezing of gait score</td>
<td>0.4±0.9</td>
<td>0-4</td>
<td>0(0-0)</td>
</tr>
<tr>
<td>UPDRS postural stability score</td>
<td>1.2±0.9</td>
<td>0-3</td>
<td>1(0-2)</td>
</tr>
<tr>
<td>UPDRS bradykinesia score</td>
<td>1.5±0.8</td>
<td>0-3</td>
<td>0(0-3)</td>
</tr>
<tr>
<td>UPDRS finger tapping score</td>
<td>1.0±0.8</td>
<td>0-3</td>
<td>0(0-2)</td>
</tr>
<tr>
<td>UPDRS dyskinesia score</td>
<td>1.7±0.6</td>
<td>0-4</td>
<td>1(0-4)</td>
</tr>
<tr>
<td>Presence of motor related disabilities:</td>
<td>Number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bradykinesia (Yes/No)</td>
<td>10/30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>freezing of gait (Yes/No)</td>
<td>9/31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gait difficulty (Yes/No)</td>
<td>11/29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>postural stability problem (Yes/No)</td>
<td>19/21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>falls (Yes/No)</td>
<td>5/35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2. Hand resting tremor analysis

As described in the system design and motor task design sections, the accelerometer signal of hand resting tremor is recorded through 3D accelerometer of the smart phone testing device. The signal profiles of the acceleration rate of hand resting tremor were analyzed to find the association between motion features of hand tremor motion and severity of Parkinson’s hand resting tremor. Amplitude of the fluctuation may vary with the change of severity of the tremor. The sample acceleration waveforms collected from participants whose UPDRS hand resting tremor scores were from 1 to 3 were shown in Figure 15. In Figure 15, the right hand column pictures show the comparison of acceleration waveforms of hand resting tremor from patients with different
UPDRS hand resting tremor scores. The pictures in right column are power spectrum density (PSD) plots according to the left acceleration waveform. The magnitude of PSD of hand motion acceleration demonstrated obvious difference between patients whose UPDRS hand resting tremor score were from 1 to 3. In the sample patients UPDRS hand resting tremor score = 1, shown in Figure 15 (A) right hand, the acceleration of hand motion was around 1 m/s². The corresponding power spectrum mainly dominated around 5 Hz, and the peak power was up to 20 (m/s²)². When hand resting tremor was severe, the acceleration rate of hand motion and the power spectrum density both exhibited substantial increasing tendency. As observed in Figure 15 (B), when the severity of hand resting tremor went up to 2, the average acceleration of hand motion was about two times greater than those patients whose hand resting tremor UPDRS score = 1 in Figure 15 (A). The power spectrum also displayed larger value, around 40 (m/s²)², and the peak power appeared at higher frequency at around 7 Hz, which showed in Figure 15 (B). From hand resting showed in Figure 15 (B) that tremor UPDRS score increase from 2 to 3, the peak power spectrum increased from 40 (m/s²)² to around 60 (m/s²)², and continuous large acceleration of hand tremor, mainly range from 3 ~ 5 m/s, was observed in Figure 15 (C). Therefore, from demonstration of the acceleration signal profile in hand resting tremor test, collected motion signal could capture the difference between hand motion data of PD patients who were at different severity stage of hand resting tremor. There is one point that needs to be pointed out. In previous studies about characteristic of Parkinson’s hand resting tremor, it was reported that the hand resting tremor mainly predominate between 4 ~ 6 Hz (111). In this study, our collected hand resting tremor data demonstrated the same characteristic. As demonstrated in right hand column pictures of
Figure 15, the hand resting tremor also mainly predominated between 4 ~ 6 Hz. This evidence also validated our method with the previous experimental result. Therefore, these acceleration waveform analysis and power spectrum anal results indicate that our smart phone based approach can effectively capture motion features of hand resting tremor and differentiate the motion patterns among different severities.

Figure 15

Acceleration waveform and power spectrum density (PSD) plot of hand resting tremor at different severity level. A) Hand resting tremor UPDRS score = 1; B) Hand resting tremor UPDRS score = 2; (C) Hand resting tremor UPDRS score = 3.
Statistics of extracted motion features from hand resting tremor test were shown in Table 13, in which the difference of motion features were compared between patients whose UPDRS hand resting tremor score < 2 and patients whose UPDRS hand resting tremor score ≥ 2. The average acceleration of those whose UPDRS hand resting tremor score < 2 was 0.6±0.2 m/s², and 1.7±0.4 m/s² for those UPDRS hand resting tremor score ≥ 2. In spectrum analysis, frequency response showed that the hand resting tremor was predominated in the frequency range between 4~6 Hz. The total power of hand resting tremor signal between 0 ~ 20 Hz was 100.7 (m/s²)² for patients whose UPDRS tremor score < 2, and 259.4 (m/s²)² for those whose UPDRS tremor score ≥ 2. The peak power was 53.7±13.2 for patients whose UPDRS tremor score < 2, and 75.2±16.6 for patients whose UPDRS tremor score ≥ 2. These comparison results indicated that motion features of hand resting tremor represent significant difference between different severities of hand resting tremor. For those patients suffer severe hand tremor (UPDRS tremor score ≥2), the power of acceleration was between 4~6 Hz (PF4_6), and total power (PF0_20), power ratio (PR), peak power (PEAK_POWER), and average acceleration (AVG_ACC) were significant greater than those with mild hand tremor (UPDRS tremor score < 2).

Table 13

Extracted motion features from hand resting tremor test, results were divided into two groups, UPDRS hand resting tremor <2, and UPDRS hand resting tremor ≥ 2. (The meaning of each motion feature is described in Table 8)

<table>
<thead>
<tr>
<th>Hand resting tremor motion features</th>
<th>UPDRS tremor score &lt; 2</th>
<th>UPDRS tremor score ≥ 2</th>
<th>P-value</th>
<th>Significance (α=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF4_6</td>
<td>6.1±2.1</td>
<td>14.4±5.2</td>
<td>0.04</td>
<td>*</td>
</tr>
<tr>
<td>%PF4_6</td>
<td>0.07±0.01</td>
<td>0.06±0.02</td>
<td>0.54</td>
<td></td>
</tr>
</tbody>
</table>
### Table 9

<table>
<thead>
<tr>
<th>PR</th>
<th>0.79±0.4</th>
<th>1.1±0.35</th>
<th>0.09</th>
<th>*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF0_20</td>
<td>100.7±25.9</td>
<td>259.4±56.0</td>
<td>0.014</td>
<td>*</td>
</tr>
<tr>
<td>PEAK_POWER</td>
<td>53.7±13.2</td>
<td>75.2±16.6</td>
<td>0.039</td>
<td>*</td>
</tr>
<tr>
<td>AVG_ACC</td>
<td>0.6±0.2</td>
<td>1.7±0.4</td>
<td>0.006</td>
<td>*</td>
</tr>
</tbody>
</table>

#### 3.3. Gait analysis

In the course of Parkinson’s disease development, motor disabilities in lower body play substantial effects on impairing walking, balance, postural stability, and even induce to falling. To effectively assess the status of PD in home based monitoring, the PD patients’ motor performance in lower body was investigated through measuring gait performance. To measure gait performance, the accelerations in three directions were collected during patients’ walking and turning. Gait features in turning and walking, as listed in Table 9, were extracted by using the gait signal processing analytics, which were discussed in CHATPER 3, section 2.2.2. In order to give an intuitively introduction about acceleration changes during walking, acceleration waveforms of sample patients with different gait difficulty severities were first shown in Figure 16. Then the extracted gait features were compared between patients whose UPDRS gait difficulty score < 2 and those whose ≥ 2 in student T test.

The sample acceleration waveforms of patients during working were shown in Figure 16. In Figure 16, the demonstrated gait waveforms were captured from four typical patients with UPDRS gait difficulty score at 0, 1, 2, and 3 respectively. Black dot line on each figure marked each gait cycle, based on automatically analysis result from designed analytics. Figure 16 (A) showed the gait acceleration waveform of PD patients who had UPDRS gait score = 0. The gait profile exhibited consistent repeating pattern, and the swing and stance phrase showed clear boundaries. The peak acceleration during...
each gait also illustrated consistent value, and the positive peak instant acceleration was up to 8 m/s², while the negative peak instant acceleration was up to 12 m/s². When gait difficulty was worse, the gait pattern and acceleration values exhibited obvious difference among acceleration waveforms. In Figure 16 (B), which is from a PD patient with UPDRS gait difficulty score at 1, gait pattern showed different traits. A consistent gait cycle was still observed in this patient and the boundaries between each gait cycle were still clear. But the peak accelerations during walking were much lower - below 5 m/s². For a patient whose gait difficulty was evaluated at 3, shown in Figure 16 (C), the gait cycle became blurry and the acceleration profile showed inconsistent and unstable pattern. The peak acceleration during walking was primarily around 2 m/s², however in some steps the peak acceleration can suddenly climbed to 10 m/s². Figure 16 (D) showed the data from a patient with gait difficulty score at 3, coming along with freezing of gait (FOG). It can be seen that this patient’s gait cycle was discontinuous, and there was a long gap from 3.6s to 5.3s, and from 6.2s to 8.2 s, during which strong resistance to moving appeared.
Figure 16

Acceleration waveforms in walking. A) UPDRS gait score = 0; B) UPDRS gait score = 1; (C) UPDRS gait score = 2; (D) UPDRS gait score = 3.
Based on the intuitive illustration of acceleration waveforms and discussions, quantitative features of gait were extracted. As described in Table 9, the listed motion features during walking and turning were extracted from walking and turning from all 40 patients. These motion features were compared between patients who do not have gait difficulty (UPDRS gait difficulty score < 2) and who have gait difficulty (UPDRS gait difficulty score ≥ 2). The comparison results were shown in Table 14. The average gait cycle time (CT) of patients not having gait difficulty was 1.1±0.32s, smaller than the average gait cycle time at 1.22±0.49s from patients having gait difficulty. The stride length (SL) and walking speed (SP) showed significant greater value on patients not having gait difficulty than patients having gait difficulty. The average stride length (SL) of patients without gait difficulty was 1.26±0.17m and was 1.07±0.29m for patients with gait difficulty. The average walking speed of patients without gait difficulty was faster
than the patients with gait difficulty, 1.15±0.20m/s vs. 0.87±0.28m/s. The average acceleration value during walking straight was 5.2±1.1m/s² for patients without gait difficulty, while 3.6±1.7m/s² for patients with gait difficulty. Except the walking cycle time (CT), all other three walking features SL, SP, and AVG_ACC were significant different between patients having gait difficulty and not having gait difficulty.

On turning task, the number of steps completing a whole round and turning speed was calculated from the collected motion data. For patients without gait difficulty, the average steps for completing a whole round was 3.1±0.9 steps, and the average turning speed was 79.1±8.49 degree/s. As expected, for patients with gait difficulty, 5.4±1.1 steps were needed to complete a whole round and the average turning speed was 53.7±6.98 degree/s. The difference of numbers of turning steps and turning speed were significant between patients with and without gait difficulty.

Table 14

Extracted motion features from walking and turning test, the results are divided into two groups, UPDRS gait score <2, and UPDRS gait score ≥ 2. (The meaning of each motion feature is described in Table 9)

<table>
<thead>
<tr>
<th>Gait Features</th>
<th>UPDRS gait score &lt; 2</th>
<th>UPDRS gait score ≥ 2</th>
<th>P-value</th>
<th>Significance (α=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking straight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT(s)</td>
<td>1.1±0.32</td>
<td>1.22±0.49</td>
<td>0.076</td>
<td></td>
</tr>
<tr>
<td>SL(m)</td>
<td>1.26±0.17</td>
<td>1.07±0.29</td>
<td>0.035</td>
<td>*</td>
</tr>
<tr>
<td>SP(m/s)</td>
<td>1.15±0.20</td>
<td>0.87±0.28</td>
<td>0.026</td>
<td>*</td>
</tr>
<tr>
<td>AVG_ACC(m/s²)</td>
<td>5.2±1.1</td>
<td>3.6±1.7</td>
<td>0.038</td>
<td>*</td>
</tr>
<tr>
<td>Turning 360°</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUM_TURN</td>
<td>3.1±0.9</td>
<td>5.4±1.1</td>
<td>0.042</td>
<td>*</td>
</tr>
<tr>
<td>TURN_SP(degree/s)</td>
<td>79.1±8.49</td>
<td>53.7±6.98</td>
<td>0.039</td>
<td>*</td>
</tr>
</tbody>
</table>
3.4. Finger tapping analysis

In finger tapping test, the participants were required to use their index figure to continuously tap a target on smart phone screen as soon as possible for 10 seconds. Timestamp of each tapping was recorded by the smart phone. From the recorded timestamp, the numbers of tapping screen was counted, and the average interval and frequency of tapping were derived. Because finger tapping test is a typical clinical measurement for bradykinesia, the calculated statistics were compared between patients who have bradykinesia and those who do not, shown in Figure 17. Patients who do not have bradykinesia have averagely 25.4±2.8 times tapping in 10 seconds, while patients who do have bradykinesia have 16.7±3.3 times. The average interval between two tapings was 0.4±0.08s for patients without bradykinesia and 0.67±0.11s for patients with bradykinesia. This result suggests that finger tapping speed can be significantly affected by bradykinesia, which potentially decreases the agility finger as well as the speed of finger movement.
3.5. Predicative models evaluation

As discussed in 3.2~3.4, the motion features extracted from hand resting tremor, waling, turning and finger tapping, show potential to capture the difference between different severities of PD symptoms. In this section, these motion features were further used to construct predicative models to rate disease stages, to detect critical parkinsonian symptoms, and even to estimate the severity of some motor disabilities. Using the methods described in 2.2.3 in this chapter, estimations to Hoehn&Yahr stage, hand
resting tremor, gait difficulty, bradykinesia, postural stability and freezing of gait were attempted in this study.

3.5.1. Disease stage estimation

In clinical practice, the Hoehn&Yahr (H&Y) stage is widely used for assessing the stage of Parkinson’s disease. In home based PD evaluation, the estimation of Hoehn&Yahr stage is an indicator of current disease status for PD patients. Therefore, a predictive model to estimate H&Y stage was first constructed using Lasso regression(126). Regression results are shown in Figure 18. The correlation coefficient of the regression model for H&Y estimation was $r = 0.81$, the averaged absolute error was 0.26, and the root mean squared error was 0.34. The scatter plot of this regression model, in Figure 18(A), exhibited a strong correlation between predicted H&Y stage and actual H&Y stage. The box plot, in Figure 18(B), showed the range of estimated stage and error of each H&Y stage. For patients at actual H&Y stage 1, 1.5, 2, 2.5, 3, and 4, the average estimated H&Y stage were $1.30 \pm 0.3$, $1.65 \pm 0.15$, $2.01 \pm 0.19$, $2.43 \pm 0.21$, $2.99 \pm 0.16$ and $3.7 \pm 0.12$ respectively. This regression model showed strong correlation between extracted motion features and H&Y stage, and the accuracy of the estimation results was sufficient for estimating Parkinson’s disease stage in this smartphone based approach.
Figure 18

Result of regression model to estimate the H&Y stage. (A) The scatter plot on predicated vs. actual H&Y motor stage, with correlated efficient $R^2=0.81$. (B) The box plot to show the range of estimated H&Y stage with average error, grouped in each H&Y stage.

(A)
3.5.2. Detecting Motor disabilities

For Parkinson’s disease, the hand tremor, gait difficulty, bradykinesia, and postural stability are critical symptoms. With the progress of disease and decline of motor performance, the motor disabilities can future induce to freezing of gait and fall, which could greatly impair living quality of PD patients. In this designed system, the above critical symptoms of PD plus freezing of gait and fall were detected using the extracted motion features from acceleration captured by smart phone. Six classification models were constructed to detect whether an individual suffers hand resting tremor, gait difficulty, postural stability, freezing of gait, bradykinesia, freezing of gait or predicating falls. These classification models were trained using Support Vector Machine (SVM) approach (61, 124). The precision and recall of each model were calculated to evaluate the accuracy and to provide the benchmark for validation of this smart phone based PD evaluation approach.
The evaluation results of these six models are shown in Table 15. For hand resting tremor detection, recall and precision were 0.77 and 0.82 respectively. The accuracy of bradykinesia detection was at the same level as hand resting tremor, with the recall of 0.77 and precision of 0.83. On detecting lower body motor disabilities, especially the walking associated disabilities, the results showed higher accuracies, which were above 80% in both recall and precision value. High accuracy in detecting the walking related disabilities might result from that features extracted in walking and turning tasks are highly correlated to walking related disabilities. As listed in Table 15, in gait difficulty, freezing of gait and postural stability detection, the recall were 0.89, 0.87 and 0.84 respectively, and accordingly the precision value were 0.81, 0.87 and 0.90. For fall detection, the recall was 0.75, and the precision was 0.76. The F measure combines precision and recall in evaluating the overall performance of the classification model. In all these six models, the models with lowest F measure, 0.77, were for bradykinesia and fall detection. F measure of models for gait difficulty, freezing of gait, and postural stability detection were all above 0.85, which means the very high accuracy to detect the existence of the symptoms. Overall, these classification results indicated high accuracy for detecting some key Parkinson’s disease related motor disabilities from using the motion data collected from our smart phone based system. The analytics for processing and analyzing motion data were also proved expected functionality and promising future in home based PD assessment and monitoring. Using the smart phone application and the functionality of analytics, physicians can find appearance of patients’ new symptoms at earlier time, and patients can also have better understanding of their current disease status and progress tendency.
Table 15

Classification results of detecting motor disabilities

<table>
<thead>
<tr>
<th></th>
<th>Hand resting tremor</th>
<th>Bradykinesia</th>
<th>Gait difficulty</th>
<th>Freezing of Gait</th>
<th>Postural Stability</th>
<th>Fall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recall</td>
<td>0.77</td>
<td>0.73</td>
<td>0.89</td>
<td>0.87</td>
<td>0.84</td>
<td>0.75</td>
</tr>
<tr>
<td>Precision</td>
<td>0.82</td>
<td>0.83</td>
<td>0.81</td>
<td>0.87</td>
<td>0.90</td>
<td>0.76</td>
</tr>
<tr>
<td>F Measure</td>
<td>0.79</td>
<td>0.77</td>
<td>0.85</td>
<td>0.87</td>
<td>0.86</td>
<td>0.77</td>
</tr>
<tr>
<td>ROC Area</td>
<td>0.74</td>
<td>0.78</td>
<td>0.85</td>
<td>0.84</td>
<td>0.87</td>
<td>0.76</td>
</tr>
</tbody>
</table>

3.5.3. Estimating UPDRS score of motor disabilities

Section 3.5.2 discussed the results of using our smart phone based system to detect substantial motor disability symptoms. However, these functionalities are based on binary classification, which can only indicate whether a patient has or not have a symptom. It can hardly tell how severe one symptom is. In current Parkinson’s disease assessment, UPDRS measurement is a widely accepted standard for assessing severity of parkinsonian symptoms. In order to make this smart phone system more compatible with UPDRS measurement, motion features captured by the smart phone are required to be converted in order to predicate UPDRS scores. Otherwise, information captured by this system is less meaningful for physicians and patients to really obtain the disease severity and further track the disease progress. In order to bridge this conversion, UPDRS hand resting tremor score, gait difficulty score, postural stability score and bradykinesia score have been estimated using Lasso regression. The accuracy and the estimation error of each regression model were discussed in this section.
Figure 19

The result of regression model to estimate UPDRS hand resting tremor score. (A) The scatter plot on predicted vs. actual hand resting tremor score. (B) The box plot to show the range of estimated score and the estimation error.

(A)
Results of estimation of hand resting tremor score are shown in Figure 19. The correlation coefficient of the regression model on hand resting tremor score estimation was $r = 0.74$, and the averaged absolute error was 0.55. The box plot showing the estimation range and error of estimated tremor score in Figure 19 (B) displayed that the average estimation on patients with actual hand resting tremor score of 0 were $0.27 \pm 0.21$, the average estimation for patients with actual hand resting tremor score of 1 were $0.93 \pm 0.17$, the average estimation for patients with actual hand resting tremor score of 2 were $2.01 \pm 0.15$, and the average estimation score were 2.94 for patients whose actual hand resting tremor score were $3 \pm 0.24$. Because the UPDRS scores are integer value, by rounding the estimated hand resting tremor score by regression model, the severity of hand resting tremor can be estimated effectively.
Figure 20

The result of regression model to estimate UPDRS gait score. (A) The scatter plot of estimated vs. actual gait score. (B) The box plot to show the range of estimated gait score and the average estimation error.
Figure 20 showed the results of estimation on UPDRS gait score using our constructed regression model. The correlation coefficient of regression model for gait score estimation was $r = 0.79$, which suggests a strong correlation between extracted motion features and the UPDRS gait difficulty score. The average absolute estimation error was 0.46. Since the UPDRS scores are all integer value, most of the estimation error can be eliminated by rounding the output of the regression model. The box plot, Figure 20 (B), demonstrated the output range regression model for groups of patients with UPDRS gait difficulty score of 0, 1, 2 and 3. The average estimation on gait difficulty score was $0.24 \pm 0.11$ for patients with actual gait difficulty score of 0, $0.89 \pm 0.28$ for patients with actual gait difficulty score of 1, $1.83 \pm 0.25$ for patients with actual gait difficulty score of 2, and $2.93 \pm 0.22$ for patients with actual gait difficulty score of 3.
Figure 21

The result of regression model in estimating UPDRS postural stability score. (A) The scatter plot showing the predicted vs. actual postural stability score. (B) The box plot to show the range of estimated postural stability score and the average estimation error.
Figure 21 showed the results of regression model in estimating UPDRS postural stability score. The correlation coefficient of regression model for postural stability score estimation was $r = 0.76$, and the average absolute error was 0.38. The box plot, in Figure 21 (B), illustrated that the average value of estimated gait score were $0.34 \pm 0.15$, $1.06 \pm 0.24$, $2.05 \pm 0.20$, and $2.99 \pm 0.23$ for patient groups with actual postural stability score of 0, 1, 2, and 3 respectively.

In this section, estimation of UPDRS scores on hand resting tremor, gait difficulty and postural stability were investigated and the results suggested that using motion features captured by our smart phone system are feasible to be used to estimate severities of some parkinsonian motor disabilities’. Correlation coefficient from 0.6 ~ 0.8 suggests strong association. In this study, all these regression models showed strong associations between motor disabilities of Parkinson’s disease and motion features captured using our
designed smart phone system. These strong associations and accuracy results indicated possibility and feasibility of using this smart phone system to provide clinical meaningful information in Parkinson’s disease home based monitoring.

4. Discussion

It is expected that home based disease monitoring will be increasingly applied in the coming years with widely implementation of healthcare information technologies (82). Monitoring and evaluation of Parkinson’s disease at home could reduce costs, enable follow-up of disease status change after specific medical treatments, and facilitate longitudinal research study by tracking disease progress. In this context, we developed a home based evaluation and monitoring system for Parkinson’s disease assessment. This system takes advantage of the current smart phone as the platform to provide integrated functions including data collection, storage, analysis and information transmission. To achieve this purpose, we developed the patient end application on smart phone, server end analytics, and tested this system on Parkinson’s patients through evaluating the accuracy of this system.

While the home monitoring enables longitudinal disease monitoring and home based evaluation, it also places stringent constraints on the system: cost, size, unobtrusiveness, ease of use and maintenance of signal quality. The system developed in this study work is simple to use, safe and does not require extra setting and equipments. The only equipment required is a smart phone with built-in 3D accelerometer. During disease evaluation, patients only need to briefly interrupt their daily activities, bind the smart phone to their hands and ankles while completing some simple walking, turning
and finger tapping activities. The system has a user-friendly interface that records display collected motion signals and supports wireless communication with server side.

In the experimental validation, we collected motion data from 40 parkinsonian subjects, analyzed these motion data and compared it with clinical experts’ evaluation on the patients’ disease status to study the correlation between using motion features. The validation results indicated that this smart phone based system can effectively capture the important motion features from acceleration signals to differentiate PD severity and identify critical symptoms. The predicative models constructed in this study to estimate disease severity indicated high accuracy and promising future. The motion features extracted from motion acceleration signals are more objective and quantitative than subjective rating performed by physicians in PD assessment. The accurate rates to detect hand resting tremor, bradykinesia, gait difficulty, freezing of gait, postural stability and fall were 79%, 77%, 85%, 87%, 86%, and 76% respectively. All these accuracies are between 70~90%, which indicate moderate diagnostic accuracy. The correlation coefficient for estimating of Parkinson’s disease stage is $r = 0.81, 0.74$ for hand resting tremor, $0.79$ for gait difficulty and $0.76$ for postural stability. The correlation coefficient results indicated strong association between the motion features extracted from acceleration signals and the severity of symptoms. The number of experimental subjects, 40 in this study, to some extends, limits the accuracy of symptoms diagnostic and disease severity estimation. In future study, with the increase of available data, these predictive models will be refined to achieve higher accuracy.

One limitation of the study is that the proposed system for home based PD monitoring only has limited in clinical validation, and lacks home setting validation. The
present work was more dedicated to describe a new design and development of a novel system, and to provide preliminary patient tests data to show that the system is useful in motor disability measurement and to prove the future feasibility of using this system in remote home based PD evaluation and monitoring. It is not a demonstration that this system will be clinically successful in monitoring Parkinson’s patients. This would require broader and more sufficient clinical studies, which requires more dedicated patient tests on both clinical setting and home setting. Because of limitation of funding, patient resources and the restrict requirement of FDA approval, the clinical validation aim is beyond the scope of this study.

Moreover, another limitation of this study is the lack of sufficient validation on the effect of intra-individual variation on assessing severity of Parkinson’s disease by using smart phone. Because the pattern of motion features might differ from patient to patient even though they are at the same severity level, using general decision support models for assessing PD severity on all patients is more bias induced. Furthermore, it is possible that for same PD patient, the motion features may also represent different signature at different situations, such as environmental or physiological changes. These variations can affect the accuracy of assessment, and reduce the usefulness of this system for home-based PD monitoring. To reduce the influence of intra-individual variation on PD assessment, more sophisticate design of experiment will be needed in future to validate analytical algorithms and decision support models. One validation approach is to group similar patients into one experimental group based on demographic and disease characteristics. In each group, the motion data will be analyzed and compared with rated UPDRS scores. The predicative models and analytical algorithm will be built specifically
for each patient group. By this way, this group based validation can provide more sufficient and extensive information to prove the usefulness of smart phone based evaluation in home-based PD assessment and monitoring. The other validation needed in future is to test a same patient in a period of time and sample multiple motion data, in order to collect and test the change of collected motion data with the change of patient living situation or other physiological situation change. However, these two validations rely on recruiting more patients and requiring enough funding support. With current limitations in funding and time frame, these validations have not been accomplished in current stage of this study, and are proposed in next stage of this study.
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