EARLY DIAGNOSIS AND OBJECTIVE ASSESSMENT OF PATIENTS WITH NEURAL AND CARDIOVASCULAR DISEASES

Ákos Jobbágy

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Introduction

Many cardiovascular and neural diseases remain undetected until the symptoms are stressed. Usually this means a progressive stage of the disease. Early diagnosis and the corresponding treatment would mean a better quality of life for the patient and a more effective and cost saving health care system for the society.

As the expected life time increases the problem of sustaining the good health of the society needs to be addressed. World life expectancy more than doubled over the past two centuries, from roughly 25 years to about 65 for men and 70 for women. The change in life expectancy for women published in [Oeppen and Vaupel, 2002] is shown in Figure 1.

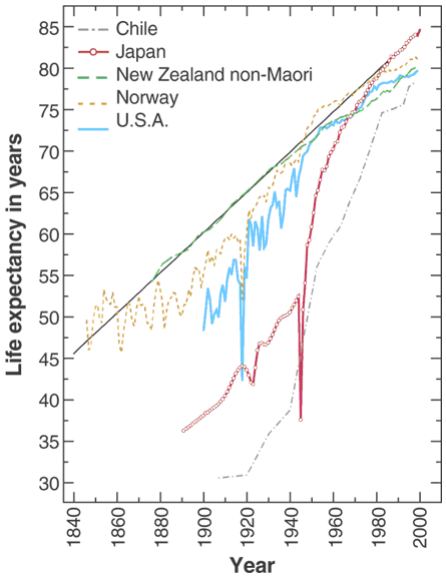


Figure 1 Change in life expectancy for women in 5 countries.

It is estimated that life expectancy further increases. National health care systems should be accommodated; the prevalence rates of many diseases substantially change over age. In Japan, where the expected life time is longer than in other developed countries (78 year for men and 85 for women in 2002), sustaining of good health is promoted by home health monitoring [Togawa, 1998]. The average medical expenditure per person is significantly higher for the elderly than for younger people. In Japan the increase in national medical expenditure by far exceeded the increase in GDP in the last decade of the XXth century. Home health monitoring accounts for an increasing share in Japan's medical expenditure. It is estimated that in the United States 20 – 30 % of patients receive inappropriate care [Starfield, 2000]. Many diseases can be treated more effectively and at a lower cost if early signs are detected. The continuous monitoring requires appropriate instrumentation, including sensors

and signal processing. However, the monitored person gets a better care only if the processed patient data are seen by medical experts in time.

In Hungary cardiovascular diseases are the leading cause of death, being responsible for about half of the deaths [Farsang 1997], [www.bel2.sote.hu/hipertonia], [Nagy 2002]. Furthermore, hypertonia and arteriosclerosis affect a high percentage of the population. It is estimated that 30 % of the Hungarian population has hypertonia, over age 65 this ratio increases to approximately 65 % [Losonczy and Rosivall 1997]. Diagnosis in the early stage would make it possible to start medication and treatment to prevent the deterioration of the patients. The presently existing blood pressure meters either require trained operator or do not assure accurate measurement [NHBPEP/NHLBI/AHA Working Meeting on Blood Pressure Measurement, 2002]. An easy-to-use and accurate device would help in early detection and home self-monitoring. This latter would mean an effective aid for the general practitioner to monitor the patient; giving a feedback for treatment and medication. Good solutions exist to transmit medical recordings of the patient to the doctor. [Kékes, 2003] describes a tele-ECG system, [Celler et al., 1999] shows that home telecare improves care and reduces cost. Further advantage of such systems is that the medical expert and the patient do not have to be at the same place. [Anliker et al., 2004] describes a wearable device that permanently monitors physiological parameters.

The early diagnosis of Parkinson's disease and the continuous monitoring of the patients' state would result in a more effective medication. The diagnosis – especially the early diagnosis – of neural diseases is a sophisticated problem. There are symptoms common for different neural diseases. Elderly people above age 65 may exhibit symptoms of parkinsonism (Parkinson's syndrome) in mild form even if they are not affected by the disease. [Duncan and Wilson, 1989] noticed that nearly one-half of the neurologically normal elderly seen in a community had at least one feature of parkinsonism. At least 20 % of Parkinsonian patients are misdiagnosed in the early stage [Findley, 1993], [Groset, 2001], [Schrag et al., 2002]. This usually means a wrong medication causing unnecessary discomfort to the patient and expenses to society. In the United States Parkinson's disease affects more than one million people. 15 % of Parkinsonian patients are diagnosed under 40, incidence increases with age [www.pdf.org/AboutPDF/index.cfm, the web page of the Parkinson's Disease Foundation].

The research work co-ordinated and led by me at the Department of Measurement and Information Systems, Budapest University of Technology and Economics has aimed at objectively characterising persons' state based on the measured data. The research work has been

aided by medical doctors. Co-operation with the Semmelweis University, Szt. Imre Hospital, National Rehabilitation Institute and Szt. János Hospital has been extremely helpful.

The human control mechanisms are very sophisticated and the related models are rarely quantitative. For the engineer it is rather unusual to experience that even the same person under seemingly identical conditions exhibits different observables without a known reason. Instead of strict rules being applied for non-living systems, we can usually identify tendencies and relate probabilities to them at the present level of knowledge while modelling living systems. The more we know of the human organism the better we realise that its operation is difficult to understand and describe by the general methods originally developed for non-living systems. Many parallel control loops exist, the majority of relations are nonlinear and taking into account all effects that influence a certain parameter would result in a model too complex to be handled by the present computational systems and also by the present experts. Certainly the ability of both experts and computers to handle complex problems will increase thus leading to a better understanding of biological systems and human organism. The complex models will be built up by using the simplified ones created and validated by contemporary researchers.

This dissertation summarises the results of the research work in two fields. The first is the analysis of human movement in order to objectively diagnose and assess the actual state of patients with neural diseases. The score of a patient performing movement patterns is influenced also by the central nervous system not only by the muscles. This is the reason why detailed analysis of finger-, hand- and arm movements can reveal neural diseases and also help determine the actual state of patients. This latter could be helpful to set the optimal medication. ***The research work led by me has resulted in*** a better understanding of human movements and made possible to define the ***measurement technique*** and ***feature extraction algorithms*** necessary to quantify the performance during movement. The results can be applied in the clinical routine as well. This required the ***development of a motion analyser*** that is affordable for this purpose. The passive marker-based motion analysis is an appropriate procedure as the markers are lightweight thus do not influence the movement tested. The cheap analyser and the assessment method my research group offers to clinicians are supposed to be applicable to gather data from a great number of patients. The evaluation of such data will lead to an objective diagnosing tool for screening tests and early diagnosis. The method has been applied to assess also stroke patients during rehabilitation.

The second field in which the dissertation gives valuable results aims at testing the cardiovascular system. Hypertension is called the “silent killer”, as it causes no easily detect-

able primer symptoms. When the secondary symptoms appear and the patient visits the doctor, organs might be severely and incurably damaged. Regular check-up of the population would be necessary. Devices applicable for self measurement [O'Brien, 2001 (b)] and providing the necessary accuracy would help involve people to care for their own health. Self measurement is advantageous also for patients already diagnosed to have hypertension. The majority of present day (semi)automatic blood pressure meters offered for home use apply the oscillometric technique. This method detects the mean pressure in the artery and calculates only an estimate of the systolic and of the diastolic pressure. British and American standards for home blood pressure meters allow substantial deviation between the displayed values and the results measured by a trained operator manually [O'Brien et al., 2001], [O'Brien, 2001(a)], [Asmar et al., 2000]. Self blood pressure measurement might be complementary to 24-hour ambulatory blood pressure monitoring (AABPM). Usually oscillometric blood pressure meters give correct results for those with normal values and may give erroneous results for those with cardiovascular diseases. ***The method I suggest assures accurate systolic and diastolic readings without a trained operator.*** Furthermore, the state of the arteries can also be assessed during the measurement. This parameter is usually more important than the systolic and diastolic pressures. For the widespread application a device has been developed that can be used by persons at home without the aid of medical experts. The results of daily measurements are stored in the device for two months so that the general practitioner gets detailed and objective information about the patient's state between visits. Should the device detect an emergency situation or should the trend of the daily measurements show a possible deterioration of the patient's state, the device is able to transmit a request for attention via mobile phone. If the national health care system equipped patients living at home alone with these devices then patients would get a better, more efficient health service. Furthermore, operating such a system would cost much less for the society.

The national health care system needs to be modified to improve the presently inauspicious health state of Hungarian people. My results offer the technical background for it in two fields.

The first chapter gives an introduction to image-based movement analysis. A brief history is given, followed by an overview of the devices used in biolocomotion studies. The overview comprises the Passive Marker-based Analyser for Movement, PAM, developed at the Dept. Measurement and Information Systems, Budapest University of Technology and Economics. The chapter summarises the biomedical applications of image-based movement analysis.

The second chapter describes the movement patterns and the feature extraction methods I have been using to characterise the motor functions of patients. ***I suggest a scoring method applicable to the movement patterns.*** The method is clinically applicable; it is expected to help understand the effect of different neurological diseases on human motor control.

Chapters 3 and 4 give the details of the research I have been conducting and coordinating in the field of movement analysis. Chapter 3 describes the early detection and staging of Parkinsonian patients. Chapter 4 summarises a measurement method to assess the actual state of stroke patients during rehabilitation.

Chapters 5 – 6 concern indirect blood pressure measurement. Chapter 5 is an overview of presently used procedures with an emphasis on the oscillometric method. Chapter 6 depicts my research work that resulted in a ***new indirect blood pressure measurement method***. The method exploits the extra information retrieved from the photoplethysmographic (PPG) signal recorded at the fingertip. Contrary to the oscillometric method, the new method ***directly*** measures the systolic and diastolic pressures. The simultaneous recording of ECG and PPG signal gives the possibility to assess the rigidity of the brachial arteries. Chapter 7 summarises the new results and formulates the theses. There are 176 references listed, adapted to the rapid increase in electronic accessibility quite many of them are available on the web. Details of presently existing rating scales for Parkinsonian and stroke patients are given in the appendix.

Further details about the research work on human movement analysis are available at the web:

http://home.mit.bme.hu/~jobbagy/parkinson/parkinson.htm.

Movies shot during movement analysis of both Parkinsonian and stroke patients and healthy subjects are accessible. The trajectories of markers are also given in separate files.

The web portal at the address below offers a free service for neurologists who want to use the tests described in this dissertation.

http://aisrv.mit.bme.hu/~zsombor/pamweb

1 Movement analysis

Neurologists observed specific changes in the movement co-ordination of their patients – compared to healthy control subjects – a long time ago. In the early, preclinical phase the subtle changes cannot be detected by visual inspection. Similarly, variations in the performance of a patient resulting from slow progress of the disease remain undetected for the human observer. Evaluation of movement aids the diagnosis – even early diagnosis – and assessment of the actual state of patients if

- the movement patterns are well defined,
- movements are recorded with satisfactory sampling rate and spatial resolution,
- appropriate feature extraction methods generate meaningful parameters.

Neurologists use a number of movement patterns to test their patients. The recordings at the Department of Measurement and Information Systems revealed that the movement patterns are usually not defined accurately enough. This deteriorates the reproducibility of these tests.

Passive marker-based motion analysis is especially suitable for testing human movements. The markers are lightweight (1...10 gram), and no wires are needed between the markers and the analyser. The markers and the analysis cause absolutely no discomfort to the persons. The performance of commercially available motion analysers by far exceeds the requirements needed to record and evaluate the movement of patients with neural diseases. As a consequence, these devices are too expensive for the task. I developed a simple device that is applicable for movement analysis and affordable for routine medical and clinical use.

The tracking of markers has made it possible to characterise the performance of a person on the basis of the complete movement. This is a substantial improvement compared to evaluation based on contact sensors. I have defined parameters that characterise both the swiftness and the regularity of movements.

1.1 History, methods, device types

Movement has been considered an important attribute of objects as well as living creatures. It is difficult to assess parameters of movement based on visual observation. Although the human image processing ability is excellent, it is valid only for static images. Details of a

movement can be accurately estimated based on human observation only if it is slow enough. Methods applied for describing and explaining movements date back to Pythagoras and other Greek philosophers. Characteristic statements are cited in [Cappozzo et al. eds.1992]: "Movement is harmony (the heavenly spheres, music)." "Space and time are not absolute concepts but only philosophically detectable bodies."

Although it made no fixed output, the camera obscura was able to render movement perceptible. Figure 1.1 gives an example.

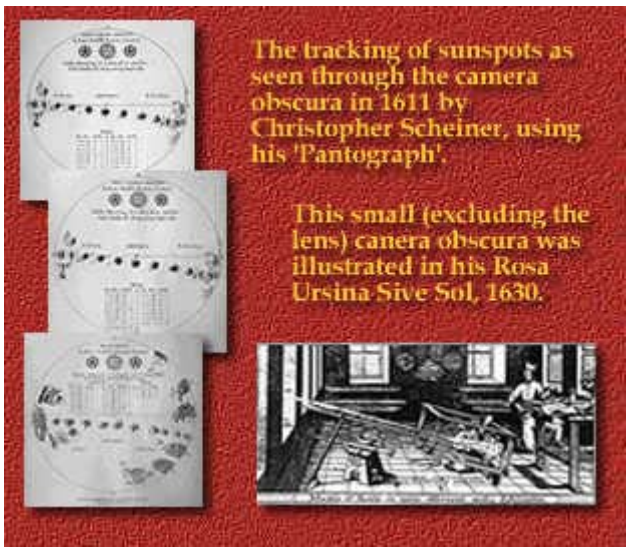


Figure 1.1. Camera obscura. Source: www.precinemahistory.net/1600.htm

Methods and devices to measure and quantify movements have been available since the XIXth century. The first "fixed photograph" was taken in 1826 by Niépce, "View from the window at Le Gras", see Figure 1.2. The equipment (called heliograph) was a camera obscura, the exposition time was eight hours. A number of experts and scientists - some of them famous for activities in different fields - contributed to the development of photography and the projection of photographs. During the XIXth century, Daguerre, Brewster, Roget, Wheatstone, Plateau, Stampfer, von Uchatius, Horner, Talbot, Moigno, von Madler, Herschel, Bayard, Childe, Hunt, Houdin, Muller, von Marten, St.Victor, Clarke, Langenheim, Evrard, Archer, Duboseq, Masher, Martin, Quinet, Melhiush, Cutting, Disderi, Poitevin, Relandrin, Fenton, Skaife, Tornachon, Chevalier, Rose, Desvignes, Ponti, Du Mont, Shaw, Parkes, Holmes, Sellers, Pepper, Dircks, Du Hauron, Laing, Molteni, Smith Beale, Lincoln, Pollock, Hyatt, Maddox, Linnett, Brown, Maxwell, Heyl, Ross, Janssen, Rudge, Donisthorpe, Edison, Reynaud, Skladanowsky, Beale, Lumière brothers, Casler, Dickson, Mach, Le Prince, Stirn, Anschutz, Friese-Greene, Evans, Ives, Demeny, Paul, Acres, Jenkins, Richard, Wray, Latham, Armat, Bloch, Smith, Pathe, Messter, Bunzli, Continsouza, Goodwin, Kamm, Eastman,

Braune, Fischer, Bernstein, Marey and Muybridge all added something to photography and to image-based motion capture. Many interesting details can be found on the website:

www.precinemahistory.net created by Paul Burns.

Figure 1.2. The first "fixed photograph", *View from the window at Le Gras* (in Saint-Loup-de-Varennes).

Two citations prove that the commercial value of motion picture was not realised at the time of its birth. "The cinema is an invention without a future" - Louis Lumière.

"Our invention can be exploited for a certain time as a scientific curiosity, but apart from that, it has no commercial future whatsoever." - Auguste Lumière.

I would like to stress the role of Etienne-Jules Marey (Figure 1.3) and Eadweard James Muybridge (Figure 1.4) (born as Edward James Muggeridge) in capturing motion on still images. Both lived between 1830 and 1904.

Figure 1.3. Etienne-Jules Marey, 1830 - 1904. www.ctie.monash.edu.au/hargrave/marey.html

In 1859 Marey defended his thesis for Doctor of Medicine, but already from 1854 on he studied human movements. His research interest focused on both internal (intracardiac pressure, arterial pulse, pulmonary ventilation and muscle contraction) and external body movements. He created different mechanical and optical tools to study motion; the best known is the chronophotographic box that was able to take 60 images per second. Further details are in [http://web.inter.nl.net/users/anima/chronoph/marey/index.htm]. Its modified version, the photographic rifle could take images at intervals of 1/100 seconds using a rotating wheel with 10 spokes. Marey was not interested in replaying the motion; he used photography to study

quantitatively human and animal motion. In 1892, ***three years prior to the first public projection by the Lumière brothers*** Marey invented the *cinecamera* and in 1895 he was elected president of the French Academy of Sciences. He is considered to be the father of biomechanics by many researchers in this field.

Figure 1.4. Eadweard Muybridge, 1830 - 1904.

Eadweard Muybridge (see Figure 1.4) became famous by applying "serial photography" to capture fast motion. He was commissioned by Leland Stanford to decide whether or not there is a moment when all feet of a galloping horse leave the ground. To do so, he could reach a 1/2000 s exposure time. The photographs surprised the experts; different concepts had been widely accepted concerning the galloping. Figure 1.5 shows twelve moments of the galloping horse 'Occident'. Images of another horse are on the front cover of the Scientific American, issued October 19, 1878.

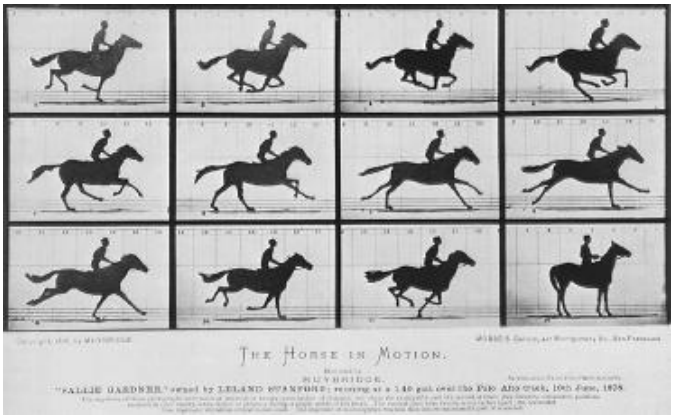


Figure 1.5. Phases of a galloping horse, taken by E. Muybridge in 1877.

Muybridge applied his method of serial photography to record phases of different human and animal locomotion. Between 1872 and 1885 he shot more than 100,000 images. He published a great number of image series in three books. A collection of his work is republished [Muybridge, 1973]. Twelve phases of a head spring are shown from front and side view in Figure 1.6. Not a scientist but rather a brilliant technician, Muybridge was

acknowledged even by the greatest contributors of the early era of studying biolocomotion. Further interesting details can be found at:
http://photo.ucr.edu/photographers/muybridge/contents.html.

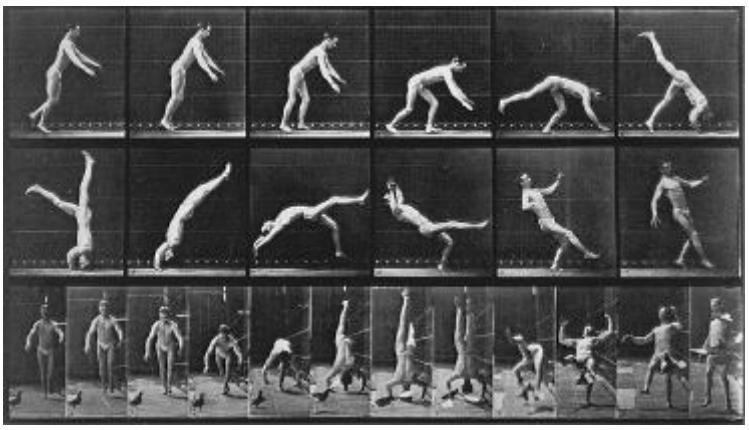


Figure 1.6. Head-spring, a Flying Pigeon Interfering 1885.

Biolocomotion studies date back to cinematography (Marey) and kymography (Ludwig). A number of paintings and sculptures demonstrate that visual (human) assessment of motion is very difficult and even such excellent observers as artists frequently portrait moving humans and animals in not existing positions. [Cappozzo et al. eds, 1992] gives a good summary of the first century of research on biolocomotion using moving pictures.

Presently available equipment range from simple home video cameras with 25 frames/s up to sophisticated equipment with more than 10,000 frames/s. The Phantom® V5.0 system from Photo-Sonics Inc. offers 1024 x 1024 resolution with 1000 full frame/s speed. Reducing the resolution allows for increasing the recording speed, with 32 x 256 resolution the maximum is 60,000 frames/s. Photron APX from Digital West Imaging is able to record 2,000 frames per second with 1024 x 1024 resolution and 120,000 frames per second with 128 x 16 resolution. The cellular neural network (CNN) technology offers local image processing for each pixel. 128 x 128 resolution and 1,000 frames/s recording speed is available [Orzó L., Tőkés Sz., Roska T., 2002], [http://lab.analogic.sztaki.hu/publications.html], further improvement is expected.

Presently image-based motion analysis is by far the most widespread for studying biolocomotion. Mechanical solutions like goniometers have a very limited field of application. Ultrasound based devices (e.g. Zebris) and magnetic devices (e.g. Flock of Birds, Ascension) are able to track a limited number of markers with low sampling rate. They are applied mainly in rehabilitation. Polhemus offers magnetic and laser based devices [www.polhemus.com].

Manual tracking of markers is offered by the cost-effective APAS system [www.sportscience.org].

1.2 Image-based movement analysis

Image-based movement analysis for biomedical purposes requires the identification of anatomical landmark points on humans or on animals. After identification, these points are tracked, i.e. the co-ordinates of these points are determined on the images. Movement analysis is based on the trajectories of the landmark points. Marker free analysis [Lanshammar, 2001, Courtney et al., 2001, Marchesetti et al, 2004] would be very advantageous; however, at present the method is not elaborated enough, the achievable accuracy is modest.

1.2.1 Marker-based analysis

Marker-based movement analysis uses markers that are attached to the anatomical landmark points, cf. Figure 1.7.

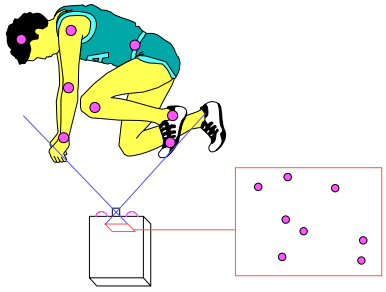


Figure 1.7 Marker placement and feature extraction in motion analysis.

The markers are tracked, based on the position of markers the positions of the anatomical landmark points are determined. The marker should keep its relative position to the anatomical landmark point during the analysed movement. Basically as a result of skin displacement this relative position does not remain constant. The best practice is to attach markers to the tested human or animal by ribbons that are tight enough; stripes equipped with adhesive layers on both sides should be avoided. The markers applied in biolocomotion studies are lightweight; they minimally influence the analysed movements.

In image-based analysis the markers must be seen by the camera(s) otherwise their position cannot be determined. A good summary of marker-based movement analysis is given in [Furnée, 1989, Cappozzo et al., (eds.), 1992].

Markers

In general motion analysis requires an appropriate model and measurements should be carried out according to it. The important – landmark - points can be tracked if markers are attached to them. Markers are *carriers* then, after acquiring a picture, only the midpoint coordinates are important, provided the midpoint always fully determines the position of the corresponding landmark point.

In general the marker images are excessively bright thus providing a means for feature extraction: by thresholding the luminosity the marker images can be separated from their surroundings.

There are basically two types of markers, active and passive ones. *Active markers* emit light. Their advantage is that the identification of a marker is easy; it is possible to light only one marker at a time. The disadvantage is that active markers either require an energy source or there must be wiring between the markers and the motion analyser. The use of active markers in biolocomotion studies is inconvenient in most cases. Another – less bothering – drawback of active markers is the time shift between sampling their positions. It is an inherent feature, as markers are lighted one after the other.

Passive markers have the important advantage that they mean almost no discomfort for the human or animal, as they are lightweight (< 10 gram) and need no wired connection. The form of the marker must be selected so that its projection to the sensor plane has always the same shape. It follows that the marker shape should result in a circular projection: spherical shape is needed for three-dimensional applications, hemispheres and disks are also satisfactory for two-dimensional use. The relative brightness of markers compared to their environment (it can also be expressed as ambient light suppression) is increased in two ways: the cover of a passive marker is made of retroreflective material and a stroboscopic infrared illumination is applied.

The main drawback of passive markers is that they need to be identified on each frame because the relative positions of the markers may change as a result of their displacement. When the trajectories of two markers cross each other the identification of the markers after the crossing requires a priori knowledge about the studied movement. If there is an object between the marker and the camera the marker image is missing from the sensor. This is called occlusion. Based on a priori knowledge and interpolation it is possible to determine the missing part of a trajectory. The longer is the missing part the greater distortion might result from the interpolation.

Cameras

In marker-based motion analysis a camera consists of the following parts:

- light source for illumination,
- optical lens(es),
- shutter,
- light sensor,
- interface circuitry.

The aim is to get a picture, on which the intensity of a marker image is much greater than its environment (the ambient light suppression is high). This assures that all the markers can be sampled simultaneously (the marker images can be extracted from the image by thresholding the intensity). This aim cannot be achieved in general but might well be approximated with restrictions that can usually be fulfilled in practical applications. The most important restriction is that the markers remain within a defined volume. The smaller is this volume the better the aforementioned aim can be approximated. Selecting the proper wavelength of the applied illumination assures the relative brightness of marker images. The most widely used solution is to apply infrared illumination in harmony with the frequency dependent properties of the retroreflective cover of markers.

The ambient light suppression can be substantially increased if the aperture time is only a fraction of the time that elapses between two consecutive frames. It can be achieved by *shuttering* and *stroboscopic illumination,* synchronised to the frame rate. This solution has a further advantage: assures equidistant, simultaneous sampling and reduces smearing.

During the tests reported in this dissertation the PRIMAS [Furnée, 1989] and the PAM analysers were used. PRIMAS uses high-quality HTH cameras (100 samples/s) with electronic shuttering (0.25 ms) and 604 x 288 resolution. PAM uses the SONY TR8100E DV camera equipped with a 1-ms infrared flash. PAM processes every field (50 samples/s), thus the resolution is 768 x 288.

1.2.2 Image processing to determine the marker positions

The first image-based motion analysers used electron tubes as sensors. The identification and location of markers required hardware supplement. The video/digital co-ordinate converter used in several devices was first reported by Furnée [1967]. Video/digital co-ordinate converters use mainly one-level thresholding, one-bit A/D conversion. Multiple level thresh-

olding - several bit A/D conversion - results in a smaller quantisation error but at the same time increases the computational load considerably.

Present day digital video cameras and PCs are fast enough. They mean a good alternative to the hardware feature extraction if processing of grey-scaled images is needed. The CNN technology also offers an effective solution to extracting marker positions from video stream shot at high speed.

Since the mid-1990 the computational power of processors has allowed determining the marker positions without hardware feature extraction. The bright marker images can be extracted by processing each pixel of the grabbed images. Marker images are derived based on the difference in brightness. Binary images can be generated by thresholding the brightness of pixels; the marker (centre) position is determined by simple geometric centroid estimation [Jobbágy, 1994]. The position is determined with a higher accuracy if the marker images are processed as grey-scale set of pixels. [Baca, 1997] gives a method for marker position estimation by fitting a Gaussian surface to the marker image. Improving hardware thresholding in image processing [Furnée and Jobbágy, 1993], the threshold level can be adaptively set on each frame. Also, the distorted marker images and ghost markers can be identified and filtered out relatively simply.

Two-level image processing is able to offer high resolution and accuracy with relatively low computational burden. First the intensity distribution of the image is determined and based on it a threshold level is set. The pixels with brightness above the threshold level are processed as grey-scale spots.

1.2.3 The necessary sampling rate for recording human movements

The human eye is able to retain an image for about 1/15 s [Winter, 1990]. This is why film (24 frames/s) or television (25 frames/s, 50 fields/s: PAL) seem to reproduce movements smoothly. The lowest sampling rate applied in gait studies is 24 samples/s. [Winter, 1982] showed that kinetic and energy analysis can be done with negligible error using this sampling frequency.

I determined the sampling rate necessary for the evaluation of the finger-tapping movement with the help of PRIMAS. Data gathered with 100/s sampling rate was processed and the parameters characterizing the movement were determined using the complete database as well as the reduced databases. The database was reduced in two steps, each time eliminating every second data. The database after the first reduction corresponds to a 50/s and after the

second reduction to a 25/s sampling rate. In this way after each test there were three databases describing the same finger-tapping movement. Strong agreement has been found between parameter values computed based on the first (100/s) and second (50/s) databases. These parameter values were markedly different from those calculated from the third database (25/s) [Fogarasi, 1999], [Jobbágy et al., 2005]. These results are in accordance with the frequency domain analysis of the time functions achieved with 100/s sampling rate: components above 25 Hz were negligible. Figure 1.8 shows the Fourier transform of the movement of a marker attached to the little finger of a young healthy subject. Similar energy distribution over frequency was detected also for other healthy subjects. Parkinsonian patients usually had energy distribution up to lower (typical value 16 Hz) frequencies (see Figure 1.9).

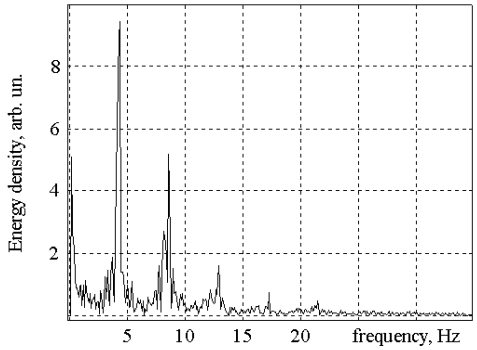


Figure 1.8. Fourier transform of the movement of the little finger during finger-tapping test (young healthy subject). Energy density is negligible above 22 Hz.

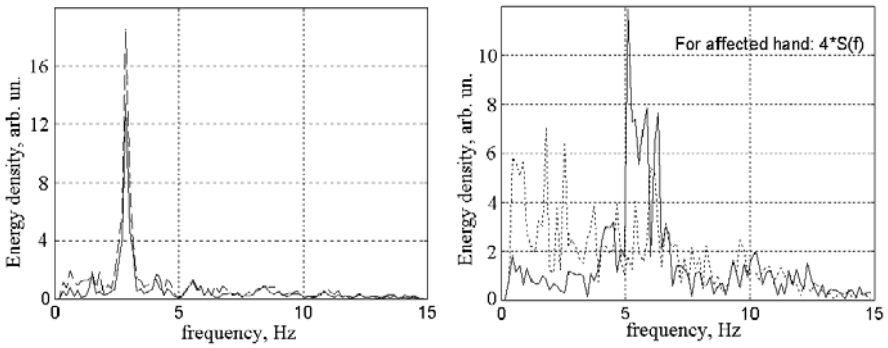


Figure 1.9. Frequency spectra of time functions of both index fingers of a young healthy patient (left) and of a Parkinsonian patient (right, affected hand: dotted line) during tapping test.

1.3 Devices

1.3.1 General purpose motion analysers

A number of image-based and marker-based motion analysers were developed but only a few have become commercially available. [Furnée, 1989] gives an excellent summary of the devices using some kind of hardware aid to extract marker images from the full image.

The Precision Image-based Motion Analyser (PRIMAS) was developed at Delft University of Technology [Furnée, 1989], [Jobbágy and Furnée, 1994]. The good spatio-temporal resolution and the relatively low price of the device make it adequate for human movement analysis. The 3D calibration of the device is unique. It is based on a set of markers placed on a plate allowing a relatively easy calibration in parallel with the measurement to compensate lens distortion. Analogue input channels for EMG or force plate sensors are available. Although a new version of the analyser was developed, at present PRIMAS is not available on the market. PRIMAS offers maximum 100 full frames/s, the resolution is 604 x 288.

VICON is widely used in biolocomotion studies. Gait, posture and balance are studied with this device mainly in research laboratories. Similarly to other analysers VICON [www.vicon.com] is also used in virtual reality applications, sport and ergonomic studies, and in projects related to entertainment (development of video games, animation, filming, etc.). Maximum 24 cameras and 128 analogue channels (to measure EMG and output of force plate sensors) can be connected to the central unit. The cameras have high resolution (1 Mpixel, 1000 x 1000), the maximum frame rate is 250/s. This allows for an excellent resolution, very rarely needed in human or animal locomotion studies for medical purposes. Lower resolution (50-60 frames/s) cameras are also available. The software offers automatic tracking of markers, cubic splines are used to estimate the missing intervals in trajectories.
MacReflex and ProReflex from Qualysis are able to reach 1000 frames/s sampling rate [Corley et al., 1993], [www.qualisys.com], [http://www.innovision-systems.com].

Similar products are offered by MotionAnalysis [www.motionanalysis.com].

The Motus Measurement System from Peak Performance [www.peakperform.com] offers sampling rate from 25 Hz up to 200 Hz (PAL), even high-speed cameras (up to 2000 Hz) can be interfaced. Force measurement and EMG devices can also be integrated.

ELITE can handle cameras up to 100 frames/s; it has analogue inputs for EMG or force plate sensors [Ferrigno et al., 1990].

Further image-based motion analysers are available. High-Speed Video Motion Analyser (HSVMA) from Ultravision is a real-time uncompressed video recording and processing software.

KODAK Ektapro offers ultra high speed, 12,000 frames/s with 239 x 192 resolution. This resolution offers even the study of a falling drop [Rothert et al., 2003].

PAM processes each field of a standard PAL video stream; this corresponds to 50 samples/s. The resolution of PAM is 768 x 288, it provides 2D information.

Non image-based motion analysing devices using magnetic [Bull et al., 1997] or ultrasound sensors [Schimke et al., 1998, www.zebris.de] are applied in different biomedical research.

The primary parameter provided by a video-based and marker-based motion analyser is the position of markers. The parameters to be determined (e.g. torque, velocity, acceleration, jerk) usually require numerical differentiation. This operation means an extremely high noise amplification factor, thus the accuracy of position data is an important issue.

Many factors influence the resolution and accuracy of video based analysers: marker size (expressed in percentage of field of view, FOV), optical projection, lens distortion, parameters of the sensor (mostly CCD), the video/digital co-ordinate- or A/D conversion, the calibration procedure (especially in case of 3D analysis) and the applied image processing algorithms.

Resolution and accuracy are not limited to the number of pixels on the sensor. When a marker image spreads over a number of pixels, then sub-pixel resolution and accuracy can be achieved by appropriate algorithms [Baca, 1996], [Jobbágy, 1994].

Motion analysers are often characterised by the spatio-temporal resolution, which takes into account the resolution both in space and time. [Furnée, 1989] gives an overview of different definitions and introduces the spatio-temporal quality factor, Q:

$$Q = \frac{\sqrt{f_s}}{p}$$

where f_s is the sampling frequency and p is the precision, expressed as a percentage of the FOV. There are analysers that make it possible for the user to increase the sampling rate if the number of effective pixels is reduced. Applications in human movement research rarely require higher than 50 /s sampling frequency. The resolution in space depends on the movement studied, the marker sizes and the FOV.

1.3.2 A device for routine clinical applications (PAM)

A Passive Marker-based Movement Analyser (PAM) has been developed at the Dept. Measurement and Information Systems; based mainly on commercially available elements [Jobbágy et al., 2004]. A digital video camera (SONY TR8100E), able to operate in the infra-red range, an optical filter and a notebook with IEEE 1394 interface are the commercially available elements. An infrared LED ring (containing 18 LEDs) with the necessary control circuitry was developed. The peak sensitivity of the CCD sensor was measured to be at 885 nm, the LEDs were selected in accordance with it (SFH 485, max. radiation at 880 nm). The control circuit synchronises the flashing of the LEDs to the vertical synchron signal of the camera. A 5-ms delay assures that flashing starts when the CCD chip is sensitive. The 1-ms flashing assures a short enough sampling time and increases ambient light suppression thus results in sharp marker images. Both even and odd fields are evaluated using appropriate marker image processing. In this way 50 images can be taken in each second. The system is inexpensive (compared to high performance motion analysers), portable and easily applicable in the medical/clinical environment.

The infrared LEDs aid the separation of marker images from the rest of the image; they increase ambient light suppression. Figure 1.10 shows two fields (odd and even) separately and also these fields together as one frame taken by PAM in the infrared range. The displacement of the markers between two fields (during 20 ms) can be observed on the frame displaying both odd and even fields.

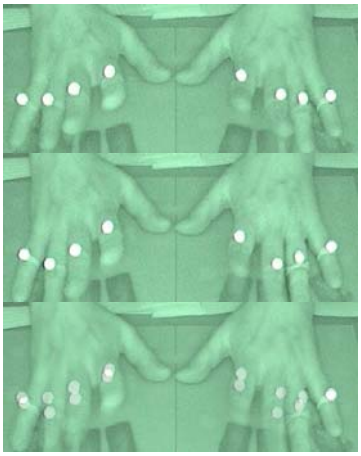


Figure 1.10. The odd field (top), even field (middle) and the two fields displayed as one frame (bottom) recorded with the PAM during finger-tapping.

Figure 1.11 shows the intensity histogram of the top image of Figure 1.10. The A/D converter of the camera gives 780 when a pixel has maximum intensity. The pixels belonging to

the marker image are excessively bright; their intensity values are between 680 and 720. The measurement set-up used for the tapping-test is shown in Figure 1.12. As the camera - hand relative position is the same during the tests then a two dimensional analyzer is enough to evaluate hand movements.

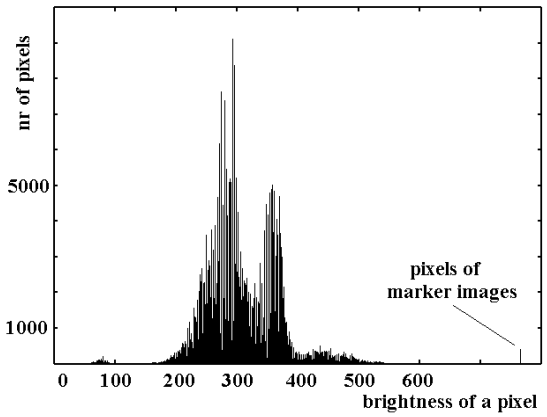


Figure 1.11. Intensity histogram of a field taken by PAM.

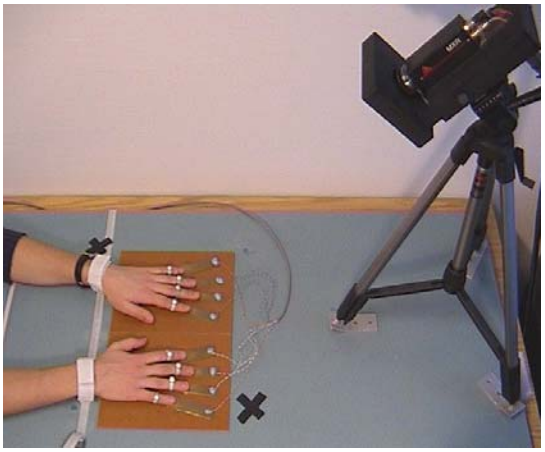


Figure 1.12. The measurement set-up for the tapping-test.

1.3.3 Resolution, accuracy and precision of motion analysers

In the following I use the terms precision and accuracy for image-based motion analysers as defined in [Walton, 1986].

Precision is the degree of mutual agreement among repeated observations made under identical conditions. Precision is a measure of random error.

Accuracy is the degree of agreement between individual measurements and accepted reference values. Accuracy is a measure of systematic error.

Resolution of a motion analyser is the smallest detectable displacement or the longest undetectable displacement.

These parameters cannot be given as single constants for an image-based analyser, because they strongly depend on the marker image size. If the marker image covers more pixels, accuracy, precision and resolution are more favourable. The nonlinearity of the lens also influences these parameters; worst results can be expected when marker images appear in the corners of the FOV.

Measurements carried out to characterise marker-based motion analysers use static markers as well as markers moving along given paths. Detailed analysis of resolution, accuracy and precision of image-based motion analysers is given in [Jobbágy et al., 1998].

Each application requires a dedicated preliminary evaluation to check if the analyser is able to meet the requirements. The analysis of human movements in the medical care rarely demands high accuracy or precision.

Evaluation of a typical image-based motion analyser (PRIMAS)

Attaching a 9-mm diameter marker (this size is used in testing finger movements) to a micrometer the ***resolution*** of PRIMAS was found to be 1/12000 of the FOV. The resolution estimated by simulation is in the order of 1/15000.

The resolution of PAM was found to be 1/16000 of the FOV, using 9-mm diameter markers in a 60 cm x 45 cm FOV.

Precision characterises the stability (reproducibility) of the system. High precision is necessary, but not satisfactory condition for high accuracy.

Scenes with static markers were observed by the analyser under test, PRIMAS. Two types of measurement were made, (a) long-term measurement series started at power on with low sampling rate (1 hour recording time, 2 frames/s) and (b) short-term measurement series with high sampling rate (10 s recording time, 100 frames/s). The (a) type test reveals if thermal changes influence the position results while the (b) type test characterises system noise.

Following power-on, the change within an hour in the measured horizontal position of the marker is approximately 90 % of the pixel side. Taking into account the given set-up it is equal to 1.5 mm imaginary displacement meaning a 1/670 ratio of the horizontal side of FOV. The change in the measured vertical position was negligible, within noise limits.

A number of 10-s recordings were made using 100 frames/s sampling rate. The centre (x and y co-ordinates) of a static marker is measured and the results are plotted. A typical distribution of the measured centres along the sensor plane is shown in Figure 1.13.

It is clear that the distribution is not normal. It is difficult to characterise the precision of a device with a single value. The maximum deviation in the described experiment is 1/7500 (horizontally) and 1/7200 (vertically) compared to the appropriate side of the FOV. Precision depends on the marker image size; it improves if the marker image increases. Precision is closely related to noise.

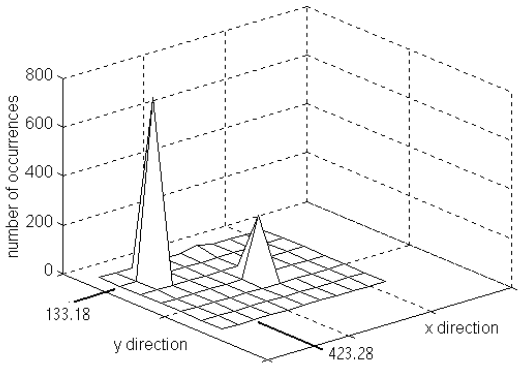


Figure 1.13. Distribution of the estimated centre points.

The system noise was investigated by subtracting grey-scaled images taken from the same scene. An 8-bit A/D converter was built in the PRIMAS, which converted the intensity of a 64 x 16 pixel area of the CCD sensor. Figure 1.14 shows a typical differential image for the PRIMAS analyser. There were two markers in the field of view, though these cannot be located after subtraction.

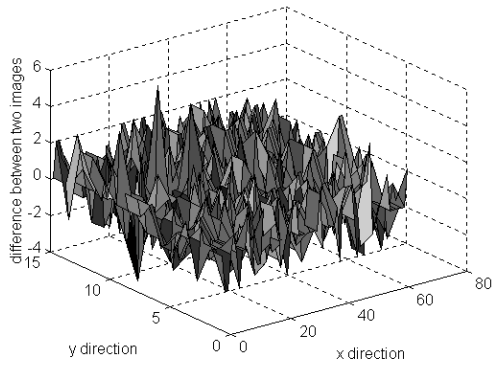


Figure 1.14. Noise of a CCD sensor: the difference of two images taken from the same scene.

Let the intensity value of the (i, j)th pixel of the CCD sensor for two images be $I_1(i, j)$ and $I_2(i, j)$, $0 \le I \le 255$, $1 \le i \le 604$, $1 \le j \le 288$. The intensity value of a pixel after subtraction is $\Delta I_{12}(i, j) = I_1(i, j) - I_2(i, j)$. In the ideal case ΔI_{12} would be zero for all pixels. The maximum values for ΔI_{12} were found to be $\pm$ 5, independent of the scene and illumination. This noise results in different calculated values for the centre of a static marker. Testing of ***accuracy*** usually requires an etalon. When testing motion analysers the absolute positions of the markers are generally not known with great enough accuracy. A widely used solution is to move a marker along a well defined trajectory, in the majority of cases this is a straight line. Accuracy is characterised on the basis of the deviations from the straight line. This test can be applied without knowing the exact marker positions.

A marker was moved horizontally with the help of a printing head and a straight line was fitted to the measured marker centre co-ordinates as shown in Figure 1.15. From these figures it is clear that the accuracy of the measurement is limited by the lens distortion. There are effective calibration procedures, which improve accuracy substantially.

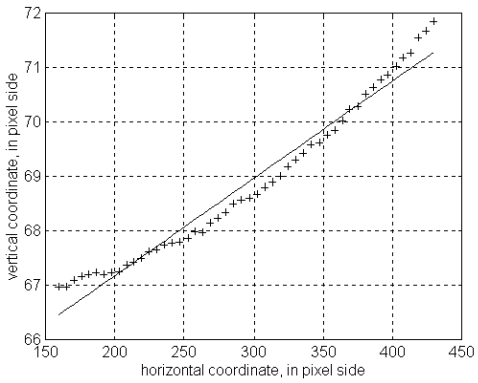


Figure 1.15. Measured positions of a nearly horizontally moving marker and a fitted straight line.

Numerical data of a biomedical application

The set-up used for the *finger-tapping test* is analysed in the following. This movement mimics piano playing; detailed description is given in 2.1.1 .

Markers are attached to the eight moving fingers with elastic ribbons. Marker size is limited, not to influence the movement. We used 9-mm diameter markers. The distance of the camera from the table is fixed. This assures the reproducibility and comparability of measurement results. FOV had to be selected so that all fingers of a subject should be seen during the movement. This requires that the horizontal size of the FOV be at least 50 cm, the actual value was 64 cm. Taking into account the ratio of horizontal and vertical sides of the FOV this means 48 cm for the vertical side. The sensor of the CCD camera of PRIMAS has 604

columns and 288 rows, the 9-mm diameter marker results in a marker image covering an area on the sensor equivalent to 30 ... 40 pixels. This means sub-pixel resolution can be achieved. When binary images are generated (the video signal is thresholded to extract the marker image), the covered pixel co-ordinates can be averaged or the more accurate ring-fitting can be used [Jobbágy, 1994].

During the finger-tapping test noise limits resolution to 0.2 mm. The accuracy was measured by moving the 9-mm diameter marker along a 30 cm line. The average distance between the fitted straight line and the measurement points was found to be 0.15 pixel side. In proportion to the diagonal of the FOV it means a 1/5000 (0.15 mm) accuracy. The measurement was repeated with smaller displacement, 5 cm. The accuracy in this case is approximately 1/4000 of the total displacement (0.013 mm). These parameters are sufficient for finger- hand- and arm movement measurements even without lens distortion compensation.

The PAM analyser was tested using similar measurement set-up [Hamar, 2004]. The results are close to the parameters of PRIMAS. The system noise limits the resolution during finger-tapping test to 0.3 mm (FOV: 64 cm x 48 cm). Both accuracy and short-time precision are the same as for PRIMAS. No warming-up effect was found. This means, PAM is also applicable for human finger-, hand- and arm movement assessment.

1.4 Biomedical/clinical applications of movement analysis

Movement coordination is affected by the actual state of a person or an animal. Changes in movement coordination can reveal and help in staging neural diseases.

Human movements are analysed from different aspects. *Kinematics* deals with displacement, velocity, acceleration – sometimes even with jerk. Both linear and angular variables can be used to characterise the movement of body segments or joints. A spatial reference is needed, either an absolute or a relative one. *Kinetics* deals with the internal and external forces that cause the movement. The internal forces mainly derive from muscle activation while external forces originate from the interaction between human or animal and the environment. [Winter, 1990] emphasises the role of *anthropometry* that gives data on the shape and mass of body segments and *muscle and joint biomechanics*.

Image-based motion analysis helps acquire kinematic data. Very often the movement analyser must be synchronised to devices providing further information on the currently studied movement. Force plates, accelerometers, treadmills and electromyographs are most frequently used but other signals of physiological origin may also be captured. Examples are: electrocar-

diogram, electroencephalogram, photoplethysmogram, spirogram, output signals of impedance measuring equipment, etc. Further signals from different sensors might give valuable information; consider the force sensors embedded into different prostheses or timing signals of schedulers.

The aim and the process of the measurement have to be explained to the tested person. The analysis of a given movement gives meaningful and comparable results only if the measurement procedure is defined in detail. This must comprise the movement pattern as well as the arrangement of the measuring devices. To get parameters characterising the given movement accurately and reliably enough for comparative evaluation, well defined parameters and signal processing algorithms are needed. Internationally accepted standards would help. There are only a few recommendations for such standards and even these are not defined to the necessary extent.

1.4.1 Rehabilitation

Movement analysis is a useful aid in rehabilitation. A number of gait analysis laboratories exist to give a feedback to physiotherapists, neurologists and the patients themselves. There are manufacturers of prostheses (Otto Bock Healthcare is a good example) that have been applying movement analysis to trim their products. This procedure complements the adjustment based on the patient's evaluation. Especially with a new prosthesis, it is very difficult for the patient to estimate its practicability.

There are no standard measurement procedures. Neither are standard devices available. This impedes the introduction of standard rehabilitation methods. The CAMARC program aimed at defining standard interfaces for the data exchange among laboratories.

Recommendation for a standard (CAMARC program)

The CAMARC (Computer Aided Movement Analysis in a Rehabilitation Context) programs I and II suggested a solution for the standardisation problem [Leo, 1994]. Different laboratories are equipped with different instrumentation; it would be an unrealistic plan to change this situation. The CAMARC recommendation is to use a *standard protocol* for the exchange of data. This allows for the use of different instrumentation and even different signal processing; the conversion programs assure the comparability of results.

The recommendation defines the laboratory axes, force plate axes; bone embedded (anatomical) frames, marker placement and marker mounting. The pre-processed gait data file

(PGD file) format is also specified. The CAMARC recommendation for the anatomical frame construction for the pelvis and femur are given in Figure 1.16. For the pelvis, RPSIS and LPSIS stand for right and left posterior superior iliac spines, RASIS and LASIS denote the right and left anterior superior iliac spines. For the femur, FH means the femoral head; LE and ME are the lateral and medial epicondyles.

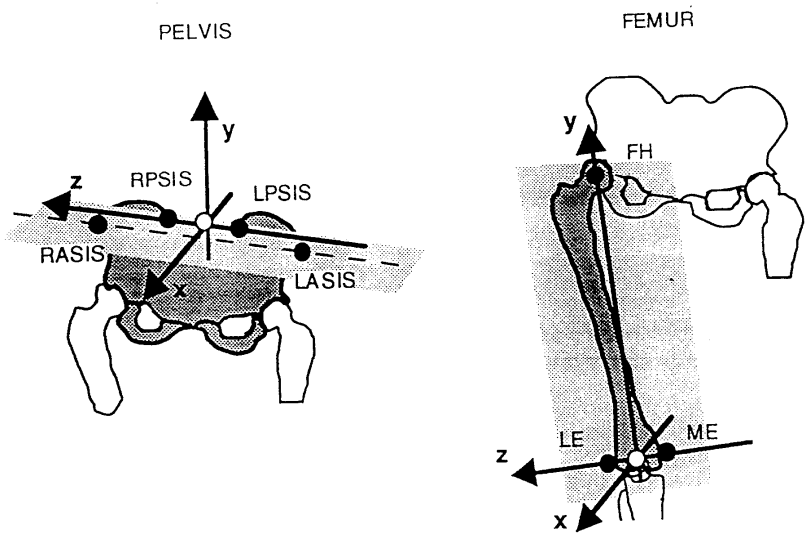


Figure 1.16. Anatomical frame construction for the pelvis and femur. CAMARC recommendation.

The CAMARC project integrated clinical and research centres as well as manufacturers and users like insurance companies. The resulting recommendation for standardised movement analysis in rehabilitation (agreed clinical and experimental protocols) is a pioneering work. Even the details are well defined; a good example is the attachment of markers to anatomical landmark points. However, there is still a lot to be done to have a widely accepted functional assessment method of the motor (dis)ability of the motor impaired and/or the elderly. A related database had been created. The database was meant to provide age-related normal values and also a comprehensive knowledge base for the quantitative classification of motor impairment. Further details are available in [Leo, 1994].

Staging of stroke patients

Presently existing tests [Hamilton, 1987], [Collen et al., 1991] measure the self supporting ability of patients (see appendix). Many everyday functions (dressing, eating, washing oneself) can be learnt to be performed with one hand only. As a result these tests do not provide an objective measure for the rehabilitation process when dysfunctions are unilateral.

In co-operation with National Institute for Medical Rehabilitation, Budapest (OORI) a measurement series was taken from stroke patients using the PAM movement analyser. The details are given in section 4.

Characterisation of hand tremor

Tremor of the hand is present even for young healthy subjects. Objective and quantitative characterisation is greatly helped by movement analysis. PAM is suitable for this purpose. Healthy subjects (aged 22 – 71) were tested, one passive marker was attached to the index finger. Recordings were made with stretched arms, supported elbow and supported wrist, both eyes open and closed. Characteristic trajectories are given in 2.2.7.

1.4.2 Assessment of the actual state of patients with neural diseases

A number of different tests are applied that assess the actual state of patients with neural diseases based on movement analysis. The United Parkinson's Disease Rating Scale (UPDRS) advises to measure the following movements: turning in bed, walking, action or postural tremor of hands, rigidity, finger taps, hand movements, rapid alternating movements of hands, leg agility, arising from chair, gait, postural stability, body bradykinesia and hypokinesia.

In case of stroke patients movements needed for daily activity are measured: sit to stand, clothing, eating, etc. There are several standard tests for quantifying the level of bradykinesia, rigidity, spasticity and paraplegia: Rivermead, Ashworth, Barthel, Hand Movement Scale (HMS), and FIM. These scales measure the motor functions of the limbs and the level of self sufficiency [Hermsdörfer et al., 1999], [Fazekas et al., 2002]. Rehabilitation proves to be more effective if aided by a feedback from the actual performance of the patient. Robot aided rehabilitation is reported by [Fazekas et al., 2004], [Foley, 2004].

Visual assessment gives coarse resolution; only experienced physiotherapists are able to evaluate the patients' state in this way. Simple devices are widely used to give better reproducibility: nine-hole peg test, contact sensors, MIDI keyboard, etc. These devices do not track the whole movement, they usually measure the total time of the movement (e.g. nine-hole peg test) or defined parts of it (e.g. time intervals between consecutive table contacts during finger-tapping test). The application of a movement analyser gives information about the whole movement. This helps the objective assessment of the movement co-ordination – thus the actual state – of patients with neural diseases.

1.4.3 Long-term monitoring of the locomotor activity of rats

The psychophysiological state of small animals (rats) can be characterised based on their movement patterns. Such a complex indirect measurement can be divided into two parts [Morawski, 1994]:

(a) conversion to transfer measurement information into the domain of "easily interpretable" phenomenon; from the signal processing point of view, generation of raw data,

(b) processing of the raw data, interpretation of the results.

The movement of rats kept in special transparent (plastic) tube-like cages was continuously tracked for a few days at the Institute of Human Physiology and Clinical Experimental Department, Semmelweis University Budapest. The rats were in head-up position and they could move back and forth and turn around the longitudinal axis of their trunk freely but they could not turn to head-down position. The cages were 60 cm long; a ladder was incorporated to aid movement up and down. The animals could eat and drink at one end (the top one for the tilted cage) of the cage, see Figure 1.17. Details are given in [Monos et al., 1989]. The position-time function in the cage is the raw data that was generated from the position of reflective markers attached to the animals. There were two groups of rats, one kept in cages tilted by approximately 45 degrees and one, the control group, kept in horizontal cages. Processing of the raw data led to the qualification of the movement patterns of *normal rats*, i.e. animals without any medication and known illness.

Figure 1.17. Experimental set-up.

Two types of instruments are often used to measure animal behaviour. Implantable transponders require surgical intervention. This is justified when not only position information but also monitoring of physiological data is necessary. Brain temperature, gross motor activity

and heart rate can be monitored with different devices of Mini Mitter Co. [www.minimitter.com]. Another solution is to mount IR light emitters and photodetectors on the cage, interruption of the beam shows the actual position of the animal. Models of Columbus Instruments are representative of this latter kind of animal activity meters [www.colinst.com]. The resolution of these devices is limited, the usual beam spacing is 20 ... 30 mm, the beam diameter is 2...3 mm. Using a mirror, a single camera can provide position data in 3D [Kaminsky et al., 1997].

In our experiment feature extraction was needed in order *to characterise the movement patterns of normal rats with a few parameters only* derived from the position-time functions. These parameters can be used later to characterise animal movement patterns that deviate from normal as a result of illness, medication or other controlled biological effects. During the feature extraction process parameters have been searched for which are similar for both groups (rats in tilted and horizontal cages) and also for parameters which are different.

The behavioural activity of small animals like rats might be a very sensitive parameter for investigating possible biological effects. In drug screening studies animal behaviour serves as indicator, an example is given in [Pradhan and Aurnasmitha, 1991].

The rat movement under the given circumstances is a stochastic phenomenon, shorter than daily periods cannot be revealed. Rats were found to be substantially more active when the ambient light intensity is low. ***The integral features characterise the behaviour of rats.*** There is a daily periodicity in distance travelled cumulated for longer time intervals (1 hour ... 3 hours). The position distribution histogram is similar for an average normal rat both in the tilted and in the horizontal cages. Further details are given in [Jobbágy et al., 2002].

2 Characterising the motor functions of patients based on movement analysis

Different movement patterns of patients are analysed in the health service. The aim is either to characterise the movement itself or to acquire information on disorders affecting the motor system. Probably the most frequently used examination is gait analysis but prosthesis adjustment, rehabilitation-, sports- and ergonomic studies are also greatly helped by movement analysis.

2.1 Movement patterns tested in our research

The early diagnosis and assessment of patients with neural diseases is more reliable if several movement patterns are involved in the test [Jobbágy et al., 1998, Rao et al., 2003]. During the research work, aiming at the assessment of Parkinsonian and stroke patients, the following movement patterns were used.

2.1.1 Finger-tapping

Tapping test has been applied to assess the accessory muscular control and motor ability as early as the 19th century. Hollingworth [1914] reports an experiment on female subjects using an electric counter to characterise the influence of menstruation. Tapping tests have been widely used since, some examples are: quantification of ataxia [Notermans et al., 1994], estimation of the severity of Parkinson's disease [Muir et al., 1995, Jobbágy et al., 1998], assessment of patients recovering from acute stroke [Heller et al., 1987], testing of patients with alcoholic Korsakoff's syndrome [Welch et al., 1997], quantification of Alzheimer's disease [Ott et al., 1995], characterization of the upper limb motor function [Giovannoni et al., 1999]. Horton [1999] found that subjects with higher intelligence had better neuropsychological test score performances except for the finger-tapping with the dominant hand test. [Dash and Telles, 1999] used the finger-tapping test to assess motor speed. There was a significant increase in performance following 10 days of yoga in children and 30 days of yoga in adults. [Volkow et al., 1998] found strong correlation between dopamine D2 receptors and the motor task characterised by the finger-tapping test.

In the clinical practice the finger-tapping movement is very often evaluated visually. This means a coarse resolution; only substantial differences can be detected. Simple contact sensors are reported to help the objective assessment [Muir et al., 1995]. There are many versions of the upper limb tapping test: hand-tapping, finger-tapping with one or more fingers, single hand - both hands, with or without a scheduler signal, etc. The presently used feature extraction methods for the tapping tests do not always provide measures useful in rehabilitation or in medication. [Heller et al., 1987] report that measurement of finger-tapping rate was not useful in testing stroke patients, the Frenchay Arm Test, the Nine Hole Peg Test and grip strength measurement could be used to record the recovery curves of patients. [Shimoyama et al. 1990] found that only the time-sequential histogram of tapping intervals could distinguish the motor dysfunctions studied. [Acreneaux et al. 1997] report that "hand to thigh tapping", "table tapping" and "finger tapping to adjacent thumb" quantify the performance of the tested subjects differently.

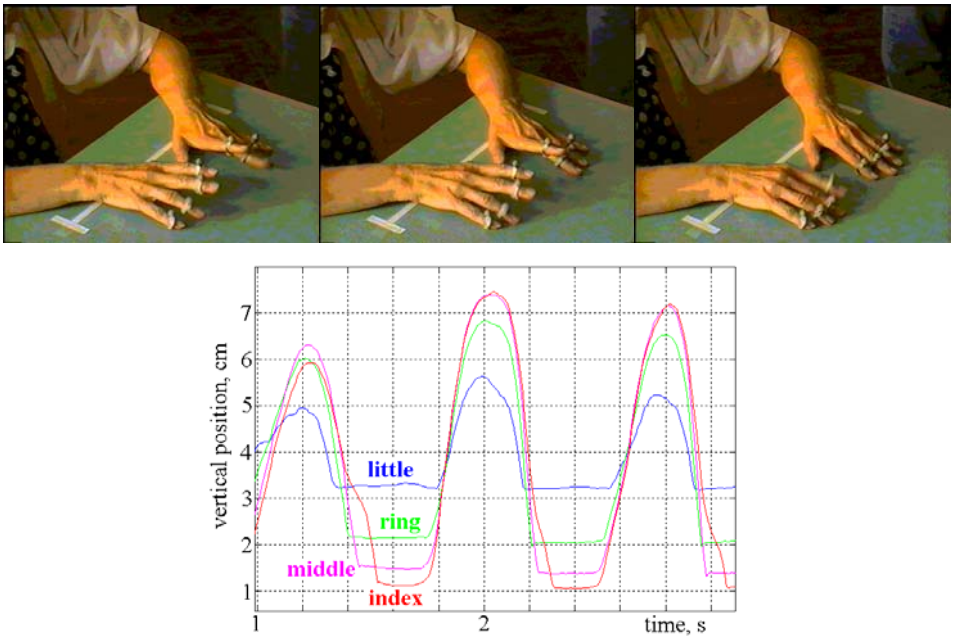


Figure 2.1. Three phases of the finger-tapping movement (above) and the trajectories of markers (on the left hand) recorded (bottom).

I found that to help reproducibility the movement pattern and the instructions given to persons had to be defined in detail. Tested persons put their hands on the table in prone position, with fingers approximately 1 cm apart from each other. 9-mm diameter markers are attached to the middle phalanxes of their fingers. Elbows are on the table. Persons lift their fingers (except thumbs) and then hit the table in the following order: little, ring, middle, and index finger. Persons are asked to perform the movement as fast as they can (most important instruction and expectation) so that they lift their fingers as high as they can. ***The priority of***

speed must be explained. Increasing the amplitude slows down the movement. However, persons should not try to increase speed by minimising the amplitude of finger lifting. Both hands should complete the same movement. This mimics piano playing. Three phases of the movement can be seen in Figure 2.1.

In the beginning of my research the finger-tapping test lasted for 8 s (21 tests of Parkinsonians, 25 tests of young and 17 tests of senior healthy subjects). A number of finger-tapping tests lasted for 30 s (4 tests of Parkinsonians and all the 106 tests that were part of a measurement series taken from five young and one senior healthy subject). Based on the evaluation of these recordings ***I suggest using 20-s long finger tapping tests***. More than two hundred 20-s long tests were recorded from stroke patients and healthy subjects. The evaluation of the first recordings taken from Parkinsonian patients showed that the wrists were not held in the same position during the tests. An elastic ribbon was applied to keep the wrists close to the table (see Figure 1.12). This is rather a warning for the tested person not to forget to keep the wrists on the table.

2.1.2 Hand tapping

The persons put their hands on the table in prone position; the fingers on each hand are close to each other, elbows are on the table. Persons lift their hands (wrists remain on the table) and then hit the table again. Persons are asked to perform the movement as fast as they can while lifting their hands as high as they can. Again, speed is the highest priority expectation.

2.1.3 Pinching and circling

This movement comprises six separate movement patterns. The four single hand or forearm movements are: pinching with the right hand, pinching with the left hand, circling with the right forearm, circling with the left forearm. The two parallel movements are: pinching with one hand while circling with the forearm of the other upper limb, cf. Figure 2.2. 9-mm diameter markers are attached to the index fingers (both for pinching and circling) and to the thumb (for pinching).

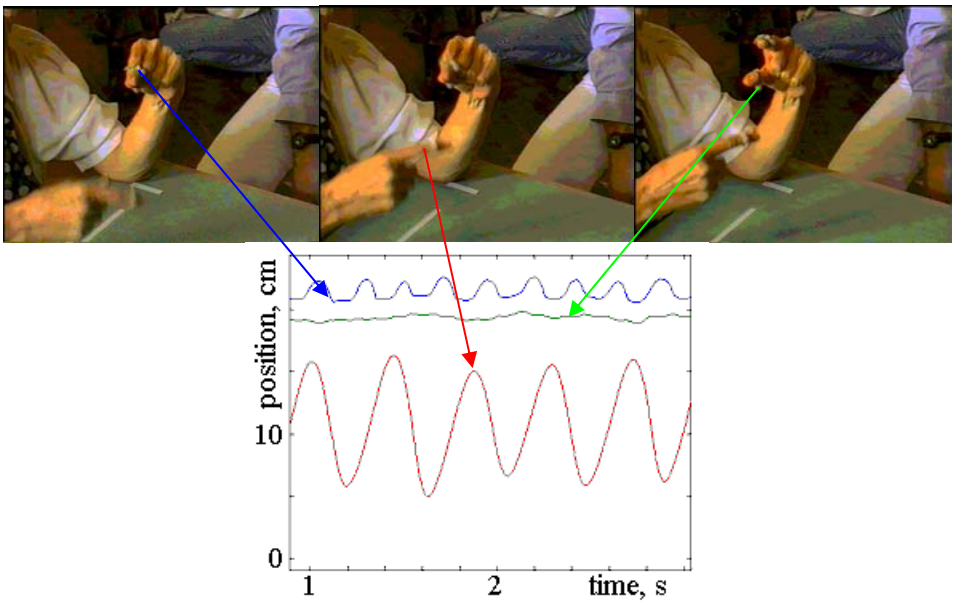


Figure 2.2. Three phases of the pinching and circling movement (above) and the marker trajectories recorded during the movement (bottom).

2.1.4 Twiddling

Patients twiddle their hands in front of their trunks, forearms are nearly horizontal. The 38-mm diameter markers are attached to the forearms, approximately 15 cm far from the carpal bones, cf. Figure 2.3. The trajectories of the markers for a Parkinsonian patient and for a young healthy subject are shown in Figure 2.4 .

Figure 2.3. Three phases of the twiddling movement.

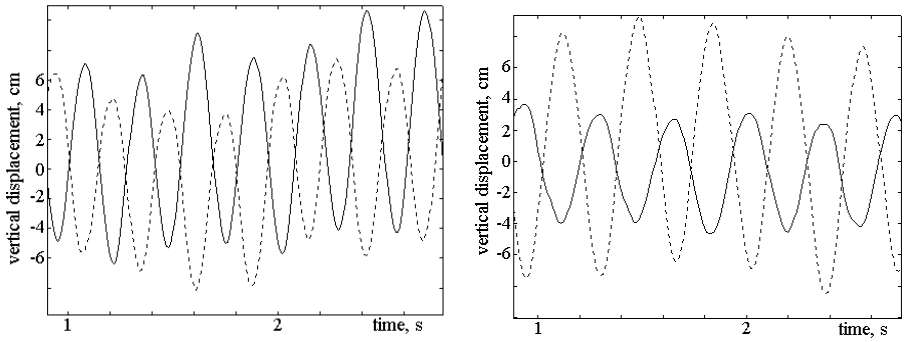


Figure 2.4. Twiddling movement. Left: Young healthy subject. Right: Parkinsonian patient. Right hand (affected one for the Parkinsonian patient) shown with solid line.

2.1.5 Pointing movements

Persons put their index finger on a marked point on the table, this is the initial position.

Slow pointing: From the initial position the person lifts the finger and very slowly (within 15 … 20 seconds) reaches and touches another marked point on the table, approximately 40 cm far from the initial position.

Fast pointing: Persons touch two marked points alternately as fast as they can. Each marked point is touched 5 times. The two marked points are approximately 40 cm far from each other. The trajectories of a marker attached to the index finger of a stroke patient and of a senior healthy subject are given in Figure 2.5. The stroke patient completed the 5 cycles within 23 seconds while the healthy subject within 3 seconds.

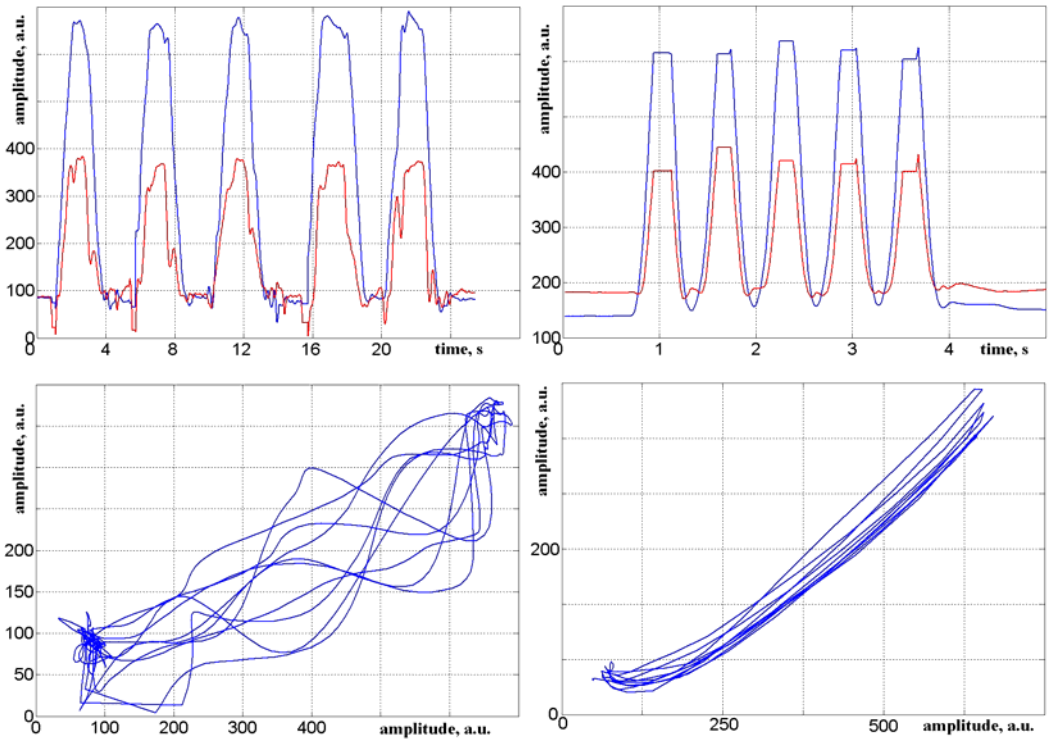


Figure 2.5. Trajectories of pointing movement. Time functions of X and Y projections (top) X-Y diagrams (bottom). Stroke patient (left), senior healthy subject (right).

The reaching and grasping movement is similar to pointing [Rearick et al., 2002]. [Morris, 2000] states that people with PD are slow to reach to stationary targets but they are able to reach forward and grasp moving objects, such as a moving ball at normal speed. The supposed reason is that the moving object triggers lower-level brain-stem or spinal cord reflexes. The reaching ability of Parkinsonians deteriorates if the position of a moving object cannot be estimated based on the trajectory of the object.

2.1.6 Tap heel on ground

The person is sitting on a chair. He/she lifts one foot and then hits the floor with this foot. The 38-mm diameter markers are attached to the foot above the ankle. The movement is shown in Figure 2.6, the marker trajectories of a Parkinsonian and a young healthy subject in Figure 2.7.

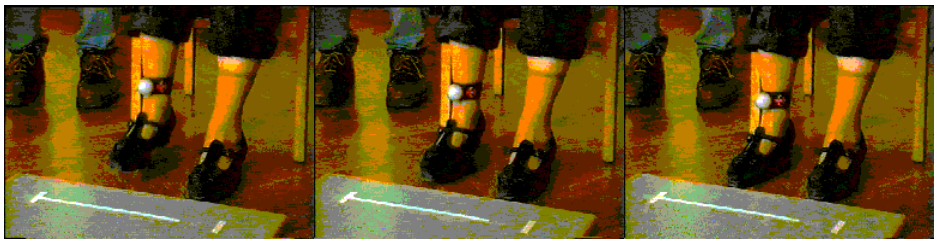


Figure 2.6. Three phases of the movement: tap heel on ground.

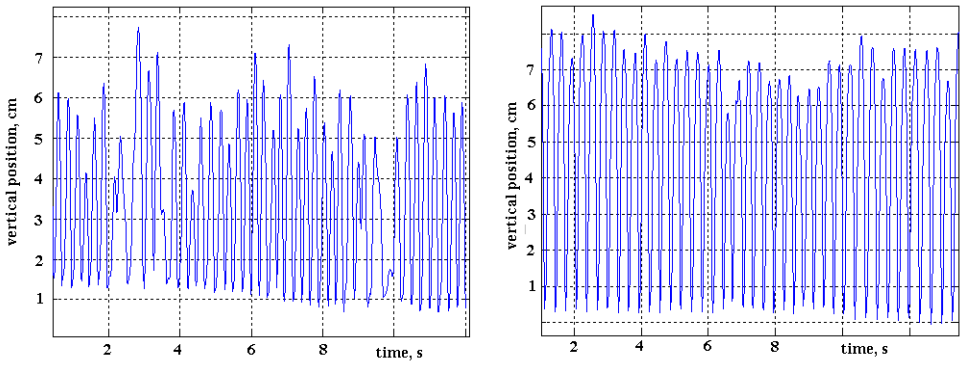


Figure 2.7. Marker trajectories during tap heel on ground. Parkinsonian patient (P15, left) young healthy control subject (right).

2.1.7 Hand tremor

Tremor is a rhythmic, involuntary oscillatory muscular contraction, affecting a part of the body [www.ninds.nih.gov/disorders/tremor/tremor.htm]. Tremor can be present in various parts of the body, legs, body, head, trunk, even vocal cords. However, most frequently it occurs in the arms and hands. There are many types and classification methods for tremor; NINDS Tremor Information Page enlists five categories: resting, postural, kinetic or intention (action), task-specific and psychogenic. There are different types of postural tremor: physiological, essential, cerebellar postural, post-traumatic, alcoholic tremor, tremor with basal ganglia disease, tremor with peripheral neuropathy. Psychogenic tremor disappears when the person is distracted. Further details are given in [Saga, 2003].

All normal persons exhibit physiologic tremor. In the majority of cases it cannot be detected by visual observation. Tracking a marker attached to the body part to be analysed

makes it possible to quantify the tremor. Presently the highest frequency component of tremor is supposed to be 15 Hz thus it is possible to use the PAM analyser for this purpose. Marker was attached to the index finger of persons. The measurement set-up assured high resolution, the typical value was 0.1 mm. Tested persons were either seated or were standing on a platform. In both cases measurements were made with eyes open or close and arms stretched or supported, either at the wrist or at the elbow. Typical displacement curves of a marker during a measurement procedure are given in Figure 2.8, the power spectra of the time functions of the vertical displacement can be seen in Figure 2.9. The subfigures to the left show results with eyes open while to the right with eyes close. Recordings with unsupported hands (top), with supported wrists (middle) and supported elbow (bottom) are given. Closing the eyes causes a substantially greater shift in position when the arm is stretched without support. However, this does not influence the power spectrum.

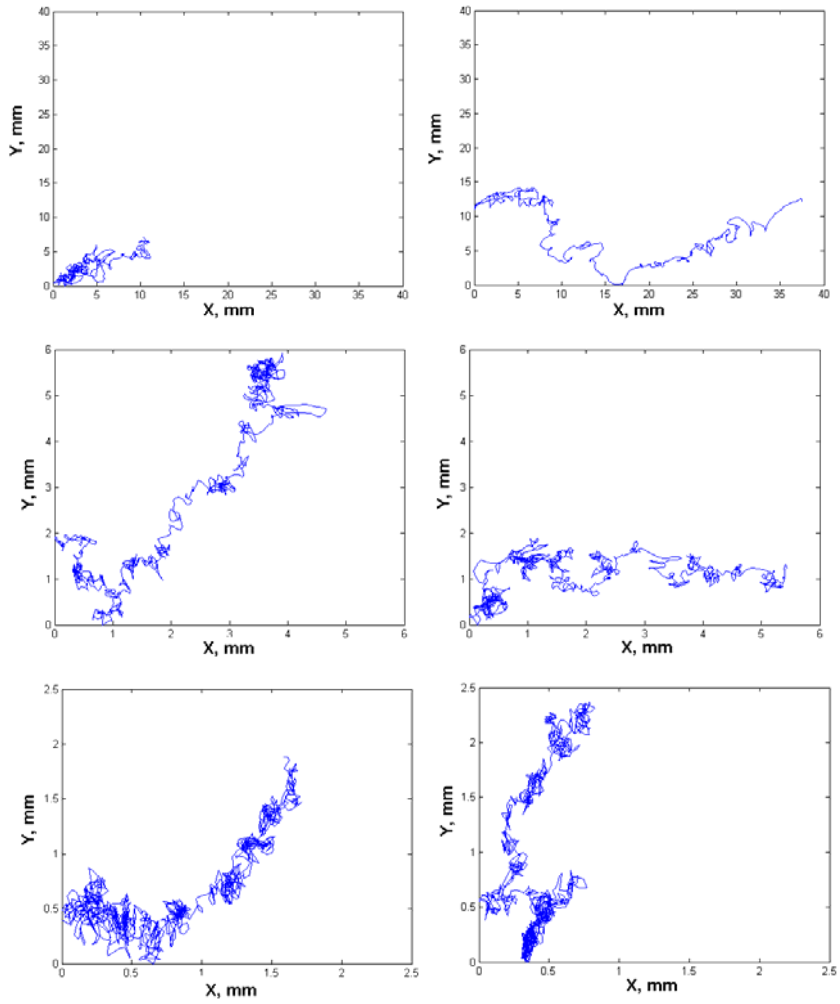


Figure 2.8. Hand tremor of a senior healthy subject. Left side: eyes open, right side: eyes closed. Top: stretched arm, middle: supported elbow, bottom: supported wrist. Scaling is the same in a row.

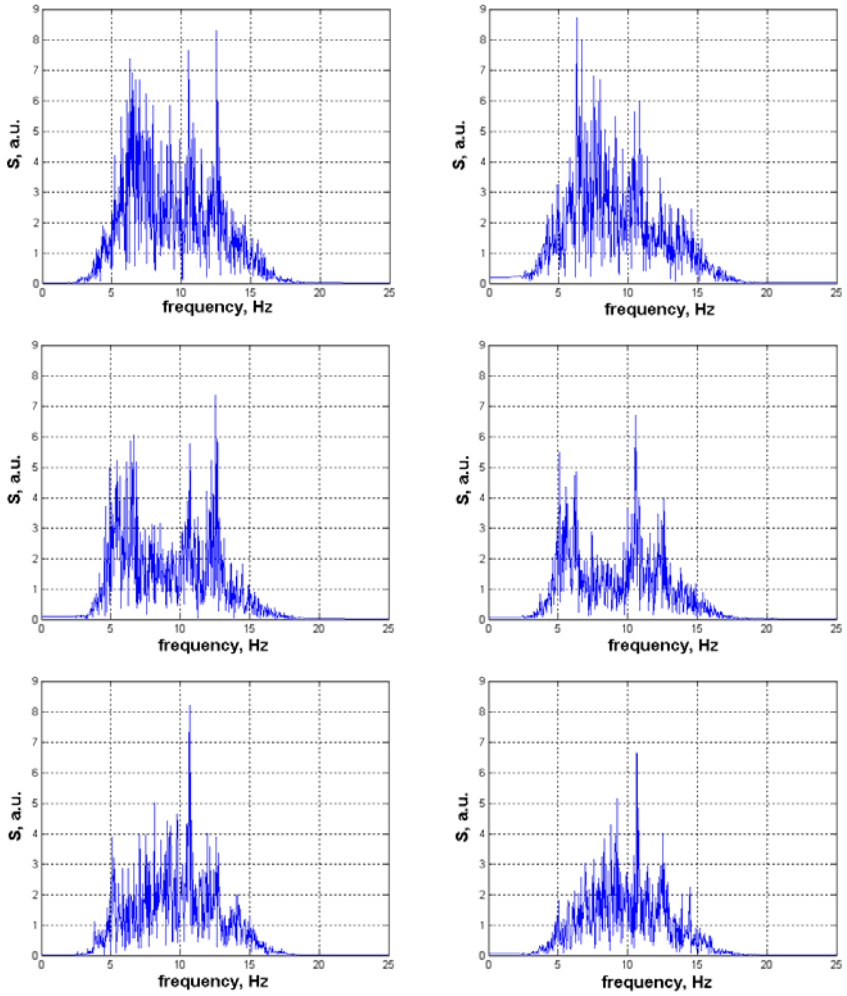


Figure 2.9. Power spectra of vertical displacement – time functions of the recordings shown in Figure 2.8.

2.2 Feature extraction methods I suggest

The primary input data are marker trajectories. Several feature extraction methods were used to find the proper parameters characterising the performance of tested persons during the different movements. The following features were determined: frequency spectrum, measure of periodicity, average speed, maximum speed within a cycle, measures of fractal behaviour. For quasi-periodic movements (finger-tapping, hand-tapping, twiddling, fast pointing, tap heel on ground), average speed of the movement is expressed by amplitude * frequency.

To quantify the measure of periodicity (regularity) of quasi-periodic movements the recorded marker trajectories should be broken down into periodic components (basis functions). ***I suggest using basis functions of any waveform***, not only sinusoidal. If a movement can be fully described by one basis function – irrespectively of its waveform – then it is a periodic movement. If the movement is not periodic then additional periodic functions are needed to

describe the movement as the sum of periodic functions. The singular value decomposition, SVD, is an appropriate method that can handle basis functions of any waveform [Kanjilal et al., 1994]. The details of the method are given in 2.2.1.

As a general rule, I found that the same person executes the movement with higher regularity when the speed is lower. This justifies using the product of speed and regularity to quantify movement co-ordination.

2.2.1 Parameters to characterise movements

The frequency spectrum of the position-time function of a marker can be determined by the Fourier transform. Speed of the movement can be an integral or a momentary feature, average or maximum values can be determined. The parameter best characterising the speed is different for each movement pattern.

The measure of periodicity of the quasi-periodic movement can be well quantified by using the singular value decomposition, SVD method [Kanjilal et al., 1997], [Stokes et al., 1999]. Contrary to the Fourier analysis, the signal is broken down to periodic functions of any kind not only sinusoidal. The vertical coordinates of the sampled marker positions (with ℓ samples) can be regarded as a vector, y:

$$y = y(1)\ y(2) \ldots y(k) \ldots y(\ell)$$

Let y(pi) mark the beginning of the i^{th} period. Samples belonging to a period are considered to be row vectors r(i).

$$r(1) = [y(p1)\ y(p1+1) \ldots y(p2-1)]$$

$$r(2) = [y(p2)\ y(p2+1) \ldots y(p3-1)]$$

$$\vdots$$

$$r(m) = [y(pm)\ y(pm+1) \ldots y(pm+c)]$$

The SVD method requires that each period contain exactly the same number of samples, i.e. the length of r(i) vectors must be the same. The time period is not necessarily constant during the completion of a movement pattern. As a first step the time function must be segmented into periods. For the finger-tapping test, I aligned the periods at the maximum vertical positions of the markers in each tapping cycle (see Figure 2.10 and Figure 2.11). For other movement patterns the segmentation is done similarly. The i^{th} row vector r(i) contains the marker positions belonging to the i^{th} cycle. The duration of a cycle varies over the test, so varies the length of the corresponding row vector.

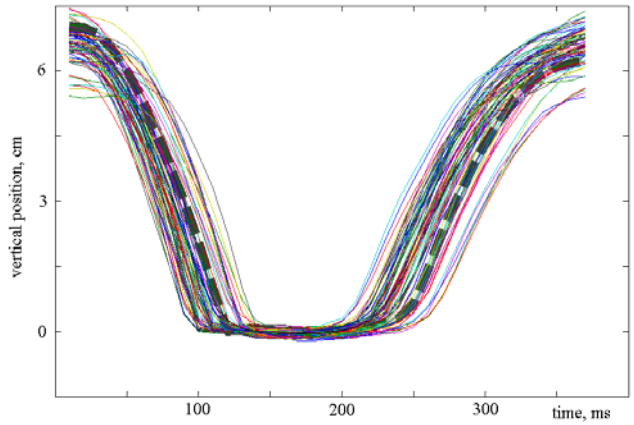


Figure 2.10. Aligned trajectories of a marker attached to the index finger of a healthy subject (thin solid lines) and the base vector determined by SVD analysis (thick dotted line) csptap2, 4. finger.

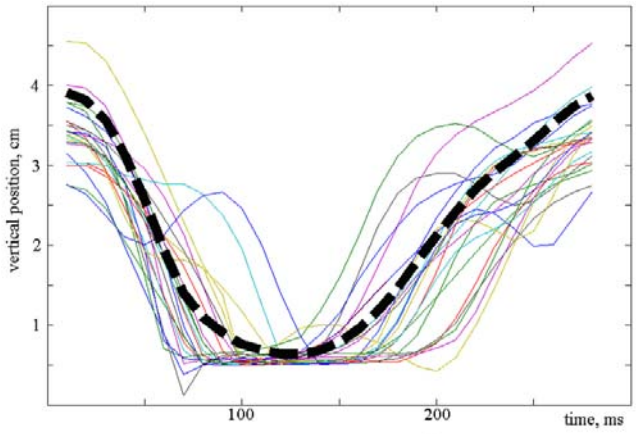


Figure 2.11. Aligned trajectories of a marker attached to the right middle finger of a Parkinsonian (P09, thin solid lines) and the base vector determined by SVD analysis (thick dotted line).

The equal length of all r(i) row vectors is assured by resampling the data in each row. The median (denoted by n) of the lengths of the row vectors will be the length of each resampled vector.

$$\text{length}\ [r(i)] = \begin{cases} (i < m) : pj - pi,\ j = i + 1 \\ (i = m) : c + 1 \end{cases}$$

$$n = \text{median}\ \{\text{length}\ [r(i)]\}$$

Resampling is accomplished by linear interpolation. The first and last elements of the re-sampled row vectors are the same as in the original row vectors, yr(i,1) = y(pi), yr(i,n) = y(p(i+1)-1) except for the last row vector, where yr(m,n) = y(pm+c). The elements of the re-sampled row vectors yr(i,j) are interpolated between the original y(pi+k-1) and y(pi+k) points,

$$k = \text{entier}(n/\text{length}(r(i))*j),\ 2 \le j \le n.$$

The matrix so created is:

$$X = \begin{bmatrix} yr(1,1) & yr(1,2) \cdots & yr(1,n) \\ yr(2,1) & yr(2,2) \cdots & yr(2,n) \\ \vdots & & \\ yr(m,1) & yr(m,2) \cdots & yr(m,n) \end{bmatrix}$$

When the matrix is composed the SVD function of MATLAB® (The MathWorks Inc.) is used. This determines the matrices S, V and Σ so that $X = S\Sigma V^T$. A detailed description of the SVD method is given in [Kanjilal and Palit, 1994]. Σ is a diagonal matrix, its σ_i elements can be regarded as weighting factors of the basis functions that are needed to describe the periods identified in the sampled data y and represented by the row vectors of X. The columns of V can be regarded as basis functions. Adding up the v_j basis functions weighted by $u_i\sigma_i$ we get the i^{th} period of the signal, i.e. the i^{th} row of X. The periodicity of movement (PM) is characterised by the rate of the dominant basis function within all functions necessary to describe the complete record, i.e. all periods. This is calculated on the basis of the diagonals of Σ, σ_i.

$$PM = \frac{\sigma_1^2}{\sum_{i=1}^{n} \sigma_i^2}$$

If σ_1 is dominant (σ_i are arranged in decreasing order) then the movement is nearly periodical and the first column of V (v_1) is the dominant basis function. If all σ_i except σ_1 are zero then the movement is strictly periodic, it can be fully described with no more than one base vector. As a result, the parameter value PM equals 1. In case of a nearly periodic movement σ_1 is dominant but further σ_i elements are non-zero. The PM parameter value decreases as further vectors are needed to describe the movement.

Figure 2.10 and Figure 2.11 show periods of finger movements together with the base vector determined by the SVD method. It is clear that the movement of the young healthy subject is more regular than the movement of the Parkinsonian patient. Figure 2.12 and Figure 2.13 show the relative weights of vectors and the weight of the base vector in different periods determined by SVD analysis for a marker movement during finger-tapping test of a healthy subject and a Parkinsonian. The figures demonstrate the application of the SVD method to quantify regularity.

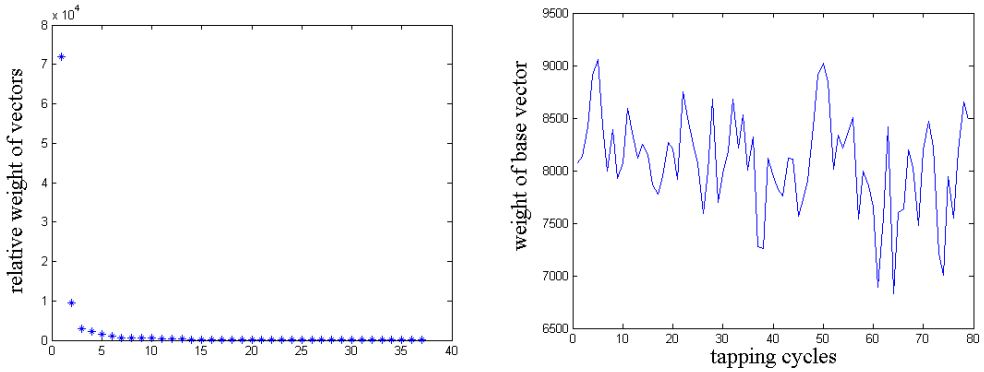


Figure 2.12. The relative weights of all SVD vectors (left) and the weight of the base vector (right) for the 79 cycles of the index finger of a young healthy subject during a 20-s finger-tapping test.

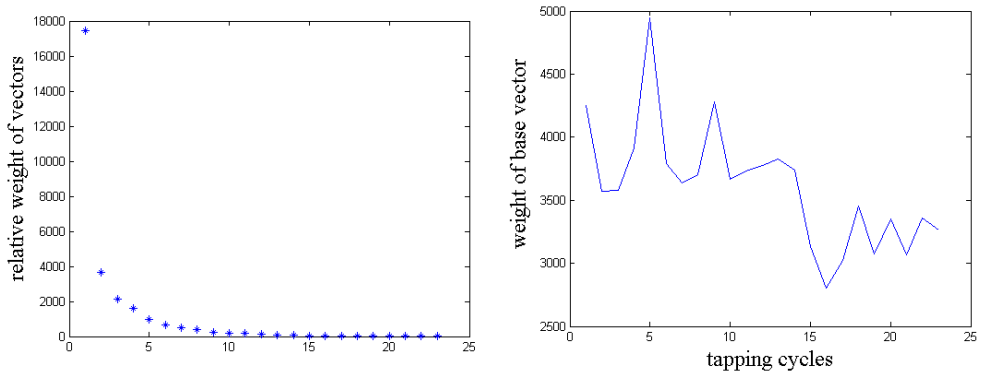


Figure 2.13. The relative weights of all SVD vectors (left) and the weight of the base vector (right) for the 23 cycles of the index finger of a Parkinsonian during an 8-s finger-tapping test.

2.2.2 Finger-tapping and hand-tapping

Greater amplitude or greater frequency during finger-tapping means faster finger movement, it might be considered as better performance. It is easier to execute the movement faster with smaller amplitude, the amplitude * frequency of tapping is suggested as an appropriate parameter to characterise the speed. This feature, called amxfr, is determined for each tapping cycle and then averaged over the whole test.

$$\text{amxfr} = \frac{\sum_{i=1}^{n} \frac{A_i}{T_i}}{n}$$

where A_i : amplitude of the i^{th} tapping cycle in cm,

T_i : time period of the i^{th} tapping cycle in s,

n: number of tapping cycles during the whole test,

amxfr is in cm/s.

The regularity of the movement is characterised by calculating PM for each tapping finger. The performance of a finger is characterised by the product of amxfr and PM. Increasing the speed usually decreases the regularity of the movement. ***I suggest characterising the performance of a finger during the finger-tapping test by the product of the parameters expressing speed (amxfr) and regularity (PM).*** Based on more than 300 finger-tapping tests I devise the Finger-Tapping Test Score (FTTS) [Jobbágy et al., 2005]:

$$FTTS = (PM - 0.6) * amxfr.$$

PM was greater than 0.6 for all fingers of all healthy subjects and for nearly all Parkinsonian and stroke patients. Subtraction of 0.6 adjusts the proper relative weight of PM to amxfr. PM is dimensionless, thus FTTS is given in cm/s. If the finger-tapping test is applied to a great number of patients then it may turn out that the relative weight of PM and amxfr must be modified.

Based on the scores of the fingers, scores can be calculated for the hands and for the person. One hand can be characterised by averaging or adding the results of two or three fingers. As the amplitude of the little finger is usually much smaller than the amplitude of the other fingers, the parameters referring to the little fingers are suggested to be excluded from averaging. However, in case of a given patient, little fingers can be interesting and their performance can be included in personalised scores.

The maximum speed within each finger-tapping cycle during lifting and striking can easily be determined from the position-time functions of markers.

The fractal behaviour of the marker trajectories could be characteristic for the tapping person. The method suggested in [Eke et al., 2002] was applied using the MATLAB functions that were available in 2004 as part of the computer program 'FracTool' at the given web-site: www.elet2.sote.hu/eke/FRACTPHYS/. The time functions of the markers did not show convincing self similarity (fractal behaviour).

The evaluation of the hand-tapping movement is very similar to the evaluation of finger-tapping. However, speed and regularity of the movement can only be defined for a hand; it must not be interpreted for separate fingers. The performance of the person can be calculated by taking into account the performance of both hands.

During finger-tapping the smoothness of the movement can also have diagnostic value. There were some stroke patients who exhibited a nearly periodic movement with a trembling around the maximum vertical position of the finger (cf. Figure 4.14). The deviation from a smooth trajectory can be taken into account as a modifier for FTTS.

Another deviation from the ideal finger-tapping is when tested subjects perform rather hand tapping (lift all fingers at the same time and also hit the table with all fingers at the same time). This deviation from ideal finger-tapping is not taken into account in FTTS. It can also happen that tested subjects hit the table with their fingers in a bad sequence: e.g. hit the table with the index finger earlier than with the middle finger. Depending on the frequency of erroneous sequences of fingers a multiplier can be used to lessen FTTS. Further details on smoothness and erroneous finger sequence are given in (Nepusz, 2005). The suggested algorithm is applicable for stroke patients as given in 4.3.

2.2.3 Twiddling

During this movement neither the periodicity of movement nor the amplitude varies substantially. Table 3.5 shows that the periodicity of movement is about the same for Parkinsonians and healthy subjects, and the standard deviation of this parameter is very small. The speed and the symmetry of the movement (difference in amplitudes for the two forearms) are characteristic for the tested person. Parkinsonians with symptoms on one side only produce quite different amplitudes for the two sides: the forearm with no symptoms circles around the affected forearm. The two parameters are:

*twiddling speed, twisp (*cycles per second)*:*

$$\text{twisp} = 1 - \frac{4 - \text{twiddling frequency}}{4 + \text{twiddling frequency}} = \frac{2 * \text{twiddling frequency}}{4 + \text{twiddling frequency}}$$

In the majority of cases, the twiddling frequency is between 0.5 and 4 Hz thus twisp is between 0.2 and 1. The normalisation helps when the results of different tests are used to characterise the actual state of a patient.

symmetry of twiddling, twisym:

$$\text{twisym} = 1 - \left| \frac{(A_r - A_l)}{(A_r + A_l)} \right|$$

where A_r and A_l are the amplitudes calculated as the difference between the maximum and the minimum vertical positions of the markers attached to the right and left forearms. The maximum and minimum positions are determined in each cycle and the amplitudes so calculated are averaged for the time of the twiddling test. The regularity of the twiddling movement has not been found to have diagnostic value.

2.2.4 Pinching and circling

The six movement patterns are the following:

- four simple movement patterns involving only one hand or forearm: circling with right forearm, circling with left forearm, pinching with right hand, pinching with left hand,
- two complex movement patterns composed of two parallel movements each: pinching with right hand and circling with left forearm, pinching with left hand and circling with right forearm.

Basically two types of parameters characterise these movements: periodicity of movement and speed of movement. The effect of the movement of the other hand and symmetry are considered in both parameter types [Jobbágy et al., 1997].

Periodicity of movement

For all eight movements PM (see 2.2.1) is calculated. Twelve parameters are needed. The first four parameters express the average periodicity of pinching and circling, both as a single movement and as part of a parallel movement. It is expected that a neural disease deteriorates the periodicity of pinching as well as circling.

$$\text{pinsgl} = \frac{\text{PM(single pinching left hand)} + \text{PM(single pinching right hand)}}{2}$$

$$\text{cirsgl} = \frac{\text{PM(single circling left hand)} + \text{PM(single circling right hand)}}{2}$$

$$\text{pinpar} = \frac{\text{PM(parallel pinching left hand)} + \text{PM(parallel pinching right hand)}}{2}$$

$$\text{cirpar} = \frac{\text{PM(parallel circling left hand)} + \text{PM(parallel circling right hand)}}{2}$$

The second four parameters express the effect of parallel movement on pinching and then on circling. They show the difference in periodicity of a movement (pinching or circling) when it is performed as a single movement and when in parallel with it another movement is also performed. It is expected that the periodicity of a movement decreases when in parallel with it another movement is performed. It is also expected that the decrease is more significant for patients with neural diseases.

$$\text{pinparsgl(r)} = \text{PM(single pinching right hand)} - \text{PM(parallel pinching right hand)}$$

$$\text{pinparsgl(l)} = \text{PM(single pinching left hand)} - \text{PM(parallel pinching left hand)}$$

$$\text{cirparsgl(r)} = \text{PM(single circling right hand)} - \text{PM(parallel circling right hand)}$$

$$\text{cirparsgl(r)} = \text{PM(single circling left hand)} - \text{PM(parallel circling left hand)}$$

The last four parameters express the difference between the two sides. They express the difference while performing the same movement with the right and left forearm and hand. These parameters give a quantitative measure for unilaterality.

$$\text{pinsindif} = \text{PM(single pinching right hand)} - \text{PM(single pinching left hand)}$$

$$\text{cirsindif} = \text{PM(single circling right hand)} - \text{PM(single circling left hand)}$$

$$\text{pinpardif} = \text{PM(parallel pinching right hand)} - \text{PM(parallel pinching left hand)}$$

$$\text{cirpardif} = \text{PM(parallel circling right hand)} - \text{PM(parallel circling left hand)}$$

Speed of movement

The speed of single and parallel movements is calculated for both pinching and circling.

$$\text{frqpinsgl} = \frac{4 - \frac{\text{freq right hand single pinching} + \text{freq left hand single pinching}}{2}}{4 + \frac{\text{freq right hand single pinching} + \text{freq left hand single pinching}}{2}}$$

$$\text{frqcirsgl} = \frac{4 - \frac{\text{freq right hand single circling} + \text{freq left hand single circling}}{2}}{4 + \frac{\text{freq right hand single circling} + \text{freq left hand single circling}}{2}}$$

$$\text{frqpinpar} = \frac{4 - \frac{\text{freq right hand parallel pinching} + \text{freq left hand parallel pinching}}{2}}{4 + \frac{\text{freq right hand parallel pinching} + \text{freq left hand parallel pinching}}{2}}$$

$$\text{frqcirpar} = \frac{4 - \frac{\text{freq right hand parallel circling} + \text{freq left hand parallel circling}}{2}}{4 + \frac{\text{freq right hand parallel circling} + \text{freq left hand parallel circling}}{2}}$$

The measure of slowing down during parallel movement compared to single movement.

$$\text{sldwnsglpin(r)} = \frac{\text{freq right hand single pinching - freq right hand parallel pinching}}{\text{freq right hand single pinching + freq right hand parallel pinching}}$$

$$\text{sldwnsglpin(l)} = \frac{\text{freq left hand single pinching - freq left hand parallel pinching}}{\text{freq left hand single pinching + freq left hand parallel pinching}}$$

$$\text{sldwnsglcir(r)} = \frac{\text{freq right hand single circling - freq right hand parallel circling}}{\text{freq right hand single circling + freq right hand parallel circling}}$$

$$\text{sldwnsglpin(r)} = \frac{\text{freq right hand single pinching - freq right hand parallel circling}}{\text{freq right hand single pinching + freq right hand parallel circling}}$$

The difference between the speeds of the same movement performed with right or left hand or forearm.

$$\text{frqdifsglpin} = \left| \frac{\text{freq right hand single pinching - freq left hand single pinching}}{\text{freq right hand single pinching + freq left hand single pinching}} \right|$$

$$\text{frqdifsglcir} = \left| \frac{\text{freq right hand single circling - freq left hand single circling}}{\text{freq right hand single circling + freq left hand single circling}} \right|$$

$$\text{frqdifparpin} = \left| \frac{\text{freq right hand parallel pinching - freq left hand parallel pinching}}{\text{freq right hand parallel pinching + freq left hand parallel pinching}} \right|$$

$$\text{frqdifparcir} = \left| \frac{\text{freq right hand parallel circling - freq left hand parallel circling}}{\text{freq right hand parallel circling + freq left hand parallel circling}} \right|$$

These parameters can be used in any combination to characterise the actual performance of the tested person. Based on the recordings taken from Parkinsonian patients and healthy control subjects ***I suggest composing the Pinching and Circling Test Score (PCTS) as the sum of the 24 parameters defined above.*** PCTS should be personalised for patients with neural disease. For the Parkinsonian patients tested at my laboratory the parameters defined for pinching movement were found to have a stronger diagnosing ability then circling movement.

2.2.5 Slow- and fast pointing

During *slow pointing* basically the tremor of the hand is measured. This is calculated based on the frequency spectrum of the marker movement. Frequency components between 2 and 16 Hz are searched for. This test is similar to the assessment of hand tremor that is usually measured on the stretched as well as on the supported (either at the elbow or at the wrist) arm. Further details are given in 2.2.7.

The score for *fast pointing* takes into account both the speed and the regularity of the movement. Contrary to finger-tapping, hand-tapping and pinching, the amplitude is (should be) constant. The two end-points of the movement (table contacts) should be the same during the whole test; change in the amplitude means an improper execution. Speed, accuracy and regularity are contradictory requirements; the Pointing Test Score (PTS) should take all these features into account. Furthermore, similarly to the finger-tapping test score, in addition to regularity, also the smoothness of the movement should be considered:

$$PTS = fr \times PM \times (1 - h_{sm}) \times (1 - h_{ac})$$

where fr is the average frequency calculated as the reciprocal value of the average time-period during the movement (moving the finger from one point to the other and back), PM characterises the similarity of the five periods, h_{sm} expresses the smoothness of the movement and h_{ac} the accuracy of hitting the marked points. Smoothness is quantified by the deviation of the average marker trajectory from the best fit of a second order curve. There is no "known good" position of the marker at the two end-points. The marker is fixed to the middle phalanx of the index finger, so it is 2 – 3 cm far from the fingertip. The distance between the marked end-point on the table and the marker also depends on the angle of the index finger to the table surface at table contact. Accuracy is characterised by the standard deviation of marker positions at the two end points. Both h_{sm} and h_{ac} are normalised, these errors can result in a maximum decline in PTS by 20 % each. The movement is nearly perpendicular to the optical axis of the camera. It follows that deviations from the marked end points will be differently projected on the sensor of the camera; deviation that falls on the straight line from the marked end point to the camera will not be perceived. Tested persons must be asked to hit the marked points accurately; substantial deviation from the marked points means the movement is not performed correctly and the score might be misleading.

2.2.6 Tap heel on ground

The score takes into account the speed and the regularity of the movement very similarly to the score of hand-tapping. The recording of the movement requires the placement of the camera from the table (where finger-, hand- and arm movements are tested) to the floor. This means an increased testing time. As a result, during my research work only 4 Parkinsonians and 3 control subjects performed this test. I suggest including this test in a second phase, after the finger-, hand- and arm tests are widely accepted and routinely used in neurological wards of hospitals.

2.2.7 Hand tremor

The slow change in the position of the stretched or supported arm is not considered to be tremor. The time function of a marker attached to an anatomical landmark point of a person is bypass filtered, the suggested corner frequencies are 2 Hz and 22 Hz. A number of parameters are used to characterise hand tremor, [Beuter et al., 2004] revises 10 possible ones. Based on more than 60 measurements on 10 healthy subjects with PAM [Melicher, 2005] found the following parameters most informative:

median frequency,

standard deviation of the median frequency,

wobble,

frequency of the two highest energy component in the spectrum,

axes of the ellipsis covering the marker trajectories in the X-Y plane,

amplitude of tremor.

Fitting a circle or an ellipse to the bypass filtered marker trajectory can help characterising hand tremor, see Figure 2.14.

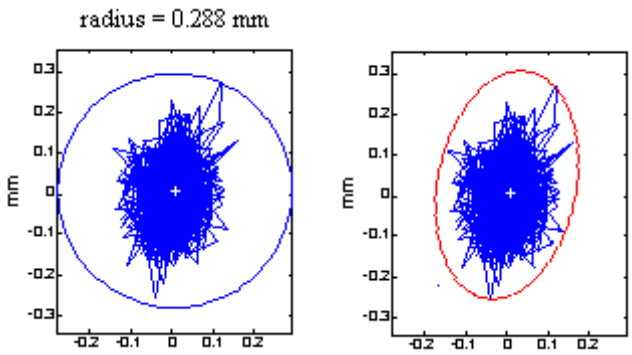


Figure 2.14. Fitting a circle (left) or an ellipse (right) can be used to characterise hand tremor.

2.3 Human factors influencing the movements recorded

Movement co-ordination ability of a person is not constant. Figure 3.16 shows the result of a 6-week finger-tapping test series taken from a young healthy subject. The FTTS score of his right and left hand exhibits a substantial variation. The movement co-ordination performance of professional sportsmen may also change even within a very short time. There are plenty of examples in tennis, table-tennis, fencing, etc. The movement co-ordination performance of a patient is also not constant. This limits the repeatability of movement tests: the performance may change although the stage of the patient's disease remains the same. I suggest ***personalising the tests***, this means:

- the selection of movement patterns that best characterise the tested person,
- comparison of the actual performance to previous results of the same person.

There are persons who have experience in completing coordinated hand or finger movements (***experienced persons***). The performance of an experienced person is substantially better than that of the non-experienced persons. This must be taken into account when testing the movement patterns of a person. When the performance of an experienced person decreases as a result of a disease, it may be still better than that of a non-experienced healthy subject. Experienced persons show smaller standard deviation in movement scores than non-experienced persons. Figure 3.15 shows that the performance of an experienced young healthy control subject is stable during a 4-week finger-tapping test series.

Some persons improve their performance considerably as they learn the movement and get accustomed to the test environment (***learning effect***). The first 2-3 recordings taken from persons may prove to be inaccurate for assessing their actual state. Figure 3.17 shows a 2-week test series of an experienced young healthy subject. The FTTS score increases during the first three tests and does not vary much later. Before making the recordings the task must be explained in detail and the tested persons must learn the movement. This harmonises with the results of [Wu et al. 1999] suggesting that at least two or three tapping tests are needed to determine the baseline value of the tapping test.

The actual psychophysiological state of the tested persons affects their movement co-ordination. Visual feedback also influences the results; measurements taken with eyes open and closed prove it. Control subjects achieved better results with eyes open and watching the finger movement than with eyes closed. The diagnostic ability of movement analysis is better if tested persons have to share their attention. A simple mean is to request tested subjects to

read while performing the test. [Orova et al., 2005] investigated how the finger-tapping test result varies for the same subject with *eyes open and closed* and also the *effect of reading*. The influence of closing the eyes and drawing the tested subject's attention to another task (reading) is different from subject to subject. As a rule, the performance reflected by FTTS deteriorates when eyes are closed but the standard deviation of the results gets smaller. Reading in parallel with finger-tapping also deteriorates FTTS and lowers the standard deviation. Healthy subjects' FTTS results with eyes closed and in parallel with reading are much better than the FTTS results of stroke patients and Parkinsonians.

Although subjects are asked to perform the movement as fast as they can, not every subject does so. Even experienced subjects were not always fast enough. The FTTS score of an experienced young healthy subject (CsP, separately calculated for his right and left hand) is the result of excellent regularity but only average speed. This was very stable during his 4-week test series, as given in Figure 3.15.

A not-experienced young healthy subject did not exhibit stability in his FTTS results during a 6-week period. However, he produced higher average amplitudes (Figure 3.16) than the experienced young subject. This raises the question of defining the movement in more details. I made even attempts to use mechanical aids to restrict tested persons' hand- and finger movements but these aids did not help. Extra fast movement may mean a bad sequence of fingers during the finger-tapping test. This effect is analysed in 4.3.3.

3 Early detection and staging of Parkinsonian patients

Parkinson's disease (PD) is a neurodegenerative disease without a known cause and cure. The symptoms had been mentioned together with possible treatment already in the ancient Indian medical practice of Ayurveda 2500 years BC. The conditions in detail were first described by James Parkinson [Parkinson 1817]. The term Parkinson's disease was first used by the French neurologist Jean-Martin Charcot (1825-1893) about 4 decades after Parkinson had published the essay. The disease is caused by the degeneration of the basal ganglia of the brain resulting in a reduced dopamine production. The dopamine producing cells in the brain are located in the substantia nigra. Dopamine is required for the information flow between cells controlling movement. By the time the symptoms are pronounced enough to set up the diagnosis 60 - 80 % of the dopamine producing cells are not functioning. Parkinson's disease is among the most common neurodegenerative diseases [Factor and Weiner, 2002]. The incidence of the disease increases with age. In the US and Canada Parkinson's disease affects about 1 % of the population over age 65 and 2 % over 70. In the US about 50,000 new cases are diagnosed each year, the total number of Parkinsonian patients is between half a million and one million at any given time [Conley et al., 1999, www.mayoclinic.com]. Further information about the disease can be found at: [www.parkinson.ca/pd/nd.html], [www.parkinson.org].

Early diagnosis and staging of Parkinsonian patients is extremely difficult. There are no blood tests or simple medical imaging procedures to confirm the onset of the disease unambiguously. PET or SPECT examination could reveal the loss of dopamine production but these examinations are not applicable for screening or widespread clinical usage. The early diagnosis of Parkinson's disease - like other extrapyramidal disorders - requires special functional imaging, different from conventional brain functional imaging [Diaz et al., 2000].

Early diagnosis would make it possible to start the treatment when the loss in dopamine production cells has just begun. Parkinson's disease has a wide range of early symptoms that are similar to those of other neurological diseases; this makes difficult the correct diagnosis. According to international statistics, the diagnosis of more than 20 % of the patients in an early phase of a neurological disease is false [Hughes et al., 1992]. Typically, the diagnosis for a great number of patients is uncertain in the first 2-3 years of the disease [Findley, 1993].

3.1 Rating scales

Different rating scales exist for Parkinsonian patients; a good summary is available at [www.parkinsonsdisease.com/pcp/rating.htm]. However, these contain rather subjective elements. In 1967, before levodopa or the dopamine agonists were used for medication, medical doctors Margaret Hoehn and Melvin Yahr published a paper [Hoehn and Yahr, 1967] rating Parkinsonian patients on a 6-point scale: 0, 1, 2, 3, 4, 5. The Hoehn-Yahr staging is given in Appendix 1.

The Hoehn and Yahr Scale rates one aspect of the disease: mobility. It does not rate other aspects of Parkinson's disease such as:

1. Anxiety and Depression
2. Dyskinesias
3. Intellectual Decline and Memory Loss
4. Unusual Behaviour
5. Swallowing Difficulty
6. Sleep Difficulty
7. Bladder Difficulty

Later the Hoehn – Yahr staging was modified and new rating systems were introduced: the United Parkinson's Disease Rating Scale (UPDRS) and the Schwab and England Activities of Daily Living scale (the questionnaires are given in Appendix 1). The UPDRS scale is calculated on the basis of the answers given to 42 questions. The actual performance is determined by visual observation or it is done by the patients themselves. The Movement Disorders Society has recently published a recommendation to develop a new version of UPDRS together with an official appendix that includes other, more detailed, and optionally used scales to determine severity of the impairments [Movement Disorders Society, 2003].

There are some further, not so widely used rating scales [Marinus et al., 2002], examples are: Activities of Daily Living (ADL), Sickness Impact Profile (SIP), Parkinson's Disease Questionnaire (PDQ-39) [Damiano et al., 1999], etc. A study was conducted in Canada to assess the change in quality of life brought by the disease for patients. The Parkinson's Impact Scale (PIMS) is determined on the basis of a one page questionnaire filled in by the patient [Calne et al., 1996], [Schulzer et al., 2003]. [Welsh et al., 2003] suggests a Parkinson's Disease Quality of Life scale (PDQUALIF). These rating scales do not help in the early detection of the disease; neither in the differential diagnosis. However, they help in determining the progress of the disease.

3.2 Assessment based on movement analysis

Assessing the motor functions of patients helps the diagnosis as well as the staging. Movement analysis helps both the early diagnosis and the staging by assessing the four basic motor signs of the disease: tremor at rest, rigidity, bradykinesia and postural instability [Marjama-Lyons and Koller, 2001], [Montgomary, 1996], [Jobbágy et al., 1997], [Jobbágy et al., 1998], [Jobbágy et al., 2000]. [Pandyan et al., 2004] reports a method to test spasticity. In the early stage these motor signs are usually unilateral, often affecting only one limb. Other Parkinsonian syndromes (e.g. multiple system atrophy, MSA, [Wenning et al., 2000]) and ageing may result in symptoms similar to those caused by primary Parkinson' disease. Especially early in the disease it is often difficult to set-up a correct diagnosis which would be important for the treatment and medication. It is estimated that 25 % of Parkinsonian patients presenting symptoms of classic idiopathic Parkinson's Disease (CIPD) are incorrectly diagnosed. It is also estimated that 15 % of these patients have atypical Parkinson's disease [Cram, 2002]. Post-mortem analysis revealed that the selectivity and specificity to differentiate between Parkinson's disease and MSA was around 90 % even after collecting medical data from the onset of the disease until death.

The Posturo-Locomotion-Manual (PLM) test was introduced nearly twenty years ago [Ingvarsson et al., 1986]. The test defines a movement pattern in detail. It starts with bending to pick up a box, standing up (this is the postural phase), walking a distance with the box (1.82 m, the locomotor phase) and then placing the box on a shelf (manual phase). The score of the patient is determined by movement analysis [Steg et al., 1989]; a new application is reported by [Curtis et al., 2001].

[Fama and Sullivan, 2002] report motor tests and cognitive tests in which 16 men with Parkinson's disease and 48 normal age-matched control subjects participated. During the motor tests hand and finger movements were videotaped and evaluated. Fine finger movements (turning a spindle) were used to assess rigidity and simple arm and hand movements were used to test motor sequencing. The scores were determined by the number of correctly performed movements meaning a relatively poor resolution.

[Rao et al., 2003] searched the MEDLINE database for all English-language articles related to the diagnosis of Parkinson's disease published from January 1966 to April 2001. (The paper also references the research work led by me.) The reference lists of all articles retrieved

were also searched for additional relevant sources. In conclusion it is stated, that ***"Nearly 200 years after it was first described, the accurate clinical diagnosis of Parkinson's disease remains a significant challenge."***

I have been testing the motor functions of Parkinsonian patients, stroke patients and healthy control subjects since 1995. The aim of the research work has been to establish a medically/clinically applicable test including the measurement set-up and the necessary signal processing algorithms. Easy operation of the measurement device – not requiring technical expertise – was a key expectation. The progress of the research has required a strong co-operation between neurologists and engineers. Passive marker-based motion analysis has been an appropriate tool for the research. Definition of movement patterns, application of motion analysis (fabricating markers, defining the anatomical landmark points where markers should be attached to, assuring the reproducibility of the tests, deciding the instructions given for the tested persons) and the evaluation algorithms have been validated by several hundred tests taken by my research group with the participation of Parkinsonian patients and healthy control subjects. The suggested procedure is simple-to-use; the device developed for the test (PAM) is affordable even for the neurological wards of Hungarian hospitals. The suggested parameters have been found to characterise the actual state of persons correctly. By evaluating the recordings of patients with neurological diseases a reference data base is being created. This will help the early diagnosis and the staging of patients based on movement analysis.

3.3 The subjects and patients tested

10 Parkinsonian patients were assessed 18 times with a battery of tests. There were 6 male and 4 female Parkinsonians, age between 45 and 78 (mean: 66.9, standard deviation 8.5). The patients were qualified according to the Hoehn-Yahr staging by neurologists; the results are given in Table 3.1. Four Parkinsonians were also tested about a year after the first test. Three patients repeated the tests two years after the first test. This has been taken into account while calculating the mean and standard deviation of age. The tests were supervised by Dr. P. Harcos, head neurologist.

There were 26 young and 12 senior persons in the healthy control group. The statistical data of the two groups are given in Table 3.2. Within the healthy subjects there were some who had experience in completing coordinated hand-, or finger movements. Some have been

playing the piano some have been doing free-hand drawing. They are called “experienced” persons.

The patients completed the following movements each time: finger-tapping, twiddling, pinching & circling. Seven times the patients repeated the finger-tapping test after a short break, resulting in 25 recordings of finger-tapping from Parkinsonians altogether. 21 young and 11 senior healthy subjects were assessed using the same battery of tests, resulting in 42 (25 + 17) recordings of finger-tapping. In addition, one senior and five young healthy subjects completed only the finger-tapping test a number of times within half a year. These subjects completed the finger-tapping test 7, 8, 14, 15, 31 and 31 times. Altogether the 38 control subjects performed the finger-tapping test 148 times.

The twiddling movement was recorded from 10 Parkinsonian patients (22 recordings) and 32 healthy control subjects (57 recordings). The pinching and circling test was recorded from 10 Parkinsonian patients (16 recordings) and 32 control subjects (33 recordings).

Patient nr.	Age	Gender	Hoehn-Yahr stage	handedness
P1	53	m	1-2	r
P2	69	m	3	r
P3	55	m	1	r
P4	76	m	1	r
P5	45	f	2	r
P6	69	f	1	r
P7	65	f	0-1 (newly diagnosed)	r
P8	65	m	0-1 (newly diagnosed)	r
P9 (same as P4)	77	m	1	r
P10	72	f	2	l
P11 (same as P2)	70	m	3	r
P12 (same as P8)	66	m	1	r
P13 (same as P10)	72	f	2	l
P14	65	m	1	r
P15 (same as P8)	67	m	1	r
P16 (same as P7)	67	f	1	r
P17 (same as P4)	78	m	1	r
P18 (same as P10)	73	f	2	l

Table 3.1. Parkinsonians tested

	age		gender: male/all	handedness right/all	experienced
	mean	std. dev.			
young	23	2.2	19/21	17/21	5/21
senior	54,2	3,7	10/11	10/11	1/11

Table 3.2. Young and senior healthy subjects tested

3.4 Recordings

3.4.1 Finger-tapping

Figure 3.1 - Figure 3.7 show the trajectories of markers attached to the fingers on both hands of 7 persons. The upper subfigures show 1.5-s parts of the movement of the ring- (solid lines), middle- (dashed lines) and index (dotted lines) fingers. The lower subfigures show 8-s parts of the movement of the middle fingers. Within one figure the two upper – and also the two lower – subfigures have the same scaling. The figures show the movement of persons according to Table 3.3. ***The figures clearly demonstrate that the progress of Parkinson's disease impairs the finger-tapping movement.***

Figure 3.1	young healthy subject, 23-year old male
Figure 3.2	senior healthy subject, 53-year old male
Figure 3.3	Parkinsonian patient, 65-year old female, just diagnosed
Figure 3.4	Parkinsonian patient, 65-year old male, just diagnosed
Figure 3.5	Parkinsonian patient, 53-year old male, Hoehn-Yahr stage 1,5
Figure 3.6	Parkinsonian patient, 45-year old female, Hoehn-Yahr stage 2
Figure 3.7	Parkinsonian patient, 69-year old male, Hoehn-Yahr stage 3

Table 3.3. Persons, whose finger-tapping movements are displayed in Figure Figure 3.1 – Figure 3.7.

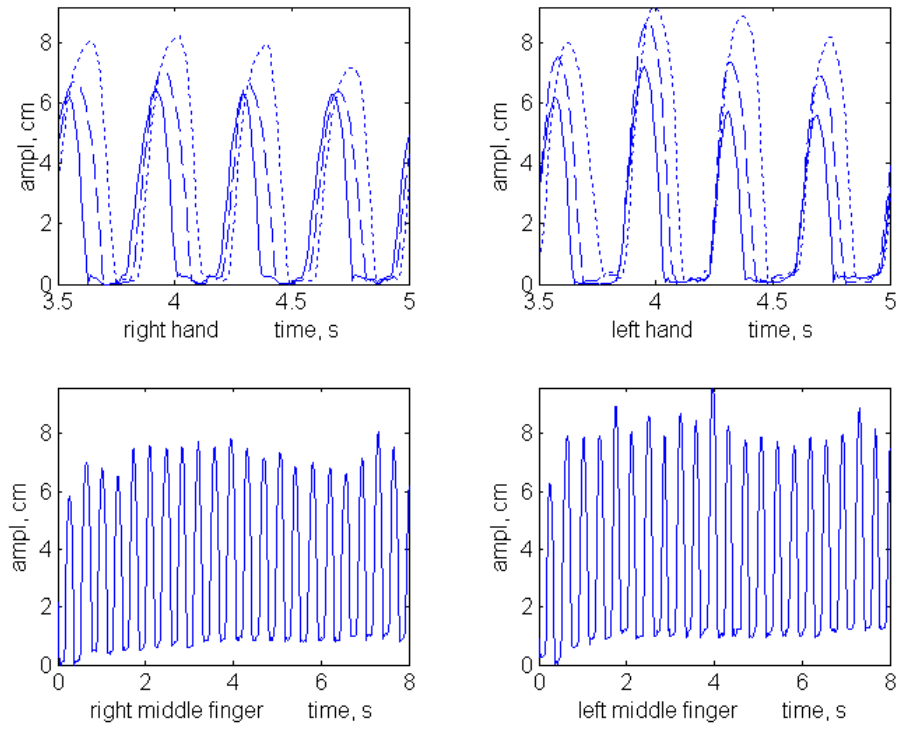


Figure 3.1. Healthy young subject (CsP). (Solid = ring-, dashed = middle-, dotted = index finger.)

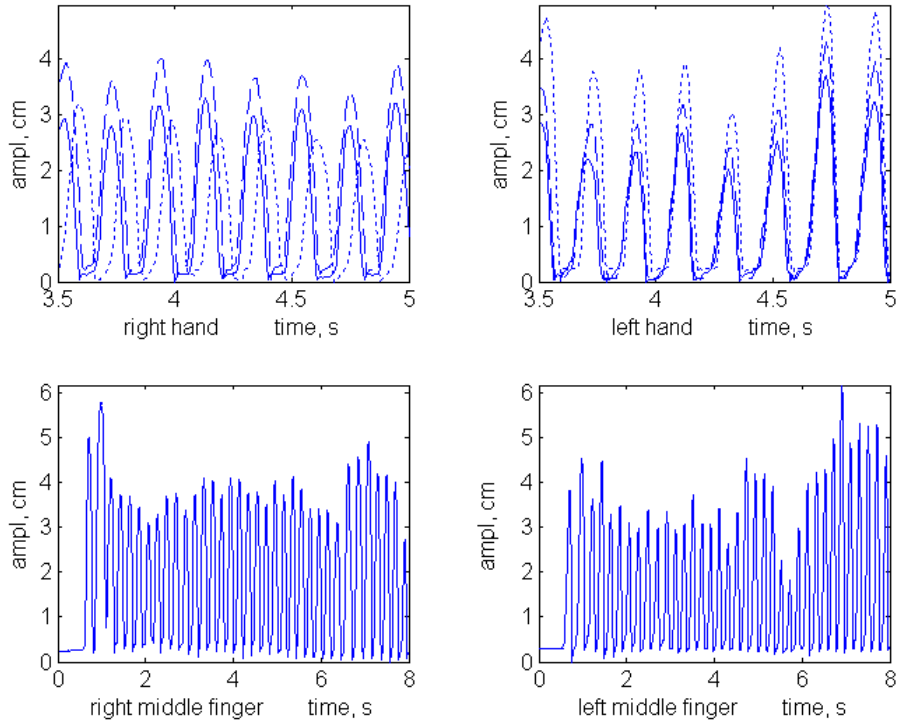


Figure 3.2. Healthy senior subject (S04). (Solid = ring-, dashed = middle-, dotted = index finger.)

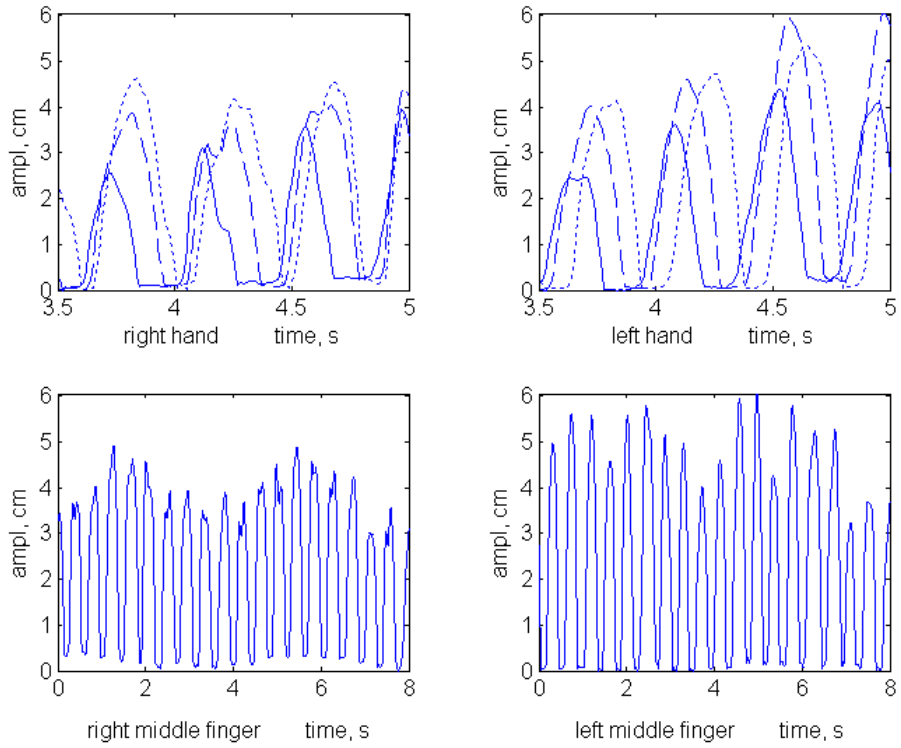


Figure 3.3. Parkinsonian patient, just diagnosed (P07). (Solid = ring-, dashed = middle-, dotted = index finger.)

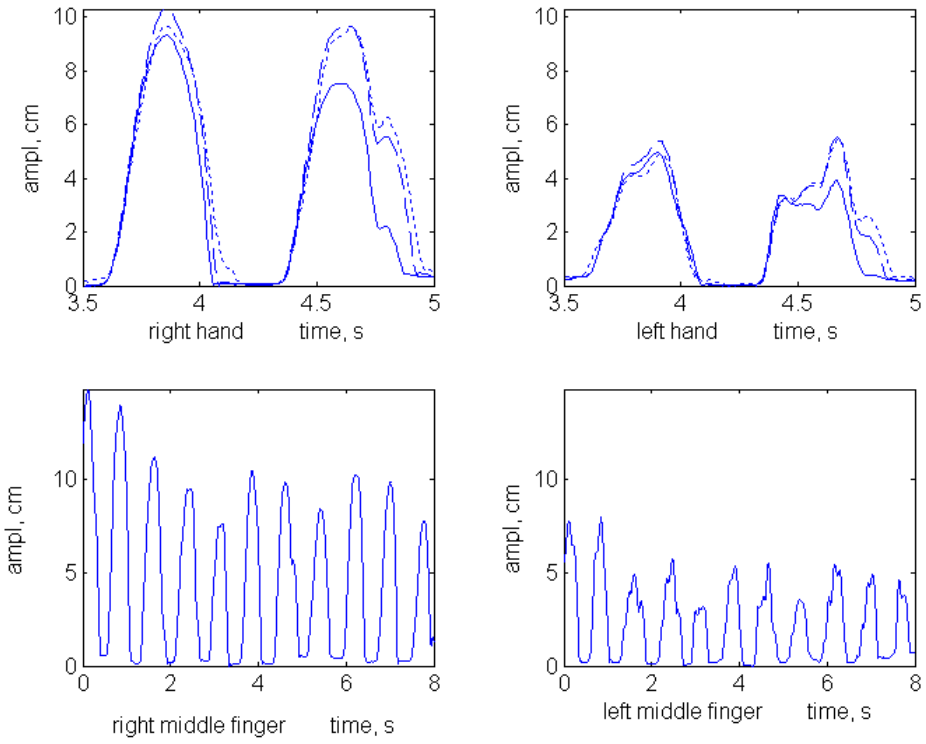


Figure 3.4. Parkinsonian patient, just diagnosed (P08). (Solid = ring-, dashed = middle-, dotted = index finger.)

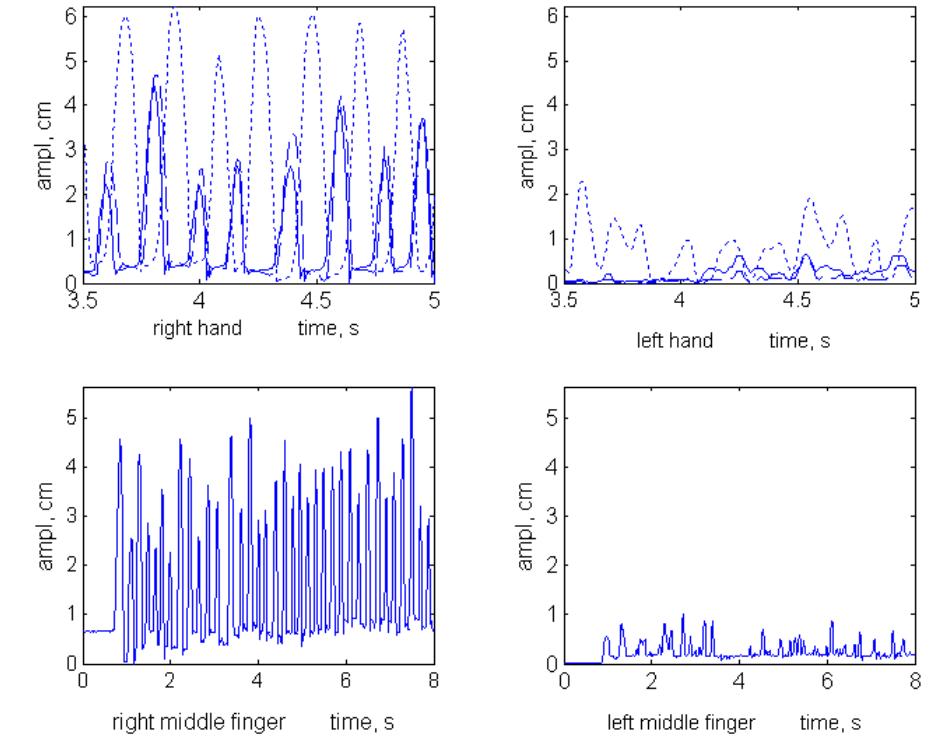


Figure 3.5. Parkinsonian patient, stage Hoehn-Yahr 1 (P01). (Solid = ring-, dashed = middle-, dotted = index finger.)

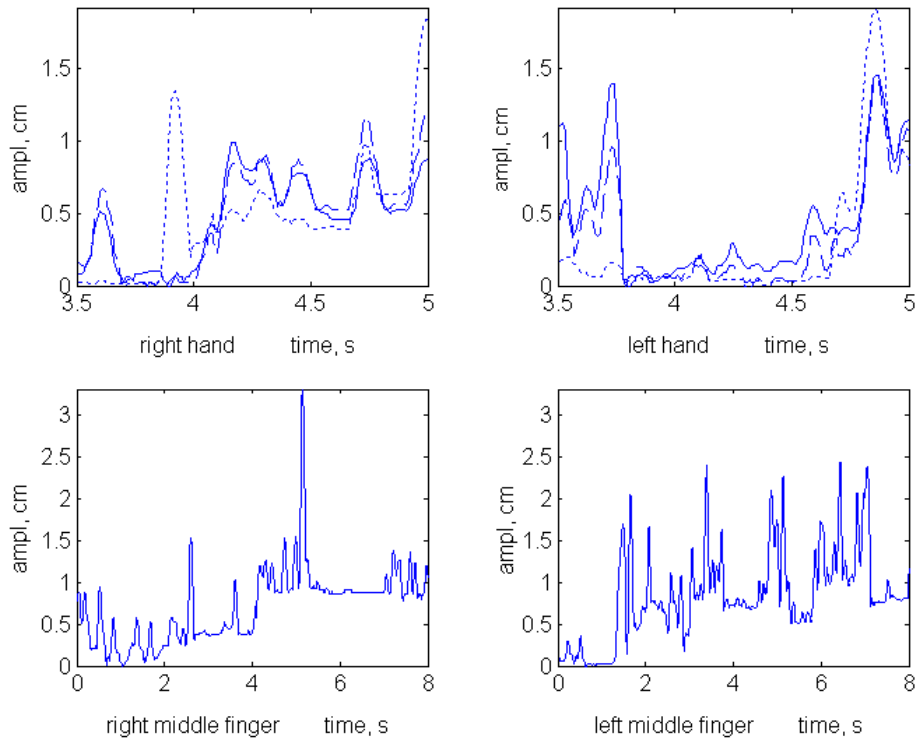


Figure 3.6. Parkinsonian patient, stage Hoehn-Yahr 2 (P05). (Solid = ring-, dashed = middle-, dotted = index finger.)

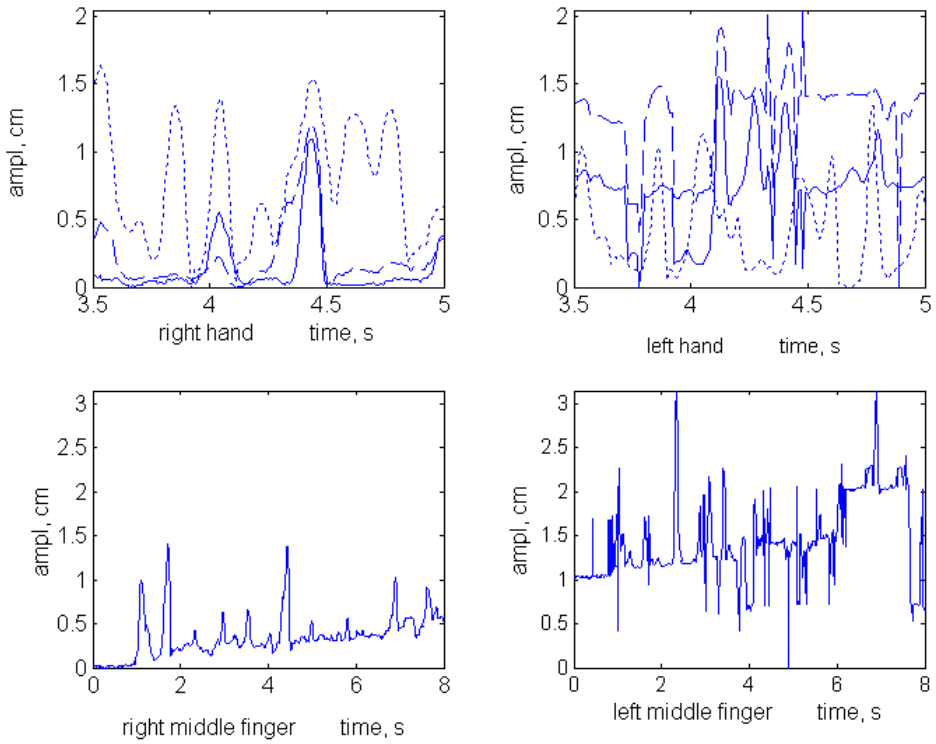


Figure 3.7. Parkinsonian patient, stage Hoehn-Yahr 3 (P02). (Solid = ring-, dashed = middle-, dotted = index finger.)

Paced tapping tests were applied so that only the index fingers had to be lifted and then put back to the table. The left and right index fingers had to be lifted alternately: while the left index finger was moving upwards the right had to move downwards. At each tick of the pacing signal tested persons had to change the position of their index fingers. This means a pacing signal with f_p frequency required a finger movement with $f_p/2$ frequency. f_p was changed (increased or decreased) in every 6 second. In Figure 3.8 thick black lines show the actual f_p value, red (right index finger) and blue (left index finger) lines show the average tapping frequency calculated for 6 seconds.

The pacing frequency started from 3 Hz and was increased in 0.5 Hz steps until 7 Hz for healthy subjects, from 1 Hz to 3 Hz (in 0.5 Hz steps) for Parkinsonians. Healthy subjects could easily follow the pacing signal. Although healthy subjects also exhibited the festination phenomenon [Nagasaki et al., 1996, Giladi et al., 2001] this was more accented for Parkinsonians. In Figure 3.8 the frequency increase compared to the pacing frequency is always less than 10 per cent for the young healthy subject while it reaches 44 per cent at 3 Hz pacing signal for a Parkinsonian patient being in the early stage. Festination – or hastening – of Parkinsonians is reported also for lip movement tests [Konczak et al., 1997].

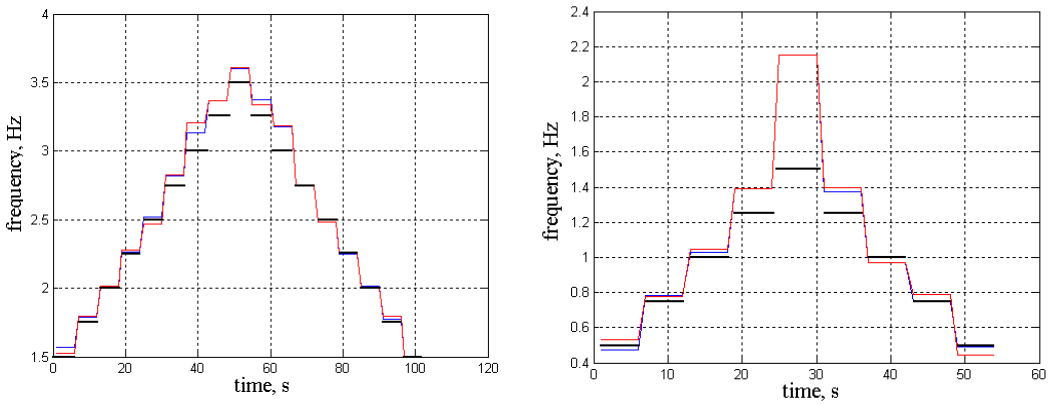


Figure 3.8**. Alternative paced tapping with right and left index finger. Young healthy subject (F12 left), Parkinsonian patient in H-Y 0-1 (P08 right).**

The amplitude of tapping changes (as a rule, decreases) with faster pacing. Figure 3.9 shows the amplitudes of the left and right index fingers during the tests of Figure 3.8.

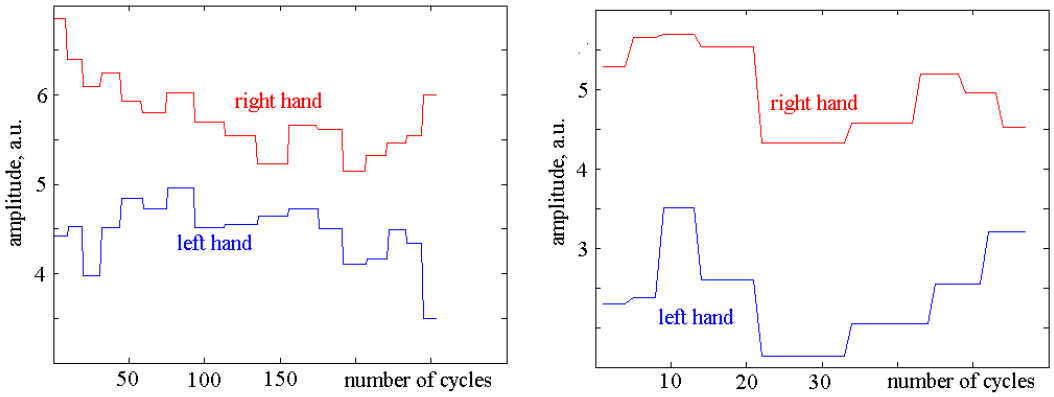


Figure 3.9. Amplitudes of the left and right index fingers during the tests shown in Figure 3.8. Young healthy subject (F12, left), Parkinsonian patient (P08, right).

The phase shift between the movement of the two index fingers changes as the tapping frequency changes. This is given for a young healthy subject (F11) in Figure 3.10. However, definition of the phase is not obvious as the tapping frequency is not exactly the same for the two fingers. The phase shift change observed is similar to the phase shift change during gait on a treadmill with varying speed, reported by [Wagenaar and van Emmerik, 1994]. Both Parkinsonians and healthy subjects tend to synchronise the initially out-of-phase tapping as frequency increases. Moreover, there is a marked difference in the phase shift versus frequency function for the two groups. It helps the assessment of Parkinsonian patients.

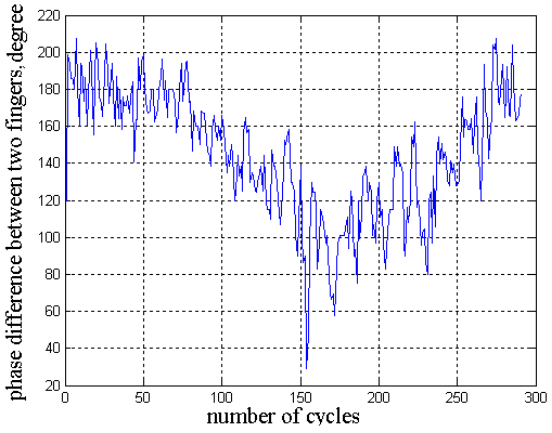


Figure 3.10. The phase shift between the two tapping index fingers during a paced test. Young healthy subject (F11).

3.4.2 Twiddling

Figure 3.11 shows the trajectories of markers attached to both forearms of a young healthy subject (F01, left) and of a Parkinsonian patient in Hoehn-Yahr stage 1 (P09, right). Solid

lines show the movement of the marker attached to the right forearm; dashed lines show the movement of the marker attached to the left forearm. The twiddling frequency is almost four cycles per second for F01 and about three cycles per second for P09. The vertical displacement is about the same for the left and right forearm of F01. P09 circles around his left forearm with his right forearm.

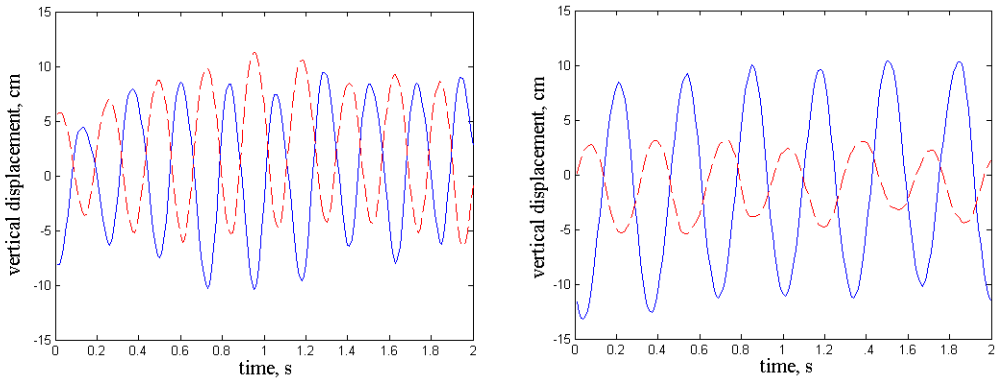


Figure 3.11. Twiddling movement of young healthy subject (F01, left) and Parkinsonian patient (P09, right). Solid line: right forearm, dashed line: left forearm.

3.4.3 Pinching and circling

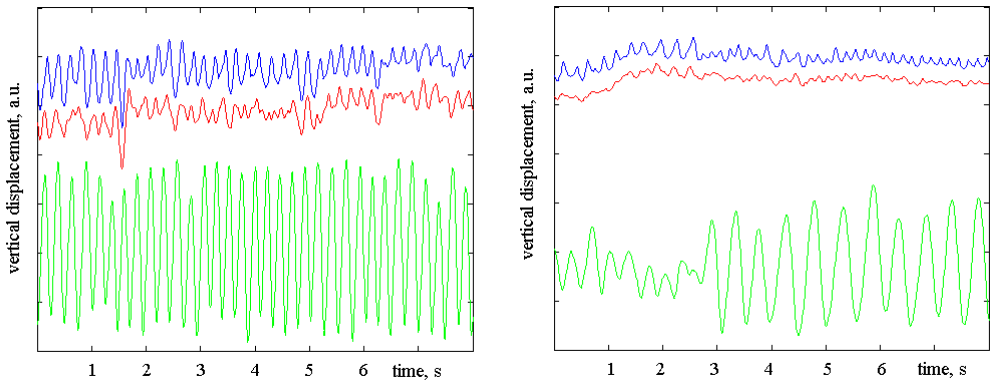


Figure 3.12. Pinching and circling movement of a young healthy subject (F17, left) and of a Parkinsonian (P14, right).

To assess the pinching movement, markers are attached to the thumb and to the index finger. It can be seen in Figure 3.12 that the thumb may also move, so pinching amplitude is determined as the difference between the positions of markers attached to the thumb and the index finger. There are substantial differences between the movement of the young healthy subject and the Parkinsonian patient regarding the amplitude stability of circling as well as the frequency of the simultaneous movement.

3.5 Staging of patients

Human image processing ability is excellent as long as the images are static. Visual evaluation of a movement can give only a rough qualification; quantitative analysis requires proper instrumentation [Cappozzo et al. (eds.), 1992]. In case of the finger-tapping test, the time intervals between table contacts of fingers can be measured with simple contact sensors. Marker-based motion analysis makes it possible to assess details of a movement on a still image, cf. Figure 3.1 – Figure 3.7. The recorded trajectories give information about the finger movement also *between* table contacts. This allows for a finer quantification of the movement of the tested person.

There are different rating scales for patients with neural diseases (see Appendix). These rating scales are rather subjective and usually concentrate on daily activities. Measurements with a movement analyser give objective results. However, the two assessment methods are different; ***there is no direct transformation between their results***. The objective assessment can greatly help the medical doctor in setting the medication and treatment.

3.5.1 The finger-tapping test

Quantification of the finger-tapping test

I suggest a characterisation method of the finger-tapping movement based on processing the position - time functions of the markers. The tested person gets a good score if the *average tapping speed* is high (measured by amplitude x frequency of the vertical marker position) and the movement is close to periodic (measured by PM), i.e. the *regularity of the movement* is good. The Finger-Tapping Test Score (FTTS) for a finger takes both parameters into account (for details cf. 2.2).

Based on the *maximum speed* and the *fractal behaviour* no parameter has been found to aid the staging of Parkinsonian patients. Neither was the *frequency spectrum* of the position-time function of a marker characteristic for a person [Jobbágy et al., 1998].

Figure 3.13 shows the FTTS parameters for the tested healthy senior subjects, Figure 3.14 shows FTTS for the tested Parkinsonian patients. Bright bars stand for the right hands and dark bars for the left ones. The FTTS for a hand is calculated by adding the FTTS values of the ring-, middle- and index fingers. The average value for the senior healthy subjects is around 20 cm/s for both hands. Only S09 and S11 exhibit substantial differences between the

two hands, the difference is less than 1:2. The Parkinsonian patients are ordered according to their Hoehn-Yahr staging established by a neurologist. A horizontal bar spans over the results of the same patient. P07 and P08 were first tested when they were diagnosed (actually the tests helped in setting up the Parkinsonian diagnosis). The FTTS of P07 is about the same as the FTTS of the worst performing senior healthy subject (S07, second test). The left hand of P08 is affected by the disease, the related FTTS is much worse than the worst FTTS of senior healthy subjects. The FTTS of the right hand of the patient (P08, P12, P15 stand for the same person) is varying, but it is never much worse than the average of healthy subjects. The FTTS of P03 is also quite close to the average FTTS of senior healthy subjects. He had worse results in pinching & circling. P14 and P06 performed similar to P08 with the difference that their right hands were affected by the disease. P04 (same as P09 and P17) gradually increased his performance, the FTTS of his left hand remained much worse than that of his right hand. The FTTS of the right hand of P01 is as good as that of a healthy senior subject, while the FTTS of the left hand is worse by a factor of 1:8. Parkinsonians with Hoehn-Yahr staging 2 or 3 could reach very small FTTS values.

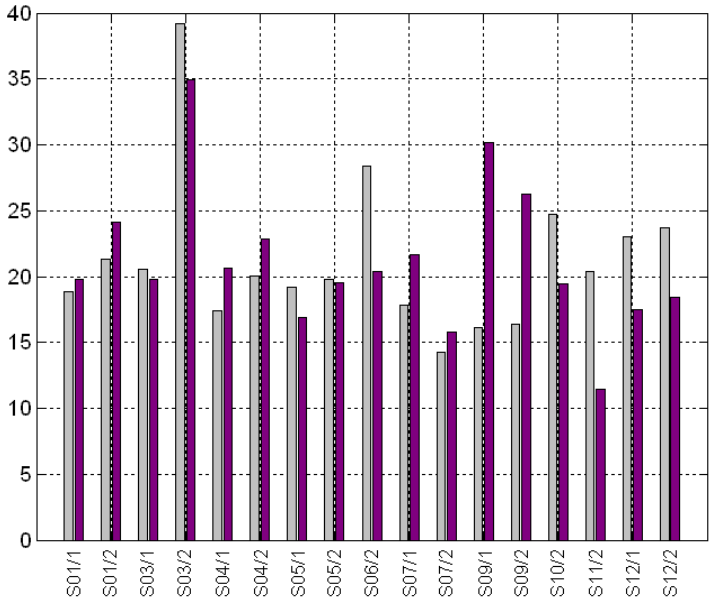


Figure 3.13. FTTS scores for the hands of senior healthy subjects. Bright bar stands for left hand, dark bar for right hand.

I do not recommend using a modifier characterising the smoothness of the movement of Parkinsonians. Contrary to stroke patients when the movement of Parkinsonians was far from periodic, deviations were stochastic. Erroneous finger sequence was also not characteristic for this patient group.

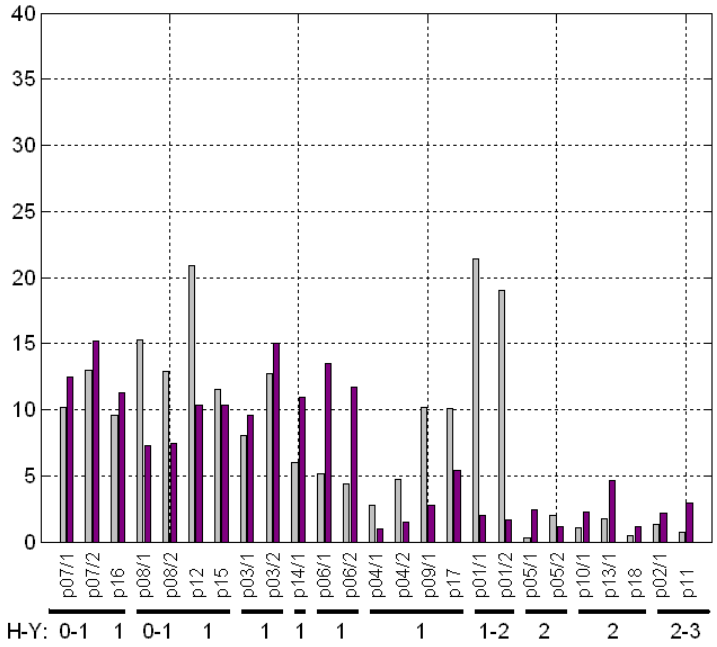


Figure 3.14. FTTS scores for the hands of Parkinsonian patients. Horizontal bar spans over the recordings of the same patient. Hoehn - Yahr staging of patients is shown below the bars. Bright bar stands for left hand, dark bar for right hand.

Repeatability of the finger-tapping test

Figure 3.15 shows the repeatability of the test for a young healthy subject (CsP). CsP is an experienced person (he has learnt to play the piano). He was very good at the periodicity of movement (PM) while he was around average regarding the speed (amxfr). The (standard deviation)/mean values of FTTS for the healthy control subjects, who participated in the measurement series are separately given in Table 3.4.

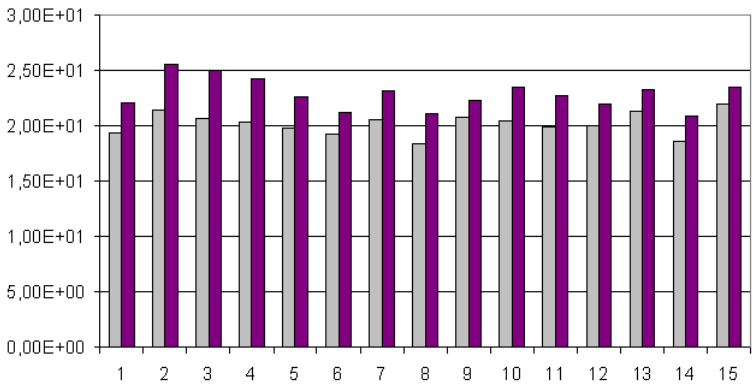


Figure 3.15. FTTS scores for the hands of an experienced young healthy subject (CsP) taken during a 4-week period.

Experienced persons exhibit better repeatability. Figure 3.16 shows the FTTS values of a non-experienced young healthy subject (MP) who exhibited the worst repeatability among healthy subjects.

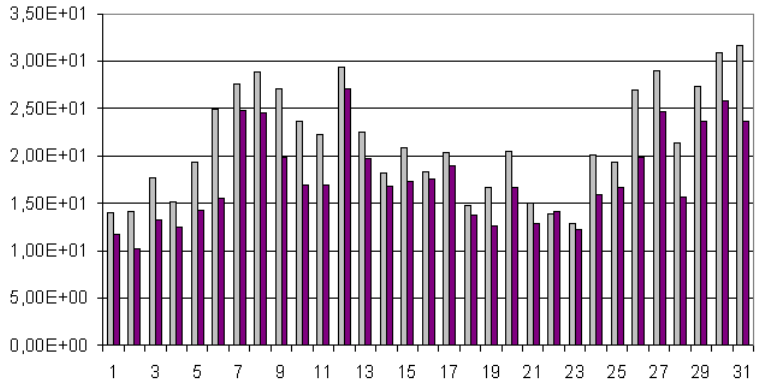


Figure 3.16. FTTS scores for the hands of a young healthy subject (MP) during a 6-week period. Bright bars stand for left, dark ones for right hands.

KRI increased her performance substantially up to the third test. In the beginning she was excited. Omitting the first two tests the (standard deviation)/mean value is as good as for other experienced subjects. RM was tested on two different days. The standard deviation of her performance on the same day was much smaller than the standard deviation of all her tests.

					(standard deviation)/mean	
subject	age	sex	experienced	nr. of tests	right hand	left hand
CsP	22	m	Y	15	0.05	0.06
FA	22	f	Y	14	0.06	0.08
RM	21	f	N	7	0.24	0.30
				(first 3)	0.08	0.03
				(last 4)	0.11	0.16
KRI	22	f	Y	8	0.21	0.24
				(omitting 1,2)	0.04	0.05
MP	23	m	N	31	0.26	0.27
JA	52	m	Y	31	0.08	0.06
10 senior			**N**	**17**	**0.27**	**0.26**
16 young			**2 out of 16**	**25**	**0.19**	**0.18**

Table 3.4. Results of the measurement series of healthy subjects.

The selectivity of the finger-tapping test

The diagnosis of Parkinson's disease is challenging [Rao et al, 2003]. Staging of Parkinsonian patients is also difficult. ***The movement disorders of Parkinsonian patients are rather unique.*** The finger-tapping test helps in the assessment of Parkinsonian patients; it even aids the early diagnosis. Analysis of further movement patterns increases the accuracy of the diagnosis and the selectivity of the assessment of patients. [Jobbágy et al., 1997, Jobbágy et al.,

2000] give the details of assessing Parkinsonian patients based on three different hand- and finger movements: (1) finger-tapping, (2) twiddling and (3) pinching and circling.

For the early diagnosis the separate assessment of fingers during finger-tapping is recommended, i.e. calculation of FTTS for all the eight fingers.

The learning effect

The test series I was supervising show that some persons – even experienced healthy subjects - improve their performance substantially as they learn the movement and get accustomed to the test environment. This means that the first 2-3 recordings taken from a person may prove to be inaccurate for assessing his/her actual state. Figure 3.17 shows an example for the learning effect. There is a marked increase in FTTS in the beginning and from the third test on the FTTS values are quite stable.

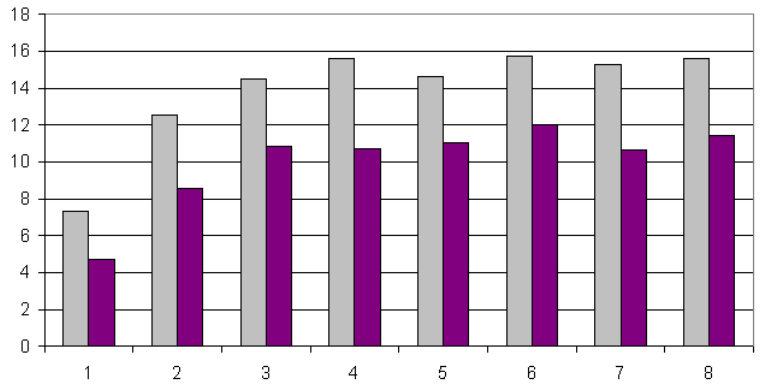


Figure 3.17. The learning effect. FTTS scores for the hands of a young healthy subject (KRI) during a 2-week period. Bright bars: left, dark bars: right hands.

The experienced persons

The performance of the experienced group is substantially better than that of other healthy subjects. This must be taken into account when using the finger-tapping test to characterise the actual state of a person. Should the performance of an experienced person decrease as a result of Parkinson's disease, it may be still better than that of a non-experienced healthy subject.

Different scores of fingers on the same hand

For healthy subjects usually

- the performance of the middle and ring finger is better than the scores of the index and little finger,
- the performance of the dominating hand is better than the score of the other hand,
- the performance of the middle and ring fingers are very similar to each other.

These observations are not valid for the majority of Parkinsonian patients.

Often one finger drops out of the movement: it remains on the table for one period while other fingers are lifted and put back. This stuck-in effect is not uncommon even for healthy subjects. Figure 3.18 shows a part of the finger-tapping of a young healthy subject. There is a tapping cycle when the left little finger remains on the table while the left ring finger performs a "normal" cycle. The left middle and index fingers also performed a "normal" cycle; they are not shown in the figure.

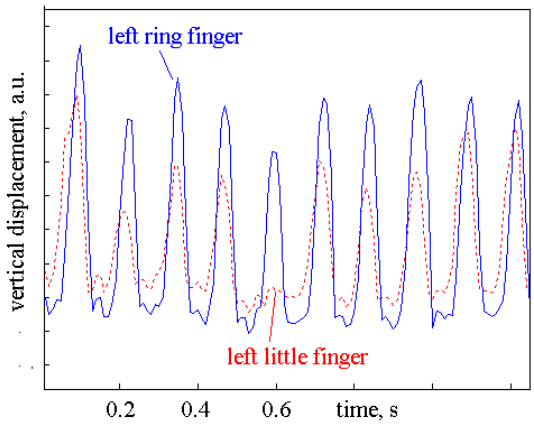


Figure 3.18. Stuck-in little finger during finger-tapping. Young healthy subject.

The order of the tapping fingers

The movement shown in Figure 3.2 results in a good FTTS score, although the movement is rather hand-tapping than finger-tapping, especially with the left hand. During hand-tapping the result of a finger (FTTS score) is almost always better than during finger-tapping. This can be observed by the experimenter, the correct movement pattern must be explained again to the tested person. Some persons miss the correct sequence of fingers; e.g. the index finger hits the table earlier than the middle finger. This happens occasionally with Parkinsonian patients, I find it negligible in the majority of cases. However, it can be taken into account when personalising the tests. Further analysis is given in 4.3.3.

3.5.2 Twiddling

	periodicity of movement, PM			frequency (twisp)			difference in amplitude (twisym)		
	average	st.dev.	st.dev/ average	average	st. dev.	st.dev/ average	average	st. dev.	st.dev/ average
young healthy subjects	0.983	0.017	0.018	0.912	0.073	0.080	0.911	0.069	0.076
senior healthy subjects	0.974	0.028	0.029	0.962	0.044	0.045	0.922	0.067	0.072
Parkinsonian patients	0.982	0.009	0.010	0.797	0.107	0.134	0.808	0.153	0.189

Table 3.5. Parameters characterising the twiddling movement.

Periodicity of movement is not applicable for characterising twiddling. The average value is about the same for both Parkinsonians and healthy subjects and the standard deviation is very small. The standard deviation/average is about 1 % for Parkinsonians, 2 % for young- and 3 % for senior healthy subjects. The lowest scores were reached by healthy subjects (0.896: S09, 0.909: Y02, 0.935: Y05, 0.946: S03). The worst score among Parkinsonians was 0.959: P8.

Low frequency is characteristic for the Parkinsonian group; their average is significantly smaller than the average frequency of the healthy subjects. However, there were healthy subjects who performed the movement slowly. The lowest frequencies were 1.7 Hz (P18) and 1.8 Hz (P17). The lowest frequencies for healthy subjects were 2.3 Hz (Y36) and 2.7 Hz (Y21). The standard deviation/average of twisp for the senior healthy subjects is 4.5 %, for the young healthy subjects 8 % and for the Parkinsonians 13.4 %.

The parameter characterising the difference in amplitude of the two forearms is substantially smaller for Parkinsonians than for healthy subjects. However, it must be emphasised that this parameter highlights the difference between the two forearms. While symptoms are unilateral, this parameter gets worse with the progress of the disease. When symptoms start to be present on both sides this parameter improves!

3.5.3 Pinching and circling

Pinching movement was found to have much better diagnosing ability than circling movement. The most probable reason is that circling is a simple movement; the Parkinson's disease only slightly affects it. It must also be noted that as a result of two-dimensional recording only the projection of the movement is available. If the disease distorts circling to be a periodic up and down movement of the forearm it is still seen as an ideal circling movement.

The slowing down – caused by performing the same movement in parallel with an other movement – of Parkinsonian patients was not greater than that observed for healthy subjects. This is contrary to expectations. This result is expected to help neurologists better understand the disease and model its effect on movement co-ordination.

Figure 3.19 shows the pinching and circling scores of 13 Parkinsonian patients. PCTS was computed by adding up the 12 parameters characterising mainly pinching (see 2.2.4). All Parkinsonian patients scored worse than the average of healthy subjects. However, the standard deviation of PCTS for healthy subjects is substantial. The average and standard deviation for senior healthy subjects is 2.938 + 3.056, while for young healthy subjects it is 2.731 +

2.728. ***I suggest using the parameters most meaningful for the tested person from the set detailed in 2.2.4 and not the combined PCTS.***

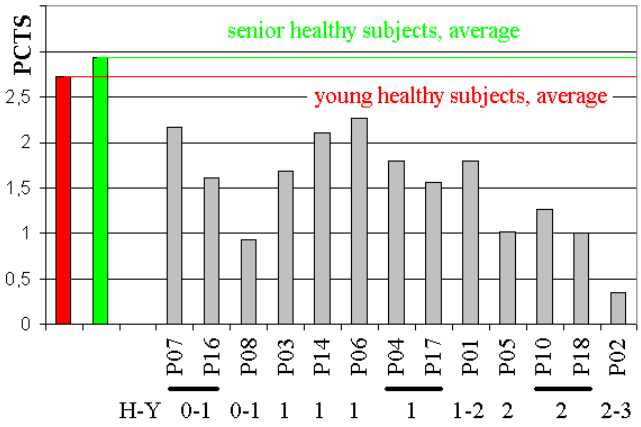


Figure 3.19. The pinching and circling scores of Parkinsonian patients. Average for young and senior healthy subjects are shown.

3.5.4 Personalisation of tests

Our measurements taken from Parkinsonian patients strengthen that this disease develops and progresses uniquely in every patient. I found no single movement pattern that would measure adequately the movement disorders of all the 10 Parkinsonians involved in our tests.

For a Parkinsonian patient those tests should be selected that manifest the movement disorders best. P7 was very good in finger-tapping, based on this movement she would not have been diagnosed as Parkinsonian. Her performance was worst in twiddling; it was about the average of Parkinsonians. She scored between the Parkinsonian average and the average of healthy subjects in pinching and circling. To track her actual state the twiddling and the pinching and circling test is suggested.

The parameters I defined for characterising the performance during different movement patterns can be broken down to sub-parameters. As an example, FTTS of single fingers as well as of a hand might be used. Medical/clinical practice will show the most commonly applicable sub-parameters.

3.6 Conclusions

Passive marker-based movement analysis is an appropriate method for the quantitative assessment of the actual state of Parkinsonian patients. The method effectively assists also the

early detection of the disease: screening tests can easily be assembled using the movement patterns defined in 2.1. The exact diagnosis of Parkinson's disease in the early phase is difficult because other neurological diseases have similar early symptoms. The diagnosis in the early stage is supposed to be false for more than 20 % of neurological diseases [Hughes et al., 1992].

The suggested measurement method is completely harmless, it does not cause any inconvenience for the tested person. The test including finger-tapping, twiddling, pinching and circling lasts for about 15 minutes.

A simple movement analyser is enough for the tests. The minimum requirement is the 50 frames/s sampling rate. Lens distortion and the resolution of the image sensor are not critical, commercial DV cameras are suitable for the task. PAM (cf. 1.3.2) is especially appropriate for this analysis as no special knowledge is required to operate it.

Finger-, hand- and arm movements can be defined so that a single camera, i.e. two dimensional analysis of the movement is enough. Usually the vertical projection of the marker trajectory is recorded and analysed.

No single movement is enough for the assessment of Parkinsonians. Patients exhibit unique symptoms, as a result, both the tested movements and the evaluation should be personalised. After evaluating all tested movements of a Parkinsonian, those ones should be selected for the assessment of his/her actual state in which the patient's score is lower than the average for healthy control subjects.

A clinically applicable analyser – PAM with appropriate human interface – will be used in Hungarian hospitals. In the frame of the T049357 nr project of OTKA (Hungarian Scientific Research Fund) *"Objective assessment of movement co-ordination disorders"* a great number of Parkinsonian and stroke patients will be tested using a new version of PAM. The device will be equipped with a simple operator interface that enables medical doctors, nurses and physiotherapists to test patients with neural diseases without involving technical personnel. The assessment of Parkinsonians by neurologists will be compared to the results gained by PAM. Based on this comparison, the evaluating algorithms of PAM can be modified. The device will be applicable both for screening and early detection and for aiding the optimal medication of Parkinsonian patients.

4 Assessment of stroke patients

There are different rating scales for stroke patients. [ed. Herndon, 1997] gives a good summary and evaluation. In the clinical practice, most applied scales rate the self supporting ability of patients (Barthel Index [Mahoney and Barthel, 1965], Functional Independence Measure (FIM) [Cavanagh et al., 2000], Activity Index, the Orgogozo Scale, Scandinavian Stroke Scale, Canadian Neurologic Scale, Hemispheric Stroke Scale, European Stroke Scale, Rivermead Scale [Wade et al., 1992], Ashworth Scale etc.) Examples can be found in the appendix. [Williams et al., 1999] gives the development of a stroke-specific quality of life scale. These scales and the measurement methods behind them focus on the functions most important for the daily activities. As an example, the Barthel Index is determined by assessing the following activities: level of self-supporting in feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfer (bed to chair and back), mobility on level surfaces, stairs. The FIM consists of 18 parameters, each can be between 1 and 7, higher value meaning greater ability. Both physical and cognitive score can be derived from the FIM and the sum of all 18 parameters can also be used. [Cavanagh et al., 2000] describes the different possible multidimensional interpretations of FIM. The rigidity or paralysis of the thumb thus results in a much worse score than the rigidity or paralysis of any other finger. The aim of my research has been to objectively characterise movement disorders. Based on it, the functional rating can be done with better resolution and accuracy; the measure of disability can also be determined.

4.1 The tested subjects

In the Brain Injury Unit of the National Institute for Medical Rehabilitation 16 patients (9 females, 7 males) participated in the finger- and hand movement assessment. The age of patients was between 23 – 85 years (average: 42.8, average for females 48.6, average for males 35.4). All patients were right handed, 10 had hemiparesis on the left, 6 on the right side. The average span between the onset of the disease and the selection for the test was 18 weeks (minimum 2, maximum 55, more than 26 weeks for three patients). [Herczeg et al., 2004] gives further details about the patients. The patients had hemiparesis resulting from upper motoneuron laesion. Twelve patients performed the tests twice on the same day, with at least 30 minutes break among the tests. The actual performance of four patients was assessed twice a week during a four-week period.

ident.	age	sex	affected side	onset of stroke	Rivermead	FIM	Barthel
J01	49	F	L	Dec. 29. 2002.	14	115	100
J02	25	M	R	Apr. 08. 2003.	10	126	100
J03	25	F	L	Oct. 07. 2002.	9	75	65
J04	35	F	R	Jan. 01. 2003.	9	109	85
J05	23	M	L	Jun. 21. 2003.	2	116	90
J06	24	M	L	Jun. 25. 2003.	13	124	90
J07	26	M	R	Oct. 19. 2003.	0	32	10
J08	39	M	L	Jun. 12. 2003.	15	116	100
J09	59	M	R	Oct. 30. 2003.	4	104	70
J10	59	F	R	May 28. 2003.	8	103	100
J11	79	F	R	Nov. 04. 2003.	8	115	55
J12	23	F	L	Oct. 09. 2003.	15	47	15
J13	52	M	L	Sep. 20. 2003.	0	20	20
J14	29	F	L	Oct. 29. 2003.	1	25	10
J15	85	F	L	Nov. 2003.	11	90	35
J16	53	F	L	Nov. 25. 2003.	8	99	80

Table 4.1. Stroke patients who participated in the test at National Rehabilitation Institute in 2003. All patients were right-handed.

4.2 Recordings

Recordings were taken in the National Institute for Medical Rehabilitation in the period 11th November – 17th December, 2003. The tests were conducted by I. Baumgartner, physiotherapist, and supervised by Dr. G. Fazekas, neurologist. Hemiparetic inpatients were selected if they were able to understand and perform the movement task. A written consent signed by the patient was a must for inclusion. Dementia or loss of ability to move fingers were reasons to exclude a patient.

Patients performed three movements. These are: finger-tapping test (2.1.1), pointing with right and left hand (2.1.5). Using conventional tests (Hand Movement Scale (HM), Modified Ashworth Scale, Functional Independence Measure (FIM) and Rivermead Scale), neurologists assessed the motor function of arm and hand in parallel with the instrumental movement analysis.

During the finger-tapping test the elastic ribbon (to keep the wrists on the table) was not used for all stroke patients. As a consequence of rigidity, some patients were unable to tap with their fingers while their hands were on the table. As a result, in some cases (see e.g. Figure 4.6) the hand slipped on the table to or from the camera.

Figure 4.1 - Figure 4.4 show the finger-tapping movement of 4 patients who were tested twice on the same day. The FTTS results and conventional ratings are given in Table 4.2. The patients are ordered according to the FTTS results averaged for two hands. J06 had much bet-

ter, while J14 had much worse FTTS than it could have been expected based on functional rating methods. Comparison of FTTS and PTS to functional (conventional) ratings is given in 4.3.1.

patient ID	FTTS result (average of 2 tests)	Barthel scale	FIM scale	Rivermead scale (upper extremity)
J08	23.1	100	42	15
J06	14.2	10	13	0
J14	2.9	90	42	13
J15	0.9	10	6	1

Table 4.2. FTTS and conventional test results of four stroke patients assessed twice on the same day.

Figure 4.1 - Figure 4.4 allow the detailed analysis of the performance of patients because movements are expressed in still images. X-Y plots are given for the pointing movements, finger-tapping is characterised by time functions. 1.5-s parts of the movement are displayed for the ring-, middle- and index fingers, 8-s parts for the middle fingers, for both hands. The FTTS and separately the PM values are shown for all eight fingers moving during finger-tapping. These figures reflect the movements quite well and help the assessment of the actual state of patients.

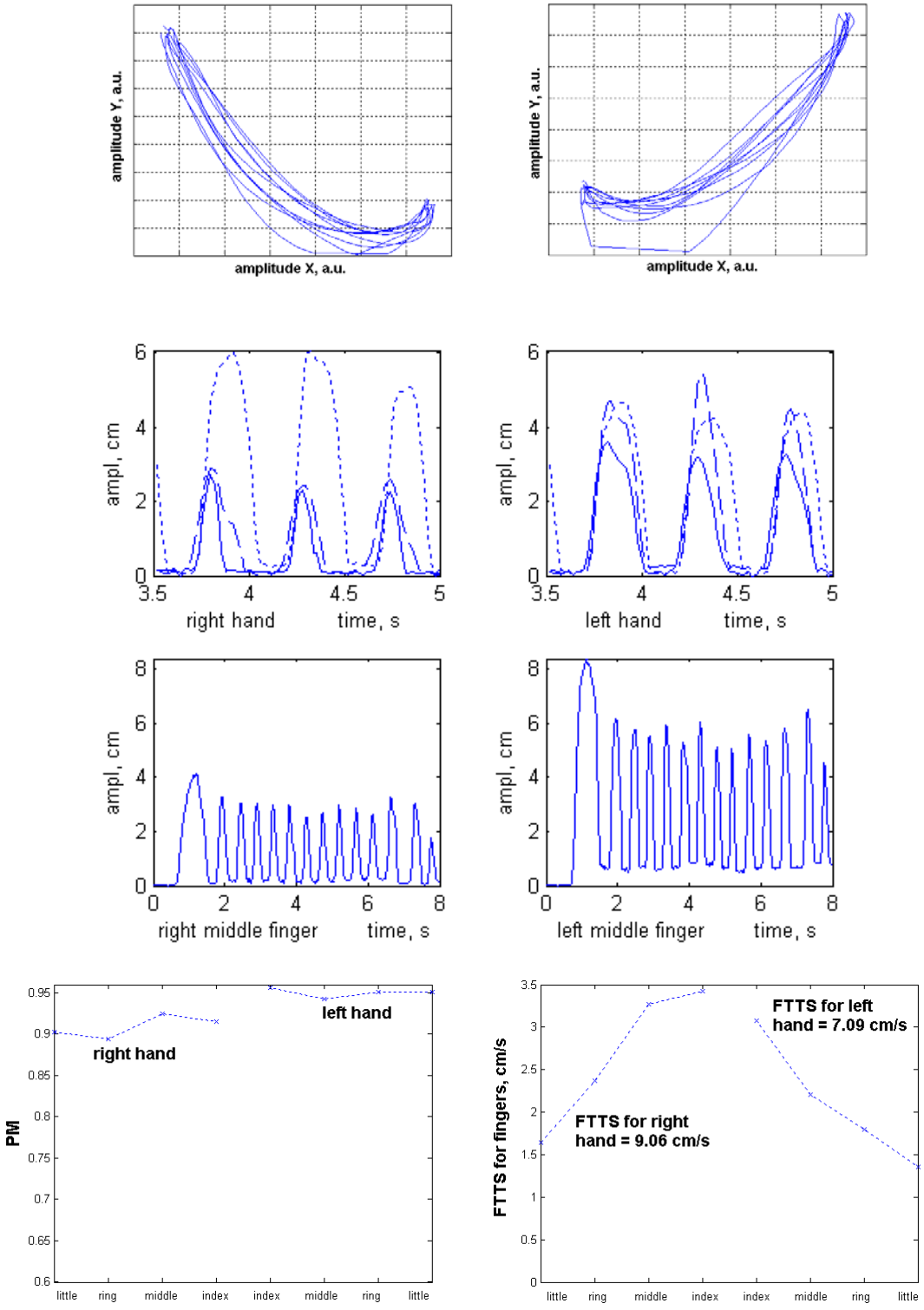


Figure 4.1. Stroke patient (J08). X-Y plots of pointing movement (top),time functions (middle) and PM and FTTS values (bottom) of fingers during finger-tapping.

The PTS was 0.51 for the right and 0.37 for the left arm.

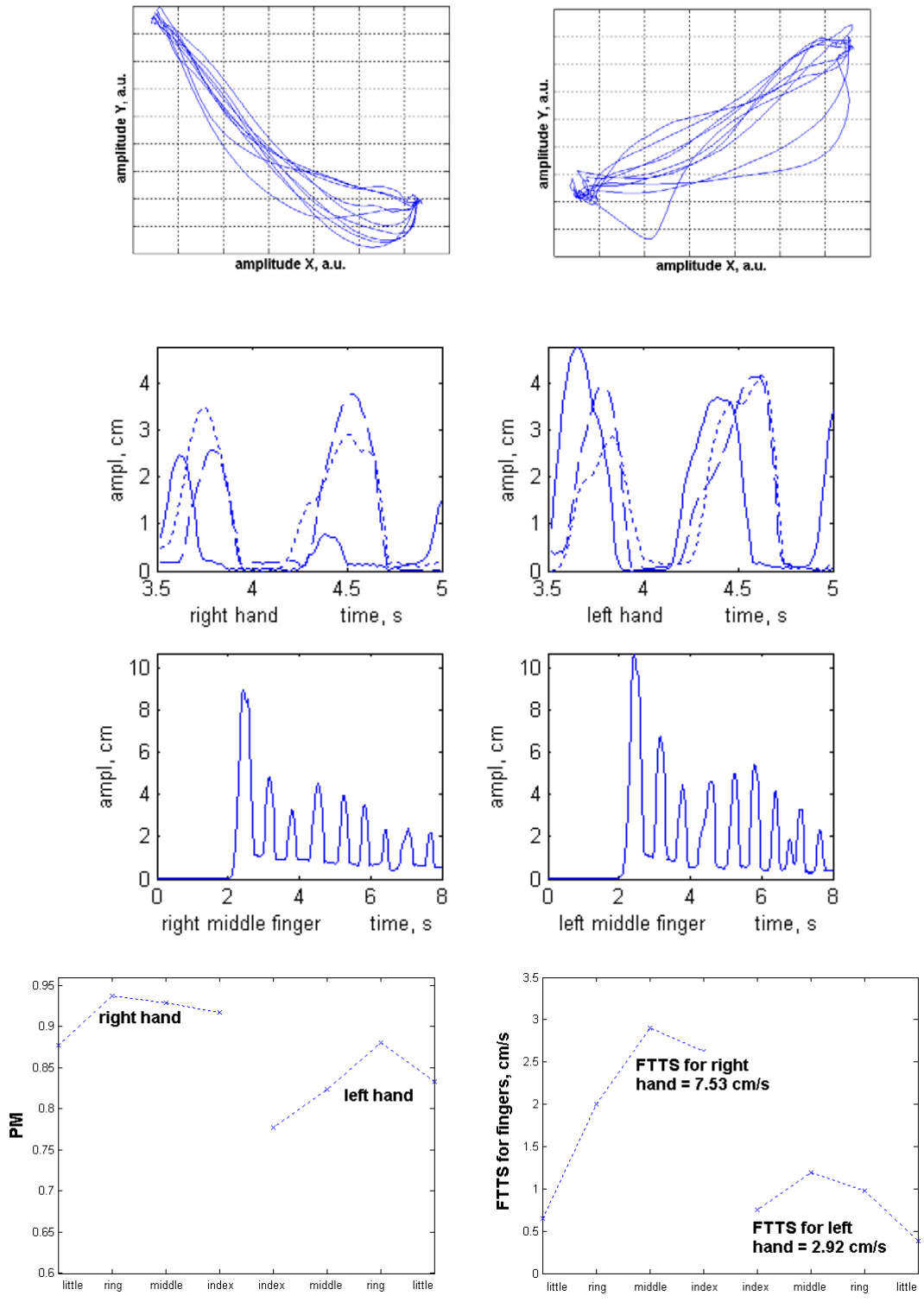


Figure 4.2. Stroke patient (J06). X-Y plots of pointing movement (top), time functions (middle) and PM and FTS values (bottom) of fingers during finger-tapping.

The PTS was 0.45 for the right and 0.29 for the left arm.

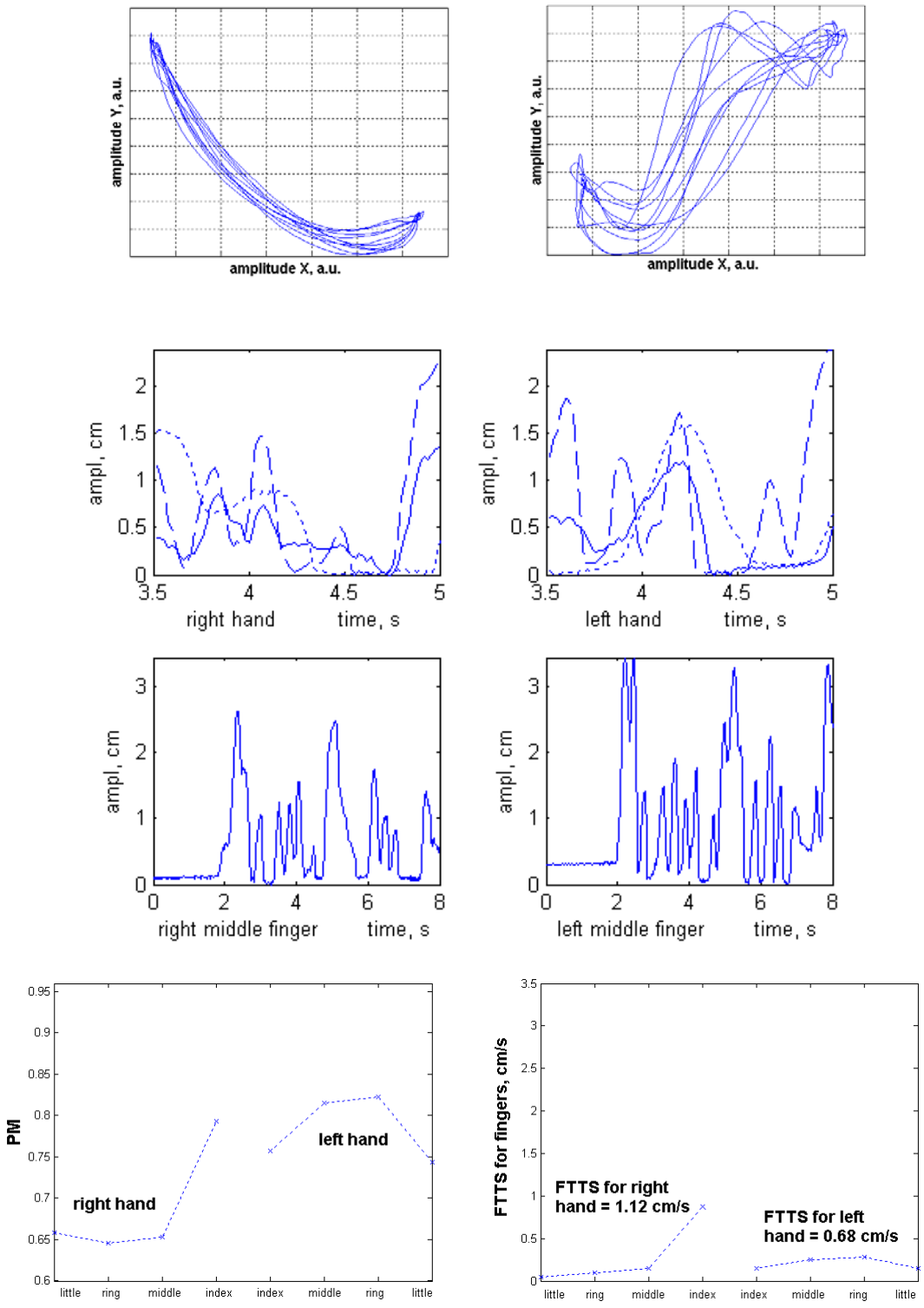


Figure 4.3. Stroke patient (J14). X-Y plots of pointing movement (top), time functions (middle) and PM and FTTS values (bottom) of fingers during finger-tapping.

The PTS was 0.35 for the right and 0.13 for the left arm.

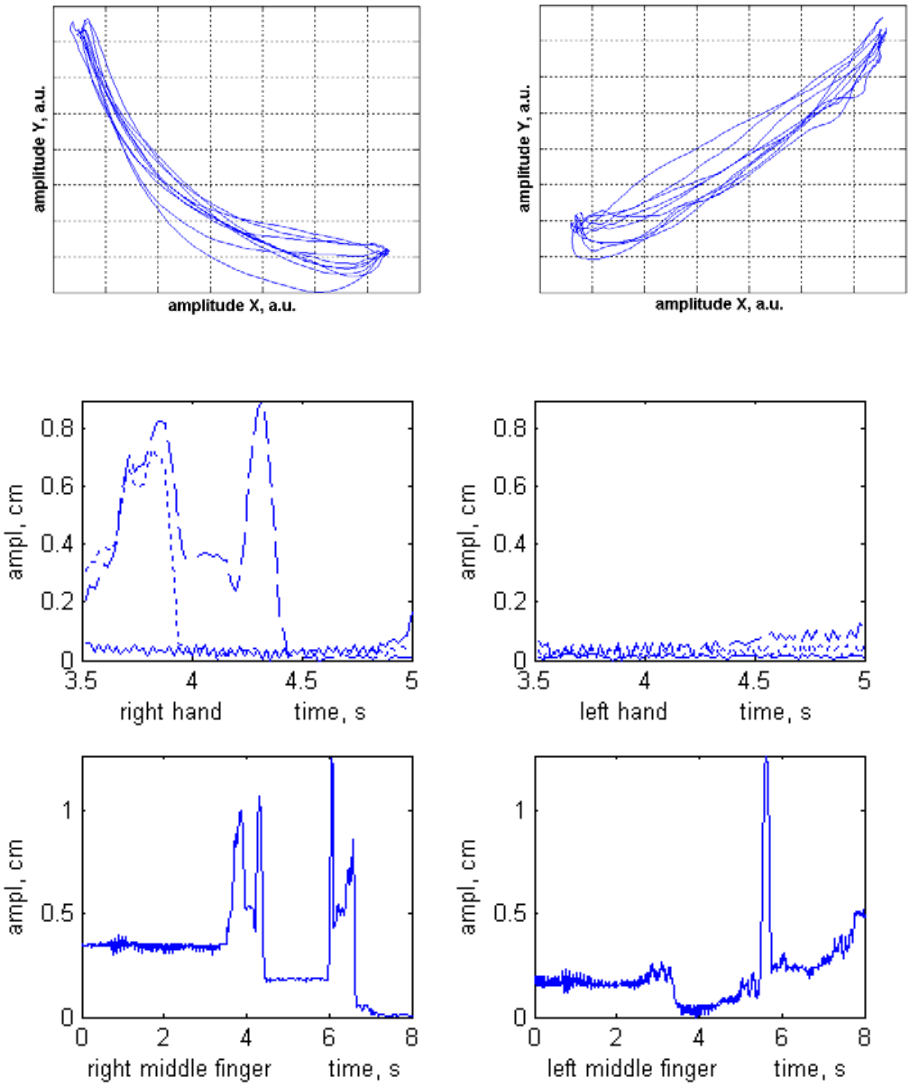


Figure 4.4. Stroke patient (J15). X-Y plots of pointing movement (top) and time functions (bottom) of fingers during finger-tapping.

Patient J15 performed the finger-tapping so irregularly with his left index and right ring finger that for these fingers the SVD method could not be applied. The PTS was 0.273 for the right and 0.125 for the left arm.

Figure 4.5 - Figure 4.8 show the finger-tapping and the pointing movement of two patients (J04, J11) who were tested for a 4-week period. The figures show the performance on the first and about three weeks later on the last test.

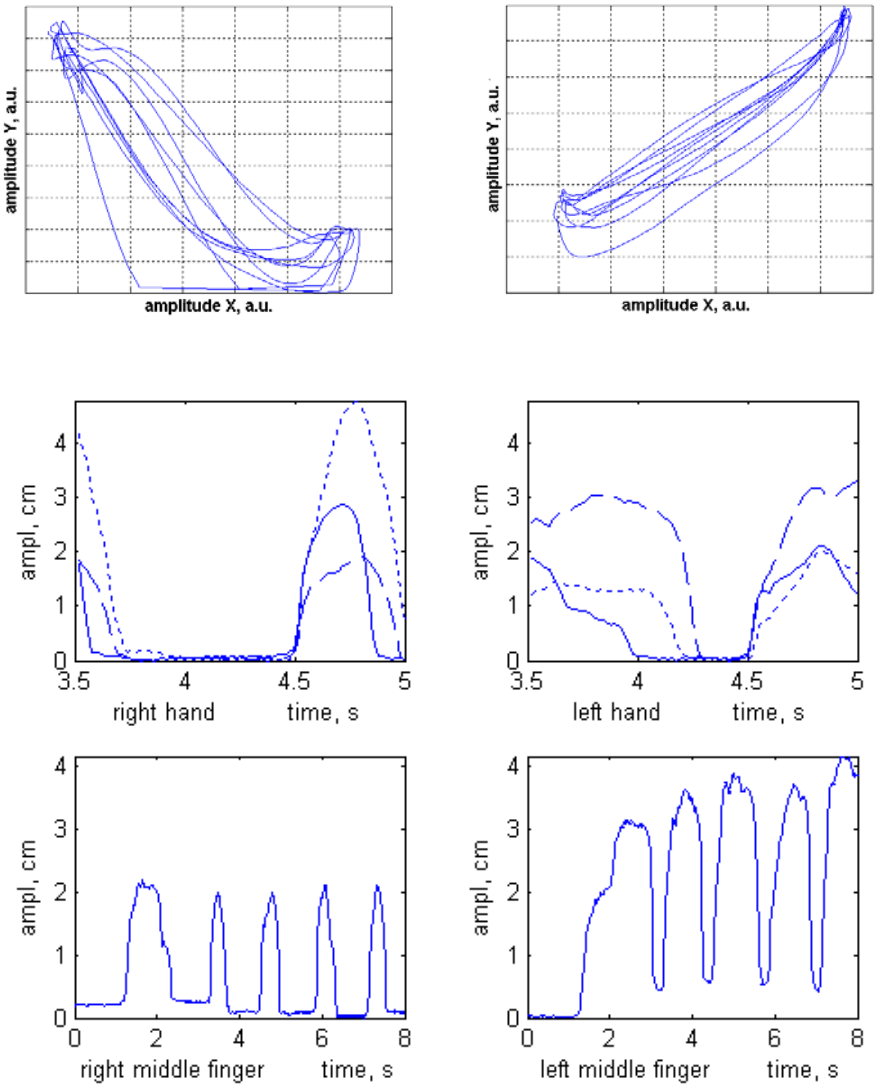


Figure 4.5. Stroke patient (J04). X-Y plots of pointing movement and time functions of finger-tapping on the first day of testing.

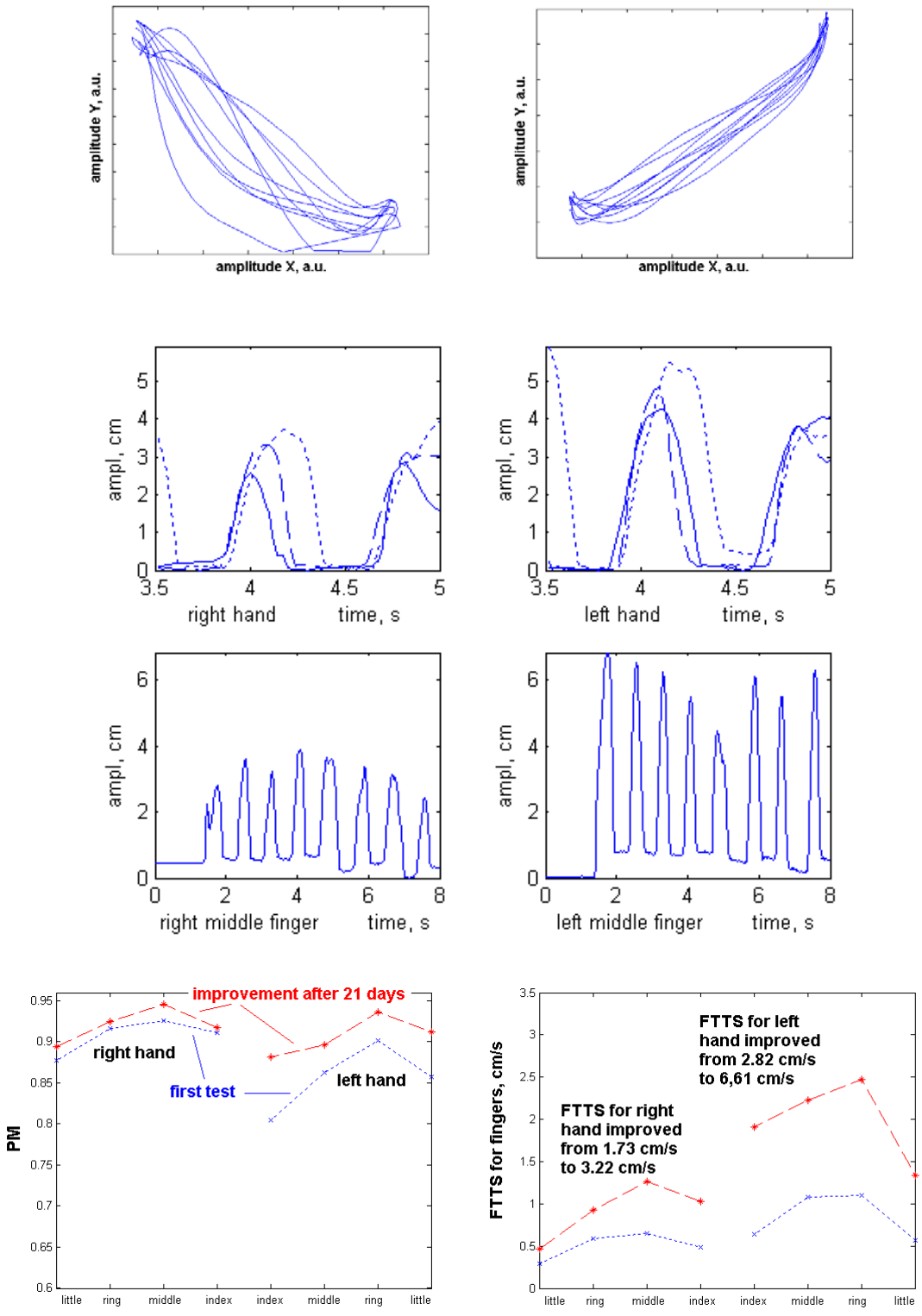


Figure 4.6. Stroke patient (J04). X-Y plots of pointing (top), time functions of finger-tapping (middle) on the last day of testing and improvement of the regularity (PM) and the FTTS in finger-tapping (bottom) (21 days after Figure 4.5).

PTS improved from 0.50 to 0.60 (left arm) and from 0.39 to 0.44 (right arm).

J04 improved the PTS from 0.33 to 0.44 for her right arm. PTS remained the same, 0.60 for her left arm. Regarding FTTS, improvement of the performance in Figure 4.6 is evident for the affected hand. The score for both hands improved substantially, the relative performance of the fingers remained unchanged. The ring finger scored the best. Both FTTS and PTS show substantial improvement in the actual state of J11 (Figure 4.7 and Figure 4.8).

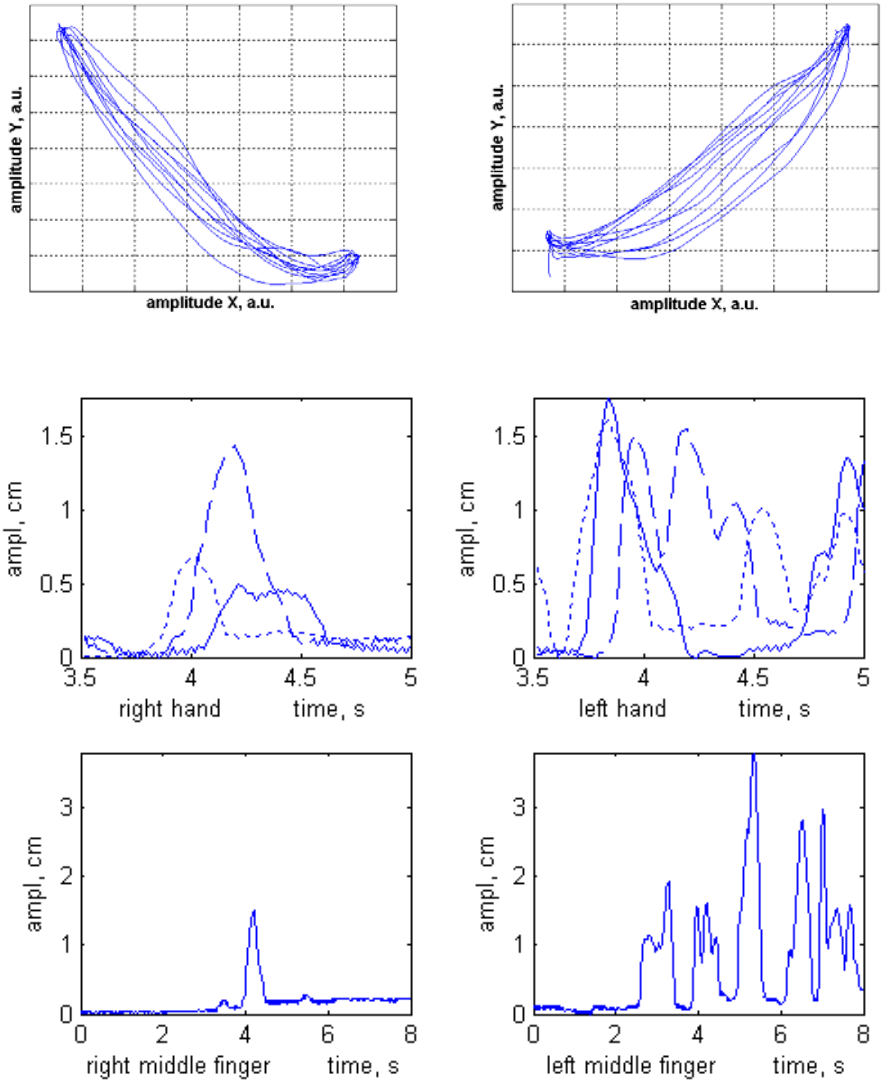


Figure 4.7. Stroke patient (J11). X-Y plots of pointing movement and time functions of finger-tapping on the first day of testing.

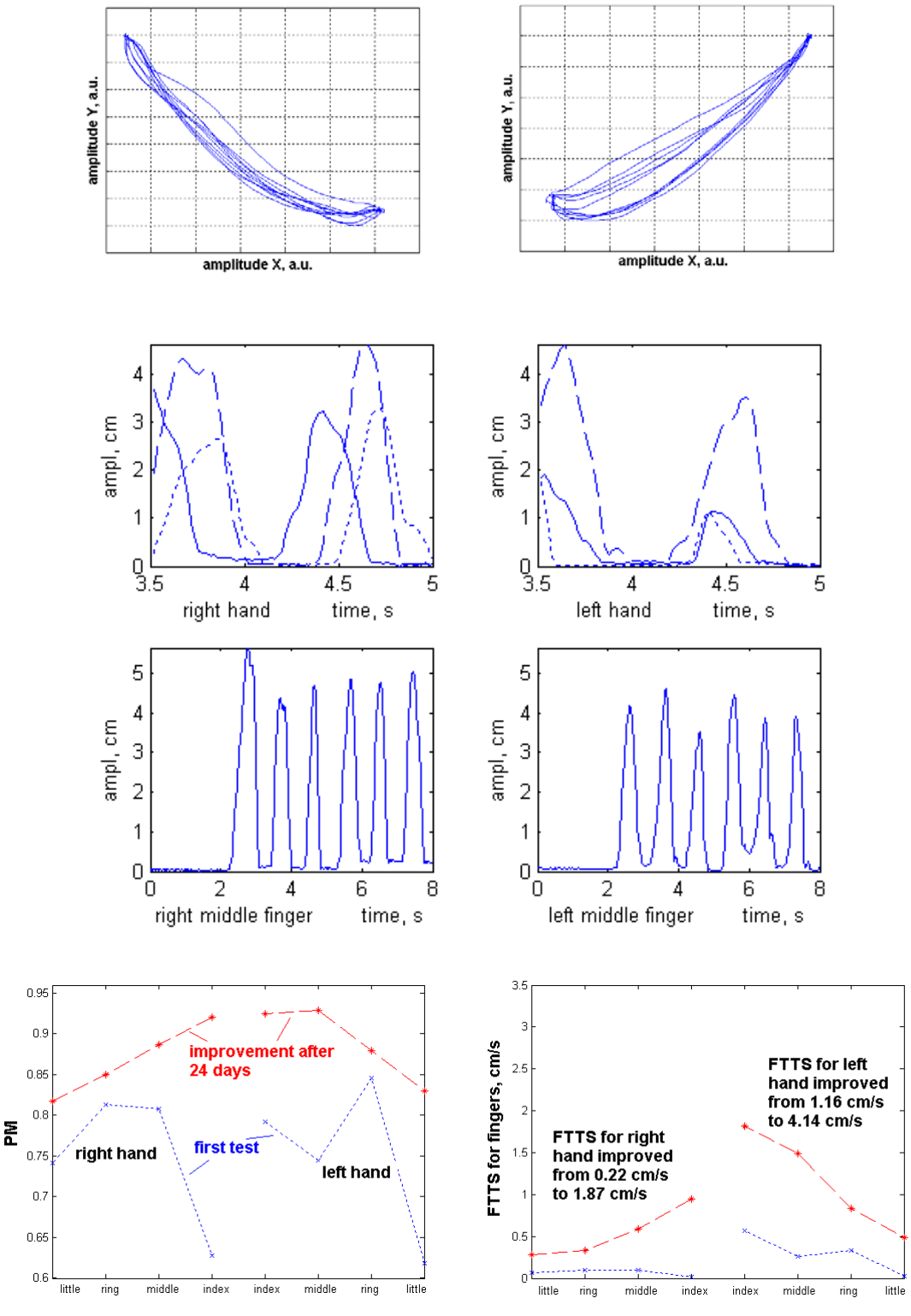


Figure 4.8. Stroke patient (J11). X-Y plots of pointing (top), time functions of finger-tapping (middle) on the last day of testing and improvement of the regularity (PM) and the FTTS in finger-tapping (bottom) (24 days after Figure 4.7).

The PTS improved from 0.14 to 0.26 for the right and from 0.18 to 0.26 for the left arm.

4.3 Staging of patients

4.3.1 Comparison to conventional ratings

Stroke patients were assessed by physiotherapists. The result of the manual assessment of stroke patients is given in Table 4.1. and in Figure 4.9. The figure proves that the FIM, the Rivermead scale and the Barthel index measure different abilities. Nevertheless, all three scales reflect mainly the level of self-supporting ability, which can be maintained even with partly paralysed fingers and arms. On the contrary, FTTS is determined separately for each finger manifesting the movement disorder in it.

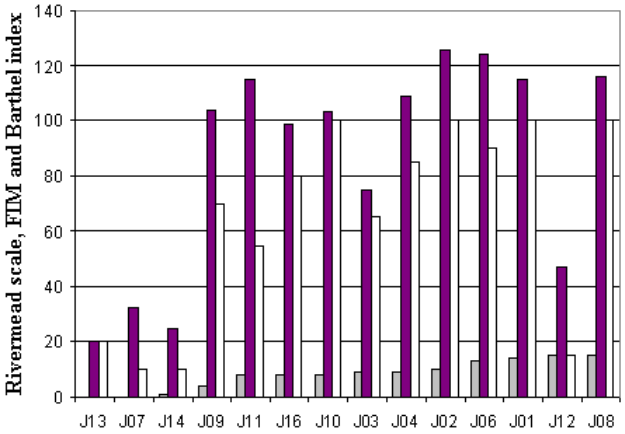


Figure 4.9. Result of manual assessment of stroke patients. Dark bars stand for FIM, on its left side the Rivermead scale, on its right side the Barthel index.

For the 14 stroke patients tested the FIM and the Barthel index shows an excellent correlation while the Rivermead scale is different from them. Rankings of patients based on the three conventional rating methods show the following correlation with each other:

	FIM	Rivermead scale
Barthel index	0.92 ($p < 0.001$)	0.61 ($p < 0.03$)
FIM		0.65 ($p < 0.02$)

Figure 4.10 shows the FTTS results of 14 patients. For the patients who were tested several times (during 2 – 3 weeks), the result of the first test is included. Patients are ordered according to the Rivermead scale for the upper extremity. J03 had the best result in FTTS while she got only average score in the Rivermead test. The results of J03 deviate most from a linear relationship between Rivermead scale and FTTS. Her thumb was spastic, she could not grip tightly. This explains the relatively bad Rivermead score (9 out of 15). Thumbs do not move

during finger-tapping. Thus the thumb related handicap did not prevent the patient from achieving a good FTTS.

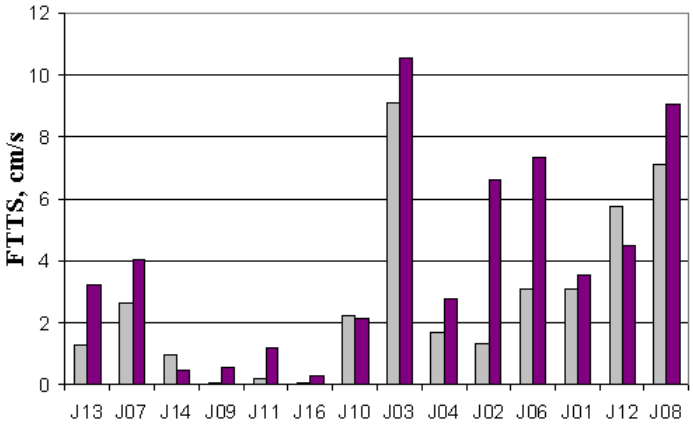


Figure 4.10. FTTS of stroke patients. Bright bar stands for hand on affected side. Patients are ordered according to the Rivermead Scale of their upper extremities.

Figure 4.11. shows the PTS of patients.

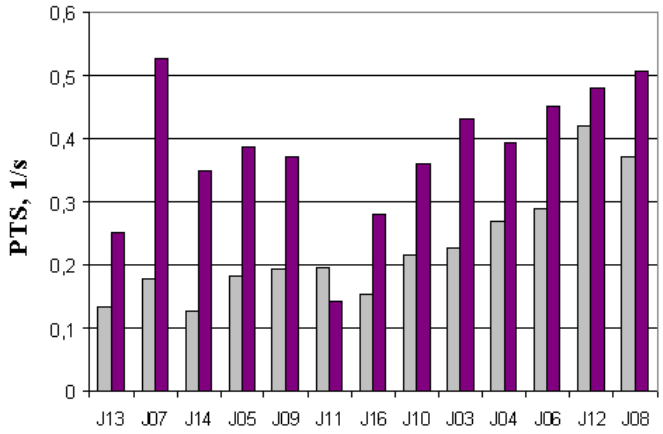


Figure 4.11. Pointing test score (PTS) of stroke patients. Bright bars stand for affected arm. Patients are ordered according to their Rivermead score.

FTTS and PTS give similar ranking of the 14 stroke patients as the Rivermead scale but different from FIM and Barthel index.

Rivermead – FTTS affected hand: $r = 0.50$, $p < 0.07$

Rivermead – PTS affected side: $r = 0.50$, $p < 0.07$

	FIM	Barthel index
FTTS affected hand	$r = -0.05$ ($p > 0.85$)	$r = 0.06$ ($p > 0.85$)
PTS affected side	$r = 0.05$ ($p > 0.85$)	$r = -0.03$ ($p > 0.90$)

FTTS and PTS of the affected side rank the patients similarly: $r = 0.55$ ($p < 0.05$). Strong correlation was found between the FTTS value of the affected and not affected hand: $r = 0.85$ ($p < 0.001$). The reason is the low speed of the movement of both hands. Parkinsonians achieved quite different speed with the affected and not affected hands during finger-tapping. Stroke patients performed their movement with the same speed with both hands. As expected, weak correlation was between the PTS values for the affected and not affected side: $r = 0.42$, $p > 0.14$.

During the parallel movement of the two hands during finger-tapping synchronisation exists that assures the same speed for both hands. Pointing movement involves one arm at a time, not affected side outperforms the affected one. Figure 4.12 summarises the relations between conventional rating scales and FTTS as well as PTS.

I have to emphasise that FTTS and PTS give a different measure of movement disorder than the conventional rating scales. Both FTTS and PTS provide neurologists with a new, objective rating method of stroke patients. This new method is about to be validated in medical/clinical environment, cf. 4.4.

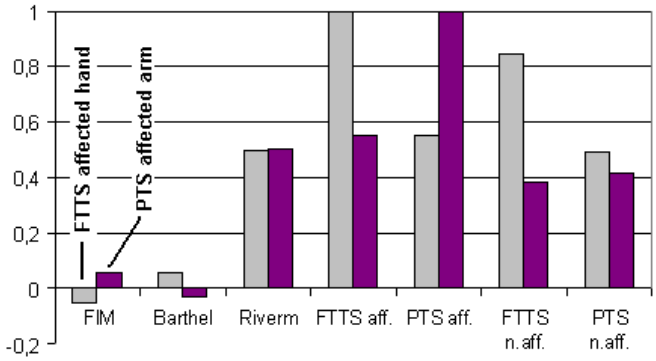


Figure 4.12. Correlation of FTTS and PTS with conventional rating methods.

Three patients (J14, J12 and J10) had better FTTS for the affected side. J11 had better PTS for the affected side. No patient performed better on the affected side both during finger-tapping and pointing. The performance of the affected side can be compared to the performance of the non-affected side by calculating the following ratio (see Figure 4.13):

$$\frac{\text{FTTS(affected side)} * \text{PTS(affected side)}}{\text{FTTS(non - affected side)} * \text{PTS(non - affected side)}}$$

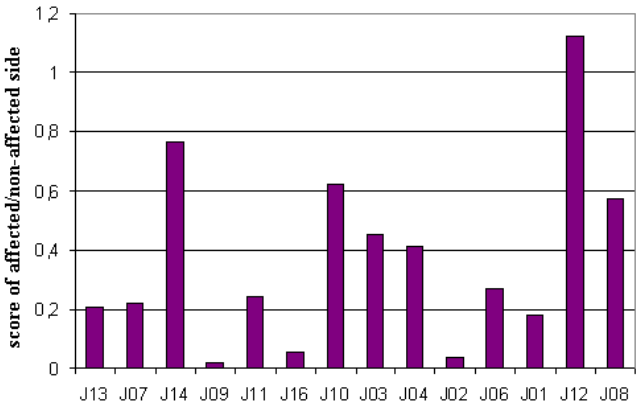


Figure 4.13. Ratio of PTS and FTTS scores on affected side and non-affected side.

J12 – a mildly paralysed stroke patient – had altogether better performance on her affected side, as a result of the finger-tapping test. There was almost no phase shift between the ring- and middle fingers on the left (affected) hand. However, this did not result in a bad sequence of fingers. All the bad sequences were detected between the little- and ring fingers, more frequently on the right (not affected) hand. The bad sequences were independent of the coupled movement of the ring- and middle fingers of the left hand. As the patient's performance was relatively good, the right hand performing "finger-tapping" had a slightly worse FTTS than the "partly hand-tapping" left hand. The right is her dominant hand, which is also the non-affected one. The measurement of the phase shift between adjacent fingers would require a better time resolution than the one offered by PAM (20 ms between frames). In the majority of cases, especially regarding patients with worse than mild paralysis, the measurement of this phase shift is not necessary.

4.3.2 The smoothness of the movement

FTTS does not take into account the smoothness of the movement. Stroke patients may exhibit nearly periodic but distorted movement. Figure 4.14 shows the trajectories of the middle finger during finger-tapping test. The cycles of the Parkinsonian patient (left) are all different from each other; the regularity (periodicity) of the movement is low. The cycles of the stroke patient (right) are quite similar to each other, even though the movement is not normal: there is a tremble around the vertical maximum position.

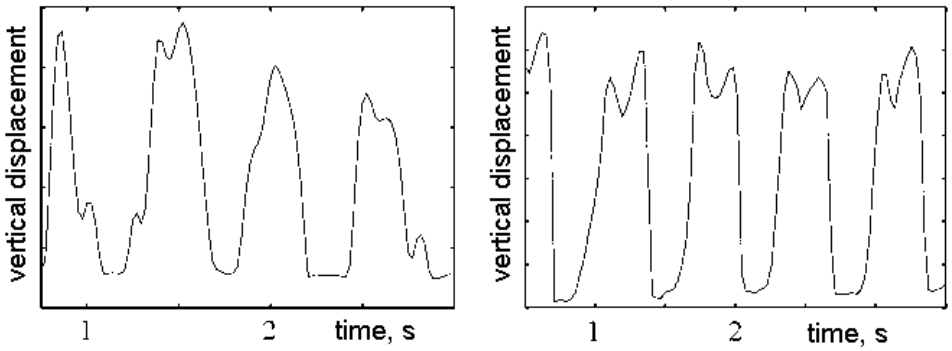


Figure 4.14. Movement of the middle finger during finger-tapping test; Parkinsonian (left) and stroke patient (right).

The smoothness of the movement can be taken into account while personalising the tests and the evaluation. [Kovács and Nepusz, 2005] suggest fitting a parabola to the rising and the falling part of each cycle and characterise the smoothness by calculating the deviation of these parts of the trajectories from the fitted curve.

4.3.3 Bad sequence during the finger-tapping test

During the finger-tapping test the frequency of errors in the sequence (a finger hitting the tabletop earlier than necessary) increases with speed. Table 4.3 shows the relative frequency of bad sequences of 5 healthy subjects and 4 stroke patients. Number of errors at each location is divided by the maximum number of errors at the same location for each person. All persons included in Table 4.3 performed the finger-tapping test at least 4 times. This means a minimum of one hundred sequences, for healthy subjects a minimum of two hundred sequences. As an average, 21 young healthy subjects had erroneous sequences in 7 % of all sequences. The same error rate was 17 % for 14 senior healthy subjects and 19 % for 16 stroke patients. In the majority of cases the bad sequence can be attributed to one finger, e.g. the ring finger hits the table earlier than the little finger. CsP had only two erroneous sequences, thus "averaging" is not possible. J04 had erroneous sequences with both hands; the ring finger hit the table earlier than the little finger. The frequency of bad sequence depends on the speed of tapping. Further details are given in [Nepusz, 2005]. ***I do not consider the bad sequence a diagnostic parameter for patients with neural diseases in general.*** However, it can be useful during personalisation of tests.

person	location of error in sequence					
	little-ring (left)	ring-middle (left)	middle-index (left)	middle-index (right)	ring-middle (right)	little-ring (right)
stroke patients						
J03	0.19	0.09	0	0.05	0.05	1
J04	1	0	0	0.17	0.11	0.96
J11	1	0.11	0.22	0.60	0.11	0.23
J12	0.25	0	0	0	0	1
young healthy subjects						
CsP	0	0	0	1*	0	0.86*
F06	1	0	0	0	0	0
FA	0.16	0	0	0.01	0.01	1
RM	0.18	0	0.03	0.17	0.09	1
senior healthy subject						
JA	1	0	0	0	0	0.59

*: CsP had only two erroneous sequences

Table 4.3. Relative frequency of bad sequences of healthy subjects and stroke patients during finger-tapping.

4.3.4 Assessment of increasing performance of patients

The improvement in the FTTS for J04 is given in Figure 4.15. The extent is notable: the FTTS on the 22. day is better by 86 % (right, affected hand) and 136 % (left, non-affected hand). The relative scores of the fingers remained unchanged. Both the regularity (cf. Figure 4.6) and the speed of tapping increased for both hands, for all fingers.

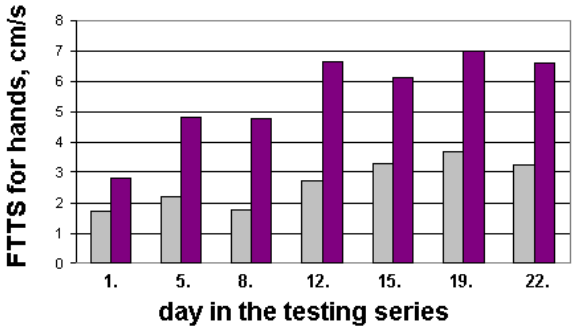


Figure 4.15. Improvement of the FTTS for J04 in 21 days. Bright bar stands for the right (affected) hand, dark ones for the left.

The change in PTS is significantly different. Figure 4.16 shows that there was no real improvement for the right (affected) arm while there was a substantial increase for the left arm, the score nearly doubled. These results provide neurologists with detailed information concerning the actual state of patients.

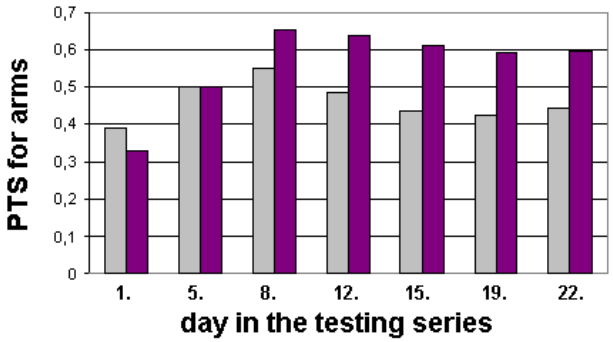


Figure 4.16. Change in PTS for J04 in 21 days. Bright bars stand for the right (affected) hand, dark ones for the left.

4.4 Conclusions

By using passive marker-based movement analysis, it is possible to assess the actual state of stroke patients with high resolution. The rehabilitation process can be quantitatively characterised using the finger-tapping and the pointing tests. Impairment and physical disability can be objectively characterised.

Patients must co-operate to achieve reliable results. It must be taken into account that the actual mental state influences the performance. Malingering patients can be revealed by repeating the tests; scatter of results is suspicious.

Stroke patients perform differently from Parkinsonian patients. The objective measurements show that the movement disorders of stroke patients are more regular. Tests repeated on the same day show better reproducibility. The relative scores of fingers during the finger-tapping test show much less variation than in the case of Parkinsonians.

The role of the physiotherapist is decisive. The movement analyser assures high resolution and good reproducibility but it is the physiotherapist who convinces the patients about the importance of the measurement procedure and calms them down if necessary.

The measurement technique and the evaluation methods described in this thesis is being validated in the frame of an OTKA (Hungarian National Research Fund) project *Objective assessment of movement disorders* (T 049357, 2005- 2008). Parkinsonian and stroke patients are assessed in the Szt. Imre Hospital and in the National Medical Rehabilitation Institute.

5 Non-invasive methods for blood pressure measurement

Blood pressure is an important physiological parameter [Fonyó, 1999, Monos, 2004]. A single measurement does not give enough information to qualify the blood pressure of a person, usually not even to discriminate normal value from pathologic one. The blood pressure is varying during the day, 20...30 mmHg differences are not uncommon even for healthy subjects. The white-coat effect is also well known. Many have increased blood pressure values at the doctor's office. Self-measurement of blood pressure at home eliminates the white-coat effect, makes possible the measurement always at the same phase of the daily activity and promotes the devotion of a person to be involved in the health keeping process. Inaccurate or low reproducibility meters prevent subjects from being motivated and the measurement results do not help the medical treatment. Consequently***, it is important to provide accurate blood pressure meters for self-monitoring***.

We experienced erroneous blood pressure readings (>10 mmHg deviation from the reference systolic value) of different oscillometric devices in about one-sixth of the measurements while testing 51 mainly young healthy subjects at rest. We used the photoplethysmographic (PPG) signal [Bhattacharya et al., 2001], [Lygouras et al., 2001] to determine the reference arterial systolic pressure. When the cuff pressure is higher than the systolic pressure no pulsation is present in the PPG signal distal from the cuff. The error rate we measured harmonises with the literature [Shuler et al., 1998], [Merrick et al., 1997], [Kikuya et al., 2002]. Both the AAMI (Association for the Advancement of Medical Instrumentation, [www.aami.org]) in the United States and the BHS (British Hypertension Society) [www.bhsoc.org] published standards for grading sphygmomanometers. Both standards define the mercury sphygmomanometer as the reference device and allow substantial deviation from it. The best grade (A) in the BHS standard allows 40 % of the results deviate from the reference by more than 5 mmHg, 15 % of the results by more than 10 mmHg and 5 % of the results by more than 15 mmHg. A clinical review of a number of presently used blood pressure meters revealed that the majority of devices could not meet even these requirements [O ‘Brien et al., 2001]. Guidelines are available for self-monitoring the blood pressure [Asmar and Zanchetti, 2001].

The present definition of blood pressure implies that momentary value is measured. Even if the measured value is accurate, there is no possibility to express the short-term variability. Should there be any physical or psychological impact on blood pressure; present day

devices are unable to detect it. ***I suggest a more informative parameter that gives the mean value and standard deviation for a short time period. Also, I suggest a method to detect if the tested person is relaxed and so blood pressure measurement gives consistent result.*** I am fully aware that my results will contribute to a more effective treatment of cardiovascular diseases only if medical doctors approve them. It has been a real biomedical engineering research project requiring a good co-operation between engineers and medical doctors. Up to now the engineers' contribution was dominating; from now on medical doctors should take over.

5.1 The oscillometric method

Different biomechanical models have been proposed to aid indirect blood pressure measurement. Two kinds of models are used. One is for the complete cardiovascular system including the heart, arteries and veins. Such models use terms like stroke volume, cardiac output, peripheral resistance, etc. The other kind of models is valid for a section of arteries; these models use terms like vessel wall elasticity, local pressure, and pulse wave velocity.

[Ursino and Cristalli, 1996] present a mathematical lumped parameter model of the oscillometric technique for indirect blood pressure measurement. Their simulations indicate that the critical parameters are vessel wall viscoelastic properties and pressure pulse amplitude. Changes in these parameters can result in 15 – 20 % error during calculation of the systolic and diastolic value according to the oscillometric method.

The oscillometric method is based on the observation first published by E-J. Marey in 1876. He observed that the amplitude of oscillation in cuff pressure increases up to a maximum and then decreases at a slower rate when the cuff pressure is decreased from above systolic to below diastolic pressure. The majority of present-day cuff-based (semi-)automatic blood pressure meters utilise this observation. The oscillometric method requires neither extra sensor nor operator expertise to detect the equality of the cuff pressure to different levels of arterial pressure (systolic, diastolic, and mean). ***The primary measured parameter is the arterial mean pressure*** indicated by the maximal oscillometric amplitude [Drzewiecki, 1995]. Figure 5.1 shows oscillometric changes in upper arm cuff pressure during slow deflation. The cuff pressure values are high-pass filtered.

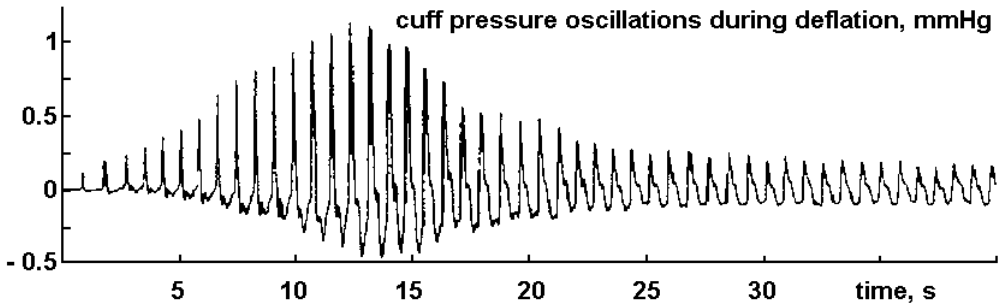


Figure 5.1. Oscillations in cuff pressure during slow deflation.

Systolic and diastolic pressure values are calculated based mainly on the amplitudes of pressure oscillations. The ratio of amplitudes (SM = systolic/mean, DM = diastolic/mean) were determined by supposing average values for physiological parameters. When the cuff is on the upper arm, SM = 0.4 ... 0.6 and DM = 0.70 ... 0.85 are reported. [Drzewiecki et al., 1994] gives a theoretical analysis and suggests a model for arterial mechanics. The values corresponding to the model are: SM = 0.593, DM = 0.717. SM and DM show little variation over the normal range of blood pressure. However, at high values of systolic pressure SM should be lowered and at low values of diastolic pressure DM should be lowered. [Ursino and Cristalli, 1996] analyses different physiological parameters that effect SM and DM.

Our detailed analysis of cuff pressure - time functions revealed that ***the value of SM and DM vary from measurement to measurement even for the same person tested at rest!*** The actual values of these parameters are unknown during an oscillometric blood pressure measurement. Consequently, the oscillometric blood pressure meters give only an ***estimate*** for the arterial systolic and diastolic pressures. The difference in two adjacent oscillation amplitudes during deflation is also applied to determine systolic and diastolic pressure. The method is called derivative oscillometry [Drzewiecki, 1995]; its accuracy is about the same as that of conventional oscillometry.

New oscillometric blood pressure measuring devices take into account not only the amplitude but also the shape of oscillometric pulses. The application of shape evaluation substantially decreases the ratio of results with unacceptable (> 15 %) error.

The oscillometric method is used in the majority of presently available devices applicable for home use. These devices are simple-to-use but not accurate enough. ***I recommend using additional information*** – derived from the PPG signal of the tested subject – ***to increase the accuracy of cuff-based blood pressure measurement***.

5.2 Other methods

Indirect, cuff-based methods measure the cuff pressure and detect when it is equal to the systolic or diastolic pressure. Korotkoff suggested using the sound of turbulent flow. If cuff pressure is between the diastolic and systolic value, the artery is completely occluded during a fraction of the heart cycle. When the pressure in the artery exceeds the cuff pressure, the artery bursts out and a turbulent flow commences. If the cuff is inflated above systolic pressure and then deflated, appearance of the Korotkoff sound signals the systolic value and vanishing of these sounds indicates the diastolic pressure. Five phases of the Korotkoff sounds are defined as the cuff is deflated. For most subjects the beginning of phase I indicates the systolic pressure. There is no consensus whether phase IV or V should be related to the diastolic pressure. Partly because of noise, the detection of these sounds is a challenge. It was also found that Korotkoff sounds – although with a different frequency spectrum – may be present even if the cuff pressure is lower than the diastolic value. According to this, the US standard defines two diastolic pressures [Carr and Brown, 1981]. [Cunningham, 2003] summarises the different theories about the origin of Korotkoff sounds. These are: cavitation theory, arterial wall theory, turbulence theory, water hammer theory and transmission of heart sounds theory.

Blood flow and movement of artery wall can be detected using different methods [Geddes and Baker, 1989], [Webster (ed.), 1995]. Ultrasound based equipment is able to sense both arterial flow and vessel wall displacement. These devices are sensitive to positioning; integration of the sensors into blood pressure meters for home use has not been solved.

An indirect method for continuously measuring the arterial pressure is described in [Peñaz, 1973] and [Togawa et al., 1997].

5.3 Accuracy of non-invasive methods

[Jones et al., 2003] gives three sources of error: the inherent biological variability, the white coat effect and the inaccuracies related to suboptimal technique. Apart from the invasive monitors and a few expensive and bulky devices (e.g. tonometers) blood pressure meters give a momentary value. Even if this value is accurate, it might be misleading, as detailed in 6.1. In this section I limit the analysis on the possible difference between the momentary blood pressure and its value calculated by non-invasive methods.

Presently used non-invasive methods use a cuff. The cuff is inflated above systolic value in some seconds and then deflated relatively slowly. The usual deflation rate is 3 – 4 mmHg/s. Complete occlusion of the artery influences blood pressure, the actual alteration varies from person to person. Even the same person may react differently to this interference.

The automatic detection and evaluation of Korotkoff sounds has not reached the effectiveness of human operators. Different evaluations of such devices are available. In summary we can conclude that devices applying this method can show results that deviate from the reference value by 10 … 15 %. Quite often they also fail to complete the measurement.

The clinical evaluations of oscillometric devices harmonise with the British and American standards. The specification of the accuracy is not simple for two reasons. Firstly, there is no gold standard to compare measurements to. Secondly, the accuracy of devices varies from person to person and also for the same person under different psychophysiological states.

Standards issued by the British Hypertension Society (BHS) [O'Brien et al., 2002], and the Association for the Advancement of Medical Instrumentation (AAMI) are slightly different.

The reference value is the one obtained by trained medical personnel using a conventional sphygmomanometer. It follows that objective evaluation of the accuracy of a given device would require a person with constant blood pressure.

The effect of occlusion by the cuff is different from person to person. Figure 5.2 shows the blood pressure change in a young and in a senior healthy male subject during slow inflation and deflation. A tonometer (COLIN CBM 7000) was applied to the radial artery at the wrist on the same side where the upper arm cuff was placed. The change in blood pressure resulting from occlusion of the brachial artery is significant in both subjects though the type of the change is different.

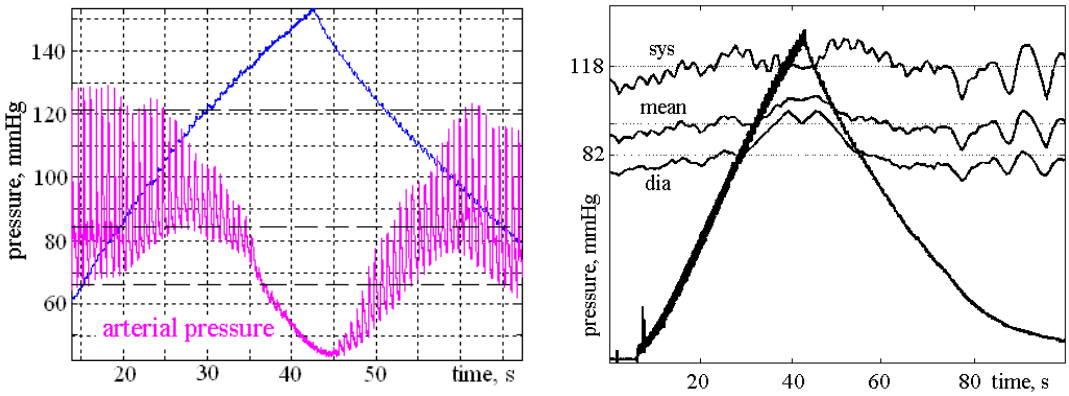


Figure 5.2. Effect of occlusion by the cuff. Young healthy subject (left) reacts differently from senior healthy subject (right).

Occlusion of the brachial artery does not change blood pressure in the other arm. The sensor of the tonometer was attached to the wrist on the right arm while the upper arm cuff to the left arm of a young healthy subject. The effect of occlusion could not be detected (see Figure 5.3).

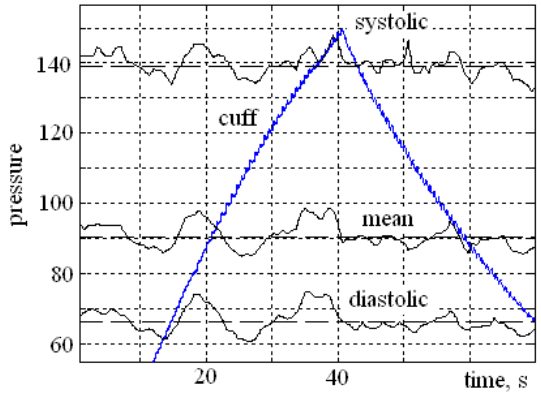


Figure 5.3. Occlusion by the cuff does not affect blood pressure in the other arm.

The error resulting from a given method is also not easy to characterise. Methods that use a slowly deflated cuff have an inherent ± 3…5 mmHg error (methodical error). Averaging for a number of heart cycles would decrease this error. The inaccuracy of the oscillometric method changes from person to person. It can be different for the same person under different physical and mental conditions.

More accurate blood pressure monitors can substantially increase the effectiveness of treatment. According to [Jones et al., 2003] only 5 mmHg systematic error prevents 21 million American people from a beneficial antihypertensive medication (underestimation) or forces 27 million American people to get antihypertensive medication needlessly.

5.4 Testing oscillometric devices

Figure 5.4 shows the result of 59 measurements on 14 healthy subjects (22 ... 52-year-old males). We used an automatic blood pressure meter with a wrist cuff (OMRON MX3) and simultaneously measured the PPG signal at the fingertip. In the majority of measurements during deflation the first pulse in the PPG signal appeared at higher cuff pressure than the systolic pressure reported by the meter.

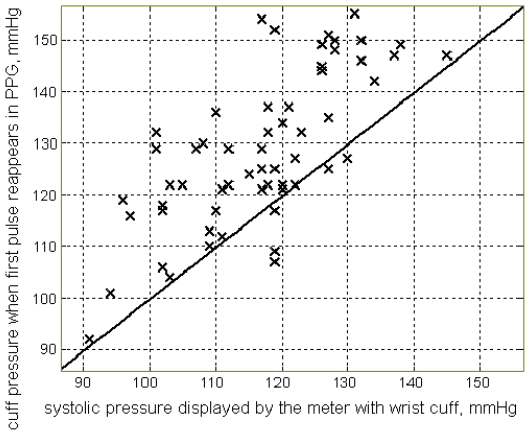


Figure 5.4. Systolic blood pressure values displayed by a meter with a wrist cuff and cuff pressure where the first pulse appeared in PPG signal during deflation.

To test the reproducibility of the OMRON MX3 meter three measurements were made with 5-minute pauses on 8 subjects. We calculated the average difference of the maximal and minimal systolic pressure out of the three measurements. The average difference in the systolic values determined by the MX3 meter was 15.1 mmHg. Considering the cuff pressure when the first pulse reappeared in the PPG signal as the systolic value this difference dropped to 7.5 mmHg. (The small cuff size prevents the application of slow inflation.)

When the cuff is on the upper arm the first opening of the brachial artery during deflation remains usually undetected in the PPG signal taken at the fingertip. Figure 5.5 shows the results of 47 measurements taken from subjects without any known cardiovascular disease.

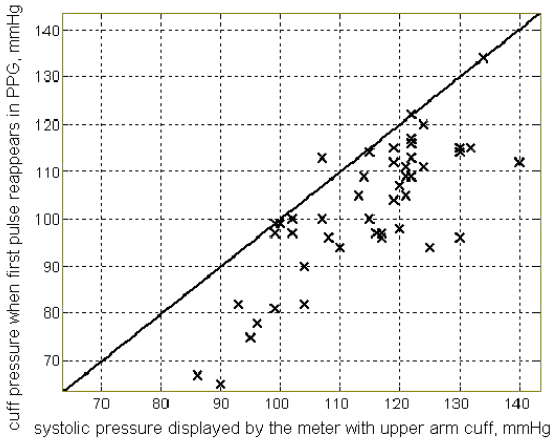


Figure 5.5. Systolic blood pressure values displayed by a meter with an upper arm cuff and cuff pressure where the first pulse reappeared in PPG signal during deflation.

The time delay between the first opening of the brachial artery and the first pulse detected in the PPG signal at the fingertip depends on the duration of total occlusion of the artery. The longer is the total occlusion the longer is the time delay. The maximal cuff pressure influences the duration of total occlusion while using commercial blood pressure meters. The maximal

cuff pressure on an OMRON M4 meter was set to values 20 ... 90 mmHg higher than the estimated systolic value of the actually tested person thus influencing the duration of total occlusion. Figure 5.6 shows the results for four subjects. We completed four or five measurements on each subject with 5-minute pauses. Based on these measurements ***I claim that the momentary value of systolic pressure in the brachial artery depends on the duration of complete occlusion.*** This causes a highly non-linear distortion in presently used indirect blood pressure measurements.

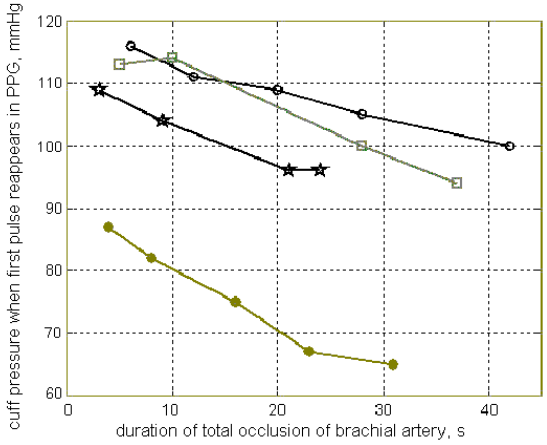


Figure 5.6. The appearance of the first pulse detected in the PPG signal depends on the time of total occlusion of the artery.

During upper arm cuff-based measurements the PPG signal taken from the fingertip can be used to detect the systolic pressure when the upper arm cuff is inflated slowly. The systolic pressure can be determined from the decreasing PPG signal amplitudes. Further details are given in 6. Figure 5.7 shows the result of 24 measurements taken from 9 healthy subjects. The average inflation speed was 5 mmHg/s. Slower inflation rate would decrease the methodical error.

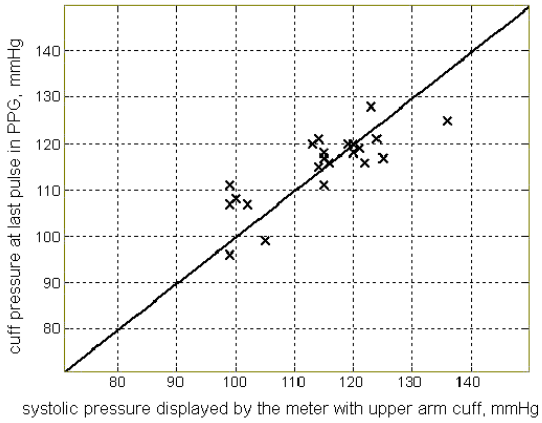


Figure 5.7. Systolic blood pressure values displayed by a meter with an upper arm cuff and cuff pressure where the last pulse was detected in PPG signal during slow inflation.

6 New method for non-invasive blood pressure measurement

The method should require neither medical expertise nor expensive equipment and should give accurate and reproducible results. The necessary hardware and software must fit into a device for home health monitoring. These requirements account for an upper arm cuff-based method. Compared to the oscillometric method, extra information is gained from an Einthoven I (or II) lead ECG and a PPG signal taken from the fingertip.

6.1 Averaging

Blood pressure of a person changes during the day. Knowing blood pressure changes during the day is valuable diagnostic information. 24-hour monitoring might be applied to assess the blood pressure profile. Even 24-hour monitoring does not give information on short-term variation in blood pressure which is not necessarily negligible. Beat-to-beat change in systolic pressure – mainly as a result of breathing – easily reaches 10 mmHg. Figure 6.1. shows a 5-s part of a recording taken from a young healthy subject at rest. Blood pressure was monitored continuously by a COLIN CBM 7000 tonometer. This device uses a pressure sensor fixed to the artery at the wrist. Pressure value is calibrated with the help of an upper arm cuff by determining the mean arterial pressure indicated by the maximal pressure oscillations. For 5 … 15 minutes following the calibration the accuracy of the tonometer is satisfactory for measuring short-term variation.

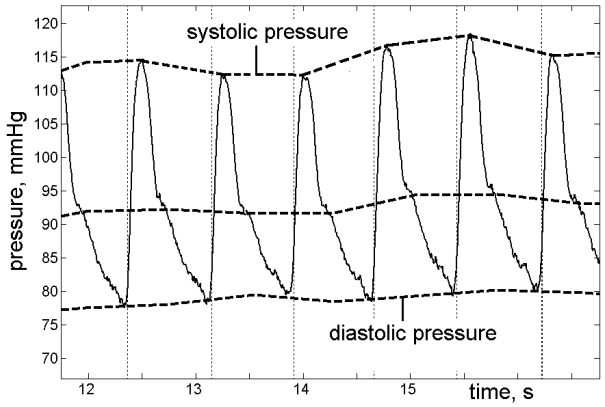


Figure 6.1. Systolic and diastolic pressure substantially changes even within a short time. Recording was taken with a COLIN radial artery tonometer from a young healthy male subject.

Short-term variations in blood pressure are mainly due to breathing. Figure 6.2 shows a recording taken from a healthy senior subject at rest. The systolic pressure was measured with the COLIN tonometer, the air flow with a PISTON spirometer. There seems to be a linkage between air flow and the delay between ECG and PPG signal, ΔT_{EP} – and thus systolic pressure –, further details are given in 6.2.2. Within 5 s the systolic pressure change can be as high as 10 mmHg!

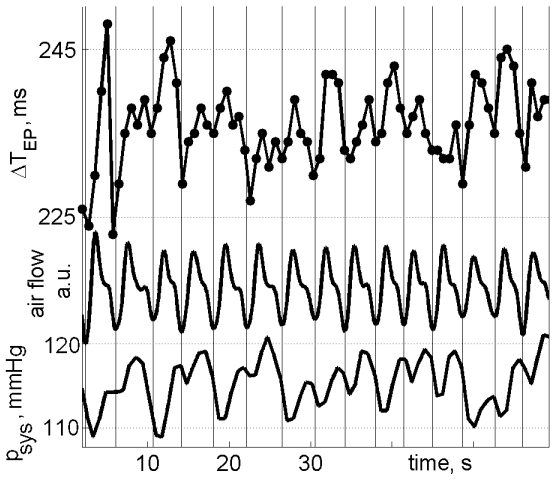


Figure 6.2. Short-term variation in systolic pressure as a result of breathing.

It follows that the ***momentary value*** – measured and/or calculated by the majority of presently used devices and methods – ***is not an optimal measure of blood pressure***. Not only the mean but also the standard deviation of the systolic pressure helps diagnose the cardiovascular system of a person. I recommend averaging for 30 seconds; this means about 30 heart cycles, thus about 30 momentary systolic and diastolic values. A recording of ECG and PPG is made with completely deflated cuff at the beginning of the measurement. This makes possible also averaging, based on the ECG and PPG signals. If the tested person is at rest, then averaging for 30 seconds filters out the effect of breathing. At the same time, the changes in the systolic pressure (best characterised by the standard deviation) are also informative for medical experts.

6.2 The photoplethysmographic (PPG) signal as an aid

The PPG signal reflects the volume changes in a body segment caused by blood saturation. The operation of the PPG sensor can be based on either transmission or reflection. In our research work a reflection-type sensor was applied. 805-nm infrared light emitting diode and a phototransistor with matched spectral sensitivity were used. The mechanical construction of

the sensor made it possible to measure the PPG signal on the finger-tip but also on the palm and the wrist. The intensity of the reflected signal increases when the volume of blood under the sensor increases.

The PPG signal might be measured on the upper arm; [Lindberg and Öberg, 1991] suggests 560-nm wavelength (green) to increase the signal/noise ratio. We were unable to designate an anatomical landmark point on the upper arm so that pulsation in the PPG signal could be reliably detected during inflation right until the complete occlusion of the brachial artery.

The pattern of hand arteries varies from subject to subject; [Platzer, 1996] defines six main types. It is not possible to designate an anatomical landmark point on the hand to record the PPG signal reliably for everyone. The PPG signal was measured at different places when the cuff was on the wrist. No place was found distal from but as close as possible to the cuff (on the palm) where pulses in the PPG signal appeared earlier during deflation than in the PPG signal observed at the fingertip. As a result, the PPG sensor was attached to the fingertip of the tested subjects.

A measurement set-up was used built around a PCL-818 (Advantech Co. Ltd.) PC peripheral card. Four channels (cuff pressure, ECG, 2 PPGs) were sampled at 1 ksamples/s each. The resolution of ECG and PPGs on both hands was 9 effective bits ($\Delta U/U_{pp}$). The cuff pressure was measured with 0.05 mmHg resolution. This high resolution was assured by measuring average time period instead of the output frequency of the pressure sensor.

The DC component of the PPG signal depends on several physiological parameters of the tested person, it must be filtered out. The variation in the PPG signal might be much smaller than the DC level, thus high-pass filtering must be done before amplifying the signal to the level required by the A/D converter. However, the usual AC coupling cannot be applied. It would distort the signal also in the pass-band and introduce a time constant causing very long settling time after a change in the sensor's output signal. The DC component was cancelled by using an integrating feedback. It acts as a high-pass filter and also gives the possibility to switch off the feedback for a short time. In this case the PPG signal is available without any distortion while the DC component is still filtered out: the integrator holds its output voltage for a while even when the feedback loop is switched off. Periodically switching the feedback loop on and off assures that the DC component of the output signal is negligible while the signal is not distorted during most of the time.

The PPG signal can also be used to characterise arterial distensibility. [Nitzan et al., 2002] shows that the time delay between ECG R peak and the pulse wave arrival to the toe, and the difference in the transit time of the blood pressure pulse waves to the toe and to the finger

decrease with age but do not depend on the diastolic pressure. Our measurements show that both the initial value (deflated cuff) and the increase in ΔT_{EP} (monitoring PPG signal at the fingertip) during a cuff-based blood pressure measurement is greater in senior (50...60 year old) males than in young (22...25 year old) males. We calculated the difference in ΔT_{EP} for the two arms during cuff-based measurements. No age dependent results were found. The changes in transit time difference, as a function of cuff pressure are different during inflation and deflation.

6.2.1 Pulse wave velocity

The velocity of the pulse wave, progressing through the arteries depends also on blood pressure. Many attempts have been made to make use of pulse wave velocity during blood pressure measurement. Pulse wave velocity can be calculated by measuring ECG and PPG signal, thus blood pressure variation can be estimated even without using a cuff [Jobbágy, 2001], [Chen et al., 2000], [Lacković and Šantić, 2001], [Lu et al., 1992], [Pruett et al., 1988].

$$PWV = \frac{L}{\Delta T_{PT}} = \sqrt{\frac{Eh}{\rho d}} \tag{1}$$

$$E = E_0 e^{aBP} \tag{2}$$

$$BP = \frac{1}{a}[\ln(\frac{L^2 \rho d}{E_0 h}) - 2\ln(\Delta T_{PT})] \tag{3}$$

where PWV is pulse wave velocity, E is the Young modulus of arterial wall (E_0 is its value at a given BP_0), BP is blood pressure, h is the thickness, d is the inner radius of the artery, ρ is blood density, α is constant, L is the distance between the heart and the fingertip and ΔT_{PT} is the pulse transit time. The systole has two periods, the isovolumetric and the auxotonic ones [Fonyó, 1999]. The former lasts until the pressure in the left ventricle exceeds the diastolic pressure in the aorta. ΔT_{EP} is the sum of the pre-ejection time, ΔT_{PE} and the pulse transit time, ΔT_{PT}.

$$\Delta T_{EP} = \Delta T_{PE} + \Delta T_{PT} \tag{4}$$

Pulse wave velocity, as defined in (1) is an average over the distance from the heart to the fingertip. The diameter of the vessel changes as the pulse wave travels along it. This changes the Young modulus at the actual position of the pressure wave. The relation between the local

pressure and flow in the artery is described in [Khir et al., 2001]. ΔT_{PT} cannot be measured easily; in general ΔT_{EP} is used instead.

6.2.2 Time delay between ECG and PPG signal

As shown in Figure 6.3, ΔT_{EPb} is the time delay from the R peak of the ECG to the peak value in PPG signal. To calculate the pulse wave velocity – and to characterise the pulse wave propagation along the artery – I suggest using ΔT_{EPa}. This is the time it takes the pulse wave to propagate from the left ventricle to the fingertip. Instead of the easily detectable peak this requires the detection of the rise in the PPG signal. Further on I use $\Delta T_{EP} = \Delta T_{EPa}$ to refer to time delay between ECG and PPG signal.

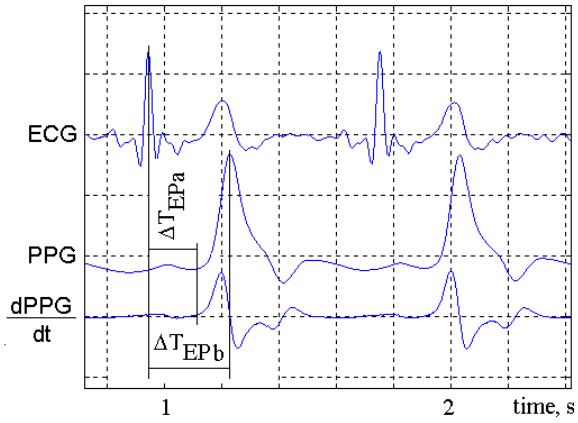
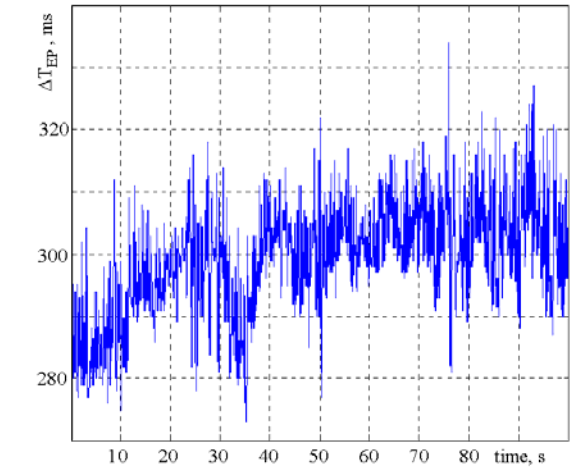


Figure 6.3. Definition of ΔT_{EP}.

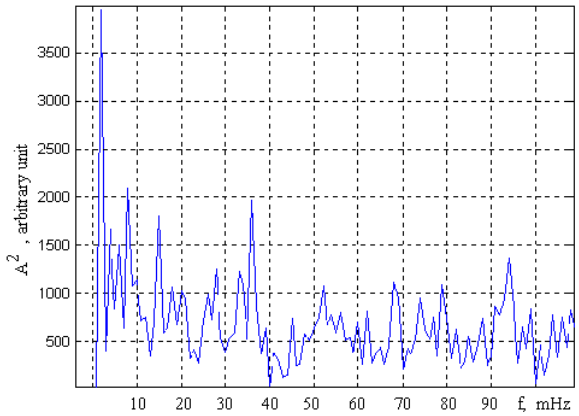
ΔT_{EP} is influenced also by factors other than blood pressure. This causes substantial error when estimating blood pressure based ***only*** on ΔT_{EP}. [Chen et al., 2001] suggests intermittent calibration with a cuff-based meter in every 5 minute. [Nitzan et al., 2001] shows that VLF fluctuations in PPG signal (and consequently in ΔT_{EP}) originate in the activity of the sympathetic nervous system. When PPG signal is taken from both hands the effect of the VLF fluctuations can be reduced by subtraction [Jobbágy et al., 2002]. Relation between heart rate and pulse transit time – defined similarly to ΔT_{EPa} – during paced respiration is reported by [Drinnan et al., 2001].

Figure 6.4a. shows a typical $\Delta T_{EP}(t)$ time function calculated from a part of a 1000-s recording. The young healthy male subject was sitting in an armchair, no cuff was applied. The spectral analysis shows that the dominant frequency was below 10 mHz in harmony with the slow elevation of ΔT_{EP}; most likely resulting from the decrease in systolic blood pressure. Peaks around 0.04 Hz and 0.1 Hz (see Figure 6.4b.) are the low frequency (LF) and the very

low frequency (VLF) components usually observed in blood pressure variation [Seydnejad and Kitney, 2001].



(a)



(b)

Figure 6.4. $\Delta T_{EP}(t)$ variation without applying a cuff. Values calculated from a part of a 1000-s recording (a) and the corresponding frequency spectrum (b).

6.2.3 PPG signal during slow inflation and deflation

The PPG signal indicates volume changes in the arteries. While cuff pressure is higher than systolic pressure no pulsation might be present in PPG distal from the cuff. Based on the PPG signal systolic pressure can be ***determined*** (not calculated).

Breathing influences ΔT_{EP}. Figure 6.5 shows different breathing profiles and the time function of ΔT_{EP} and t_{RR}. The coherence is obvious. There is a basically linear relationship between air flow during breathing and ΔT_{EP}, see Figure 6.6. Further details of the measure-

ment are given in [Szekrényesi, 2003]. The effect of breathing on baroreflex measurements is reported by [Bowers and Murray, 2004].

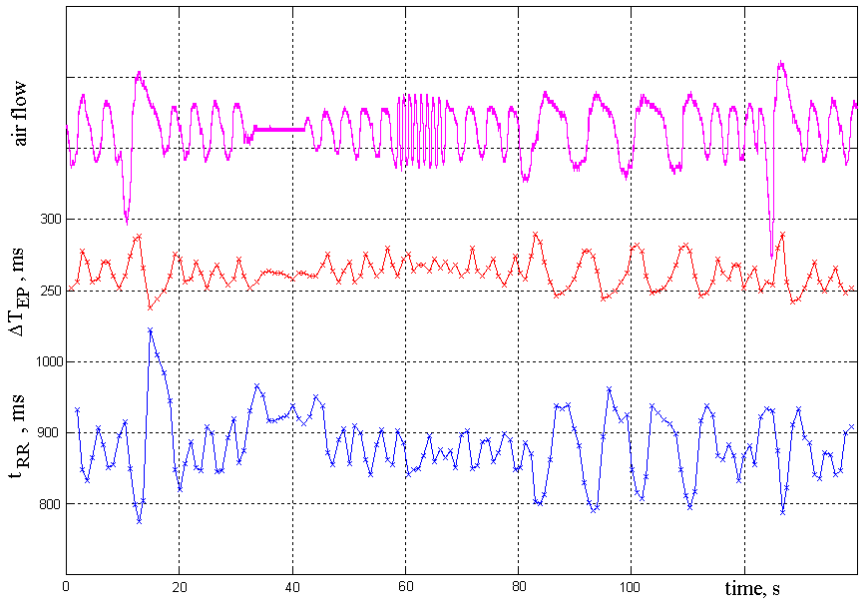


Figure 6.5. Breathing influences heart rate (t_{RR}) and the delay between ECG and PPG signal (ΔT_{EP}).

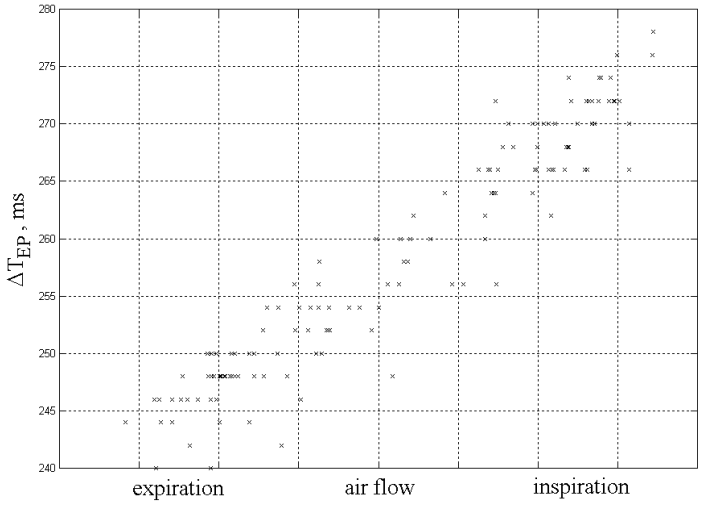


Figure 6.6. Relation between air flow and ΔT_{EP}. Young healthy subject at rest.

Breathing – air flow – modulates ΔT_{EP} during inflation and deflation, as it is shown in Figure 6.7. Modulation of air flow disappears when breath is held, see Figure 6.8.

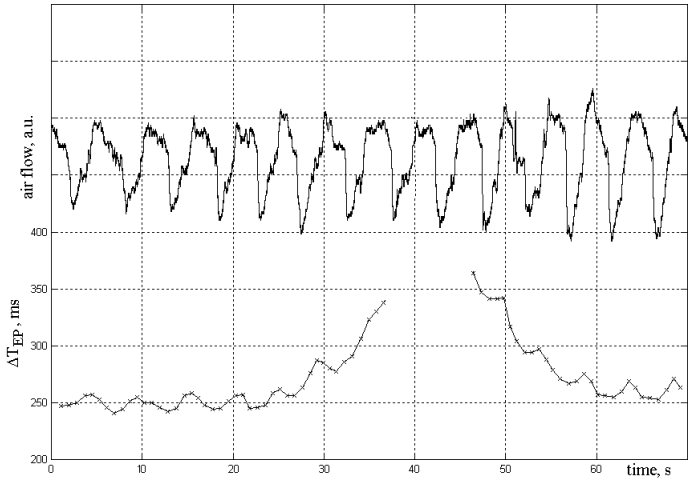


Figure 6.7. ΔT_{EP} modulated by air flow during slow inflation and deflation. Young healthy subject at rest.

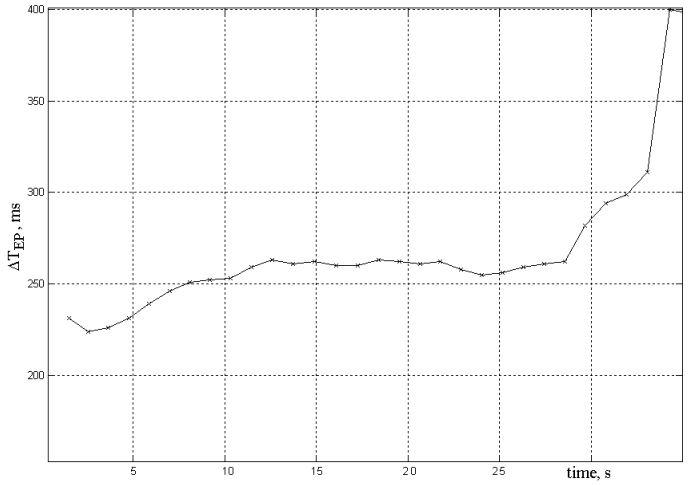


Figure 6.8. ΔT_{EP} during slow inflation. Young healthy subject, holding breath.

The modulation caused by breathing can be removed from the ΔT_{EP} time function if air flow is also measured. There is a delay between changes in air flow and changes in ΔT_{EP}. It must also be taken into account that ΔT_{EP} is a momentary value but it is influenced by the thoraxic pressure (and thus air flow) while the pulse wave is travelling in the thorax. For normal breathing high correlation was found between ΔT_{EP} and the integral of air flow for a time interval. Two parameters, the duration of the time interval (T_i) and the delay (T_d) between the end of this interval and the moment the pulse wave reaches the fingertip were varied to find maximum correlation between the integral of air flow and ΔT_{EP}. Definition of T_i and T_d are given in Figure 6.9.

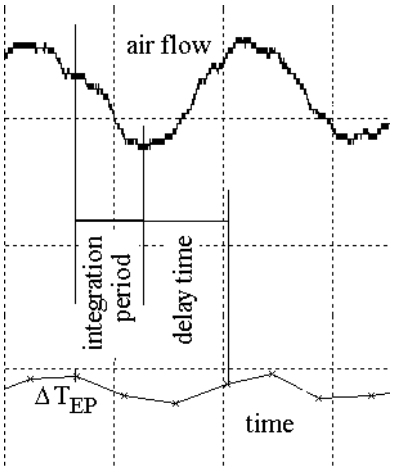


Figure 6.9. Definition of delay time and integration period for the compensation of the modulation in ΔT_{EP} caused by breathing.

Figure 6.10 shows the achievable correlation between the integral of air flow for a period and ΔT_{EP} (young healthy subject, normal breathing). The maximal achievable correlation is high, 0.81, when T_d = 1.6 s and T_i = 2.6 s. During paced breathing an even higher correlation can be attained (0.92 … 0.96). Further details are given in [Szekrényesi, 2003].

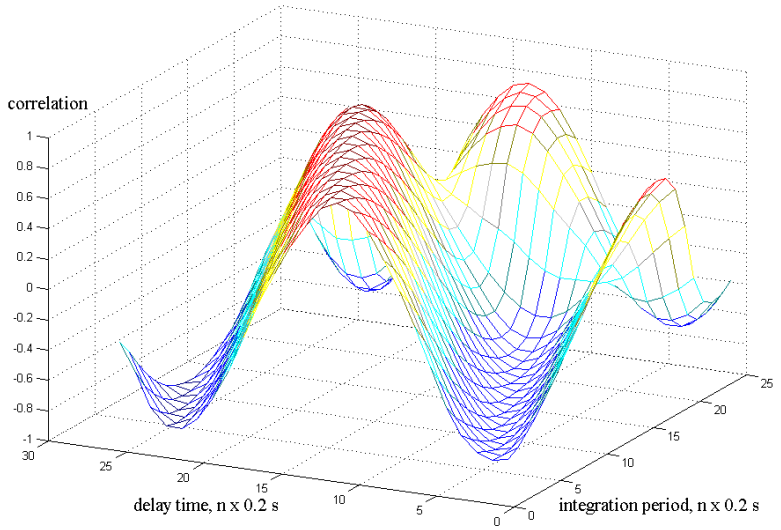


Figure 6.10. Correlation between ΔT_{EP} and the integral of air flow over a time interval. Length of integration period and delay of pulse wave arrival at the fingertip to this interval are varied to find maximal correlation.

Figure 6.11 shows the pressure - time function of an upper arm cuff and the PPG signal taken simultaneously from the fingertip of a young healthy subject at rest. An OMRON M4 blood pressure meter was used for the measurement. The cuff of the automatic meter was inflated slowly by reducing the control voltage of the built-in motor. The systolic pressure (117 mmHg) displayed by the oscillometric meter correlates well with the cuff pressure that was measured during inflation when the last pulse appeared in the PPG signal.

It was frequently experienced that the cuff pressure was different when the last pulsation in PPG signal was detected (p_{il}) during slow inflation from the cuff pressure when the first pulse reappeared (p_{df}) during slow deflation ($p_{il} > p_{df}$). This can also be seen in Figure 6.11 where p_{df} = 107 mmHg, by 10 mmHg less than p_{il}. The most probable reason is that when the pressure of the cuff wrapped around the upper arm decreases below the systolic pressure *the first pulse and the following 1-2 pulses remain undetected in the PPG signal* taken at the fingertip. Measurements were taken on the same person in parallel with a COLIN tonometer and with our measurement set-up (slowly inflated and deflated cuff, ECG and PPG signal recorded at the fingertip). *When the cuff was inflated slowly, pulses in the PPG signal taken from the fingertip were present until the cuff pressure exceeded the systolic pressure.*

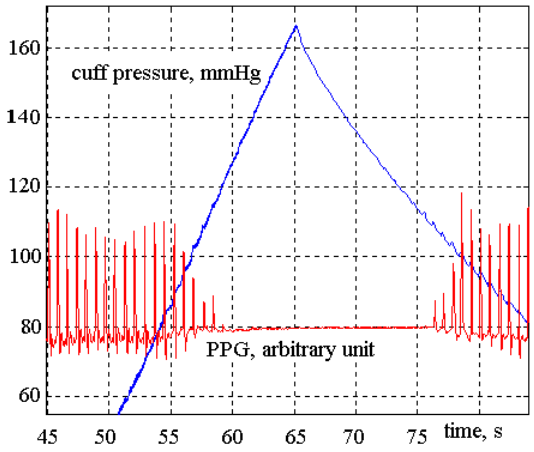


Figure 6.11. Cuff pressure and PPG signal time function during measurement with an upper arm cuff.

The amplitude of the PPG signal changes as cuff pressure changes, the amplitude change is steep around the diastolic pressure. Pulses in the PPG signal disappear when cuff pressure exceeds the systolic pressure. ***Based on these phenomena evaluation of the PPG signal helps determine the diastolic and systolic pressure.***

The PPG signal can also be used to check if the cuff is wrapped up and inflated properly, see 6.3.5. It is possible to stop the inflation when cuff pressure exceeds the systolic pressure.

6.3 The suggested new method

The method eliminates the disadvantages of presently used indirect methods: does not give false result if the tested person is not relaxed, directly measures (and not calculates) systolic and diastolic pressures, uses slow inflation thus reduces the interference caused by the cuff

and assesses the short-term variation in systolic pressure. The method is especially suitable for devices applied in home health monitoring.

6.3.1 Testing the relaxation before the measurement

In the first phase (minimum 30 heart cycles) the cuff is completely deflated. During this interval the ECG and PPG signals are recorded to make a decision if the person is relaxed enough to start the measurement. The decision is based upon the analysis of the heart rate (HR). Figure 6.12 demonstrates the variation in heart rate for a young (left) and a senior (right) healthy male at rest. Moving window of 30 heart cycles is used. Windows overlap, the step is 5. The i^{th} point in Figure 6.12 stands for the interval between the $(i*5)^{th}$ to $(i*5+30)^{th}$ heart cycles.

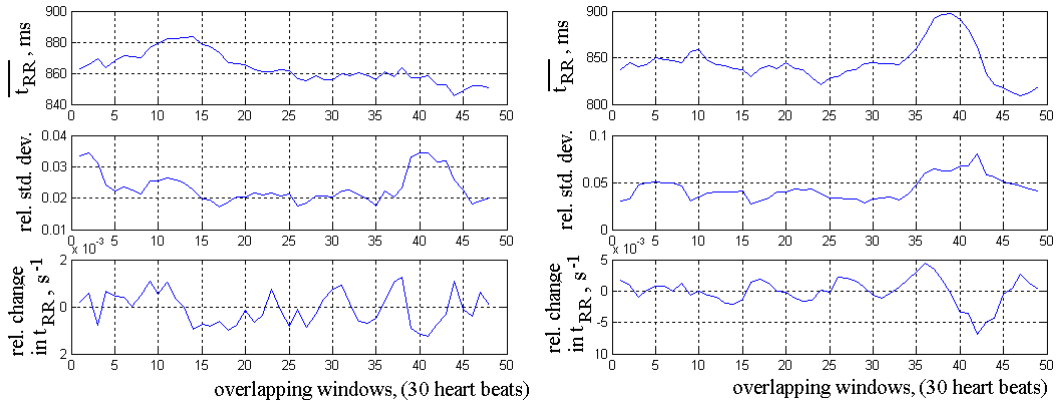


Figure 6.12. Variation in heart rate. Healthy subjects at rest, senior (left) and young (right) males.

On top is the average t_{RR} calculated for the heart cycles in the window. The middle diagram shows the standard deviation over mean for HR in the given window. The bottom figure shows the slope of the straight line fitted to the relative changes of the t_{RR} values in the window.

$$\text{relative change in } t_{RR} = \frac{\frac{|t_{RRf} - t_{RRl}|}{\overline{t_{RR}}}}{t_{window}} = \frac{\frac{|t_{RRf} - t_{RRl}|}{\overline{t_{RR}}}}{30 * \overline{t_{RR}}} = \frac{|t_{RRf} - t_{RRl}|}{30 * \left(\overline{t_{RR}}\right)^2}$$

where t_{RRf} is the first, t_{RRl} is the last value of the fitted line in the window.

Based on more than 200 measurements on 5 senior (age between 40 … 65) and 15 young (age between 23 … 27) healthy males at rest both the relative standard deviation and the relative change in t_{RR} values were found to be smaller for the senior group. ***As a general threshold level, the person is considered to be relaxed and measurement can start if for 30 heart***

cycles the relative standard deviation of t_{RR} is less than 0.05 and the relative change in t_{RR} is less than 0.005 s^{-1}. This latter means an average maximum 5 ms change in t_{RR} within adjacent beats for all 30 beats if the heart rate at the beginning of the test is 60 bpm.

Figure 6.13 shows the changes in heart rate of two young healthy males following short physical stress. They run on the stairs for 4 minutes immediately before the measurement. For subject A it took about two and a half minutes (25*5+30 s) to calm down. By this time the standard deviation over mean of t_{RR} values became less than 0.05. The relative change in t_{RR} was less than the threshold level already after one minute (7*5+30 s). This subject was tested several times. At rest – without any physical stress – he had a pulse rate around 60 bpm, i.e. t_{RR} was close to 1000 ms. It is clear from the figure that even 3 minutes after a short physical stress the pulse rate is above 80 bpm as t_{RR} is less than 750 ms. Under this condition the systolic pressure measured during slow inflation was about 15 mmHg higher than the average of systolic pressures at 60 bpm heart rate. At the time of measurement the actual systolic pressure of the subject was really higher than at rest. Technically the measurement error (the difference between the actual and the measured values) was small; nevertheless the result could be misleading if taken as the value at rest. Subject B behaved differently. The relative standard deviation is about 0.05 even at the end of the 3-minute recording and the relative change in t_{RR} gets only slightly within the given limits by the end. After about two minutes at rest the heart rate starts to increase again.

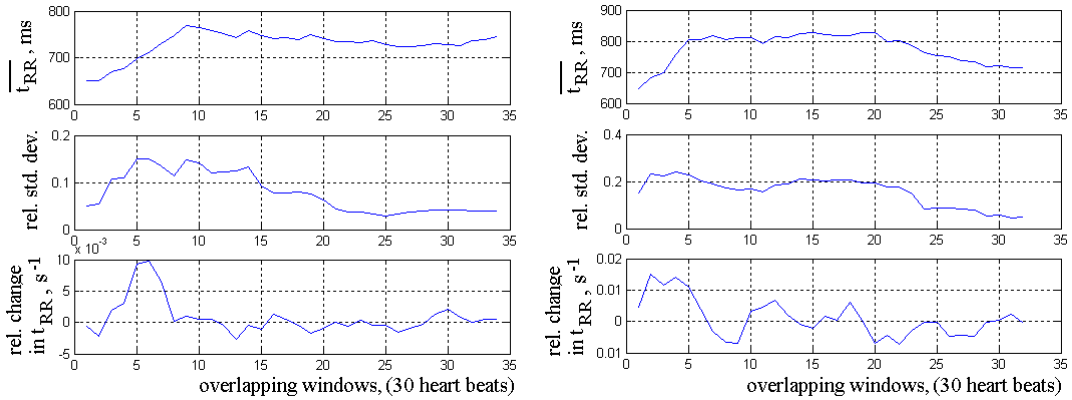


Figure 6.13. Time period of heart cycle (t_{RR}) after physical stress. Young healthy subjects.

I suggest using personalised limits to decide whether the subject is relaxed enough to start the measurement. This makes possible a more accurate assessment than using general rules. The limits can be based on the analysis of the variations in t_{RR} and the decision algorithm can be stored in a home health monitoring device.

6.3.2 The cuff pressure profile

The widely used method is to inflate the cuff pressure fast above the systolic pressure and deflate the cuff at a rate of about 3 – 4 mmHg/s to below diastolic value. The motor performing inflation is stopped during the measurement of the pressure oscillations in the cuff. A substantial noise source is switched off; however, the occlusion of the artery changes the pressure to be measured (see 5.3)!

During inflation ΔT_{EP} increases as the cuff pressure increases. The main reason is that the pulse wave slows down at the section narrowed down by the cuff. The increase in ΔT_{EP} starts at low cuff pressure and the change in it is steepest when the cuff pressure equals the diastolic pressure. Our measurements intimate that the occlusion changes the biomechanical properties of the arteries. The ΔT_{EP} vs. cuff pressure function is steeper during deflation than inflation for the majority of tested persons [Jobbágy et al., 2002]. A diagram for a senior healthy male is given in Figure 6.14. This is typical for healthy senior subjects. ΔT_{EP} recorded for the right arm (without cuff) was subtracted from ΔT_{EP} recorded for the left arm (cuff was on the upper left arm). This reduced the effect of breathing on ΔT_{EP}.

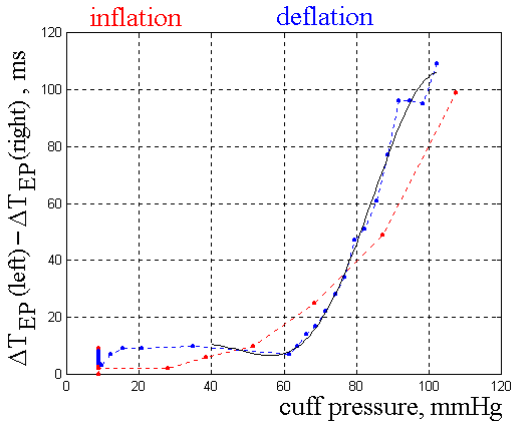


Figure 6.14. ΔT_{EP} vs. cuff pressure is different during inflation and deflation. ΔT_{EP} at the right arm is subtracted to reduce influence of breathing.

The almost linear change in PPG signal amplitude around the diastolic pressure during inflation is usually not present during deflation. For this reason ***I suggest determining the systolic and diastolic pressure during slow inflation of the cuff.***

In Figure 6.14 the ΔT_{EP} vs. cuff pressure function is steeper during deflation than during inflation. This presumes a change in the elasticity of the artery caused by the occlusion. I found that compared to young subjects, healthy seniors exhibit greater change in steepness for the ΔT_{EP}(cuff pressure) function during deflation compared to inflation. Based on this observation quantitative assessment of the rigidity of the arteries is being developed.

6.3.3 Determining the systolic pressure

The amplitude of the PPG signal decreases as cuff pressure increases. The tested persons put their lower arm on the table in supine position. The hand is supported so that the lower arm is at approximately 15 degrees to the table. Figure 6.15 shows a part of a typical recording. The amplitude of a pulse in PPG signal is defined as the amplitude difference between the zero derivatives.

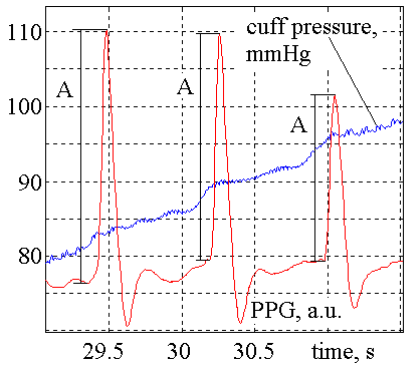


Figure 6.15. Definition of the amplitude of pulses in PPG signal.

The amplitudes of the pulses in PPG signal until the total occlusion during slow inflation are shown in Figure 6.16. ***The cessation of the pulsation in PPG signal indicates when cuff pressure is equal to systolic pressure.*** This gives a momentary value (see 6.1); it can be misleading as a result of oscillations in PPG amplitude. Oscillations in the PPG amplitude – and slope – are mainly due to breathing. The effect of breathing can be reduced by fitting a straight line for the declining section. The zero pressure crossing of the straight line is an estimate of the average systolic pressure over the time while the cuff pressure increases from diastolic to systolic pressure. The slope of slow inflation I have been using is about 3 mmHg/s, the usual difference between systolic and diastolic pressure is more than 30 mmHg thus the time for averaging is longer than 10 s. The standard deviation of systolic pressure over a short time period is estimated based on the standard deviation of ΔT_{EP} when $p_{cuff} = 0$. In general:

$$\frac{\sigma_{p_{sys}}}{p_{sys}} = k \frac{\sigma_{\Delta T_{EP}}}{\Delta T_{EP}}$$

k was found to be different for different persons. A rough estimate is k = 1, in home health monitoring devices personalised values for k can be stored. Even without an accurate value, ***changes*** in the relative standard deviation of systolic pressure estimated using the same k value have diagnostic information.

More effective filtering can be based on the identification of the effect of breathing on PPG amplitude at the beginning of the measurement when $p_{cuff} = 0$.

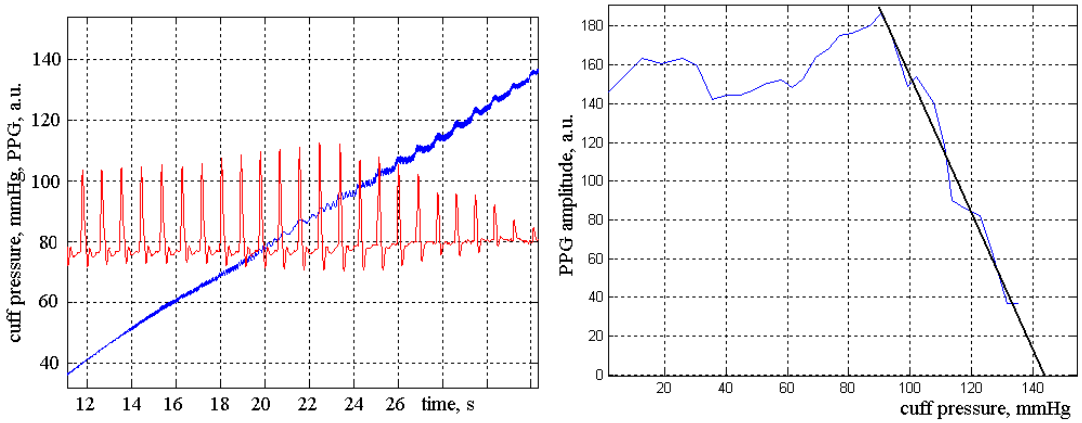


Figure 6.16. Amplitude of pulses in PPG signal as cuff pressure slowly increases.

6.3.4 Determining the diastolic pressure

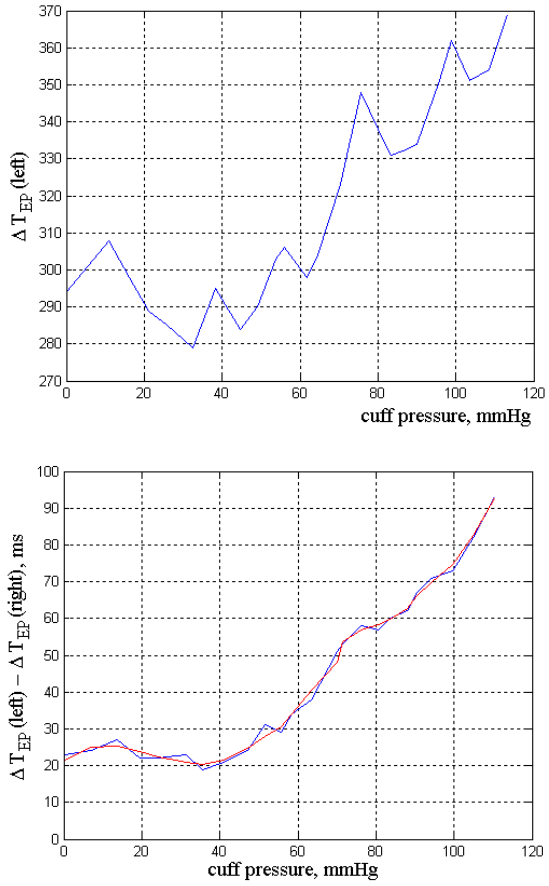


Figure 6.17. ΔT_{EP} increases as cuff pressure increases during slow inflation. Top: ΔT_{EP} for the left arm (where cuff is attached to), bottom: difference of ΔT_{EP} of the two arms before and after low-pass filtering.

Pulse wave velocity decreases as cuff pressure increases. The increase is maximal when cuff pressure is equal to diastolic pressure. Based on it, the diastolic pressure can be determined. As described in 6.2.3, breathing modulates ΔT_{EP}. Without also measuring air-flow breathed in and out by the tested person, filtering out the effect of breathing is not easy. ***I suggest recording the ΔT_{EP} on both arms and subtracting the two signals.*** Subtraction reduces the effect of breathing. Figure 6.17 shows ΔT_{EP} recorded for the left arm (above), where the cuff was attached to, and the difference of ΔT_{EP} of the two arms before (blue) and after (red) low-pass filtering (second order Butterworth, f_c = 0.4 Hz), (bottom).

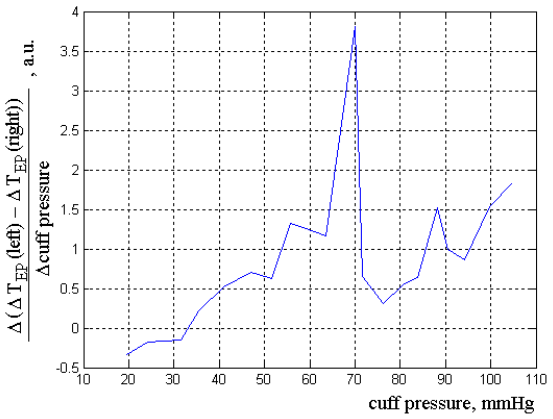


Figure 6.18. The rate of increase in ΔT_{EP} as cuff pressure increases during slow inflation. Maximum increase is when cuff pressure equals diastolic pressure.

Subtraction of ΔT_{EP} of the arm without the cuff substantially reduces the effect of breathing. ***The diastolic pressure is estimated to be equal to the cuff pressure, where the rate of change in ΔT_{EP} is maximal during slow inflation.*** For the measurement shown in Figure 6.17 the diastolic pressure is estimated to be 70 mmHg. Calculation of the ***rate of change*** in ΔT_{EP} means that impacts which are constant during the measurement are eliminated by the subtraction. This means that the preejection time ΔT_{PE} does not effect the measurement.

6.3.5 Testing the proper placement of the cuff

Based on the PPG signal the *proper fitting and inflation of the cuff can also be checked.* When cuff pressure is above the arterial pressure, pulsation in the PPG signal should cease. In Figure 6.19 pulses in PPG signal are present during the whole measurement process. This indicates that the cuff was unable to occlude the artery. It was deliberately prevented by placing a small wooden plate under the cuff. However, based on the amplitude changes of the oscillometric pulses the automatic blood pressure meter did not give error indication, calcu-

lated and displayed values as systolic and diastolic blood pressures. Resulting from the improper occlusion, the displayed systolic pressure was by 15 mmHg (12 %) above the real value. Reference systolic pressure value was determined 5 minutes before this experiment using the method reported in 6.3.3.

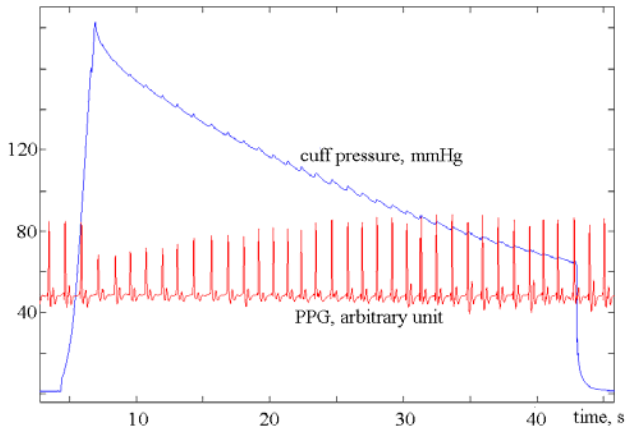


Figure 6.19. Time functions of cuff pressure and PPG signal during measurement. Loosely wrapped up cuff, pulses in PPG signal do not disappear.

6.4 Results using the suggested method

560 recordings were made from 93 persons using slow inflation. Three persons were tested in parallel with a COLIN CBM7000 tonometer that continuously measured arterial pressure. Following a calibration with an upper-arm cuff, for 5 … 15 minutes this device is considered to give reference values. The systolic and diastolic pressure measured as described in 6.3.3 and 6.3.4 were close to within ± 5 mmHg to the 20-s average of the continuously measured values.

Although it is included in the standards (see section 5), I do not consider the results as reference values that are measured by a trained person with a manual sphygmomanometer. I did not use this method to validate my results.

Measurement series were completed from relaxed healthy subjects. 10 measurements were made using an oscillometric meter with slow inflation and simultaneously recording ECG and PPG in every 5 minute. Several times during parallel measurement the oscillometric meter was unable to calculate p_{sys} and p_{dia}, it gave an error message. Using the method I suggest it was always possible to determine p_{sys} and p_{dia}. When another measurement result within 5

minutes was available from the same person, p_{sys} and p_{dia} determined by the method described in 6.3.3 and 6.3.4 correlated with it.

The method I suggest is being built into ten devices meant for home health monitoring. In 2006 ten patients with cardiovascular disease will use these devices for six months. Self-measurements will be performed twice a day. The devices request the patient to complete measurements at pre-programmed times. If the patient does not make the scheduled measurement or the result is extremely unfavourable the device sends an SMS to the given telephone to request help. If the results are acceptable, they are stored for 2 months. Patients take the results of two months with them to their general practitioner. The doctor gets detailed information on the blood pressure of the patient between two visits. In addition, a 10-s ECG record (Einthoven lead I or II) and oxygen saturation level will be stored in parallel with blood pressure measurement values.

The ten patients will make about 600 measurements. This will help validate the suggested blood pressure measurement method.

7 New results of the dissertation

1. ***I developed a measurement procedure and an algorithm to quantify the performance in quasi-periodic human movements ([Jobbágy et al., 2005], [Jobbágy et al., 1998], [Jobbágy et al., 2004], [Jobbágy et al., 1999], [Jobbágy et al., 1996].***

The performance during the repeated execution of a movement pattern is determined by regularity (periodicity) and speed. These features are conflicting (it is easier to maintain regularity at a lower speed), I suggest using the product of them.

performance = (regularity – c) x speed

Constant c is used to set equal weight to regularity and speed.

I showed experimentally that in the frequency domain of most frequently used quasi-periodic movements there is no diagnostically important information for the assessment of the actual state of Parkinsonian patients.

1.1. I demonstrated that the SVD (Singular Value Decomposition) method is applicable for the quantification of regularity. With the help of the SVD method a set of $\underline{v}_j$ basis vectors are determined. The linear combinations of these vectors define all (k nr) performed cycles. All cycles contain m sampled data. (This is assured by resampling if necessary.) For the definition of a given cycle different weights ($u_{ij}\sigma_j$) belong to the $\underline{v}_j$ basis vectors. σ_j (j = 1, …, m) values are identical for all cycles, the u_{ij} weight belongs to the $\underline{v}_j$ basis vector in the i^{th} cycle. The i^{th} cycle, $\underline{p}_i$ is determined as:

$$\underline{p}_i = \sum_{j=1}^{m} u_{ij}\sigma_j \underline{v}_j$$

Increasing regularity is indicated by the increasing weight of the dominant basis vector in describing the complete movement. Having ordered the σ_j weights according to their values, the Periodicity of Movement (PM) can be computed:

$$PM = \frac{\sigma_1^2}{\sum_{j=1}^{m}\sigma_j^2}$$

For periodic movement $\sigma_{j\,(j\neq 1)} = 0$, thus PM = 1.

1.2. I showed that speed can be quantified by the product of average amplitude and average frequency of the trajectory run by the observed point of a part of the body (finger, hand, and arm). The speed, amxfr is:

$$\text{amxfr} = \overline{\text{amplitude}} * \overline{\text{frequency}}$$

2. ***I worked out a procedure to assess the movement patterns of patients with neural diseases and to personalise these tests ([Jobbágy et al., 2005], [Jobbágy et al., 1998], [Jobbágy et al., 2004], [Jobbágy et al., 2000], [Jobbágy et al., 1997], [Jobbágy et al., 1996], [Jobbágy et al., 1995], [Jobbágy, Harcos, Fazekas, 2005]).***

I showed and experimentally justified that quantification of the finger-tapping test helps assess the actual state of patients with neural diseases. I showed and experimentally justified that tracking markers in two dimensions is satisfactory to evaluate the finger-tapping movement.

Disorders in movement of Parkinsonians and stroke patients are different. Parkinsonians exhibit stochastic deviations. There are patients in both groups who have significantly worse results for one finger than for the other fingers on the same hand during finger-tapping test. Taking all these into account I defined the FTTS (Finger-Tapping Test Score) parameter to quantify the performance of the finger-tapping test.

2.1. FTTS = (PM – c) x amxfr

Constant c serves for setting the proper relative weight of regularity and speed. Based on the 300 finger-tapping recordings we made the suggested value for c is 0.6. I confirmed experimentally that this parameter expresses properly the performance of Parkinsonian and stroke patients during the finger-tapping test.

2.2. FTTS is defined for ***one finger***. I showed that the ***performance of a hand*** can be quantified by the sum of the FTTS values of the ring-, middle- and index finger.

2.3. For stroke patients FTTS must be augmented to consider also the smoothness and the possible incorrect order of fingers:

$$\text{FTTS} = (\text{PM} - c) \times \text{amxfr} \times (1 - h_s) \times (1 - h_o)$$

where h_s is smoothness error and h_o expresses the incorrect order of fingers.

2.4. I showed that the product of PM and amxfr can be used also for the quantification of other measurements when the tested subject has to repeat a given movement pattern. For the assessment of Parkinsonians such are the twiddling, pinching and circling movements.

3. I worked out an indirect measurement method that characterises blood pressure better than presently used methods ([Jobbágy, 2004], [Jobbágy et al., 2004], [Jobbágy et al., 2002], [Jobbágy et al., 2001]).

The method requires the measurement of the

- cuff pressure during slow inflation,
- Einthoven I. or II. lead ECG,
- PPG signal at the fingertip.

The measurement method integrates the following new results.

3.1. If the tested person is not at rest during blood-pressure measurement then the result can be misleading. Before the measurement it must be analysed, whether the tested person is relaxed. It can be determined by evaluating the variation in the delay between ECG and PPG signals (ΔT_{EP}) and in heart rate (heart rate variability, HRV) when the cuff is fully deflated.

I worked out a ***general criterion***: measurement can start if the relative standard deviation of the period (t_{RR}) of 30 consecutive heart cycles is less than 0.05 and the absolute value of the slope of the straight line fitted to the t_{RR} values in the same time-window is less than 0.005 s^{-1}.

The relaxed state – needed for the correct measurement – can be more accurately determined if ***personalised criteria*** are used.

3.2. The diastolic pressure can be determined by analysing ΔT_{EP} for the arm where cuff is attached to. ΔT_{EP} increases as cuff pressure increases. The modulation effect of breathing must be filtered out from the $\Delta T_{EP}(p_{cuff})$ function. I suggest recording ΔT_{EP} also for the arm without cuff and subtracting it from ΔT_{EP} of the arm where cuff is attached to. ***The maximal change in the slope of the $\Delta T_{EP}(p_{cuff})$ function detected during slow inflation designates the diastolic pressure.***

3.3. The ***systolic pressure can be directly detected*** during slow inflation based on the PPG signal. ***The cessation of the pulsation in PPG signal designates the momentary systolic pressure.*** Breathing modulates also the amplitude of the PPG signal. I showed that the effect of this modulation can be reduced by fitting a straight line to the PPG amplitude – cuff pressure function in between the diastolic pressure and the pressure belonging to the cessation of the PPG pulsation.

3.4. I suggest using the average and standard deviation of the systolic pressure calculated for a short time period instead of momentary value. The standard deviation of the systolic pressure can be estimated on the basis of the $\Delta T_{EP}(t)$ function recorded at the beginning of the measurement procedure, when $p_{cuff} = 0$.

$$\frac{\sigma_{p_{sys}}}{\overline{p_{sys}}} = k \frac{\sigma_{\Delta T_{EP}}}{\overline{\Delta T_{EP}}}$$

Based on this, changes in the relative standard deviation of p_{sys} can be tracked for a person.

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10 Appendix

1. Rating scales for Parkinsonian patients

Hoehn and Yahr Staging of Parkinson's Disease

1. Stage One
    1. Signs and symptoms on one side only
    2. Symptoms mild
    3. Symptoms inconvenient but not disabling
    4. Usually presents with tremor of one limb
    5. Friends have noticed changes in posture, locomotion and facial expression
2. Stage Two
    1. Symptoms are bilateral
    2. Minimal disability
    3. Posture and gait affected
3. Stage Three
    1. Significant slowing of body movements
    2. Early impairment of equilibrium on walking or standing
    3. Generalized dysfunction that is moderately severe
4. Stage Four
    1. Severe symptoms
    2. Can still walk to a limited extent
    3. Rigidity and bradykinesia
    4. No longer able to live alone
    5. Tremor may be less than earlier stages
5. Stage Five
    1. Cachectic stage
    2. Invalidism complete
    3. Cannot stand or walk
    4. Requires constant nursing care

United Parkinson's Disease Rating Scale (UPDRS)

A. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment

0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)

0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florrid psychosis. Not able to care for self.

3. Depression

1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative

0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

B. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. Speech

0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation

0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

8. Handwriting

0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting food and handling utensils

0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing

0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene

0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes

0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)

0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking

0 = None.
1 = Rare freezing when walking; may have starthesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking

0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)

0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism

0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

C. MOTOR EXAMINATION

18. Speech

0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression

0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression.
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)

0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands

0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succession.)

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)

0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture

0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)

0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)

0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

D. COMPLICATIONS OF THERAPY (In the past week)

i. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)

0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)

0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?

0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)

0 = No
1 = Yes

ii. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?

0 = No
1 = Yes

37. Are "off" periods unpredictable?

0 = No
1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?

0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?

0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

iii. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?

0 = No
1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?

0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis?

(Record the patient's blood pressure, height and weight on the scoring form)

0 = No
1 = Yes

II. MODIFIED HOEHN AND YAHR STAGING

STAGE 0 = No signs of disease.
STAGE 1 = Unilateral disease.
STAGE 1.5 = Unilateral plus axial involvement.
STAGE 2 = Bilateral disease, without impairment of balance.
STAGE 2.5 = Mild bilateral disease, with recovery on pull test.
STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.
STAGE 4 = Severe disability; still able to walk or stand unassisted.
STAGE 5 = Wheelchair bound or bedridden unless aided.

III. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
50% = More dependent. Help with half, slower, etc. Difficulty with everything.
40% = Very dependent. Can assist with all chores, but few alone.
30% = With effort, now and then does a few chores alone or begins alone. Much help needed.
20% = Nothing alone. Can be a slight help with some chores. Severe invalid.
10% = Totally dependent, helpless. Complete invalid.
0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

2. Rating scales for stroke patients

The Barthel index

Feeding
0 = unable
5 = needs help cutting, spreading butter, etc., or requires modified diet
10 = independent

Bathing
0 = dependent
5 = independent (or in shower)

Grooming
0 = needs to help with personal care
5 = independent face/hair/teeth/shaving (implements provided)

Dressing
0 = dependent
5 = needs help but can do about half unaided
10 = independent (including buttons, zips, laces, etc.)

Bowels
0 = incontinent (or needs to be given enemas)
5 = occasional accident
10 = continent

Bladder
0 = incontinent, or catheterized and unable to manage alone
5 = occasional accident
10 = continent

Toilet Use
0 = dependent
5 = needs some help, but can do something alone
10 = independent (on and off, dressing, wiping)

Transfers (bed to chair, and back))
0 = unable, no sitting balance
5 = major help (one or two people, physical), can sit
10 = minor help (verbal or physical)
15 = independent

Mobility (on level surfaces)
0 = immobile or < 50 yards
5 = wheelchair independent, including corners, > 50 yards
10 = walks with help of one person (verbal or physical) > 50 yards
15 = independent (but may use any aid; for example, stick) > 50 yards

Stairs
0 = unable
5 = needs help (verbal, physical, carrying aid)
10 = independent

Functional Independence Measure.

Eighteen items are equally weighted; each is rated from 1 (completely dependent) to 7 (independent without device). The items included feeding, upper-limb dressing, lower-limb dressing, bowel management, bladder management, feeding, bathing, walking, stairs, tub transfer, toilet transfer, bed transfer, comprehension, expression, problem solving, social interaction, and memory.

The **Rivermead Mobility Index** is a measure of disability related to bodiliy mobility. It demonstrates the patient's ability to move her or his own body. It does not measure the effective use of a wheelchair or the mobility when aided by someone else. It was developed for patients who had suffered a head injury or stroke at the Rivermead Rehabilitation Centre in Oxford, England.

No	Parameter	Question
1	Turning over in bed	Do you turn over from your back to side without help?
2	Lying to sitting	From lying in bed do you get up to sit on the edge of the bed on your own?
3	Sitting balance	Do you sit on the edge of the bed without holding on for 10 seconds?
4	Sitting to standing	Do you stand up (from any chair) in less than 15 seconds and stand there for 15 seconds (using hands and with an aid if necessary)?
5	Standing unsupported	Observe standing fore 10 seconds without any aid or support.
6	Transfer	Do you manage to move from bed to chair and back without any help?
7	Walking inside with an aid if needed	Do you walk 10 meters with an aid or furniture if necessary but with no standby help?
8	Stairs	Do you manage a flight or stairs without help?
9	Walking outside (even ground)	Do you walk around outside on pavements without help?
10	Walking inside with no aid?	Do you walk 10 meters inside with no calliper splint aid or use of furniture and no standby help?
11	Picking off floor	If you drop something on the floor do you manage to walk 5 meters pick it up and then walk back?
12	Walking outside (uneven ground)	Do you walk over uneven ground (grass gravel dirt snow ice etc.) without help?
13	Bathing	Do you get in and out of bath or shower unsupervised and wash self?
14	Up and down 4 steps	Do you manage to go up and down 4 steps with no rail and without help but using an aid if necessary?
15	Running	Do you run 10 meters without limping in 4 seconds (a fast walk is acceptable)?

response: yes = 1, no = 0

Rivermead motor index = sum(points for all 15 questions)