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Ocular Microtremor Measurement,
Characterization & Analysis

2010

by

Mohammed Ali Al-Kalbani

A thesis submitted in conformity with the
requirements for the degree of Doctor of
Philosophy

Clinical Medicine

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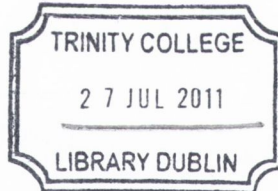
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Summary

Ocular Microtremor (OMT) is a high frequency tremor of the eye present in all normal subjects even if the eye is apparently still. It is one of the fixational eye movements. Changes in the OMT frequency and pattern have been observed in a number of clinical conditions involving the brainstem. The OMT amplitude is in the range from 2.5 arcsec up to 33 arcsec with a mean dominant frequency of around 85 Hz.

Nearly all quantitative clinical investigation of OMT is carried out by the piezoelectric measurement technique (PZT system) which is based on the voltage change produced by a piezoelectric element in contact with the scleral surface of the eye. Current PZT systems suffer from a number of limitations. In this thesis the PZT system was modified to address limitations of the system regarding variable loading of the eye with the PZT probe, probe usability and acceptability and signal distortion due to the low dynamic range of the system. The newly developed PZT system has been tested using an OMT simulator and a number of clinical investigations were carried using it in both normal subjects and patients.

One of the difficulties in OMT signal processing is that the other fixational eye movements contaminate the OMT records. Current methods used to extract OMT signal from recorded eye movement traces result in some information loss in the OMT pattern. The signal recovery problem in OMT measurement appears to lend itself well to the application of a wavelet denoising method. In this thesis we examine the performance of the current OMT signal recovery methods. A wavelet denoising method is employed here for the first time for the recovery of OMT and its performance is compared to the other techniques reported in the literature.

OMT pattern analysis is one approach to differentiating between normal subjects and patients cases in clinical investigations. A number of papers show the clinical significance of looking at the 'bursts' and 'baseline' features of the OMT signal, but analysis to date

has relied on visual inspection. The thesis introduces an automated approach of burst/baseline identification based on a time-varying filter using the Gabor transform.

The work also includes a fundamental examination of the nature of the OMT signal and if assumptions of stationarity and/or linearity are valid. This work will help in the development of diagnostic markers of OMT, in the choice of appropriate signal analysis methods and the development of OMT models. This includes a comprehensive assessment of a range of OMT clinical markers, including some newly introduced ones in separating normal OMT records from abnormal OMT, particularly stroke patients. While many markers have been explored in the literature they have not been systematically compared in this way before.

Due to the fact PZT system is an invasive approach, a non contacting method is more desirable in clinical investigation. One potential non-contacting measurement technique is laser speckle metrology. To develop speckle methods for OMT measurement, fundamental investigation is required into the phenomenon of 'biospeckle', seen where laser light is incident on a biological target. This thesis presents a platform for the investigation of speckle using a high speed CCD camera and demonstrates that biospeckle need not rule out the use of speckle methods in OMT measurement. The laser speckle correlation technique is demonstrated to have potential in OMT measurement using an OMT simulator and a realistic in vitro biological target.

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Preface

Ocular Microtremor (OMT) is one of the three fixational eye movements present even when the eyes are apparently still. The other fixational movements are drift and microsaccades. OMT is the fastest of these movements and has the smallest amplitude. OMT causes eye displacement of the order of a micron with a frequency of around 85Hz for normal subjects.

The potential for OMT to have some role in vision was considered in the dynamic theory of vision (30), which suggested that the OMT vibration sweeps images on the retina over several receptors, improving the visual acuity. More recent findings about the OMT amplitude contradict this theory as the image shifts due to OMT was found to be only of the order of one photo-receptor (15).

Most clinical studies in OMT did not focus on its role in vision, but rather as a clinical indicator of neurological function. Coakley demonstrated a number of clinical cases where changes in OMT reflect changes in the condition of the brainstem, particularly in patients in coma (31). This was followed by investigations carried by other authors to demonstrate the value of OMT as a clinical indicator for different clinical conditions, such as multiple sclerosis (34), monitoring depth of anesthesia (36), idiopathic Parkinson's disease (37) and acute stroke (35).

Most clinical investigation in OMT has been carried out using the piezoelectric probe measurement method (PZT system) first introduced by Bengi and Thomas in 1968 (38). The PZT probe is sensitive to all fixational eye movements (OMT, microsaccades and drift). In current PZT system design low pass filtering is used to remove microsaccades from the PZT probe signal output prior to digitization. As the microsaccades have higher amplitude than OMT and the frequencies of both overlap, filtering causes a distortion of the signal due to the ringing response of the filters and microsaccades can cause signal saturation. A second limitation of the PZT system is that the current method of advancing

the piezoelectric probe to the eye requires a level of high skill by the operator and introduces a variation in the OMT amplitude measurement. Finally the probe tip that comes in contact with eye is not made from a biocompatible material, which would not be in line with current design practice. Part of this thesis describes, implements and validates improvements to the current PZT system in overcoming these three limitations.

It is important to consider signal stationarity and linearity when selecting a suitable signal analysis method or modeling method. For example when analyzing a stationary signal use of the fast Fourier transform may be sufficient to estimate frequency content while with a nonstationary signal it may be more appropriate to monitor the change of signal frequency with time (such as joint time–frequency analysis). Also nonlinear measures such as entropy could be more suitable in analyzing a nonlinear signal. Many biomedical signals are found to be nonstationary and/or nonlinear. There has been no report in the literature investigating OMT stationarity and linearity assumptions. Part of this thesis investigates those two assumptions.

As explained earlier the PZT probe senses the full fixational eye movement, OMT, drift and microsaccades. Current methods in recovering the OMT signal are based on basic filtering or on analyzing segments free of microsaccades. There is no report in the literature about examining the performance of the current OMT recovery methods. Part of this thesis introduces new OMT recovery methods and compares them against performance of the current methods.

Current methods of analyzing the OMT signal are based on OMT feature extraction (bursts and baseline) and on the dominant frequency peak changes between the different clinical conditions. There is no report in the literature of a full comparison between the OMT analysis methods. This thesis introduces new analysis methods and compares the efficacy of new and existing markers in discriminating between normal subjects and clinically abnormal OMT.

As mentioned earlier, most clinical investigations are based on the PZT system which is contacting measurement system. For patient comfort and to avoid the loading of the eye

that cause change in the OMT signal, a non contacting OMT measurement system is required. Boyle in 2001 (14) investigated the possibility of speckle interferometry in OMT measurement. His work did not investigate the biospeckle activity (a time varying speckle produced by living organisms) caused by the eye sclera, which could acts as source of noise in the speckle measurement methods. Also Boyle's work raises the question if it is possible to use the other speckle metrology methods (such as speckle correlation) for OMT measurement. Compared to speckle interferometry the speckle correlation method, is simpler to implement and provides x-y direction measurement of OMT signal (speckle interferometry only provides one direction measurement). The final part of this thesis examines the biospeckle activity using a high speed CCD camera and also investigates the possibility of using the speckle correlation as new candidate in OMT measurement.

The thesis is divided into seven chapters. The first chapter introduces the relevant background literature. Chapter 2 describes new developments in the current PZT measurement system. Chapter 3 examines the signal recovery methods. Chapter 4 examines the stationarity and linearity assumptions. Chapter 5 and Chapter 6 describe and validate the developments carried in this thesis in OMT signal analysis. Finally Chapter 7 investigates the biospeckle activity and examines the possibility of using the speckle correlation method in OMT measurement.

List of abbreviations:

A

- ❖ A A F T : Amplitude adjusted Fourier transform.
- ❖ A D C : Analog to digital converter.
- ❖ A M D : Absolute mean difference.
- ❖ $A M I$: Average mutual information.
- ❖ A R : Autoregressive.
- ❖ A R S : AR spectrum.
- ❖ A R M A : Autoregressive-moving average.
- ❖ A T V F : Adaptive time varying filter.
- ❖ A U C : Area under curve.

B

- ❖ B S P R : Burst spectral power ratio.

C

- ❖ C A B G : Coronary artery bypass grafting.
- ❖ C C : Correlation coefficient.
- ❖ C_{TH} : Gabor coefficients threshold.
- ❖ $C_{m,n}$: Gabor coefficients.
- ❖ C_v : Coefficient of variation.

D

- ❖ D A S : Discontinuous adventitious sound.
- ❖ d b : Daubechies wavelet.
- ❖ D F S : Digitally filtered shuffled.
- ❖ D P I : Dual Purkinje image.
- ❖ D W T : Discrete wavelet transform.

E

- ❖ E C G : Electrocardiogram.
- ❖ E E G : Electroencephalograph.

F

- ❖ F B a : Frequency content of baseline.
- ❖ F B I wavelet : U.S. Federal Bureau of investigation wavelet.
- ❖ F B u : Frequency content of bursts.
- ❖ F O A : Fractional octave analysis.
- ❖ F T : Fourier transform.
- ❖ F F T : Fast Fourier transform.

H

- ❖ HF: High frequency.
- ❖ HRV: Heart rate variability.

I

- ❖ IAAFT: Iterated amplitude adjusted Fourier transform.
- ❖ ICA: Independent component analysis.
- ❖ IEC: International Electrotechnical Commission.

K

- ❖ κ : Kappa value.

L

- ❖ LASCA: Laser speckle contrast analysis.
- ❖ LF: Low frequency.

M

- ❖ MA: Moving average.
- ❖ MDBa: The mean duration of baseline.
- ❖ MDBu: The mean duration of bursts.
- ❖ MF: Middle frequency.
- ❖ MIF: Mean instantaneous frequency.
- ❖ MPE: Maximum permissible exposure.
- ❖ MUSIC: Multiple signal classification.

N

- ❖ NBu: Number of bursts occurring per second.
- ❖ NPC: Normal peak count.

O

- ❖ OMT: Ocular microtremor.

P

- ❖ PC: Peak count.
- ❖ Pe: Permutation entropy.
- ❖ PROBa: Percentage of record occupied by baseline.
- ❖ PSD: Power spectral density.
- ❖ PZT: Piezoelectric.

R

- ❖ RMS: Root mean square.
- ❖ RMSE: Root mean square error.
- ❖ ROC: Receiver operating characteristics.

- ❖ RS: Random shuffling.
- ❖ r_{sym} : Symmetrical rank.

S

- ❖ SC: Speckle correlation.
- ❖ SE : standard error.
- ❖ SI: Speckle interferometry.
- ❖ SNR: Signal to noise ratio.
- ❖ SPR : Spectral power ratio.
- ❖ Stderror: Standard deviation error.
- ❖ STFT: Short time Fourier transform.

T

- ❖ T : Threshold.
- ❖ tiAAFT: Truncated iterated amplitude adjusted Fourier transform.
- ❖ TR : Time reversal.

U

- ❖ UWT: Undecimated wavelet transform.

W

- ❖ WPC: Wavelet peak count.

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Ch1

1 Literature Review

1.1 OMT

1.1.1 Introduction

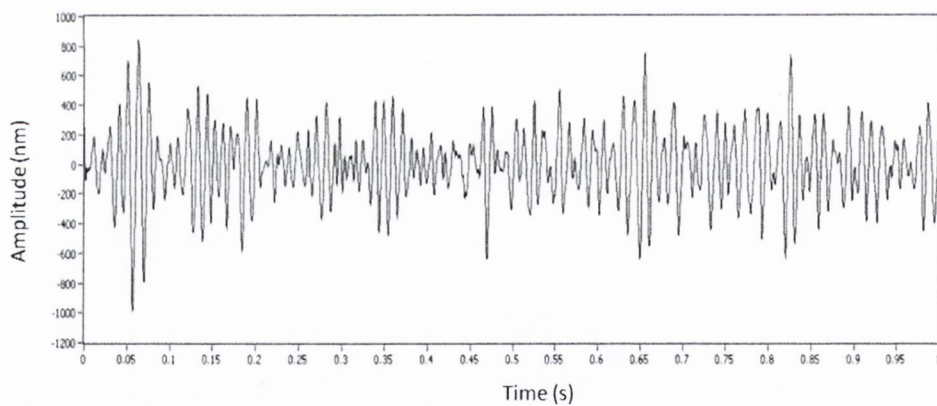


Figure 1. Ocular Microtremor (OMT) signal taken from normal subject.

Ocular microtremor (OMT) is a continual high frequency involuntary eye movement present in normal subjects even when the eye appears to be at rest. The eye displacement

caused by OMT is from 150nm to 2500nm (see appendix 2.5 arcsec to 30 arcsec¹) oscillating at a frequency of about 85Hz for normal subjects. Figure 1 shows a typical filtered OMT 1s trace taken from a normal subject and Figure 2 shows a typical OMT frequency spectrum plot peaking at 79.3Hz from a normal subject.

OMT (also referred to as tremor) is the highest frequency lowest amplitude oscillatory component of fixational eye movements. It was first discovered by Alder and Fliegelman in 1934 (39). OMT activity has been noted not only in humans but also in animals: in cats (40), rabbits (41) and rats (42).

The next two sections give an introduction to the different types of eye movements and the anatomy of the eye. This is followed by a detailed explanation of different aspects of OMT.

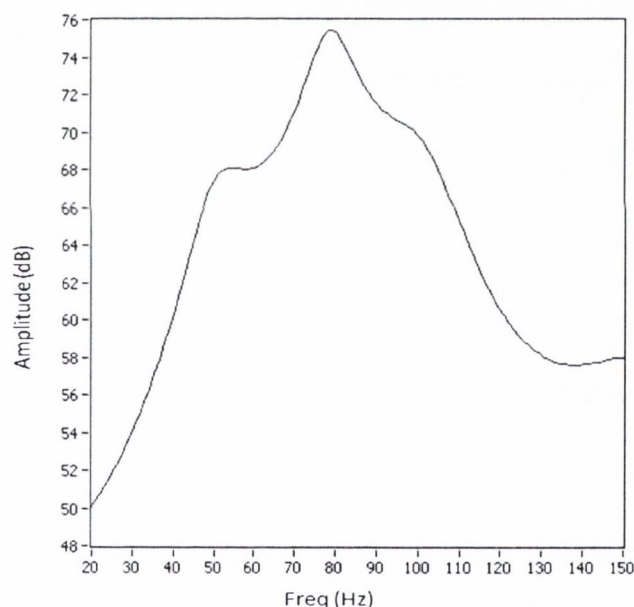


Figure 2. A typical OMT frequency spectrum of 15s signal from normal subject using the AR method (order:47, peaking at 79.3Hz).

¹ See the appendix to see the relationship between the two figures.

1.1.2 Eye movements

There are a number of eye movement types such as: Vestibular, Optokinetic, Pursuit, Saccade, Rapid phase, Vergence and fixational eye movements. Table 1 lists the eye movements and their functions. In this work we are interested in fixational eye movements and OMT in particular.

Type of eye movement	Functions
Fixational	Maintains the image of a stationary target on the eye fovea
Saccade	Places the image of the target on the eye fovea
Rapid phase	Resets the eye rotation and direct the gaze to a new visual target.
Vergence	Simultaneous movement of the eyes towards or away from one another to place the image on both foveas.
Vestibular	Maintains the image stable on the retina during short head movement
Optokinetic	Maintains the image stable on the retina during full head movement
Pursuit	Maintains the image of a moving object on the eye fovea

Table 1. Eye movements and their functions (13)

1.1.3 Eye anatomy

The eyeball is moved by three pairs of muscles (lateral rectus, medial rectus, superior rectus, inferior rectus, superior oblique and the inferior oblique) that insert on the outer surface of the eye (see Figure 3). They allow for three dimensional eye movements. The lateral and medial rectus muscles rotate the eye in the horizontal plane. When the two eyes are directed to a target the eye on the target side is rotated by the lateral rectus and the other eye by the medial rectus. The superior and inferior rectus muscles elevate and depress the eyes, especially when the visual axes are rotated away from the nose. The superior and inferior oblique muscles act as elevators and depressors when the visual axes are rotated towards the body central axis. The ocular muscles show a continuous small activity (even when the eye is apparently at rest) called the tonic activity.

The brain controls eye movements by coordinating the output of the lower motor neurons that form cranial nerves III, IV and VI. Cranial nerve III (oculomotor) controls the superior, medial, inferior rectus and inferior oblique. The oculomotor centre is close to the

brain center that is also responsible for maintaining consciousness (43). The lateral rectus and the superior oblique are controlled by cranial nerves VI (abducens) and IV (trochlear, respectively. The cranial nerves III and IV are located in the lower midbrain and VI is located in the lower pons (See Figure 4). The three cranial nerves are also responsible for controlling the elevation of upper eyelid (4).

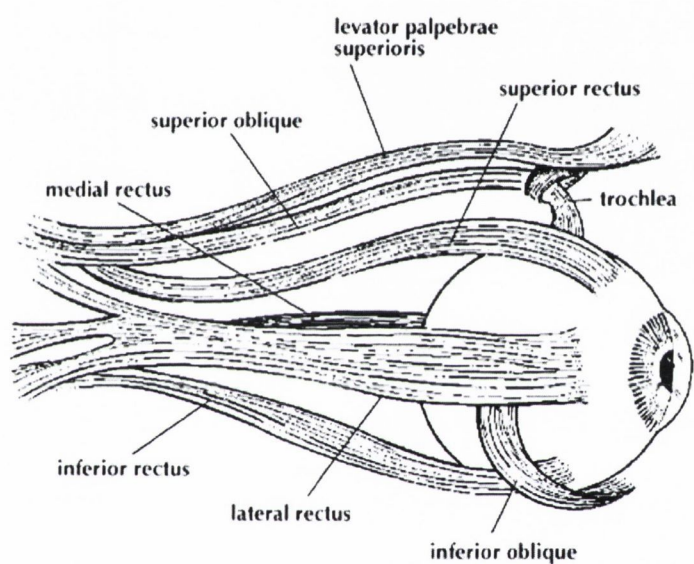


Figure 3. The extra-ocular muscles of the right eye (1)

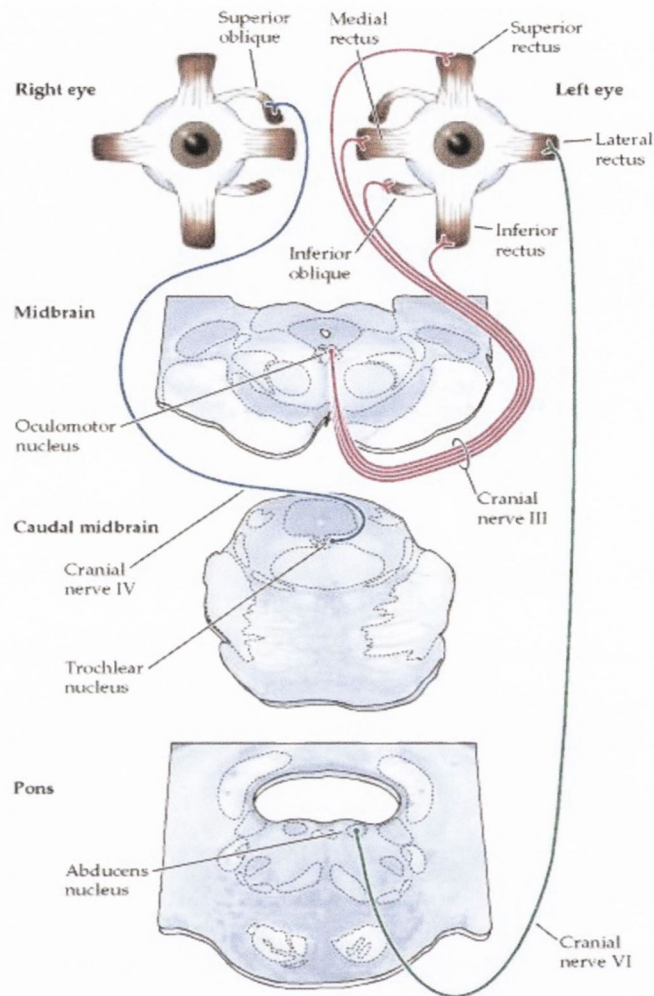


Figure 4. The structure of the cranial nerve nuclei (III, IV and VI) that controls the extra-ocular muscles that result in the different eye movements (5).

1.1.4 Fixational eye movements

The eye undergoes continual three dimensional low amplitude movements even during eye fixation². Three types of fixational movements have been described: Ocular Microtremor (OMT), drift and microsaccades. These fixational eye movements occur involuntarily and unconsciously (44).

² Maintenance of the visual gaze on a single location.

1.1.4.1 Microsaccades

Microsaccades are rapid small amplitude fixational eye movements. The mean peak to peak amplitude of microsaccades is $10\mu\text{m}$ (3 min of arc/sec) and can reach up to $110\mu\text{m}$ (30 min of arc/sec) (4). The average duration of an inter-saccadic interval is between 0.5s-5s, and varies between individuals (45). The occurrence of microsaccades are correlated between the two eyes (0.6-0.9 correlation factor), while this is not in the case of drift and OMT. Martina-Conde et al (46) found that microsaccades counteract visual fading during fixation.

1.1.4.2 Drift

Drift is a low velocity movement of the eye when fixating. The eye drift frequency is around 2 Hz and with a maximum frequency of 30Hz (47). Nachmias in 1959 (48) believed it to be a source of noise in maintaining a stable image on the retina. Kowler in 1991 (49) contradicts that and hypothesises that drift helps in adjusting the eye position in visual tasks.

1.1.4.3 OMT

Ocular microtremor, as introduced above, is very fine continuous movement of the eye with displacement about 150nm to 2500nm peak to peak and oscillating at a frequency of 85 Hz in normal subjects. The OMT frequency band is from 20 Hz to 150 Hz (7). The lower cutoff of OMT frequency is an arbitrary value chosen by Sheahan (7) due to the fact that current PZT measurement systems (used in most OMT clinical investigation), filter 0Hz-20Hz band to remove the eye drift.

1.1.5 OMT origin

OMT activity is believed to be generated by fluctuations in the tension of opposing muscles (26), (50). As the OMT signal is of very low amplitude it would be reasonable to

believe that it could be a mechanical response caused by interference from an external source, such as head movements, heart beats or environmental noise transferred to the measurement system. A number of published works contradict this hypothesis and show that OMT is neurogenic in origin. In an experiment done by Coakley in 1983 (31), the subject was a patient with one normal eye and one paralyzed (unilateral ophthalmoplegia). He recorded OMT from both eyes, but noted that there was OMT activity present in the normal eye and not in the paralyzed eye. Similar results were observed by Bolger in 1994 (51). Bolger also noted that there was abnormal low frequency signal with subjects having unilateral denervation of the medial rectus in one eye compared to normal OMT in the other normal eye. This implies that normal innervations are required for OMT activity to be present which concludes that OMT is of neurogenic in origin. Coakley (31) and Eizenman (26) suggested that the frequency of OMT is predominantly determined by the distribution of firing frequencies among oculomotor neurons. A similar frequency band (60-100Hz, gamma frequency) to OMT has been noted in the local field potentials recorded in the region of the subthalamic nucleus in patients with Parkinson's disease (52). Further investigation is required to determine if there is any correlation between the two activities, which will help in understanding more about the OMT activity.

Eizenman in 1983 (26) modeled the OMT frequency spectrum as a cyclo-stationary process based on the average frequency spectrum shape of OMT signal, implying that the statistical properties of the signal vary cyclically with time (53). He used the corneal reflex method (54) in measuring OMT with seven normal subjects. The analysis was based on computing the power spectra of OMT and drift over inter-microsaccadic segments (more than 100 segments for each patient record) longer than 1024ms duration. He noted that the power spectrum divides into two regions 0-40Hz and 40-100Hz. The first region (0-40Hz) showed a power decline of $1/f^2$ (where f is the frequency) and was modeled as Poisson process representing the random firing of the motor units. He also noted that there were number of narrow spectral peaks in that region, which were believed to be due to artifacts of the system vibration, the line frequency and its harmonics. In the second region (40-100Hz), a significant broad peak power was noted which was modeled as a cyclo-

stationary process due to clock-like firing of the motor unit during fixation. One of limitations in Eizenman's modeling is that it is based on the comparison of only seven normal subjects. This may not be adequate to represent the whole population and certainly not the clinical conditions impacting on OMT.

Sheahan in 1992 (6) investigated two mathematical models for OMT, neurological and mechanical to fit the OMT and drift spectrum taken from normal subjects. Both models model the OMT signal superimposed with eye drift but free from microsaccades. The neurological model models OMT as a mechanical response of a non-resonant eyeball to the random firing of fibers in the musculature. The mechanical model is based on Robinson models for eye movements (55). Sheahan's model is based on assuming the eyeball undergoes a slightly under-damped high frequency resonance. The investigation concluded that the mechanical model provides a close approximation to measured OMT spectra with a deviation in the low frequency region (about 0-40Hz) which was attributed to drift contamination in the measured signal spectra (see Figure 5). The neurological model failed to predict both the low frequency region and the spectral peak at 70-80Hz. Both Sheahan models are based on assumptions of an underlying linear OMT generation mechanism.

In Eizenman and Sheahan work, both models are based on using the frequency spectra information obtained from normal subjects to understand the origin of OMT signal during fixation. The difference between the two approaches is that Sheahan tried to model the full frequency range of OMT and drift (0-150Hz) using the two models suggested (neurological and mechanical) and obtained the parameters that gave the closest fit to observed spectra. Both models used by Sheahan failed to predict the 0-40Hz frequency region in measured spectrum which was thought to be due to the drift artifact superimposed in it. On the other hand Eizenman modeled the frequency spectra as being generated by two distinct processes and divided the spectra into two regions (0-40Hz and 40-100Hz).

The models described by Eizenman and Sheahan are based on linear system assumption. The validity of this assumption has not been examined as will be explained later.

1.1.6 OMT correlation between the eyes

Initial findings in the correlation of OMT between the two eyes reported by different authors suggested that there was no correlation in the OMT activity between the eyes (19), (50), (51). Abakumova in 1975 reported there was no clear correlation (based in visual observation of the data) in the times of occurrence of the OMT bursts pattern between the eyes, but he did not investigate it (27). Sheahan remarked on the non correlation of the time domain signals between the eyes (most signals tested had a p-value below 0.1) and suggested that the OMT generation process is separate in each eye (50). She used linear Pearson's correlation coefficient³ to investigate the degree of correlation between the two eyes. In this investigation she looked at the correlation between the eyes of the power (mean square of the signal) and dominant frequency (using peak count and AR spectrum) where she used six OMT signals taken from different normal subjects. In which she divided the signals to 1s microsaccades free segments and calculated for each the power and dominant frequency. Then finally she calculated the correlation coefficient between the eyes of the three measures for the six normal subjects. However, she noted a weak positive correlation of the high frequency component of the OMT signal between the two eyes. Spauchus in 1999, claimed that there was a high degree of correlation between the eyes as measured using partial coherence (Coherence estimates the linear time invariant relationship between signals and partial coherence estimates coherence between signals taking in account relationship of the signals with a reference signal (56)) (57). In Spauchus study he used the head movement as the reference signal for the partial coherence between the two eyes, which useful in removing any coherence due head movements.

³ A measure of similarity between two data.

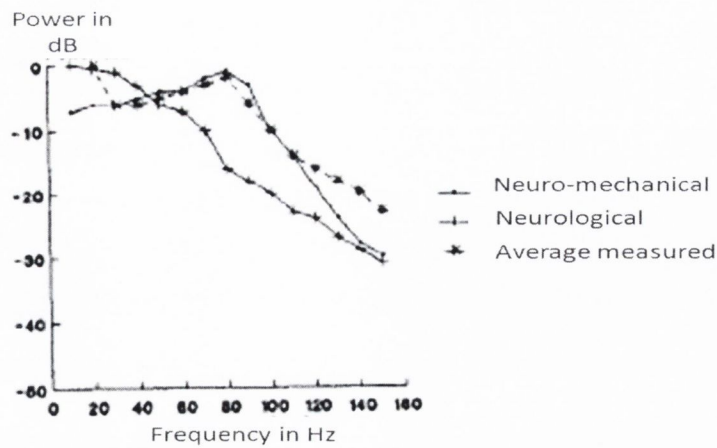


Figure 5. The mean OMT power spectra measured from 10 healthy subjects and the predicted spectra of the neurological and neuro-mechanical models (6)

1.1.7 OMT and vision

Figure 6 shows a schematic diagram of the human eye. The light emitted or reflected from objects, allows the eye to capture the position, shape and the colour of the object viewed. The retina detects the light focused on the photoreceptors cells: rods and cones. Rods function mainly in low illumination while the cones are used mostly in daytime vision and in the perception of colour. The center of the retina is the fovea. The fovea is the part of the retina with the highest acuity due to the high density of photoreceptors. The photoreceptors convert the light pattern into neuronal signals which are sent by the optic nerve to the brain.

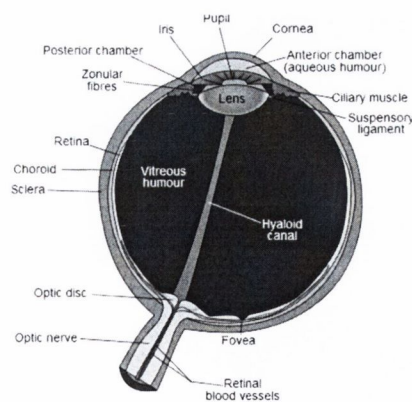


Figure 6. Schematic diagram of the human eye(from (4)).

The first studies to investigate the role of OMT in vision were carried out by Marshall et al (30), Jones et al (58) and Ratliff (59) in 1942, 1947 and 1952, respectively. The authors suggest that the fixational eye movements continuously scan the images on the retina. This is the dynamic theory of vision, which states that eye movements are responsible for hyperacuity⁴ (60). The theory suggests that OMT is sufficient to sweep the image over the retina cones. Later reported findings about OMT amplitude showed it be within the inter-cone distance (7), (51), (14), (26), and too small to have a role in hyperacuity.

One of the recent findings suggests that fixational eye movements (Microsaccades, drift and OMT) have a role in counteracting image fading caused by neural adaptation (47). Since microsaccades occur less often (about 0.5-5s) than the other fixational movements, this suggests that drift and microtremor may play a role in preventing visual fading.

Boyle in 1999 (61), used a mathematical model to investigate the role of OMT in vision. Boyle used a simulated fixational eye movement trace in his investigation. He modeled the impact of blurring while varying the OMT amplitude and the eye photoreceptor cone spacing ratio. He concluded that any significant increase in the OMT amplitude known observed values relative to cone spacing would be likely to blur features resolvable by the photoreceptor cones (61). As the ratio of OMT amplitude to the cone spacing ratio is known to be less than one he concluded that an increase in tremor amplitude of the order a micron would affect the visual process. Also his findings support that OMT hypothesis of that one of the factors in the cone spacing limits.

Recent work By Mattias et al in 2003 (60) took another approach by studying hyperacuity with the combination of the three fixational eye movements (Microsaccades, drift and OMT) and reexamining the dynamic theory of vision. This study did not investigate the particular role of OMT in hyperacuity but rather the combination of three fixational movements. The study is based on modeling the eye retina and comparing the response of

⁴ Hyperacuity (also called vernier acuity) is the ability of the eye to resolve certain stimuli with resolution better than that imposed by the Nyquist sampling theorem. Its resolution is about 5 to 10 higher than normal visual acuity.

a resting and moving eye. His findings concluded that the combination of the three fixational eye movements would improve visual performance in the retinal periphery but not in the central retina (optical blurring limits hyperacuity). Another recent paper by Daqing et al in 2009 (62) took the same approach as Mattias and studied the role of the combined fixation eye movements in the enhancement of visual acuity. The study is based on using a visual neural model to take account of the temporal statistics of the firing neurons (as eye movement generates additive random stimuli to photoreceptors). They concluded that the combined eye movements contribute to overcoming the inherent resolution limits of the photoreceptors and enhance the sharpness and resolution of images.

One of the major limiting factors in studies of the role of OMT in vision is the measurement system. Accurate recording of microtremor frequency and amplitude are required. Also the measurement is required to be noncontacting so as not to distort vision during visual tasks in the tests. Current systems, as will be explained later, suffer from these limitations but some new promising laser speckle measurement systems may overcome them (14), (63), (64).

1.1.8 Clinical markers in OMT

Extracting useful clinical information from physiological signals (such as Electroencephalography, Electrocardiography and Electromyography signals) requires reliable signal processing techniques. Accurate detection of differences between normal subjects and patients may improve diagnosis and the treatment of the patient under test. Common diagnostic techniques used by medical researchers in physiological signals include extraction of information from the time-domain, frequency-domain (e.g FFT, Welch spectrum and Linear Predictive spectrum), joint time-frequency domain (e.g STFT, Gabor transform and Wavelet transform) and the use of nonlinear measures (e.g Lyapunov exponent, Correlation dimensions and entropy measures).

OMT amplitude has not been used as clinical marker in OMT clinical studies. This due to the fact that most clinical investigation is based on the PZT system, which has low

accuracy in amplitude measurement (65). In the OMT literature two main clinical markers have been used: OMT features and OMT frequency content. The OMT features are divided into two activities: an irregular baseline tremor and higher amplitude bursts as shown in Figure 7. The OMT features are assessed in clinical investigations in terms of the burst and baseline frequency content, duration and frequency of occurrence. The second method for analysis of the OMT signal is based on looking at the frequency content and determining the dominant frequency. There are four methods reported in the literature used for estimating the dominant frequency: peak count (by finding the mean number of peaks per second), Fourier fast transform (FFT) spectrum, Welch spectrum and the Autoregressive (AR) spectrum (50). In normal healthy subjects the mean frequency of OMT was found to be 84Hz (33) using the peak count method. In clinical investigations the mean OMT frequency was found to be reduced in several clinical conditions.

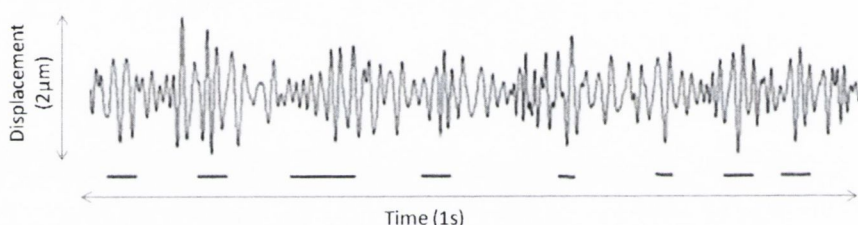


Figure 7. One second OMT signal (bursts episodes are underlined) .

1.1.9 OMT clinical studies

Shakanovich and Thomas in 1974 were the first to study OMT in unconscious patients (41). They noted that there was a decrease in OMT activity in those patients compared to conscious subjects. This led to further investigation of the relation of OMT activity to brainstem function, particularly in the prognosis of the unconscious patient, such as patients in coma (27), (66), (67), (68), (69), (32). The largest study in coma patients was done by Coakley with 101 patients (31). Of those patients most showing a low OMT frequency did not recover from the coma. Serial records from the patients were found to correlate with patient condition with an increase in OMT frequency being correlated with an improvement in the patient's condition and vice versa. OMT activity was lost and only

the presence of residual abnormal activity was noted in a dead patient brainstem (31), (51). Recent findings by Bolger found that OMT frequency is reduced in patients with neurologic disorders such as Multiple sclerosis (34) and idiopathic Parkinson's disease (37).

Bolger in 1999 demonstrated that there was a difference in the spectral content of OMT records of five patients with third nerve palsy when compared with normal eyes (70). Recent findings by Collins (71) agree with these observations.

The OMT signal amplitude diminishes with increasing depth of anesthesia (36), (72). By monitoring the changes in frequency with time the OMT signal has been shown to accurately track depth of anesthesia from unconsciousness to consciousness (36). Coakley in 1976 found that the OMT frequency and amplitude diminishes during sleep and returns on awakening. This study was based on monitoring the OMT activity in four sleeping normal subjects (73). The authors noted that the OMT features during sleep was quite different to that seen during coma (67), (66). During sleep changes in the amplitude were the most obvious feature, while in the coma patient's low frequency dominates the record.

Collins in 2008 found that the OMT frequency is reduced in patients with confirmed stroke compared to neurologically normal subjects (35). She concluded the possibility of using OMT as an adjunct to the diagnosis of stroke, in the acute assessment of stroke evolution and as a potential prognostic indicator in acute stroke (74).

1.1.10 Factors that affect OMT activity

A number of studies were carried out to determine the factors that may have an influence on the OMT activity and which must be considered in the design and statistical tests of clinical studies with OMT.

- ❖ Age: Bolger has studied the changes in OMT frequency content with age. His study was based on records taken from 72 normal healthy volunteers aged from 21 to 88 years. There was a significant drop in the overall frequency and the frequency

content of bursts with age ($p < 0.002$ and $p < 0.001$, respectively) (75). Also he noted that there was a highly significant drop in the overall frequency, the frequency content of bursts and the frequency content of baseline ($p < 0.0001$) in subjects older than 60 years old.

- ❖ Caffeine intake: Collins has reported that there is a small but significant change ($p < 0.001$) in OMT activity 30 minutes after caffeine intake from 85.9Hz (SD 3.4 Hz) to 87.9Hz (SD 3.3 Hz) (76).
- ❖ Fixation: Bolger in 1994 found that there was no significant difference in OMT frequency and power with seven normal subjects between fixating and non eye fixating during the OMT recording (51). This contradicted findings by Bengi and Thomas with five normal subjects where they found a reduction in OMT amplitude in a non fixating compared to a fixating subject (77). Both studies used the PZT system.
- ❖ Loading: Bengi and Thomas in 1973 (77) did an experiment to investigate the effect of loading the eye on OMT. In this experiment the loading of the eye was achieved by increasing the weight of a contacting piezoelectric OMT measurement probe (5-15 g.cm² added inertias). Increasing the loading to the eye (through a contacting measurement method or some other source), will result in a reduction of the OMT amplitude and high frequency spectra power (77). This is expected as the extra load will increase the damping of eyeball rotation, which therefore decreases the amplitude of the OMT displacement.
- ❖ Illumination: A small significant drop in OMT frequency spectral density was noted by Bolger for OMT measured in the dark compared to normal room lighting (51). As in the case of fixation, no change in the frequency spectral density was detected in the work by Bengi and Thomas (77). This is may be due to the fact that in Bengi and Thomas study did not carry out a statistical test of significance, and small differences in the frequency spectral density between the dark and light might have not been detected.

1.2 OMT measurement Techniques

A number of techniques have been reported for measuring OMT activity. To design a technique to measure the OMT signal requires an understanding of the signal measured and what could affect the measurement.

1.2.1 OMT amplitude and frequency

Due to the limitations of the techniques used in OMT measurement, there is no accurate measure of OMT amplitude, and the values reported by different authors are only approximate measures. Also the values quoted by different authors vary from one study to another. Table 2 below lists the OMT amplitude average and range reported by different authors. The highest mean amplitude was reported by Alder and Fliegelman (2) of 134 arcsec and the lowest was reported by Sheahan (7) of peak to peak amplitude range from 2.5 arcsec up to 3.3 arcsec.

Alder and Fligelman (1934) was the first to estimate OMT frequency. As the frequency content is of great importance in OMT clinical studies, different authors have investigated the average or the range of the OMT frequency for normal subjects. Table 3 shows the estimate of the OMT frequency for normal subjects reported by different authors. Most authors quote figures round 85Hz (Table 3). The differences between these estimates are generally attributed to differences in the methods used to measure and analyze the OMT signal and the number of subjects included in the estimate. Bolger has used the highest number of normal subjects (105) in his OMT studies.

Author	Techniques	Average amplitude	Amplitude range	Reference
Alder & Fliegelman (1934)	Reflection mirror	134 arcsec	-	(2)
Raltiff & Riggs (1950)	Optical lever	17.5 arcsec	-	(15)
Ditchburn (1953)	Optical lever	-	5-16 arcsec	(17)
Riggs (1954)	Corneal reflection	-	5-16 arcsec	(19)
Yerbus (1967)	Optical lever	-	20-40 arcsec	(20)
Steinman (1973)	Optical lever	-	5-30 arcsec	(23)
Eizenman (1985)	Corneal reflection	6 arcsec	-	(26)
Sheahan (1993)	PZT system	-	2.5-33 arcsec	(7)
Bolger (1994)	PZT system	4 arcsec	-	(9)
Boyle (2001)	Speckle interferometry	12 arcsec	-	(14)
Ramdane (2004)	IRIS system	-	5-30 arcsec	(5)

Table 2. Variation of the OMT amplitude reported by different authors.

Author	No. of subjects	Technique	Analysis Method	Frequency (Hz)
Alder & Fliegelman 1934 (2)	1	Reflection mirror	Manual peak count	50-100Hz
Ratiff and Riggs 1950 (15)	5	Optical lever	Manual peak count	30-70Hz
Ditchburn & Ginsborg 1953 (17)	2	Optical lever	Manual peak count	30-80Hz
Riggs et al 1954 (19)	6	Corneal reflection	Manual peak count	60-80Hz
Matin 1964 (21)	1	Contact lens	Spectral analysis	85Hz mean
Shaknovich & Thomas 1973 (24)	7	PZT system	Spectral analysis	100Hz mean
Abakumova 1975 (27)	7	PZT system	Manual peak count	85-105Hz(95Hz mean)
Davis & Plant 1978 (29)	1	PZT system	Manual peak count	100Hz mean
Coakley 1981 (31)	41	PZT system	Manual peak count	88-124Hz(101Hz mean)
Michalik 1987 (32)	34	PZT system	Spectral analysis	87.4Hz mean
Bolger et al 1999 (33)	105	PZT system	Automated peak count	70-103Hz(83.68Hz mean)
Collins et al 2008 (35)	20	PZT system	Automated peak count	88.9Hz mean

Table 3. OMT frequency estimation of healthy subjects reported by different authors.

1.2.1.1 Specification required for OMT measurement system

The specification requirement advised by Sheahan (7) to measure the OMT signal in terms of dynamic range and bandwidth is 25-2500nm (0.41-41.3 arcsec) and 20-150 Hz, respectively. The specification was derived from OMT amplitude and frequency estimates reported by different authors. The specified dynamic range of 40 dB (covering 25nm-2500nm) is not unusual in biomedical instruments (7), (78), (79). The frequency band of interest in OMT (20Hz - 150Hz) was chosen by Sheahan based on observation in literature (see Table 3 for figures reported in the literature).

By comparison with EEG system requirements (as the OMT and EEG signals are both neurological measures(7)) Sheahan stated that the amplitude response and frequency response of the system should be linear and not fall below 2dB of the peak value within the system bandwidth. Also the system should user friendly and safe for clinical investigations.

1.2.1.2 Other movements that effects OMT measurement

The design of the OMT measurement system must take into account that there are a number of movements present, which can be divided into two categories. The first are eye fixation movements (drift and microsaccades). Both of these movements are higher amplitude than OMT. Microsaccades are rapid small- amplitude movements, which occur at an approximate mean rate of 1 to 2 per second. The drift is a continual low frequency movement (about 2 Hz). Both movements have amplitudes less than 110 μ m (30.3 arc-minutes) (4). As drift frequencies do not overlap with the OMT frequency range (20Hz-150Hz), simple high pass filtering will be sufficient to attenuate drift. On the other hand microsaccade activity overlaps the OMT frequency band, which causes difficulty in filtering of movements.

The second category is due to artifacts other than eye movements, such as head movements and heartbeats. Those movements can be reduced by mounting the transducer

in a headrest that moves with the head (e.g using a head-band around the forehead to mount the instrument) as reported by number of authors (7), (80). The head movements can then be filtered out due to the low frequency of the head movement compared to the OMT. The other possible solution is to have a second transducer (such as magnetic tracking device and sophisticated algorithms used in eye trackers (81) to measure the head movements. The difficulty in this approach is correlating and scaling the head movement and eye movement signals to subtract out the signal associated with head movements.

1.2.2 Techniques implemented to measure OMT

There are number of techniques reported in the literature used to measure OMT:

1.2.2.1 Reflection mirror

The first method used in measuring OMT employed the optical lever technique and was introduced by Adler and Fliegelman in 1934 (2) and further improved by Ratliff and Riggs (1950) (15). The method is based on detecting the changes of the angle reflection of a light beam reflected from a very small, flat (plane) mirror mounted on a contact lens worn on the eye (15), (2). The reflected beam was captured using a series of photographs taken on photographic film. In this method a change in the angle of incidence (due to the eye movement) will result in double that change in the angle of the reflected beam, increasing the spatial resolution of the system (48). Alder and Fliegelman did not take account of this magnifying effect so they had scaling error in their results which was pointed out by Ratliff and Riggs. The system resolution was quoted as one arcmin (about $3.64\mu\text{m}$ arc displacement) (82).

One of the disadvantages of this method is that it is an invasive technique that may cause discomfort to the patient and limits the recording time of the OMT measurement. Also mechanically loading of the eye may cause changes to the characteristics of the measured signal. It has been reported that mechanically loading the eye causes changes to microsaccade characteristics (83). Although the reflection mirror system was reported to

detect OMT the resolution of the system does not meet the required ideal spatial resolution for measuring the OMT signal (25nm)(50).

1.2.2.2 Corneal reflection

This method is based on directing a collimated beam of infrared light on the cornea and using the reflection from the cornea to measure eye rotation. The virtual image formed by the convex surface of the cornea (the 'Purkinje' image) may be tracked to follow eye movements. Eizenman in 1984 (54) modified the corneal reflection method to achieve a resolution capable of measuring fixational eye movements. The system resolution is 30 arcsec (about $1.82\mu\text{m}$ arc displacement). Figure 8 shows the optical configuration of the system. Eizenman used an infrared emitting diode as the source (S) and directed it to the eye (10mm beam diameter at the eye) using a collimated lenses (L_1 and L_2) and mirror (DM). The reflected image is captured using a collecting lens (L_3) and a set of six front surface gold mirrors (M_1 - M_6), the reflected image is captured using a linear array of photodetectors (10),(26). The system was tested using an artificial eye. Eizenman reported that the measurement results from the human eye of the fixation movements (drift, microsaccades and OMT) generally agrees with findings using other measurement systems.

The most recent versions of this device use two ocular reflections to separate eye rotation from head movements (translation movement). One of the methods, known as the dual Purkinje image (DPI) is based on monitoring the first Purkinje image and the fourth Purkinje (the image formed by the reflection from the back of the ocular lens). The system is not sensitive to translational movement due to the fact that both reflections (from the lens and the cornea) move together through exactly the same distance with eyeball translation but show different displacements with eyeball rotation. The DPI measures the difference between the two images by adjusting a series of mirrors using servomotors so that the two images are kept superimposed on electronic photoreceptors. The adjustment required to the mirrors is proportional to the eye rotation and is independent of head translation. The resolution of this system is 10 to 20 arcsec (about 606nm to $1.21\mu\text{m}$ arc

displacement) (84) but the head needs to be stabilized. Other methods use the first Purkinje image and the center of the pupil as the two points of reference to measure the eye rotation and to separate out head movements (1).

Both approaches have similar resolutions. Purkinje based systems are noninvasive, but the spatial resolution does not meet the specification requirement for measuring the OMT signal.

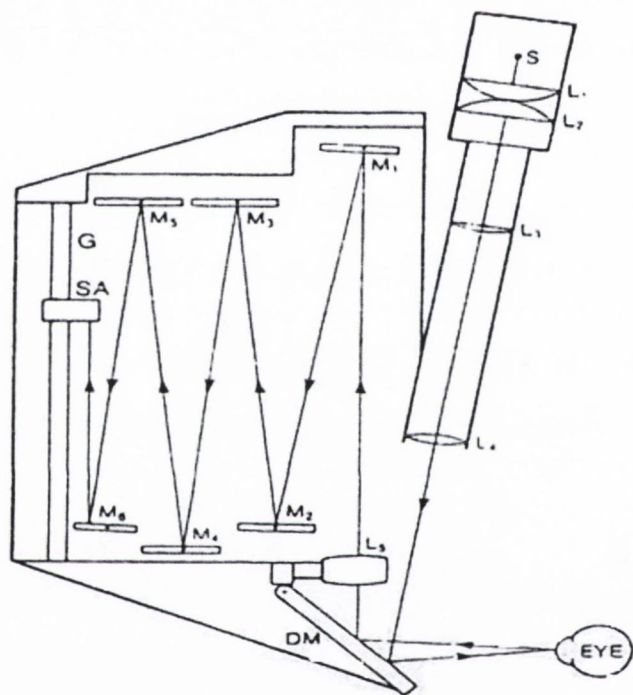


Figure 8. Schematic diagram of the corneal reflex system used by Eizenamn (1984 (10)). M₁-M₆: Golden mirrors, L₁-L₅: Lenses, S: Source (gallium infra-red emitting diode), DM: dichroic mirror, SA: sensor array.

1.2.2.3 IRIS system

This method has been reported for OMT measurement by one author (12). The method is based on the reflection of infrared (IR) light by the area on both sides of the boundary

between the white sclera and darker iris. Two infrared sensors are positioned to detect the reflection from the two areas. The voltage difference between the two sensors is proportional to the eye movement. The IRIS system can detect the eye movements in one axis (e.g horizontal or vertical). One of the drawbacks of this system is that it can induce certain artifacts in the recorded signals depending on the sensor placement (85) (a decrease in apparent peak saccadic velocity when the sensor is close to the eye sclera or introduction of a nonlinear component in the signal when the sensor is close to the eye pupil). The best resolution of the system is quoted as 2 minutes of arc (about $7.3\mu\text{m}$ arc displacement) (5) which does not meet the resolution required for OMT measurement.

1.2.2.4 Scleral search coil

In this method the subject under test is fitted with a large diameter soft contact lens which has a fine wire coil embedded in it (86), (87). A time varying magnetic field is applied to the eye under test using two pairs of large horizontal and vertical coils. When the eye moves within the field an alternating voltage is induced in the search coil proportional to the sine of the angle between the plane of the search coil and the direction of the magnetic field. The system is not sensitive to small translational head movement since the magnetic field is fairly homogenous (88). The resolution of the system is 5 arcsec (about 303nm arc displacement).

Due to the mechanical loading of the eye cornea by the contact lens with the search coil, this may cause temporal deformation of the cornea and reduction of visual acuity (83), (89). Frens and Van Der Geest found that the mechanical loading by the search coil caused microsaccades to last longer (by about 8%) and become slower (by about 5%) (90).

1.2.2.5 Capacitance gauge

In this method a fixed plate of a capacitor is placed near the eyeball surface. The eyeball will act as the second earthed moving plate of a variable capacitor. The capacitance changes due to the eye movements cause frequency modulation of an r.f. oscillator. The

OMT signal is directly proportional to the frequency modulation. Bengi and Thomas (38) were the first to introduce the capacitance gauge in OMT measurement. The authors reported that the system meets the resolution requirement to measure the OMT, but did not state the resolution (38).

Although the method may meet the spatial resolution requirements, a highly trained operator is needed to precisely position the plate as close as possible to the eye. Also the system is very sensitive to translational movements of the head which requires the head to be held still. Variation in plate positioning changes the system sensitivity, making absolute OMT amplitude measurement difficult.

1.2.2.6 PZT system



Figure 9. Photograph of the PZT system being used for OMT measurement as developed by Sheahan (7)

Nearly all quantitative clinical investigation of OMT has been carried out using the PZT method, which was first developed by Bengi and Thomas (38). The method is based on measuring the voltage change produced by a piezoelectric element when it is in contact with the eye. There are two approaches to measure OMT: open eyelid and closed eyelid. In the open eyelid approach the probe is placed on the surface of the sclera of the eye (38). Sheahan in 1993 gave a detailed performance specification of the PZT system developed by her, as will be explained later (7). Figure 9 shows a photograph of the closed eyelid

PZT system during a typical OMT recording using the system developed by Sheahan in 1993. The first clinical study using the PZT open eyelid technique was done by Coakley in 1983 to measure OMT during sleep and anesthesia. Thomas and Coakley (91) were the first to introduce the closed eyelid method, where the piezoelectric probe is placed on top of the closed eyelids. Although this method is vulnerable to the noise added by the levator palpebrae muscle, the muscle is completely relaxed when the eyelid is closed suggesting that the resulting noise should not be high (92). The resolution of the open eyelid system is 10nm (about 0.17 arcsec) (7). The advantage of the closed eyelid method over the other technique is that it is easier to do studies with patients under the following conditions: sleeping, anaesthetized or in coma. The disadvantages of the closed eyelid method is that the OMT signal detected is noisier (65) (could be due to the blood flow within the eyelids) and visual tasks studies cannot implemented using the closed eyelid technique. Work by Thomas and Coakley showed that the frequency measured by the closed eyelid technique is lower when both eyes are closed than when one is kept open during the recording (91). There has been no investigation as to whether the measured OMT amplitude would be damped or the spectral content changed by transmission through the eyelids.

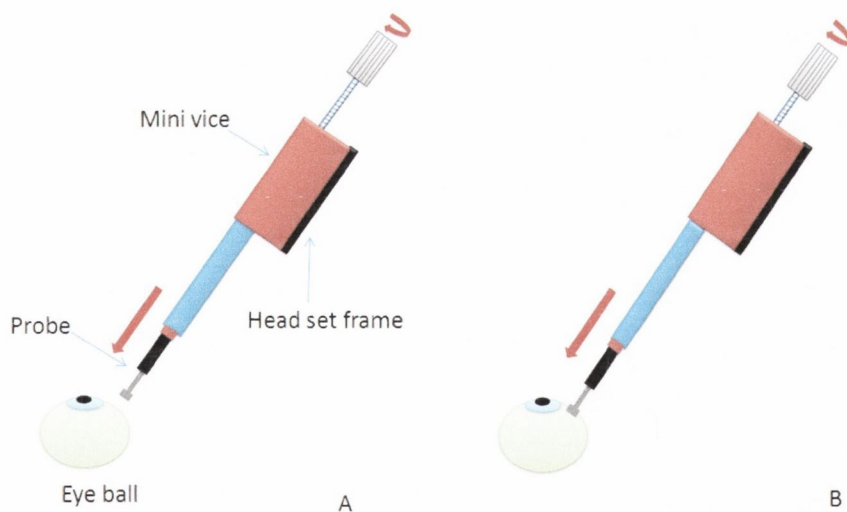


Figure 10. The screw mechanism in the current PZT system. A. The probe is advanced by turns of the mini vice. B. Once the probe comes in contact with the eye sclera, further turns of the mini vice will increase the pressure applied by the probe to the eye.

1.2.2.6.1 Existing PZT systems

The first OMT PZT system introduced by Bengi and Thomas in 1968 (38) was based on using a piezoelectric element with one end covered with a rubber (latex) cap for comfort where it comes in contact with the eye. The system forms a cantilever and the voltage generated by the piezoelectric element was proportional to small eye rotation. The probe was brought in contact with the eye using a micrometer screw mechanism and attached to a Perspex headband. The measurement of the horizontal or vertical component of tremor was achieved by changing the sensing orientation of the piezoelectric element. The output of the probe was amplified using a field effect transistor amplifier (gain 14) and bandpass filtered (20-140Hz). Next the signal was differentiated (to represent the output in velocity) and displayed. The resolution of the method was 1 arcsec (about 60.6 nm).

One of the difficulties in the system introduced by Bengi and Thomas was that it was subject to translational movements by the globe (29). A second drawback of the technique was that as the probes are securely attached to the headset the probes cannot be sterilized (or disinfected). Also the piezoelectric element is very brittle and rapid eye movement could potentially shatter and damage the eye. The technique was further modified by Davis & Plant in 1978 (29). They introduced a removable probe tip that could be sterilized by ethylene oxide (or replaced with a sterilized probe), which overcame the sterilization issue with the first system. The probe was set in a hockey mask to reduce the head movements. The piezoelectric element was secured in a tube (to prevent it from breaking) and the eye movement is transmitted to the element by the removable probe head. Detailed performance specifications of the OMT measurement system were not provided by Bengi & Thomas or by Davis & Plant. Sheahan in 1993 (7), filled this gap by reporting a fully detailed design and performance of a PZT system. The PZT system developed by Sheahan is based on having a removable probe attached to a headband. The 3D positioning of the probe was provided using three mini-vices. The probe is brought in contact with the eye by a screw mechanism (mini vice). Figure 10 shows the screw mechanism used to advance the probe to the eye sclera during the recording procedure. In this method the probe is first

brought in contact with the sclera and then an additional $\frac{1}{4}$ turn of the mini vice was applied once the eye was contacted (equivalent to about a 0.2mm advance). As the OMT signal is within the audible range⁵, Sheahan used audio feedback to help the operator to know when the probe is in contact with the sclera (the OMT activity which around 80Hz has distinguishable sound to an expert examiner)(50). This done by playing the amplified captured OMT signal by the PZT probe into a headphones held by the operator.

The output of the probe was fed to a signal conditioning unit. Comprising:

- Input stage: A high impedance (10M) buffer and differential amplifier.
- 8-pole Butterworth high pass filter (3dB point is at 16 Hz).
- 4-pole Butterworth low pass filter (3dB point is at 170Hz).
- Delay equalizer: to minimize phase non-linearity caused by the probe and the above circuits.

The output of the conditioning unit was then acquired on a personal computer and on a cassette tape for analysis. She used an OMT simulator to test the performance of the system (such as the dynamic range, frequency response, phase response and amplitude response).

1.2.2.7 In-plane speckle interferometry

Optical metrology techniques in general have a number of important advantages over current methodologies: i.e. sensitive, noncontact and non-invasive (93). Speckle interferometry is based on having two laser beams directed onto one point on the sclera of the eye. As the sclera surface is not mirror like (optically rough) this causes the formation of laser speckle. The speckle fluctuations are captured using a photodiode and then further

⁵ Human Ear audible range, roughly round 20Hz to 20kHz.

processed to recover the OMT signal. This method was first introduced for OMT measurement systems by Boyle (14), (61) in 1999 with tested resolution of up to 100nm (about 1.7arcsec) using eye safe laser power levels. The optical configuration used was an in-plane, phase modulating⁶ speckle interferometer using a photodiode to measure OMT and with the eye sclera (the white of the eye) as the target (Figure 11). The laser beam used was a red He.Ne laser (continual wave, $\lambda=632.8\text{nm}$).

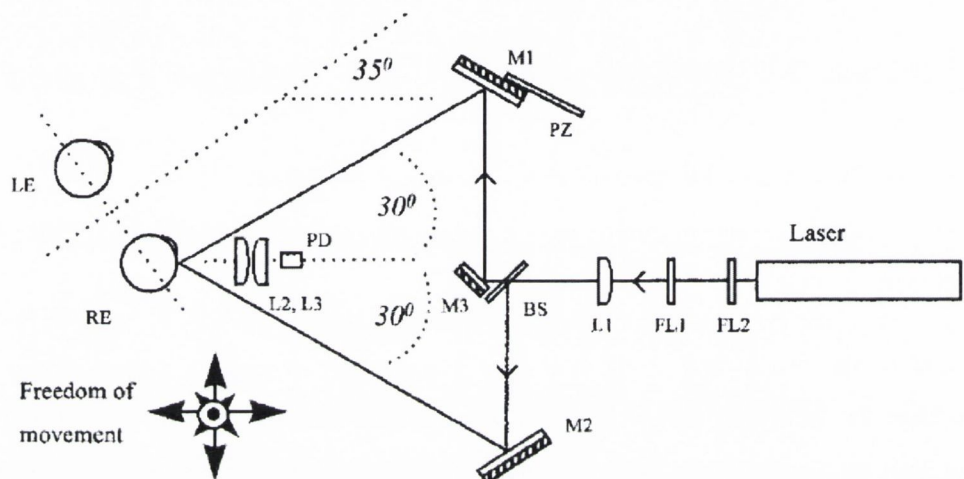


Figure 11. shows an in-plane, phase modulating speckle interferometry using a photodiode to measure the OMT by using the eye sclera (the white of the eye) as the target. FL1, FL2, filters; L1, focusing lens; BS, beam splitter; M1, phase-modulating mirror; PZ, piezoelectric element; M2, M3, fixed mirrors; RE, right eye; L2, L3, collecting lenses; PD, photodiode (14).

The resolution of the system was 100nm which is about 4 times less than the ideal resolution for the OMT measurement(7), but sufficient to capture it. The setup was tested using a calibrated piezoelectric driven OMT simulator with a white plastic surface to represent the eye sclera. Further testing was performed using a small bovine scleral sample to take into account the effect of the biospeckle⁷ in the measurement of the simulated signal. Boyle et al [17] noted that there were a number of distinctive low frequency noisy

⁶ Phase modulation was used to remove the directional ambiguity in the measurement system.

⁷ Biospeckle is term given to the speckle from a biological surface.

phases with the biological sample as a target during the signal simulation measurements which were not noted with the plastic target (61). It was concluded that they arose from biospeckle fluctuations. One of the limitations in Boyle's work is that he did not investigate the effect of the biospeckle activity in the OMT measurement as the biospeckle fluctuations act as source of noise which could distort the displacement information of interest in the speckle measurement techniques.

Boyle concluded that the sclera surface generated sufficient stable to allow implantation of speckle OMT measurement technique. However the tests did not include simulation of head movements, tear flow and sclera blood flow.

To further confirm the feasibility of this approach a third test was also performed, whereby a 140Hz sinusoidal signal was superimposed on the measurement of the *in-vivo* eye. The spectrum of the measured signal showed a spike at 140Hz, indicating that the system operated correctly *in-vivo*.

The setup was further developed using a laser diode ($\lambda=638\text{nm}$) coupled by phase maintaining fibers with integrated phase modulation that allowed construction of a more compact portable device (94), (95). The system has not yet been tested *in-vivo*. Additional simulation tests were performed (96) using eye drop solution (Brolene Propamidine) to simulate eye tears by applying it to the plastic surface during the OMT recording. This resulted in an error in the displacement measurement of 1.9%. The author concludes that there is no apparent effect of tear flow on the measurement results. The test of the tear flow does not simulate the effect of having a biological sclera as the target, which could cause a higher level of disagreement between the measured and the simulated signals.

1.3 Measurement techniques- Areas for investigation

1.3.1 PZT system

Although most clinical studies of OMT have been carried out using the PZT techniques there are number of limitations to it.

The procedure cause some discomfort to the subject as anesthetic eye drops must be first introduced to the eye, the eye is under pressure from the piezoelectric probe during measurement and the eyelids must be held open. Subject discomfort sets a limit to the measurement time. Loading of the eye by the probe affects visual acuity, as it dampens eye movements and may cause slight deformation of the eye cornea. This limits potential studies incorporating visual tasks to investigate the relation between OMT activity and vision. The probe part which comes in contact with the eye (Sheahan used silicone rubber layer to cover the piezoelectric probe tip) is not a biocompatible material, which would not be in line with current design practice. Measurement of OMT amplitude is not accurately reported by the current PZT systems, as there are variations in the measurement between and within operators (97). Also the dynamic range of the current system is not enough to capture all the movements (microsaccades and drift) picked up by the PZT probe, as the signal is pre analogue bandpass filtered prior to digitization. This introduces artifacts to the OMT signal due to the characteristics of those movements The new PZT probe designed and built in the work presented here addresses the effect of loading on OMT measurement, dynamic range improvement and probe tip biocompatibility.

1.3.1.1 Variation on the pressure of the probe to the eye

As explained earlier Thomas and Bengi investigated the effect of loading the eye by the PZT probe (77). The investigation was based on applying different probe inertias on the eye of one normal subject. Their findings were that as we increase the loading applied to the eye will result in reduction of the OMT amplitude and high frequency spectra power. This is because the extra load will increase the eyeball inertia, and therefore decrease the

amplitude of the OMT displacement. From their findings one can conclude that loading by the PZT probe needs to be as low as possible (so as not to affect the characteristics of the OMT signal) and constant between trials (to reduce variation due to the different loadings).

Advancing the probe using the screw mechanism has drawbacks in terms of the measurement variability and patient safety. To position the probe on the sclera with the screw mechanism requires some skill and ensuring that there is no significant variation in the pressure applied to the sclera by the probe is difficult. Sheahan was the first to investigate the variation in the OMT frequency in a normal population (97). The investigation was based on measuring OMT with the PZT screw mechanism with experienced and relatively inexperienced operators. The results showed that intra-subject coefficients of variations for the estimated OMT frequency (by peak count) was about 5% with an experienced operator and about 14% with a relatively inexperienced operators. Those variations are due to number factors such as the actual OMT variation and technical difference due the system and the operator. The larger variability seen with the inexperienced operators may be due to larger variations in probe-eye contact pressure in this group.

She also found that the amplitude variation for a given probe varied by about 25% between measurements using the OMT simulator with a skilled operator. This test was carried out using two probes with the simulator head covered by bovine sclera (50). This variation in amplitude is high and introduces difficulties in estimating the actual OMT amplitude. That's why there isn't up until now any clinical value of the OMT amplitude in clinical studies.

1.3.1.2 Dynamic range

Current PZT systems have a dynamic range of 25nm-2500nm, which is adequate for recording OMT signal only after the signal from the PZT probe has been analogue bandpass filtered (e.g Butterworth) to remove other eye movements (microsaccades and

drift). This will cause a distortion to the signal due the ringing response of the filter to microsaccades and the signal will be saturated, as simulated in Figure 12. Figure 13 shows a block diagram of the current PZT system layout(7). This issue is addressed more in Chapter 3.

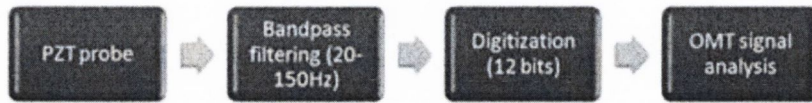


Figure 13. A block diagram of the current PZT system.

1.3.1.3 Probe tip

Many materials that come in contact with tissue are required to be biocompatible, such as artificial hips, contact lenses and artificial pacemakers. Biocompatible materials are designed to interact with biological systems without causing foreign-body reactions, injuries or toxic reactions (98).

As explained above, current methods have a probe tip which comes into contact with the eye made from materials that are not biocompatible. As the PZT probe comes in contact with the eye, it is prudent to choose the tip material considering the current thinking on contact lenses design which are made from biocompatible materials. The advantage of biocompatible contact lenses is their good physiological response with reduced induction of tears, sclera/corneal desiccation and protein deposits (99).

A second point taken from the contact lens guidelines is that contact lens should never be shared with anyone else as there is danger of cross-contamination (e.g. patients with keratoconus) between the eyes (100). In the current PZT probes the probe tip is not removable (attached to the probe) which may cause cross contamination when the same probe is used between subjects.

1.3.1.4 Proposed modifications to PZT system

Part of the thesis will investigate three of the limitations in the current PZT system. First the screw mechanism will be redesigned to be more user friendly and to reduce the sources of variation in OMT measurement. Also experiments will be carried out to understand the effect of probe pressure on both amplitude and frequency on OMT measurement. Those developments and tests will be investigated in Chapter 2. Second, Chapter 2 will also investigate the possibility of using a 24 bit resolution ADC to provide a 102dB dynamic range to digitize the eye movement signal directly from the PZT probe without analog pre-filtering. The improved dynamic range will lead to the possibility of capturing both OMT and microsaccades using the PZT probe. Finally the work will also involve developing a PZT probe with a disposable tip made from a biocompatible material.

1.3.2 Speckle techniques

1.3.2.1 Speckle Metrology

Speckle metrology is a growing optical measurement technique used in many fields such as mechanical and medical measurements. Laser speckle is a phenomenon seen where laser light scatters from a rough (nonspecular) object resulting in a random pattern of dark and bright spots (speckles) to form. The random speckle is formed by interference of a set of wavefronts having the same frequency but different phases, resulting in a distribution whose amplitude (therefore intensity) varies randomly (101).

The speckle phenomena was first noted in 1962 by Rigden and Gordon of Bell laboratories (102) but was only studied in detail from a theoretical viewpoint in 1984 by Dainty (103) and then further developed in practical applications. A typical pattern of speckle is shown in Figure 14. One of the applications of speckle techniques is in strain measurements, where the absolute difference is found between a reference speckle image of light scattered off an object and a second speckle image of light scattered off the object under strain. The

difference image will show bright and dark fringes with the fringe spacing corresponding to deformation of the object by a fraction of a wavelength (104).

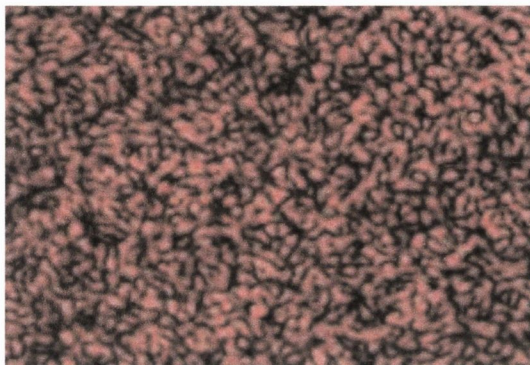


Figure 14. A typical pattern of speckle.

A fully developed speckle pattern (i.e. unity contrast, discussed later) will appear only if the height variations of the diffuser (rough surface) are greater than the wavelength of the laser beam used. A small movement of the diffuser will cause fluctuations of the speckle pattern. These fluctuations are caused by the changes of the path lengths of the interfering wavefronts caused by the movement of the scatterers, but the speckle pattern after movement will remain correlated to the pattern before movement. For a large movement the speckles decorrelate and the speckle pattern change completely. This property is used in velocity measurements (105).

One of the important second-order statistics characteristics of the speckle pattern is the speckle size. The speckle size determines the limits for speckle measurement techniques in terms of resolution and quality. The speckle size is determined by the optical configuration of the imaging lens (such as magnification and lens F number), which can be chosen to provide a specified speckle to pixel (detector pixel) ratio, depending on the desired application.

The speckle to pixel ratio is also important in techniques based on detecting changes in the local speckle contrast. If the ratio is small (the speckle size is smaller than the pixels), more than one speckle is sampled by each pixel causing speckle averaging and loss of contrast information. If the ratio is high (the speckle size is too large compared to the pixel size), very few speckles will be available and will be insufficient for contrast analysis. The speckle size can be easily controlled by varying either the magnification of the lens or the aperture of the imaging optics.

The local speckle contrast is defined as the ratio of the standard deviation to the mean intensity of the image. The speckle contrast value is between 0 and 1. A fully blurred speckle pattern caused by fast moving object will have a contrast value of 0. For a stationary diffuser object the contrast value is higher than for a moving object. If the integration time of the detector is too slow to capture the speckle fluctuations, the image will be blurred due to averaging of the speckle and this will cause a reduction in the local speckle contrast. Using a shorter exposure time would freeze the speckle fluctuations and results in a higher local speckle contrast (106).

The local speckle contrast not only provides information about the quality of the speckle image but also can image the velocity distribution in a field view by mapping the contrast variation within the image. This has been used in the development of laser speckle contrast analysis (LASCA). The LASCA can provide a real time flowmetry monitoring system and has been used particularly in blood flow measurements (107-112). Also a similar technique has been used in monitoring the heartbeats from a vein, where by plotting variation in the local speckle contrast with time the minimum contrast indicates an occurrence of a heartbeat (113-114). LASCA is based on using a CCD camera and a frame grabber to capture the speckle pattern from the area of interest. The speckle contrast is calculated for equal sub-matrices from the image to form a false-color map of the velocities within the imaged area (as the velocities are related to contrast changes in the sub-matrix from frame to frame).

1.3.2.2 Speckle applications and techniques:

The speckle pattern reflected from a static rough surface has a unique pattern (like a fingerprint) that reflects the microstructure of the specific surface of the illuminated area. This property has been used to measure the roughness of objects using speckle techniques (115),(116),(117),(118).

There are two types of speckle changes. The first one is 'speckle translation' where the speckle pattern moves with the diffuser as a whole and the pattern remains unchanged for a considerable time. The second type is the boiling of speckle where the speckle pattern changes over time not only because of the motion of the diffuser but also because of Brownian motion within the object illuminated (119). The boiling speckle regime is the deformation, disappearance and reappearance of the speckle spots like a vapor bubbles in boiling water. Speckle demonstrating both translation and boiling changes simultaneously may degrade the recorded speckle image information for metrology purposes (120).

Speckle metrology techniques have the same sensitivity as classical and holographic interferometry (121). In the measurement of OMT we are interested in in-plane displacement as the rotation of the eye at a point on the eyeball can be approximated by in-plane displacement. There are two main speckle techniques to measure in-plane displacement, speckle correlation (122),(123),(124) and speckle interferometry (125),(126),(127).

1.3.2.3 Speckle Correlation

The speckle correlation technique (also called digital speckle photography, electronic speckle photography or digital image correlation) is based on using an electronic detector (e.g. CCD camera) to capture the speckle pattern fluctuations from frame to frame. It is an improved version of the original speckle photography method where the speckle pattern is recorded by means of electronic detector instead of a photographic plate. Figure 15 shows a typical optical setup of the speckle configuration.

point where the path difference is $|L_1-L_2| = n\lambda$ (where n is an integer) and it reaches a minimum when $|L_1-L_2| = (2n+1)\lambda/2$. This will result in bright and dark pattern interference fringes that represent the optical path difference of the combined beams. The difference in the path length could be due the delay of one of the combined beams relative to the other or to a change in the shape of phase front. This phenomenon is used in detecting fine movements of objects using the pattern interference fringes. In speckle interferometers, the individual speckles go through these bright to dark transitions caused by the movement of the surface of interest by $\lambda/2\sin\beta$. The speckle intensity at a point will vary sinusoidally from a maximum:

$$I_{max} = I_1 + I_2 + 2\sqrt{(I_1I_2)} \qquad \text{Equation 1}$$

To a minimum:

$$I_{min} = I_1 + I_2 - 2\sqrt{(I_1I_2)} \qquad \text{Equation 2}$$

where I_1 and I_2 are the intensity of each of the combined (interference) waves.

In the in-plane speckle interferometry technique the object to be measured is illuminated by two coherent beams incident at β to the surface normal as shown in Figure 16 (125).

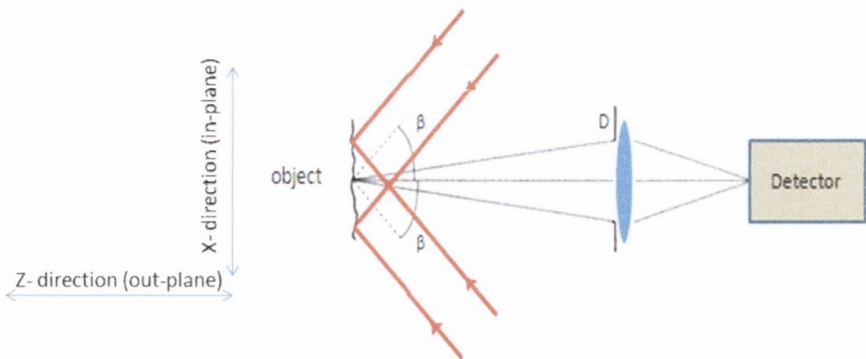


Figure 16. The optical setup for speckle Interferometry used in measuring in-plane displacement. The object is illuminated by two coherent light beams at the same angle β to the surface normal and imaged by a lens on to the detector (diode or CCD camera).

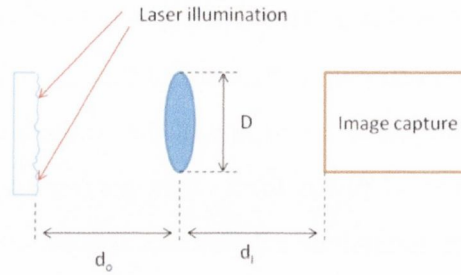


Figure 15. Schematic diagram of the speckle correlation (d_o =distance to object, d_i = distance to image and D = lens aperture).

For in-plane displacement measurement a camera with a frame rate adequate to capture the motion of the moving object is used to record the speckle pattern changes during the motion. Using a frame grabber the images of the speckle fluctuations are extracted from the data captured by the CCD camera. The displacement between a frame (reference image) to preceding frame (displacement image) is calculated by taking a sub-matrix (e.g. 15x15 pixels) from the middle of the reference image (frame n). Next a sweep (2D correlation) through the displaced speckle image (frame $n+1$) is carried out seeking the highest correlation coefficient. Finally from the location of the correlation peak the displacement is found. This cycle is repeated to the last frame to regenerate the relative motion observed. The sub-image size determines the spatial resolution. With this technique sub-speckle sized displacement has been tracked (128).

1.3.2.4 In-plane Speckle Interferometry

Interferometry techniques are regarded as one of the most sensitive non contacting methods used to measure small displacements. The techniques can reach a sensitivity of fractions of the wavelength (λ) used in the optical setup. The basic idea of interferometry is of splitting a coherent monochromatic beam into two beams (or more) and recombining them. When the two beams travel through different optical paths (L_1 and L_2) with no change in the frequency, the irradiance of the combined beams will depend on the difference of the path length of the two beams. The irradiance reaches a maximum at the

In the setup above two independent speckle fields S_1 and S_2 will be generated by each beam and combined coherently to form a third speckle field S_3 (which is the speckle pattern captured by the detector in speckle interferometry technique). The field S_3 consists of speckle from the interference of $S_1 + S_2$. If the object moves in the out-plane direction (z-direction, Figure 16), then both interfering beams will have a path difference of $\delta(1+\cos\beta)$, (where δ is the displacement and β incident beams angle in Figure 16) which results in no change in the path length of S_3 . If the object moves in the y-direction there will also be no change in the path length of S_3 . However if the object moves in the x-direction(in-plane), one of the interfering beams increases in path length by $\delta\sin\beta$ while the other one will decrease by the same amount. This will result in changes in S_3 which becomes re-correlated with itself whenever,

$$2\delta\sin\beta \approx n\lambda \quad \text{Equation 3}$$

where λ is the wavelength of the laser beam and n is 0,1,2,3...

1.3.3 Speckle interferometry versus speckle correlation

A major technical difference between speckle correlation and interferometry is that speckle correlation relies on the use of an imaging detector whereas in speckle interferometry data from a point detector is adequate, as changes in individual speckles, rather than changes in the movement of the overall speckle pattern are tracked. In-plane speckle interferometers process interference signals; correlation methods process images. In-plane speckle interferometers also tend to need more complex optical elements (such as phase modulators) to remove the directional ambiguity in the interference signal.

The resolution of the speckle correlation technique during motion depends on the average speckle size and the CCD camera specifications (such as pixel size, quantum efficiency and resolution) (129). In an in-plane speckle interferometer the resolution depends on the beam source wavelength and the incident beam angles.

Speckle interferometry can resolve motion in one direction only (e.g. in-plane) component, while the speckle correlation can resolve x-y motion. Speckle correlation techniques will be sensitive to disturbances caused by unwanted out of plane movements as these movements will also cause changes in the speckle pattern. Speckle interferometry is not affected by this, as it is sensitive only to in-plane movement in one direction (its own plane). On the other hand speckle correlation technique are less sensitive to external vibrations and to other environmental effects (121).

The sensitivity of the speckle interferometry technique depends on the wavelength of the laser (λ) and the incident beams angle β to the normal of the objects surface. Sensitivity of the speckle correlation technique is limited by the average speckle size and the detector specification of the CCD camera used (speckle to pixel size ratio as discussed earlier) (130).

Ulyanov (131) stated that the resolution of the speckle correlation and the speckle interferometry are identical for in-plane measurements. Ulyanov used the theoretical resolution limit for each method and proved that they were identical. Also Ulyanov stated that the speckle correlation technique is only limited by the pixel size of the camera and is independent of the speckle size in the presence of biospeckle (will be introduced in the next section). This is due to the fact that the speckle size is comparable with the wavelength of the incident beam in the case of a biological object. We are unsure as to which technique would have the better resolution as Ulyanov's mathematical model did not include the biospeckle phenomena in this simulation as a source of noise.

1.3.3.1 Biomedical applications of speckle metrology

Table 4 shows a table of some biomedical applications of speckle metrology using speckle correlation (SC) or speckle interferometry (SI).

Application	Technique	Reference
Investigation of the interior in plane deformation of the crystalline lens of a human eye	SC	(8)
Relationship between cardiac displacements and the chest wall movements	SC	(16)
Measurement of the chest wall movements during the ECG	SC	(18)
Monitoring the human pulse	SI	(22)
Measuring the bio-tissue vibration	SI	(25)
Surface displacement of embalmed human femurs under load	SI	(26, 28)

Table 4. Some speckle correlation (SC) and speckle interferometry (SI) biomedical applications.

1.3.4 Biospeckle

Biospeckle is a time-varying speckle produced by living organisms. Although biospeckle is a source of noise in tissue images, it also carries useful information about the biological or physiological activity of living tissue such as blood flow (which can be mapped as variation in the speckle contrast) and tissue structure motility (132). The relationship between the biospeckle activity and the motion of the diffuser was first studied by Okamoto and Asakura in 1995 (133).

Bio-speckle has different spatio-temporal properties different from those of speckle from inanimate objects due to the effect of multiple scattering (133), such as the depolarization of the incident light (134). The multiple scattering causes speckle statistics changes especially to the second-order statistics of the speckle pattern and speckle fluctuations (93).

The cause of the multiple scattering is due to the fact that most tissues are randomly inhomogeneous media, for example tissue such as the eye cornea, gastric mucous membranes and very superficial skin layers (134).

Biospeckle techniques have been implemented in a range of biomedical applications, such the measurement of the blood flow in skin tissue (135-140), muscular activity (141) and ocular retinal blood flow (132, 142-146). There have also been studies of biospeckle fluctuations using botanical specimens. Oulamara in 1989 have shown that biospeckle

from some fruits have low and high frequency fluctuations resulting from the movement of fast mineral particles and slow plastids (147), which expected to be similar to the effect of tear flow on the speckle pattern. This is an important thing to take in consideration in the development speckle approach in the measurement of OMT.

1.3.5 Speckle metrology- areas for investigation

The work by Boyle in using the speckle interferometry in the OMT measurement was based on a photodiode system (14). This system configuration limits the measurement to one dimension and monitoring of the 2D speckle pattern changes is lost. Only a single point in the speckle pattern was sampled. The pattern itself was not visualized. Using a high frame rate CCD camera will resolve the issue. This will be technically challenging because of the power restrictions required to keep to eye safe exposure limits and the frame rate requirements to capture the fast OMT movement.

The introduction of the second dimension will also allow the study of time-varying speckle, enabling the study of the bio-speckle of the eye and speckle contrast. The effects of boiling speckle and multiple scattering phenomena which have been observed in most biological tissues could be quantified and analyzed. Speckle from the sclera has never been observed *in-vivo* or *in-vitro*. Speckle contrast measurement analysis will allow the study of the quality of the speckle pattern images in the presence of biospeckle activity. The results may suggest the possibility of using speckle correlation techniques to measure the OMT signal. Introduction of speckle correlation to OMT would allow for a more compact and simpler method than the interferometry technique. This is due to that fact the correlation method is based on single beam illumination, while the speckle interferometry requires two beams to be aligned to one spot with the same angle to the surface normal of the target. Speckle interferometry techniques also require using phase modulation and demodulation (or similar process) during the measurement process. The speckle correlation technique is less sensitive to room vibrations making it more favorable for clinical use.

Chapter 7 in this thesis investigates the biospeckle activity in-vitro produced from the eye sclera using a high speed CCD camera and also investigates the possibility of using speckle correlation techniques in OMT measurement.

1.4 OMT signal processing approaches

1.4.1 OMT signal extraction techniques

The signal captured by the PZT system is a composite of three superimposed involuntary eye movements (described earlier): OMT, microsaccades, and slow drifting eye movement (see Figure 17). The measurement system has an inherent high pass characteristic with a cut-off of approximately 5Hz due to characteristics of the piezoelectric bimorph response, which cause some filtering of the eye drift.

Filtering the drift artifact from the captured signal could be easily done by simple high pass filtering as the amplitude of the drift artifact is about the same amplitude as OMT and does not overlap with the frequency range of interest (20-150Hz).

On the other hand the microsaccades (rapid flicks) captured by the PZT system have a RMS amplitude an order of magnitude greater than OMT. The frequency band of the microsaccades and OMT slightly overlaps as the step caused by the microsaccades has frequencies overlapping with OMT frequency (Eizenman 1985(148)). Standard high pass filtering (FIR or IIR filters) of microsaccades causes distortion of the signal due to the “ringing” response of the filter (149) to microsaccades.

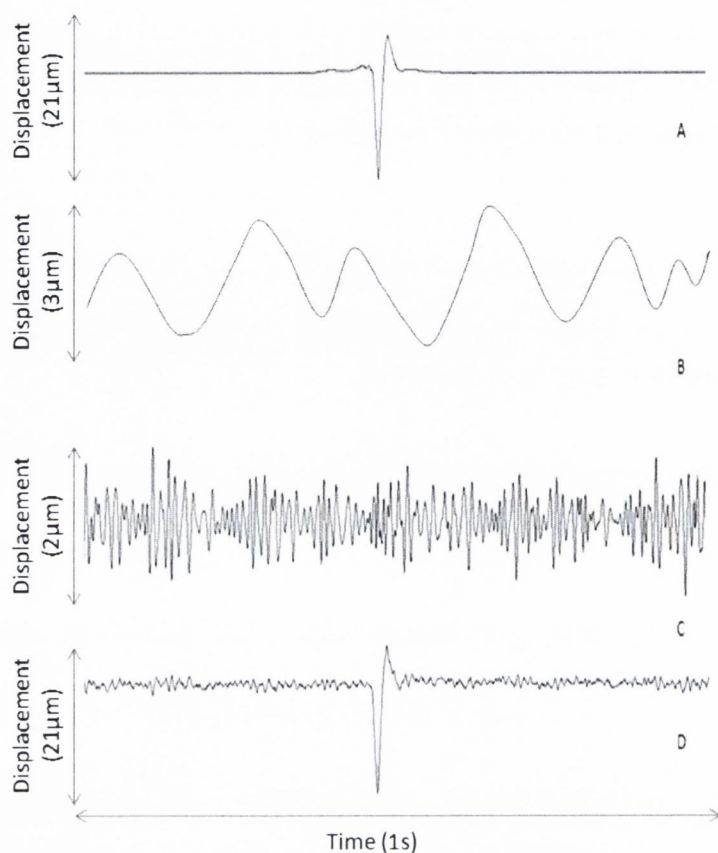


Figure 17. A) Microsaccades. B) Drift artifacts. C) OMT. D) Composite signal. The scale is not the same for all.

One of the current methods implemented by most authors to remove microsaccades is by simple visual inspection of a trace (27, 31, 57, 150) or by automated methods that threshold the signal (148) (7, 34, 36-37, 151)). In this method the identified microsaccades are then removed from the trace (by simply cutting it) and next the free microsaccades periods are rejoined to form a continuous signal. This method suffers some limitations. First, the signal is distorted where the microsaccades have been removed. Second, as segments of the trace are removed with the microsaccades, errors arise in temporal measures of the signal pattern. In particular, errors are introduced into the mean period between OMT bursts in the trace, a parameter of clinical interest (27), (51). Simple cutting of the microsaccades also limits application of joint frequency-time analysis, a potentially fruitful approach to OMT signal characterization (36).

Another method for removing microsaccades from the OMT signal, is based on using multiresolution signal decomposition by wavelet (12), (152). The multiresolution method is based on dividing the signal into number of frequency bands and then filtering the unwanted bands in the wavelet domain (40-150Hz is the unfiltered band and the rest is filtered). Ramdane-Cherif used the IRIS system (based on infrared light reflection technique(153)) to capture the OMT signal. The signal trace captured by their system incorporates OMT, microsaccades, blinks and drift (see Figure 18). The drawback of this method is that the microsaccades and OMT frequency bands overlap slightly (148) and this causes a distortion to the OMT filtered signal. The author does not give detail of the performance of the multiresolution recovery method, nor do the results provide frequency spectra information (a conventional method in analysis of OMT) to allow comparison to spectra in the literature. The author uses a fixed AR model order variation as classifier in his investigation in Schizophrenia (12), which had not been reported previously in the literature.

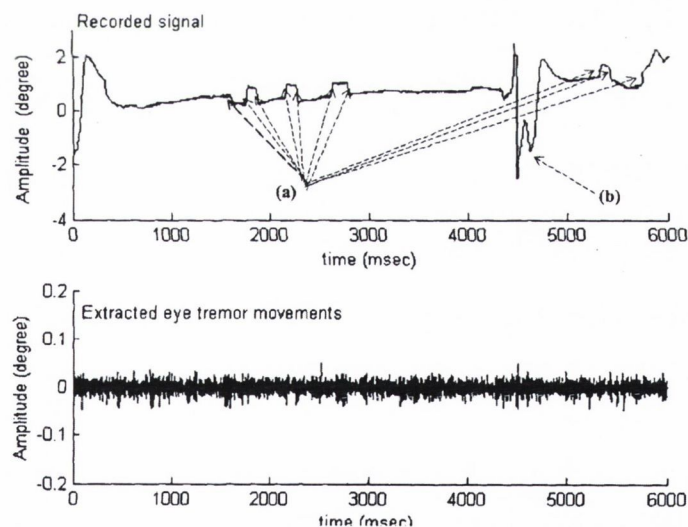


Figure 18. In top is the eye movement signal captured by the IRIS system. a)Microsaccades b)blinks. In bottom is the extracted OMT signal using the Multiresolution method (12).

1.4.2 OMT frequency analysis

1.4.2.1 Peak count

A very simple time domain analysis method is based on the peak count. The peak count gives an estimate of the spectrum dominant frequency component of the analyzed signal (154), (155), (156). The technique is based on counting the number of peaks per unit time. The peak count is used widely in sound analysis and in the analysis of biomedical signals such as EMG (157), (158).

The peak count is one of the most useful analysis methods employed in OMT clinical investigations (31), (34), (75), (159), (71) due to its reproducibility under static conditions⁸ (50), (36). In early work the estimate of the dominant frequency in OMT was found by visually counting the number of peaks per unit time (31), (150), (17), (27) which was time consuming and had limited reproducibility. Sheahan in 1991 introduced an automated method based on counting the sign changes in the differentiated OMT signal (50). To minimize the effect of noise, she discounted the peaks with amplitude less than 23dB of the root mean square value of the OMT signal processed. This is based on the assumption that a good display system has a signal to noise ratio of 23dB or more (160). She tested the manual and automated peak count method with simulated methods and concluded that they corresponded well, although the automated method was more sensitive to small peaks not resolvable by visual inspection (50).

One drawback of this method is that it is very vulnerable to additive noise, DC offset and 50Hz hum (161), (162), (163). High frequency noise increases the number of peaks detected overestimating the dominant high frequency. High amplitude low frequency noise will cause fewer peaks to be detected and underestimating the dominant high frequency. In the case of noisy OMT patients records this will cause statistical false negative errors due to the error in the frequency estimate. On the other hand high amplitude low frequency

⁸ Conditions that causes no significant difference in OMT frequency.

noise will cause fewer peaks detected and may cause false positives with normal subjects OMT signal due to the error in the frequency estimate by the peak count. Also the technique is only suitable for narrowband stationary signals as it based on averaging the number of peaks per second in estimating the dominant frequency, which could provide inaccurate result with wideband signals (162),(164), (165), (166).

1.4.2.2 OMT power spectrum

A power spectrum describes the energy distribution of a signal in the frequency domain. The power spectrum density (PSD) is the normalized power spectrum (the power spectrum divided by the size of the frequency interval to remove the dependence on the interval). The PSD describes the power of signal is distributed with frequency. There are two methods used to estimate the PSD (167): nonparametric and parametric.

1.4.2.2.1 Nonparametric approach

Marple in 1987 (168) classified the nonparametric (also called classical) techniques for estimating the spectrum of a signals into direct and indirect methods. Direct methods are based on using direct transforms (generally FFT) in estimating the PSD of the signals that are called periodograms. Indirect methods (also called correlogram) are based on applying a correlation estimate to the signal and then transforming (e.g FFT). The periodogram is the more popular approach and the indirect correlogram is not widely used, due to its computational time disadvantage.

One of the most popular periodogram methods is the Welch spectrum that was first proposed by Welch (169) and then further modified using a segmentation technique developed by Bartlett. (170). The method is based on dividing the signal into equal overlapping time segments and a windowed Fourier transform is applied to each segment separately. The transforms are then averaged. The overlapping allows more segments per data length for averaging which decreases spectral estimation error (171). The spectral resolution of the Welch method is limited by the number of samples per segment.

The Welch spectrum has been applied to spectral estimation in a number of biomedical applications such as the analysis of the spectral content of the EEG signals (172), (173), (174).

In the OMT literature classical methods have been used in analyzing the OMT spectral content. Both conventional FFT with non-overlapping (32), (29), (57) (26), and overlapping FFT (11), (50) have been applied to spectral estimation of OMT signals.

1.4.2.2.2 Parametric approach

The parametric approach assumes that the signal being analyzed is the output of a mathematical model driven by a white noise. The model does not attempt to directly model the underlying physiological signal, anatomic or physical elements of the system. It simply attempts to model the relationship between the input (white noise) and output (signal analyzed) of the process. This referred to as the black-box approach. An important step in this method is the choice of a model that reflects the behavior of the system(175). Some examples of these models are the autoregressive model (AR), moving average (MA), autoregressive-moving average (ARMA) and multiple signal classification (MUSIC-based on spectral estimation).

The AR model is a linear prediction approach which uses the model's previous outputs to attempt to predict the next output. AR spectra analysis is based on modeling the signal as white noise which passed a set of filters (depending on the model order) called autoregressive or feedback filters. By estimating the filters parameters (coefficients), the estimate of the spectra is found using the frequency response of those filters. The model order is important when estimating the PSD of the signal. A low order results in a smoothed spectrum and too high an order will increase the spectrum resolution but introduce spikes in the spectrum (176). See the appendix for more details on the AR model.

An advantage of the parametric approach over the nonparametric is that the parametric approach has more statistical consistency even with short segments of data. Also it does not need a window in order to decrease spectral leakage and the frequency resolution is independent of the number of samples (175). The drawback of parametric techniques is that they are complex to implement and necessitate finding a suitable model that fits with the signal analyzed. Also the performance of the technique degrades rapidly in the presence of noise, especially with a small number of data points (175).

Many real-world systems can be modeled accurately with an AR model. In biomedical signals the AR model has been used in EEG (177), (178), HRV of ECG (175), EMG (179), (180) and speech analysis (181), (182). Sheahan was the first to use the parametric approach in estimating the PSD of OMT (11). She used the Lattice reduction algorithm (167) to calculate the coefficients of the autoregressive filters with a fixed model order of 30 for a 10s signal duration. She compared it with the nonparametric PSD approach (FFT with segment 50% overlapping method). The comparison was based on using simulated OMT signals with known spectral content. The signals were generated using four band-pass ARMA filters (the AR method was not used in order not to bias the results), representing low frequency (LF, 15-25Hz), middle frequency (MF, 20-60Hz), high frequency (HF, 55-95Hz) and wideband noise (12-230Hz) (Figure 19). The findings of her simulation were that the parametric approach (AR) was superior in estimating the frequency of simulated OMT signal to the conventional nonparametric Fourier analysis. The error associated between the true spectra peak and the estimated peak was 7Hz and 14Hz for the AR and FFT methods, respectively. She also compared the mean frequency of the high frequency peak obtained from healthy subjects using the Fourier and the AR model to the peak count estimate of the dominant high frequency component. She found that the classical Fourier method showed the most variation in estimating the dominant frequency peak with clinically OMT static conditions (33). She also found that the peak count provided the most accurate estimation of the dominant frequency spectra peak with simulated signals compared to the AR and FFT estimations.

Ramdane in 2004 (12) used the AR model in an OMT clinical study related to Schizophrenia. Unlike Sheahan, she used the AR coefficient's mean value and deviation as the clinical marker, studying the difference between the groups of healthy, schizophrenic treated and schizophrenic untreated subjects. She used the Yule-Walker method (183) to estimate the AR coefficients and the Akaike Information Criterion (184) to select a model order. The optimal order was found to be 18. She showed that it was possible to divide the two classes (healthy and schizophrenic) into two groups using the AR coefficients deviation and the model order as markers. The author concluded that the method provides a simple and reliable method to analyze the OMT signals. There was no explanation to as why the author used the AR coefficients as a classifier instead of using them to estimate the OMT spectrum as Sheahan did (11). This would have been useful in comparing the study with spectral clinical findings reported by other authors, though Ramdane method could be computationally faster and more sensitive to clinical changes. Also one of the disadvantages in Ramdane was that classification using AR coefficients (looking at the variation in the coefficients) requires a fixed model order (18 was used). This may not model the signal well in all cases as there is a high variation in the characteristics of the abnormal OMT signals. A low model order leads to poor signal description and a high model order will increase variance in the model parameters (185).

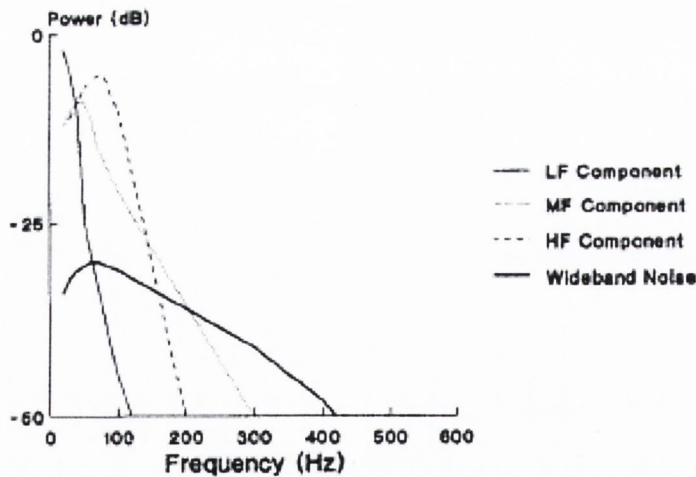


Figure 19. The frequency response of the ARMA bandpass filters used to simulate the OMT signal (11). LF=low frequency, MF=middle frequency and HF= high frequency.

1.4.2.3 Joint time frequency domain

The OMT frequency analysis techniques reported in the literature are based on deriving the spectral estimate for a fixed and often relatively long duration, with the assumption that the OMT process generates a stationary frequency spectrum over these periods. The usual methods used to characterize a statistically stationary signal are either time or frequency domain analysis. Unfortunately most real life signals are not stationary and the signal frequency varies with time. Gabor in 1946 (186) found a solution to this issue by introducing a joint time- frequency representation of the signal, which always tracks the variation of the frequency with time.

The standard tool used to build the joint time-frequency representation is the Short-Time Fourier Transform (STFT). One of the limitations of the STFT is that it is based on a fixed window to generate the joint time-frequency representation. One of the techniques used to overcome this problem is to use a time-scale representation with a wavelet transform. The wavelet technique overcomes the limitation of the STFT by using a multi-scale window (more detail in the wavelet section).

Joint time-frequency approaches are increasingly used in analyzing and denoising non-stationary biomedical signals such as electroencephalograph (187), electrocardiograph (188), lung sounds (189), instantaneous heart rate (190), joint sounds (191) and speech (192). There was only one work reporting use of the joint time-frequency representation to study the variation of OMT frequency with time. Heaney in 2004 used the peak count repeatedly to estimate the dominant frequency of 2.5s epochs to build a time-frequency plot (36). The plot was used to study the variation of OMT frequency with patient depth of anesthesia over time. The technique used by Heaney brings to attention one of the uses of the Joint time-frequency domain and the potential of developing the method for clinical studies with new techniques such the Wavelet transform. The introduction of the joint domain will be useful in OMT studies, such as in the studies of the role of the OMT in vision (e.g. doing visual tasks and to try to correlate them with changes in the OMT activity).

1.4.3 OMT feature extractions approaches and analysis

1.4.3.1 OMT features

As explained earlier, the OMT signal consists of an irregular baseline tremor with intermittent episodes of higher amplitude bursts as shown in Figure 7. The burst periods have the shape of an amplitude modulated near-sinusoidal oscillation with a frequency of about 75Hz to 115Hz for normal OMT subjects (31). The OMT baseline activity has an irregular low amplitude pattern with a frequency range from 70 Hz to 126 Hz (159) for normal subjects.

The OMT burst/baseline features has been analyzed by visual inspection using the following 6 parameters (9):

- ❖ Number of bursts occurring per second.
- ❖ The mean duration of bursts.
- ❖ Percentage of record occupied by baseline.
- ❖ Frequency content of bursts.
- ❖ The mean duration of baseline.
- ❖ Frequency content of baseline.

Bolger in 1992 investigated the optimal OMT signal duration for OMT feature analysis to provide a reliable measure in clinical investigations (159). This important result provides limits of the minimum records duration that can be analyzed reliably for burst/baseline measures. He used the reliability coefficient (R) which is described in detail by Fleiss (193). R is calculated from:

$$R = \frac{\sigma_b^2}{\sigma_b^2 + \sigma_w^2} \quad \text{Equation 4}$$

Where σ_b^2 is the variance between the subjects and σ_w^2 is the variance within the subject. From the reliability guidelines used by Fleiss (193), a value greater than $R=75\%$ will

provide excellent reliability corresponding to a ratio of 1.7 of ∂_b to ∂_w . Table 5 shows the OMT time duration required to get an R_{min} of 75% (within a 95% confidence interval) using the different OMT feature parameters reported by Bolger. He concluded that a 5 second OMT signal time duration would be a reasonable balance of the measurement precision and analytic effort.

Abkumova in 1975 was the first to bring the signal features of OMT to attention in his study of abnormal pupil reflex in neurological patients (27). He tested 22 neurological patients with abnormal pupil reflex and 7 normal healthy subjects. He noted that there is no clear correlation of the occurrence of OMT bursts between the eyes (right and the left). The analysis of OMT was based on visual inspection. He also noted the occurrence of a rare OMT features (he called it pathological burst) in the patients group only, which is similar to bursts described earlier but with higher amplitude and irregular shape. He concluded that there is a strong correlation between the abnormality of the OMT features and abnormal pupil reflex.

Coakley in 1986 studied the relation between brain stem function and OMT (194). He found that in patients with motor neuron disease there was a loss of OMT bursts and baseline activities but he did not investigate the frequency or amplitude difference in the bursts/baseline parameters between the control and the patients with the disease. Bolger in 1999 examined changes in OMT activity in patients with idiopathic Parkinson's disease compared to normal control subjects (37). He used the six OMT features parameters (listed earlier) and the overall mean OMT frequency in his study. The study was carried out using OMT data from 22 normal subjects and 22 patients with Parkinson's disease. The results showed that with Parkinson's OMT records there was a significant decrease in the overall frequency ($p=0.00001$), frequency content of baseline ($p=0.0013$), frequency content of burst ($p=0.0422$), number of bursts ($p=0.0001$) and the duration of bursts ($p=0.0002$) when compared to normal OMT records. Also there was significant increase in baseline duration ($p=0.00001$) and the percentage of record occupied by the baseline ($p=0.00001$).

1.4.3.2 Examining OMT features

Most published work in OMT examines only changes in the overall frequency content of the signal as a diagnostic marker. Identification of bursts and baseline patterns has to date been carried out by visual inspection and has a number of drawbacks. It requires skill, is a time consuming process and it is not a reproducible method.

Also the analysis of the identified features using the six different parameters listed earlier (such as frequency of bursts and frequency content of baseline) is based on manual analysis by the examiner (such as manual peak counting of the average number of peaks per burst to estimate the frequency content of a burst). Analysis of OMT features suffers the same problems as burst identification mentioned above. These difficulties illustrate the need for a reproducible and automated approach for analyzing the OMT features.

1.5 Signal processing- areas for investigation

1.5.1 Introduction to wavelet method

1.5.1.1 Wavelet transform

Traditional Fourier transform analysis has a major drawback in that temporal information is lost. The drawback is not that important when the signal properties do not change over time (stationary signal). However, most biomedical signals show non stationary or transitory characteristics such as trends, drift, sudden changes and changes of events. Those characteristics are of clinical importance in biomedical signal analysis.

The Short Time Fourier Transform simultaneously characterizes a signal in time and frequency. However the precision of the time and frequency in the STFT is determined by the size of the window (Figure 20) (195). This is a drawback of the STFT as most biomedical signals require good resolution of both time and frequency simultaneously.

The term wavelet was first introduced by Alfred Harr in 1910 (196), but only received limited attention. Wavelet analysis is now a rapidly growing signal processing method. Wavelet analysis methods have theoretical properties that can allow a better interpretation of biomedical data than conventional methods. Wavelet could be used as tool for denoising (197), data compression(198), trend analysis (199), (200) and feature extraction (201).

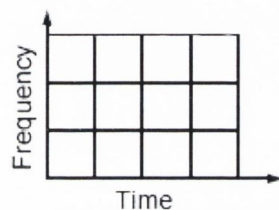


Figure 20. Shows how the STFT applies a fixed window size analysis along the Time-Frequency plot.

The motivation for developing the wavelet transform is based on the desire to overcome the drawbacks of the Fourier analysis and the STFT process (202). The wavelet method has an advantage over the STFT using a windowing technique with variable size regions. The wavelet method uses long time intervals where low frequency information is of interest and short ones where high frequency information (Figure 21) is of interest. This advantage works well in periodic signals and in extracting deterministic and stochastic components (203).

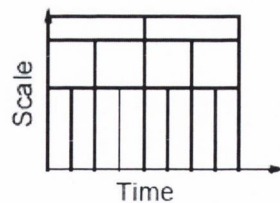


Figure 21. Shows how the Wavelet transform applies a variable window size analysis along the Time-Frequency plot.

The wavelet method is based on a time-scale representation of the signal instead of the time-frequency as in the STFT case. The relation between frequency and the scale is (204):

$$F_s = \frac{F_c}{s \cdot \Delta} \quad \text{Equation 5}$$

where, s is the scale, Δ is the sampling period, F_c is the centre frequency of the wavelet and F_s is the pseudo- frequency corresponding to the scale s . Wavelet analysis is also called constant Q (Q factor) technique, as the relation between the F_c and the bandwidth remains constant through the scales.

1.5.1.2 Wavelet and Biomedical signals

The Fourier transform has been widely used in analyzing deterministic and quasi-deterministic signals. As most biological signals are non-stationary, the Fourier transform is not favorable as a tool in the analysis of those signals, because changes in the frequency spectrum with time are lost (205-207). A number of approaches have been used to overcome this difficulty such as using the Fourier transform with a Gaussian window (Gabor transform). Another approach was based on using the Wigner-Ville distribution, which was first introduced by Wigner and developed by Ville(208-209).

Among these new approaches the wavelet transform has emerged over the recent years as one of the best tools for analyzing biomedical signals. This is due to the fact that the Wavelet transform can provide a better resolution of the time and frequency at the same time (210).

The wavelet transform has been implemented with a combination of independent component analysis (ICA) for the suppression of artifacts in the EEG brain signals (211). The wavelet transform has also been used in EEG signals to perform distribution analysis and signal classification (212), (213).

In the ECG the shape of the signal at a given point of time is related to the activity of the cardiological process at that time. The wavelet transform has provided time-frequency data

(time-scale) that characterizes the shape of the ECG signal (214-215). Also the wavelet analysis provides unique patterns for individual diseases when using Heart Rate Variability (HRV) as a diagnostic marker (216).

1.5.2 OMT signal recovery and wavelet

One of the growing developments in analyzing biomedical signals is based on using the wavelet transform to remove noise from signals (denoising). Wavelet denoising can achieve much higher denoising quality than conventional methods (217). This is due to the fact that the wavelet transform provides detailed time-frequency (time-scale) information, which allows for better discrimination between the noise and the signal of interest, even in the presence of non-stationarity characteristics, seen in many biomedical signals (197).

The wavelet denoising technique is based on transforming the signal in the wavelet transform, then thresholding (or masking) the wavelet coefficients, where the coefficients lower than threshold represent the noise to be filtered. Then the signal free of noise is recovered by applying an inverse wavelet transform to the thresholded coefficients.

The wavelet denoising technique may provide an alternative technique to recovering the OMT signal from other eye movements with higher fidelity in both the time and frequency domains. Chapter 3 examines the performance of the current OMT signal recovery techniques in both time and frequency domains and investigates the possibility of using new methods in OMT signal recovery such as the wavelet denoising method.

1.5.3 Stationarity

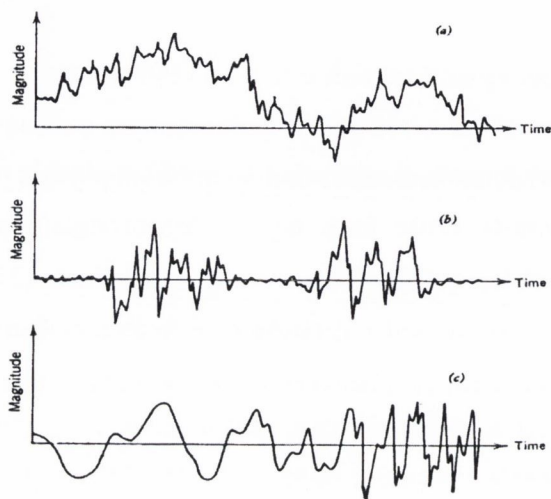


Figure 22 Signals that are nonstationary in the mean (a), variance (b), and frequency content (c).

A stationary signal is a random signal where statistical properties such as the mean, variance and correlation do not vary with time. Signals that have statistical properties that change over time are regarded as non-stationary signals. Figure 22 shows a process that has a nonstationary mean and variance (218).

Nonstationary signals are divided by the spectral content changes into two groups: evolutionary and transient. Evolutionary signals have time varying spectrum and transient signals have short time events such as edges, peaks, bursts. If a non stationary signal can be divided into short equal segments over which the statistics of interest are not varying, then the signal is a quasi-stationary. This is known as a short time analysis.

Many biomedical signals are non-stationary, for example electromyography, electroencephalography, vibromyographic, phonocardiogram, viobroarthrographic and speech signals (219),(220). The biomedical signals that relate to the cardiac system, such

as electrocardiogram, phonocardiograph and carotid pulse are mostly periodic and regarded as cyclo-stationary signals (the signal pattern repeats at regular intervals).

1.5.3.1 Stationarity of biomedical signals

Characterization of biomedical signals as stationary or non-stationary is critical when analyzing the signal. For example when using the Fourier transform to analyze a signal, it is assumed that the signal is periodic. In practice the periodicity condition is relaxed by windowing the signal of interest. The FFT method is insensitive to the time varying features (such as frequency) of nonstationary signal, but provides an average estimate of the PSD (221). The same applies to statistical analysis and to stochastic modeling (such as AR and ARMA) (222). The fixed analysis window used in these methods restricts the frequency and time resolution (energy concentration) due to the uncertainty principle (223-224). A method to solve this is to use short windows for high frequencies (as they have a short time span) and wider windows for low frequencies (as they have longer time span). This idea of having a varying window-width led to the invention of the wavelet transforms. This method is more appropriate to use in the case of nonstationary signals.

Nearly all clinically significant changes observed in OMT relate to measures of the dominant frequency. The analysis techniques used to date for OMT are generally used in estimating the dominant frequency of stationary signals, such as use of the AR spectrum (12), (11) and Welch spectrum (50), (57), (14). The same goes for the simple peak count method, which is one of the clinically useful and frequently used method of OMT dominant frequency estimation (31), (34), (75), (159),(71).

Significantly, all these spectral estimations techniques are best suited for stationary signals, yet the stationarity of the OMT time series has not been investigated in any detail. In the case where the OMT signal is non stationary and variations in the OMT frequency with time are present, then the peak count, AR spectrum and Welch spectrum estimates of the dominant frequency will be less precise depending on the degree of non-stationarity of the signal analyzed (225). This due to the fact that the variation of the frequency with time

will be averaged out (in the case of peak count) or neglected (where the frequency spectrum peak is determined by the AR and FFT methods).

The difference between the OMT burst activity and OMT baseline activity in both amplitude and frequency with time could imply that signal is nonstationary. Due to these facts an investigation of the OMT stationarity is required. In this work we investigate the stationarity of the OMT signal in chapter 4.

1.5.4 Nonlinearity

Nonlinear signals are signals that cannot be modeled by Gaussian linear stochastic process (226). The study of nonlinearity in signals is motivated by two reasons. First it helps uncover underlying nonlinear components in the system and whether a realistic model of the process requires a nonlinear element. For example in the modeling of the smooth pursuit (227) and saccadic (228) eye movements a nonlinear model was found to give a closer fit to the measured data than a linear model. This is of interest to OMT modeling as the nonlinear behavior in those movements could be due to how the eye extra-ocular work which also generates OMT signal. Secondly, if the system has nonlinear components then nonlinear measures (such as correlation dimension (229-230), Lyapunov exponent (231-232) or signal complexity (233-234)), may help classify and identify the abnormalities in the system.

A change in some monitored nonlinear parameter of a biomedical signal could potentially be a marker of a change in the health condition of the monitored patient. This hypothesis has led to the use of nonlinear measures in the analysis and modeling of a number of biomedical signals such as hand tremor(235), electrocardiogram (ECG)(236), heart variability (HRV) (237) and electroencephalogram (EEG) (238). For example the cardiovascular system exhibits nonlinear activity and standard HRV measures (such as mean, standard deviation and root mean square of successive RR interval difference) may not be able to detect these nonlinear changes (239). Such as in monitoring of CABG

(coronary artery bypass grafting) patients, the short-term fractal scaling exponent (α) was found to be more sensitive to it than classical methods (e.g FFT) (240).

1.5.4.1 Surrogate data test

Surrogate data (or surrogates for short) is a method used to test for nonlinearity in a time series (241). The technique is based on generating time series which have all the linear properties of the original time series, but which distort the nonlinear deterministic structure in the time series tested.

The surrogate data nonlinearity statistical test is based on computing the statistical difference between the original time series and a linearised version of the data (surrogates). The discriminating statistic is found using nonlinear measures such as correlation dimension (242), Lyapunov exponent (243), time reversal (244) and average mutual information of the signal (245).

The two main null hypotheses used for statistical testing of non-linearity are 'simple' and 'composite'. The simple null hypothesis assumes that the time series is a linear stochastic process. The composite null hypotheses test assumes the time series is a linear stochastic process driven by Gaussian white noise.

The most commonly used techniques for generating surrogates are random shuffling (RS) (246), Fourier transform (FT) (246), amplitude adjusted Fourier transform (AAFT) (247), iterated AAFT (iAAFT) (248), digitally filtered shuffled (DFS) (249) and truncated iAAFT (tiAAFT) (250).

1.5.4.2 OMT and nonlinearity

In the literature, there has not been any investigation of the nonlinearity of OMT data and models of OMT generation system are based on linear models such as the neurological and neuro-mechanical model introduced by Sheahan (6). Clinical investigations with patients have shown some cases where an abnormality (an irregular signal pattern) in the OMT

signal was present, but which was not well differentiated from normal OMT signals using frequency spectra measures (such as peak count or linear predictive spectrum) (251). There is some loose evidence that OMT from some patients can be more ‘irregular’ than normal OMT. The first question is if the OMT data from normal subjects and/or patients should be regarded as nonlinear. Secondly, if present, are such irregular structures in the OMT signal due to nonlinear components in the OMT generation mechanism. If this is true then it will lead to the introduction of new methods for analyzing OMT sensitive to changes due to nonlinearity. This will also imply a nonlinear approach should be considered to build a more realistic OMT model for a better understanding of the OMT generation process. Chapter 4 in this thesis examines the linearity assumption of OMT. Also Chapter 6 examines the possibility of using one of the signal complexity measures (Permutation entropy) as new clinical marker of OMT.

1.5.5 OMT features extraction

1.5.5.1 Gabor transform

Most biomedical signals are regarded as nonstationary (such as speech signals, ECG and EEG). In general the frequency of these signals varies with time. Classical Fourier transform analysis can determine the frequency components of signals, but cannot indicate where or for how long those frequencies existed within the signal.

One of the advantages of the Gabor Transform Spectrogram over the Short-time Fourier Transform is that it is invertible (the time domain signal can be constructed from the Gabor transform). The invertible property of Gabor is used in implementing a time-varying filter by modifying the Gabor time-frequency domain information (by either masking or thresholding the Gabor coefficients) and then applying the discrete Gabor expansion to return to time domain signal. This technique (called a Gabor time-varying filter) is used frequently in filtering of noise as in general noise information is represented

by low Gabor transform coefficients, and can be filtered by thresholding the coefficients (252).

The Gabor transform has been implemented in a number of biomedical signals such as the analysis of frequency rhythms of EEG (253), the study of frequency band behavior during epileptic seizure (254) and in heart beat reduction noise (Gabor time-varying filter) in lung sound measurement (189).

1.5.5.2 Automated OMT features extraction

The difficulty in the differentiation of OMT baseline activity (70 Hz-126 Hz(159)) from burst activity (75 Hz- 115 Hz(31)) is that both frequency ranges overlap and normal band pass filtering will not work. One of the possible solutions would be to identify the burst of OMT using a joint time-frequency representation of the time domain OMT signal. The OMT burst will appear having a high energy level in the joint domain as the bursts have higher amplitude, near-sinusoidal oscillation compared to the low amplitude irregular oscillation of baseline. The Gabor time varying filter is a possible solution for recovering the high energy coefficients of the time-frequency domain using a suitable threshold. This would provide an automated method for identifying the OMT features (bursts and baseline). Chapter 5 investigates the possibility of using a Gabor time varying filter to extract the high energy information (higher Gabor coefficients) of the joint time-frequency domain and compares this approach to burst identification by human observers.

1.5.6 OMT analysis approaches

Advances in signal analysis have enhanced the diagnostic potential of physiological signals in clinical studies by introducing new techniques and characterizing the role of the old and new techniques. Those advances in signal analysis will improve the potential of the OMT signal as a clinical marker in clinical trials. In this work we implement new analysis methods in analyzing the OMT signal in clinical investigations.

Sheahan has examined three OMT frequency markers (peak count, Welch spectrum and AR spectrum) (11), (50). The study was limited in three aspects. First the comparison was carried out on simulated signals and not on real patient data. Secondly the study did not examine the OMT features. Thirdly the investigation was based on OMT signal simulation with stationarity and linearity assumptions.

A comprehensive study of the efficiency of the standard OMT clinical markers in determining normal subjects and patients in OMT clinical investigations has not been yet carried out. Secondly there are several new markers could be implemented in OMT such as signal complexity measures. These two issues are carried out in chapter 6 in this thesis.

1.6 Conclusion

There are number of clinical studies in ocular microtremor reported in the literature that clearly demonstrate the potential of OMT as a clinical marker in a range of clinical conditions including coma, Parkinson's disease and stroke. Despite this, OMT has received little attention in terms of measurement techniques, processing approaches and in investigation of fundamental signal characteristics

Current OMT measurement methods suffer from a number of limitations in terms of both usability and patient acceptability. Most clinical studies are based on using the PZT system, which makes it important to further develop the system to overcome limitations concerning dynamic range, biocompatibility of the probe tips and measurement amplitude variation. On the other hand the PZT system procedure involves the PZT probe coming in contact with the eye which may cause patient discomfort and may alter the OMT signal due to the loading of the eye. Having a noncontacting OMT measurement system will be of great benefit to OMT clinical studies. In the development of noncontact OMT measurement method, work by Boyle (14) has shown the possibility of using speckle interferometry in OMT measurement, but additional research is needed to determine the effect of the biospeckle phenomenon produced by eye sclera on speckle based OMT

measurement. Also study is needed of the speckle correlation technique which may lead to the development of a much simpler noncontacting OMT measurement approach than the optically more complex speckle interferometry method used by Boyle.

A number of biomedical signals have been reported in the literature as being nonstationary and/or nonlinear. There is no work reported in the literature testing assumptions of OMT signal stationarity and linearity. Knowledge of stationarity/linearity is of importance when selecting appropriate signal analyzing method or in building OMT model to understand the OMT mechanism.

One of the challenges in processing the OMT signals is recovering it from the full fixational eye movement trace (including drift and microsaccades) captured by the PZT probe. Current OMT signal recovery methods are based on relatively basic signal processing concepts and have a number of limitations. Some more recently developed signal processing techniques may have the potential to overcome these limitations. Therefore it will be of benefit to develop new methods for recovering the OMT signal and to compare these new methods with the current recovery methods.

The OMT features (bursts and baseline) have been shown to be of value in clinical investigations. However current methods of estimating burst/baseline are based on visual inspection, which is time consuming and not reproducible. Joint time frequency analysis might be the key to develop an automated feature extraction method that will overcome the limitations of visual inspection, which has not been investigated in the literature.

Clinical assessment of the OMT signal is based on measures of the dominant frequency of OMT spectrum and on measures of the OMT burst/baseline features. However there is no comprehensive report in the literature examining the relative performance of these measures in distinguishing between normal subjects and patient OMT. Such an examination will be of importance in choosing appropriate OMT clinical markers.

Ch2

20MT PZT system

2.1 Introduction

This chapter explains the design and build of the measurement system used to record the OMT signal in experiments described elsewhere in this thesis. The measurement system is based on the piezoelectric technique (PZT system) used previously by a number of authors (7), (38), (27), (29). The chapter starts by addressing the limitations of the current PZT systems used for OMT measurement and then describes the modifications implemented here to overcome some of these limitations. The work also investigates the impact of the variation of the probe mass on OMT measurement.

2.2 Proposed modification to the current PZT system

Although nearly all quantitative clinical investigation of OMT has been carried out by the PZT system (open eyelid in particular), the current design suffers from a number of limitations that are discussed in detail in the literature review.

2.2.1 Probe advancing

Current PZT system requires considerable operator skill to bring the bimorph probe correctly into contact with the eye sclera, using the manually advanced screw mechanism

(see Figure 10), and the pressure applied to the eye may differ from measurement to measurement.

The work done here implements a new technique for advancing the probe to the sclera based on gravity feed to overcome the difficulties with screw method used by Sheahan (7).

The effect of probe loading has not been studied in detail. Work by Bengi and the Thomas (77) was the only study that investigated the loading effect, but was limited in looking at the loading effect in the frequency spectra power shape. Also the probe pressure variation may be implicated in measurement variation seen with Sheahan PZT system (7). The work will include investigation of effect of the probe mass on changes in OMT frequency power and amplitude. This result will be useful in choosing an optimal probe mass for the new developed PZT system.

2.2.2 Dynamic range



Figure 23. The proposed modification to the new system to have a higher dynamic range that will overcome the dynamic range issue.

The PZT probe can sense all three fixational eye movements (microsaccades, drift and OMT). The PZT systems are designed with a dynamic range of 25nm-2500nm (40 dB) (7) to record only OMT. The limiting factor on the dynamic range was that a 12bit ADC was used in the design. To capture all the fixational movement without filtering them, the dynamic range has to be at least 73 dB (or 25nm- 110 μ m, adapted from the amplitudes of the fixational eye movements reported in (47)).

Improvements in available analogue to digital converter technology since the system designed by Sheahan (50) was built will allow a wider dynamic range to be implemented,

capable of digitizing all three fixational movements without a requirement for pre-filtering in the analogue domain. This will be useful to clinically study the other fixational movements and how they interact with OMT and in future investigations of PZT probe behavior with eye movements. Recent developments in digital signal processing provides a number of ways that may be useful in to separating the different eye movements from each other such as Wavelet denoising and blind source separation. To be able to investigate the full potential of such techniques the signal from the PZT probe has to be digitized without affecting OMT and microsaccades content of the signal captured by the PZT system (higher dynamic range). This approach is applied in the new development of the PZT system as shown in the block diagram Figure 23 (compared to the block diagram of the current PZT system in Figure 13).

2.2.3 Probe tip

The probe tip that comes in contact with the eye should be made from a biocompatible material. PZT systems tips described in literature (50), (38), (67), (27), (29) are not made from biocompatible materials, which would not be considered best practice in modern designs.

A disposable tip is required to avoid the risk of cross contamination between patients. The tip should be capable of being disinfected or sterilized between trials with same patient. In this work we develop a simple removable biocompatible tip, which can be changed between patients.

2.3 Redesigned PZT system

2.3.1 System requirement

The specification requirement for the OMT system design is based on the specification advised by Sheahan in 1993 (7) with an increased dynamic range. To capture all the fixation movement the dynamic range of the ADC has to be at least 73 dB (25nm- 110 μ m)

adapted from the amplitudes of the fixation eye movements reported in (47). A 24 bit depth ADC is sufficient to provide dynamic range.

The frequency bandwidth is required to be from 20Hz to 150Hz. The amplitude response should be linear and frequency response should not fall below 2dB of the peak value within the system bandwidth. The phase response has to be as linear as possible.

The system should be portable for clinical use and safe for patient measurements. It should also acquire OMT signals from both eyes simultaneously for cross comparison. The cross-talk between the acquired signals from both eyes should be below the acceptable noise level of the system.

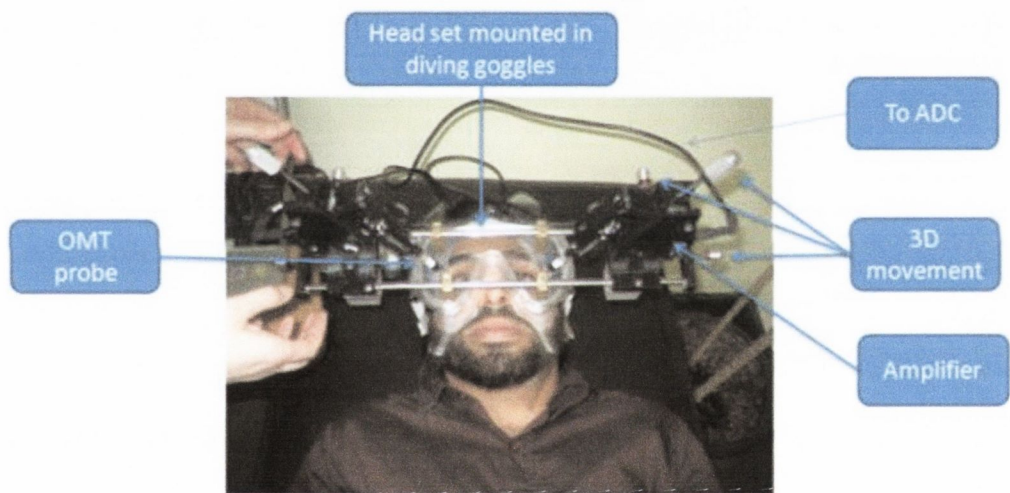


Figure 24. New developed OMT PZT system headset.

2.3.2 New PZT system development

At the start of the development of the new PZT system described here, a basic bench-top prototype model was available to the author, This prototype was based on Sheahan's PZT system design, but was not suitable for clinical use (255), (50).

This prototype was evaluated in terms of patient acceptability and usability. From this evaluation, a new PZT system was designed and built by the author. The main new

developments to Sheahan's design were on the probe biocompatibility, advancing the probe to the eye mechanism and increasing the dynamic range.

With aid of PhD clinical researcher (NC) the new PZT system design was evaluated. Five more design/evaluation iterations followed to improve the system with respect to:

- ❖ Patient safety.
- ❖ Patient comfort.
- ❖ System stability.
- ❖ User acceptability.
- ❖ Dynamic range.
- ❖ Probe positioning mechanism.

For example probe weight was reduced for patient comfort and safety, bearings were introduced in moving parts for easy probe positioning and headset materials and construction were changed to improve system stability.

The user interface software was built in LabVIEW (3) with an interface for use by the clinical investigators. The software allows the user to record, processes and analyse eye movement data from the PZT system (the processing and analysis of data will be explained in the following chapters).

Clinical investigations using the new PZT system were carried by the PhD clinical researcher (NC) in both normal subjects and patients. The OMT data used in this thesis was recorded primarily by one user (NC), unless noted otherwise. The redesign, construction, testing and evaluation for both hardware and software (processing and analysis) of the new PZT system were all carried by author.

Figure 24 shows the newly developed OMT PZT system, where the headset is mounted on diving goggles. The probe can be removed between tests and during OMT measurement the pressure applied to the eye is by gravity feed and depends only on the mass of the probe. A more detailed explanation of the different parts of the system is given below.

2.3.3 Probes

The new PZT system probes were developed using series⁹ piezoelectric bimorphs¹⁰ (custom SV07, 25mm long by 2mm wide by 0.5-0.6 mm thick, Sensor Technology Ltd. Ontario, Canada). The series bimorphs plates are bonded with opposing poling axes facing each other. In the system design, the bimorph leads are soldered to a male 3.5mm stereo jack and 10mm of the bimorph is glued (15mm free end) to the jack forming a cantilever mode of operation (See Figure 25). The jack allows easy removal and attachment of the probe from the headset mechanism for the probe disinfection process.

One of the important things to take in consideration in the design of the PZT probe is the mechanical resonant frequency of the probe as it forms a cantilever mode of operation. The resonant frequency of the probe has to be not within the OMT passband frequency (20Hz-150Hz) range so that we have a linear amplitude response. The mechanical resonant frequency of the bimorph is calculated from the following equation (256):

$$\text{Resonant frequency(Hz)} = 0.16 \left(\frac{h}{L^2} \right) \left(\frac{1}{\sqrt{s_{11}^E \rho}} \right) \quad \text{Equation 6}$$

Where:

ρ is the density of the piezoelectric ceramic (Kg/m²)

s_{11}^E is the compliance (m/N) piezoelectric ceramic.

h is the thickness (m) piezoelectric bimorph.

L is the free end length of bimorph (m)

Increasing the free end of the bimorph will increase the sensitivity (proportional to L^2/h^2) of the probe but will reduce the resonant frequency and make the probe easier to break

⁹ The piezoelectric layers of the bimorph are electrically in series.

¹⁰ Bimorph is a cantilever that made of two active layers.

(bimorph is brittle). Using the above equation the mechanical resonant frequency of the probe is about 1070Hz, well above the flat frequency band required in the OMT measurement system.

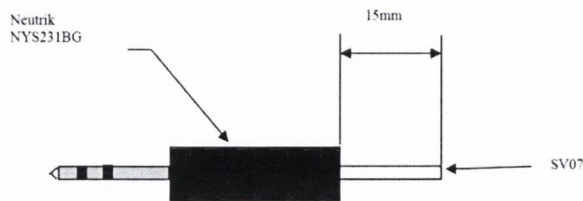


Figure 25. Probe used in the OMT PZT system using a stereo jack with bimorph attached to it.

The free end of the probe is covered with disposable (between patients) sheaths made from biocompatible medical grade silicone (MDX4-4210, Dow Corning). The sheath ends are made wide (4mm diameter) to reduce the pressure on the sclera during measurement (see Figure 26). The silicone sheaths are custom made using aluminum molds and heated in an oven at 75 °C for 30 minutes (for fast curing). The silicone protects the eye from the bimorph (even if the bimorph breaks) and satisfies the infection control requirement of being disposable and biocompatible. The silicone cap is held to the probe tightly by applying silicone (MDX4-4210) around the proximal end of the cap and probe for secure and easy replacement. This process was done every time the cap was replaced.

The probe with the cap secured to it is disinfected by soaking the silicone part of it in fresh disinfection solution (Opti-Free EXPRESS, Sicon) for at least 6 hours before use.

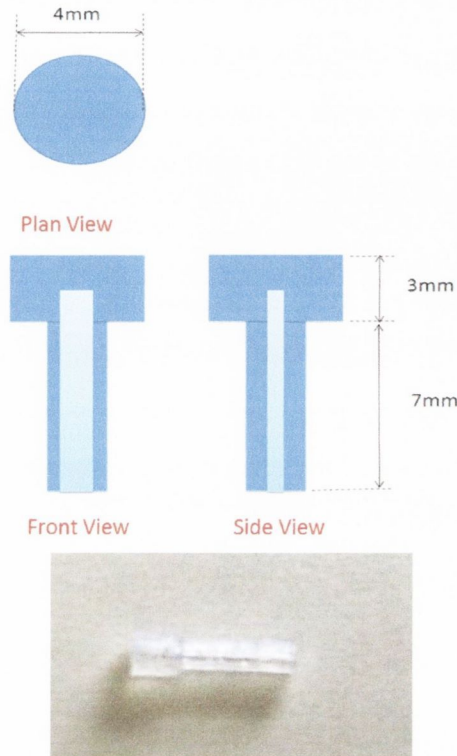


Figure 26. Schematic diagram of the tap and photo of silicone tip.

2.3.4 Headset

Figure 27 shows the sliding mechanism of the newly developed PZT system. The OMT probes are plugged and unplugged to the headset by means of a female 3.5mm stereo jack fixed to a precision linear ball slider. The slider is controlled by a mini vice (See Figure 27 and Figure 28). Once the probe comes in contact with the eye sclera, further turns of the mini vice will not advance the probe any further and the probe rests on the sclera (see Figure 29 for more clarity). The pressure of the probe into the sclera in this state will depend on the mass of the probe and the slider part attached to it (a total of 14g). The slider with mini vice has a safety pin to prevent applying force to the slider that might increase the pressure applied to the eye. The release of the probe from the eye can be done quickly by moving the slider up by hand or by the unscrewing the mini vice.

In this design the gravity feed probe fixed the slider replaces the screw mechanism used to advance the probe in Sheahan's design and allows for constant pressure to be applied to the sclera between trials. Unlike the screw mechanism the probe is not held rigidly against the eye. This provides a safety margin if the eye is accidentally brought towards the probe (such as gross eye movements) as the probe will move on its slider (the probe has 38 mm to 10 mm free movement).

The PZT headset and other PZT system components schematic drawings design were build in AutoCAD (257). The headset provides 3D positioning of the probes which are mounted in diving goggles. The goggles reduce unwanted head movements and reduce the risk of injury from the probe caused by sudden head movements as the goggles allow the whole system to move with the head.

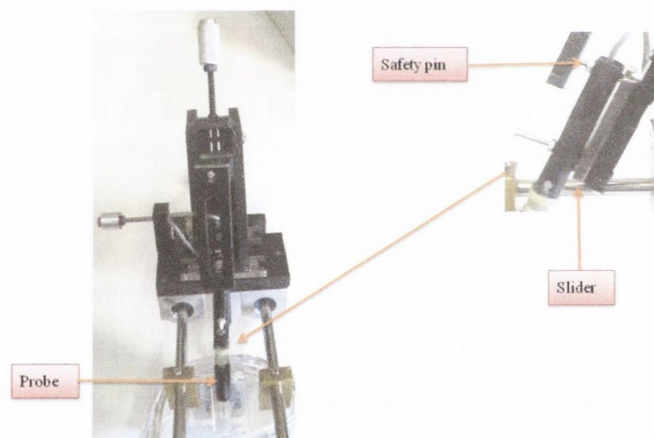


Figure 27. The sliding mechanism for the PZT system that provides gravity dependence in the pressure applied to the eye during the recording. .

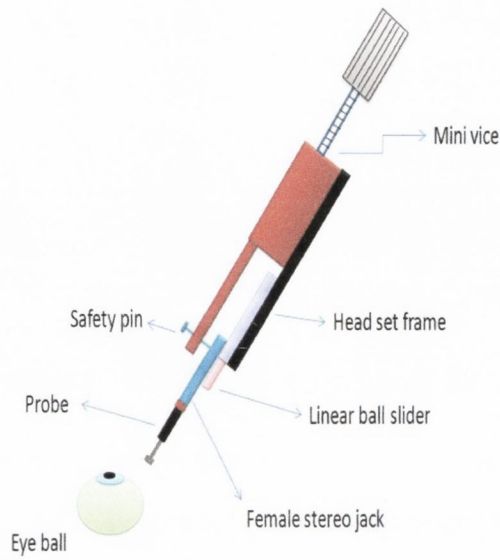


Figure 28. The sliding mechanism in the new PZT system.

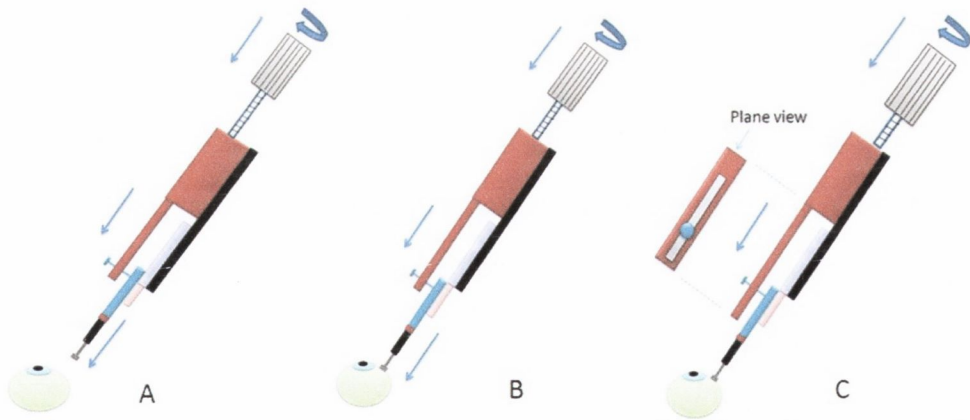


Figure 29. A. The probe is first advanced by the sliding of the slider, which is controlled by a mini vice. B. Once the probe comes in contact with the eye sclera, the probe will rest on the eye sclera by gravity. C. further advancing the mini vice will not advance the probe as the safety pin is not attached to the mini vice (see plane view).

2.3.5 Circuitry

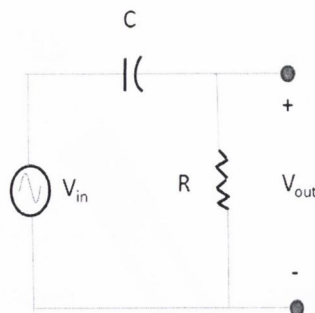


Figure 30. Equivalent circuit (Passive first order high pass filter) of the piezoelectric bimorph.

The bimorph probe forms a voltage source with a capacitance in series, which implies that the probe with the input impedance of the amplifier circuitry forms a first order high pass filter (see Figure 30). The first order high pass filter 3dB point (f_0) is calculated from:

$$f_0 = \frac{1}{2\pi RC} \quad \text{Equation 7}$$

Where C is the probe capacitance and the R is the input impedance of the circuit. The power response of the filter is calculated as follows (258):

$$\frac{\text{Power out}}{\text{Power in}} = \frac{1}{1 + \left(\frac{f_0}{f}\right)^2} \quad \text{Equation 8}$$

where f is the frequency in Hz. The combination of the above equation gives:

$$\frac{\text{Power out}}{\text{Power in}} = \frac{1}{1 + \left(\frac{1}{2\pi fRC}\right)^2} \quad \text{Equation 9}$$

The mean capacitance of the bimorphs was measured to be about 7.7nF. We seek a power response within -2dB (0.64) between 0.5 Hz to 200Hz (the OMT signal activity is between 20-150Hz). This means that input impedance should be higher than the following (using the above equation):

$$R = \frac{2}{3\pi fC} \quad \text{Equation 10}$$

Which implies that input impedance should be greater than $55\text{M}\Omega$ with $f=0.5\text{Hz}$. This was achieved using a high input impedance instrumentation amplifier (BB. INA114). The gain was set to 100 for both probes (left and right eyes). The amplifier circuits are brought as close as possible to the bimorph probes to reduce noise and all the leads and circuits are shielded to reduce 50/60Hz supply interference. The two circuits from the right and left eyes probes are kept apart to reduce cross-channel interference.

The outputs from the two instrumentation amplifiers are fed directly to a USB analog to digital convertor (NI USB-9233). The A/D samples at up to 50k bytes/s, with a 24-bit resolution (102 dB dynamic range), which allows acquisition of the PZT system signal without pre filtering. The A/D board includes a variable anti-aliasing filter, which is important as no low pass filter is included in the circuit design. The sampling frequency is set to 2500 samples/s. The captured signals are displayed on screen and recorded in .txt file format for digital signal processing. Figure 31 shows the block diagram of the new PZT system circuitry.

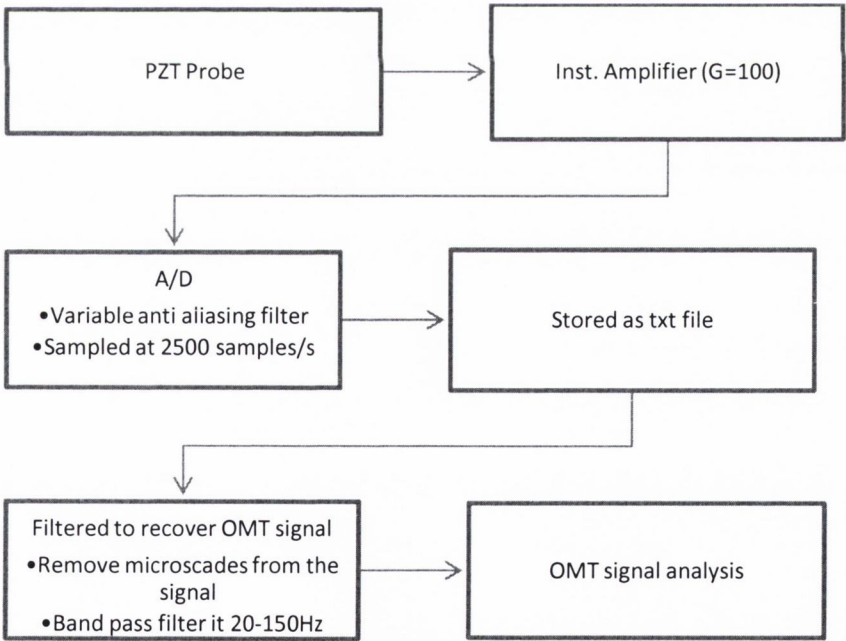


Figure 31. Block diagram of the new PZT system circuitry.

2.3.6 Electrical safety

The PZT system was tested and passed electric safety in compliance with International Electrotechnical Commission (IEC) standards (IEC 60601-1) for the design of medical devices (259). The testing was done in St. James's Hospital with approval from the department of Medical Physics & Bioengineering using a RIGEL electrical safety analyzer.

2.3.7 OMT recording and analysis software

For the PZT system two programs (OMT reader program and OMT writer program) are custom made to assist clinicians in their OMT studies. Those programs were written using LabVIEW (3).

2.3.7.1 OMT writer software

The OMT writer program allows the user to display the two signals captured by the PZT system from the right and the left eye in real time. It also provides a real time frequency spectrum of the two signals for the user, which is useful for monitoring the frequency content of the signal acquired and to determine if there is noise disturbing the recording. The program stores the signals in a .txt file format, with time recording duration control. It also allows acquisition and storage of a third signal (used in clinical investigation for ECG signal capture and also to capture trigger signals for clinical studies involving EEG and visual tasks).

2.3.7.2 OMT reader software

The reader program allows the user to choose the file stored by the OMT writer program and the part of the signal to be analyzed. The user has two options in choosing a method to recover the OMT signal from the full eye movement signal, using the wavelet technique (default) or the cutting method (more detail about these techniques will be described in detail in the OMT recovery chapter). The program allows the user to use a digital notch filter to remove 50 Hz hum if present. The recovered OMT signal is displayed in the time

domain and in the time-frequency domain. The program gives a frequency spectrum plot of the signal using a user selection of either: normal FFT, Welch spectrum or AR spectrum. The frequency of the spectrum peak of the OMT signal and the number of peaks per second is also shown. Figure 32 shows the OMT reader program.

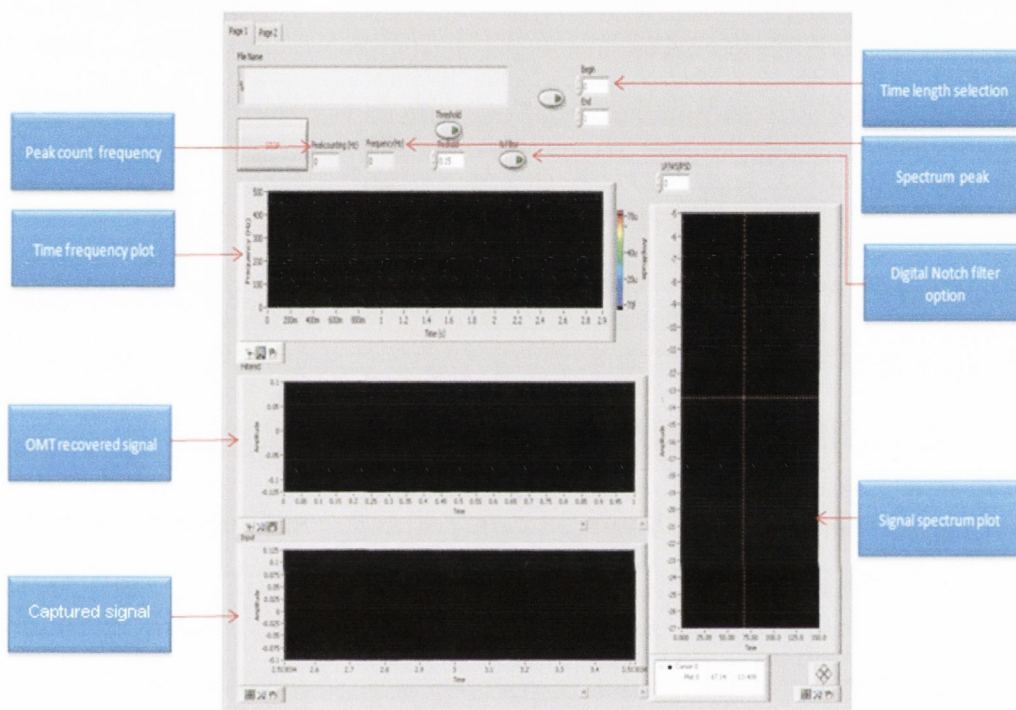


Figure 32. OMT reader program.

2.3.8 Procedure for OMT recording

As the newly developed OMT PZT system is based on gravity pressure probe placement on the eye sclera the subjects are asked to lie supine on a bed during the OMT recording¹¹. Both eyes are anesthetized using Proxymetacaine Hydrochloride 0.5%, with two drops per eye for comfort during the recording procedure. Adhesive tape pieces are applied to the

¹¹ Note that supine recording is the norm with PZT systems.

subject's eyes. One end of each piece of tape is kept free and the other ends secured to the lower and upper eyelids to ensure a clear view of the eye sclera when retracted. This allows placement of the probe without eyelash and eyelid interference in the recording. Next the headset is securely mounted on the head using Velcro straps and the subject is asked to look straight ahead and to hold the head as still as possible. The probes are then brought close to the eye sclera and next the eyelids are retracted using the adhesive tape which is then secured to the cheek and forehead. The probes are brought in touch with sclera near the sclera-corneal junction and the digital recording process is set for 30s duration. After measurement the probes are immediately removed from the eye and the headset is also removed. The full procedure takes about 5 minutes.

2.4 System test

2.4.1 Methods

2.4.1.1 OMT simulator

To test the performance of the developed PZT system an OMT simulator is used. The simulator is based on the scleral surface simulator used by Sheahan(50), which was further developed by Boyle (61). The simulator is made of a white plastic disc to model the eye sclera, mounted on three piezoelectric bimorphs as shown in Figure 33. As the bimorphs bend into an arc rather than rotate about a fixed point, the three simulator bimorphs are made twice as long as the average radius of human eyeball to give a close approximation for the OMT arc displacement (50). The outer bimorphs are used to drive the mounted disc and the third is used as a reference for the calibration of the simulator.

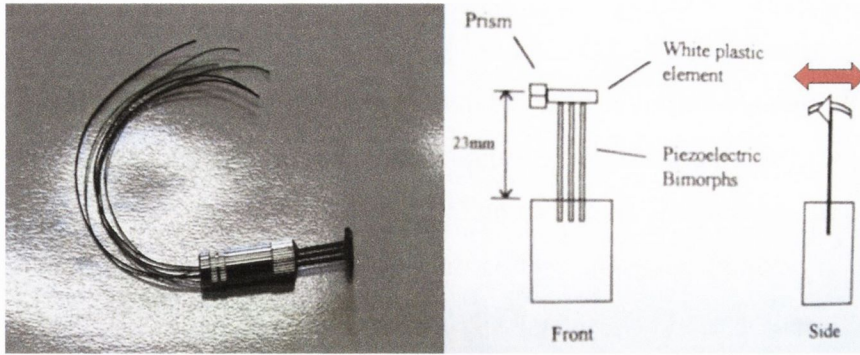


Figure 33. The OMT simulator to the left and the OMT layout to the right

A small prism (Melles Griot, 4.5mm along hypotenuse edge by 3.2mm deep) is used to calibrate the simulator using a He-Ne laser Michelson interferometer. The amplitude, phase and the frequency response are tested over the OMT range (20Hz-150Hz).

2.4.1.1.1 OMT simulator displacement calibration

The calibration of the simulator is based on the tangential displacement versus the output voltage from the reference (middle) bimorph. The calibration is carried using a Michelson interferometer with a He-Ne (632.8nm) laser as a source. The setup is arranged so that it measures only the active displacement component of the simulator (see Figure 34). The laser beam is directed to a beam splitter (50:50) which divides into two beams. One of the beams is directed to the simulator prism and one to a fixed mirror as a reference beam. The reflected beam from the prism is parallel to the incident beam throughout the motion of the simulator. The interference fringes formed by the recombination of the two beams are detected by a photodiode.

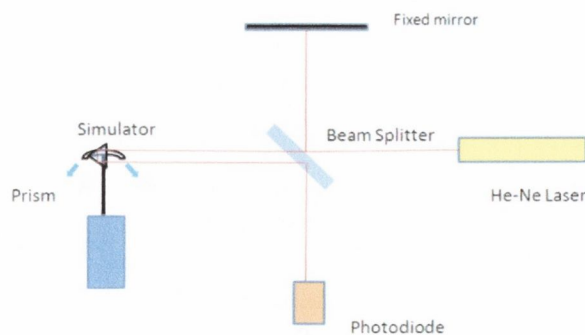


Figure 34. Calibration setup for the OMT simulator using Michelson interferometer.

For the calibration procedure a 20Hz sinusoidal signal of 10Vp-p is used to drive the simulator. The photodiode output and the simulator reference output are displayed together on an oscilloscope. The output from the photodiode will appear as series of peaks (a peak to peak represents a transition from bright to dark to bright interface fringe), with a discontinuity (every 25ms) when the simulator reverses direction (see Figure 34). Each peak to peak represents a $\frac{1}{4} \lambda$ (158.2nm) displacement of the simulator. This fact is used to calibrate the simulator by noting the change in reference voltage output from the first peak after a discontinuity to subsequent peaks and the corresponding displacement change. Figure 37 shows a plot of the simulator displacement verses the reference output.

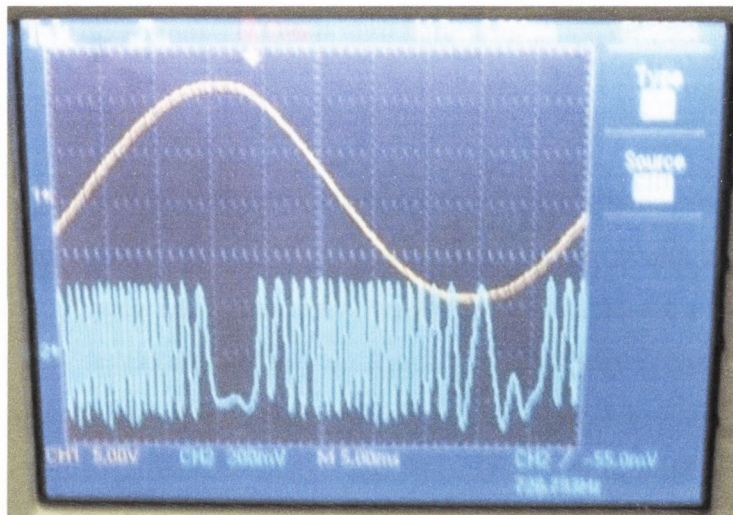


Figure 35. The oscilloscope display, with the simulator reference output in top and the photodiode output in the bottom.

2.4.1.2 Performance verification tests

Using the OMT simulator, five probes of the new PZT system were tested for their frequency response and phase response from 20Hz to 150Hz to see if they meet the system design specifications stated above. The amplitude response of 10 probes was also tested to see the variation between probes. The system was tested in-vivo with a normal subject to assess the increased dynamic range and to determine qualitatively if microsaccades and drift could be captured without causing system saturation.

2.4.1.3 Measurement of sources of variation in the new PZT system

To quantify measurement variations in the new PZT system, the coefficient of variation (C_v) is used as measure of dispersion. The coefficient of variation is calculated as follows:

$$C_v = \frac{\text{standard deviation}}{\text{mean}} \quad \text{Equation 11}$$

The following experiments were carried out with an inexperienced operator using the newly developed PZT system.

2.4.1.3.1 Amplitude variation due to the loading of the simulator

This experiment was carried out to see the effect on the amplitude response of the simulator when it is loaded by the probe (14g). The simulator was driven with a sinusoidal signal (80Hz) over a 0-24Vp-p range. The reference output amplitude of the simulator was compared in the loaded and unloaded cases

2.4.1.3.2 Variation in the probe sensitivity due to loading

This experiment was carried out to test the variation of the measurement probe sensitivity with different pressures applied by the probe to the sclera simulator. The simulator is set at 80 Hz with a constant peak to peak displacement of 1 μ m (corresponding to ~1.77V pk-pk output from the simulator reference). The mass is varied from 14g (probe minimum mass) to 36g and the probe output noted. Note that the displacement of the simulator is damped due to the loading of the probe to the simulator. A constant 1 μ m pk-pk displacement was achieved by varying the amplitude of the sinusoidal signal driving to the simulator at each load to maintain a constant simulator reference voltage output.

As described in the literature that Sheahan found 11% coefficient of variation for the OMT amplitude with an inexperienced operator (50). For cross comparison between Sheahan PZT system with screw mechanism and the new developed system with the sliding mechanism, an additional test with an inexperienced operator was done using a similar experimental setup. The 14g probe was used with the simulator set to 80Hz sinusoidal

signal with peak to peak displacement of 1 μ m. The operator was asked to bring the probe in contact with the simulator and measure the amplitude of the captured signal. This procedure was repeated for ten times and then the coefficient of variance was calculated using the ten amplitude measures.

2.4.1.3.3 Variation in in-vivo OMT amplitude and frequency due to the different loading

This experiment was done to see the actual variation *in-vivo* in measured OMT amplitude and frequency with probe mass. One healthy volunteer aged 27 years old was recruited for this investigation and the recording was done with a relatively inexperienced operator. The subject was asked to not drink any source of caffeine or eat anything four hours before the testing. Two OMT records at 30 minutes intervals were taken on five separate days. During the recordings the subject was asked to fixate on a fixed target and the room illumination was kept as constant as possible. The loading on the eye sclera by the probe and extra masses were randomly changed between each test (14g, 15.2g, 16g, 16.5g and 18.5g). Load was varied only on the right eye while the left eye was loaded only with the 'standard' 14g probe. OMT was recorded from both eyes simultaneously for a 20s period. The probes used in the in vivo experiment were first calibrated using the OMT simulator and the output of the probes in volts was converted to displacement in μ m. The same probes were also used for the right and left eyes during all the experiment.

The signals captured by the PZT system were further digitally processed using the newly developed wavelet denoising technique to recover the OMT signal (described in more detail in Chapter 3) (149). The signal was then digitally bandpass filtered from 20-150Hz to remove drift and noise.

To investigate the variation in amplitude within each record, the coefficient of variation of the OMT amplitude RMS value was calculated for each OMT record of the right eye. This done by dividing the 40s records (20s first trial and 20s second trial) into 5s segments and the RMS amplitude was found for each segment. Then the RMS mean of the segments and the standard deviation was calculated for each 40s (first trial + second trial).

To investigate the variation in the OMT dominant frequency, the linear predictive spectrum method was used to estimate the OMT frequency spectra peak for each record. The model order was determined for each record by the Akaike information criterion (a detailed explanation will follow in Chapter 6).

To investigate the variation in OMT dominant frequency within each record, the coefficient of variation of the OMT dominant frequency was calculated for the OMT record of the right eye. This was done by dividing the 40s records (20s first trial and 20s second trial) into 5s segments¹² and the OMT spectrum was calculated for each segment using the Linear predictive spectrum (as above). The frequency spectrum peak was noted for each segment. Then the mean and the standard deviation were calculated for each 40s. Then the coefficient of variation was calculated for each day using the right eye records.

2.4.2 Results and discussion

2.4.2.1 OMT simulator

Figure 36 shows the frequency response of the simulator when loaded by the 14g PZT system probe,) and when unloaded. The frequency response is nearly flat over the frequency range of interest (20-150Hz). Figure 37 shows the results of the simulator amplitude calibration. The response is linear with a calibration factor of approximately 0.57 nm /mV.

¹² 5s OMT duration would be a reasonable balance of the measurement precision and analytic effort

159. Bolger C SN, Coakley D, Malone J. High frequency eye tremor: reliability of measurement. Clin Phys Physiol Meas. 1992 13(12):151-9.

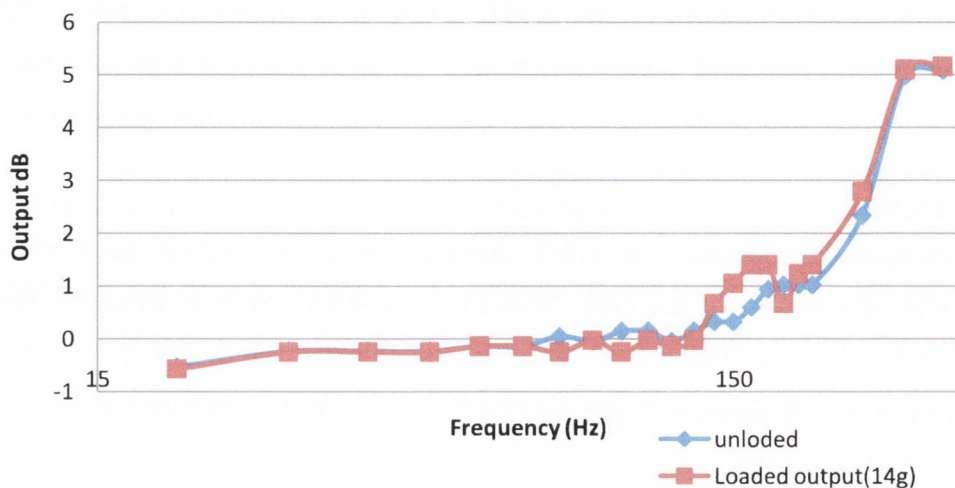


Figure 36. The frequency response of the simulator in unloaded and loaded conditions.

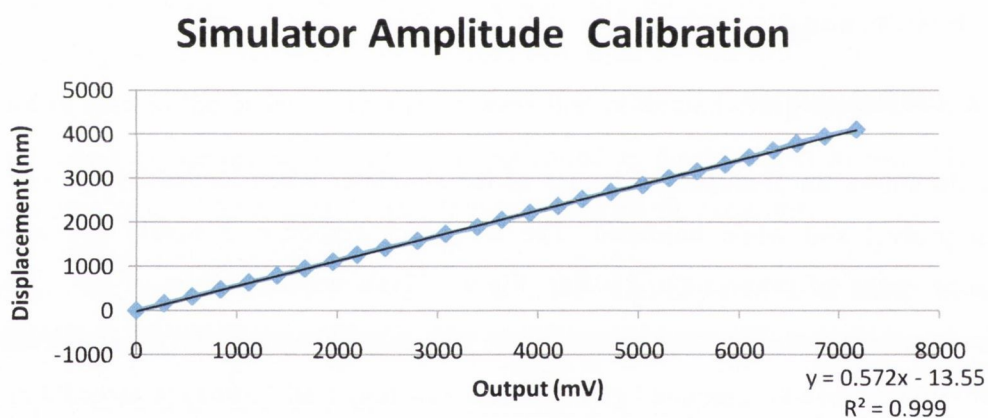


Figure 37. Simulator amplitude peak to peak displacement calibration

2.4.2.2 Performance verification tests

2.4.2.2.1 Probe

Figure 38 shows the frequency response of five PZT system probes. The response is nearly flat with small peaks of 0.4dB magnitude over the OMT frequency range of interest which are acceptable (7). Figure 39 shows the phase response of the same five probes. The

response variation was about linear ($R=0.61$), which meets the requirement being as linear as possible (7). From linear regression, the probe amplitude response was found to be linear with an average R value of 0.992 from ten probes (see Figure 40). From the amplitude response of the 10 probes tested it can be seen that there is a variation between the probes. The average calibration factor of the probes is about $3.21\text{mV}/\mu\text{m}$ with standard deviation of $0.95\text{mV}/\mu\text{m}$. The high standard deviation suggests that each probe needs to be calibrated independently with the simulator for accurate OMT amplitude measurement.

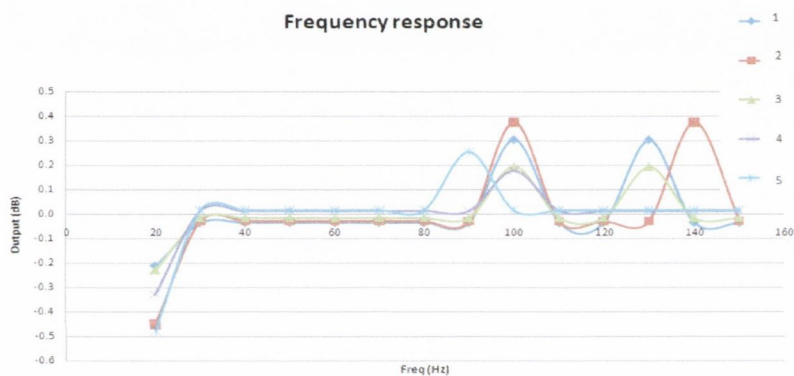


Figure 38. Frequency response of five PZT system probes.

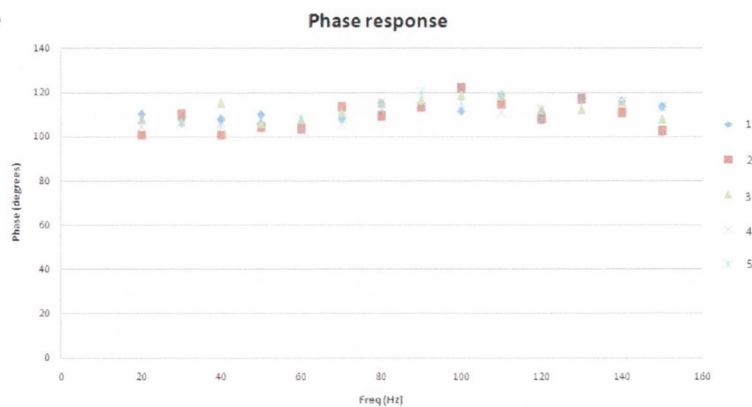


Figure 39. The phase response of five PZT system probes.

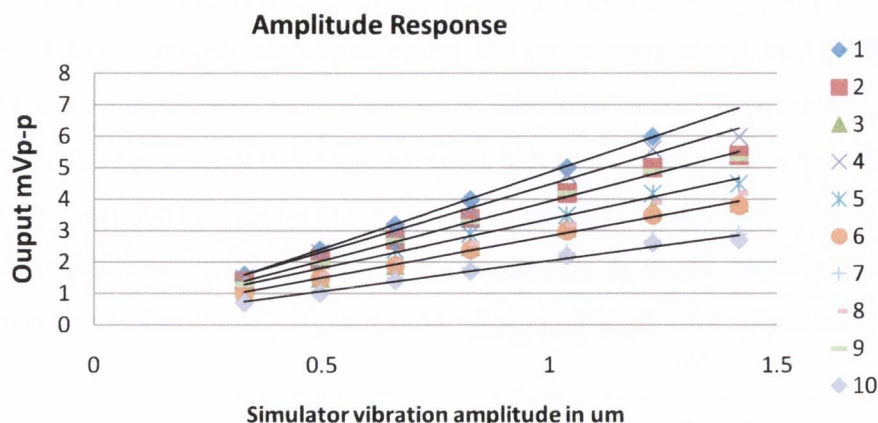


Figure 40. The amplitude response of 10 PZT system probes (1-10). Average R value of 0.992 and the average calibration factor of the probes is about 3.21mV/μm with standard deviation of 0.95mV/μm.

2.4.2.2.2 Performance of the new PZT system

Figure 41 shows the newly developed PZT system during an OMT recording. The new sliding mechanism has two advantages over the screw mechanism used in previous systems. First it does not require a highly skilled operator. Second, a constant pressure is applied to the sclera and this may reduce the error due to variation of the pressure applied. This will help increase the accuracy of OMT amplitude measurement using the PZT system.

Figure 42 shows a one second trace of the signal captured from a healthy subject using the new PZT system. The figure demonstrates the three fixation eye movements: microsaccades, OMT and drift. The system can capture the three movements, unlike the old system where the filtering was done in the analogue domain and caused a ringing response and saturation clipping due to the fast, high amplitude of the microsaccades compared to OMT (149). This will allow the application of advanced signal processing to recover the OMT signal in the digital domain as will be explained later. Also, microsaccade information could be retrieved for clinical studies that need to simultaneously investigate OMT and microsaccades.

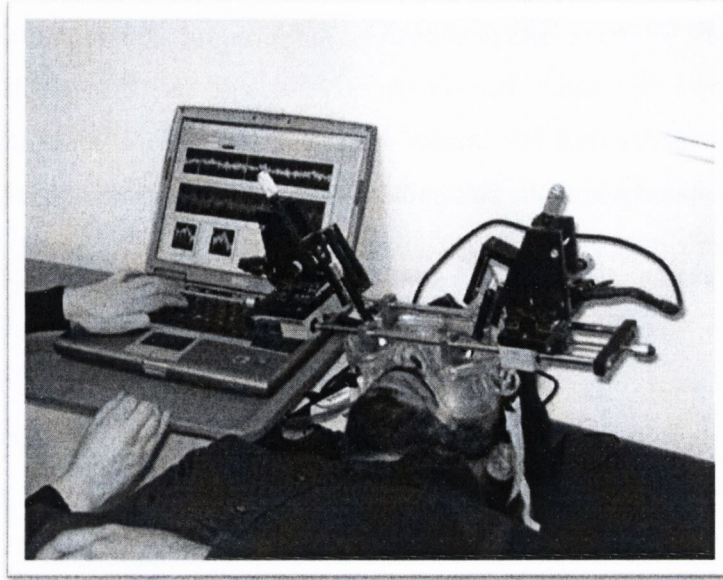


Figure 41. The new PZT system during OMT recording

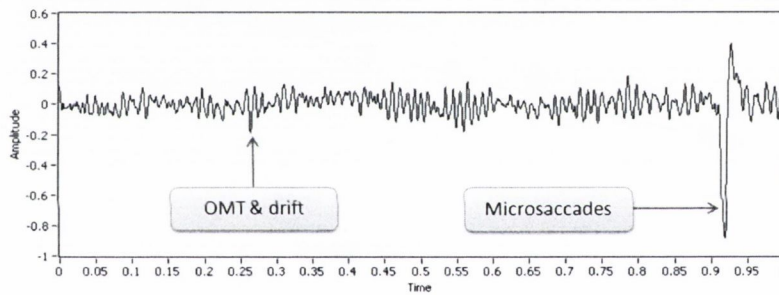


Figure 42. Shows a one second OMT signal captured by the new PZT system

2.4.2.3 Measurement of sources of variation in the new PZT system

2.4.2.3.1 Amplitude variation due to the loading of the simulator

Figure 43 shows the amplitude response over the range of interest 25nm – 2500nm of the simulator with input sinusoidal signal (80Hz) voltage plotted verses the simulator reference output. Two conditions were tested: unloaded and loaded (with the OMT probe: 14g). Both cases show a linear amplitude response (note that we here measuring the simulator reference voltage not the PZT probe output). The unloaded case is tested as it is

necessary to use the simulator with noncontact OMT measurement techniques such as described in Chapter 7. The results demonstrate that the simulator response remains linear when it is loaded by a test probe, although the drive voltage must be increased to achieve a given displacement under load conditions. A given displacement under loaded/unloaded conditions is set by reference to the calibration curve in Figure 37 relating simulator output voltage to displacement.

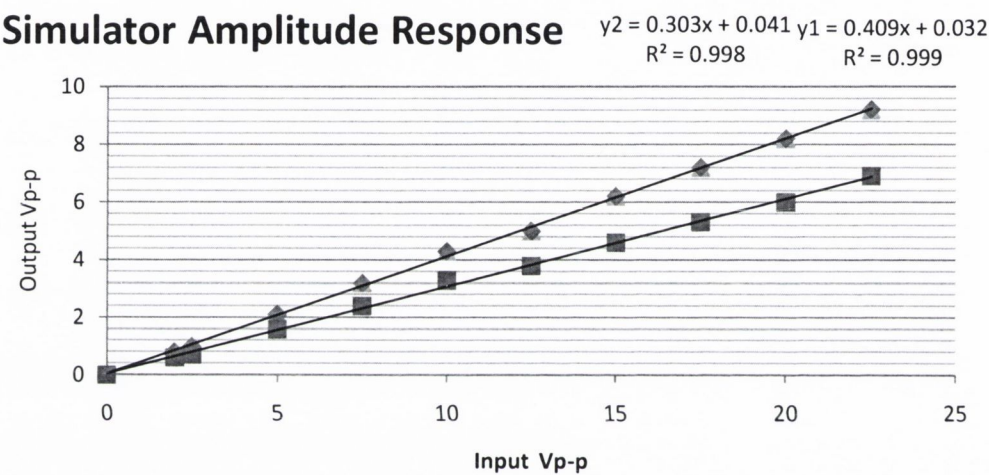


Figure 43. The simulator amplitude response with blue points (y1) represents the response of being unloaded and the red points (y2) of being loaded with OMT PZT probe.

2.4.2.3.2 Variation in the probe sensitivity due to loading

Figure 44 shows the variation in the probe output with different loads (probe + mass added) using the gravity sliding technique with the simulator set to 80Hz with peak to peak displacement of 1µm. Four of the five probes showed voltage outputs within an 8% variation relative to the standard 14g probe voltage output for 14g-29.2g loads. A fifth probe showed a voltage variation of 22%. The results also show an average variation

increase of 23% with a 35.6g load for all the probes relative to the voltage output for a standard 14g probe. This suggests that for patient comfort and safety the probe mass should be as low possible. The total mass loaded on the subject’s eye is set 14 ± 1 g with the gravity sliding mechanism and standard probe used in this PZT system.

The additional test with an inexperienced operator to investigate amplitude variation with ten trails, showed that the average amplitude coefficient of variation was 4%. In each trial the sliding mechanism was used to bring the probe in contact with simulator (setting: 80Hz with peak to peak displacement of $1\mu\text{m}$) and measure the amplitude of the simulator movement using the PZT probe (14g).

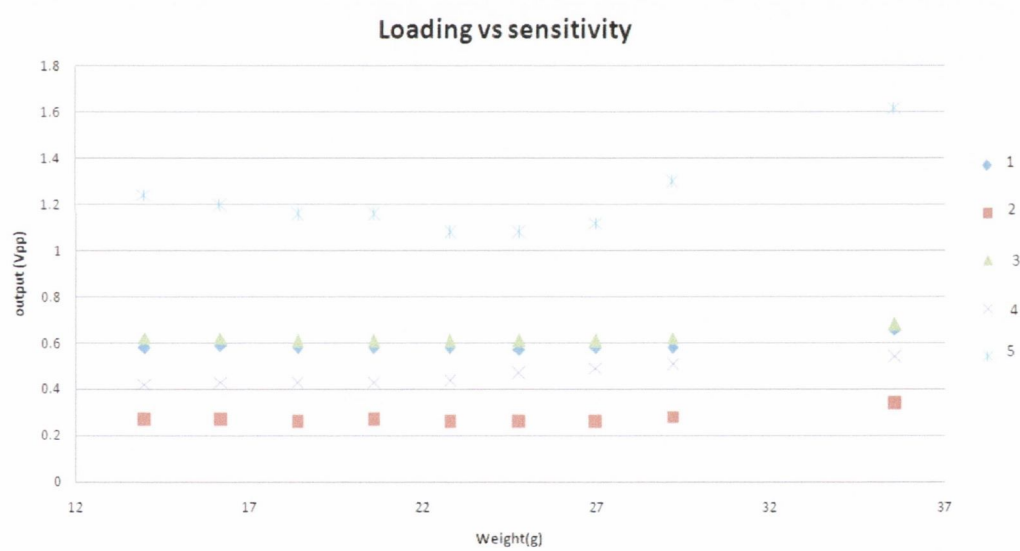


Figure 44. A plot of five different probes with different loading mass verses the probe output voltage with constant simulator displacement.

2.4.2.3.3 Variation in OMT amplitude and frequency due to the different loadings

	Right eye		Left eye	
	Load(g)	RMS(μ m)	Load(g)	RMS(μ m)
1	14	0.68	14	0.70
2	15.2	0.66	14	0.73
3	16	0.71	14	0.68
4	16.5	0.69	14	0.71
5	18.5	0.75	14	0.70

Table 6. Variation in OMT amplitude with load

Table 6 shows the OMT average RMS value from the two trials with different loads applied by the probe. There is no clear relationship between RMS OMT amplitude and load in the right eye. Neither is there any clear relationship between the loaded and unloaded eyes in terms of amplitude difference. By comparing the difference in the average RMS value between the two eyes, to the load applied to the right eye, association regression analysis showed no statistically significance ($p=0.260$) at an α -level of 0.05. This could be due either that the difference is too small and a larger masses needs to be used (which might cause volunteer discomfort) or that variations due other factors such as probe sensing orientation variation and OMT day to day variation are higher.

On the other hand there was an increase in the variation of amplitude within records (standard deviation of RMS value within a single record) as the load was increased. Figure 45 shows the coefficient of variation of the OMT amplitude RMS for each 40s day record. With probe masses of 14 g and 15.2g the average coefficients of variation were about the same (8.5% and 8.4 %, respectively). From 16g and upwards the figure increases. The increased variability may be due the discomfort of the volunteer (felt by the volunteer during the measurement recording) as the loading is increased or to some unknown physiological response of the eye to loading. Using the lowest mass probe is preferable, as the variation is at its lowest.

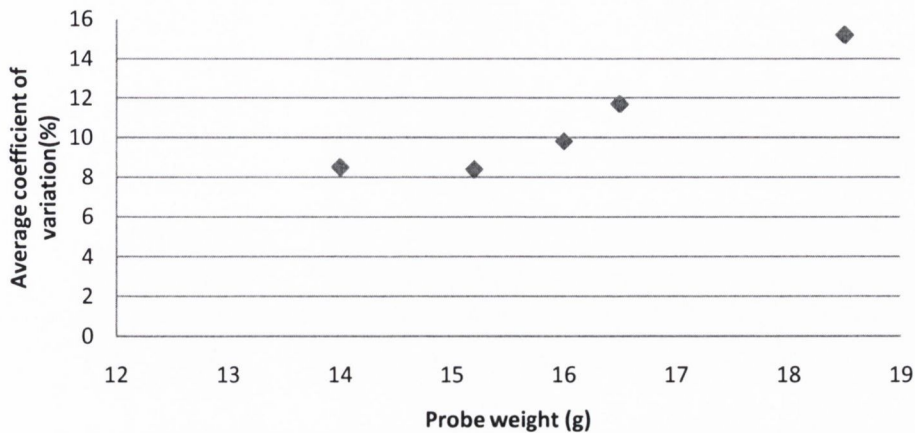


Figure 45. Graph of variation in the average amplitude coefficient of variation with probe mass

	Right eye		Left eye	
	Load(g)	Freq(Hz)	Load(g)	Freq(Hz)
1	14	83	14	84.1
2	15.2	79.3	14	82.7
3	16	81.5	14	82.4
4	16.5	83.4	14	79.3
5	18.5	84.6	14	81.7

Table 7. Variation in OMT frequency with load

Table 7 shows the mean average frequency spectral peak between the two trials of each load applied. By comparing the difference in the average OMT dominant frequency between the two eyes, to the load applied to the right eye, regression analysis showed no statistically significant association ($p=0.182$) at an α -level of 0.05. Work done by Bengi and Thomas (77) reported that as we increase the loading of the eye will results in reduction of the high frequency spectra power, but their investigation was based only limited to visual observation of the frequency spectra power plots and quantitative measures of difference were not reported.

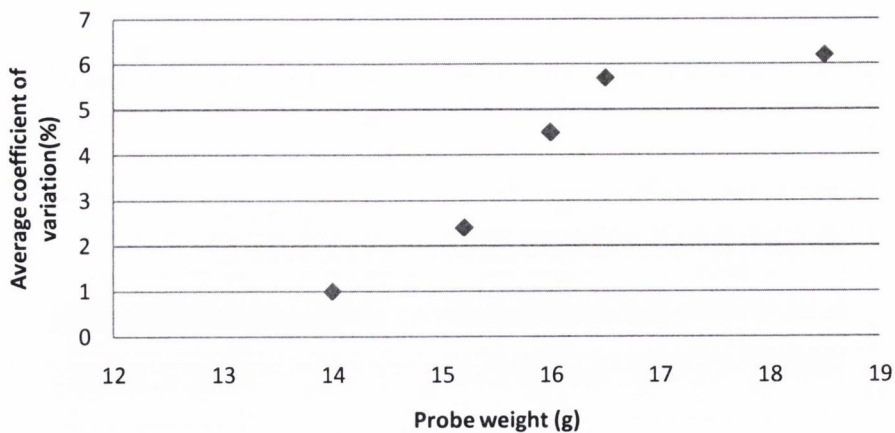


Figure 46. Graph of variation in the frequency average coefficient of variation with probe load.

As in the case in the amplitude there was increase in the dominant frequency variation within the records with load. Figure 46 shows the average coefficient of variation of dominant frequency for each 40s record using different probe loads. As the probe mass increases there was an increase in the dominant frequency variation. The lowest variation (1%) was with 14g. As in the case of OMT amplitude, those variations are possibly due the subject discomfort as the weigh is increased or due to some a physiological response of the eye to loading.

One of the limitations in this study was the sample size: more volunteers, OMT records and load variation were required, but due to discomfort, the study was limited to one subject. Also the recordings were done in five different days (two records per day) for patient comfort, which may affect the results due day to day variation. The 14g probe was the lowest mass investigated and was preferable to the others tested due to its low variation in OMT frequency and amplitude. Lower mass probes would need to be investigated to see if results improve at less than 14g. It also shows the importance in having constant pressure as variation in the pressure applied to the eye will lead in increase in the variation in the OMT amplitude and frequency.

2.5 Conclusion

A new PZT system based on a gravity feed sliding mechanism instead of the previously used screw mechanism was tested and proven capable of measuring the OMT signal. The technique has been used in a number of OMT clinical trials (260),(261),(74),(262),(263). The system proved to be user friendly and incorporates various safety features for the patient. The system could easily be made smaller and light mass and adapted with other devices for simultaneous measurements, such as the commercially available IR systems for microsaccade tracking.

The new PZT system has a wider dynamic range giving it an advantage over the existing systems; this will be useful in three ways. First it will help in understanding the interaction between the grosser eye movement such as microsaccades, drift and the PZT probe. Second, it helps clarify the relation of OMT with other fixational movements, such as in vision. Finally it will allow implementation of new advanced signal processing techniques for recovery and signal analysis in the digital domain.

In the investigation of PZT probe loading effects the results can be discussed in terms of impact on OMT amplitude and frequency measurement

2.5.1 OMT amplitude

With the PZT system, there are two possible components to variations of amplitude measures due to probe loading: (i) changes of the probe sensitivity with pressure and (ii) changes in the way eye interacts with probe, either by simple mechanical loading or by some physiological 'reaction' from the eye:

- i) With an experienced operator, Sheahan (50) measured the coefficient of variation for OMT amplitude in a simulated set up as 25% with the simulator head covered by bovine sclera and as 11% with a plastic target. From our results with a plastic target used in a very similar experimental setup, the coefficient of variation was 4%. The difference could be due to the variation in

pressure applied by the screw mechanism compared to the constant pressure applied by sliding mechanism. Certainly, it was demonstrated here that the amplitude sensitivity of probes varies with load, with a coefficient of variation of >8% found with loads from 14g to 29.2g (relative to the 14 g probe mass).

- ii) From the *in-vivo* test, the results showed there was no significant difference between RMS OMT amplitude with loading applied but on the other hand the result showed an increase in variability of amplitude with pressure. This emphasizes the importance of keeping the pressure applied by the probe low and constant.

2.5.2 OMT frequency

Sheahan found a 14% variation between records of the same patient in OMT frequency estimation with an inexperienced operator compared to 5% with experienced operator *in-vivo* tests. The results presented here show that variation in dominant frequency (using the linear predictive spectrum peak) increases with pressure from 1% with 14g to about 7% with 18.5g. Both increased load and variation in the load (such as in the screw mechanism method) seem likely to contribute to increased variation in the dominant frequency measures according to the results observed. A variable load may explain some of the differences seen between inexperienced and experienced observers in Sheahan (97).

One of the limitations in the comparison between the new PZT system and the screw mechanism is that the pressure applied by the screw mechanism to the eye using Sheahan's device is unknown but it is unlikely to have greatly exceeded that of the new device, given the intolerance of subjects to probes approaching 20g. A full check on whether the new sliding mechanism is better in reducing the amplitude and frequency variation compared to the screw mechanism would require a full replication of Sheahan's investigation of measurement variability across subjects and operators (50), but from the results presented here one can conclude the importance of constant probe pressure.

Ch3

3 Microsaccade identification & removal methods in OMT measurement

3.1 Introduction

The PZT system developed in this work has a dynamic range capable of capturing OMT signal with microsaccades present without the requirement of analogue pre-filtering of the probe output. There are a number of methods used in the literature for OMT signal recovery (as listed in the literature review), but an examination or comparison of their performance in both the time and frequency domains has not been carried out. This section of the thesis examines current methods used in microsaccade identification and removal. It examines the possibility of improving the digital signal processing of OMT records by using advanced methods that have not been previously reported in OMT literature. The investigation involves using wavelet denoising tools as a new microsaccade removal method. The chapter will include a validation test for the microsaccade identification and removal methods.

3.2 OMT signal recovery

In biomedical signals, sudden changes in the signal of interest due to secondary components have been observed in a number of physiological signals, such as EMG (spike waveforms) and in EOG (saccadic eye movements). If the analysis of the signal includes analysis of segments incorporating sudden changes then this will result in a distortion in both the frequency and time domains (264). One of the difficulties in analysing the OMT signal is the removal of microsaccades from the signal captured by the PZT system. In the recovery of the OMT signal it is important to preserve the signal continuity with minimal distortion to the signal due to the recovery method used.

Current methods are based on simple filtering or cutting of microsaccades from the PZT output. Due the fact that both methods have limitations (discussed in the literature review) a new improved method is needed(265).

The wavelet provides a compact representation that gives energy distribution of the time and frequency, which makes it ideal for automated feature identification of sudden short-duration signal changes (205). As the microsaccade information is a combination of sudden changes in the time and frequency domains, it may be possible to use wavelet in identifying the periods of microsaccades. This fact lend itself in the possibility in using the wavelet as new tool for identifying the microsaccades information and therefore remove them from the full fixation movement signal captured by the PZT, which makes it a good candidate for a new microsaccade removal technique.

3.3 Method

3.3.1 Microsaccade removal methods

Five candidate methods of OMT recovery were compared in this test in order to assess the utility of the proposed wavelet microsaccade removal method.

3.3.1.1 Wavelet method

A new approach is presented in this thesis. The method is based on treating the microsaccades as the desired signal and the other components of the signal such as drift artefacts and OMT as “noise”. Then the noise is filtered using the denoising technique based on the undecimated wavelet transform (UWT). Finally the noise (drift and the OMT) is recovered, by applying the inverse transform to the filtered information (251).

3.3.1.1.1 The denoising technique

The most commonly used of the discrete forms of the wavelet transform are the discrete wavelet transform (DWT) and undecimated wavelet transform (UWT) (202) (see the appendix for more detail on the continuous wavelet transform). The UWT has the property that it is shift invariant (or translation invariant). The shift invariance gives the UWT an advantage over the DWT of having better denoising capability (gives better balance between smoothness and accuracy). However the DWT method is more computationally efficient. In this work we use the UWT as it is better for denoising as (produces more precise information for the frequency localization (266)).

Denoising using the UWT method is described by the following three steps:

- I. Transform the noise contaminated signal $g(t)$ to obtain the UWT coefficients. The coefficients with smaller values will correspond to the noise.
- II. Threshold the UWT coefficients to set the coefficients with the lower values to zero. There are two types of thresholding (also called shrinking rules), soft and hard thresholding. The soft thresholding technique sets the UWT coefficients smaller than the threshold to zero and smoothes the larger coefficients towards zero. The hard thresholding technique sets the UWT coefficients smaller than the threshold to zero and the remaining coefficients are unchanged. The hard thresholding technique was used, as soft thresholding would smooth the signal and cause distortion to the OMT recovered signal. Figure 47 shows the difference between using the two different

thresholding methods in microsaccades denoising. The eye movement trace is from the PZT system of a healthy patient.

III. Reconstruct the signal using the inverse of UWT of the threshold coefficients.

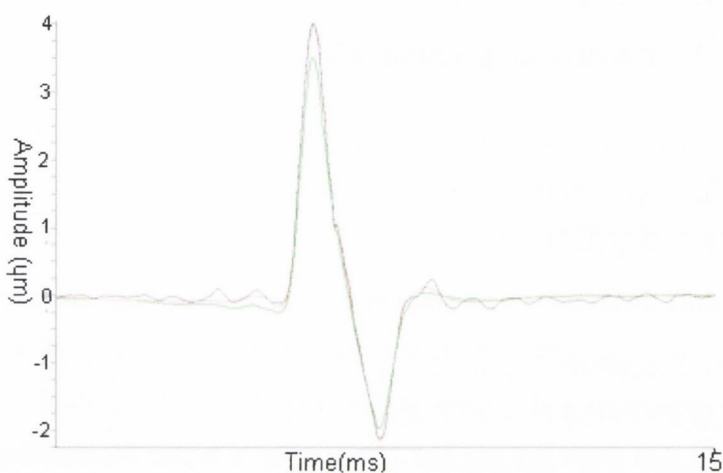


Figure 47. The black trace shows the signal from the PZT probe during a microsaccade. The red is the denoised signal using the hard thresholding. The green signal is using the soft thresholding.

3.3.1.1.2 Wavelet function selection

One of the particular problems in using wavelet theory is the selection of a suitable wavelet function as the wavelet transform is not unique (267). There are two commonly used families of discrete wavelet, orthogonal wavelets and biorthogonal wavelets. The orthogonal wavelet (e.g. Daubechies, Harr, Symmets and Coiflets) are used in applications such as signal (or image) compression and denoising. They have the advantage of being invertible, give perfect reconstruction and are easy to compute. Biorthogonal wavelets (e.g FBI “U.S. Federal Bureau of investigation wavelet” and biorthogonal) are used where linear phase is required (such as features extraction, e.g. peak detection and image edge detection), as orthogonal wavelets uses non linear phase filters.

To test a suitable wavelet function for the new OMT denoising method, a simulation test was carried out. Different wavelets functions were tested by simulating an eye movement signal (5s) of microsaccade (12 microsaccades periods with different shapes taken from control subjects and patients), drift and OMT. Next the microsaccade signal was denoised using the wavelet technique with the different functions (Harr, Daubechies, biorthogonal, symmlets and coiflets). Then the recovered microsaccade signal was cross-correlated with the original microsaccade signal and the RMSE value was also calculated for each case.

3.3.1.1.3 Rescaling method

The threshold (T) used for the denoising method is calculated as follows:

$$T = \sqrt{2\sigma^2 \log(N)}$$

where N is the size of the time series and σ^2 is the noise variance of the signal.

Rescaling methods are methods used to estimate the noise variance at each level of the wavelet transform. The first method is based on the basic model where the noise is assumed to be white with unit variance. The second method is the single level where the noise is assumed to be white, but the noise standard deviation is estimated at the first level of the wavelet (unscaled noise). The third method (Multiple levels rescaling) is based on estimating the noise standard deviation at each level independently. This implies that the noise does not have to be white. This method will allow filtering of complex noise (266), (268). Multiple levels rescaling methods have been used here to estimate the noise variance at each level, as the noise (OMT and Drift) is not white noise, as determined by initial examination using the whiteness test (the whiteness test is described in the appendix). The examination was based on testing different signals of OMT superimposed with drift free of microsaccades periods (taken from the clinical data of normal subjects (30 records) and patients (30 records)).

3.3.1.1.4 Method overview

Figure 48 shows a block diagram summarizing the OMT signal recovery using the wavelet method. After the microsaccades are removed the low frequency components such as drift artefacts are filtered using a digital high pass filter (20Hz cut-off, Elliptic filter¹³), as OMT frequency content is in the band 20Hz-150Hz.

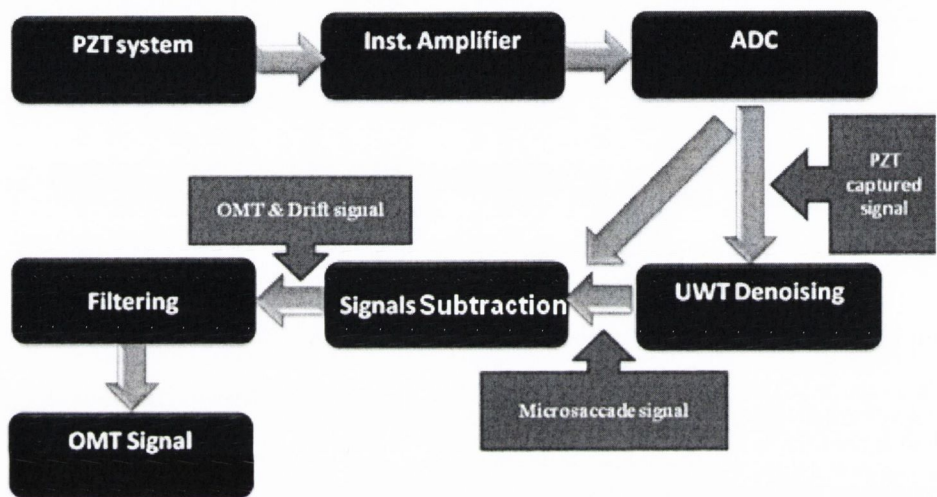


Figure 48. Block diagram of the process of OMT signal recovery.

3.3.1.2 Filtering method:

This is based on digitally filtering the signal from the PZT probe using the Elliptic filter. The filter specifications as follows:

¹³ The Elliptic filter is used here, because provides sharpest transition between the passband and stopband which useful in filtering the microsaccades information with lower order (as microsaccades have an order of amplitude higher than OMT) compared to the other filters (such as Butterworth or Chebyshev).

Filter type	Bandpass	
Sampling frequency	2500Hz	
Passband Edge Frequency	20Hz	150Hz
Passband Ripple	0.1dB	
Stopband Edge Frequency	10Hz	160Hz
Stopband Attenuation	60dB	
Filter order	20 ¹⁴	

Figure 49 shows the frequency response of the filter, which is calculated using LabVIEW digital filter design toolkit (3).

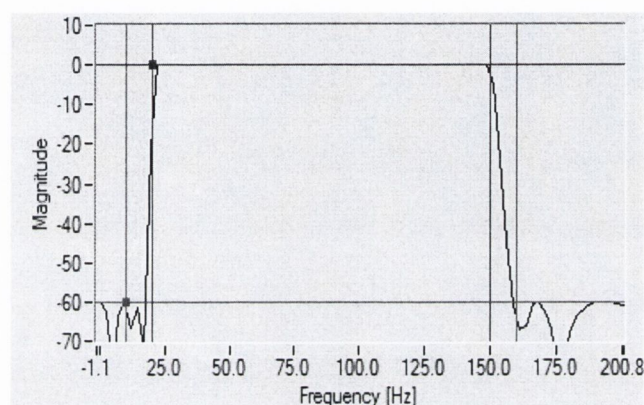


Figure 49. Shows the frequency response of the Elliptic filter.

3.3.1.3 Cutting method:

The second method is based on an automated method of removing the periods of the microsaccades. The automated method identifies the microsaccade peaks and then removes 0.03s before and after (0.06s duration removed) the identified peak locations. The remaining parts are joined together and bandpass filtered with the same filter specification as used in the filtering method described above. This method has been implemented by different authors (7, 26, 34, 36-37, 151), but as pointed out in the literature review, this leads to distortion in the frequency spectrum because of the discontinuity introduced in joining microsaccades free segments.

¹⁴ Filter order was estimated by LabVIEW digital filter design toolkit based on the listed above filter specifications.

3.3.1.4 Multiresolution method:

The third method is based on using the wavelet multiresolution method. This method is used in the analysis of signals that contain both low and high frequency components (multiple resolution). The difference between the wavelet denoising methods and the wavelet multiresolution method is that the former is based on thresholding the UWT coefficients while the latter is based on the selection of frequency (scale) bands of DWT of the original signal to reconstruct a new time domain signal from the selected bands. This method could be used in separating the drift (low frequency component) from the OMT signal (high frequency component), but it might not be expected to work in removing the microsaccades as they overlap with OMT frequency band. One author has reported use of this method but did not validate its performance (12). The steps in recovering the OMT signal using this method are summarized as follows:

- I. Obtain the DWT coefficients from the PZT system signal using wavelet bior 2-8 with 13 levels (this wavelet was chosen in a preliminary trial of different wavelets to test which one appeared to give the best performance).
- II. Construct the frequency spectrum using the DWT coefficients.
- III. Filter the unwanted bands in the wavelet domain (40-150Hz is the unfiltered band and the rest is filtered).
- IV. Reconstruct the OMT signal from the selected DWT coefficients.

For more details see (12).

3.3.1.5 ATVF method:

The fourth method is based on using a time varying filter with an adaptive threshold. It is the technique used in the automated burst extraction method introduced in this work (see Chapter 5). The difference here is that the technique includes an adaptive threshold based on locating the microsaccade periods and then seeks the optimal threshold coefficient that

will reconstruct the microsaccades signal. Then the OMT signal and drift are recovered by reconstructing the Gabor coefficients that are below the threshold.

The steps in recovering the OMT signal using this method are summarized as follows:

- I. The threshold (T) of the method is first set to 0.8.
- II. Calculate the Gabor coefficients ($C_{m,n}$) of the PZT system signal using the Gabor transform.
- III. The highest and the lowest Gabor coefficients are found (C_H and C_L , respectively) from the transferred OMT signal.
- IV. The Gabor coefficients threshold value (C_{TH}) is calculated as follows:

$$C_{TH} = ((|C_H| - |C_L|) \times T) + C_L$$

- V. Set all the coefficients as follows:
 - a. If $|C_{m,n}| \geq C_{TH}$ then $C_{m,n} = C_{m,n}$
 - b. If $|C_{m,n}| < C_{TH}$ then $C_{m,n} = 0$
- VI. Reconstruct the time domain signal from the thresholded coefficients.
- VII. Allow the user to compare the thresholded signal from the original and chose to repeat III with different threshold setting (T) chosen by the user or proceed with the following step.
- VIII. Finally bandpass filter the signal (20-150Hz) to remove drift artefacts.

3.3.2 Validation methods

3.3.2.1 Signal simulation

To validate the efficiency of the OMT recovery methods we need to compare the OMT signal recovered by the different methods to the original OMT signal without the other eye movements. The problem in using real subjects/patients records captured by the PZT system for validation is that we do not know the original OMT signal (the PZT probe

captures other eye movements with OMT). To overcome this issue simulated signals were used in this investigation.

The efficiency of each of the candidate microsaccade removal methods was tested on a total of 40 simulated traces. Twenty traces were derived from OMT of 'normal' subjects and twenty from patients (from 20 different normal subjects and 20 different patients). The patient OMT cases were taken from different patients with either: stroke, midbrain infarcts, cranial nerve VI palsy or traumatic brain injury. Both groups are aged 24-75 years old. Fifteen seconds of OMT were recorded by the PZT system by a single experienced observer (NC). All the recording took place in St. James's Hospital with approval from the hospital ethics committee.

The OMT component was then extracted using the cutting method and bandpass filtered (20-150 Hz) so as not to bias the test. The simulated eye movement signals (see example in Figure 51.f) are made by the addition, of white noise (0.01 amplitude to the RMS value of OMT), random microsaccades (2-20 microsaccades per 15s taken from recorded PZT probe signals) and a 5 Hz sine wave (to simulate drift artefacts) to the OMT component obtained (see Figure 50). The patient OMT simulated signals (see example in Figure 52.f) included a low frequency activity (higher amplitude than normal drift that could be due head movement) that has similar characteristics to the patients OMT records found in clinical situation. The low frequency activity component was taken from different patients OMT PZT probe records by low pass filtering (40Hz, as noted activity is round 18Hz) microsaccades free periods. The simulated low frequency activities are taken from PZT system records measured from patients OMT patients. The RMS amplitude of the low frequency component was set to 1.5 times that of the OMT signal RMS value (approximately the same ratio as observed in real patient OMT records).

The ratio of the microsaccades amplitude (RMS value) to the OMT signal amplitude (RMS value) was set randomly from 4.8 to 26.4 (the ratio was calculated using the OMT data collected for this study). The ratio was set as the sensitivity of the individual probes used by the PZT system are not the same (for more information see Chapter 2).

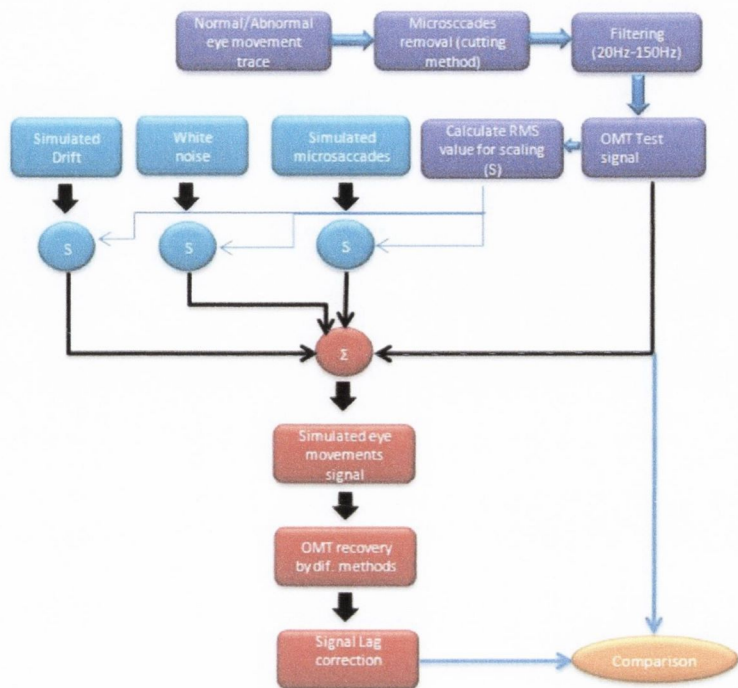


Figure 50. Test of candidate microsaccade removal techniques.

3.3.2.2 Comparison tests

The signal comparison between the recovered signal and the original signal involves a delayer to fix the time lag¹⁵ between the compared signals which are different in each recovery method. Comparison was made using four methods:

3.3.2.2.1 Time domain comparison:

The first method looks at time domain statistical parameters. These methods are used by different authors (269-272) as a distortion measure for Electrocardiogram signal (ECG). The first parameter is based on measuring the signal to noise ratio (SNR) in dB of the original OMT signal before addition of the other movements to the processed signal, which is expressed as follows (272):

¹⁵ The time lag between the signals was found manually by the user for each case.

$$SNR = 10 \log_{10} \left(\frac{\sum_{n=1}^N [x(n) - \bar{x}]^2}{\sum_{n=1}^N [x(n) - \tilde{x}(n)]^2} \right) \quad \text{Equation 12}$$

Where $x(n)$ and $\tilde{x}(n)$ are the OMT original signal and the processed signal, respectively. The $\bar{x}$ is the mean value of the original signal. The SNR term will go from positive to negative as the sum of the square difference between the original signal and the processed signal gets higher or lower than the sum of square difference between the original signal and the mean (variance). This implies as the SNR term goes towards negative the more distorted the processed signal.

The second parameter is based on the cross correlation (271), which evaluates the similarity between the original signal and the filtered signal. The cross correlation (CC) is expressed as follows

$$CC = \frac{\frac{1}{N} \sum_{n=1}^N (x(n) - \bar{x})(\tilde{x}(n) - \mu)}{\sqrt{\frac{1}{N} \sum_{n=1}^N (x(n) - \bar{x})^2} \sqrt{\frac{1}{N} \sum_{n=1}^N (\tilde{x}(n) - \mu)^2}} \quad \text{Equation 13}$$

Where $x(n)$ and $\tilde{x}(n)$ are the OMT original signal and the processed signal, respectively. Also $\bar{x}$ and μ are the mean values of the original and the processed signals, respectively.

The time domain comparison will provide a measure of how reliable and efficient the candidate processing methods are in preserving the temporal features used for detection and classification of the OMT signal such as the OMT features.

3.3.2.2.2 MIF comparison:

The second test is based on looking at mean instantaneous frequency (MIF). The mean instantaneous spectrogram is based on the Gabor transform (see Chapter 5 for more details). The MIF comparison test will reveal how much distortion is caused in the joint time-frequency domain. This measure is important when looking at OMT features analysis and also when doing cross-correlation between different records (e.g left and right eyes) or auto correlation function.

The first comparison of MIF is based on looking at the absolute mean difference (MIF-AMD) between the original signal (OMT test signal in Figure 50) and the processed signal (recovered OMT signal). The second measure is based on looking at the local error measure. This looks at the standard deviation error (MIFStderror), which is defined as follows (270)

$$MIFStderror = \sqrt{\frac{1}{N-1} \sum_{n=1}^N [e(n) - \bar{e}]^2} \quad \text{Equation 14}$$

Where $e(n)$ and $\bar{e}$ are the error and the mean error between the MIF of the original OMT signal and the processed one, respectively. N is the number of samples. The third measure in the MIF is based on the cross correlation (CC) (271), which evaluates the association between the MIF of the original signal and the processed signal.

3.3.2.2.3 FOA comparison:

This signal comparison approach is based on the fractional octave analysis (FOA), which defines the spectral band powers at defined octaves (the octaves are set from 20Hz to 150Hz with 1/6 bandwidth, using banks of band pass filters with constant Q factor. The FOA spectrum is present as a bar chart. Each bar in the histogram represent the band filter centered at the octave frequencies 29.5Hz, 33.1Hz, 37.2Hz, 41.7Hz, 46.8Hz, 53Hz, 59Hz, 66Hz, 74Hz, 83Hz, 94Hz, 105Hz, 118Hz, 132Hz and 149Hz. In the validation test the FOA of the OMT signal before it had been corrupted was compared with the FOA of the OMT signal recovered using each method. The measure is based on looking at the Absolute mean difference (FOA-AMD) between each band in the histogram plot of the processed signal compared to the FOA of the original signal.

The FOA comparison provides information about the band power distortion in the frequency region of interest (20Hz-150Hz).

3.3.2.2.4 OMT clinical parameters:

The two methods most frequently used in analyzing the OMT signal used in OMT clinical investigation (148), (50), (36), (34), (51), (273), (262), (263) are the Peak Count (PC) and the Autoregressive (AR) spectrum (for more details see chapter 6). In this comparison we look at the absolute mean difference (AMD) between the original OMT signal and the processed OMT signal for the spectral high power peak estimated using both the peak count (PC-AMD) and the AR spectrum (ARS-AMD).

These measures will provide information about how reliable the microsaccade removal methods are in clinical investigation when using the PC or the AR spectrum.

The four tests described above (Time, MIF, FOA and clinical parameters) will reveal distortions of the time, frequency and joint time-frequency domains caused by the various OMT recovering methods tested.

3.3.3 Computational platform

The simulation and analysis was carried on an Intel(k) Core(TM)2 CPU T7200@2.00 GHz with 2.00 GB of Ram. All the analysis was done in MATLAB [29] and LabVIEW [30].

3.4 Results

In the process of selecting a suitable wavelet function, Table 8 shows cross-correlation between the original microsaccades signal and the recovered one. From all the methods Daubechies (db03) has the highest correlation factor of 0.973 and RMSE of 35nm.

Wavelet function	RMSE(nm)	CC	Wavelet function	RMSE(nm)	CC	Wavelet function	RMSE(nm)	CC
db02	44	0.965	Harr	42	0.959	coit1	64	0.968
db03	35	0.973	bior1-3	49	0.967	coit2	58	0.965
db04	68	0.97	bior1-5	52	0.966	coit3	64	0.963
db05	72	0.967	bior2-2	64	0.954	coit4	68	0.96
db06	77	0.97	bior2-4	69	0.956	coit5	72	0.957
db07	80	0.967	bior2-6	72	0.958	sym2	44	0.965
db08	85	0.965	bior2-8	74	0.959	sym3	59	0.972
db09	87	0.963	bior3-1	109	0.926	sym4	58	0.964
db10	92	0.963	bior3-3	99	0.947	sym5	66	0.961
db11	101	0.961	bior3-5	93	0.956	sym6	63	0.962
db12	104	0.956	bior3-7	94	0.955	sym7	67	0.96
db13	103	0.953	bior3-9	95	0.956	sym8	68	0.961
db14	103	0.953	FBI	65	0.958			

Table 8. Cross-correlation and RMSE between the original microscades signal (5s signal with 12 microscades periods) and the denoised microscades signal (dB= Daubechies, bior=biorthogonal, sym=symmlets, coit=coiflets) .

3.4.1 Time domain comparison

Figure 51 shows an OMT signal (1s period from a normal subject) recovered using the five microsaccades removal methods. Due to the high amplitude of the microsaccades artefacts, a ringing response distortion to the OMT signal was seen in the filtering method. In the cutting method the recovered OMT signal loses some information (only 0.88s of the 1s trace was left). This loss of information is crucial when we look at the OMT features parameters. The same applies to the signal recovered by the ATVF (Figure 51.b). On the other hand the wavelet method (Figure 51.a), the OMT signal is recovered without introducing gaps in the signal and appears similar to the original.

Figure 52 shows OMT signal recovery (1 s period from a patient) using the five methods. Traces Figure 52.g and Figure 52.f shows the OMT signal (from normal subject) and the simulated eye movement signal, respectively. Using the filtering method (Figure 52.e), the OMT signal is highly distorted as the amplitude of the patients OMT signal was lower (as

observed from the original records used here taken from patients) than normal subject OMT signals and that will increase the distortion caused by the filter ringing response. Using the cutting method (Figure 52.d), there was not much difference in normal subject and patients OMT signal recovery as it based simply on cutting the microsaccade periods and then bandpass filtering the remaining signal (microsaccades free). Using the multiresolution method (Figure 52.c), the signal was corrupted as the multiresolution was based on filtering the frequency bands components of the microsaccades, which overlaps with patients OMT signal band. Using the ATVF (Figure 52.b), the method was able to recover the OMT signal with about the same level of distortion as the multiresolution method. The same applies with the wavelet method (Figure 52.a).

Table 9 is the mean of the SNR with the normal subjects and patients OMT signals using the different recovery methods. In the normal subjects filtering case the mean of SNR was very low and becomes far worse in the patients OMT records. The cutting method was not tested here as the processed and original signals are not comparable on sample to sample basis. The multiresolution method with normal subject OMT records, gave a SNR of about 0.84 dB, but gets noisier than the cutting method in the patients OMT records. The same applies for the ATVF but with better results in the normal subjects' records (1.94 dB). The wavelet recovery method gives the best SNR for both normal subjects and patients records.

Table 10 shows the mean of the cross correlation factor between the processed signal and the original signal for both groups (normal subjects and patients). For the normal subjects records the wavelet has the highest correlation factor of 0.93 followed by the ATFV method with 0.704. The multiresolution method mean of the cross correlation factor of 0.598, but the filtered method has a correlation factor of 0.201. With the patients records group the only method with a high correlation factor is the wavelet method with mean of 0.812.

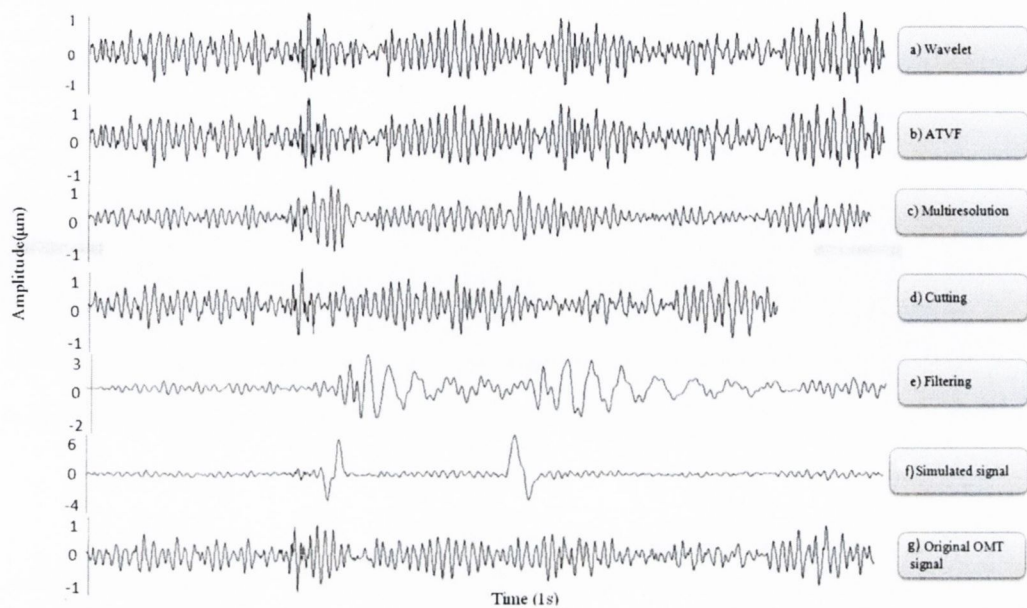


Figure 51. The recovered normal OMT signal with wavelet method (a), ATVF method (b), Multiresolution method (c), cutting method (d) and filtering method (e). In (f) is the simulated corrupted signal and (g) is the original normal OMT signal (1s). [note scale differences and also a. b and c are inverted].

Methods	Mean SNR-T-normal (dB)	Mean SNR-T-patients (dB)
Filtering	-13.5	-20.6
Multireslation	0.835	-8.5
ATVF	1.94	-8.01
Wavelet	8.56	4.895

Table 9. The mean of the SNR of the normal and patients OMT records (20 records each case).

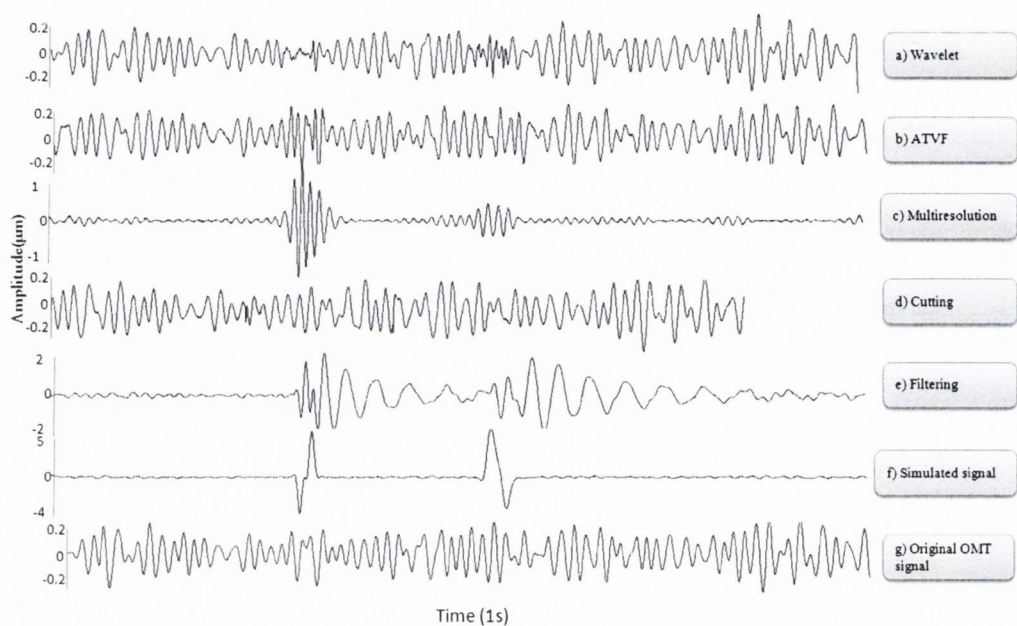


Figure 52. The recovered patient OMT signal with wavelet method (a), ATVF method (b), Multiresolution method (c), cutting method (d) and filtering method (e). In (f) is the simulated corrupted signal and (g) is the original patient OMT signal (1s). [note scale differences].

Methods	Mean (dB)	SNR-T-normal	Mean (dB)	SNR-T-patients
Filtering	0.201		0.036	
Multireslation	0.598		0.063	
ATVF	0.704		0.234	
Wavelet	0.93		0.812	

Table 10. The mean of the cross correlation of the normal and patients OMT records (20 records each case).

3.4.2 Mean instantaneous frequency (MIF)

Figure 53 and Figure 54 shows a 5s MIF of a normal subject and a patient OMT signal respectively. The MIF signal shown in black in both figures is that of the original OMT signal. Using the filtering method, the original MIF and the recovered MIF, are not well correlated especially in the patient record case. Using the multiresolution method (Figure 53.d and Figure 54.d (in red)), the MIF is better than the filtering method for the normal subject record case and shows a poorer correlation in the patient record case. On the other hand using the ATVF (Figure 53.e and Figure 54.e) and Wavelet method (Figure 53.f and Figure 54.f), gives more desirable results when comparing the MIF of the original and the recovered signal.

Table 11 shown the means of the cross correlation (CC), absolute mean error (AMD) and error standard deviation (stderror) of the MIF of 20 (15s each) normal subjects OMT records. The cutting method not been examined as it involves losing some time domain information because of the period removal. The filtering and the multiresolution recovery methods also have poor CC. The wavelet recovery method provides the highest CC factor of 0.83 and the best AMD and stderror. Table 12 shows the mean CC, AMD and stderror of the MIF of 20 patient OMT records. Looking at the values, the quality of the recovery methods of the MIF is lower with the patients OMT cases, especially when using the multiresolution method. The same applies for the ATVF as the CC has dropped by half, though it gives a reasonable AMD compared to the other methods. Overall the wavelet method was able to achieve good results over the three measures of MIF.

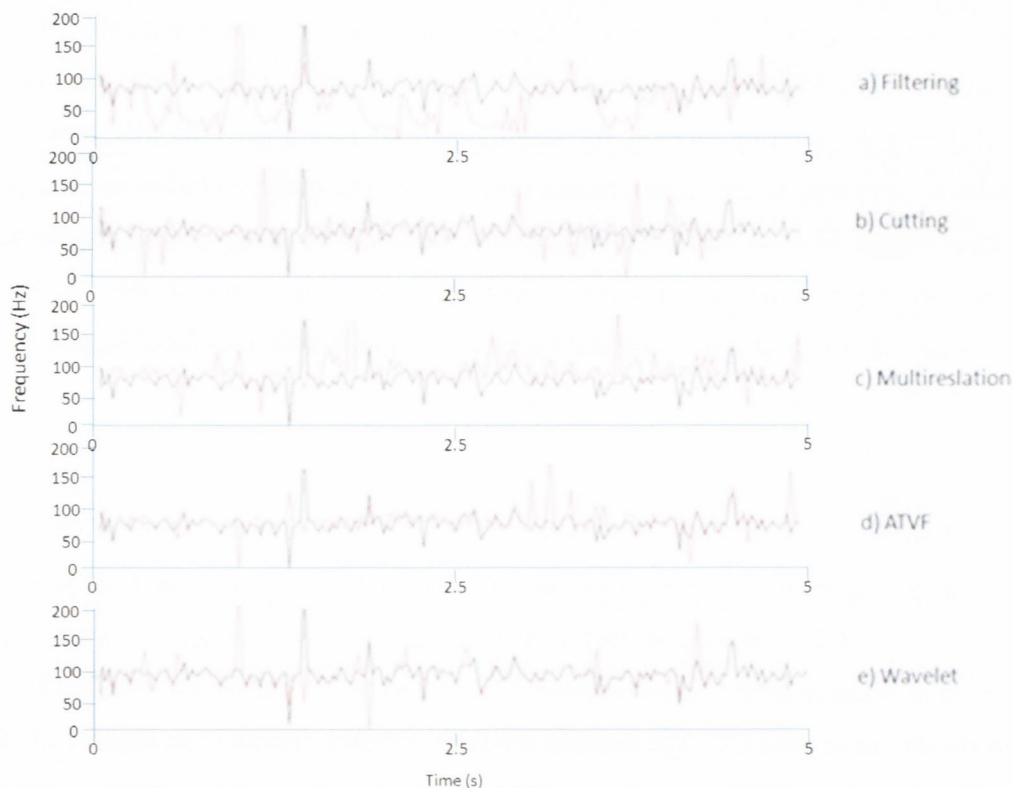


Figure 53. The MIF of the original normal OMT signal is shown in black form 0-200Hz of 5s and in red is the recovered signal by the different methods. a) The MIF of the OMT recovered signal using the filtering method. b) The MIF of the OMT recovered signal using the cutting method. c) The MIF of the OMT recovered signal using the multiresolution method. d) The MIF of the OMT recovered signal using the ATVF. e) The MIF of the OMT recovered signal using the Wavelet method

Methods	CC	AMD(Hz)	Stderror(Hz)
Filtering	0.242	28.08	47.45
Multireslation	0.313	20.02	36.73
ATVF	0.675	11.38	38.18
Wavelet	0.833	7.28	30.87

Table 11. The means (20 cases each) of cross-correlation (CC) , absoul mean difference (AMD) and the Stderror (standard deviation error) of the MIF for the normal OMT case.

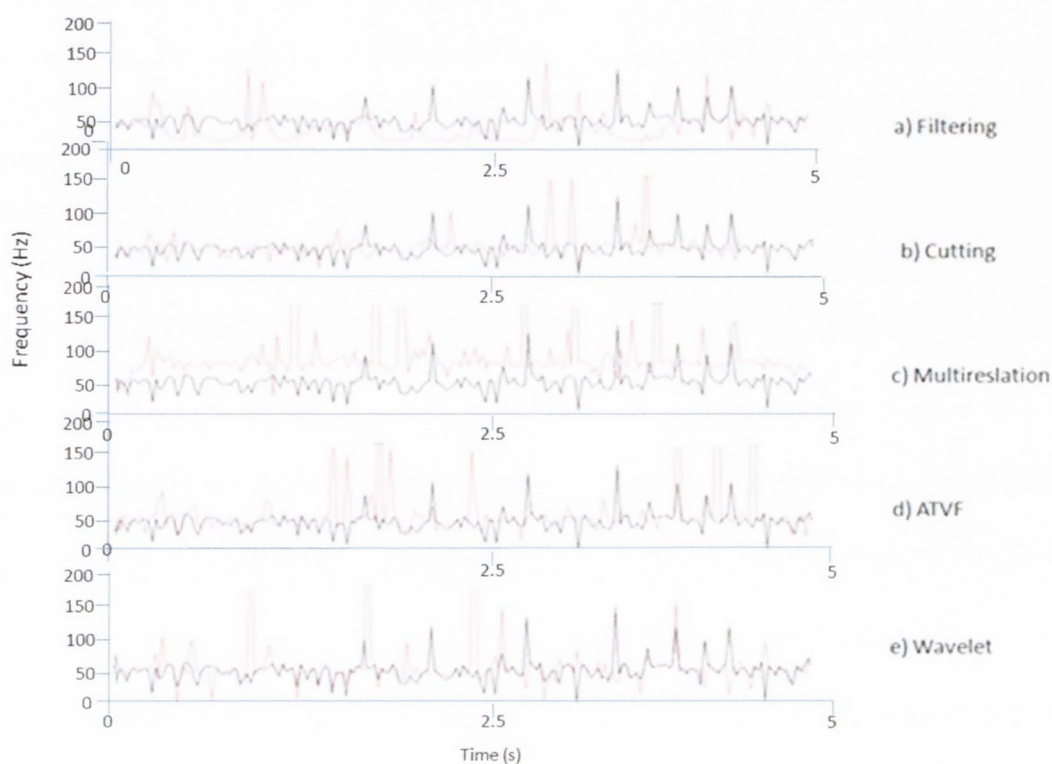


Figure 54. The MIF of the original patient OMT signal is shown in black form 0-200Hz of 5s.a) In red is the MIF of the simulated eye movements signal. b) The MIF of the OMT recovered signal using the filtering method. c) The MIF of the OMT recovered signal using the cutting method. d) The MIF of the OMT recovered signal using the multiresolution method. e) The MIF of the OMT recovered signal using the ATVF. f) The MIF of the OMT recovered signal using the Wavelet method.

Methods	CC	AMD(Hz)	Stderror(Hz)
Filtering	0.13	25.87	51.28
Multireslation	0.069	74.7	116.3
ATVF	0.297	17.63	52.39
Wavelet	0.569	14.04	47.63

Table 12. The means (20 cases each) of cross-correlation (CC) , absoult mean differnce (AMD) and the Stderror (standard deviation error) of the MIF for the abnormal case.

3.4.3 Fractional octave analysis (FOA)

Figure 55, Figure 56 and Figure 57 shows the FOA histogram plot (20-150Hz) of an example normal subject OMT record. Figure 55 is the FOA plot of the original OMT and Figure 56.a is the simulated eye movement signal. Using the filtering method (shown in Figure 56.b), the recovered signal remains distorted by the low frequency component. With the cutting method (shown in Figure 56.c), the recovered signal has similar FOA plot with a slight increase in the low frequency component and the high component remain unchanged. Using the multiresolution method, the high frequency component was fully recovered but with high drop in the low frequency component. Visual inspection of the ATVF method shows a FOA plot pattern similar to that of the original signal with a decrease in the low frequency components and a small alteration in the high frequency components. The wavelet method provides a very close match to the original FOA histogram in both high and low frequency components as reflected in the results in Table 13.

Figure 58 shows the FOA histogram plot of a patient OMT record (original OMT). Figure 59.a is the simulated eye movement signal. Using the filtering method (shown in Figure 59.b), did not recover the spectral features of the original signal. The cutting method (Figure 59.c) was able to recover the original patients OMT signal with a slight increase in the low frequency component. The recovered signal is highly distorted using the multiresolution method, as the method is based on recovering the frequency band of OMT signal that do not overlap with microsaccades, which is not the case. Although the ATVF (Figure 60.b) was able to recover the original signal, there is a small distortion across all the bands of interest. The same applies to the wavelet, but with lower lowest variation in the FOA, especially in the dominant frequency bands.

Figure 57.a and Figure 60.a show the FOA plot of the signal recovered using the multiresolution method of normal subject and patients records, respectively. From the two figures you can see that the low frequency bands are suppressed as the method is based on dividing the spectrum in to a number of frequency (scale) bands in the wavelet domain and

then constructing the recovered signal from the high frequency bands (suppressing the low frequency bands).

Table 13 shows the means of the FOA-AMD of 20 normal subjects and patients OMT records. For the normal subjects OMT records the wavelet method had the lowest variation in the FOA (FOA-AMD 0.345). The cutting method and the ATVF also had a low variation in the FOA (1.2 and 2.79 respectively). Although the multiresolution was capable of giving better results in the time and MIF comparisons, the FOA-AMD is the highest among the others as the multiresolution method is based on removing the lower frequency bands which has most microsaccade activity.

In the case of patients OMT records, there is more noise added to the simulated signal, the FOA-AMD are higher for all the recovery methods. The wavelet method shows the best performance in terms of the lowest variation in FOA along the bands of interest (20-150Hz) of the recovered signal (6.91). The cutting method (8.59) also gives a reasonable distortion level. Unlike the normal subjects OMT records the ATVF is more distorted as seen by the high increase in the FOA-AMD.

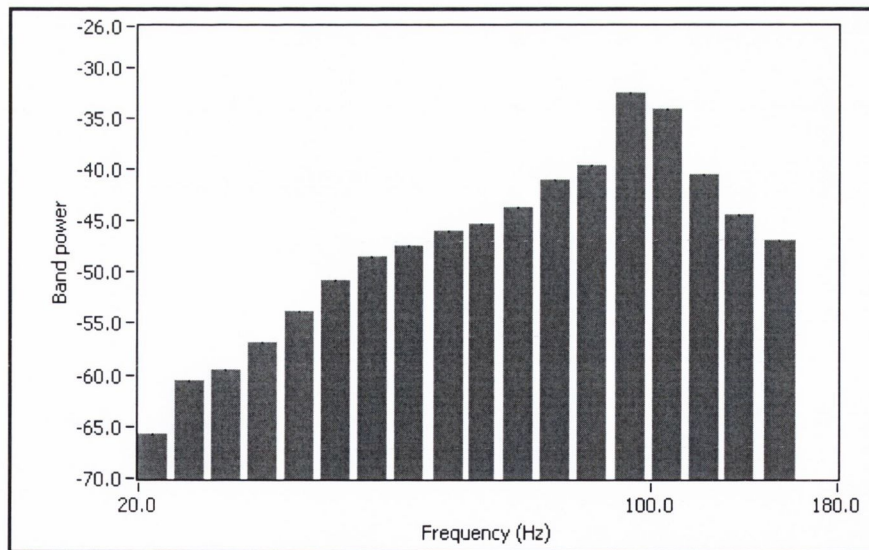


Figure 55. The FOA (20Hz-150Hz with bands power in dB) of the original OMT signal (15s) taken from a normal subject.

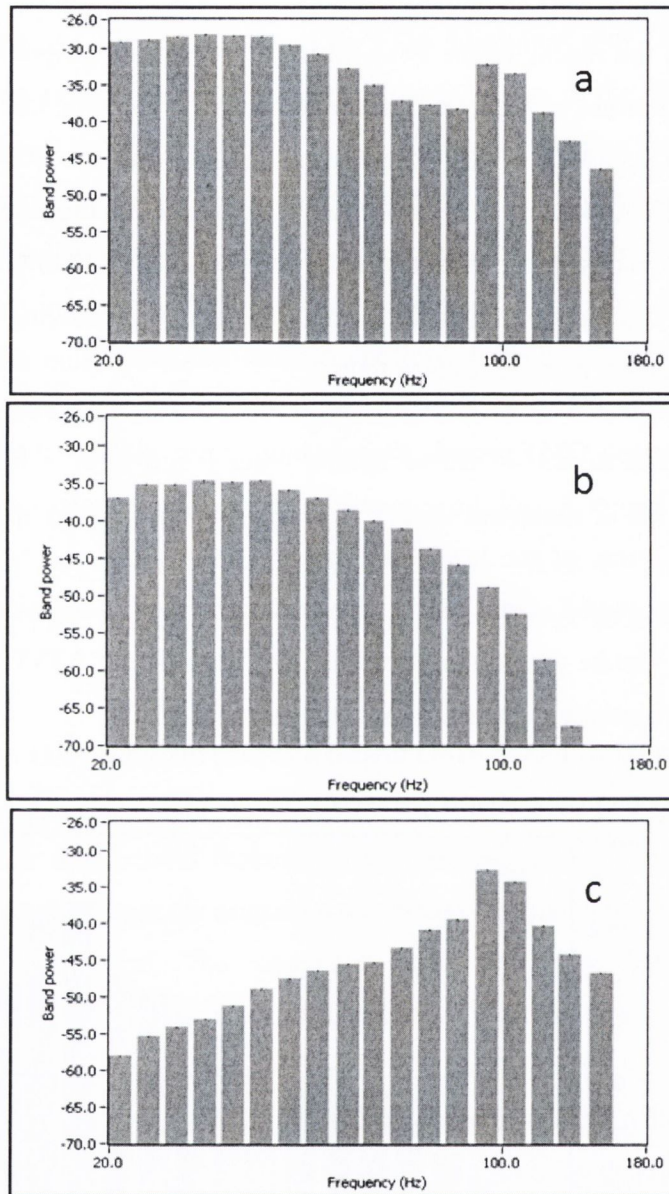


Figure 56. The FOA plot (20Hz-150Hz with bands power in dB) of the simulated and recovered OMT signal (15s) taken from a normal subject. a) FOA of the simulated eye movements signal. b) FOA of the OMT recovered signal using the filtering method. c) FOA of the OMT recovered signal using the cutting method.

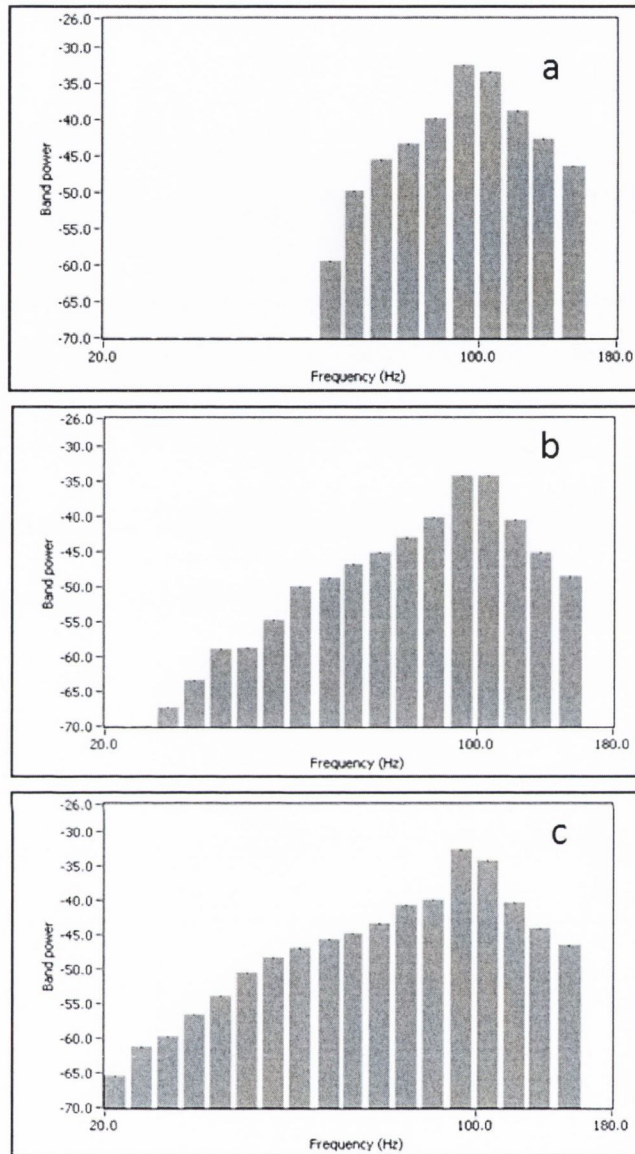


Figure 57. The FOA plot (20Hz-150Hz with bands power in dB) of the recovered OMT signal (15s) taken from a normal subject. a) FOA of the OMT recovered signal using the multiresolution method. b) FOA of the OMT recovered signal using the ATV. c) FOA of the OMT recovered signal using the Wavelet method

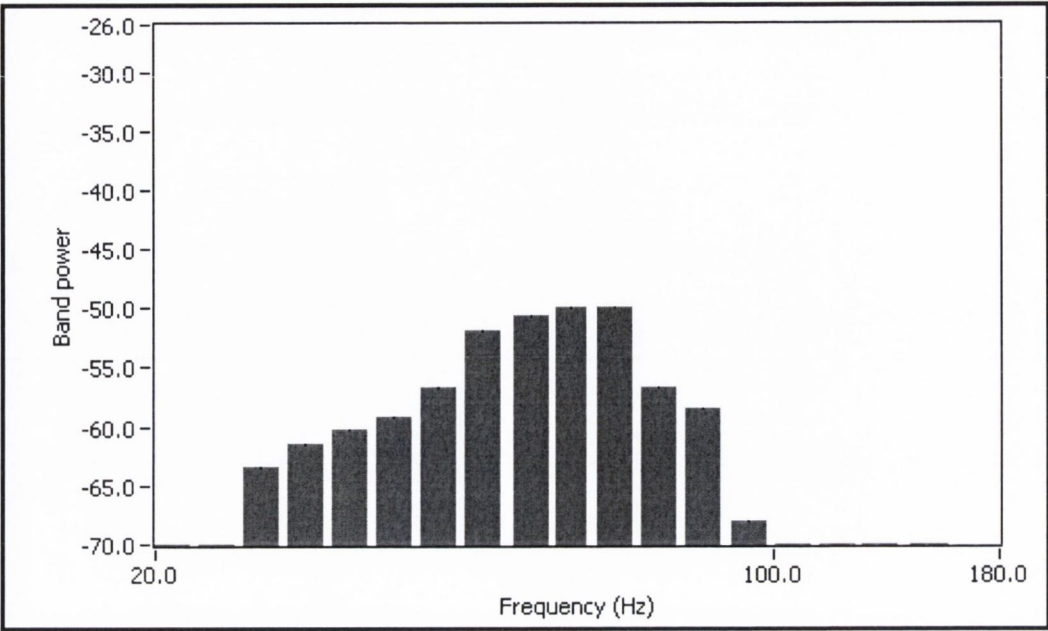


Figure 58. FOA (20Hz-150Hz with bands power in dB) of the original OMT signal (15s) taken from a patient.

Methods	Normal subjects FOA-AMD	Patients FOA-AMD
Filtering	16.07	27.5
Cutting	1.2	8.59
Multireslation	26.3	41.17
ATVF	2.79	16.11
Wavelet	0.345	6.91

Table 13. The means (20 each case) of the Mean absolute error of the FOA bands between the original OMT signal and the recovered one using the different methods.

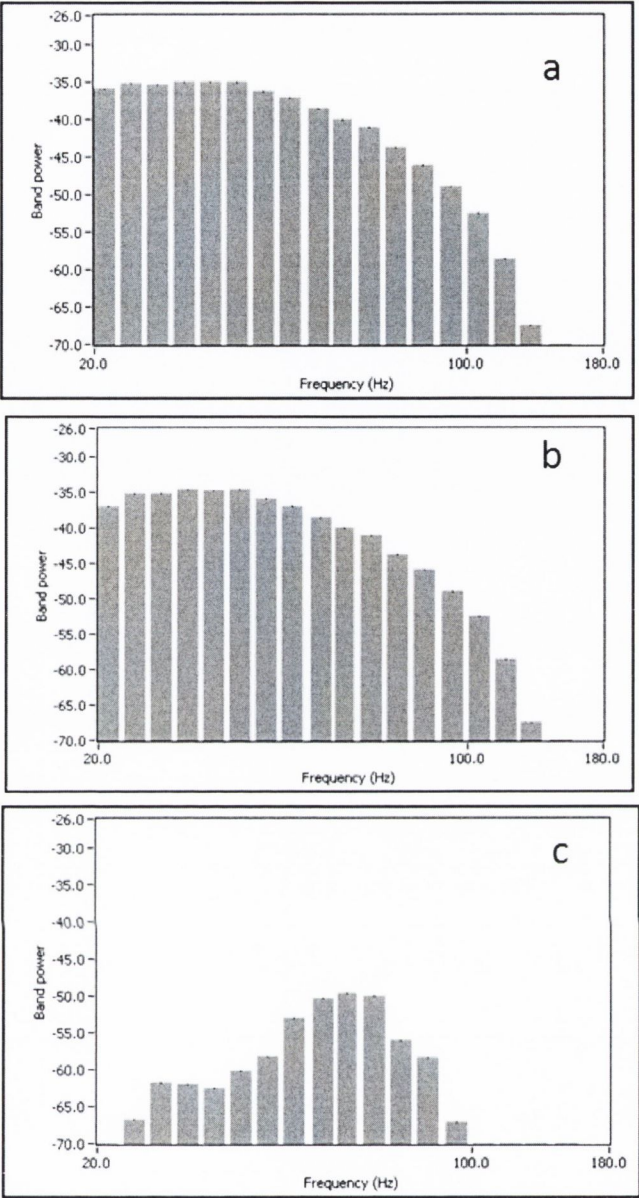


Figure 59. The FOA plot (20Hz-150Hz with bands power in dB) of the simulated and recovered OMT signal (15s) taken from a patient. a) FOA of the simulated eye movements signal. b) FOA of the OMT recovered signal using the filtering method. c) FOA of the OMT recovered signal using the cutting method.

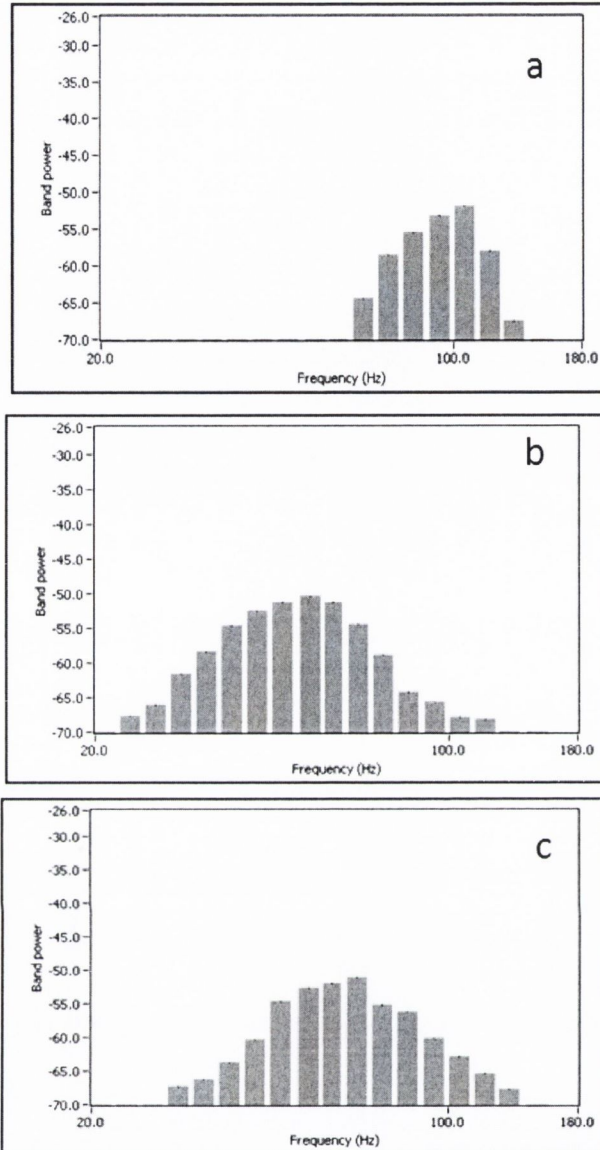


Figure 60. The FOA plot (20Hz-150Hz with bands power in dB) of the recovered OMT signal (15s) taken from a patient subject. a) FOA of the OMT recovered signal using the multiresolution method. b) FOA of the OMT recovered signal using the ATVF. c) FOA of the OMT recovered signal using the Wavelet method

3.4.4 OMT clinical parameters

Table 14 shows the PC absolute mean difference (PC-AMD) and AR spectrum peak absolute mean difference (ARS-AMD) of the two simulated groups (normal subjects and patients OMT records) for the different OMR recovery methods tested. The difference comparison is between the high spectral power peak estimation of the original signal compared to the same estimate for the processed signal using the Peak Count (PC) method or the Autoregressive (AR) spectrum. The wavelet method and the cutting method have achieved the best OMT signal recovery, showing the lowest variation in the spectral high peak estimation using the PC and the AR spectrum. The filtering method and the multiresolution method have both given a wide difference in the PC and the AR spectrum compared to the original signal. The ATVF achieved good results in the AR method but showed a higher difference in the PC method.

Methods	Normal subjects		Patients	
	PC-AMD (Hz)	AR-AMD(Hz)	PC-AMD(Hz)	AR-AMD(Hz)
Filtering	81	47	83	63
Cutting	1.3	0.8	2.3	1.7
Multireslation	36	10	55	53
ATVF	23	2.9	38	5.3
Wavelet	1.2	0.8	1.9	1.6

Table 14. The absolute mean difference of PC and AR spectrum comparing the original signal to the processed signal.

3.5 Discussion

3.5.1 Filtering method

As microsaccades are higher amplitude than the desired OMT signal, normal filtering 20-150Hz band (finite impulse response filter or infinite impulse response filter) of the eye movement signal will distort the OMT signal. Also the step caused by the microsaccades has frequencies which overlap with OMT frequency (148). By looking at the results from the time domain (SNR and CC), frequency domain (FOA-AMD) and joint time frequency analysis (CC, Stderror and AMD), filtering demonstrated poor results that will affect

diagnostic analysis in clinical examination. The results from looking at the two important diagnostic tools in the OMT clinical investigation (PC and AR spectrum) suggest that filtering is an unsuitable method of microsaccade removal in clinical tests.

One of the limitations in examining the filtering method in this work is that the test is restricted in only using a high order Elliptic filter. The order chose was designed to remove the high amplitude microsaccades, which affects the filter stability and introduces nonlinearity frequency dependent time delay (274). Investigating an optimal filter (finite impulse response filter or infinite impulse response filter) in both type and order may improve the results of the validation test carried in this work, though the issues with high amplitude and frequency overlap of microsaccades would not be solved with normal filtering.

3.5.2 Cutting method

Most clinical investigations use this method to recover the OMT signal (70), (36), (34), (275), (7). This method was able to recover the OMT signal (normal subjects and patients records) with low distortion in the spectral plot as shown in the FOA-AMD (in the normal subjects case 1.2dB difference and in the patients OMT case 8.59dB difference). The cutting method is clearly superior to ordinary filtering as the spectral peak is one of the most useful parameters in clinical assessment of OMT. This agrees with the results seen when looking at the clinically used parameters (PC and AR spectrum). The results from the AR spectrum (ARS-AMD) showed a mean variation of less than 1.7Hz between the processed and original signals using the cutting method. The same applies to the PC-AMD which showed an absolute mean difference of 2.3Hz. Unfortunately, the drawback of the cutting method is that because the method is based on microsaccade period removal, there is loss of information as seen in the time domain and joint time-frequency domain comparison. One of the key OMT analysis methods in clinical investigation is examination of the OMT features (burst and baseline) parameters (276). These parameters will be distorted (or difficulties will be introduced in analyzing them) by the cutting methods as some of the time domain information is lost.

The discontinuity in the OMT signal causes difficulties in characterizing and modeling the OMT signal. Microsaccades removal with the cutting method results in short OMT segments. Joining these segments to provide a sufficiently long data series for analysis may bias results, as summation of segments will introduce an increase in the low frequency component of the OMT signal due to offsets between the segments.

3.5.3 Multiresolution method

Although this method was used in the literature in the OMT investigation of the schizophrenia patients (5), the effectiveness of this method was not assessed. The results show that the method is not suitable as a recovery method. This is due to the fact that the microsaccades frequencies overlap the lower band of the OMT frequency range and the method is based on filtering the lower frequency band of captured signal. In pathological cases, where the dominant frequency tends to be lower, this problem will have most impact with multiresolution method. This is clearly the case when looking at the PC-AMD and AR-AMD as shown in Table 14. With both PC and AR spectrum the difference between the original signal and the filtered signal was shown to be as high as 55Hz and 53Hz respectively. This high difference will cause difficulties in detection and characterization of the OMT signal in clinical investigations (such as patients with stroke, midbrain infarcts, cranial nerve VI palsy or traumatic brain injury).

The performance of this method could be improved by introducing an adaptive band filtering selection, though still the overlap of the OMT frequency and microsaccades frequency will be an issue.

3.5.4 ATVF method

This a new OMT signal recovery method introduced in this work. Results show that this is better in recovering the OMT signal than the filtering and the multiresolution methods. In the time domain comparison of the first group (normal subjects OMT signal recovery) the ATVF showed good results compared to the other methods in terms of the CC and SNR (0.704 and 1.94dB). Unfortunately this is not the same for the second group (patients OMT

signal recovery) as the performance has dropped ($CC=0.234$ and $SNR= -8.01$ dB). The same is noted when looking at the MIF and FOA. Looking at the PC-AMD and the ARS-AMD the method is better in the normal subjects' records than the patients' one. Also there is less difference in the ARS-AMD than the PC-AMD.

The overall performance of the recovery method is much better for normal subjects OMT records than patients OMT records in all domains (time, frequency and joint time-frequency). Further work is required to improve the threshold selection to cope with differences between normal subjects and patients' records.

3.5.5 Wavelet method

There is no report in the literature in using the wavelet denoising as method for OMT signal recovery (251). The main idea of this method is to use the wavelet denoising method to get as-close a fit as possible to the microsaccades information (filter OMT, drift and noise), which are represented by the high wavelet coefficients. Then by subtracting the recovered microsaccade signal from the original signal (full movement signal), the OMT information could be easily recovered by normal low pass filtering (20 Hz cutoff to remove drift information).

One of the key points in this method is the selection of an appropriate wavelet function. The selection process in this work is based on a simulated signal made of different microsaccades shapes observed from the original clinical data (captured by the PZT system described in Chapter 2) used in this chapter in both normal subjects and patients. From Table 8 one can conclude that the db03, showed better results in terms of the correlation and RMSE compared to the other tested functions, although the difference in correlation value between the different functions is small.

The wavelet method shows good results in the time domain with the lowest mean cross correlation factor seen in the patients records of 0.812 and SNR of 4.90 dB. This is better compared to the other methods. The same applies when looking at the frequency and the joint time-frequency domain with FOA and MIF. This advantage is also reflected in the

results of the clinically used parameters PC-AMD and ARS-AMD (1.9Hz and 1.6Hz). This is about the same results as the cutting method but with the advantage of not having the correlation domain lost, which is required for pattern analysis and for examining the cross correlation between the two eyes.

Although the wavelet method showed better results in all the validation tests carried compared to the other recovery methods, the MIF with patient records showed poor results (CC=0.569, AMD=14Hz and Stderror=48Hz) in comparison with normal subjects records (CC=0.833, AMD=7Hz and Stderror=31Hz). The same was noted for the time domain, FOA and clinical parameters compressions. This due to the difference in the signal features (in both time domain and frequency domain) of the patient records compared to normal subjects. This points out one of the limitations of this system in clinical investigation, which requires further improvement in having both threshold and wavelet function selections to cope with changes in signal features.

The wavelet method introduced was applied in a number clinical investigation (35, 74, 76, 261, 263, 273). One of the key advantages of recovering the OMT signal using the wavelet method is the preservation of the continuity of the time series with minimal distortion due to the signal recovery. This will allow investigation of the OMT signal generation mechanism in more detail.

3.6 Conclusion

The chapter implemented five methods to recover OMT from the PZT signal. Three (filtering, cutting and multiresolution methods) have already been used in the literature in recovering the OMT signal and the other two (ATVF and wavelet methods) are newly implemented methods. The five methods were examined in terms of performance in recovering the OMT signal in the time, frequency and joint domains. The examination was based on a simulated OMT signal of normal subjects and patients OMT characteristics. The results are in favour of the wavelet method as a tool to recover the OMT signal from the eye movement signal with lowest distortion level.

In some relatively rare clinically abnormal OMT records seen by the author, in addition to the expected drop in OMT frequency, an atypical low frequency, high amplitude background is present in the PZT signal. The origin of this 'artefact' is unknown and may originate from abnormal high amplitude eye movements or from head movements. The type of wavelet function (e.g. Harr or Daubechies) and the number of levels used for reconstruction have to be defined a priori in the wavelet method and this choice may influence the final results. It is unlikely that the wavelet method chosen to extract microsaccades from a typical normal or typical pathological trace could extract microsaccades from these typical traces. These atypical abnormal waveforms were not considered here and their prevalence has not yet been quantified. Further work could be done to build an adaptive wavelet method to cope with variations in the characteristics of OMT signals.

Ch4

4 Investigation of OMT signal characteristics

4.1 Introduction

4.1.1 OMT signal and stationarity

Stationarity has not been investigated in the literature for the OMT signal for normal subjects or for patients with clinical conditions. Stationarity tests in normal subject OMT signals may not be valid for all OMT signals as there are differences in frequency and burst characteristics between normal subjects and patient OMT signals. As the stationarity of OMT has received little attention, we propose here to test OMT signal stationarity in normal subjects and patient cases. A new developed OMT signal recovery method for eye movements captured by the PZT system was introduced in Chapter 3 and its performance was validated and compared to current methods. The method is based on recovering the OMT signal using a wavelet denoising technique (251). Using wavelet microsaccade removal has provided the advantage of not losing time domain signal continuity, as long

runs of continuous data that the new method provides simplify and increase the power of statistical methods used to test stationarity.

4.1.2 OMT signal and nonlinearity

The OMT signal trace shows some features which may hint at an underlying non linear process driving the movement. Despite this, in the OMT literature, there has been no attempt to investigate OMT nonlinearity. Equally, no attempt has yet been made to extract non linear measures from the OMT signal as potential clinical markers.

As explained in the literature the OMT signal is divided into burst and baseline activities. In particular the irregular waxing and waning of sinusoidal bursts in OMT has a form that invites comparison with behavior seen in chaotic systems (277), (278), (279).

If we can detect underlying non linear processes in the OMT signal, then this will be of significance in developing models and hypotheses on the physiological origins of OMT. In addition, uncovering a non linear element in OMT may lead to new clinically useful measures (such as nonlinear entropy measures) of OMT and challenge some of the linear analysis approaches used at present (such as FFT or the AR spectrum).

A common approach to test the linearity of physiological signals is to generate the surrogate data of the signal tested and then to apply a null hypothesis statistical test to prove or disprove linearity. This approach will be discussed in great detail later.

4.2 Methods

4.2.1 OMT signal data collection

The data was collected using the PZT system (described in Chapter 2) with a single experienced observer (NC). The PZT system has a linear amplitude response, with a flat frequency response between 20 Hz to 150Hz. The signal is digitized using a 24bit ADC with 2500 samples per second. For the following tests 100 OMT traces of 15 seconds duration were acquired. Fifty OMT signals were taken from normal subjects (25 subjects,

2 records each, one from the right eye and one from the left eye) and fifty from patients (25 patients, 2 records each one from the right eye and one from the left eye). The patient records were taken from patients with either: stroke, midbrain infarcts, cranial nerve VI palsy or traumatic brain injury. All the recording took a place in St. James's Hospital with approval from the hospital ethical committee. The estimate of the mean frequency spectral peak (using the peak count) is $84.6 \pm 5.6\text{Hz}$ and $69.4 \pm 10.2\text{Hz}$ for the normal subjects and patients groups, respectively.

The signals captured by the PZT were further digitally processed using the wavelet denoising technique to recover the OMT signal (described in more detail in Chapter 3) (251). The signal was digitally band pass filtered from 20Hz to 150Hz to remove the drift and the noise from the OMT signal.

4.2.2 Computational platform

The tests were designed and implemented on a Intel(k) Core(TM)2 CPU T7200@2.00 GHz with 2.00 GB of Ram in MATLAB (280) and LabView (3).

4.2.3 Stationarity tests:

There are two methods available to investigate the stationarity of the OMT signal: parametric and nonparametric tests (281-285).

Nonparametric tests are more widely used, because one does not make any assumptions about the signal tested. Nonparametric tests require 5% to 35% more data than the parametric tests to arrive at the same statistical conclusion with the same confidence interval (286). On the other hand, the parametric tests require valid assumptions about the system such as normality, equal mean, equal variance etc (287) for the subsegments analyzed. In this investigation of OMT signal stationarity nonparametric stationarity tests were implemented.

4.2.3.1 Nonparametric tests

There are number of nonparametric stationarity tests used by different authors but the two most commonly used are the run test and the reverse arrangements test (278). Of those two tests the reverse arrangements test has been found to be more powerful in detecting the non-stationarity of time series signals (218).

4.2.3.2 Reverse arrangements test:

The reverse arrangement test was used for stationarity testing. In this test the OMT time series X_t is divided into N subsequences. The minimum value of N is 10 to provide a statistically significant result (288). The duration of the subsequences for stationarity testing should exceed the period of its lowest frequency component (218, 288-289). The low frequency cut off of the OMT signal is 20Hz; this will suggest a window size of 50ms as a lower limit for the stationarity testing. As a precaution 100ms (250 samples) was chosen as the minimum window size. The upper limit was chosen to be 1.4 second (3500 samples) as the longest subsequence duration possible of the total OMT signal duration (15s) that will provide enough subsequences ($N=10$) to be significant. Stationarity tests were performed on non-overlapping window sizes ranging from 0.1 to 1.4s.

For each subsequence the mean square value was computed. The mean square value of each subsequence is equal to $\mu_1, \mu_2, \mu_3, \mu_4, \dots, \mu_N$. Let h_{ij} to be as follows:

$$h_{ij} = \begin{cases} 1 & \text{if } \mu_i > \mu_j \text{ for } i > j \\ 0 & \text{otherwise} \end{cases}$$

and

$$A = \sum_{i=1}^{N-1} A_i \quad \text{where} \quad A_i = \sum_{j=i+1}^N h_{ij} \quad \text{Equation 15}$$

The confidence interval is calculated using the reverse arrangements distribution (218). The reverse arrangements distribution is a normal distribution with mean value (μ_A) and variance (σ_A) as follows (290):

$$A = \frac{N(N-1)}{4} \quad \text{Equation 16}$$

$$\sigma_A^2 = \frac{N(2N+5)(N-1)}{72} \quad \text{Equation 17}$$

The hypothesis of the stationarity of the signal is accepted at the significant level of α if:

$$Z_{1-\frac{\alpha}{2}} < Z_A < Z_{\frac{\alpha}{2}}$$

where Z_A is,

$$Z_A = \frac{A - \mu_A}{\sigma_A} \quad \text{Equation 18}$$

4.2.3.3 Regression test

Using the OMT signals (from both normal subjects and patients) which were classified to be nonstationary by the reverse arrangement test, the source of non-stationarity is investigated here. In this investigation we are interested in using the regression statistical test to determine if the variables (such the OMT mean) vary with time. This done by statistical testing if the variables data has zero slope when plotted against time. Zero slope implies that variable does not change with time linearly (while taking outliers into consideration) and therefore implies that the variable is not a source of nonstationarity in the tested signal as does not change with time.

To investigate the fundamental source of nonstationarity, the time invariants were tested for three variables: the mean (Y_m), variance (Y_v), and OMT dominant frequency content (Y_f) (by peak count) by regression analysis (289). Of the number of ways we could examine the stationarity of the frequency content, the peak count was chosen as it is the favored method in analysis of OMT dominant frequency content (33). The nonstationary signals are divided to equal non-overlapping subsequences and for each subsequence the three variables were calculated. With regression analysis the calculated values are tested

independently with the null hypothesis that each variable does not vary with time using the least square line with zero slope ($B_1=0$).

The test statistics as follows; the null hypotheses (H_0), that variable Y is independent of time $X(t)$ if $B_1=0$:

$$H_0: B_1=0$$

$$H_a: B_1 \neq 0$$

The hypothesis is tested using the t-score test with $n-2$ (n is the number of subsequences) degrees of freedom. The hypothesis is tested using a 95% confidence interval where t_{score} is calculated as follows:

$t_{score} = \frac{B_1}{SE}$ where SE is the standard error from the regression output calculated as follows:

$$SE = \sqrt{\frac{\sum_{t=0}^N (Y_t - \hat{Y}_t)^2}{(N-2)(X_t - \bar{X})^2}} \quad \text{Equation 19}$$

Where;

- Y_t is the dependent variable (Y_m , Y_v or Y_f).
- $\hat{Y}_t$ is the estimated value using B_1 from the regression analysis.
- X_t is the observed value of the independent variable.
- $\bar{X}$ is the mean of independent variable.
- N is the number of observations.

The overall test is done as follows:

- ❖ Divide each of the nonstationary signals into equal non-overlapping subsequences ($n=15$).
- ❖ Calculate the mean (Y_m), variance (Y_v), and OMT dominant frequency content (Y_f) for each subsequence.

- ❖ Check if there are outliers and check normality and equal variance assumptions.
- ❖ Calculate the slope B_i and the standard error (SE) for each variable.
- ❖ Calculate the t score for each variable and test the hypothesis with $N-2$ degrees of freedom.

4.2.4 Nonlinearity test

One of the strategies in determining if a time series is nonlinear is by generating data that has the same time duration and maintains all the linear properties of the original time series and removes any nonlinear deterministic structure by complex phase randomization in the frequency domain. The generated data are called the surrogate data (or surrogates for short). It is one of the most reliable methods for testing the nonlinearity of time series (248-249). In this test the null hypothesis tested is that the time series is the result of a Gaussian linear stochastic process and therefore the surrogates are generated consistent with the hypothesis. The most commonly used techniques for generating surrogates are random shuffling (RS) (246), Fourier transform (FT) (246), amplitude adjusted Fourier transform (AAFT) (247), iterated AAFT (iAAFT) (248), digitally filtered shuffled (DFS) (249) and truncated iAAFT (tiAAFT) (250).

4.2.4.1 Generating surrogates for OMT signal

As discussed above, there are a number of methods for generating the surrogate data. The difficulty arises when dealing with the OMT signal is that the signal cannot be assumed to be stationary. Applying either RS, FT, AAFT or iAAFT in generating the surrogate may give rise to statistical Type I error (rejection of the linearity hypothesis where it is true), as the rejection could be due to non-stationarity (241, 244, 250). On the other hand tiAAFT solve this issue by applying phase randomizing only for the high frequency content of the Fourier transform, therefore the long time scales of the data (the low frequency of the spectrum) are preserved in the surrogate. Hence the algorithm preserves the non-stationarity within the surrogates, so that the outcome statistic result is not biased by the non-stationarity term (250).

The algorithm of the tiAAFT is implemented on the OMT signal as follows:

- a. First the OMT signal amplitude is rescaled to a normal distribution by generating a Gaussian white noise and sorting it from the ranking of the OMT signal. Let $x(t)$ be the rescaled OMT signal.
- b. Construct the Fourier transform $X(\omega)$ surrogate of $x(t)$, where ω is the frequency.
- c. Generate random phase $\beta(\omega)$ for $\omega > f_t$ and $\beta(\omega) = 0$ elsewhere, where the f_t is the truncated frequency.
- d. Then the randomized Fourier transform amplitudes are adjusted back to the amplitudes of $X(\omega)$, to adjust the power spectrum to that of the original signal power spectrum.
- e. Next the inverse Fourier transform is applied to the result of step d.
- f. After that the data are rescaled to the distribution of the original OMT signal and sorting it from the ranking of the $X(\omega)$.
- g. Finally steps c to f are iterated until the difference between the power spectrum of the surrogates and the original signal is small.

For more information see (241).

For a significance level of $(1-\alpha) \times 100\%$, we must at least generate $N = \frac{2}{\alpha} - 1$ surrogates for a two sided test. Using more surrogates can increase the power of the test (244). In the OMT linearity testing using a 95% confidence interval 39 surrogates were generated ($N = \frac{2}{0.05} - 1$) for each OMT signal tested (both normal subjects and patients records). Then the nonlinearity statistic test was carried out for each signal.

4.2.4.2 Nonlinearity statistic measure

To attempt to reject the statistical hypotheses of linearity, a nonlinear parameter is required for comparison. If the nonlinear parameter value of the signal is within the confidence interval of the probability distribution of the surrogates then the signal is linear (hypothesis is accepted), as the nonlinear deterministic structure (if any) should be removed when generating the surrogate data. The nonlinear statistic measure used in this study is based on the time reversal (TR), as it is a computational simple traditional measure of nonlinearity (291). A time series is said to be reversible if its probabilistic properties don't change with respect to time reversal (291). A linear stochastic process always has symmetric statistics under time reversal, which implies that time irreversibility is an indicator for nonlinearity. This fact is used in the linear/nonlinearity discrimination by statistical testing the time series with the surrogate data generated, with the null hypothesis being that the time series is reversible (linear stochastic process).

For tested OMT records, the time reversal was calculated for the surrogates ($s_i, i=1,2,\dots,N$, where N is the number of the surrogates generated) and the original OMT signal, as follows:

$$TR(\tau) = \frac{1}{N-\tau} \sum_{n=\tau+1}^N (s_n - s_{n-\tau})^3 \quad \text{Equation 20}$$

Where τ is the time lag estimated from the first clear minimum of the average mutual information plot of the signals (292). The average mutual information (AMI) is calculated as follows:

$$AMI(x_t, x_{t+T}) = \sum_{t=0}^l P(x_t, x_{t+T}) \log_2 \left(\frac{P(x_t, x_{t+T})}{P(x_t)P(x_{t+T})} \right) \quad \text{Equation 21}$$

where:

- T is the time delay in steps of (1/2500s).
- x_t is the original signal.
- x_{t+T} the time delayed signal with T .
- $P(x_t), P(x_{t+T})$ are the probability of x_t and x_{t+T} , respectively.

➤ (x_t, x_{t+T}) is the joint probability of x_t and x_{t+T}

4.2.4.3 Hypothesis testing

As we cannot assume normality of the results (has not been tested) from the time reversal calculation, Z score statistics would not be valid. Alternatively a rank order test can be used (246).

Let TR_o be the time reversal of the original OMT signal and $TR_{s,i}$ be the time reversal of the surrogates ($i=1,2,\dots,N$). Then TR_o and $TR_{s,i}$ is sorted in increasing order and the position of TR_o (rank, r) is noted. The symmetrical rank (r_{sym}) is calculated as follows:

$$r_{sym} (\%) = \frac{\left| \frac{N+1}{2} - r \right|}{\frac{N+1}{2}}$$

The null hypothesis (OMT signal is linear) is rejected if $r_{sym} \geq 95\%$ (293).

4.3 Results

4.3.1 Stationarity test

Table 15 shows the results from the stationarity test with the mean square value using the reverse arrangements test with OMT records from normal subjects and from patients. With the normal subjects cases using a 100ms window length the statistical null hypothesis of stationarity is rejected with 95% confidence interval in about 30% of the OMT records, In the case of the patients records using a 100ms window length, the percentage of nonstationarity is higher than normal subjects with more than half of the records (60%) shows nonstationarity. As expected the results shows that a shorter segment duration results in increasing the percentage of nonstationarity in the OMT records as shown in Table 15.

Window length	Non-stationarity	
	Normal subjects	Patients
100ms	15/50 (30%)	30/50 (60%)
250ms	14/50 (28%)	28/50 (56%)
500ms	14/50 (28%)	26/50 (52%)
750ms	10/50 (20%)	27/50 (54%)
1s	8/50 (16%)	20/50 (40%)
1.4s	5/50 (10%)	15/50 (30%)

Table 15. The percentage of nonstationary signals out 50 OMT traces from normal subjects and 50 OMT traces from patients using the reverse arrangements test with the mean square value of the records.

Figure 61 shows a Venn diagram of the sources of nonstationarity in the signals classified by the reverse arrangements tests as non stationary using a 100ms window size (15 cases from normal subjects and 30 from patients). The source of non stationary (Mean, Variance or Frequency) was tested using regression analysis. The overlaps in the Venn diagram show the cases where combinations of sources (Mean & Variance, Mean & Frequency, Variance & Frequency and Mean & Frequency & Variance) were attributed as the source of non stationarity for both normal subjects and patients records. There were a number of undetermined cases where Mean, Variance and Frequency could not account for the non stationarity seen (7% of both groups).

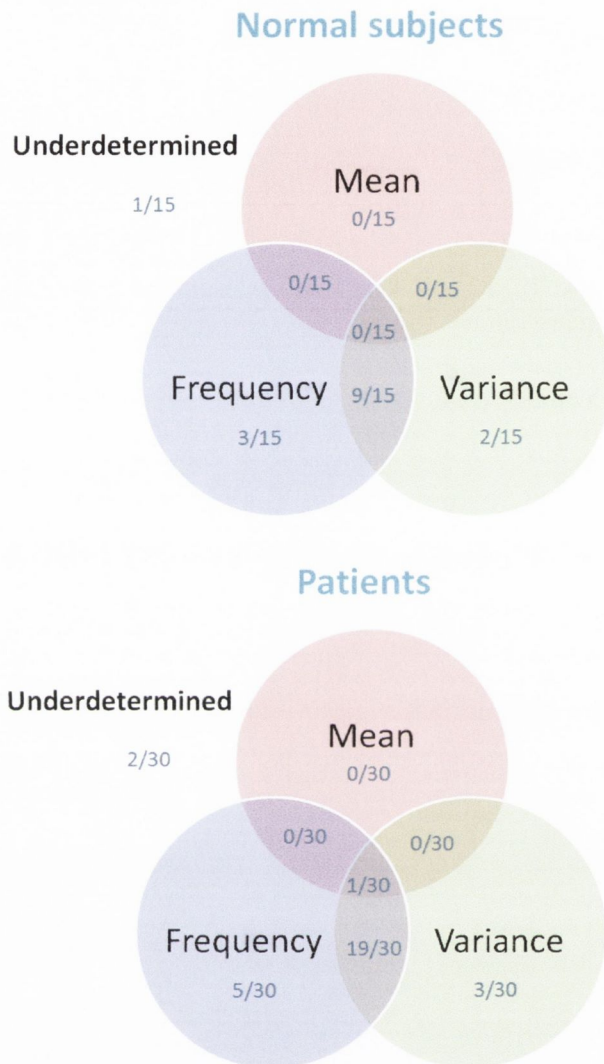


Figure 61. Venn diagram of the different investigated sources (mean, variance and frequency and their combinations) of nonstationarity in the OMT signals (15 nonstationary signals from normal subjects and 30 nonstationary signals from patients) that are found to be non-stationary with 100ms window size.

4.3.2 Linearity tests

For a 95% confidence interval it was necessary to generate at least 39 surrogates (244) for a two sided linearity test. Due to the long computational time required for the linearity test only 39 surrogates were generated using tiAAFT for each OMT signal test. 60 OMT signals (15s each) were used randomly from the 100 signals described earlier with (30 from normal subject data and 30 from the patient data).

Table 2 shows the results of the linearity test of the normal subjects and patients cases. For the normal subjects OMT records there was 4 cases were the hypothesis of linearity was rejected. The results also show that for about a third of the patient OMT records, the hypothesis was not accepted.

OMT time series from	Hypothesis accepted (signal linear)
Normal subjects	26 out of 30
Patients	21 out of 30

Table 16. Shows the results of the linearity test using OMT records from normal subjects and patients.

4.4 Discussion

4.4.1 OMT Stationarity

Using the nonparametric reverse arrangements test shows that OMT stationarity cannot be assumed in all cases from data taken for normal subjects and patients. In the case of OMT signals taken from normal subjects there were 15 signals out of 50 where the hypothesis of stationarity was rejected using the reverse arrangements test with 100ms window length. Using a longer duration window length the numbers of cases of nonstationarity were fewer, with just five nonstationary cases with a 1.4s window. The number of nonstationarity cases (15) was with the OMT signals taken from patients records with changes in OMT activity. The hypothesis of patients OMT records being stationarity was rejected in 30 out of 50 cases using 100ms segment duration, in 26 cases with 500ms duration and in 15 cases with 1.4s duration.

In nonstationary signals using a long window duration for analysis, slow varying trends could appear stationary (288). The results shows that there is a significant difference in using different window sizes with the stationarity test ($p < 0.05$) using a 95% confidence interval. Table 15 shows that as the window length of the subsequences is increased the number of cases of nonstationarity decreases, which agrees with results seen by different authors (other than OMT) when increasing window duration in the stationarity test (278), (288), (294). This suggests that increasing the width of the OMT analyzing window is more favorable to reduce estimated frequency spectra variability when using frequency analyzing methods such as the peak count, AR spectrum and Welch spectrum, although this will affect the temporal resolution of the methods and also those parameters that changes with time might be of importance in assessing the system behavior or clinical condition. Window length that can provide 100% stationarity was not observed in this study. The maximum duration that could be tested with a 15s records length in the reverse arrangement method was 1.4s. The stationarity tests are more reliable using a short window sizes as the longer the window duration then there will be not enough segments for the test to be significant (M) with limited OMT duration of 15s.

The result of testing the source of nonstationarity with the mean, variance, frequency and their combinations using the regression analysis, is demonstrated in Figure 61. Most of the nonstationarity in the OMT signals is due to temporally unstable variance and/or frequency in both the normal subjects and patients groups. The mean in most cases was time invariant, which expected due to the high pass filtering that will tend to force the mean to be zero (294). For the normal subjects and patients, nonstationary in 7% of signals was not due to the mean, variance or frequency (undetermined). In these cases there was no evidence from the scatter plot of mean, variance and frequency versus time of outliers or data scatter that could have masked a non zero slope (295). Similar results of undetermined cases were noted in the literature in the study of mechanomyogram (289) and paediatric aspiration (288) signals with the investigation of source of nonstationarity using the regression analysis. The authors reported that the undetermined cases could be related to nonlinearity within the signal.

One of the limitations in testing the source of nonstationarity due to frequency content is that the peak count only estimates the mean frequency spectral peak, but does not represent all the potential temporal changes in the frequency spectral content. Further work could be done by applying regression analysis through the frequency spectrum estimated at each interval.

One of the possible reasons for nonstationarity in the OMT signal could be the generation mechanism of the OMT burst and baseline features. As the amplitude of the OMT burst activity is higher than the baseline this will introduce variance changes with time. Also the burst frequency activity (e.g. mean 83.5 Hz, stdv 4.5Hz in normal subjects) is different than the baseline frequency activity (e.g mean 87.7 Hz, stdv 18.7Hz in normal subjects) so the variation in the baseline frequency will introduce nonstationarity in the frequency content of the OMT signal. This may explain the increase in the number of nonstationary cases in the patients versus normal subjects records, as differences in the OMT bursts and baseline features of the normal subjects compared to the patients OMT signals have been reported by a number of authors (51), (31), (27) and were also noted in this work. Increasing the segment duration in the stationarity test will introduce averaging between burst and baseline activity and will cause the reverse arrangements test to accept the hypothesis of stationarity. This was shown by the reduction in the number of nonstationary cases when the OMT segment test duration was increased from 100ms to 1.4s.

The results show that the assumption of stationarity of OMT is not valid and suggest that the current analyzing methods (FFT, Welch spectrum, peak count, and linear predictive spectrum) should be examined further to take in to account nonstationarity as they are more suited for frequency content that is time invariant. One of the possible solutions to this is to modify the current analysis methods by dividing the recorded OMT signals into segments and apply a stationarity test to each segment. Then only those segments that pass the stationarity test are analyzed. The same approach has been applied in cardiovascular variability signals to overcome the limitations of spectral analysis due nonstationarity (296). The disadvantage of this method was that the temporal information will be lost due to the truncation of nonstationarity segments. This method might not be appropriate in

OMT analysis due to loss of valuable information such as OMT burst and baseline features. Also the nonstationarity in the OMT signal could be a potential source of information about a change in the clinical state during those changes, especially changes of OMT frequency with time. A more appropriate method may be to introduce new analysis methods that are not based on the stationarity assumption. One of the preferred methods of dealing with biomedical signals is the Wavelet transform. The wavelet method is less affected by nonstationarity as it is based on varying the window-width as discussed in the literature review, which could be used to introduce the joint time-frequency (scale) in the OMT analysis, so that monitor the changes of frequency with time and try to relate it to the clinical state of the subject examined. The potential of using the joint time-frequency analysis for OMT was discussed in the literature review.

4.4.2 Nonlinearity test

For the nonlinearity test the modified AAFT (tiAAFT) was used to generate the surrogate data, as the possibility of statistical Type I error (rejection the linearity hypothesis where its true) due nonstationarity of the OMT signal in some cases is minimized. Using a 95% confidence interval the nonlinearity test shows that about 14% of cases were nonlinear for OMT records taken from normal subjects and 30% of cases were nonlinear for OMT records taken from patients. This implies that not all the OMT records could be assumed to be linear.

In OMT simulation, a linear model of the OMT signal generation mechanism will not be realistic due to the nonlinearity of the OMT signal in some cases. The increase of the nonlinearity cases in the patients records compared to the normal subjects records is an important fact to be taken in to account when modeling the OMT signal. Further investigation will be required to understand the source of nonlinearity in some of the OMT cases.

On the other hand, the nonlinearity found in the OMT signal will encourage us to test the usability of the nonlinear measures as OMT clinical markers. Current methods of analyzing the OMT signal are based on linear measures. The fact that the number of

nonlinear cases in the patients OMT records was higher than the normal subjects OMT records supports the use of nonlinear measures in OMT clinical studies. Chapter 6 tests one such measure in an OMT clinical investigation.

4.5 Conclusion

This chapter investigates the characteristics of the OMT signal in terms of stationarity and nonlinearity. These findings could help in building a more realistic OMT model that will help understanding of the origin of OMT and the OMT generation process. The findings also question the appropriateness of the current OMT analysis methods that are based on the assumption of stationary or linear signal and support the idea of implementing new methods to reflect these findings.

Ch5

50MT feature extraction

5.1 Introduction

For clinical applications quantitative parameters of a demonstrated value must be extracted from the OMT trace. Peak counting, frequency analysis and simple visual inspection have been employed in the past. One clinical measure that has demonstrated value in OMT clinical investigation is the identification of the OMT features (bursts and baseline) in the signal (27), (37). Published work on OMT features is based on six parameters: number of bursts, mean duration of bursts, frequency content of bursts, percentage of baseline duration, mean duration of baseline and the frequency content of baseline. Changes in these parameters have been noted in the OMT records from patients with abnormal pupil reflex (27), motor neuron disease (194), idiopathic Parkinson's disease (37) and with ageing (75).

The OMT features are identified by visual inspection. Identification of the burst and baseline activity of OMT signal in this way is time consuming, laborious and subject to observer variability. This limits the use of OMT feature analysis as a diagnostic tool in clinical studies and limits the duration of signals that can be practically examined.

Here we propose an automated burst extraction method. The proposed method is tested by comparison with visual inspection by skilled and unskilled observers.

Automation of burst extraction is expected to speed analysis and calculation of burst/baseline parameters and to improve reproducibility between studies. In addition, the automated method will simplify quantification of the correlation of burst occurrence between the two eyes. To date little work has been done on this area, although based on visual judgment, Abkumova (27) suggested that no strong correlation exists. More definitive evidence would be interesting from a neurophysiological perspective.

5.2 OMT burst extraction

5.2.1 Basis of method

OMT bursts have higher amplitude than baseline and have a near-sinusoidal shape. There is a small spread in the frequency content during each burst, similar to that of a sine wave carrier amplitude-modulated by a low frequency (about 5Hz). Simple time domain filtering will not work in separating OMT baseline activity (70 Hz to 126 Hz(159)) from burst activity (75 Hz to 115 Hz(31)) as both frequency ranges overlap.

Examination of a joint time frequency spectrogram of OMT using the Gabor transform illustrates a potential mechanism of burst extraction (see Figure 62). Bursts appear with higher energy levels than baseline, implying they are represented by higher Gabor coefficients. If the Gabor coefficients for an OMT trace are first calculated and then appropriately thresholded, reconstruction of the signal using the thresholded coefficients will return a trace with an estimate of burst activity alone.

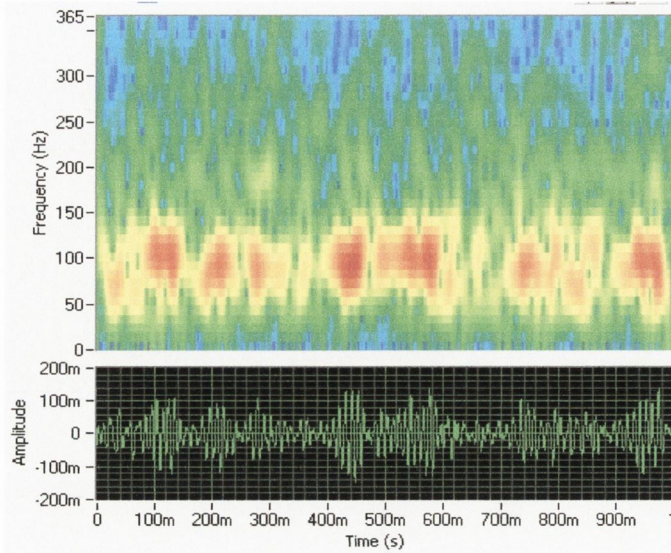


Figure 62. A spectrogram of 1s of OMT signal (microsaccades and drift artifacts has been filtered out).

5.2.2 The Gabor transform

The OMT recovered signal $g(t)$ can be represented by the Gabor expansion as a linear combination of the time-frequency elementary functions :

$$g(t) = \sum_{m=0}^{M-1} \sum_{n=0}^{N-1} C_{m,n} h_{m,n}(t) \quad \text{Equation 22}$$

where $h_{m,n}(t)$ is the time-frequency elementary function and $C_{m,n}$ are the Gabor coefficients. N is the number of frequency bins and M is the number of samples in the time domain.

The Gabor coefficients $C_{m,n}$ can be calculated using the Gabor transform:

$$C_{m,n} = \sum_{t=0}^{l-1} g(t) \beta^*[t - mdM] e^{-j2\pi nt/N} \quad \text{Equation 23}$$

where $\beta(t)$ is the analysis window and l is the signal length. The time-frequency elementary function can be calculated using:

$$h_{m,n}(t) = w[t - mdM] e^{j2\pi nt/N} \quad \text{Equation 24}$$

Where $w(t)$ is the window function and the time sampling interval is dM ($dM = \text{signal length} / M$). For more details about the Gabor transform, see (252), (208),(297), (298), (299).

5.3 Method

5.3.1 The Automated method

The following steps are implemented in the program used to identify and separate the burst regions from the OMT signal:

- The eye movements signal from PZT system (introduced in Chapter 2) is first filtered to remove drift and microsaccades using the wavelet denoising method (described in Chapter 3) and to extract OMT.
- Then the Gabor coefficients ($C_{m,n}$) of the signal are calculated using the Gabor transform.
- Next the highest and the lowest Gabor coefficients are found (C_H and C_L , respectively). The high Gabor coefficients (high energy region of the joint time-frequency spectrogram plot) are found to represent the burst activity.
- After that the threshold value (C_{TH}) is calculated as follows:

$$C_{TH} = ((C_H - C_L) \times T) + C_L$$

where the threshold (T) was chosen to be 0.9 (this will be justified later).

- Next the program runs through all the coefficients and implements the following
 - If $|C_{m,n}| \geq C_{TH}$ then $C_{m,n} = C_{m,n}$
 - If $|C_{m,n}| < C_{TH}$ then $C_{m,n} = 0$
- Next the inverse Gabor transform is applied to the modified coefficients. The signal will appear in the time domain with zeroed regions (the thresholded coefficients) representing baseline activity regions and the remaining regions of the OMT signal are the bursts.

5.3.2 OMT clinical data

The OMT clinical data used in the validation of the burst identification automated method were collected using the PZT system with a single experienced observer (NC). The OMT

recording duration was 15s, sampled at 2500 samples per second and recorded from both eyes simultaneously. The data was collected from ten different normal control subjects and ten different patients with either: stroke, midbrain infarcts, cranial nerve VI palsy or traumatic brain injury¹⁶, all of which cause changes in OMT activity. Both groups were aged from 24-75 years old and all recordings took place in St. James's Hospital with approval from the hospital ethic committee.

The signals captured by the PZT system are filtered using the wavelet method (introduced in Chapter 3) to recover the OMT signal (149).

5.3.3 Correlation of the burst occurrence between the two eyes

First the bursts signal was extracted from the OMT signal $y(n)$ using the automated Gabor method. Then from the extracted signal a new 'burst present' binary signal $u_{burst}(n)$ was generated with:

$$u_{burst}(n) = \begin{cases} 1 & \text{if } y(n) \text{ is a sample from a burst} \\ 0 & \text{if } y(n) \text{ is a sample from baseline} \end{cases}$$

This was done for both eyes obtained simultaneously using the PZT system from 10 normal subjects and 10 patients (15s each). Then the correlation coefficient (CC) was calculated with (271):

$$CC = \frac{1/N \sum_{n=1}^N ((u_{burstR}(n) - \bar{u}_{burstR})(u_{burstL}(n) - \bar{u}_{burstL}))}{\sqrt{\frac{1}{N} \sum_{n=1}^N (u_{burstR}(n) - \bar{u}_{burstR})^2} \sqrt{\frac{1}{N} \sum_{n=1}^N (u_{burstL}(n) - \bar{u}_{burstL})^2}} \quad \text{Equation 25}$$

Where;

$u_{burstR}(n)$ and $u_{burstL}(n)$ are the 'burst present' (0s and 1s) signals from the right and left eyes.

¹⁶ Different conditions so that the performance of the automated method could be tested using a number of patients conditions, which strengthen the effectiveness of the validation test.

$\bar{u}_{burstR}$ and $\bar{u}_{burstL}$ are the signal means and N is the number of samples.

Next the average correlation coefficient was calculated for all the records (n=20) and the highest correlation coefficient was noted .

5.3.4 Method validation

To validate the effectiveness of the new automated Gabor method it was compared to visual inspection to identify the number of bursts and their periods.

5.3.4.1 Number of bursts

To assess the automated method with respect to the variability in observers in identifying bursts in a signal, twenty volunteers (with little background in signal processing, but experienced in examining signals such as clinical EEG and ECG) were chosen to count the number of bursts in six signals (1s each) of three different normal subjects and three different patients. The volunteers were given instructions on how to identify an OMT burst. The mean and the standard deviation of the number of bursts identified were then calculated and compared with results obtained from the automated method. The automated method was implemented using different thresholding (0.89, 0.90, 0.91, 0.92, and 0.93). This was to investigate the variation in the number of bursts identified with changes in threshold. The variability of burst identification with threshold setting was then compared with the inter observer variability of the unskilled observers.

5.3.4.2 Identifying periods of bursts

In this test the automated method is validated against two skilled OMT features examiners. The two expert examiners (examiner A & examiner B) experienced in OMT visual inspection were asked to visually mark periods of bursts in the same 3 s trace (1s record from three different patients) of OMT of a normal subject (the same normal subject's OMT records used in the above test).

To investigate intra-examiner repeatability, the examiners were also asked to repeat the test on the following day. For comparison, the signal was processed with the automated method with a threshold setting of 0.9 (this will be justified later).

Agreement between the automated method and the examiners was tested by generating a signal $x(n)$ of the same duration and sampling rate (3s at 2500Hz) with:

$$x(n) = \begin{cases} 1 & \text{if } y(n) \text{ element of a burst} \\ 0 & \text{if } y(n) \text{ element of a baseline} \end{cases}$$

The agreements between the results were also examined using the Kappa statistic, which is useful to rule out chance agreement. The Kappa statistic is commonly used in medical literature. The method is based on comparing the observed proportion of agreement between two results made by two different observers (A_{obs}) with the proportion of agreement that would be expected by chance (A_{exp}). The Kappa value (κ) is calculated as follows:

$$\kappa = \frac{A_{obs} - A_{exp}}{1 - A_{exp}} \quad \text{Equation 26}$$

The Kappa magnitude value strength are judged by Landis and Koch as follows (300) (301):

- Poor if $\kappa \leq 0.20$
- Slight if $0.21 \leq \kappa \leq 0.40$
- Moderate if $0.41 \leq \kappa \leq 0.60$
- Substantial if $0.61 \leq \kappa \leq 0.80$
- Almost perfect if $0.81 \leq \kappa \leq 1.00$

To see the effect of varying the threshold used in the automated method with the agreement to the two examiners, the threshold is varied from 0.85 to 0.95 in steps of 0.005. The Kappa value is calculated between the automated method using different thresholds and the visually score of burst from the first day of the two expert examiners (examiner A & examiner B).

The number of bursts identified by the skilled examiners was also compared to the number of bursts found by the automated method.

5.3.5 Computational platform

The automated method program was build and tested on computational platform Intel(k) Core™ 2 CPU T7200@2.00 GHz with 2.00 GB of Ram. All the analysis was carried out in LabVIEW (3) and Minitab (302).

5.4 Results

5.4.1 New method results

By applying the thresholding method to the original OMT signal after filtering with an empirically determined threshold setting of 0.9 the method was able to identify the periods where the bursts occurred. The six main burst-related parameters described previously (51) could be calculated from the period of bursts in the OMT signal identified in this way.

Figure 63 shows the spectrogram of the thresholded signal, demonstrating removal of periods with lower power level (baseline and background noise). Figure 64 shows an OMT signal before and after processing.

By applying the method to signals obtained from simultaneous recording from the left and right eye, the results appear to agree with previous findings that there is no obvious correlation between the times of occurrence of the bursts in the records from the two eyes (see Figure 65) (27). Using the records from the normal subjects (10) and patients (10) patients the average correlationt coefficent between the two eyes was 0.10 with the highest at 0.32.

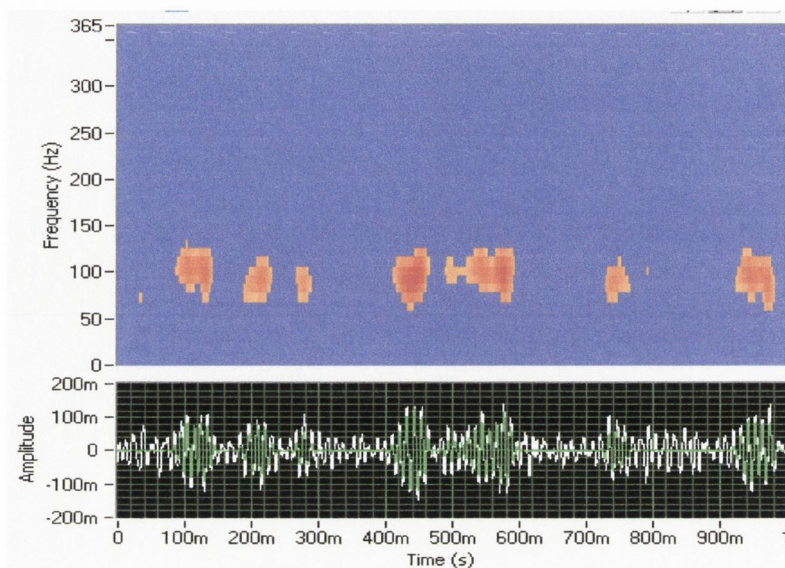


Figure 63. The spectrogram using the Gabor transform of the same signal in Figure 62.

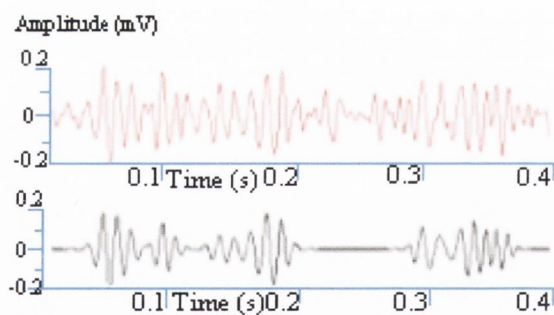


Figure 64. The upper trace is of OMT and the lower trace shows the same signal after thresholding using the method described here.

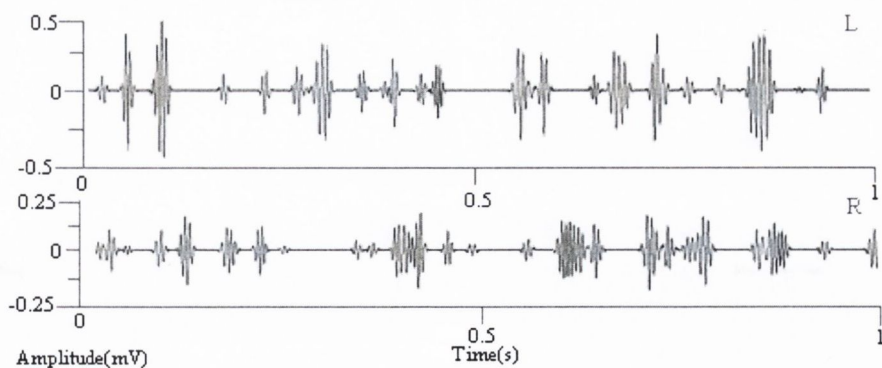


Figure 65. Thresholded OMT signal of the right eye (R) and the left eye (L).

5.4.2 Validation results

Table 17 shows the burst count variation with the threshold setting. As the threshold increases the number of bursts identified by the automated method decreases. This is because the filtered bursts have Gabor coefficients that are no longer within the threshold limits. This illustrates the importance of choosing an appropriate threshold.

Threshold	Number of bursts	
	Normal subjects	Patients
0.89	26	22
0.9	24	19
0.91	23	18
0.92	22	17
0.93	16	10
Mean N. bursts by inexperienced examiners	24.3 (Sdv 1.53)	16.0 (Sdv 8.52)
Mean N. bursts by Experienced examiners (A & B)	22.5 (Sdv 2.18)	N/A

Table 17. Burst count variation with the threshold setting using normal subjects and patients OMT signals (3s).

Results from the twenty inexperienced observers with six OMT signals (3 from normal subjects and 3 from patients, 1s each), shows that the mean number of bursts with normal subject records was 21.5 with a standard deviation of 4.32, while the automated method with thresholds from 0.89-0.92 has mean number of bursts of 24.3 with a standard deviation of 1.53. For the patients OMT signal the mean number of busts was 16.0 with a

standard deviation of 8.52, while the automated method with thresholds from 0.89-0.92 has a mean number of bursts of 19 with a standard deviation of 1.87.

On the other hand the results from the experienced examiners A and B with normal subjects OMT signal shows that the mean (in day one and day two with two examiners) number of bursts was 22.5 with a standard deviation of 2.18. The mean day to day variation in identifying bursts was 1.41.

Table 18 shows the agreement percentage and the Kappa statistic of the comparison between the two examiners and the new automated method.

Case	% Agreement	Kappa value	Comments
Examiner A, Day 1 vs Day2	86.4%	0.736	Examiner A shows intra observer difference over one day.
Examiner B, Day 1 vs Day2	89.3%	0.762	Examiner B shows an intra observer difference over one day
Examiner A vs Examiner B	88.5%	0.758	There is a good agreement between examiners as expected for experienced examiner A & B.
Examiner B vs Automated method	86.2%	0.709	The agreement between examiner B and the automated method is comparable to intra and inter observer agreement.
Examiner A vs Automated method	90.5%	0.791	There is very good agreement between examiner A and the automated method.

Table 18. The Kappa statistic for identifying the periods of bursts.

Figure 66 shows the variation in the kappa value of the automated method compared to the two examiners (examiner A and examiner B) using thresholds from 0.85-0.95.

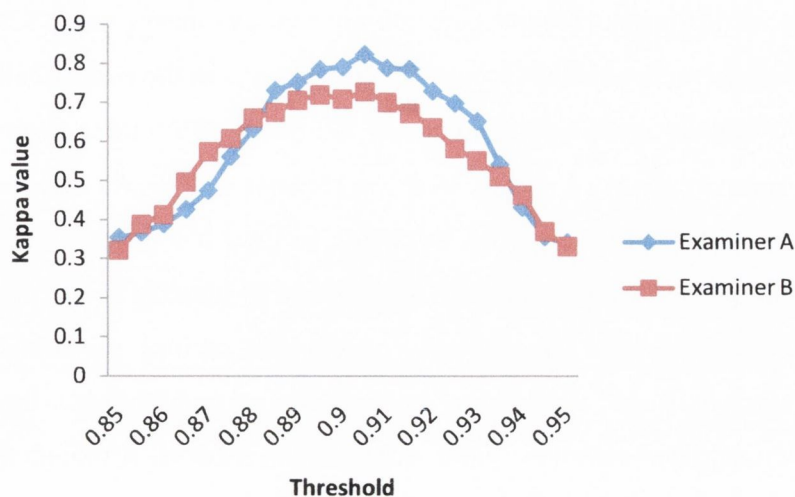


Figure 66. Plot of the variation in the Kappa value with different threshold setting of the automated approach compared with two examiners.

5.5 Discussion

The result from identifying the number bursts with inexperienced volunteers using visual inspection have shown there is a considerable variation in ‘burst’ identification within this group. The standard deviation in the number of bursts identified in normal subject’s OMT records by unskilled volunteers was 4.32 (from a mean number of bursts of 21.5 over duration of 3s). This deviation doubles in the patient OMT tested (8.52). This points to the importance of having a more robust method for identifying bursts from baseline OMT. The standard deviation in the number of bursts identified in normal subjects by skilled examiners was 2.18. By comparing the variations from the skilled compared to the unskilled we conclude that it requires skilled bursts examiners to reduce the variation in using visual inspection in clinical studies.

From the Kappa statistic, all cases (intra examiners, between examiners and automated method compared to the examiners) demonstrated a substantial strength of agreement (0.61-0.80) (300) in identifying the periods of bursts. The results show good agreement between the automated method and visual inspection by experienced examiners of OMT traces with 90.5% agreement with examiner A and 86.2% agreement with examiner B.

The burst identification agreement between the two examiners was 88.5%. This implies that the automated method shows a level of agreement with the two examiners comparable to the inter examiner agreement. Comparing the result of the intra-observer repeatability from day 1 compare to day 2 shows 86.4% agreement and 89.3% agreement of examiner A and examiner B respectively. The automatic method has the advantage of using both quantitative frequency and time domain information to identify bursts, whereas the visual inspection alone relies just on qualitative assessment of time domain information. The variability seen between and within human observers highlights the advantages of adopting a standardized automatic burst identification method. Although there was at least 20 bursts in the 3s OMT records, one of the limitations of this test was the use of short OMT records with normal subjects only.

One of the difficulties in the new automated method is the threshold setting. From Table 17 and Figure 66 we can clearly see the importance of choosing an appropriate threshold. From the plot in Figure 66 we can see that kappa level varies with the threshold setting (n shape), when comparing the automated method with the two examiners (examiner A and examiner B). Between threshold settings of 0.88 to 0.92 the Kappa value is relatively insensitive to changes in threshold. With thresholds lower or higher than that region the Kappa value decreases rapidly. The overlap of the thresholds that were within 90% of the highest achieved kappa value by the two examiners compared to automate method was between 0.89-0.915, which implies that the optimal threshold that can achieve the highest level of agreement with the examiners is within that range. It also shows from the current results that within that range (0.89-0.915) the exact threshold used are not important as a small change in the threshold will not dramatically impact on results.

The threshold selection is independent of the gain sensitivity of the OMT probe or system, as the threshold depends on the lowest and highest Gabor coefficients. The threshold settings will not then vary for probes of different sensitivities or with amplitude variations between subjects. However, transiently high Gabor coefficients could distort the method; this could be avoided by looking at the Gabor time-frequency plot and only analyzing the periods free from such noise.

In this work the threshold was chosen to be fixed at 0.9. This value was chosen empirically by comparison of the output of the automated method with thresholds set in the range 0.65-0.95 versus burst identification by an expert examiner. . A similar approach has been used in choosing an optimal threshold in filtering heart sound from lung sound (189). An adaptive threshold would be more favorable with a variability that depends on the OMT signal features properties (such as amplitude and spectrum power). This will require a full properties analysis of the bursts and baseline activities in both normal subjects and patients.

The correlation of occurrence of bursts between the eyes was not investigated in the literature. Abkumova in 1975 noted that there was no clear correlation between the two eyes regarding the occurrence of the OMT bursts, but he has no investigated it (27). The results agree with what was noted by Abkumova, but this does not rule out the possibility of frequency spectrum correlation between the eyes bursts as this was not investigated.

5.6 Conclusion

The results clearly demonstrate the possibility of replacing OMT feature analysis by visual inspection with an automated extraction method. The OMT bursts are very distinctive in the joint time-frequency domain and can be easily processed by the Gabor time varying filter. An automatic method has been developed to identify the periods of bursts in an OMT eye tremor signal. This method can form the basis of a reproducible, reliable method of extracting quantitative data on bursts from OMT for clinical applications. The method requires further improvement in threshold selection. A more sophisticated choice of threshold might improve the performance of this method. In Chapter 6 the burst identification method was implemented in a clinical scenario.

Ch6

60MT signal analysis

6.1 Introduction

OMT clinical studies have shown the value of OMT as a diagnostic measure in a number of investigations. This points to the importance of establishing reliable feature extraction techniques that can quantify the changes of the OMT signal in either time or frequency related to the clinical state of the subject.

A number of OMT clinical analysis techniques used in the literature are based on either visual inspection or on computerized automated methods. Current techniques in the analysis of OMT signal could be divided into two categories: OMT feature extraction and OMT frequency content classifiers. In the OMT literature nobody has carried out a comprehensive cross comparison of the effectiveness of different analysis techniques as classifiers of OMT data.

Collins in 2008 found that OMT frequency reduces in patients with an acute stroke compared to neurologically normal control subjects (35). She used one of the new techniques developed in this work called the wavelet peak count (WPC) as a classifier in her study. In this chapter we investigate the effectiveness of the OMT analysis techniques reported in the literature (such as peak count, AR power spectrum, Welch spectrum and the six OMT features) in differentiating the OMT records of normal subjects from acute

stroke patients. The investigation also introduces two new additional measures to the above: Permutation entropy and burst spectral power ratio.

6.1.1 Current developments

In this work a number of developments were carried out to improve the analysis of OMT signal.

6.1.1.1 OMT features

In the literature six OMT features have been reported: number of bursts occurring per second (NBu), the mean duration of bursts (MDBu), percentage of record occupied by baseline (PROBa), frequency content of bursts (FBu), mean duration of baseline (MDBa) and the frequency content of baseline (FBa)(51).

In the past the usability of this technique was limited as it is based on using visual inspection to identify the OMT features (bursts and baseline) and there is no automated method for analyzing the different OMT features. Improvements in replacing the visual inspection by an automated method (using Gabor time varying filter) were discussed in Chapter 5. In this work we use the Gabor method to identify the OMT features (bursts and baseline) and to automatically calculate the six OMT features. This will allow us to examine the effectiveness of the automated method in a clinical situation compared to the other OMT classifiers.

6.1.1.2 Burst spectral power ratio (BSPR)

The spectral power ratio (SPR) is a commonly used frequency measure for HRV (heart rate variability) signals, which is defined by the ratio of the low frequency (LF) to the high frequency (HF) content (303), (304). The LF and the HF power are calculated by integrating the spectral density function.

$$SPR = \frac{LF}{HF} = \frac{\int_{f_1}^{f_2} |X(f)|^2 df}{\int_{f_2}^{f_3} |X(f)|^2 df} \quad \text{Equation 27}$$

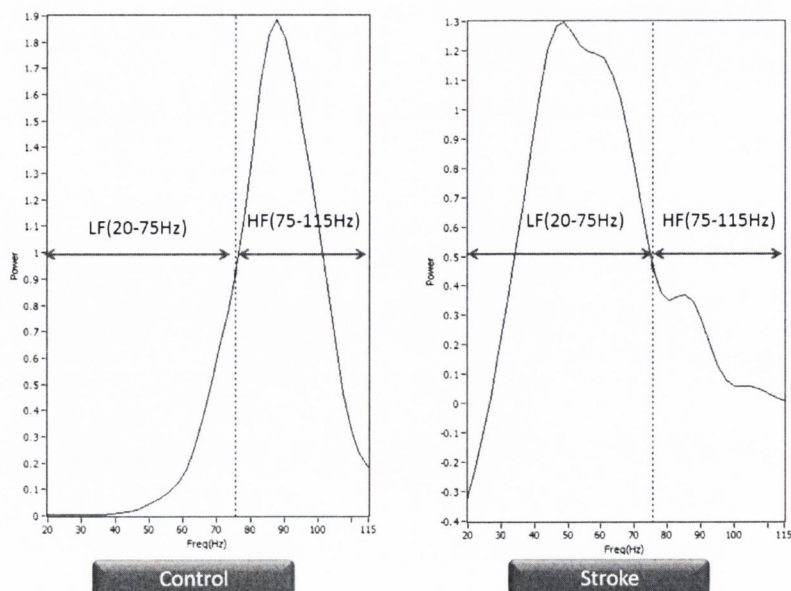


Figure 67. The burst spectral plot (AR average spectrum, order 42) of a normal subject and stroke patient.

Clinical studies have shown that the dominant OMT burst frequency shifts from a high frequency region (around 85Hz) towards a low frequency region (around 65Hz) in clinical conditions causing a reduction in OMT activity (37), (75). This was also noted here in stroke OMT records from the initial tests. Within a given OMT burst the frequency spread is quite small, while the frequency difference between individual bursts is quite large. This spread in the burst frequency activity might reduce the efficiency of burst frequency as clinical measure. This could be avoided by using the high frequency and low frequency spectral regions of OMT signal to develop the SPR in OMT bursts.

The HF of the OMT burst spectrum is taken to be from 75Hz to 115Hz (as the reported figure from the literature by Coakely (31) for normal subjects) and the LF is the frequency range from 20Hz to 75Hz. Unlike the case of HRV where the spectral ratio is based on the sympathovagal balance¹⁷, the choice of using SPR is based only on observed spectral

¹⁷ The balance between the sympathetic and parasympathetic activity.

differences seen between the two regions. Further study is required to understand the physiological origin of the spectra changes in OMT bursts.

As an example Figure 67 shows AR spectrum of entire OMT burst activity of a signal (one from control subject and one from stroke patient). The burst activity in normal subjects is between 75 to 115 Hz (31). The spectrum from the normal subjects shows that most frequency burst content is within the 75-115 Hz region, but in the other case with stroke patient most frequency burst content is within the second region 20-75 Hz, with a small peak in the 75-115 Hz. This suggests the possibility of using the spectral ratio in addition to FBU as classifier.

6.1.1.3 Wavelet peak count

A new approach of peak count was introduced by Mallat in 1992 (305) to overcome the current limitations of the normal peak count (NPC)¹⁸. The method is based on applying the peak count in the wavelet time-scale domain instead of the time domain. This has an advantage over the NPC because the technique is less sensitive to noise of the signal (306). This method was not implemented in the OMT signal analysis.

Here we implement the wavelet peak count (WPC) technique to estimate the dominant OMT frequency to see if it has potential as a new OMT classifier. The work here also investigates if there is a significant difference between the two peak count methods (NPC and WPC).

6.1.1.4 OMT signal complexity

Nonlinear dynamics describe a system in which the output is not proportional to the input (307). Nonlinear measures have become of increasing importance in bio-signal analysis in the last decade. Nonlinear analysis techniques have been used in the analysis of biomedical signals such as EEG (308) and HRV-signals (309).

¹⁸ The term normal peak count (NPC) was used to distinguish it from the new developed peak count method in this context.

The complexity of signals increase then decrease as a signal changes from completely random to highly ordered (277). Complexity is a measure of regularity or repeatability within the signal analyzed. The fewer the signal patterns the lower the complexity. In the EEG signal prior to the experience of a seizure the dynamical complexity of neural activity of the network changes from complex to simple (310). The main types of signal complexity measures are Lyapunov exponents, entropies and fractal dimensions.

Permutation entropy is a measure used to evaluate the regularity and the complexity of signals and was first proposed by Bandt and Pompe in 2002 (311). The permutation entropy is not strongly affected by the amplitude or additive noise of the signal analyzed which makes it more favorable than other measures such as sample entropy (310). The permutation entropy also reflects the degree of nonstationarity in a signal due to changes in its complexity (312). Permutation entropy has been used in EEG applications such as the assessment of anesthetic drug effects (313), in separating consciousness from unconsciousness (314-315) and in seizure detection (310). The permutation entropy is low when the signal has a dominant low frequency component and high when it has a dominant high frequency component. The permutation entropy is sensitive to the dominant frequency and to the bandwidth of the signal analyzed (316).

Nonlinear measures have not previously been implemented in OMT analysis. One of the possible measures is the measure of the complexity of the OMT signal by permutation entropy. The permutation entropy does not require long data length as is the case for the approximate entropy¹⁹ (310). Due to its simplicity, fast computation, less sensitivity to noise and sensitivity to the spectrum dominant frequency changes, it is a candidate for OMT signal analysis.

¹⁹ Another entropy signal complexity measure used frequently in the literature.

6.1.1.5 AR spectrum

The AR spectra analysis was introduced to OMT by Sheahan (11) and Ramdan (12). As explained in the literature the model order is important when estimating the PSD of a signal. Low order results in a smoothed spectrum and too high an order will increase the spectral resolution but introduce spikes in the spectrum (176). Although Sheahan and Ramdan used the Akaike Information Criterion (AIC) to estimate the model order both used a fixed model order across the subjects examined. Sheahan used the AIC with 10 healthy subjects to search for the optimal order between 1 to 30 and found that for data points higher than 400 (at a signal sampling rate of 1000Hz) the estimated optimal order was 30, so she fixed the optimal order to 30. The use of a fixed model order in OMT analysis may affect the estimation of PSD as the OMT may have different characteristics between individuals or groups, particularly when comparing normal subjects to patients. In this work we implement the AR method by estimating the optimal order for each signal analyzed using the AIC method.

6.2 Method

6.2.1 Techniques

There are a number of techniques used to analyze the OMT signal in both the time and frequency domains. Below are details of the techniques implemented here and tested for effectiveness as OMT signal classifiers in stroke.

6.2.1.1 OMT features

The burst spectral power ratio (BSPR) of the OMT is evaluated as follows:

- The filtered OMT signal is first thresholded using the Gabor automated burst extraction method with fixed threshold of 0.9 (as explained in Chapter 5).
- Then PSD is calculated using the AR method for the burst activity including the gaps between bursts.

- Next the HF and the LF are calculated by integrating the resulting spectrum from 75Hz to 115Hz and 20Hz to 75Hz respectively as stated in Equation 27.
- Finally the BSPR is calculated.

The six OMT features introduced by Bolger are also tested in this work. The MDBu and NBu are calculated using the OMT bursts identified using the Gabor automated burst extraction technique. The MDBa and PROBa are then calculated by identifying the baseline periods from the original signal compared to the Gabor thresholded signal. The dominant frequency of FBu and FBa are calculated using the AR method with either OMT baseline (for FBu) or OMT burst (for FBa) zero padded. Note that Bolger in his work used the peak count method to estimate FBu and FBa, which introduced a difficulty due to the short duration of bursts and the broadband nature of the baseline frequency content.

6.2.1.2 Wavelet Peak count

The WPC is calculated for the OMT signal as follows:

- I. First the filtered OMT signal is transformed to the wavelet time-scale domain using the Undecimated Wavelet transform (UWT used here instead the DWT because it has better noise discrimination as explained in the Chapter 3) with db02 wavelet.
- II. The positive amplitude value peaks are searched for as in the NPC at all the levels of the wavelet transform the wavelet transform is divided into a number of levels).
- III. For each level search the corresponding nearest peak detected in the higher level.
- IV. Threshold the peaks with amplitude less than 23dB of the root mean square value of the OMT signal processed.
- V. Finally divide the number of peaks by the signal time length.

The WPC is affected by the number of levels used. Using a large level value will reduce false peaks detected due to noise, but on the other hand requires a higher computational

time. For noise free data a small level is sufficient. Initial testing (based on visual inspection of the current OMT data used in this chapter) of different level values showed a level of 3 was appropriate for the wavelet transform setting.

6.2.1.3 OMT spectrum analysis

In this investigation we use both parametric and nonparametric approaches to estimate the power spectrum density (PSD) of OMT. For the parametric approach we apply the AR model method as reported in the literature (11). The steps below are carried out in computing the OMT PSD estimation using the AR model:

- I. Compute the AIC criterion to estimate the order model.
- II. Estimate the AR coefficients and the variance of the noise using the Yule Walker equations.
- III. Compute prediction error (θ_t) and test if they are white using the whiteness test (see the Appendix). If the prediction error is white then the model matches with the signal being analyzed.
- IV. Compute the PSD using the estimated AR coefficients.

For more details about the AR model see the Appendix.

For the nonparametric approach in estimating the PSD, here we use the Welch method to estimate the PSD of the OMT signal with 50% overlapping using a Hanning window similar to the configuration reported in the literature (11).

6.2.1.4 Permutation entropy

The time series $X_t (t=1, 2, \dots, T)$, when embedded with dimension D and time delay of $\tau = 1$ (Bandt and Pompe used 1 (311)) will form a vector $X_t = [X_t, X_{t-1}, X_{t-2}, \dots, X_{t-(D-1)}]$. If the elements of vector X_t arranged in an increasing order:

$$x_{t-R_{D-1}} \leq x_{t-R_{D-2}} \leq \dots \leq x_{t-R_0}$$

The $\pi_{D-1}^T(t) = R_0, R_1, R_2, \dots, R_{D-1}$ ($\tau = 1$) are permutations of $(0, 1, 2, \dots, D-1)$. If there exists two or more elements of the same value in the time series, then it is ordered so that the number appearing earlier is regarded to be smaller ($R_m \leq R_{m-1}$ if $x_{t-R_m} = x_{t-R_{m-1}}$).

For an example time series:

$$x_0 = 1.3, x_1 = 1.7, x_2 = 1.2, x_3 = 1.8, x_4 = 1.6, x_5 = 1.5, \dots$$

Starting at $t=5$ and using $D=5$ and $\tau=1$ then $x_{t-0\tau} = x_5 = 1.5, x_{t-1\tau} = x_4 = 1.6, x_{t-2\tau} = x_3 = 1.8, x_{t-3\tau} = x_2 = 1.2, x_{t-(D-1)\tau} = x_1 = 1.7$. Then by arranging the elements in increasing order we have $(1.2 < 1.5 < 1.6 < 1.7 < 1.8)$. This implies the permutation is $\pi_4^1(5) = (3, 0, 1, 4, 2)$.

For D different numbers there will be $D!$ different permutations ($\pi_i: i = 1, 2, \dots, D!$). Let $f(\pi) (= \#\{t | t \geq 1 + (D-1), \text{ where } t \text{ has ordinal pattern } \pi(t)\})$ be the frequency of the permutations of the time series x_t , then its probability distribution is given by:

$$p(\pi) = \frac{f(\pi)}{T-D-1} \quad \text{Equation 28}$$

Finally the permutation entropy is defined as:

$$H(D) = -\sum_{D=1}^{D!} p(\pi) \ln p(\pi) \quad \text{Equation 29}$$

The permutation entropy depends on the selection of the embedded dimension D . The selection of D must satisfy the condition $T \gg D!$, where T is the number of samples in the analyzed signal (317). For D less than 3 there will be few distinct states for OMT recordings. Large D (greater than 10) will have better results but will cause memory restrictions (318). Bandt and Pompe suggested that the embedded dimension D should be chosen between 3 and 7. For the OMT signal (15s period sampled at 512 Hz, $T=7680$) D was chosen to be 6 ($6!=720$) to satisfy the condition $T \gg D!$, which corresponds to a window of about 12 ms.

6.2.2 Comparison of analysis techniques

To compare the different OMT analyzing methods we require OMT data. The test data could be either simulated or measured. Simulated data allows generation of signals with known simulated features. With measured data the analysis techniques could be compared to a gold standard that classifies the measured signal as from normal subject or patients records. The nonstationarity and nonlinearity of the OMT signal makes it difficult to generate signals with known true features that are valid simulations of real OMT. Simulating OMT signals with stationary and linear features might bias the comparison between the classifiers. Here we use measured OMT data from a control group and from a patient group showing changes in OMT features such as the frequency content and OMT features, and which include cases of non stationarity and non linearity as noted in Chapter 4.

To test the performance of the analysis techniques (NPC, WPC, WS, ARS, BSPR, NBu, MDBu, PROBa, FBu, MDBa, FBa and Pe) in the analysis of the OMT signal, the effectiveness of the techniques as classifiers of OMT as of a ‘normal’ subject or ‘stroke’ patient is tested.

The different classifiers are examined in terms of their sensitivity, specificity (319) and their accuracy (320). Those measures quantify how effective the classifier is in distinguishing between two different groups (normal subjects and patients) compared to a gold standard. Sensitivity is the proportion of the records identified correctly as ‘positive’ (TP =true positive) that are from the patient group. Specificity is the proportion of the records identified correctly as ‘negative’ (TN =true negative) that are from the normal subjects group. Accuracy is the proportion of records that are correctly classified to the right group (normal subjects and patients). An ideal classifier will have 100% in the three measures. The three measures are calculated as follows:

$$\text{Sensitivity} = \frac{TP}{TP+FN} \quad \text{Equation 30}$$

$$\text{Specificity} = \frac{TN}{TN+FP} \quad \text{Equation 31}$$

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN} \quad \text{Equation 32}$$

The cutoff classifications of the techniques are found by plotting the receiver operating characteristics (ROC) curve and choosing the closest point in the curve to the upper left corner of the ROC as having the highest overall classification accuracy of the technique tested (321). The area under curve (AUC) of the ROC is calculated in Matlab (322) for each analysis technique to find which technique is a better classifier in this study. Also the Pearson product-moment correlation coefficients are calculated between the analyzing techniques to quantify the strength of association between them.

6.2.3 Clinical data

For the following tests 60 OMT traces of 15 seconds duration were collected using the PZT system with a single experienced observer (NC). Thirty OMT signals (control group) were from neurologically normal subjects (different individuals) and thirty from acute stroke patients (different individuals) diagnosed (gold standard, as explained earlier) clinically and radiologically within two weeks of stroke onset. All the recording took place in St. James's Hospital with approval from the hospital ethic committee.

The signals captured by the PZT were further digitally processed using the wavelet denoising technique to recover the OMT signal from unwanted signals (such as microsaccades, eye drift and noise) (251).

6.2.4 Computational platform

The testing was designed and implemented on an Intel(k) Core(TM)2 CPU T7200@2.00 GHz computational platform with 2.00 GB of RAM. All the analysis was done in MATLAB (280), LabView (3) and Minitab (302).

6.3 Results

The results below are based on using: normal peak counts (NPC) , wavelet peak counts (WPC), Welsh spectrum frequency peak (WS), AR model spectrum frequency peak (ARS)

, burst spectral power ratio (BSPR), number of bursts per second (NBu), mean duration of bursts (MDBu), percentage of record occupied by baseline (PROBa), dominant frequency content of bursts spectra (FBu), mean duration of baseline (MDBa), dominant frequency content of baseline spectra (FBa) and the Permutation entropy (Pe) in the analysis of the OMT signals. Figure 68 to Figure 72 shows results for an example individual from normal control subject group and from the stroke patients group.

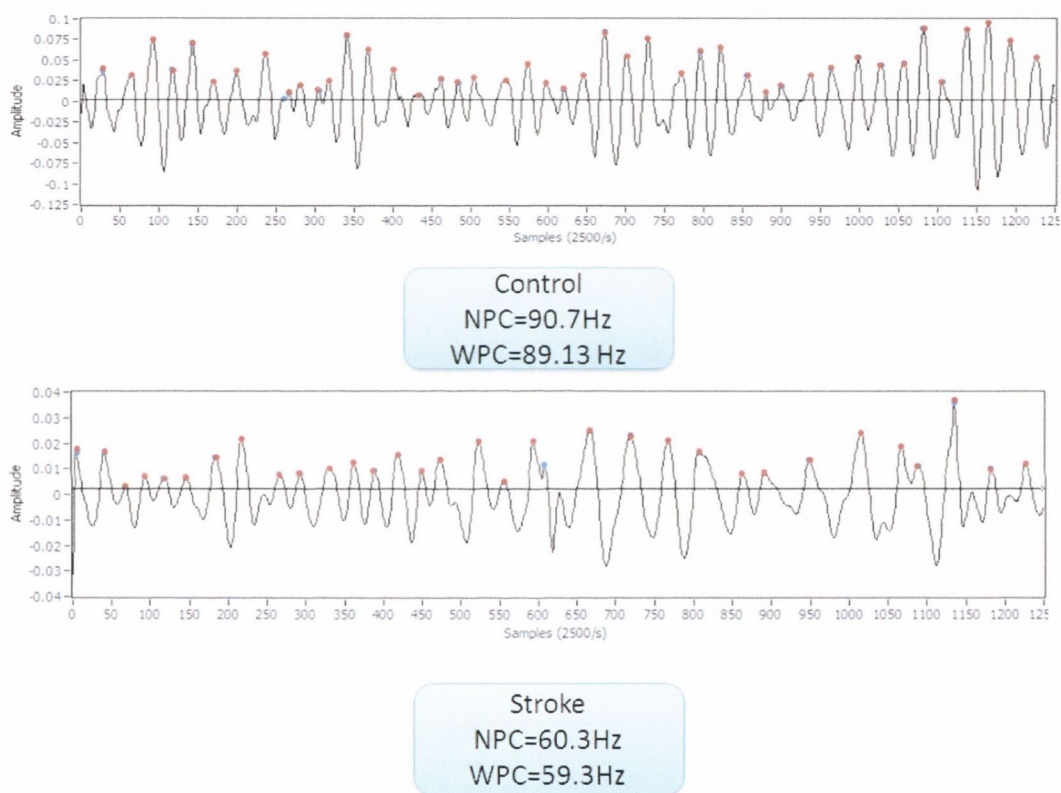


Figure 68. OMT records of 0.25s duration from control and stroke patients. The red and blue dots represent the peaks detected by the NPC and WPC, respectively. The estimated dominant frequency using the NPC and WPC listed above are for the complete 15s duration. The line crossing the signals represents the threshold line of the peak detection. Note that the blue and red dots overlap (appearing red) in all the peaks except in one case in each trace where the WPC identifies a peak not identified by the NPC fails (appearing blue).

Figure 68 shows an OMT trace of 0.25s duration for the control and for the stroke patient. The red and blue dots in top of the traces represent the peaks detected using the NPC and WPC, respectively. Most of peaks are detected by both methods and give a similar estimated dominant frequency peak for the 15s control subject (NPC=90.7Hz & WPC=89.1Hz) and stroke patient (NPC=60.3Hz & WPC=59.3Hz).

Figure 69 and Figure 70 shows 1s of the control subject and stroke patient, with OMT burst extracted using the time varying Gabor filter and the burst spectrum using the AR method. The figure also includes the different values for the OMT features.

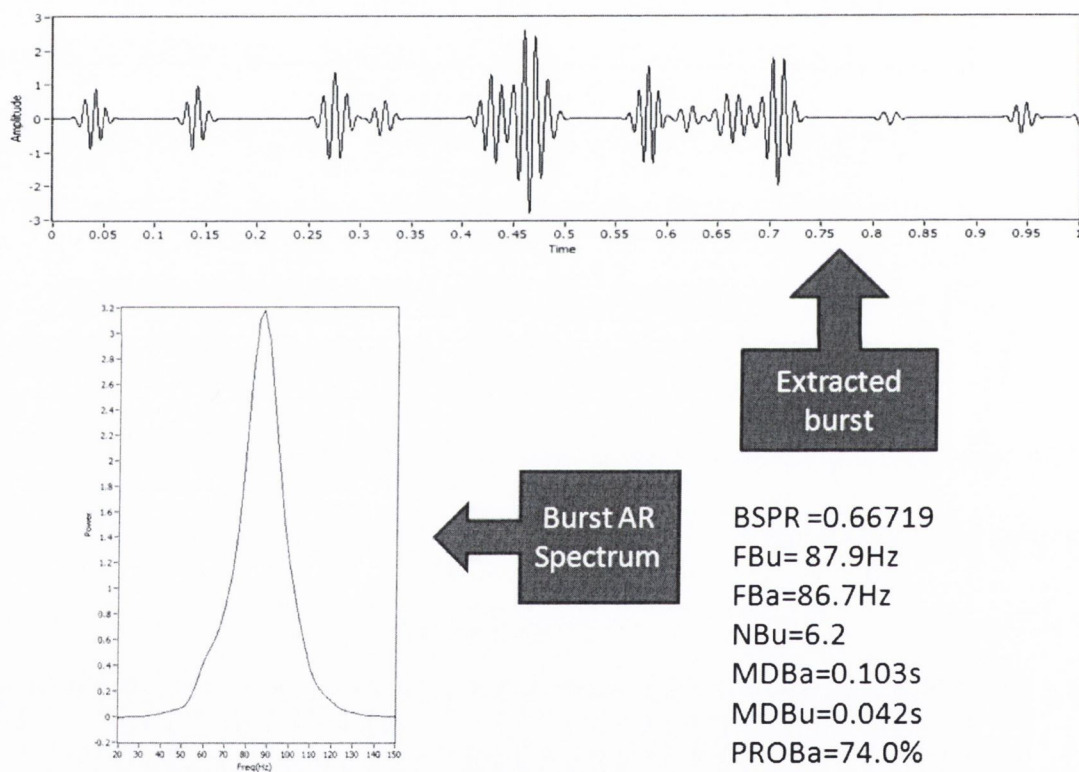


Figure 69. 1s burst extracted signal and the burst AR spectrum from the same control subject as in Figure 68. The different OMT pattern parameters are listed for the full 15s signal duration.

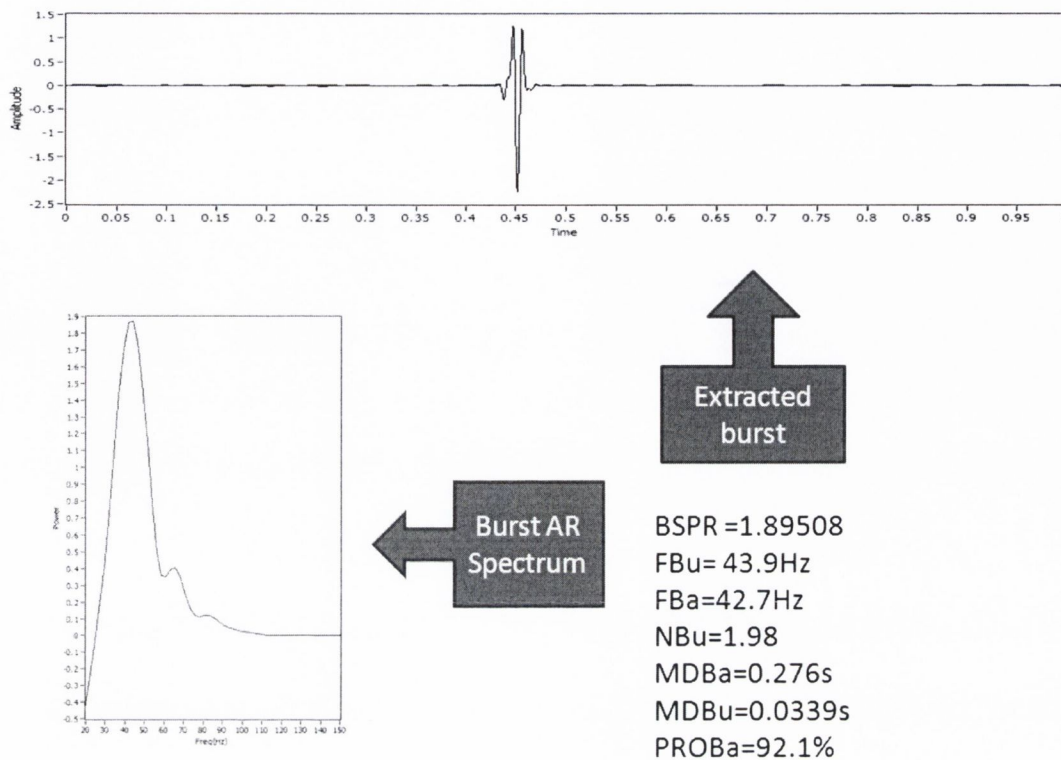


Figure 70.1s burst extracted signal and the burst AR spectrum from the same stroke patient as in Figure 3. The different OMT pattern parameters are listed for all the 15s signal duration.

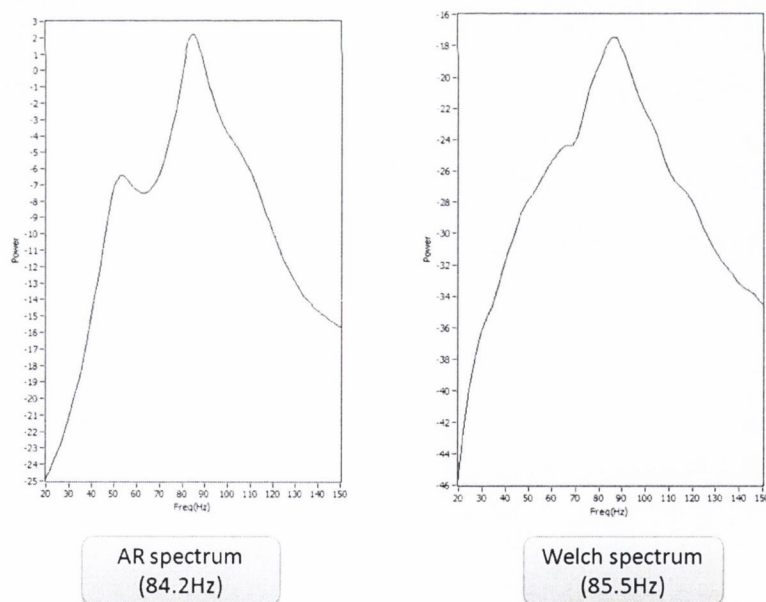


Figure 71. The AR spectrum (order 38) and the Welch spectrum (Hanning, 512 window length, 50% overlap) of 15s record from one control subject as in Figure 68, with dominant spectra peak noted (84.2 Hz & 85.5 Hz, respectively).

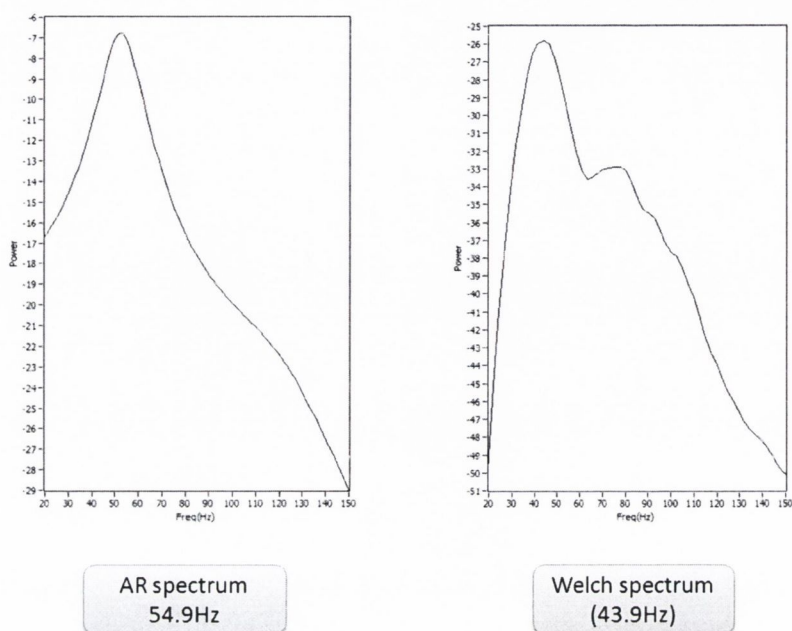


Figure 72. The AR spectrum (order 47) and the Welch spectrum (Hanning, 512 window length, 50% overlap) of 15s record from the same stroke patient as in Figure 3, with dominant spectra peak noted (54.9 Hz & 43.9 Hz, respectively).

Figure 71 and Figure 72 shows the AR and the Welch spectrums of 15s of the control subject and stroke patient. With the control subject, there was no big difference in the frequency spectra peak using the two methods (AR=84.2 Hz & WS=85.5 Hz). In the stroke patient case there was a big difference (11Hz) between the frequency spectra peak using the two methods (AR=54.9 Hz & WS=43.9 Hz).

Table 19 shows the correlation of the techniques on analysing the 60 OMT records (control and stroke groups). The highest correlation (0.997) was between the NPC and the WPC technique and with the lowest (0.199) between the MDBu and the Pe.

Methods	NPC	WPC	WS	ARS	BSPR	Pe	MDBu	MDBa	NBu	FBu	FBa
WPC	0.997										
WS	0.890	0.901									
ARS	0.872	0.882	0.923								
BSPR	-0.904	-0.907	-0.857	-0.814							
Pe	0.851	0.828	0.653	0.593	-0.725						
MDBu	0.425	0.430	0.405	0.400	-0.429	0.199					
MDBa	-0.389	-0.378	-0.325	-0.282	0.467	-0.329	-0.218				
NBu	0.452	0.445	0.414	0.359	-0.546	0.406	0.302	-0.883			
FBu	0.846	0.854	0.885	0.811	-0.886	0.695	0.424	-0.400	0.503		
FBa	0.875	0.886	0.905	0.907	-0.854	0.635	0.486	-0.269	0.369	0.825	
PROBa	-0.485	-0.478	-0.445	-0.403	0.584	-0.392	-0.399	0.877	-0.981	-0.522	-0.414

Table 19. Pearson product -moment correlation coefficients between the analyzing techniques.

Classifier	Control patients		Stroke patients		p value
	Mean	Stdv	Mean	Stdv	
NPC	91.0Hz	4.24Hz	74.1Hz	9.77Hz	0.0001
WPC	88.4Hz	4.20Hz	72.4Hz	9.66Hz	0.0001
WS	84.2Hz	8.10Hz	64.0Hz	15.7Hz	0.0003
ARS	83.6Hz	7.5Hz	64.5Hz	15.1Hz	0.0003
BSPR	0.774	0.152	1.408	0.399	0.0001
Pe	0.561	0.0210	0.503	0.0284	0.0001
MDBu	0.039s	0.003s	0.037s	0.003s	0.052
MDBa	0.139s	0.039s	0.240s	0.097s	0.0001
NBu	5.3/s	1.5/s	3.1/s	1.57/s	0.0004
FBu	86.5Hz	7.53Hz	62.0Hz	14.9Hz	0.0004
FBa	82.9Hz	5.30Hz	64.4Hz	18.1Hz	0.0004
PROBa	79.6%	6.45%	88.3%	6.16%	0.0004

Table 20. The mean and the standard deviation of the control and stroke patients using the different analysing methods. The p-values test if the means of the normal subjects and stoke patients are the same (null hypothesis) using 95% confidence interval.

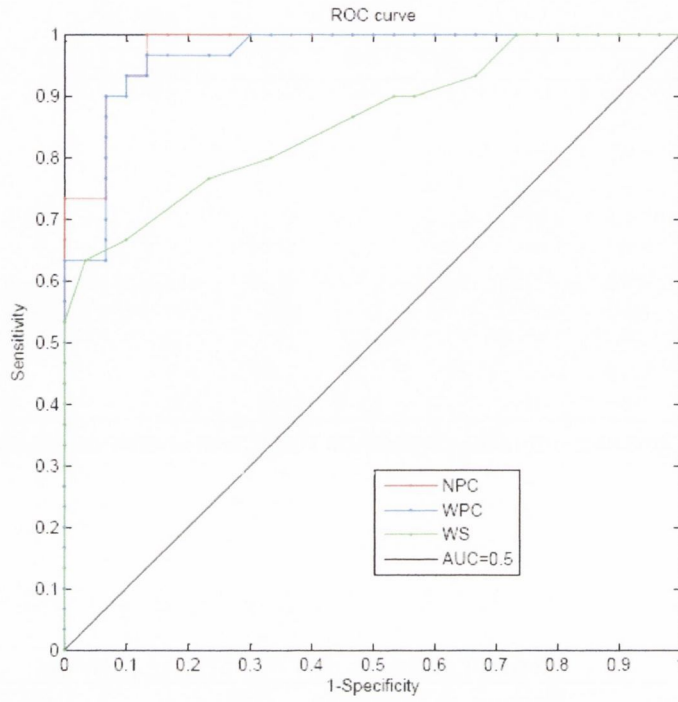


Figure 73. Receiver operator characteristic (ROC) of the NPC, WPC and WS using the control and stroke patients OMT data. The AUC line represents the area under curve of a value of 0.5.

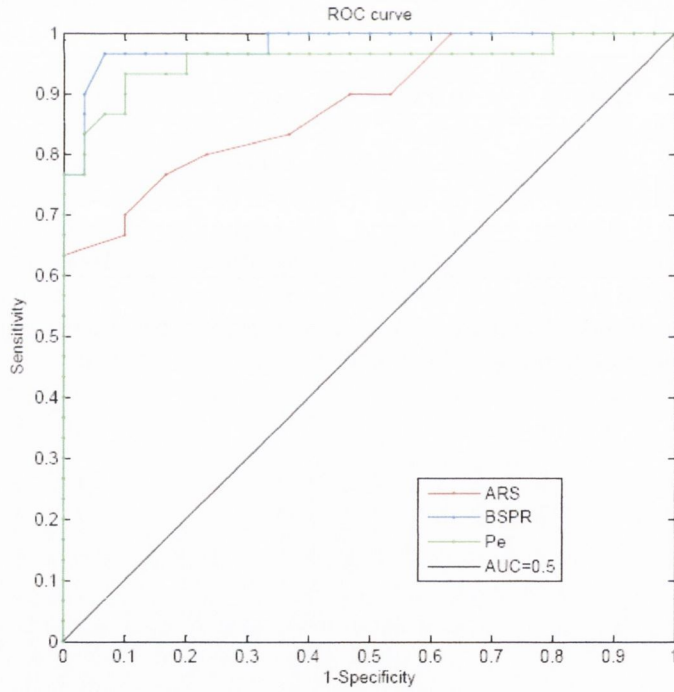


Figure 74. Receiver operator characteristic (ROC) of the ARS, BSPR and Pe using the control and stroke patients OMT data .The AUC line represents the area under curve of a value of 0.5.

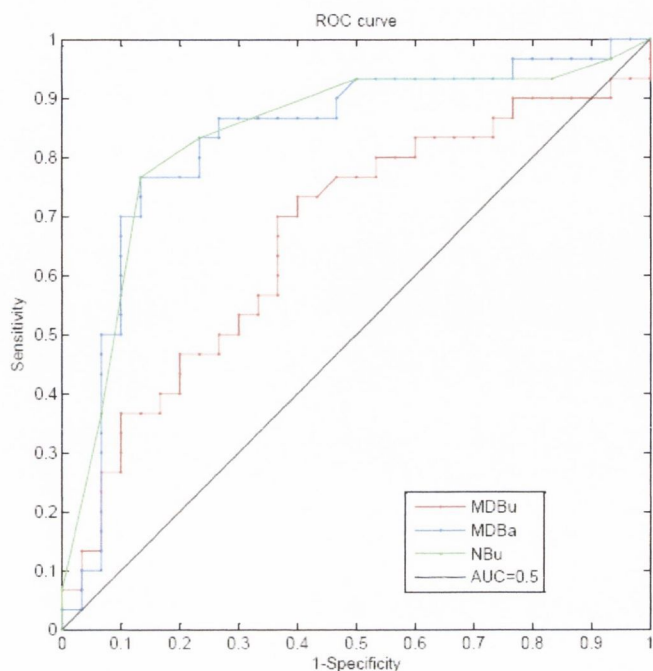


Figure 75. Receiver operator characteristic (ROC) of the NBU, MDBu and FBU using the control and stroke patients OMT data. The AUC line represents the area under curve of a value of 0.5.

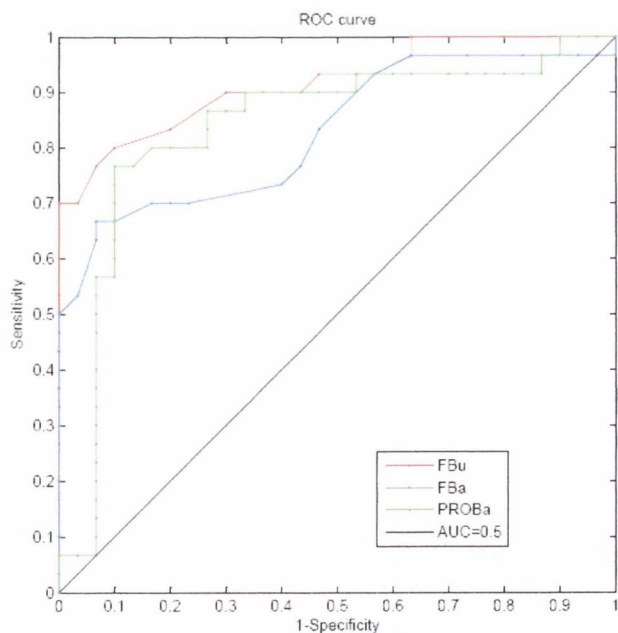


Figure 76. Receiver operator characteristic (ROC) of the FBa, MDBa and PROBa using the control and stroke patients OMT data. The AUC line represents the area under curve of a value of 0.5.

Classifier	AUC	Cutoff	Sensitivity	Specificity	Accuracy
NPC	0.97667	84.3Hz	0.903	0.931	0.917
WPC	0.96500	82.5Hz	0.903	0.931	0.917
WS	0.85944	75.7Hz	0.767	0.767	0.767
ARS	0.88333	76.90Hz	0.781	0.821	0.800
BSPR	0.98111	0.9700	0.966	0.935	0.950
Pe	0.95611	0.5322	0.931	0.903	0.917
MDBu	0.66722	0.0390s	0.679	0.656	0.667
MDBa	0.82944	0.1430s	0.788	0.852	0.817
NBu	0.83944	3.0Hz	0.788	0.852	0.817
FBu	0.91611	75.7Hz	0.818	0.889	0.850
FBa	0.82833	75.7Hz	0.737	0.909	0.800
PROBa	0.83611	83.1%	0.794	0.885	0.833

Table 21. AUC, cutoff, sensitivity, specificity and the total classification accuracy of the different OMT analyzing techniques used in the control and stroke patients data. The WS fails to have AUC above 0.5, so other measures are not included.

Table 20 lists the mean and the standard deviation of the OMT signal classifiers with control (30 records) and stroke (30records) patients data records. From the spectral measures (WS, ARS, NPC and WPC) the WPC has the lowest standard deviation in both the normal subjects and the patients groups of 4.20Hz and 9.66Hz, respectively. The WS has the highest standard deviation particularly with the patients data (15.7Hz).

Using Table 20 we can compare differences in the classifier means between the control subjects and the stroke patients. For a given classifier the p-values test if the means of the normal subjects and stoke patients are the same (null hypothesis) using 95% confidence interval. The results show that there was a shift of the OMT frequency peak from round 85Hz in the control group to around 65Hz in the stroke group. This was seen in the peak count (NPC & WPC, $p=0.0001$), WS ($p=0.0003$), ARS ($p=0.0003$) and in both the burst (FBu, $p=0.0004$) and baseline (FBa, $p=0.0004$) activity. Also the results show a decrease

in the number of bursts (NBu) and a non significant small decrease in the burst duration (MDBu, $p=0.0520$) in the stroke patients compared to the control group. The results from the stroke patients show an increase in baseline duration MDBa ($p=0.0004^{20}$) and PROBa ($p=0.0004^{21}$).

Figure 73 shows the ROC curves of the NPC, WPC, WS and the line representing the AUC (area under curve) of 0.5. Among those classifiers the NPC appear to have the highest overall classification accuracy (high AUC). Figure 74 shows the ROC curves of the ARS, BSPR, Pe and the line representing the AUC (area under curve) of 0.5. Figure 75 and Figure 76 shows the ROC of the six OMT features reported in the literature (NBu, MDBu, FBu, FBa, MDBa and PROBa). All the OMT features ROC curves have an AUC above 0.5 with the highest achieved by the BSPR. Table 21 lists the classifiers' AUC and the cutoff point to achieve the highest overall accuracy. Also it includes the sensitivity, specificity and the total classification accuracy using the obtained cutoff point from the ROC curves using the control and stroke OMT patients' records.

6.4 Discussion

6.4.1 Peak count

The normal peak count (NPC) technique is the favored method in analysis of the OMT signal in clinical investigations, due to its reproducibility under static conditions and its simplicity. The drawback of this technique is that it is sensitive to noise and accurate only for narrowband frequency activity (as it based on based on finding the average number of peaks per unit time and in the case of a signal with a wideband frequency activity there might be an error in the estimate of the dominant frequency due the presence of outliers frequency activity).

²⁰ Statistically testing weather the MDBa have the same mean for the normal subjects and stroke patients.

²¹ Statistically testing weather the PROBa have the same mean for the normal subjects and stroke patients.

The OMT signal is not always stationary and sometimes exposed to high noise. This may give misleading results in the analysis of the OMT signal with NPC. A new peak count technique (WPC) was introduced in the literature and applied to the OMT analysis which is based on applying the peak count in the wavelet domain instead of the time domain.

The Pearson product-moment correlation coefficient shows that there is a high strength of association between the NPC and WPC (0.997) in the analysis of the OMT signals from the control and stroke patients records (see Table 19). Although the NPC and WPC are good estimators of the dominant frequency, the correlation between them and the AR spectrum peak is low (0.408 and 0.365, respectively). There is no significant correlation between the peak count methods results and any of the OMT features, even the OMT frequency features FBa and FBu.

In the OMT signal classification for the control group the standard deviation is the lowest (see Table 20) for NPC and WPC compared to the other spectral measures. It also shows that there is a higher spread in the dominant frequency in the stroke group compared to the control group. The WPC has a lower standard deviation than NPC for both groups, though there was no significant difference ($p=0.806$) using the Levine's test (323).

Figure 73 shows the ROC of both the NPC and WPC. The NPC has a higher AUC than the WPC (0.910 and 0.901, respectively) which implies it is very marginally better as classifier for the control and stroke data. From the ROC data a cutoff point was found to be 87.7Hz for the NPC and 84.4Hz for the WPC. This gives a sensitivity of 0.929 to the NPC and 0.871 to the WPC, but the specificity is higher for WPC (NPC=0.875 and WPC=0.897). The total classification accuracy is higher for the NPC than the WPC (0.900 and 0.883). See Table 21.

Although, the WPC was reported to be less vulnerable to noise and more accurate than the NPC (306), the overall results show that there is no significant difference ($P=0.287$) between the means of NPC and the WPC in the analysis of OMT signals from control versus the stroke patients data, although we had expected that the WPC would show better

performance over the NPC. A complete comparison of the clinical utility of WPC versus NPC would require extending this study to conditions other than stroke.

6.4.2 AR spectrum (ARS) and Welch spectrum (WS)

The AIC criterion was used to estimate the order model for each OMT signal for the ARS method. There was only one case of the 60 data records that failed the whiteness test for the AR model, implying that the AR model would not fit that record, but would work for the other 59 OMT signals from the control and stroke patients. This points out the importance of checking if the model fits with the OMT signal, as including such data might bias the results. In the literature the AR method has been used without checking the fitness of the model.

The ARS and the WS are both estimates of the PSD of the OMT signal (one is a nonparametric and the other a parametric approach), and there was significant association between the spectral peaks found by each (correlation of 0.923, $p=0.975$). The ARS and the WS shows good correlation with the NPC and WPC frequency measures. The ARS and WS shows significant correlation with the OMT features spectral parameters: BSPR, FBu and FBa (see Table 19). There is a higher association of the spectra peak of the OMT signal (ARS) and the OMT baseline (FBa) compared to the OMT burst frequency classifiers (BSPR and FBu), this could be due to a higher proportion of the timeline being occupied by baseline than by burst activity.

From Table 20, it can be seen that the mean frequency and standard deviation is about the same for WS and ARS for the control group, but the WS has a higher spread in the stroke group due to the over estimation of the frequency content of some data compared to the other spectral estimators (NPC, WPS and ARS). Due to this, the ROC of the WS has the lowest AUC area (see Figure 73 and Table 21) in comparison with the other dominant spectral frequency estimators, which can be seen in the results for sensitivity (0.767), specificity (0.767) and accuracy (0.767).

On the other hand the ARS achieves an AUC of 0.883. With a cutoff point of 76.9Hz, the sensitivity is 0.781, specificity is 0.821 and the total classification accuracy is 0.800. This suggests that the NPC and the WPC have better classification performance than the ARS for control versus stroke data.

The results from the spectral measures (NPC, WPC, ARS and WS) in the stroke study, supports the results obtained from the comparisons done by Sheahan (11), (50), where she had seen that WS showed the most variation under clinically OMT static conditions, while peak count (NPC) was the lowest.

6.4.3 OMT features

The OMT features have been used in OMT signal analysis in a number of papers using visual inspection. The current work introduces a new technique called the burst spectral power ratio (BSPR) with aid of the automated burst extraction technique in addition to the techniques reported in the literature (FBu, NBu, MDBu, FBa, PROBa and MDBa). The time efficiency and reproducibility of the automated OMT features extraction used here, as compared to visual inspection has allowed the practical implementation of OMT features (burst and baseline) measures as analysis methods.

The BSPR, FBa and FBu have high correlation with all the dominant spectral frequency measures (NPC, WPC, ARS and WS). From the ROC plot the BSPR has the highest AUC of 0.98111, which implies that it has the best performance among all the other classifiers (see Table 21) for the current data tested. Using the ROC curve, the best cutoff point for BSPR was 0.970. This implies that an approximately equal LF/HF power split between the bands taken from Coakley (31) is close to the ideal cut off point between control and stroke patients. A slight adjustment to the interval can provide a unity cutoff ratio. This implies if the HF power is more than LF then BSPR will indicate the record is from the control group and vice verse. A cutoff of 0.970 gives a sensitivity of 0.966, specificity of 0.935 and a total classification accuracy of 0.950. The second highest AUC among the burst and baseline measures was the FBu, which was expected as both BSPR and FBu are measures of the OMT burst frequency spectra.

Of the OMT burst and baseline measures, the MDBu has the lowest performance (AUC=0.667), while the others have a higher AUC than 0.8. The new technique (BSPR) provides a better classification performance in this OMT study with control versus stroke patients and may also work well for other studies. The BSPR has an advantage over other techniques, because it analyzes only the burst frequency component which appears more stable (having a nearly a sinusoidal shape with a small spread in the frequency content during each burst (51)) than the baseline activity.

One of the limitations in the new analysing method BSPR (also FBu and FBa) is calculating the PSD spectrum with missing data (either burst information or baseline information), which distorts the frequency spectrum (324). The missing data is high in the case of BSPR and FBu due to the fact that the filtered baseline information accounts for about 80% (see Table 20) of the OMT signal. A number of methods were reported in the literature of how to deal with missing data (324), (325) , (326), which could be implemented to improve those measures.

In hart rate variability (HRV) analysis of the frequency domain, a study by Kim (327), showed that lowest error (comparing original signals PSD to simulated missing data signals PSD) in calculating the HF and LF of the HRV was the FFT with cubic spline interpolation method. In this study the experimental values were calculated by various spectrums (FFT, ARS, Welch and Lomb-Scargle) with several interpolation methods (nearest neighbor, linear, cubic spline and piecewise cubic Hermite). Similar study is required to see the effect of missing data to the BSPR, FBu and FBa of OMT and also to find the best method in calculating the frequency spectrum with the lowest error.

6.4.4 Permutation entropy (Pe)

There are no reports in the literature of the use of nonlinear measures for OMT signal analysis. In this work we introduce permutation entropy as measure of OMT signal complexity.

The results from Table 20 shows that the Pe of the OMT signal reduces in the stroke group compared to the control one. This implies that the records from the stroke group are less complex than the control group, which implies that it has fewer patterns within it.

As described earlier there is a high correlation between the Pe and the NPC or WPC (0.852 and 0.828), which implies that there is association between the complexity of the signal and the estimation of the dominant frequency by NPC and WPC.

Results from the ROC shows an AUC of 0.956 (higher than 0.5), which ranks it 4th compared the other 11 AUCs. The best performance of the Pe in classification of the control versus the stroke group is (using 0.5322 cutoff point), sensitivity of 0.966, specificity of 0.935 and total classification accuracy of 0.950.

The Pe technique provides an overall good classification technique - better than OMT spectra estimators ARS and WS with current data.

6.5 Conclusion

The chapter examines current analysis techniques used in the OMT analysis literature (NPC, WS, FBa, FBu, MDBa, MDBu, PROBa, NBu and ARS). Also it introduces new techniques: WPC, BSPR and Pe. The investigation is based on using control versus stroke patients OMT data in examining the classification performance of those techniques.

Among all the techniques used the mean duration of bursts (MDBu) is the only classifier that fails to achieve good results, which questions the suitability of this technique in OMT analysis.

There is no significant classification performance difference between the WPC and the NPC with current data. The BSPR technique achieved the best OMT classification performance for the control verses stroke patients among the other techniques. Further work is required to find an optimal HF and LF frequency bands for the BSPR and to understand the physiological origin of the shift in the dominant frequency spectrum from high to low frequency region. The results support the option of using the BSPR as a new

diagnostic tool in the OMT clinical trials and the utility of the automated features extraction using the Gabor time varying filter in achieving this.

Similar reliability test is required for other clinical investigation using the different classifiers, particularly BSPR, Pe, NPC and WPC. Also future studies could include the possibility of using the OMT analysis techniques in distinguishing between more than two groups, which will support the idea of having the OMT as diagnostic tool in clinical environment.

Chapter 4 points out that the OMT signal is not always stationary and linear. This chapter uses the tests the nonlinear complexity measure Pe as possible classifier of the stroke patients from the control. The results suggests the possibility of using nonlinear measures in the OMT signal analysis, but may require further investigation using clinical data other than stroke data. However it is of interest that the data was sensitive to this measure. Further work is required to tackle the non-stationarity of the OMT signal and look at the performance of the current classifiers when present. Also more work is required to develop ways to analyze the OMT signals taking in the account the possibility of non-stationarity, such as the use of the time-scale spectrogram by the wavelet transform.

Ch7

7 Laser speckle metrology for OMT measurement

7.1 Introduction

Laser speckle metrology is a candidate for OMT measurement. Speckle techniques could potentially provide a high resolution, non-contacting, compact and portable OMT measurement. One uncertainty is however the degree to which biospeckle and tear flow might impact on the practical utility of speckle methods.

There are two related elements in this investigation. First, the technical problem of capturing speckle images of laser light scattered from the sclera is considered. Such images have never been captured before and the laser safety and image speed requirements of an *in-vivo* OMT measurement system makes this a challenging problem. If speckle imaging under these conditions could be demonstrated, a platform would then exist to study the laser light scattering behavior of the eye and allow future refinement of speckle based OMT measurement techniques. In addition, speckle image capture is a necessary first step in many speckle metrology techniques. The second element of the investigation was to consider whether or not the biological nature of the scattering surface would

severely degrade displacement information carried by the laser speckle so that standard speckle metrology approaches would be rendered impractical.

7.2 Speckle metrology

Speckle in optics is a random high contrast granular pattern observed when an optically rough object is illuminated by a coherent source. The speckle pattern is produced by self interference of numerous waves that are reflected from the rough object. A number of techniques have been developed using speckle phenomena to measure displacement and velocity.

In applying speckle based methods for the measurement of OMT, we are essentially interested in measuring in-plane displacement as the rotation of the eye at a point on the eyeball can be approximated by an in-plane, tangential displacement. OMT causes oscillatory rotation of the eye in all directions. Most published work is based on measuring the horizontal component of OMT only, but speckle methods capturing the x-y movement will be useful in understanding the dynamics of OMT, and could be useful in investigating its role in vision. Here we are interested in speckle correlation and in-plane speckle interferometry techniques.

7.3 OMT measurement techniques

A number of techniques are reported in the literature for measuring OMT. Of them, only the PZT method has been shown to achieve a resolution that has been systematically measured to satisfy the ideal resolution required to measure OMT (7).

The open eyelid PZT system has a number of advantages over other methods including its high resolution. This has led to it being accepted as the current method of choice for OMT clinical investigations. However it does not come without disadvantages. Prior to measurement anesthetic eye drops must be administered to reduce patient discomfort. The eyes are taped open during the recording process to prevent the eyelid from touching the probe, which can lead to drying of the eye. Mechanical loading the eye during the

recording, can lead to temporary deformation of the sclera and reduction in the visual acuity. The taping and the mechanical loading also limits the recording time due to patient discomfort. Furthermore the recording duration is limited, since it is restricted to prevent drying and irritation of the eye. The accuracy of OMT amplitude measurement as determined by the PZT system is known to be poor (50).

Boyle in 2001 (14) demonstrated an in-plane phase modulation speckle interferometry technique that was able to record the OMT signal. The method was based on having two laser beams (one is phase modulated and the other is used as a reference) from the source ($\lambda=632.8$ nm) directed into one point in the sclera of the eye (as in Figure 11). The speckle fluctuations are captured using a photodiode and then further processed to recover the OMT signal.

This technique overcomes a number of the limitations of other techniques, for example it is non invasive, does not require the eye to be anaesthetized during the recording as in the PZT system and it has a high resolution compared to other non contacting methods. The resolution of the system is 100nm (about 4 times poorer than the ideal resolution for the OMT measurement (7)). The technique is being developed to allow measurement of OMT in clinical studies (94), (95), (63).

7.4 OMT and speckle metrology

As explained in the literature review, biospeckle is a time-varying speckle produced by the biological or physiological activity of living organisms. Biospeckle has different spatio-temporal properties than speckle patterns produced from inanimate objects (133), causing it to have more complex speckle statistics, especially with respect to second-order statistics such as the speckle size (93).

Although the biospeckle generated from human tissue can carry useful information on blood flow and on tissue structure motility, it is also a source of noise in tissue images (132).

In the in-plane speckle interferometry system used to measure OMT, the sclera (also called the white of the eye) is used as the target (14), (94). The sclera provides a suitable scattering target and also limits the eye laser exposure hazards as light is not directed to the retina.

The sclera is a highly scattering medium (328) but due to the blood vessels underlying the scleral surface and the bulbar conjunctiva (a transparent membrane covering anterior part of the sclera) biospeckle is expected when reflecting a laser beam from it. Tears may also contribute to biospeckle as increasing moisture level has been shown to increase biospeckle activity (329).

A quantitative measure of the temporal and spatial stability of the speckle pattern is the local speckle contrast (to be described in detail later). The higher the local speckle contrast the higher the speckle pattern image quality. Speckle contrast could also be used in examining the biospeckle activity since a higher biospeckle activity will cause a reduction of the image quality which therefore causes a reduction in the local speckle contrast.

Boyle in his work reported that there was unwanted amplitude and phase modulation in the captured speckle signal and suggested that this was due to biospeckle fluctuations, however this could not be quantified as the optical configuration used was limited to a point sampling photodiode detector. A high speed camera (CCD or CMOS) is required to investigate the biospeckle effects in the OMT measurement. A high speed camera is necessary as the investigation will require capturing the speckle translation (due to the eye movements up to 150Hz) and boiling speckle (due to the speckle fluctuations caused by tear flow, blood flow and multiple scattering). In this work we investigate the possibility of using a high speed CMOS camera to capture speckle pattern activity from an *in vitro* scleral surface under eye safe low laser power levels, which has not been attempted before. This will help in understanding the unwanted noise caused by biospeckle activity in the development of speckle based (such as speckle correlation or in-plane speckle interferometry) OMT measurement techniques. In addition, the chapter investigates *in*

vitro the possibility of using the speckle correlation technique as a new, alternative 2D OMT non-contacting measurement technique.

7.5 Speckle contrast

As laser speckle is a random phenomenon it can only be described statistically. A detailed explanation of speckle statistics theory is given by Goodman (330). In this work we will be interested the speckle contrast. The local speckle contrast ($\mathcal{C}$) is a first-order statistical measure and is defined as the ratio of the standard deviation (σ_I) of the speckle pattern intensity to the mean intensity ($\tilde{I}$).

$$\mathcal{C} = \frac{\sigma_I}{\tilde{I}} \quad \text{Equation 33}$$

If the motion of the object is faster than the exposure time of the CCD camera, rapid intensity fluctuations of the speckle pattern are formed which result in a blurred image. To quantify the blurring effect of the speckle the local speckle contrast may be used.

The following are the properties of the local speckle contrast for speckle scattered from a surface.

- ❖ The speckle contrast lies between the value of 0 and 1.
- ❖ In ‘fully developed’ speckle patterns the contrast is unity whereas a ‘partially developed’ speckle pattern has a speckle contrast ($\mathcal{C} < 1$) (331).
- ❖ Unity contrast demonstrates that there is no blurring and contrast of zero indicates that the object is moving fast enough to average all the speckles. A static object could have local speckle contrast less than 1 due to other factors such as the dark current of the detector (106) or biospeckle activity if the surface is of biological origin. Lower contrast decreases the signal to noise ratio when speckle is used for displacement measurement
- ❖ The higher the velocity of the object the smaller the contrast.

There have also been studies of biospeckle fluctuations using botanical specimens. Results have shown that local speckle contrast of the biospeckle is usually less than unity using

botanical specimens i.e. speckle is not fully developed (332). The speckle contrast is used in this work as a first order measure of the degradation of speckle quality by biospeckle of the eye sclera and the tear flow.

7.6 Methods ²²

7.6.1 OMT simulator

The OMT simulator used in this experiment is the same simulator used for the PZT system in Chapter 2. To investigate the effect of biospeckle on the speckle techniques, three different surfaces were used. The first was based on having the plastic disc on the simulator (not driven) as the target. The second target was a small sclera flap cut from a sheep's eye. The conjunctiva was retained on the flap and the sample was used within three hours of slaughter. The sclera flap was 10mm by 10mm cut by a scalpel. The flap was used immediately after cutting it, as it degraded quickly after cutting from the eyeball. The third target was the flap with the addition of artificial tears (Povidone K25 N.Pharmaceuticals). The scleral samples were placed on top of the simulator head and the simulator was driven by a signal generator. The testing with the simulator is divided into two tests, static target and OMT simulation.

7.6.1.1 Static target:

To test the effect of the biospeckle phenomena in the OMT measurements using the different speckle methods, the speckle pattern was captured with CCD camera. In this measurement the three target surfaces explained above were kept static during the recording (no signal driving the simulator).

²² All the work carried in this chapter both hardware and software was all done by the author of this thesis.

The local speckle contrast was calculated for each data record of the three static surfaces by taking each frame (whole speckle pattern) and calculating the intensity standard deviation (σ_I) and the mean intensity ($\tilde{I}$).the local speckle contrast was then calculated by finding the ratio of the standard deviation to the mean intensity as explained earlier.

7.6.1.2 OMT simulation

To test the possibility of using the speckle correlation method in the OMT measurement, the OMT simulator was used with the sclera flap attached and artificial tear flow. The simulator was driven with frequencies in the OMT range (20Hz to 150Hz) and amplitudes from 100nm-3500nm.

A second experiment was also carried using a pre-recorded OMT signal (obtained by the contacting piezoelectric technique, see Figure 82) to drive the simulator (2.4 μ m pk-pk sampled at 200Hz) with the plastic target as surface. To test the speckle correlation performance in reconstructing the signal the Pearson's correlation coefficient (CC) and the root mean square error ($RMSE$) were calculated as follows:

$$CC = \frac{\frac{1}{N} \sum_{n=1}^N (x_n - \bar{x})(\tilde{x}_n - \mu)}{\sqrt{\frac{1}{N} \sum_{n=1}^N (x_n - \bar{x})^2} \sqrt{\frac{1}{N} \sum_{n=1}^N (\tilde{x}_n - \mu)^2}} \quad \text{Equation 34}$$

$$RMSE = \sqrt{\frac{\sum_{n=1}^N (x_n - \tilde{x}_n)^2}{N}} \quad \text{Equation 35}$$

where:

x_n is the original signal (m)

$\tilde{x}_n$ is the reconstructed signal (m)

N is the number of samples.

$\bar{x}$ is the mean value of the original signal (m)

μ is the mean value of the reconstructed signal (m)

7.6.2 Optical configuration

The experimental arrangement for recording is shown in Figure 77. A speckle pattern was formed by projecting the laser beam onto the specimen surface using a He-Ne laser (5mW, $\lambda=632.8\text{nm}$, continuous wave). The beam is then spatially filtered to give a smooth Gaussian intensity profile. A collimating lens is used to control the size of the illuminated spot. The spot size used in the experiments was approximately 1mm. The laser power was controlled by adjustment of the spatial filter with collimated lens and monitored using a PD300 thermal head with Nova 2 display (Ophir Instruments Ltd.).

The laser power was set having regard to restrictions that would be necessary when using the system *in-vivo*. There are two standards that give guidelines for the Maximum Permissible Exposure (MPE) levels of laser radiation, the International Electrotechnical Commission (825-1) (333) and the American National Standards Institute (Z136.1)(334). The two standards agree in the same MPE level for the eye.

Following the guidelines, the MPE limit for the He-Ne laser ($\lambda=632.8\text{nm}$) laser was set to $250\mu\text{W}$ for a 10s exposure (64% of the MPE). See the appendix for more details.

The resulting speckle was imaged using a variable zoom lens (1X to 150X, depending on the desired resolution). The real image formed was projected to a CMOS camera (Motion Scope PCI 8000S, Redlake Inc). The resolution of the system was controlled by adjusting the ratio between the speckle size (see the appendix) and the pixel size by changing the magnification with the zoom lens. The higher the ratio the better the resolution of the system. Also the resolution could be slightly adjusted by changing the lens aperture. The speckle patterns were recorded by a high speed digital video camera with a frame rate of 500Hz (500Hz frame rate acquisition speed was sufficient to track the speckle pattern

changes in the presence of the OMT movement), on a 280 x 320 pixel CCD matrix with pixel size 7.4 μ m square. The camera output was recorded in .avi format.

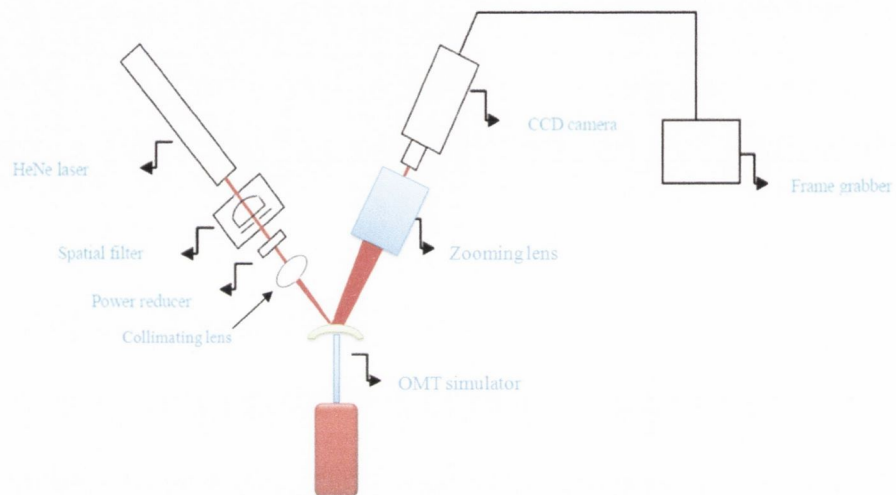


Figure 77. The experimental arrangement for the eye sclera speckle investigation.

7.6.3 Processing

7.6.3.1 Data analysis

Due to the low laser power used in this experiment, the image quality of the speckle pattern is low, such as due DC noise and environmental noise. To improve the image quality of the speckle pattern the frames captured by the camera were first denoised using a 2D Daubechies wavelet (db02) with Undecimated Wavelet Transform (UWT). The denoising setting is based on manual testing different wavelet settings (as in Chapter 3) and seeking the optimal 2D cross-correlation coefficient peak (φ_{peak} , explanation will follow) in the speckle correlation technique.

The analysis was carried out on computational platform Intel (k) Core(TM)2 CPU T7200@2.00 GHz with 2.00 GB of Ram. All the analysis was performed in MATLAB (280) and LabVIEW (3).

7.6.3.2 Speckle correlation

The motion of the simulator is obtained by the speckle correlation technique as follows:

1. From the captured data, some frame (f_2) and the preceding frame (f_1) are selected.
2. Next a sub-image (f_{1s}) is formed from the middle of the speckle pattern in frame f_1 .
3. Then a 2D cross-correlation map (335) is obtained between f_{1s} and f_2 with a step size of one pixel (the step size is the number of pixels over which f_{1s} is shifted in x-direction and y-direction to calculate the next correlation coefficient) .
4. Next the x-y pixel displacement of the object during the period from f_1 and f_2 is estimated by comparing the correlation peak (φ_{peak}) to the middle of the correlation map.
5. Finally, the pixel displacement on the CCD is related to the actual movement of the target by adjusting for the magnification of the configuration.

7.6.3.2.1 The 2D cross-correlation coefficient (φ) is calculated by (336):

$$\varphi(l, k) = \sum_{i=0}^{M-1} \sum_{j=0}^{N-1} f_{1s}(i, j) \cdot f_2^*(i + l, j + k) \quad \text{Equation 36}$$

Where $f_{1s}(i, j)$ is the reference speckle pattern sub-image (f_{1s}) with size $M \times N$ and $f_2^*(i + l, j + k)$ is the conjugate of the preceding speckle pattern image (f_2) with size $D \times E$. The limits of l and k are:

$$0 \leq l < M + D - 1$$

$$0 \leq k < N + E - 1$$

When $\varphi = l$, the two subsets (f_{1s} and f_{2s}) are correlated fully and when $\varphi = 0$, the two are not correlated. The l and k values of the highest correlation coefficient, provide its location within the correlation map.

For this investigation the denoised speckle pattern data was processed to obtain the detected motion by using sub-image size of 15x15 pixels and a step size of one pixel to calculate the 2D correlation map.

7.7 Results

7.7.1 Static target

Figure 78 shows the local speckle contrast of the three target conditions for 100 consecutive frames, under static conditions (no simulator driving signal). The plastic target has the highest local speckle contrast (the top plot in Figure 78) with mean of 0.467 and standard deviation of 0.001. In the case where the eye sclera flap was used (the middle plot in Figure 78) the mean is 0.450 and standard deviation of 0.003. the third case, using the eye sclera flap target with artificial eye tear flow (the bottom plot in Figure 78), has the lowest local speckle contrast with the mean of 0.425 and a standard deviation of 0.007.

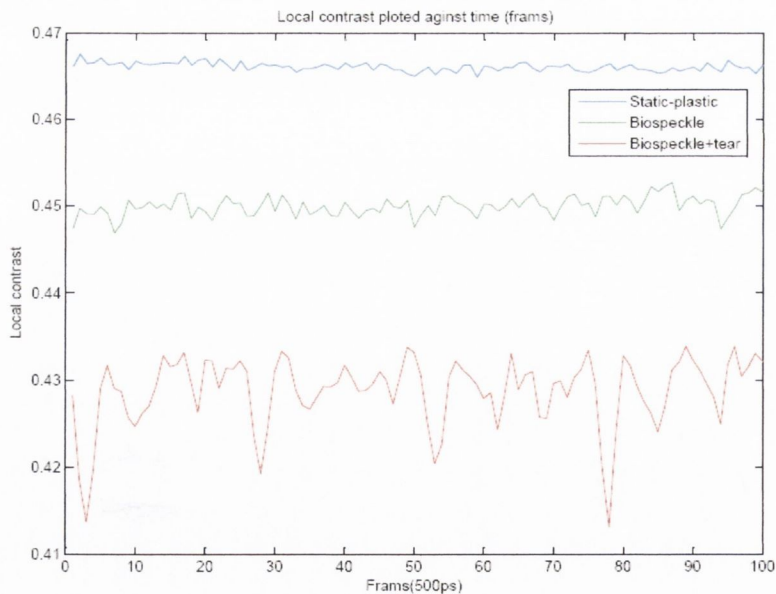


Figure 78. The local speckle contrast of the frames captured by the camera from a static object.

7.7.2 OMT simulation

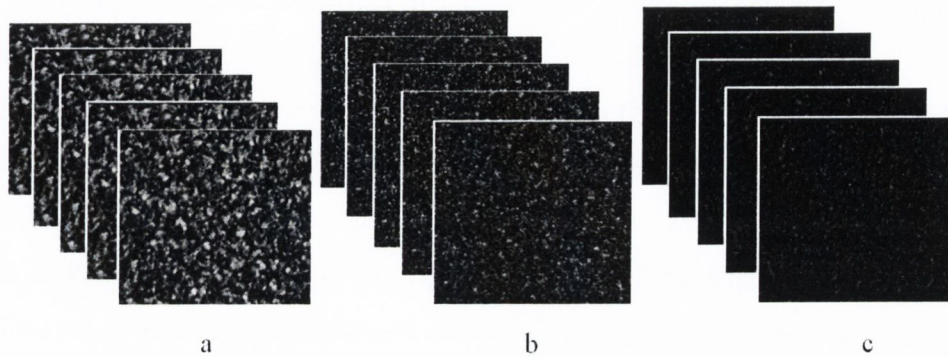


Figure 79. Shows consecutive frames acquired with camera set at 500Hz frame rate and the target driven by 80Hz sinusoidal signal of $1\mu\text{m}$ peak to peak amplitude. a) With the simulator plastic disc as the target. b) With the eye sclera flap attached to the simulator. c) With the eye sclera flap attached to the simulator and stimulated eye tear flow.

Figure 79 (a, b and c) show five consecutively acquired images from the CMOS camera running at a 500Hz frame rate with the simulator driven by 80Hz at an amplitude of $1\mu\text{m}$ peak to peak. The targets in the three conditions are a) Simulator plastic disc as the target. b) Eye sclera flap attached to the simulator. c) Eye sclera flap attached to the simulator and artificial eye tear flow. From the figure we can see that the cases with the bio samples are qualitatively less distinct. This is could be due to the multiple scattering by the biological target especially in the presence of tear flow which might cause randomization of the polarization of the coherent reflected laser resulting in less distinct speckle captured by the camera (330).

Figure 80 shows a typical a 2D cross-correlation of consecutive speckle frames (500Hz frame rate) of the scleral flap with stimulated tear and with the simulator driven at 80 Hz, $1\mu\text{m}$ peak to peak amplitude. The location of the correlation peak in Figure 80 corresponds

to the frame to frame displacement and is distinguishable from background. In this case $\varphi_{peak}=0.89$ and $\varphi_{background}<0.45$.

Using the simulator with the sclera flap attached and with artificial tear flow, the feasibility of using speckle correlation was tested. By driving the simulator at frequencies in the OMT range (20Hz and 150Hz), the speckle correlation method was able to reconstruct the displacement of the flap. Short periods of interference were noted, these were related to noise and vibration in the surrounding environment. Figure 81 shows the reconstruction of the displacement in the case where the sclera flap was attached to the simulator and driven at 80Hz with a peak to peak displacement of 2μm and where artificial tears were added to the flap. The magnification was set to 30X, which implies that each pixel shift represents 247nm displacement (with 7.4μm pixel size). The smallest peak to peak displacement that could be resolved with this optical configuration and with the moving scleral sample with tears as a target was approximately 300 nm peak-peak at 80Hz.

In the case where the pre-recorded OMT signal used to drive the simulator, the speckle correlation technique was able to reconstruct the signal with a 0.99 correlation factor (see Figure 82) and RMSE of a 122 nm.

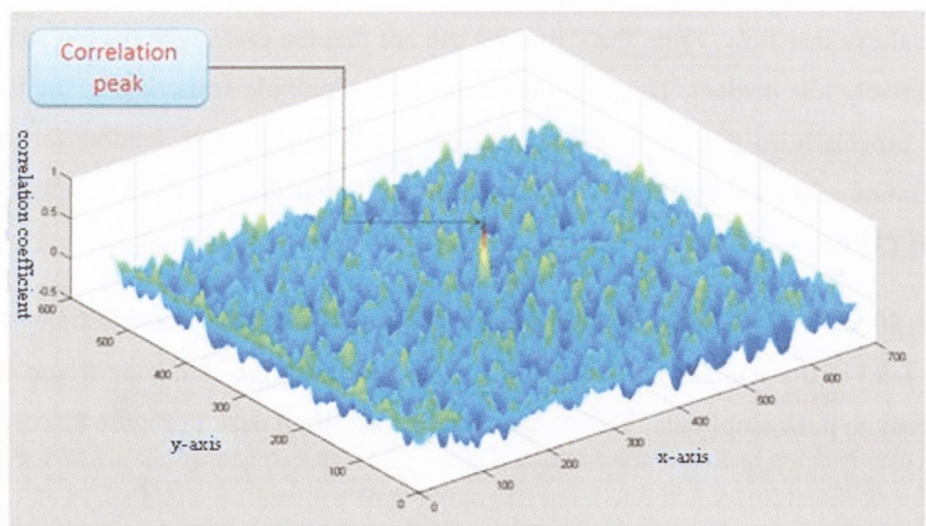


Figure 80. A typical cross-correlation of two subsequently acquired images with sclera flap and stimulated eye tear.

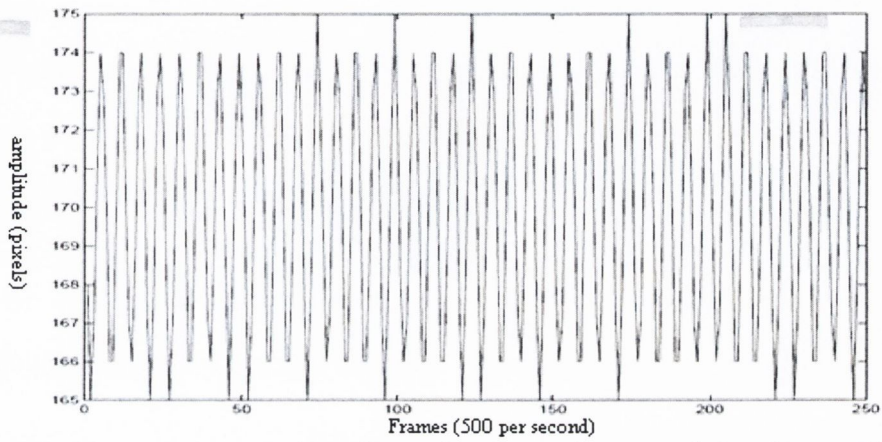


Figure 81. A sine wave (80Hz) simulated signal captured by the speckle correlation technique. The target was sclera flap with stimulated eye tear. Each pixel represents a target displacement of 247nm (30X magnification setting).

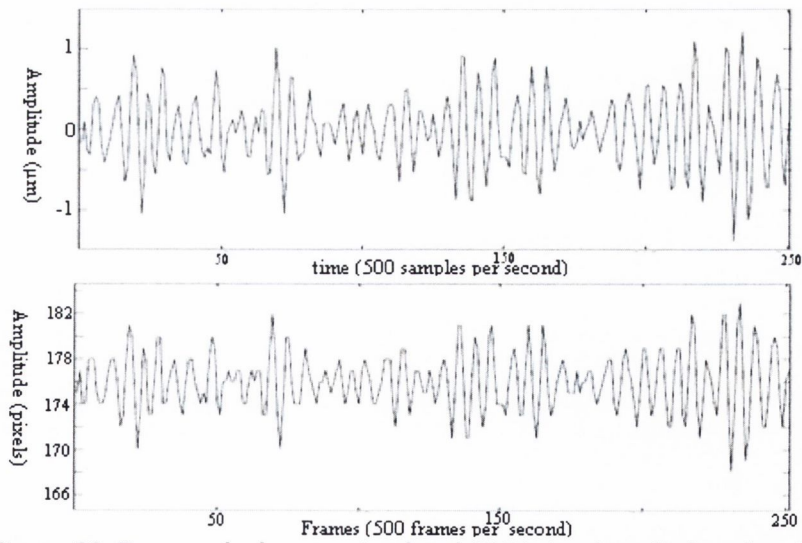


Figure 82. Top graph shows a simulated OMT signal applied to the simulator using a plastic target. In the bottom a reconstruction of the signal using the speckle correlation technique is shown.

7.8 Discussion and conclusion

7.8.1 Static target

Boyle (61) demonstrated the possibility of using the speckle interferometry in OMT measurement. The biospeckle phenomena have been shown in previous studies to be produced when speckle techniques have been used with biological samples. Due to the characteristics of the eye sclera, we expect the presence of biospeckle due to blood flow, the transparency of the bulbar conjunctiva (which will increase multiple scattering events) and eye tear flow. The presence of biospeckle activity will cause an increase in the noise level in speckle metrology methods applied to OMT measurement (such as speckle interferometry).

One of the limitations to Boyle's work was that he did not quantify the effect of biospeckle in the measurement system. This due to the fact that his system was based on using a photodiode which only can detect temporal variation of signal at a single point in the speckle pattern. In this work we overcome limitation of Boyle's system configuration by using a fast speed CCD camera to capture the speckle pattern fluctuation instead of using photodiode.

The effect of biospeckle in increasing the noise level in speckle metrology methods was quantified by comparing the local speckle contrast of speckle from an optically rough object (plastic disc) to the contrast in speckle from an *in vitro* sclera flap. Artificial tear flow was introduced to the sclera flap to additionally simulate the effect of tears.

As explained earlier, loss of local speckle contrast is a measure of the potential of biospeckle to degrade the performance of speckle metrology techniques. The results show that there is a drop of 4% in the local speckle contrast from the eye sclera compared to a white plastic surface. Artificial tear flow caused a drop of 9% in the local speckle contrast compared to the plastic surface, which agrees with findings that increase in the moisture level effects the quality of the captured speckle pattern (329). This implies that a high

production of tear flow will increase the noise level in the OMT measurement using speckle methods since lower speckle contrast leads to a decrease in the signal to noise ratio (120). This suggests that one of the factors to reduce the noise level in eye speckle images is to avoid high tear flow such as the condition when the eye is irritated. The results also show that although the local speckle contrast decreased from 0.467 with the plastic target to 0.425 with the eye sclera and tear, the speckle contrast is qualitatively stable and the speckle pattern is not excessively blurred by biospeckle activity.

7.8.2 OMT simulation

The use of a high-speed CCD camera in capturing the speckle pattern from the eye sclera at eye safe power levels has not been done before. The results presented here show that it is possible to capture the speckle pattern using the high frame rates necessary to capture displacement at OMT frequencies (up to 150Hz). This demonstrates that a high speed CCD can form the basis of a platform for studying biospeckle *in-vivo* despite the requirement to use very low eye safe laser power.

Current work demonstrates that the speckle correlation is a candidate technique for OMT measurement and as an alternative to the speckle interferometry technique reported by Boyle (14). The possibility of measuring the OMT signal with this technique may lead to a simple, portable non-contacting method. The technique would allow an x-y direction measurement of OMT signal, which has not been achieved by other OMT measurement techniques. Also, compared to the speckle interferometry technique, the system should be less sensitive to environmental noise in clinical scenarios (337).

The speckle correlation approach used here could reconstruct the movement of a biologically realistic target moving at OMT frequencies and amplitudes. Using the pre-recorded OMT signal to drive the simulator, the speckle correlation method was able to reconstruct the signal with a high correlation factor ($\mathcal{CC}=0.99$) which implies that there is high level of association between the simulated signal and reconstructed one. The correlation factor is not measure of agreement so that large systematic difference between the two signals is not reflected on it. Also the correlation factor is very sensitive to extreme

values, which may result in falls level of association (338). Visual inspection of the two tested signals showed no evidence of extreme values in the data set, which implies that the correlation factor is not effected by present of extreme values. On the other hand the root mean square error (*RMSE*) was 122nm, which is high in comparison to the to achieve an adequate resolution for OMT measurement (61). The high *RMSE* value could be due DC shift between the simulated signal and measured signal²³. *RMSE* is a good measure of accuracy, which reflects the systematic difference between the simulated signal and reconstructed signal. Unlike the correlation factor the *RMSE* has same units as the tested signals.

The speckle correlation approach described achieved a resolution of approximately 300nm. This is about 6 times poorer than the ideal resolution for OMT measurement and three times poorer than the resolution of the speckle interferometry method introduced by Boyle (14). However the system used here was not optimally configured and it is likely that improvement could be made by using a higher sensitivity camera, improving the correlation method to interpolate between pixels and by determining the best speckle to CCD pixel ratio appropriate for a biological target.

²³ Note that with large DC offset we may have good resolution but poor *RMSE* value

8 Appendix

8.1 Relation between angular eye rotation and the arc displacement

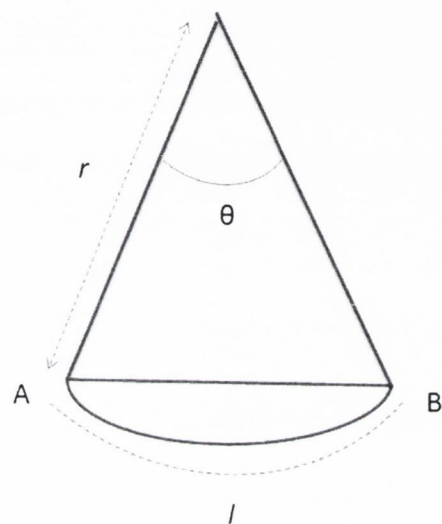


Figure 83. Arc displacement of rotating object

In most clinical books the eye movements are quoted in term of their angular of rotation (θ). If the eye rotated from point A to B as shown in Figure 83, the arc displacement (l) is calculated as follows:

$l = \frac{\pi}{180} r \theta$ Equation 37

Where r (average eyeball radius is about 12.5mm (339)) is the eyeball radius in meters and rotation angle (θ) in degrees. Table 22 shows some conversations from angular rotation to arc displacement.

Eye rotation	Arc displacement
1 degree	218μm
1 arc minute	3.6μm
1 arcsec	60.6nm

Table 22. Conversation table from angular rotation to arc displacement

8.2 Eye laser safety

The Maximum Permissible Exposure (MPE) level of the eye to laser radiation depends on the wavelength of the laser used and the exposure time. The higher the wavelength the lower the MPE since the energy is lower. Also the longer the exposure time the higher the level of radiation applied to the eye.

There are two standards that give guidelines for the MPE levels of laser radiation, the International Electrotechnical Commission (825-1) (333) and the American National Standards Institute (Z136.1)(334). The two standards agree in the same MPE level of the eye.

Following the guidelines of the two standards to calculate the safe eye laser levels, the MPE limit for the He-Ne laser ($\lambda=632.8\text{nm}$) laser in Wm^{-2} are calculated as follows:

$$MPE = \begin{cases} 10^2 C_3 C_6 & \text{if } t > T_2 \\ 18t^{0.75} C_6 & \text{if } t < T_2 \end{cases} \quad \text{Equation 38}$$

where;

$$T_2 = 10 \times 10^{0.02(\lambda-550)} \quad \text{Equation 39}$$

With $\lambda=632.8$ and $T_2=453\text{s}$. Since the experimental setup does require to excide T_2 , therefore the MPE is:

$$MPE = 18t^{-0.25} \quad \text{Equation 40}$$

With $C_6=1$, implying a direct beam viewing of the laser, although the beam is directed to the sclera of the eye, but for safety we assume the worst case scenario. Therefore the MPE for 10 seconds recording period with CCD camera is $MPE_{10s}=10.1\text{Wm}^{-2}$.

The beam intensity is averaged over a pupil area of $38.48\mu\text{m}^2$. This will give us $MPE_{10s}=388.7\mu\text{W}$. The limit to the speckle investigation is set to $250\mu\text{W}$ for 10s exposure (64% of the MPE).

8.3 Speckle size equation

The second-order statistic, speckle size, is an important parameter in the design, simulation and analysis of speckle metrology systems. In particular, the relative size of an average speckle and the pixels in a sampling CCD matrix is of interest(340).

The radius of the smallest speckle spot is estimated as follows (341):

$$r = 1.22\lambda \frac{d_I}{D} \quad \text{Equation 41}$$

where d_I and D are the image distance from the lens and the aperture of the lens respectively. The above equation is used to determine the minimum pixel size required to capture a single speckle. For the optical configuration shown in Figure 15, the equation above could be further modified to help determine the minimum pixel size using the lens equation.

$$\frac{1}{d_o} + \frac{1}{d_I} = \frac{1}{f} \quad \text{Equation 42}$$

Where d_o and f are the object distance from the lens and the focal length respectively.

Using The magnification (M) is $M = d_I/d_o$. Therefore becomes:

$$d_I = f(M + 1) \quad \text{Equation 43}$$

We can then introduce a magnification factor to speckle size equation:

$$r = 1.22(1 + M)\lambda \frac{f}{D} \quad \text{Equation 44}$$

where,

d_I : Image distance from the lens to the object

D : The aperture of the lens

M : Magnification

f : Focal length of the lens

λ : Wavelength of the laser (632.8nm)

The speckle size equation is used in the design of the optical configuration in speckle techniques to achieve the resolution required. For example with $M=30$ and using a lens with an f-number of 4 the statistical average radius speckle size is $95.7\mu\text{m}$. Using a camera with $7.4\mu\text{m}$ pixel size implies that on average each speckle will be captured by about 26 pixels, with each pixel in the camera representing 247nm of the real image.

8.4 Continuous wavelet transform

A time domain signal $g(t)$ can be transformed to the continuous wavelet domain ($W_{(s,\tau)}$) by :

$$W_{(s,\tau)} = \langle g, \varphi_{(s,\tau)} \rangle = \frac{1}{\tau} \int g(t) \varphi_{(s,\tau)}^* \left(\frac{t-s}{\tau} \right) dt \quad \text{Equation 45}$$

Where the new dimensions of the wavelet transform are s (scale) and τ (translation). The φ^* is the conjugate of the analyzing wavelet φ (also called the mother wavelet) which is described by :

$$\varphi_{(s,\tau)}(t) = \frac{1}{\tau} \varphi \left(\frac{t-s}{\tau} \right) \quad \text{Equation 46}$$

The function $\varphi(s, \tau)$ can be described as a copy of the signal wavelet φ , scaled by s and centred around the translation τ (variable scaling constant, see Figure 84). The inverse of the wavelet transform is given by:

$$g(t) = \iint W_{(s,\tau)} \varphi_{(s,\tau)}(t) d\tau ds \quad \text{Equation 47}$$

With continuous wavelets, the resulting coefficients are not invertible. For applications such as denoising, edge detection and peak detection, the signal needs to be reconstructed. To overcome this problem requires the use of the discrete wavelet tools.

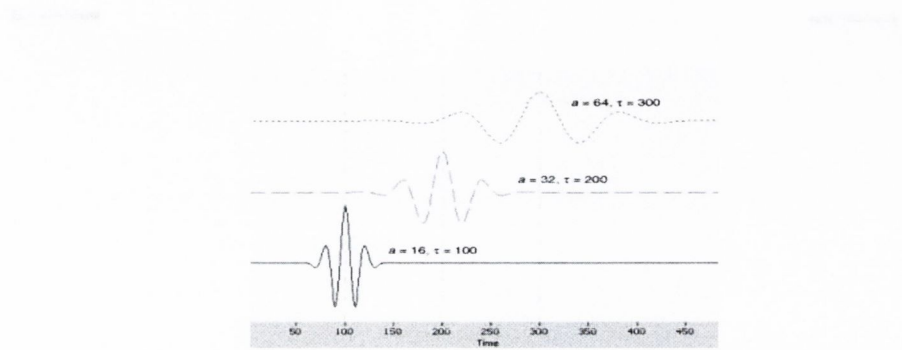


Figure 84. Function $\varphi(s,\tau)$ can be described as a copy of the signal wavelet φ , scaled by s and centred around the translation $\tau(3)$.

8.5 AR model

For a time series the AR model the predication of a value $\tilde{x}_t$ is based on the past values $x_{t-1}, x_{t-2}, x_{t-3}, \dots, x_{t-p}$ plus a predication error (e_t). The order of the AR model equals the number of past values (p) that are used to estimate x_t . Then the AR model is defined as:

$$\tilde{x}_t = - \sum_{k=1}^p a_k x_{t-k} + e_t \tag{Equation 48}$$

Where the $a_1, a_2, a_3, \dots, a_p$ are the AR coefficients. If the model (either AR or other models) and the model order models the signal with close match then the predication error (e_t) is white noise with a mean value of zero. There are number of ways to estimate the AR coefficients such as the Forward-Backword, Least-Squares, Yule-Walker, Burg-Lattice and Geometric-Lattice. In this work we use the Yule–Walker equations to estimate the AR coefficients (342), which based on solving the Hermitian Toeplitz system of equations:

$$\begin{bmatrix} r_0 & r_1 & \cdots & r_{p-2} & r_{p-1} \\ r_1 & r_0 & \cdots & r_{p-1} & r_{p-2} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ \vdots & \vdots & \cdots & r_0 & \vdots \\ r_{p-1} & r_{p-2} & \cdots & r_1 & r_0 \end{bmatrix} \begin{bmatrix} a_1 \\ a_2 \\ a_3 \\ \vdots \\ a_p \end{bmatrix} = \begin{bmatrix} r_1 \\ r_2 \\ r_3 \\ \vdots \\ r_p \end{bmatrix} \quad \text{Equation 49}$$

Where $r_m (m=0,1,2,\dots,p)$ is the autocorrelation given by

$$r_m = \frac{N}{(N-m) \sum_{n=0}^{N-1} x_n^2} \sum_{n=0}^{N-m-1} x_n x_{n+m} \quad \text{Equation 50}$$

Where N is the number of data points of signal x_t .

To obtain an AR model that fits with data analyzed the choice of the right order is important. There are number of ways that can be used to estimate the optimal order of the AR model, in this work the Akaike Information Criterion (AIC) was implemented (343). The AIC method is based on finding a model order that minimize the following:

$$AIC = N \log S + 2p \quad \text{Equation 51}$$

Where S is the average value of the sure prediction error (e_t).

8.6 Whiteness test

The whiteness test is based on the following;

Let $X(t)$ be the signal with N number of data points. To test the whiteness of the signal the auto-correlation value ($Acor(k)$) of the signal is first calculated.

$$Acor(k) = \frac{1}{\sum_{n=0}^{N-1} X(n)^2} \sum_{n=0}^{N-k-1} X(n)X(n+k) \quad (10)$$

The randomness of the signal is then tested using the chi- square (χ^2) distribution. The hypothesis examines whether or not the OMT signal $X(t)$ is white noise. The test is:

$$\epsilon = \frac{N}{A_{cor}(0)^2} \sum_{n=1}^{N-1} A_{cor}(n)^2 \quad (11)$$

Using a confidence level α , if $\epsilon < \chi_{\alpha/2}^2(N-1)$, then the signal considered is white noise (129).

9 List of publications

1. Al-Kalbani M, Collins N, Boyle G, Foran T, Hegarty F, Sheahan N, Coakley D. Piezoelectric strain gauge system development for measuring ocular microtremor. Cambridge IPEM2006; Cambridge 2006.
2. Al-Kalbani M, Collins N, Boyle G, Foran T, Hegarty F, Sheahan N, Coakley D, editors. Microtremor measurement system development. Dublin APSM meeting; 2006; Dublin.
3. Al-Kalbani M, Collins N, Finucane C, Ryle J, Boyle G, Coakley D, editors. Eye movement distortion in high resolution retinal imaging. Engineering the Eye II; 2006; Galway.
4. Al-Kalbani M, Collins N, Boyle G, Hegarty F, Foran T, Sheahan N, Coakley D. An automated ocular microtremor feature extraction using the Gabor thresholding technique. Conf Proc IEEE Eng Med Biol Soc2007. p. 2851-4.
5. Collins N, Al-Kalbani M, Boyle G, Baily C, Kilmartin D, Coakley D, editors. Characterisation of the tremor component of fixational eye movements. . Proceedings of the 14th European Conference on Eye Movements (ECEM2007); 2007 August 19 – 23; Potsdam.
6. Collins N, Al-Kalbani M, Boyle G, Harbison J, Cassidy L, Coakley D, editors. Ocular microtremor: contemporary overview and new findings in stroke and ocular palsy. British Ocular Motor Group Meeting 2007; 2007 December 7; London.
7. Al-Kalbani M, Collins N, Boyle G, Foran T, Hegarty F, Sheahan N, Coakley D, editors. Ocular microtremor measurement system. Fermanagh Bioengineering in Ireland; 2007; Fermanagh.
8. Collins N, Al-Kalbani M, Boyle G, Harbison J, Coakley D, editors. Ocular microtremor in a case of bilateral thalamic and midbrain infarct. Dublin Irish Heart Foundation Stroke Study Day; 2007; Dublin.
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10 Glossary of Terms

A

- ❖ **Accuracy in signal analysis:** Is the proportion of records that are correctly classified in to the right group (normal subjects and patients).
- ❖ **Akaike Information Criterion:** A method used to estimate the optimal AR model order.
- ❖ **Amplitude response:** A measure of a system output amplitude in response to an input signal over range of frequencies of interest.
- ❖ **Anti-aliasing filter:** Is a low pass filter which has a cut-off below the Nyquist frequency.
- ❖ **AR spectrum:** Is one of the parametric linear prediction approaches used to estimate the PSD of signals using the Autoregressive model.

B

- ❖ **Bandpass filter:** A digital or analogue component that attenuates frequency components which lie outside a particular band of frequencies.
- ❖ **Biospeckle:** Is a term given to the speckle from a biological surface.
- ❖ **Boiling Speckle:** The speckle pattern changes over time not only because of the motion of the diffuser but also because of Brownian motion within the object illuminated. The boiling speckle regime is the deformation, disappearance and reappearance of the speckle spots like a vapor bubbles in boiling water.
- ❖ **Bulbar conjunctiva:** A transparent membrane covering anterior part of the sclera.
- ❖ **Butterworth filter:** Is a type of signal processing filter design that have frequency response as possible flat in the passband frequencies.

C

- ❖ **Capacitance gauge system:** Eye movement measurement system. In this method a fixed plate of a capacitor is placed near the eyeball surface. The eyeball will act as

the second earthed moving plate of a variable capacitor. The capacitance changes due to the eye movements cause frequency modulation of an r.f. oscillator.

- ❖ **Coherence:** Estimates the linear time invariant relationship between signals.
- ❖ **Corneal reflection:** Eye movement measurement system. This method is based on directing a collimated beam of infrared light on the cornea and using the reflection from the cornea to measure eye rotation. The virtual image formed by the convex surface of the cornea (the 'Purkinje' image) may be tracked to follow eye movements.
- ❖ **Correlation coefficient:** A measure of similarity between two time series.
- ❖ **Cyclo-stationary signal:** The statistical properties of the signal vary cyclically with time.

D

- ❖ **Dominant frequency:** The frequency occurring the most.
- ❖ **Drift:** Low velocity movement of the eye when fixating.
- ❖ **Dynamic range:** A ratio (as ratio or logarithmic value) between the smallest and largest measurable quantity.

F

- ❖ **Fixation:** Maintenance of the visual gaze on a single location.
- ❖ **Fractional octave analysis (FOA):** Defines the spectral band powers at defined octaves, using banks of band pass filters with constant Q factor. The FOA spectrum is present as a bar chart.
- ❖ **Frequency response:** A measure of a system output spectrum in response to an input signal.

G

- ❖ **Gabor Transform:** A special case of the short time Fourier transform were uses a Gaussian function and it's invertible.

- ❖ **Gabor time varying filter:** A noise filter based in thresholding (or masking) coefficients in the Gabor domain.

H

- ❖ **Hard thresholding:** Technique sets the UWT coefficients smaller than the threshold to zero and the remaining coefficients are unchanged.
- ❖ **High pass filter:** A filter that attenuates low frequency, but leaves high frequencies unfiltered.
- ❖ **Hyperacuity:** Is the ability of the eye to resolve certain stimuli with resolution better than that imposed by the Nyquist sampling theorem. Its resolution is about 5 to 10 higher than normal visual acuity.

I

- ❖ **IRIS system:** Eye movement measurement system. The method is based on the reflection of infrared (IR) light by the area on both sides of the boundary between the white sclera and darker iris. Two infrared sensors are positioned to detect the reflection from the two areas. The voltage difference between the two sensors is proportional to the eye movement.

K

- ❖ **Kappa statistic:** The Kappa statistic is commonly used in medical literature to test of agreement that rules out agreement by chance.

L

- ❖ **Local speckle contrast:** Is defined as the ratio of the standard deviation to the mean intensity of the image. The speckle contrast value is between 0 and 1.
- ❖ **Low pass filter:** A filter that attenuates high frequency, but leaves low frequencies unfiltered.

M

- ❖ Microsaccades: Rapid small amplitude fixational eye movements.

N

- ❖ Nonlinear signal: Are signals that are cannot be modeled by Gaussian linear stochastic process.
- ❖ Nonstationary signal: Signals that have statistical properties that changes over time.
- ❖ Nyquist frequency: Is half of the sampling frequency.

O

- ❖ Ocular microtremor (OMT): A continual high frequency involuntary eye movement present in normal subjects even when the eye appears to be at rest.
- ❖ OMT baseline: One of the OMT signal features that has an irregular low amplitude pattern with a frequency range from 70 Hz to 126 Hz for normal subjects.
- ❖ OMT signal features: Consists of an irregular baseline tremor with intermittent episodes of higher amplitude bursts.
- ❖ OMT bursts: One of the OMT signal features that have the shape of an amplitude modulated near-sinusoidal oscillation with a frequency of about 75Hz to 115Hz for normal OMT subjects

P

- ❖ Partial coherence: Estimates coherence between signals taking in account relationship of the signals with a reference signal.
- ❖ Peak count: The technique is based on counting the number of peaks per unit time, which gives an estimate of the spectrum dominant frequency component of the analyzed signal.
- ❖ Permutation entropy: Is a measure used to evaluate the regularity and the complexity of signals.

- ❖ **Phase modulation:** A method used to remove the directional ambiguity in the speckle interferometry measurement system.
- ❖ **Signal power:** Mean square of the signal.
- ❖ **Power spectral density (PSD):** Describes how the power of a signal is distributed with frequency.
- ❖ **Purkinje image:** A virtual image formed by the convex surface of the cornea.
- ❖ **PZT system:** Eye movement measurement system. The method is based on measuring the voltage change produced by a piezoelectric element when it is in contact with the eye.
- ❖ **PZT system closed eyelid:** The piezoelectric probe in the PZT system is placed on eyelid of the eye.
- ❖ **PZT system open eyelid:** The piezoelectric probe in the PZT system is placed on the surface of the sclera of the eye.
- ❖ **PZT system screw mechanism:** The piezoelectric probe is advanced to the eye by a mini vice and once the probe comes in contact with the eye sclera, further turns of the mini vice will increase the pressure applied by the probe to the eye.
- ❖ **PZT system sliding mechanism:** The piezoelectric probe is advanced to the eye by a precision linear ball slider and once the probe comes in contact with the eye sclera, the pressure applied by the probe to the eye depends in the probe mass only.

Q

- ❖ **Quasi-stationary:** Term given when a non stationary process can be divided into short equal segments over which the statistics of interest are not varying.

R

- ❖ **Reflection mirror:** A measurement system used for eye movement's measurement. The method is based on detecting the changes of the angle reflection of a light

beam reflected from a very small, flat (plane) mirror mounted on a contact lens worn on the eye.

- ❖ Rescaling method: Are methods used to estimate the noise variance at each level of the wavelet transform.
- ❖ Reverse arrangements test: Nonparametric stationarity tests.

S

- ❖ Sampling frequency: Is the number of times per second that the amplitude of a signal is specified digitally.
- ❖ Scleral search coil: Eye movement measurement system. The method is based on applying a time varying magnetic field and when the eye moves within the field an alternating voltage is induced in a search coil which is embedded in contact lens.
- ❖ Sensitivity: Is the proportion of the records that are from patients that the classifier correctly identifies as positive.
- ❖ Soft thresholding: Technique sets the UWT coefficients smaller than the threshold to zero and smoothes the larger coefficients towards zero.
- ❖ Speckle: Is a phenomenon seen where laser light scatters from a rough (nonspecular) object resulting in a random pattern of dark and bright spots (speckles) to form.
- ❖ Speckle contrast: Is a first-order statistical measure defined as the ratio of the standard deviation of the speckle pattern intensity to the mean speckle intensity.
- ❖ Speckle correlation: Is a method based on using an electronic detector (e.g. CCD camera) to capture the speckle pattern fluctuations from frame to frame.
- ❖ Speckle interferometry: Speckle interferometry in eye movements is a method to capture fine eye movement based on having two laser beams directed onto one point on the sclera of the eye. As the sclera surface is optically rough this causes the formation of laser speckle. The speckle fluctuations are captured using a photodiode and then further processed to recover the eye movement signal.
- ❖ Speckle translation: The speckle pattern moves with the diffuser as a whole and the pattern remains unchanged for a considerable time.

- ❖ **Specificity:** Is the proportion of the records that are of normal subjects that the classifier correctly identifies as negative.
- ❖ **Stationary signal:** Is a random signal where statistical properties such as the mean, variance and correlation do not vary with time.
- ❖ **Surrogate data (or surrogates for short):** Is a method used to test for nonlinearity in a time series. The technique is based on generating time series which have all the linear properties of the original time series, but which distort the nonlinear deterministic structure in the time series tested.

W

- ❖ **Wavelet:** Is a wave-like oscillation with amplitude that starts out at zero then oscillate back to zero from increase to decrease.
- ❖ **Wavelet transform:** Is the representation of a signal by wavelets.
- ❖ **Wavelet denoising:** Is method of filtering noise based on transforming the signal in the wavelet transform, then thresholding (or masking) the wavelet coefficients, where the coefficients lower than threshold represent the noise to be filtered. Then the signal free of noise is recovered by applying an inverse wavelet transform to the thresholded coefficients.
- ❖ **Welch spectrum:** Is method used for estimating power spectrum density of a signal.

Y

- ❖ **Yule-Walker:** A method used to estimate the AR filter coefficients.

Z

- ❖ **Zero padding:** Extending a signal (or spectrum) with zeros.

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