Quantification of Tremor and Bradykinesia in Parkinson's Disease Using a Novel Ambulatory Monitoring System

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***Abstract*—An ambulatory system for quantification of tremor and bradykinesia in patients with Parkinson's disease (PD) is presented. To record movements of the upper extremities, a sensing units which included miniature gyroscopes, has been fixed to each of the forearms. An algorithm to detect and quantify tremor and another algorithm to quantify bradykinesia have been proposed and validated. Two clinical studies have been performed. In the first study, 10 PD patients and 10 control subjects participated in a 45-min protocol of 17 typical daily activities. The algorithm for tremor detection showed an overall sensitivity of 99.5% and a specificity of 94.2% in comparison to a video reference. The estimated tremor amplitude showed a high correlation to the Unified Parkinson's Disease Rating Scale (UPDRS) tremor subscore (e.g., $r = 0.87$, $p < 0.001$ for the roll axis). There was a high and significant correlation between the estimated bradykinesia related parameters estimated for the whole period of measurement and respective UPDRS subscore (e.g., $r = -0.83$, $p < 0.001$ for the roll axis). In the second study, movements of upper extremities of 11 PD patients were recorded for periods of 3–5 hr. The patients were moving freely during the measurements. The effects of selection of window size used to calculate tremor and bradykinesia related parameters on the correlation between UPDRS and these parameters were studied. By selecting a window similar to the period of the first study, similar correlations were obtained. Moreover, one of the bradykinesia related parameters showed significant correlation ($r = -0.74$, $p < 0.01$) to UPDRS with window sizes as short as 5 min. Our study provides evidence that objective, accurate and simultaneous assessment of tremor and bradykinesia can be achieved in free moving PD patients during their daily activities.**

***Index Terms*—Biomedical signal processing, bradykinesia, gyroscope, Parkinson's disease, tremor, wearable technology.**

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I. Introduction

PATIENTS with Parkinson's disease (PD) show major clinical abnormalities of movements including resting tremor, rigidity, bradykinesia, and postural instability [1], [2]. With progression of the disease the response to dopaminergic treatment becomes less stable and fluctuates over time, with an increase in rigidity, resting tremor and bradykinesia during OFF periods, and dyskinesia during ON periods. Recently, *deep brain stimulation* (DBS) in the *subthalamic nucleus* (STN) has been introduced as a treatment of patients with refractory fluctuations [3]. STN DBS results in a significant reduction of the needed medication which, in some patients, can even be completely discontinued [4]. STN DBS is effective against nearly all cardinal features of PD as long as the stimulator is turned on, whereas Parkinsonism returns shortly after turning the stimulator off. Thus, for the purpose of validating movement analysis systems, STN DBS treated PD patients provide particularly useful experimental conditions whereby Parkinsonian state of the patients can be switched on and off on demand.

Currently assessment of motor abnormalities in PD is mainly clinical, based on a number of different scales. Among them, the most widely used rating scale is the Unified Parkinson's Disease Rating Scale (UPDRS) (part III) [5]. Using various techniques, several groups have proposed objective methods to detect and quantify tremor [6]–[11] and bradykinesia [12]–[14]. Recently, there has been a growing interest in applications of body-fixed sensors (BFS) and in particular kinematic sensors for long-term monitoring of PD patients. Several groups have used *accelerometers* to detect and quantify tremor [15]–[18] and bradykinesia [8], [14], [19], [20]. A drawback of the accelerometers is that the amplitude of the measured accelerations of a moving segment depends on the position of the sensor on the segment. Another type of kinematic sensor, a gyroscope, that can measure angular velocity of the movement of a body segments, has been rarely used but may be even more useful for quantifying tremor and bradykinesia [21]: The angular velocity measured by a gyroscopic sensor attached to a moving segment is independent of the position of the sensor on the segment.

The objective of the study was to design a new ambulatory system using miniature gyroscopes attached to the forearms to quantify tremor and bradykinesia during daily activities of the patients. Two studies have been performed. In the first study, PD patients with bilateral STN DBS implantations and a control group performed a protocol of typical daily activities. Sensitivity and specificity of a new algorithm to detect tremor and

TABLE I
ACTIVITIES USED IN THE MEASUREMENT PROTOCOL OF THE FIRST STUDY

	Activity	Minimum time
1	Sitting with no movement	30s
2	Sitting and talking	60s
3	Sitting, counting in inverse starting from 100 each time subtracting 7	60s
4	Sitting, holding the 2 hand in 90°	30s
5	Sitting, alternate movement of the right hand	30s
6	Sitting, alternate movement of the left hand	30s
7	Standing, followed by walking round 2m toward a table and sitting behind it	120s
8	Sitting, writing the date, name and a series of standard phrases	60s
9	Sitting, eating and drinking	120s
10	Standing, followed by walking toward the lavatory	60s
11	Standing, brushing the teeth	60s
12	Standing, combing the hair	60s
13	Walking from the lavatory to the corridor and sitting on the chair	120s
14	Standing, walking for 20m with normal speed, turning back and sitting on the chair	120s
15	Standing, climbing the stairs, turning back and sitting on the chair	120s
16	Standing, walking for 20m with fast speed, turning back and sitting on the chair	120s
17	Lying in the bed	60s

quantify the severity of the tremor and bradykinesia were determined. During the second study, the method was applied to a group of PD patients that were free to perform daily activities at will during several hours of continuous recording while the state of the stimulation was changed from ON to OFF and back to ON again. We also studied the effect of selection of the window sizes used to calculate the parameters related to the tremor and bradykinesia on the correlation between the appropriated subscores of the UPDRS and these parameters.

II. METHOD

A. Patients and Experiment Design

Two studies and a control experiment have been performed. A group of 10 PD patients (five males) and a group of 10 age and sex-matched healthy controls participated in the first study. PD patients participating in the study had bilateral STN DBS implantation for 20 ± 3 months. The average age of the patient group was 61.5 years ($\max = 75.1$, $\min = 48.7$, $\mathrm{STD} = 7.8$) with a duration of disease of 15.6 ± 0.8 years and the average age of the control group was 63.6 years ($\max = 82.8$, $\min = 45.2$, $\mathrm{STD} = 10.5$). All PD patients had levodopa-responsive PD, without any atypical signs on examination [22], no dementia (following International Classification of Diseases-10 definition of dementia), and no significant depression. The control subjects had no neurologic disease or medical condition associated with tremor, no tremorogenic medication. They had neither orthopedic nor arthritic condition on the upper limbs limiting the recordings [21].

Movements of the upper extremities of the participants were continuously recorded while they followed a protocol of 17 tasks, each one representing a typical daily activity (see Table I). The protocol took up to 45 min. Before each measurement period, PD patients were evaluated using the UPDRS motor Section III, [5]). During the period of the measurements, all activities of the subjects were recorded on video. Each patient performed the protocol twice, once during Stim ON (when both stimulators had been turned on) and once during Stim OFF (when both stimulators had been turn off). The Stim OFF measurement was recorded between 120 and 180 min after turning STN DBS off [23].

Eleven PD patients (seven males) participated in the second study. They had an average age of 66.5 years ($\max = 82.3$, $\min = 59.6$, $\mathrm{STD} = 6.8$). In this study patients were free to move about within the hospital and to perform activities they wished. Subjects started while the STN DBS stimulation was ON. Subsequently, the stimulators were turn OFF for 3 h and then turned ON again. Typically, each measurement period was about 5 hr, including 1 h with Stim ON, followed by 3 h of Stim OFF followed by another hour of Stim ON. An UPDRS test was performed at the beginning of the measurement and was repeated at least every hour.

The studies were approved by the local Ethics Committees of the respective hospitals (Neuroscience in HUG, Internal Medicine in CHUV). All participants in the study gave informed consent prior to enrollment.

B. Measurement System

In the first study, the measurement system included a sensor attached to each of the forearms. Sensors where attached to the skin just above the wrist, using special elastic bands (made by Huguenin, CH). These bands had a layer of silicon on the side facing the skin to avoid slipping. Each sensor included three miniature uni-axial gyroscopes (Murata, ENC-03J) measuring the angular velocity of the forearms movements in roll, yaw, and pitch direction [Fig. 1(a)]. The range of the sensors after calibration was $\pm 1200\,^{\circ}/\mathrm{s}$. The weight of each sensor was 35 g and their dimensions were $35 \times 30 \times 37$ mm ($\mathrm{W} \times \mathrm{H} \times \mathrm{D}$). To record the signals during the measurements, a light portable data-logger (Physilog®, BioAGM, CH) with 8 MB memory cards and a sampling rate of 200 Hz and 12-bit resolution of A/D was carried by the subject. With this configuration, it was possible to continuously record for up to 1 h and 20 min.

To extend the period of recording and to make the system easier to use by the patients, in the second study we used a newly designed system called *Autonomous Sensing Unit Recorder* (ASUR). Each ASUR unit integrated two gyroscopes, data-logger, battery and flash memory in a single, independent small package See Fig. 1(b). By eliminating the external data-logger and interconnecting cables, this new system could be carried by the patients more comfortably for extended hours of measurements. Each unit weighted 50 g (including battery) and measured $61 \times 44 \times 19$ mm ($\mathrm{W} \times \mathrm{H} \times \mathrm{D}$). Each unit included 64 MB of flash memory and a rechargeable battery with a capacity of 1280 mAh. The units had a sampling rate of 200 Hz and could continuously record up to 14 hr. Instead of a three-dimensional (3-D) configuration, a two-dimensional configuration of the gyroscopes was used in order to minimize energy consumption as the gyroscopes were the most energy consuming parts of this circuit (30 mW for each gyroscope). Each unit included two miniature gyroscopes in the roll and pitch direction (Analog device, ADXRS300). Similar to the previous system, the range of the sensors after calibration was

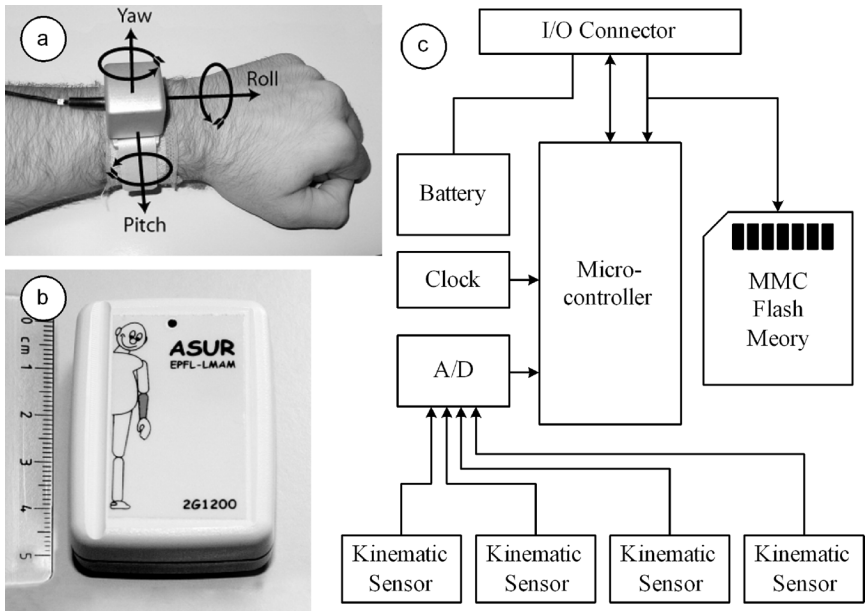

Fig. 1. (a) The 3-D gyroscopic sensor used in the first study. (b) ASUR units used in the second study. (c) ASUR units integrate kinematic sensors and data-logger. Each unit can have up to four kinematic sensors (Only two gyroscopes were used in this study).

$\pm 1200\,^{\circ}/\mathrm{s}$. The units were attached on the forearms of the subjects, using elastic bands. At the end of the measurement, recorded signals were transferred to a personal computer for the analysis.

To ensure that the changes in the architecture of the system between the first and second study did not affect the outcomes of the analysis algorithm, we performed a control experiment using both systems simultaneously on four PD patients (two males) with an age between 55 and 69 years. In this experiment, patients followed the 45-min protocol of the first study twice, once with Stim ON and once with Stim OFF, while both systems were recording their movements.

C. Detection and Quantification of Tremor

Tremor in PD is generally characterized by rhythmic movements at a frequency of approximately 4–6 Hz, which predominantly occurs at rest but also can be present during action [24]. To detect tremor, the angular velocity signals from each axis of the sensors were analyzed separately. Fig. 2(a) shows the block diagram of the method. The first step was to remove the drift of the signals using a very fast (i.e., low computation time) first-degree infinite impulse response (IIR) filter with a cutoff frequency of $f_c \approx 0.25$ Hz in the software. To detect tremors, the signal was then divided into 3-s windows. Since PD tremor normally has a duration in the range of at least a few seconds once it begins, selecting a very short window size (e.g., less than 1 s) could dramatically increase false-positives (FPs). Such a short window period would also make it difficult to compare the outcomes to the video recording, as the analysis of the video does not have a similar accuracy. On the other hand, selecting a very long window (e.g., more than 10 s) would reduce the resolution of the tremor detection and also could reduce the accuracy in the case that a short period of rest tremor followed a long period of intensive voluntary activity.

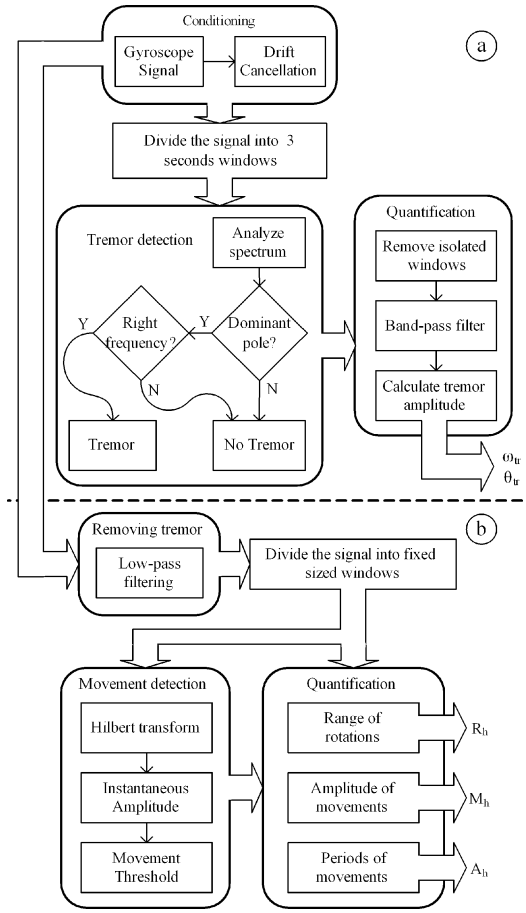

Fig. 2. The flowchart of the methods. (a) The tremor detection and quantification method. (b) Quantification of the bradykinesia.

For each window the frequency spectrum of the signal was estimated using an all-pole sixth-degree autoregressive model by

using the Burg method [25]. The amplitudes of the poles in this model are between zero and one. The pole with the highest amplitude was selected as the dominant pole. If its frequency was between 3.5 and 7.5 Hz and its amplitude was higher than 0.92 (or 92% of the maximum), the window was reported as tremor. We tried different values for the amplitude threshold. Based on our dataset and the observer's ability to detect visible tremor on the video, the value of 0.92 had the best result. With the selected window of 3 s, we observed that on rare occasions during the periods that subject had no tremor, especially while subject performed certain rhythmic activities (like brushing the teeth), some isolated windows (i.e., with no detected tremor before or after them) were misclassified as tremor. To reduce these FPs, the algorithm identified these isolated windows and removed them from the output by marking them as no-tremor. This step reduced FPs at the risk of potentially reducing true-positives (TPs). However, as extremely short periods of PD tremor are unusual, we found that benefits of this method outweighed its drawbacks.

The amplitude of the detected tremors in degrees/s (ω_{tr}) was calculated by taking the root mean square (RMS) value of the angular velocity signal from the gyroscope after filtering using a bandpass 280 degree finite impulse response (FIR) filter with cutoff frequencies of 3.5 and 7.5 Hz. The filter was used to reduce the effect of movements of the upper extremities with frequencies outside of the range of the frequencies associated with PD tremor. (Initially, a short IIR filter with similar cutoff frequency was considered; however, we found out that this filter introduced too much distortion in the signal so we decided to use a longer FIR filter with lower distortion). The amplitude of the tremor of the pitch, roll, and the yaw axes were called ω_p, ω_r, and ω_y, respectively. Considering that the sensitive axes of gyroscopes were perpendicular, the amplitude of a combination of two or all three axes could be calculated by

$$\omega_{pr} = \sqrt{\omega_p^2 + \omega_r^2} \tag{1}$$

$$\omega_{pry} = \sqrt{\omega_p^2 + \omega_r^2 + \omega_y^2} \tag{2}$$

where ω_{pr} is the combinations of the two axes of pitch and roll and ω_{pry} stands for the combination of all three axes. To calculate the amplitude of the tremor in degrees (θ_{tr}), the filtered signal was integrated over time and its RMS value was calculated. With change of the symbols, the same formulas were used for the angles of combinations of axes.

The amplitude of the signal measured by a gyroscope is not dependant on the position of the sensor on the forearm segment. However, the amplitude is influenced if the main affected limb is not the forearm (often hands or fingers in PD). In such situations sensors typically measure a reduced movement depending on the number and structure of the joints and segments between the source of the tremor and the forearm segment.

D. Quantification of Bradykinesia

The method to quantify bradykinesia included two steps: identifying periods of movement and calculating parameters related to the movements see Fig. 2(b). The method was based on estimation of related parameters for each consecutive fixed period of time. In the first study, the parameters related to bradykinesia were calculated for the whole period of measurement (approximately 45 min). In the second study, the periods of the recording were divided into a series of fixed sized windows and the parameters were calculated for each window. Several window sizes (45, 30, 15, 10, and 5 min) were considered and the effect of selection of window size on the ability of the algorithm to follow the fluctuations of the bradykinesia was studied.

To identify periods of movements, after canceling the drift of the gyroscope (as described in the previous section) an eighth-degree low-pass IIR filter with a cutoff frequency of $f_c \approx 3.5\,\mathrm{Hz}$ was applied to remove the effects of tremor. To find the *instantaneous amplitude* of the low-pass filtered signal of the gyroscope $g_{lp}(t)$, an analytical signal was constructed [26]

$$a(t) = g_{lp}(t) + i\,\overline{g_{lp}}(t) \tag{3}$$

where $\overline{g_{lp}}(t)$ represents the Hilbert transform of $g_{lp}(t)$. The instantaneous amplitude and phase of the $g_{lp}(t)$ are the amplitude and phase of $a(t)$.

Those periods of time that the instantaneous amplitude of the gyroscope signal was more than $5\,^\circ/\mathrm{s}$ were defined as the periods of movements of the upper extremities. Movements of the upper extremities slower than this threshold were hardly visible in practice and were very close to the noise or artifacts in our recorded signals. To quantify the movements, three aspects of the movements were considered: the average speed, periods and the average range of the movements. As such, the average value of three parameters were calculated for each time window: The *Mobility of hand*, M_h, standing for the average angular velocity of the upper extremity, defined as the RMS of the $g_{lp}(t)$ during the periods of movements. *Activity of the hand* or A_h was defined as the percentage of time in a selected time window that the upper extremity was moving (i.e., when $|a(t)|$ was more than the selected threshold). The third calculated parameter was the average *Range of rotation of hand*, or R_h. To calculate R_h, the range of the rotations of upper extremities (angles) were calculated by integration of the $g_{lp}(t)$ during the period of the movements.

E. Statistical Analysis and Comparison to UPDRS

We evaluated the sensitivity and specificity of the tremor detection method in comparison to video recordings since currently no alternative instrumented method could be used as a gold standard. During the first study, where subjects performed the 45-min protocol, movements of the upper extremities were recorded by video. The video was synchronized to the recorded data using a recorded audio cue (Physilog data-logger made a beep at the start and end of recording). For each PD patient n ($n = 1 \ldots 10$) the period of TP, TP_n, was defined as the period of the tremor that was both visible in the video and correctly identified by the algorithm: A reviewer carefully examined the recordings and identified the start and end of each period i of the visible tremors of the upper extremities of each patient, independent of their amplitude or direction. These periods were called $Ttr_{n,i}$. Three vectors $W_{n,a,j}$ were considered, where $a \in \{p, r, y\}$ stands for the axes of the sensor and j represents the window number (for a measurement of duration of $Trec_n$ and windows of the duration of d, j could have a value

between 1 and $Trec_n/d$). If more than half of a window j was included in *any* $Ttr_{n,i}$, the corresponding $W_{n,a,j}$ was assigned a value of one; otherwise it was assigned a value of zero. For a combination of two axes, for example roll and yaw axes, the corresponding $W_{n,r+y,j}$ was be defined as

$$W_{n,r+y,j} = \begin{cases} 1, & \text{if } W_{n,r,j} = 1 \text{ or } W_{n,y,j} = 1 \\ 0, & \text{otherwise} \end{cases} \quad (4)$$

and for the combination of all three axes, $W_{n,r+p+y,j}$ could be defined as

$$W_{n,r+p+y,j} = \begin{cases} 1, & \text{if any } W_{n,a,j} = 1,\ a \in \{p,r,y\} \\ 0, & \text{otherwise} \end{cases} . \quad (5)$$

For each patient n, the sensitivity of the tremor detection for each axis a of the sensor ($\mathrm{Sens}_{n,a}$) could be calculated by

$$\mathrm{Sens}_{n,a} = \frac{\mathrm{TP}_{n,a}}{\sum_i Ttr_{n,i}} = \frac{\sum_j d\, W_{n,a,j}}{\sum_i Ttr_{n,i}}. \quad (6)$$

Although it would be possible to calculate FPs and specificity with similar steps, such an approach would not be very accurate: Obtaining optimal images of the upper extremities from a distance was not always possible and uncertainties could arise if upper extremities were not clearly visible in some sections of the video while the algorithm detected a period of tremor. To avoid this problem [17] used the detected periods of tremor in a group of patients with Alzheimer's disease that had no sign of tremor to assess the FP rate. In our study, we used the data of healthy control subjects ($m = 1 \ldots 10$) that by definition had no tremor: Any period of detected tremor was used a FP. For the control group, the value of $W_{m,a,j}$ corresponding to all windows that algorithm detected any tremor was assigned a value of one. A value of zero was assigned to all other $W_{m,a,j}$ s. The W_m vectors corresponding to the combination of axes were calculated similar to (4) and (5). The specificity in detection of the tremor for control subject m ($\mathrm{Spec}_{m,a}$) was then

$$\mathrm{Spec}_{m,a} = \frac{\mathrm{Trec}_m - \mathrm{FP}_{m,a}}{\mathrm{Trec}_m} = \frac{\mathrm{Trec}_m - \sum_j d\, W_{m,a,j}}{\mathrm{Trec}_m}. \quad (7)$$

Finally, overall sensitivity and specificity of each axis a where calculated by:

$$\mathrm{Sens}_{\mathrm{overall},a} = \frac{\sum_n \mathrm{TP}_{n,a}}{\sum_n \sum_i Ttr_{n,i}} \quad (8)$$

$$\mathrm{Spec}_{\mathrm{overall},a} = \frac{\sum_m (\mathrm{Trec}_m - \mathrm{FP}_{m,a})}{\sum_m \mathrm{Trec}_m}. \quad (9)$$

This approach (instead of simply taking the average) reduced the effect of very low prevalence of tremor in some patients, while including all of them in the calculation of the overall values.

To study the correlations between UPDRS and the outcomes of the algorithms, two UPDRS subscores were used. A subscore of UPDRS motor section from items 20 and 21 (rest tremor and action tremor) was used to evaluate the results of the tremor quantification. For bradykinesia, the summation of the subscores 23, 24, and 25 (finger tapping, hand movement, rapid alternate movements of hand) was used. When comparing the tremor subscore of UPDRS and outcomes of the algorithm, the logarithms of the parameters were considered. As it was possible that tremors would stop for some periods of time, where an amplitude of zero was reported, instead of directly taking logarithm of the amplitudes, $\log_{10}(1+\omega_{tr})$ and $\log_{10}(1+\theta_{tr})$ were used in calculations.

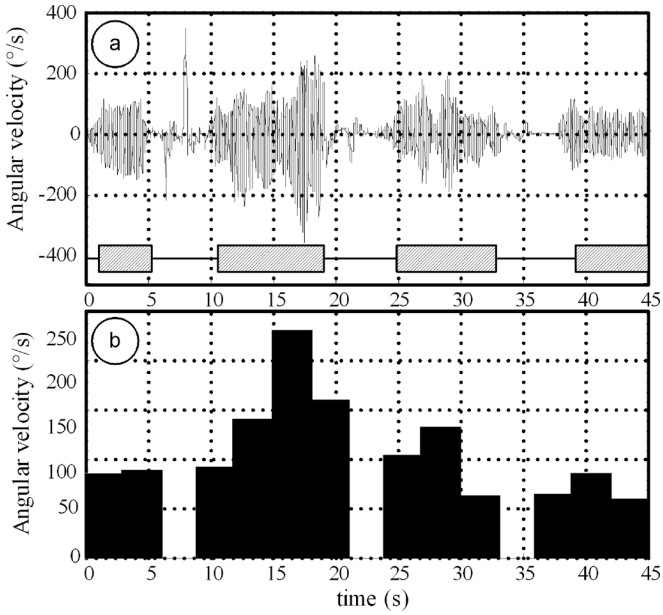

Fig. 3. A sample of the output of the tremor detection algorithm. (a) Raw signal from the gyroscope (roll axis). The boxes with hatched patterns are periods of tremor detected by visual observation (b) Output of the algorithm. Black bars are detected periods of tremor and the height of the bar shows the amplitude of the tremor.

During the second study, a patient's Parkinsonian symptoms were assessed at least once per hour, using UPDRS. To study the correlation between UPDRS and the estimated parameters related to bradykinesia and tremor, the last UPDRS during the Stim OFF was selected (typically, 3 h after turning the stimulator off and just before turning it on again). The values of the estimated parameters during time windows of 5, 10, 15, 30, and 45 min just before this UPDRS test were used to study correlations.

Wilcoxon's nonparametric rank-sum test was used to compare different parameters between the normal subjects and PD patients. To compare between the Stim ON and Stim OFF states, Wilcoxon's nonparametric paired test, sign-rank test was used. The correlation between UPDRS subscores and different parameters was estimated using Pearson's correlation. For all statistical tests, p -values above 0.05 were considered as nonsignificant.

III. Results

A. First Study: Subjects Following the Test Protocol

For each 3–s period the tremor detection algorithm provided two outputs: presence of tremor and the amplitude of the tremor. Fig. 3 shows a typical outcome. The periods of the tremor reported by video observations are also presented. Table II shows the results of estimated sensitivity and specificity of the tremor detection algorithm, for each axis and each possible combination of axes of the gyroscopes. Among the three axes of the sensor, roll axes showed the highest sensitivity

TABLE II
PERFORMANCE OF THE TREMOR DETECTION ALGORITHM COMPARING TO THE VIDEO REFERENCE. THE MEAN VALUE AND *OVERALL* VALUES ARE ALSO PRESENTED

	Subject	Pitch	Roll	Yaw	Pitch+Roll	Roll+Yaw	Pitch+Yaw	All axes	Prevalence
Sensitivity	Patient 1	68.3%	81.8%	71.1%	88.4%	88.8%	83.3%	91.1%	79.6%
	Patient 2	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	10.1%
	Patient 3	49.3%	52.3%	52.3%	81.6%	83.9%	70.0%	98.5%	12.8%
	Patient 4	56.1%	80.3%	45.0%	94.8%	86.6%	71.6%	99.6%	23.7%
	Patient 5	59.0%	0.0%	73.7%	59.0%	73.7%	100.0%	100.0%	1.3%
	Patient 6	45.9%	86.7%	70.4%	88.8%	90.9%	75.0%	92.2%	58.5%
	Patient 7	66.8%	67.4%	68.6%	85.5%	86.7%	89.1%	96.3%	26.6%
	Patient 8	66.3%	70.3%	76.5%	87.0%	95.6%	87.6%	100.0%	31.3%
	Patient 9	88.5%	100.0%	88.5%	100.0%	100.0%	88.5%	100.0%	1.4%
	Patient 10	81.7%	99.1%	45.1%	100.0%	100.0%	87.6%	100.0%	32.4%
	Average	68.2%	73.8%	69.1%	88.5%	90.6%	85.3%	97.8%	27.8%
	Overall	65.2%	82.0%	67.6%	93.4%	94.3%	84.1%	99.5%	31.4%
Specificity	Control 1	99.8%	99.7%	99.4%	99.5%	99.1%	99.1%	98.8%	-
	Control 2	98.5%	98.0%	98.3%	96.5%	96.3%	96.8%	94.8%	-
	Control 3	99.3%	99.5%	99.8%	98.7%	99.3%	99.1%	98.5%	-
	Control 4	95.8%	98.2%	97.5%	94.0%	95.7%	93.3%	91.5%	-
	Control 5	94.9%	97.3%	95.0%	92.2%	92.3%	89.9%	87.2%	-
	Control 6	96.9%	97.2%	96.4%	94.1%	93.5%	93.3%	90.4%	-
	Control 7	100.0%	98.7%	100.0%	98.7%	98.7%	100.0%	98.7%	-
	Control 8	100.0%	97.4%	99.8%	97.4%	97.2%	99.8%	97.2%	-
	Control 9	97.0%	96.9%	96.4%	94.0%	93.4%	93.5%	90.4%	-
	Control 10	96.2%	98.7%	96.5%	94.9%	95.2%	92.7%	91.4%	-
	Average	97.8%	98.1%	97.9%	96.0%	96.1%	95.8%	93.9%	-
	Overall	97.9%	98.2%	98.0%	96.2%	96.2%	95.9%	94.2%	-

TABLE III
BRADYKINESIA-RELATED PARAMETERS FOR EACH AXIS OF THE SENSORS. THE VALUES ARE SHOWN IN $\mathrm{Mean} \pm \mathrm{STD}$ FORMAT. THE p-VALUES ARE THE RESULTS OF HYPOTHESIS TEST OF EQUIVALENCE OF THE MEAN OF THE PARAMETERS IN DIFFERENT GROUPS

Param.	Axis	OFF	ON	Control	OFF v.s. Control	ON v.s. Control	ON v.s. OFF
M_h (°/s)	Pitch	26.1±8.0	40.8±12.0	54.5±8.4	0.0002	0.0036	0.0020
	Roll	35.8±9.1	56.9±10.5	74.9±10.7	0.0002	0.0028	0.0020
	Yaw	31.8±8.3	51.3±12.2	79.5±11.6	0.0002	0.0006	0.0020
R_h (°)	Pitch	3.4±1.4	4.9±1.5	6.2±1.0	0.0022	N.S.	0.0039
	Roll	3.4±1.1	5.2±1.2	6.5±1.1	0.0003	0.0140	0.0020
	Yaw	4.3±1.6	6.6±1.9	9.6±2.5	0.0002	0.0113	0.0020
A_h (%)	Pitch	43.1±6.5	44.8±6.5	49.0±5.3	N.S.	N.S.	N.S.
	Roll	50.6±10.0	49.6±8.5	53.9±5.6	N.S.	N.S.	N.S.
	Yaw	43.9±8.1	44.9±7.6	48.7±3.8	N.S.	N.S.	N.S.

TABLE IV
CORRELATION BETWEEN UPDRS TREMOR SUBSCORE AND THE PARAMETERS CALCULATED BY THE ALGORITHM. PARTIAL CORRELATION REMOVED THE EFFECT OF ON/OFF FACTOR

Axis	Pearson correlation				Partial Correlation			
	ω_{tr}		θ_{tr}		ω_{tr}		θ_{tr}	
	r	p	r	p	r	p	r	p
Pitch	0.84	0.0001	0.85	0.0001	0.78	0.0001	0.83	0.0001
Roll	0.87	0.0001	0.86	0.0001	0.81	0.0001	0.84	0.0001
Yaw	0.81	0.0001	0.82	0.0001	0.74	0.0003	0.78	0.0001
Pitch + Roll	0.87	0.0001	0.87	0.0001	0.81	0.0001	0.84	0.0001
Roll + Yaw	0.86	0.0001	0.86	0.0001	0.81	0.0001	0.84	0.0001
Pitch + Yaw	0.82	0.0001	0.87	0.0001	0.76	0.0001	0.85	0.0001
All axes	0.86	0.0001	0.86	0.0001	0.81	0.0001	0.84	0.0001

and specificity. When combining the outputs of two axes, the optimal combination always included the roll axis except for the Patients 5 and 7.

In the first study, for each subject an overall value was calculated over the entire period of measurement for each of the three bradykinesia related parameters (see Table III). The results of the hypothesis test for the equivalence of the mean between the three groups of Stim OFF, Stim ON an controls show that the M_h and R_h (but not A_h) had significant differences (except for one case) between the three groups. The correlation between the UPDRS tremor subscore and logarithm of the tremor amplitude reported by the algorithm was studied. As each PD patient performed the test both in ON and OFF state, a partial correlation coefficient was also performed to remove the effect of ON/OFF factor (see Table IV). Table V shows the results of the correlation study between UPDRS bradykinesia subscore and

TABLE V
CORRELATION BETWEEN UPDRS TREMOR SUBSCORE AND THE PARAMETERS CALCULATED BY THE ALGORITHM. PARTIAL CORRELATION WAS PERFORMED TO REMOVE THE EFFECT OF ON/OFF FACTOR

Parameter	Axis	Pearson correlation		Partial Correlation	
		r	p	r	p
M_h	Pitch	-0.54	0.0131	-0.25	N.S.
	Roll	-0.83	0.0001	-0.68	0.0014
	Yaw	-0.76	0.0001	-0.57	0.0105
R_h	Pitch	-0.47	0.0362	-0.32	N.S.
	Roll	-0.70	0.0006	-0.48	0.0380
	Yaw	-0.53	0.0163	-0.44	N.S.
A_h	Pitch	-0.55	0.0123	-0.59	0.0073
	Roll	-0.42	N.S.	-0.53	0.0186
	Yaw	-0.45	0.0466	-0.53	0.0203

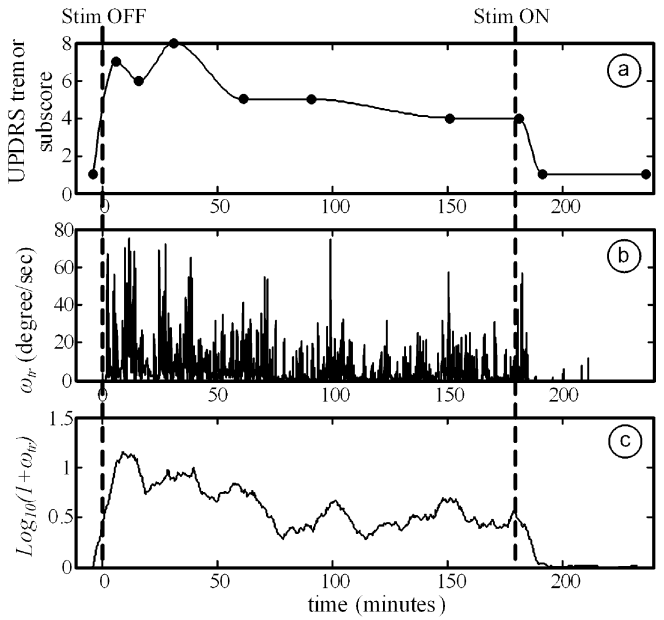

Fig. 4. (a) Black circles show the tremor subscore of each UPDRS test of a typical patient. (b) Detected tremor in roll axis. Every 3 s, a bar representing the amplitude of the tremor was drawn. (c) Logarithm of the amplitude of the tremor after running a 10-min moving average window.

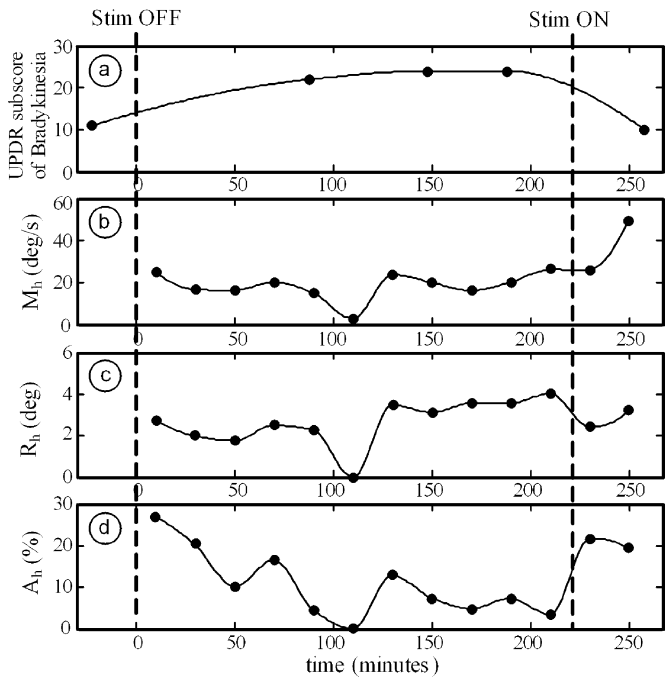

Fig. 5. (a) Black circles show bradykinesia subscores of each UPDRS test of a typical PD patient. b, c, d) M_h, R_h and A_h estimated for each 20-min window on the roll axis of the sensor.

the bradykinesia related parameters (M_h, R_h, and A_h) where significant correlations in some case were obtained.

B. Second Study: Monitoring Free Moving Patients

Fig. 4(b) shows the outcome of the tremor algorithm during monitoring of a PD patient for almost 4 hr. Recording was started when the stimulators was turned off ($t = 0$ min) and continued till 1 h after they turned on again. During this period, the patient performed several UPDRS tests. The values of the UPDRS subscore related to the tremor of hands are shown in Fig. 4(a). As the resolution of the tremor detection algorithm was much higher than resolution of the UPDRS tests, a moving average window was run over the results see Fig. 4(c). It can be observed that the results parallel the changes of the UPDRS tremor subscores. Fig. 5 shows a typical graph of the outcomes of the bradykinesia quantification method. Patient started in ON state. At $t = 0$ min stimulator was turned off and at $t = 220$ min it was turn ON again. Fig. 5(a) shows the changes in the bradykinesia subscore of the UPDRS during this period. Fig. 5(b)–(d) shows the M_h, A_h, and R_h estimated with a window size of 20 min. The first UPDRS test was done just before the beginning of the recording and the last one just after the end of the recording. As the patient became more bradykinetic, the speed of his movements decreased and the level of activity diminished. At approximately $t = 110$ min, the subject was almost completely inactive ($A_h = 0$). By turning the stimulator ON again, the average mobility of the upper extremities and the level of activity increased again.

The effect of the selection of the size of window size on the correlation between UPDRS subscores and tremor and bradykinesia related parameters is illustrated in Fig. 6 where window size was changed from 5 min to 45 min. Fig. 6(a) shows the coefficient of the correlation between the UPDRS bradykinesia subscore and the three bradykinesia related parameters estimated for all patients. Similarly, Fig. 6(b) shows the coefficient of correlation between UPDRS tremor subscore and the estimated amplitude of the tremor.

IV. Conclusion and Discussion

A. Measurement Systems

The measurement system used in the second study had several advantages over the first one: the gyroscopes used in the first study where highly sensitive to shocks and we had to recalibrate them after every few measurements, while those used in ASUR units did not have this problem. With ASUR units also it was possible to perform much longer recordings. Although the ASUR units were slightly bigger and heavier than the sensors used in the first study, we had a very positive feed-back from the patients regarding the ease of use of the system during normal activities, mainly due to elimination of the interconnecting cables. Moreover, the total weight of the ASUR setup was lower: 100 g for two ASUR units versus 400 g for the two sensors, data-logger, cables and connectors. Finally, despite the differences between size and weight and type of the gyroscopes of the two systems, by comparing the outcomes of the tremor and bradykinesia analysis algorithm in the control experiment, we did not find any significant differences.

B. Detection and Quantification of Tremor and Bradykinesia

We have found a good overall sensitivity and specificity (99.5% and 94.2%, respectively) for tremor detection using a 3-D gyroscope (see Table II). The high sensitivity of the algorithm may be partially due to the fact that it may be difficult to identify low amplitude tremor in the video, a problem also

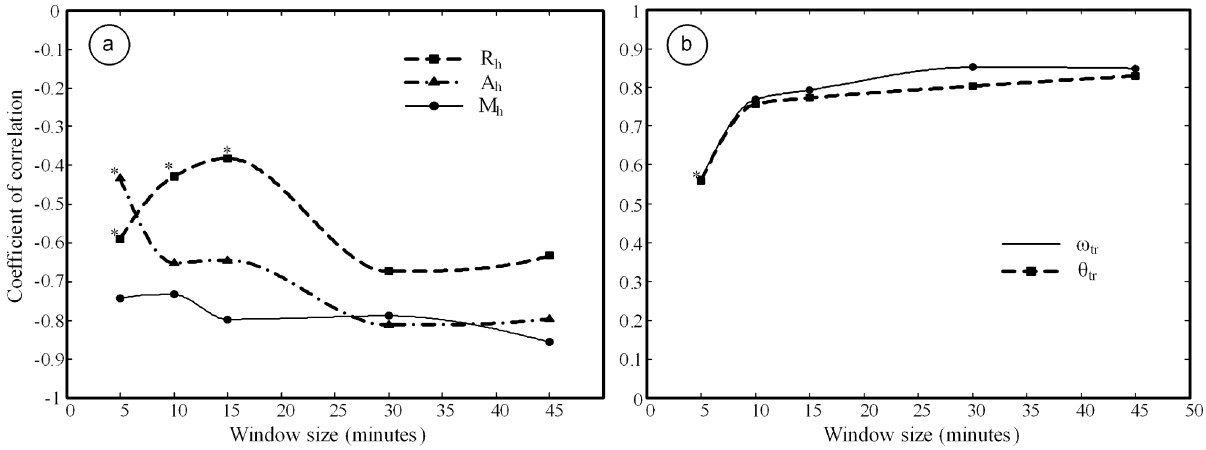

Fig. 6. (a) The effect of selection of the time window on the correlation between the UPDRS bradykinesia subscore and the outcomes. (b) The correlation between UPDRS tremor subscore and the calculated average amplitude of the tremor. The symbol * shows where correlation was not significant (i.e., $p > 0.05$).

reported by [17]. By combining the outcomes of the sensitive axes in two or three axes groups, the sensitivity was increased but specificity reduced. A reduction in specificity may have resulted from summation of the independent FPs of each single axis. Most FPs resulted from brushing the teeth and voluntary rhythmic oscillations of the upper extremities. The results suggest that even in the presence of this type of activities, the sensitivity of the method is very high.

We found a high correlation between the parameters estimated by our method and UPDRS tremor subscore (see Table IV). For example the estimated amplitude of angular velocity of tremor (ω_{tr}) in the roll axis showed a correlation with $r = 0.87$ ($p < 0.001$) with the UPDRS subscore. By removing the effect of ON/OFF factor (i.e., taking the partial correlation, see Table IV), the correlation reduced only marginally to $r = 0.81$ suggesting a high correlation between the clinical results and outcomes of the system.

We found that M_h and R_h measured in any of the axes of the sensor showed significant differences between PD patients during Stim OFF period and controls ($p < 0.002$, see Table III). At the same time, we found significant differences in these two parameters between Stim ON and Stim OFF states ($p < 0.004$). While STN DBS showed a significant improvement of these parameters, in almost all cases (except for the R_h of the pitch axis) the PD patients remained significantly different from the healthy control subjects. We also found highly significant correlation between these parameters (M_h and R_h) and UPDRS bradykinesia subscore (see Table V). However, using statistical analysis with partial correlation, we found that by removing the effect of ON/OFF factor from our data, only M_h was able to maintain high and significant correlation with the UPDRS ($r = -0.83$ and $r = -0.68$ in roll axis for normal and partial correlation). Bradykinesia refers to the slowness of the ongoing movements. As a gyroscope directly measures the angular velocity of movements and all body movements are in fact rotations around joints, these results are not unexpected. The third parameter calculated by our algorithm, A_h, was not significantly different between the three groups. This result was somewhat expected in this study as all subjects followed the same protocol of timed activities and as such, they had the same level of activity.

C. Long-Term Measurements

We evaluated the sensitivity and specificity of the method in the first study while subjects performed a protocol of typical daily activities. However, as continuous video recording for up to 5 h of free moving PD patients including clear view of their upper extremities all the time was not possible, we could not evaluate sensitivity and specificity in the second study. Instead we only compared the results to the UPDRS score of the patients to see how well the outcomes of the method could follow the changes in the state of tremor score of the patients. Results of the first study showed that the quantific parameters related to tremor and bradykinesia had a high correlation with the UPDRS subscores. Those results were obtained using a time window of 45 min. To find out if the same correlation exists with smaller windows and in general to study the effect of selection of the time window on correlations, we used the data from our second study, where subjects were free to perform any activity they preferred. With a window size of 45 min, the correlations of most of the estimated parameters to their respective UPDRS subscore were similar to those obtained in the first study (see Fig. 6). This confirms the consistency of the results obtained during the test protocol of the first study. As the windows size decreased, in general the correlations also started to decrease. Only with the smallest window sizes in some cases the correlation was no longer significant.

Fig. 6(b) shows the effect of window size on correlation between the estimated tremor amplitude and UPDRS. By averaging the reported amplitudes in the selected windows, a significant and high correlation to UPDRS was obtained for all window sizes. Only for the smallest window sizes (5 min) the correlation lost its significance. One explanation could be that the tremor of PD patients could momentarily stop due to voluntary activities. On such occasions, the mean value of the amplitude of the tremor could reduce significantly. With short window sizes the average tremor amplitude can vary a lot from one window to another which in effect, by assuming slow variations of Parkinsonian state of the patient, could reduces the correlation.

Among the parameters related to bradykinesia, M_h showed the highest correlation to UPDRS Fig. 6(a), even with the

smallest window size of 5 min ($r = -0.74$, $p < 0.01$). In the first, controlled study A_h did not show any correlation to UPDRS while in the second study, this parameter showed a high and significant correlation to UPDRS with larger window sizes ($r = -0.81$ and $r = -0.80$ for 30- and 40-min windows, $p < 0.003$). Without asking patients to do any specific set of tasks, probably patients with higher UPDRS scores tended to have less activity. As such, rather than bradykinesia, A_h could be more related to other symptoms of PD, i.e., akinesia and hypokinesia which refer to the difficulty to initiate movement and reduction of movement amplitude, respectively. As A_h represents the intensity of the activities during a certain period of time, we expect this parameter to be a good estimator of hypokinesia. Bradykinesia and hypokinesia are intrinsically related and in many cases present at the same time in PD patients. This represents the probable basis for A_h showing some correlation with the UPDRS bradykinesia subscore. However, finding an objective relationship between hypokinesia and A_h will need further study.

D. Comparison to Other Systems

Several studies have addressed the problem of using kinematics sensors for the ambulatory detection and quantification of tremor [7], [15], [17]. Hoff *et al.* [15] reported a good sensitivity and specificity (82% and 93%, respectively) comparing to video recordings. They also reported significant correlation between the duration and intensity of tremor calculated by their method and UPDRS tremor subscores in sitting and standing body postures. [17] also reported a good sensitivity (between 0% and 5.9% FPs) in detection of tremor during daily activities. Compared to these studies our method shows an even higher sensitivity and specificity (99.5% and 94.2%, respectively) and showed correlations to UPDRS even in free moving patients. Moreover, the reduction of the number of sensors from three to two (like in the ASUR units) reduced the sensitivity by only a small margin (see Table II).

There are only a few studies of bradykinesia using quantitative or ambulatory systems. [14] reported a system based on actigraphy to study the effects of drugs on hypokinesia and to determine hypokinetic periods during a day. Dunnewold [8] used a 3-D accelerometer to measure the accelerations on the wrist and compared them to movement time and tap rate scores [27]. They found significant differences between healthy controls and PD patients; however, they found moderate or no correlation to UPDRS.

E. Conclusion

We have presented a new ambulatory monitoring system to simultaneously provide objective measures of tremor and bradykinesia in PD patients. The system is simple to use and does not hinder the patients, as it consists of only two small and light (50 g) sensing units (ASUR units) attached on each forearm while offering continuous, long-term monitoring up to 14 hr. We found a high sensitivity and specificity in detection of tremor while subjects were performing typical daily activities. Also a high correlation between tremor and bradykinesia related parameters and UPDRS subscores were found. Finally, our study has shown the possibility of evaluation the bradykinesia during short intervals (as short as 5 min) while the patient performs his daily activity.

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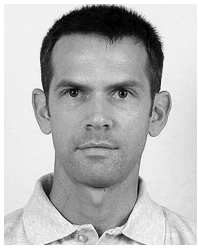

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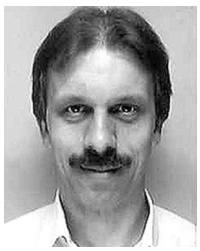

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