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UNIVERSITY OF ALBERTA

REDUCTION OF PATHOLOGICAL TREMOR BY FUNCTIONAL ELECTRICAL STIMULATION

By

MANOUCHEHR JAVIDAN

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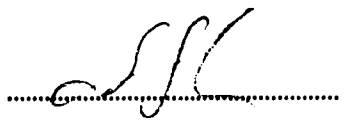

Arthur Prochazka

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THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled **REDUCTION OF PATHOLOGICAL TREMOR BY FUNCTIONAL ELECTRICAL STIMULATION** submitted by Manouchehr Javidan in partial fulfillment of the requirements for the degree of Master of Science in Experimental Medicine.

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This thesis is dedicated to my parents Gheysar and Ali for their loving care, and to my wife Farahnaz, and my children Amirali and Amir Hussein without whose understanding, patience and loving encouragement nothing would have taken place.

ABSTRACT

Tremor is a common movement disorder which may be functionally disabling to the patient. This is particularly observed in patients with progressive neurological disorders such as Parkinson's disease and multiple sclerosis. Very little is known about the pathophysiology of tremor and although several groups of medications are available for parkinsonian and essential tremor with reasonable efficacy, therapy for cerebellar tremor is still lacking.

This work presents development of a new technique to attenuate pathological tremors. Using closed loop functional stimulation (FES), tremorogenic muscles were stimulated out of phase to counteract tremor movements. The electrical stimulation of the muscles was amplitude-modulated by a filtered version of the movement signal. The filter design was based on the open loop frequency characteristics of the wrist and elbow in a group of normal subjects. This closed loop system suppressed pathological tremors by up to 70% without a significant effect on slow functional movements.

The technique was then evaluated in a selected group of patients referred with the clinical diagnosis of essential tremor, Parkinson's tremor and cerebellar tremor due to multiple sclerosis. The tremor in these patients was refractory to pharmacological treatment. On average FES suppressed essential tremor by 73%, parkinsonian tremor by 62% and cerebellar tremor by 38%. A better performance in cerebellar tremor was obtained by re-tuning the loop to 2-3 Hz.

This technique appears to be useful in suppressing pathological tremor. However, practical limitations were encountered which restrict the use of this system in its present form. In the next few chapters I will describe the pathophysiology and treatment modalities for tremor, methodology of application, open loop frequency characteristics of the wrist and elbow in normal subjects, filter design, and the results of FES in the three groups of patients. Advantages, practical limitations and the potential improvements in this technique will be discussed.

PREFACE

This thesis reports the application of a new technique in the management of tremor. It involves using closed loop Functional Electrical Stimulation of agonist-antagonist muscles to reduce tremor amplitude.

The introductory chapter of this work reviews our current understanding of the pathophysiology of the physiological and pathological tremor. This includes definitions , classification, analysis of tremor frequency and amplitude, and mechanisms of tremor generation. The theoretical and pharmacological basis of treatments for essential, parkinsonian and cerebellar tremor are discussed.

The first part of chapter II describes control theory utilised in this work. The remainder of this chapter is devoted to the description of methodology of the experiments in frequency response characteristics of load-moving muscle. This part of the work, particularly the engineering aspects of the filter design was in collaboration with Dr. Arthur Prochazka. This chapter also details the method of application of FES in normal subjects and the results of the open loop studies to obtain linear transfer function of the wrist and elbow. The latter is particularly important in the development of the filter model for closed loop stimulation in patients with pathological tremors without interfering with their functional movements.

Chapter III reports the clinical assessment in patients with essential, parkinsonian and cerebellar tremor. This includes the detailed analysis of the tremor frequency and waveform in each patient and the response to FES. An example of each group is presented. The final chapter summarizes the results and reviews the practical applications, limitations of the FES technique and patients' opinion. Chapter IV also attempts to provide guidelines for future research into this problem.

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CHAPTER I

INTRODUCTION

Tremor is a relatively common movement disorder which can be very disabling and embarrassing to the patient. Tremor may be present in both physiological and pathological conditions. Therefore, it has been very attractive to neurophysiologists and clinical neurologists who wish to understand the basic mechanisms and management of this movement disorder. However, despite a great deal of effort aimed at studying the underlying physiology, pathology, and pharmacology of tremor these aspects remain poorly understood. On the other hand clinical recognition of the tremor type is extremely important as it determines the type of treatment which may be available. Several modalities have been used for the treatment of pathological tremors in a variety of neurological disorders. These include medications, muscle loading, stereotactic surgery etc. However, only about 50% of tremors are successfully suppressed with these approaches.

Pharmacological agents were first used in the treatment of Parkinson's tremor. Atropine was introduced by Charcot (1879) and scopolamine by Erb (1908). Belladonna alkaloids and in the 1950's centrally acting anticholinergic drugs were used until the introduction of levodopa by Cotzias et al. (1967). The latter medication has become the mainstay of treatment in Parkinson's disease. Recently dopamine receptor agonists and monoamine

oxidase inhibitor-B (MAO-B) enzyme inhibitors (Deprenyl) have been introduced as adjunctive treatment. These drugs can sometimes be used as a monotherapeutic agent if levodopa fails (Lieberman and Goldstein (1982).

The effect of alcohol on reducing essential tremor was reported by Critchley in 1949. However, its use has been discouraged due to the associated morbidity and mortality. On the basis of several studies which showed the capability of beta- and alpha-adrenergics to enhance physiological and essential tremor (Marshall and Schneiden 1966, Marsden et al., 1967 and 1969), the use of β- blockers such as propranolol in the treatment of essential tremor has been reported with success (Winkler and Young, 1971, 1974; Sevitt, 1971). Owen and Marsden (1965) showed that the potentiating effect of epinephrine on Parkinson's tremor could be mediated by beta-adrenergic blockers, whereas alpha-adrenergic blockers such as phentolamine were ineffective. Intravenous propranolol was also shown to reduce accentuated physiological tremor in anxiety and thyrotoxicosis (Marsden et al., 1968). Recently, after years of limited success with a variety of pharmacological therapies for cerebellar tremor, some beneficial effects of 5-hydroxytryptophan (Rascol et al., 1981) and Isoniazid (Sabra et al., 1982) have been reported.

About 50% of pathological tremors cannot be adequately controlled by medication. Effectiveness of stereotactic surgery in alleviating Parkinson's tremor was reported by Cooper as early as 1955. There has been considerable debate on the cost and benefit as well as potential complications and recurrence of tremor after surgery. This technique is still being used in refractory tremors. The only available alternative to control such tremors has been inertial loading of the affected limb (Hewer et al., 1972). However, this generally

tends to be viewed as a last resort, and often proves unsatisfactory, because the amount of loading required to attenuate a tremor by a useful amount usually weighs the limb down to the point where voluntary movement is impeded and the limb muscles rapidly fatigue. Viscous loading has been suggested as a further alternative (Morrice et al., 1987), the idea in this case being to attach a device to the limb which would offer an impedance to movement that is proportional to limb velocity. Pilot experiments along these lines have been promising, but so far the approach has not been implemented practically. Furthermore, it is likely that purely viscous loading would not be selective enough to impede pathological tremors whose power content is in the frequency range 2-5 Hz without also significantly impeding useful movements in the 0 - 1 Hz range. A combination of inertial, resistive and viscous loading (Morrice et al., 1987) providing a mechanical impedance with a sharply tuned band-pass characteristic might be another option, but its practical implementation within acceptable size limits might prove very difficult.

In this thesis I describe a new approach whereby closed-loop functional electrical stimulation (FES) is used to activate the tremorogenic muscles out-of-phase, thereby counteracting the tremor. A signal from a displacement transducer is high-pass filtered to respond selectively to tremor movements, the filtered signal being used to amplitude-modulate electrical stimulation of the muscles producing the movement. With careful filter design, it is possible to attenuate 2 - 5 Hz tremors substantially, while only minimally attenuating functional movements in the 0 - 1 Hz range. A knowledge of the response characteristics of the load-moving muscles is an essential prerequisite for the design process, the details of which are presented in chapter II. Clinical trials are presented in

chapter III.

Before describing the details of the study, I will review the following aspects of tremor 1) definition, 2) classification, 3) characteristics, 4) mechanisms and clinical aspects 5) current management and treatment modalities.

Definition of tremor

The definition of tremor in the literature to date has been ambiguous and confusing. According to Dejerine (1914), tremor is characterized by 'involuntary rhythmic oscillations about a position of equilibrium which involve either the whole body or part of it'. The most accepted definition is that tremor is an involuntary periodic oscillation of a body part in a rhythmic and continuous manner (Findley & Gresty, 1981) that results from the alternating or synchronous contractions of reciprocally innervated antagonistic muscles (Fahn, 1972; Jankovic and fahn, 1980; Koller, 1984a).

Although it is simple to relate tremor to alternating contractions of the antagonistic muscles, synchronous contractions of such muscles may also produce tremor and this concept is more difficult to understand. Shahani and Young (1976a) related this to possible synchronous contractions differing in force and duration. Tremor has a relatively fixed periodicity and has an amplitude and waveform which are to some extent invariant over a certain period of time. These characteristics enable clinicians to distinguish tremor from other involuntary movements with irregular appearance such as myoclonus, chorea, clonus, etc.

Classification of tremor

In general, tremor can be classified as:

Rest tremor (The term "static" is discouraged) and action tremor. Action tremor is further subdivided into postural and intention (movement) tremor (Findley & Capildeo, 1984), although some authors consider movement tremor as a separate entity (Weiner & Lang, 1988).

- Rest tremor occurs in the absence of voluntary muscle movement and the affected body part is supported against gravity (Findley, 1989). It is most commonly present in Parkinson's disease.

- Action tremor occurs during a voluntary muscle contraction such as maintaining a fixed posture or performing a movement. This category includes postural and intention tremor. Postural tremor refers to tremor present when the affected body part is maintaining a sustained antigravity posture. Examples of this are physiological, enhanced physiological and essential tremor. Intention tremor is produced by dynamic goal-directed action of the limb. This classically occurs at the termination of a movement but it may also be seen at the initial or even middle part of a movement. It is most often associated with cerebellar disorders (Marshall, 1968; Fahn, 1972; Jankovic and Fahn, 1980, Marsden, 1984; Weiner and Lang, 1989).

Analysis of tremor characteristics

Tremor frequency

Determination of tremor frequency can be useful in understanding underlying mechanisms. The frequency of pathological tremor is easily measured by a small accelerometer and is

usually fairly stable. Frequency measurement coupled with waveform analysis allows separation of tremor into several broad groups. Table 1 indicates the frequency of tremor in various clinical disorders (Findley, 1988).

Table 1. Frequencies of Common Tremors

Frequency (Hz)	Type of Tremor
2.5-4	Cerebellar, "Ataxic," with cerebellar brainstem disease Oculo-palatal myoclonus
4-5	Parkinson's disease (rest tremor) Rubral Drug-induced (e.g., neuroleptics)
5.5-7	Essential Parkinson's disease (postural tremor) Drug-induced (e.g., sodium valproate)
7-12	Physiological Exaggerated physiological Drug-induced (e.g., epinephrine)

Note: Frequency characteristics are not mutually exclusive and some overlap exists between the frequency bands of different types of tremor.

Analysis of the waveform

Analytical techniques such as Fast Fourier Transformation and Power Spectral Analysis can accurately determine the distribution and amplitude of the frequency components of a tremor and their variability. This allows for a further separation of complex tremors that is often difficult by clinical examination alone (Findley et al., 1981; Findley and Gresty, 1984; Gresty & Findley, 1984). Spectral analysis of tremor was first introduced by Halliday and Redfearn (1956). According to their experiments and work by Merton et al. (1967),

Sutton and Sykes (1967a,b), and Stephens and Taylor (1974) physiological tremor is a mixture of different frequencies ranging between 6-12 Hz rather than one single frequency. In pathological tremor, however , a more consistent peak frequency is observed.

Clinical electromyography

Standard techniques such as surface or intramuscular electromyography (EMG) are usually unhelpful in the differential diagnosis of tremor. However in studying tremor, they may be used in differentiating active muscle contraction from passive movements such as ballistocardiogram artefact that is present in physiological tremor of most normal subjects (Brumlik and Yap, 1970). The EMG usually reveals either an alternating or a synchronous pattern of activity in agonist-antagonist muscles. As early as 1940, Hoefer and Putnam reported synchronous contraction of agonist-antagonist muscles in abnormal tremor, and Lippold et al. (1957) described this observation in man and concluded it to be a basis for what they called physiological tremor. The fact that synchronous bursts of activity in agonist-antagonist pairs can generate tremor is presumably due to inequalities in strength and timing of contraction (Shahani and Young, 1976a). Alternating activity is commonly seen in parkinsonian rest tremor (Findley et al., 1981), whereas the higher frequency action tremors in Parkinson's disease also show synchronous bursts of activity in agonist-antagonist muscles (Lance et al., 1963). Essential tremor classically shows synchronous activity, however alternating muscle bursts in large amplitude tremor have been reported (Sabra & Ha[illegible]). A shift of pattern (alternating to synchronous and vice versa) of muscle activity [illegible]orted in essential tremor in prolonged recordings (Findley et al., 1984).

Action tremor associated with cerebellar pathology such as that often present in multiple sclerosis shows the alternating EMG pattern. The recruitment order of individual motor

units during essential tremor bursts is different from that seen in either Parkinson's disease or physiologic tremor (Shahani & Young, 1978; Young & Shahani, 1979). However the single unit recording technique required to demonstrate these differences is not routinely used in the clinical evaluation of tremor. EMG has also been used in the assessment of various treatment modalities of tremor.

Mechanisms of Tremor Generation

Tremor can be present in normal as well as pathological conditions. Although the mechanisms underlying each type of tremor may be different, some overlap certainly exists. I will discuss these mechanisms under two major headings: physiological tremor and pathological tremor.

i) Mechanisms underlying physiological tremor

Voluntary movements of the limb can be made at various frequencies, usually up to 6 Hz (Stein and Lee, 1977). Regular oscillations of the human limb while maintaining a posture or performing a voluntary movement are usually referred to as tremor. The frequency of such oscillations falls within a narrow band of 8-12 Hz, and is referred to as physiological tremor. The mechanisms underlying physiological tremor are generally discussed in relation to the following categories:

a) Passive mechanical properties of the limb

b) Oscillation in spinal reflex arc

c) Oscillation in the "long loop" reflex pathways

d) Responses to heart beat and to grouped motoneuronal firing

e) Oscillations generated within supraspinal structures

a) Mechanical properties

The human limb by virtue of its muscles, bones, tendons, etc. is a mass-spring system with inertia and stiffness (Rack and Westbury, 1974; Marsden, 1978). Every such system tends to oscillate at a frequency called the natural resonant frequency. The greater the mass and the lower the spring stiffness, the lower the natural resonant frequency (Marsden, 1978). The natural resonant frequency of the fingers has been estimated at about 25 Hz which is higher than that of the wrist (about 9 Hz) and of the elbow (about 2 Hz) (Stiles and Randall, 1967; Joyce and Rack, 1974; Marsden, 1978). This mass-spring system is capable of developing sustained oscillations at frequency range of 8-12 similar to the natural resonant frequency of the wrist (Marsden, 1978). Partridge (1965) described the processing and filtering characteristics of muscle in response to sinusoidally varying neural inputs. He noted a progressive reduction of the amplitude of the muscle force as input signal frequencies increased, along with an increasing phase lag of force behind the command signal. These properties were likened to a low-pass filter acting on an input into the mechanical system.

In summary the two important mechanical factors related to tremor generation are the natural resonant frequency of the limb, which is a function of the load and viscoelastic muscle properties, and the filtering characteristics of the active muscle (Rack, 1978 and 1981).

b) Oscillation in the spinal reflex arc

The contribution of the stretch reflex arc to tremor was first discussed by Walsh (1924) and Sherrington (1925). Subsequently, several other studies (Halliday and Redfearn, 1956;

Lippold, 1970 and Joyce and Rack, 1974) indicated that physiological tremor is at least partially due to oscillations occurring as a result of instability of the spinal stretch reflex. It was suggested by Marsden (1978) that the frequency of oscillation was related to the time taken for nerve impulses to travel from muscle spindles to alpha motoneurons and back from the ventral horn to excite muscles. In the human monosynaptic reflex arc this time interval ranges between 15 to 60 ms. Marsden argued that a linear servo loop with too high a feedback gain tends to oscillate at a period equal to twice the delay around the loop. The frequency of oscillations is calculated as f= 1000ms/ 2 X loop delay. Thus a 10 Hz oscillation in such a system indicates a loop delay of about 50 ms (Marsden, 1978). However this simple relationship has been challenged (Prochazka and Trend, 1988).

The role of stretch reflexes in the generation of tremor, was questioned in studies that showed the persistence of tremor after surgical deafferentation (Foerster, 1936; Altenburger, 1937), in tabetic patients (Marshall and Walsh, 1956; Halliday and Redfearn, 1958; Marsden and Meadows et al., 1967) and in severe peripheral neuropathy (Marsden and Meadows et al., 1967). However, tremor amplitude tends to be smaller in most of these cases. Marsden (1984) argued that although physiological tremor can occur in the absence of afferent feedback its amplitude is probably modulated by the effect of spindle input that may synchronize motoneuron discharge. Further studies by Joyce and Rack (1974) and Joyce et al. (1974), Mathews and Muir (1980) Hagbarth and Young (1979) were all supportive of the role of the afferent input and the stretch reflex arc in tremor generation. Prochazka and Trend (1988) artificially increased spindle stretch-sensitivity with vibrators placed over the flexor and extensor muscles of the elbow. They noticed when the gain exceeded a threshold value, forearm oscillations developed. The frequency

of the oscillations was in the 3-5 Hz range at low levels of co-contraction and increased to 5-8 Hz at higher levels. This suggested that at the elbow stretch reflexes assist in the generation of 3-8 Hz rather than 8-12 Hz tremor.

c) Oscillation in the "long loop" pathways

In motor control studies, a late EMG response to muscle stretch has been identified which is called "long loop" or long latency (M2) response. Enhancement of long-latency response has been reported in Parkinson's disease (Lee and Tatton, 1975). The possibility that physiological tremor is driven by oscillations arising from instability in long-loop reflexes has also been suggested (Lance and McLeod, 1975; Marsden et al. 1976 a,b). The interaction of long latency and monosynaptic stretch reflexes to influence tremor was modelled by Stein and Oguztorelli (1976 a,b) who suggested that the presence of multiple reflex pathways with different gains and loop delays would reduce the tendency for tremor. In particular, high reflex gain in supraspinal pathways theoretically may dampen out oscillations of spinal origin.

d) Responses to heartbeat and to grouped motoneuronal firing

d.1- Response to heart beat

The effect of the ballistocardiogram on finger tremor, and oscillations occurring in time with the heartbeat have been recorded in completely denervated limbs or after paralysis with succinylcholine. However, less than 10% of the tremor recorded from outstretched fingers can be accounted for by the heartbeat (Marsden et. al., 1969). It is believed now that the ballistocardiogram exerts a very minor effect on modifying physiological or any type of pathological tremor (Weiner and Lang, 1989).

d.2- Response to grouped motoneuronal firing

Normally, motoneurons fire in an asynchronous manner, so that during voluntary activation, normal firing of motor units might not be expected to produce substantial tremor. However, firing rates of motor units at recruitment are close to the frequency of physiological tremor (Stein and Lee, 1977). Allum et al. (1978) argued that unfused twitches summating to produce tremor oscillations are produced by synchronization of a few newly recruited motor units either by chance or by a common input of central origin. During a steady maintained contraction, the most recently recruited motor units, which are larger than those recruited initially (Mori, 1975), are the most likely to give rise to rhythmical twitches of the muscle at a frequency around 10 Hz. It can be shown mathematically that the summated tensions of many motor units firing at a similar rate (10-15 Hz) will produce a net tension with small fluctuations in this same frequency range (Allum et al., 1978). This is true even if there is no synchronization at all between the units. However, Milner-Brown et al. (1973a, b and 1975) found a weak synchronization between motor units in more pronounced tremor. Allum suggested the greater the tendency for synchronization, the greater the physiological tremor. There are situations involving anxiety, adrenaline infusion or when the limb is suddenly disturbed, in which motoneuron synchronization can be demonstrated. Hagbarth and Young (1979) suggested that such a grouping of motor unit discharges often seems to be the result of the activation of stretch reflex mechanisms.

e) Oscillations generated within supraspinal structures

An influence of the brain on physiological tremor was suspected from the time of Gordon Holmes (1922) who observed the disappearance of normal postural tremor of the outstretched hands after unilateral damage to the cerebellum. An hypothesized relation

between the alpha rhythm and physiologic tremor (Lindqvist, 1941) was never confirmed. Sutton and Sykes (1967) reported the disappearance of the 9 Hz hand tremor upon closing the eyes particularly when tremor was recorded in a tracking or holding task employing visual feedback. Lamarre (1975) suggested that some physiological tremors such as those dependent upon visual feedback might be due to synchronized rhythmic activity at 7-12 Hz within the inferior olives or in the olivo-cerebello-bulbar system. Lamarre found that the tremorogenic drug harmaline induced the inferior olivary nuclei behave as a 10 Hz generator. This supports the possible existence of a rhythmic generator in the olivo-cerebello-bulbar system.

In summary, the origin of physiological tremor remains uncertain. Probably no single mechanism is solely responsible. This may in fact be due to a combination of factors including motor units rhythmicity, feedback in segmental reflex mechanisms, mechanical properties and perhaps a contribution from an autonomous central oscillator located within the neuraxis.

Enhanced physiological tremor (EPT)

This tremor could simply be due to the exaggeration of physiological tremor in a variety of clinical situations including emotional states such as anger and excitement. However, it may also be seen in pathological conditions e.g. thyrotoxicosis. This tremor has a frequency of 8-12 Hz. It is usually absent at rest and appears when maintaining a posture and is present in, but not intensified by movement (Marsden, 1978). The similarity between tremor of anxiety and fright (Graham, 1945; Redfearn, 1957) and that of thyrotoxicosis to EPT, and their reduction by β-adrenergic blockade (Marsden et al. 1968)

suggests an underlying β-adrenergic mechanisms in the genesis of these tremors. Table 2 (Weiner and Lang, 1989) indicates factors which enhance physiologic tremor:

Table 2. Factors Accentuating Physiological Tremor

Mental State	**anger, anxiety, stress, fatigue, excitement**
Metabolic	**fever, thyrotoxicosis, pheochromocytoma, hypoglycemia**
Drugs	**β-adrenergic agonists, dopamine agonists, psychiatric drugs (e.g., tricyclics), anticonvulsants (e.g., sodium valproate), endocrine drugs (e.g., thyroxine), drugs used in neuroimaging (e.g., metrizamide)**
Toxins and toxic states	**e.g., mercury, lead, alcohol and benzodiazepine withdrawal**
Dietary	**methylxanthines (coffee, tea, cola), monosodium glutamate**

2) Mechanisms of pathological tremor

a. Resting tremor of Parkinson's disease

This tremor was originally described by Parkinson in 1817 and its characteristics have since been described in detail (Denny-Brown, 1968; Selby, 1968; Struppler, 1978; Findley, 1981). EMG recordings show rhythmic activity alternating in agonist-antagonist muscles, with the frequency varying between 3-7 Hz (Shahani and Young, 1976a; Findley et al., 1981) but most often in the 4-5 Hz range. Characteristically, Fourier analysis of Parkinson's rest tremor reveals a fundamental frequency and several associated harmonics.

Findley et al. (1981a) identified two separate peaks by spectral analysis that appears to be seen consistently with tremors of basal ganglia origin (Jancovic, 1988).

Resting tremor primarily involves the distal upper extremities and occasionally proximal upper limbs and lower extremities. The involvement of head and neck is rare. It is characteristically unilateral at onset and may sometimes remain so throughout. The tremor typically attenuates or disappears with initiation of movement and recurs after a few seconds of posturing (Findley and Gresty, 1984). The tremor is not localized to one muscle group and is usually diffuse. Its amplitude is variable and may be modulated by emotional stress and intellectual concentration (Rondot et al., 1978).

Although rest tremor is the most common manifestation, as the disease progresses, a postural component may be noted in some patients (Rondot et al., 1978). Some parkinsonian patients show evidence of a second, more rapid type of tremor in the 8-10 Hz range occurring during voluntary contraction of muscles, possibly due to an exaggeration of physiological tremor (Gurfinkel and Osovets, 1973; Lance, et al., 1963). There are other tremors similar to the resting tremor of PD. These include tremor induced by narcoleptics, manganese and carbon monoxide poisoning. Action tremor seen in Wilson's disease is also similar to that seen with Parkinson's disease.

a.1 Origin of Parkinson's tremor

James Parkinson (1817) observed the disappearance of tremor on the hemiplegic side of a patient with stroke and its recurrence after improvement of hemiparesis suggesting central mechanisms underlying the parkinsonian tremor. Ever since this observation, due to the results of other studies supporting the peripheral mechanisms, the origin of resting tremor has been disputed.

Central mechanisms

Early studies showed the persistence of resting tremor in procaine-deafferented muscles and it was concluded that tremor was not directly related to proprioceptive reflexes (Walsh, 1924). Further evidence for a central origin came from the observation of the similarity of firing frequency of thalamic and basal ganglia neurons with the frequency of Parkinson's tremor (Jasper and Bertrand, 1966; Albe-Fessard et al., 1966). In addition, tremor produced by ventromedial tegmental lesions in the monkey is not affected by deafferentation (Ohye et al., 1970; Lamarre and Joffray, 1979). Studies by Lee and Stein (1981) demonstrated that mechanical perturbations could reset the phase of essential tremor but not the resting tremor of Parkinson's disease suggesting that a central oscillator rather than an unstable peripheral reflex loop may be responsible for resting tremor. Recent analysis of resting tremor suggests that it originates as a consequence of oscillation of signals within an internal feedback loop between the spinal segments and motor cortex (Teravainen and Caln, 1980).

The administration of dopamine, by way of its precursor L- dopa, may ameliorate and occasionally stop the tremor. Destruction of the pallidofugal fibres (Meyers, 1940) and even more specific, the ventral intermedius nucleus of thalamus (VIM) can also stop parkinsonian tremor (Narabayashi and Ohye, 1978). Tremor- related neuronal activities are seen specifically within the VIM. When tremor is stopped voluntarily or by passive manipulation, the rhythmic bursts in VIM disappear and start to reappear when tremor starts again (Narabayashi, 1986). A surgical lesion of 3-4 mm in diameter in VIM area results in immediate and almost complete disappearance of tremor (Narabayashi and Ohye, 1980). Apart from being a somatosensory nucleus, VIM is also considered to receive proprioceptive input from muscle and joints (Narabayashi, 1986). Narabayashi (1986),

argued that VIM is the pacemaker for tremor activity, but this postulate is not universally accepted. The inherent oscillatory properties of the thalamic cells make them behave as an intrinsic oscillator similar to inferior olive cells (Llinas and Jahnsen, 1982). Partial deafferentation of these cells, for example following damage to the dentate nucleus (Carrea and Mettler, 1947; Goldberger and Growdon, 1973; Lamarre and Dumont, 1972) can initiate this oscillatory behaviour and thalamic cells start to fire at about 6 Hz, similar to the frequency of parkinsonian tremor.

Peripheral mechanisms

The involvement of peripheral mechanisms in tremor at first sight seems difficult to support. However, some studies have indicated that dorsal root section does not abolish parkinsonian tremor but modifies its frequency and amplitude (Foerster, 1911 and 1936; Pollock and Davis, 1930). Recently Rack and Ross (1986) applied alternating flexion and extension to the limbs of Parkinson's patients and suggested the hypothesis that a self sustaining oscillation of a peripheral reflex loop analogous to clonus is primarily related to parkinsonian tremor. Microneurographic recordings of Ia fibers in parkinsonian patients did not reveal an abnormal pattern (Hagbarth et al., 1975), but other studies showed increases in tremor amplitude elicited by vibratory activation of muscle spindles and a resetting of tremor rhythm by supramaximal stimulation of a mixed nerve (Rondot and Bathien, 1976 and 1978; Rondot et al., 1978) suggesting an oscillatory spinal reflex mechanism. Recently Rack and Ross (1986) applied alternating flexion and extension to the limbs of Parkinson's patients. In some patients this entrained the resting tremor. The EMG profile was indistinguishable from a reflex response.

Neurochemical basis of Parkinson's tremor

The rest tremor of Parkinson's disease may be due to dopamine deficiency (Ehringer and Hornykiewicz, 1960; Bernheimer et al., 1973; Lloyd et al., 1975; Price et al., 1978). However, changes in other neurotransmitters such as noradrenaline, 5-HT, and GABA , various peptides and enkephalin receptors may also be responsible (Studler et al., 1982; Jenner and Marsden, 1984). Bernheimer et al.(1973) reported that the severity of tremor parallels the decrease of dopamine in the pallidum and to some degree decrease of dopamine and homovanilic acid (HVA) in the putamen. This has been disputed by Fahn et al. (1971). McGeeer et al. (1961) and Barbeau (1962) suggested that disruption of the normal dopaminergic-cholinergic balance is responsible for Parkinson's tremor. This was supported later by pharmacological manipulation of striatum in cat with cholinergic compounds to produce tremor (Conner, 1966; Lalley et al., 1970; Baker et al., 1976). So far, this mechanism appears to be the most accepted theory.

b. Essential tremor (ET)

This tremor has been defined as a benign, monosymptomatic disorder generally characterised by the presence of a postural and kinetic tremor seen particularly in the upper extremities but it may involve lower extremities, head or trunk or voice (Weiner and Lang, 1989). It usually occurs in the absence of any other neurological sign. It may be an autosomal dominant hereditary disorder (Larsson and Sjogren, 1960; Critchley, 1972) and in such instances is called familial tremor. When occurring sporadically, it is called benign essential tremor and when diagnosed after the age 65 without a familial presence, it is called senile tremor (Weiner and Lang, 1989).

Age of onset is usually late adolescence or young adulthood (Weiner and lang, 1989)

specially in sporadic cases (Elsasser, 1941). The majority of hereditary cases start after the age 50 (Larsson and Sjogren, 1960). The onset is usually insidious. Although usually tolerable, at times it interferes with eating, drinking, writing and other daily activities and it may be a source of embarrassment to the patient. It is often unilateral initially and gradually becomes bilateral with one side predominating. Essential tremor is mostly a slowly progressive disease with gradual involvement of different muscle groups, although it may remain confined to one part of the musculature.

The tremor frequency varies from 4-12 Hz and tends to slow with age (Marshall, 1962; Elbe, 1986). However, this may be related to the disease process rather than age per se. The amplitude is also variable and it is influenced by factors affecting physiological tremor (Weiner and Lang, 1989). Contrary to Parkinson's tremor, mental calculation does not increase the amplitude of essential tremor and may even attenuate it. It is usually attenuated during movement but may be increased in gain during or at the termination of movement (Findley et al., 1984) and also with emotion and fatigue (Rondot et al., 1978). Sudden, spontaneous, wide fluctuations in amplitude seen in parkinsonian rest tremor are not characteristic of essential tremor (Findley and Salisachs, 1984). There are occasional reports of the presence of resting tremor in this condition (Critchley, 1949; Koller, 1984a).

b.1 Pathophysiology of essential tremor

Virtually nothing is known of CNS mechanisms which may account for essential tremor. Neuropathological studies have so far failed to demonstrate anatomical CNS abnormalities to account for the tremor (Young, 1986). There have been some discussion about oscillatory loops within the CNS, namely olivo-cerebello-rubral or other pathways. Little

attention has been directed towards peripheral mechanisms. There have been no reports on the effect of deafferentation in patients with essential tremor (Rothwell et al., 1986). Elbe (1986) using auto and cross-spectral analysis, distinguished two components of essential tremor and concluded that both a central oscillator system and peripheral reflex mechanisms were involved. Lee and Stein (1981) reported that large mechanical perturbations of a tremulous limb can more easily reset the phase of an ongoing ET than PD rest tremor, suggesting a peripheral mechanism for ET.

In summary, it seems unlikely that any one of the central or peripheral systems could completely explain the underlying mechanisms for ET. Further quantitative tremor analysis is required to clarify this issue (Freund et al., 1986).

c. Cerebellar tremor

Cerebellar disorders are often associated with intention tremor. This is most clearly seen in the terminal portion of a movement as slow 2-3 Hz, large-amplitude oscillations of the limb (Shahani and Young, 1978). Postural tremors may show similar features, but they have a faster frequency and usually occur in one plane (Shahani and Young, 1976 a&b). Cerebellar tremor is most likely due to a lesion of the main neocerebellar outflow pathway, the dentate nucleus and its efferent fibers in the superior cerebellar peduncle (Holmes, 1904, 1917 and 1922) rather than to a lesion of the cerebellar cortex. Animal studies support this concept (Botterell and Fulton, 1938; Carrea and Mattler, 1947; Peterson et al., 1949; Ferrier and Turner, 1984).

Charcot (1868) described the action tremor of multiple sclerosis. Benedikt (1889) and Holmes (1904) suggested that lesions of the midbrain and superior cerebellar peduncle or red nucleus might cause action tremor. Ferrier and Turner (1894) had produced action

tremor in monkeys by lesioning the ipsilateral superior cerebellar peduncle. Furthermore, Sander (1898) had described intention tremor in a patient with a tumor of the ipsilateral cerebellar hemisphere, with destruction of the dentate nucleus and superior cerebellar peduncle. Holmes never observed rest tremor in his patients with cerebellar disease but mentioned a static (now referred to as postural) tremor which also involved head and trunk. Cooper (1960) mentioned relief of contralateral intention tremor by ventrolateral thalamotomy. Reflex mechanisms are rarely mentioned in relation to cerebellar tremor, though Prochazka and Trend (1988) showed that they could certainly play a role.

Treatment Modalities For Pathological Tremor

Several modalities of treatment have been used so far in the management of pathological tremor. A variety of medications, stereotactic surgery and limb weighting have had some degree of benefit. I will discuss the current available treatments for each type of tremor in the following paragraphs.

a. Parkinson's tremor (PT)

Clinical trials have usually not assessed the effect of drugs on parkinsonian tremor. On occasions, even when this was done, there were methodological problems in the assessments of tremor amplitude and frequency (Cleeves et al., 1987). A final conclusion on this issue is that of all the cardinal symptoms of Parkinson's disease, tremor responds least predictably to antiparkinsonian drugs (Boshes, 1976). Therefore, there remains an indication for stereotaxic thalamotomy in the management of this aspect of Parkinson's disease (Andrew, 1984).

a.1 Anticholinergics and Antihistamines

Anticholinergics have been used in the treatment of PD for over a century and are mildly effective in some patients (Weiner and Lang, 1989). They are not as effective for tremor as they are for akinesia and rigidity (England and Schwab 1959). Schwab and Leigh (1949) found a mean 25% improvement in 31 of 50 parkinsonian patients treated with the anticholinergic drug Parpanit. Doshay and Constable (1949) reported improvement in 65 of 117 patients with Parkinson's tremor by benzhexol (Artane). Side effects of these drugs include toxic delirium, hallucinations and depressed levels of consciousness which can be quite marked in the elderly. The peripheral nervous system complications are cycloplegia, constipation, urinary retention, and impaired sweating (Weiner and Lang, 1989). Antihistamines have been used in PD since the 1940's. Significant tremor reduction was seen in only 25% of patients (Effron and Denker, 1950). Although Anticholinergics and antihistamines retain a definite secondary place in the treatment of PD, their effect has been overshadowed by the introduction of L-dopa and dopamine agonists. However, to allow for a delay in the introduction of levodopa therapy, these drugs may be utilized in a subgroup of patients with a very slowly progressive disease, those with symptoms confined to one side of the body, and in patients with tremor as the main manifesting complaint.

a.2 Levodopa

In the late 1960's levodopa therapy for PD was introduced (Cotzias et al., 1967 and 1969) and it remains the mainstay of therapy in PD despite all the side effects arising from its chronic use.

Once absorbed, more than 95% of levodopa is decarboxylated to dopamine outside the CNS and is unable to cross the blood brain barrier except in small amounts of about 1%

(Weiner and Lang, 1989). The development of the peripheral aromatic amino acid decarboxylase inhibitors (PDI), carbidopa and benserazide used in combination with levodopa allows for a reduction of the oral levodopa required to achieve significant CNS levels. This approach also reduces the gastrointestinal side effects of this agent (Agnoli, 1974).

Again for unknown reasons tremor is the least responsive component of this motor disorder to levodopa therapy. Nor is it known why some PD patients present predominantly with tremor whereas others show rigidity and akinesia as their main symptoms (Findley, 1988). Overall improvement in tremor using levodopa alone or in combination with a PDI has been between 40% and 60% (Keenan, 1970; Rinne et al, 1972; Agnoli et al., 1974; Martinez Lage et al., 1974; Miller and Wiener, 1974; Ohmoto and Kiskisawa, 1975). The individual response to levodopa is quite variable. Interestingly, tremor can actually be aggravated by low doses of levodopa, usually at the beginning and end of the period of the action of each dose (Findley, 1988).

Parkinson's patients treated with levodopa may experience several side effects such as anorexia, nausea, vomiting, cardiac arrhythmias or hypotension. The most common CNS side effects of levodopa are dyskinesias (Weiner and Lang, 1989). Some patients develop dystonia. The second important central side effects are fluctuating levels of motor performance such as on-off phenomenon (Caln et al., 1974; Fahn, 1974). The third major complication of chronic levodopa therapy is altered behavioral states. These vary from disturbed sleep patterns and nonthreatening visual hallucinations to the less common paranoid psychotic states (Weiner and Lang, 1989). It is also worthwhile mentioning that levodopa has a tendency to lose its efficacy over time (Weiner and Lang, 1989).

a.3 Dopamine receptor agonists

These drugs directly stimulate the dopamine receptors and have the advantage of avoiding levodopa-induced side effects. They are mainly ergot derivatives such as lergotrile, bromocriptine, pergolide, lisuride and mesulergine. Non-ergot derivatives include ciladopa, 4-propyl-9-hydroxynophthoxazine (PHNO) and abeorphine. From the first group, lergotrile was not distributed because it caused hepatitis. Mesulergine and ciladopa were withdrawn because they induced tumors in rodents (Weiner and Lang, 1989). Bromocriptine affects both the presynaptic and postsynaptic dopaminergic systems (Lieberman et al., 1976; Parkes et al., 1976; Lieberman et al., 1980). Stimulation of the postsynaptic receptors in the striatum is believed to account for the efficacy of bromocriptine in PD (Weiner and lang, 1989). This drug is particularly helpful in patients experiencing long-term side effects of levodopa. The proportion of treated patients with improvement in short-term studies ranges from 25% to 100%. The long-term advantage of bromocriptine is not clear and some results have been disappointing (Lees et al., 1978; Lieberman et al., 1980). In the latter study, from the 21 patients who originally responded to bromocriptine, only 5 retained their response after two years. The most common problems with bromocriptine are hypotension, hallucinations, aggravation of dyskinesias, and occasional erythromelalgia-like skin eruption. Low-dose bromocriptine therapy in PD introduced by Techenynne et al. (1982), has not gained universal support (Calne et al., 1984; Weiner and Lang, 1989). Pergolide mesylate is more potent than bromocriptine and may be a good choice especially for motor fluctuations of PD (Lieberman et al., 1981 and 1982). Lisuride appears to act centrally as a serotonin agonist. Its side effects are similar to those of levodopa and bromocriptine (Lieberman et al., 1981; Parkes et al., 1981). The non-ergot dopamine agonists are in the stage of clinical testing and conclusive reports are yet to come. Other

medications such as amantadine working either by dopamine release from synaptic terminals or by interfering with reuptake of dopamine from synaptic cleft have relatively short term effectiveness. Amphetamines and especially of recent interest, MAO-B selective inhibitors such as Deprenyl, are in clinical usage, but little information is available regarding their effect on tremor. None of these studies has quantitatively assessed the effect of these medications on tremor.

b. Essential tremor

Many patients with ET do not require drug treatment. Sedatives, tranquilizers and antiparkinson drugs have been shown to be ineffective (Thompson et al., 1984; Barbeau, 1969; Lapresle et al.,1974).

b.1 Alcohol

Ethyl alcohol (45 to 80 ml vodka ingested orally) markedly reduces essential tremor amplitude in 10 to 15 minutes (Critchley 1949; Growdon et al., 1975). Koller and Biary (1984) found a dramatic tremor suppression by small amount of ethanol in some patients. However, there are patients with a family history of tremor or with sporadic ET who have no response to ethanol. The risk of tolerance and addiction makes the use of alcohol as a regular therapy inadvisable.

b.2 β- Blockers

It was first noticed by Dr. Gerald F. Winkler, that one of his patient's tremor was remarkably improved during treatment with propranolol for paroxysmal atrial tachycardia. The efficacy of propranolol on essential tremor was subsequently confirmed in numerous studies (Winkler & Young, 1974a&b; Murray, 1972; Teravainen et al, 1976). A single dose of propranolol can produce up to 50% reduction in tremor 90 minutes after ingestion and

the effect may last up to eight hours (Calzetti et al., 1983). Propranolol is in fact the most beneficial beta blocker for the treatment of ET. It is effective in more than 70% of patients (Weiner& Lang, 1989). However it has side effects such as depression, insomnia, and hallucinations (Greenblatt et al. 1974).

b.3 Primidone

This drug has been used as an anticonvulsant for many years and is effective in reducing ET with an efficacy similar to propranolol (Findley et al., 1985). A single oral dose of primidone (250 mg) can decrease tremor by up to 60% for 1-7 hours following ingestion (Koller and Royse, 1986). The anti-tremor mechanism of primidone is not known.

b.4 α-Blockers

The use of alpha adrenergic blockers such as Thymoxamine to reduce ET was introduced by Mai and Olsen (1981), but this has been criticized (Koller, 1986; Caccia, 1985). Miscellaneous drugs such as amantadine (antiviral agent), 5HTP (serotonin precursor), clozapine (weak dopamine receptor antagonist), Progabide (GABA agonist) and the antidepressant Trazadone have also been tested but the results are preliminary.

In patients who do not respond to medical management, thalamotomy with a selective lesion in the VL and posterior lateral and the subthalamic regions has been used (Guiot, 1960; Cooper, 1962). However, surgery is seldom recommended for this monosymptomatic condition due to the small but definite risk of motor or sensory complications.

Cerebellar tremor

To this date, the only therapy of value in cerebellar tremor has been the weighting of the limb to dampen severe intention tremor (Hewer et al., 1972). Recently, a series of investigations have examined the use of isoniazid in cerebellar tremor due to multiple

sclerosis. The initial report of its benefit (Sabra et al., 1982) has not been confirmed in subsequent studies (Hallet et al, 1984 and Koller, 1984b). Jankovic (1986) concluded that despite a subjective feeling of improvement in some patients, there was no objective functional improvement. Stereotactic thalamotomy has been used in severe disabling midbrain tremor, but even in the most successful cases significant dysfunction persisted (Lang and Weiner, 1989).

CHAPTER II

REDUCTION OF TREMOR BY FUNCTIONAL ELECTRICAL STIMULATION: I- METHODOLOGY AND RESULTS IN NORMAL SUBJECTS

Objectives of the study

In this study we explored the possibility of suppressing pathological tremors using closed-loop functional electrical stimulation (FES) to activate the tremorogenic muscles out-of-phase. A displacement signal arising from the tremor movements monitored with a transducer was filtered so as to be "tuned" to the tremor frequency at the wrist or elbow. The filtered signal was used to amplitude-modulate the electrical stimulation. An essential part of the design process was first to measure the open-loop frequency response characteristics of the forearm and hand to stimulation of the elbow and wrist flexors and extensors in a number of normal subjects. These data allowed us to identify closed-loop configurations which attenuated 2-5 Hz tremors substantially, while only minimally attenuating functional movements in the 0 - 1 Hz range. There was a fairly delicate balance between efficacy and the risk of instability. However designs were identified which offered enough tremor suppression and adequate immunity to muscle/load variations in order for the technique to be considered seriously for clinical application. As the methodology of this technique is based on the control system, first I will describe the basic theory of the feed back loop.

Introduction to the control theory approach utilised in this work

The task of a control system is to force the controlled variable (the "output", e.g. displacement), to follow variations in a command signal (the "input"). This is achieved by driving an actuator (e.g. muscle) with a signal which is proportional to the difference or "error" between the output and input. The greater the error, the more the actuator works to counteract it. The system operates automatically by virtue of a closed loop structure: a sensor transduces the output signal and feeds it back to a comparator, where it is subtracted from the input signal to yield the error signal, which in turn drives the actuator to modify the output.

The first three things one usually asks about a control system are 1) what is its gain: how much does it amplify the command signal? 2) how well does it resist perturbations imposed from the outside? 3) is it stable, marginally stable, or unstable? To answer these questions, one must analyze the loop by characterising the responsiveness of each of its main elements: the actuator, the sensor, and the comparator. Each element receives its input from the element behind it in the loop and its output becomes the input for the next element in line (e.g. the comparator receives its input from the sensor and sends its output to the actuator). To characterise each element, we need to describe how its output varies with respect to its input. The main purpose of systems analysis is to identify so-called "transfer functions", that is to say mathematical functions which, when multiplied by the input signal, will predict the output signal. The simplest such function is a constant. In this case the output of the element is simply proportional to the input. However, in many cases elements respond dynamically, that is their output is not only

proportional to the input, but also to its rate of change (velocity), and perhaps to higher derivatives as well (acceleration, etc.).

Before we discuss the tools used to analyze dynamic systems, let us develop the transfer function of a simple control loop with proportional elements. In Fig. 1 the transfer functions of the actuator and sensor are the constants G and H respectively.

Now output = G x error.

but error = (input - H x output)

so output = G (input - H x output)

i.e. output + GH x output = G x input

i.e. output (1 + GH) = G x input

rearranging, $$\text{output} = \frac{G}{1 + GH} \text{ input}$$

The transfer function, or gain of this simple closed loop is

$$TF = \frac{G}{1 + GH} \quad \text{.....(1)}$$

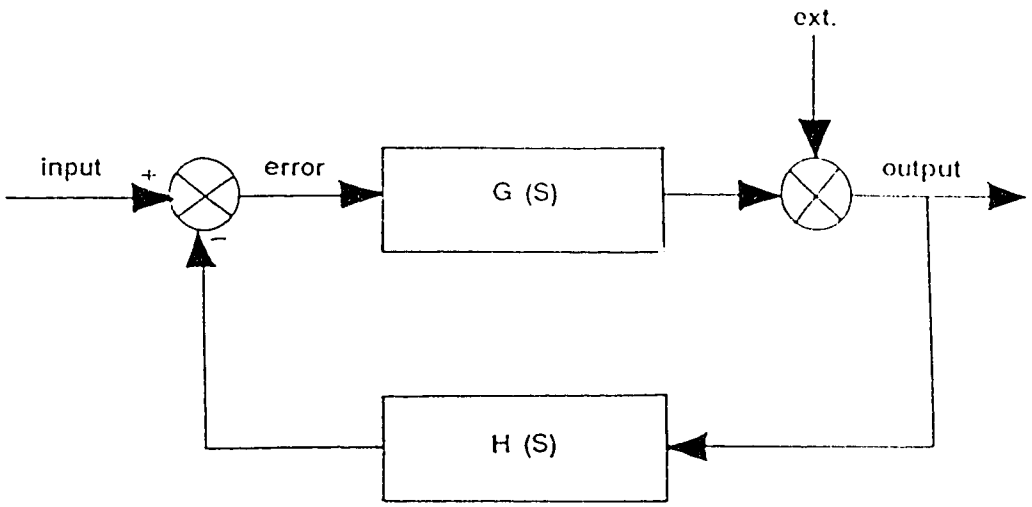

Figure 1. Schematic of the general organization of a feedback control loop.

Thus if G = 10 and H = 1, the gain is 10/11. How well does this loop resist external perturbations? Consider an external perturbation ext added to the output of the actuator. For simplicity, let us assume that the input is zero (the command is to hold the output at zero level). If the loop were inoperative, ext would be the final value of the output. However, with the loop in action,

$$\text{error} = (0 - H \times \text{output})$$

and

$$\text{output} - \underline{\text{ext}} = (G \times \text{error})$$

therefore

$$\text{output} - \underline{\text{ext}} = -GH \times \text{output}$$

so

$$\text{output} = \frac{\underline{\text{ext}}}{1+GH} \quad \text{.....(2)}$$

So with the loop operating, the final value of the output is only 1/(1+GH) of that in the absence of feedback control. Thus for G = 10 and H = 1, the effect of the external perturbation is reduced to 1/11 of that without feedback. The larger the term GH (referred to as the open loop gain), the greater the resistance to external perturbations.

In the system described in this thesis, the patient's tremor may be viewed as the external perturbation. A feedback loop is set up to stimulate the patient's own muscles (the actuator) to resist the perturbation. A loop gain GH of 10 would thus usefully attenuate the tremor to 1/11 of its amplitude in the absence of the loop.

Generally the elements of a feedback loop have dynamic response characteristics; the output is related to the input by a differential equation such as:

$$\text{output} = A\,(\text{input}) + B\,\frac{d(\text{input})}{dt} + C\,\frac{d^2(\text{input})}{dt^2} + \text{etc.} \quad \ldots(3)$$

This is not in the desired form of a discrete transfer function which can be multiplied by the input to give the output. However, the desired form can be achieved if all the variables and differential terms in the equation are transformed into Laplace variables. Equation 3 then becomes:

$$\text{output} = A\,(\text{input}) + B\,s\,(\text{input}) + C\,s^2\,(\text{input}) + \text{etc.}$$

$$= \text{input}\,(A + Bs + Cs^2 + \text{etc})$$

Each element in the loop can now be described by algebraic equations of this kind, replacing the constants G and H in equations 1 and 2 above by the functions G(s) and H(s).

As stated above, in the technique to be described, the subject's movements, both voluntary and involuntary, were viewed as the external perturbation. The aim was to set up an external artificial loop which would stimulate the patient's own muscles to impede the

involuntary tremorous components of movement, but not the slow, intended components. This was achieved by ensuring that the open loop gain G(S)H(S) was large in the frequency range 2.5-5 Hz (tremor range), and small in the range 0-2.5 Hz (voluntary movement range). Now G(s) was in fact the transfer function of the electrically stimulated muscles moving the hand and forearm. The first task therefore was empirically to establish this relationship in a number of subjects for both wrist and elbow. The next step was to design feedback functions H(s) which would give the overall open loop transfer function G(s)H(s) the desired bandpass property (low from 0-2.5 Hz, high above 2.5 Hz). Note that in this system, the input is fixed to zero. In other words the intention is that tremor is held to zero quite effectively whereas voluntary movements are held to zero ineffectively.

Methodology of The Experiments

Frequency response characterisation of load-moving muscle

Experimental approach The first step in the procedure was to establish the frequency response characteristics of the muscles moving the hand and the forearm. The responses to modulated electrical stimulation of antagonist groups of flexor and extensor muscles acting about the wrist and elbow were analyzed in 7 normal subjects, using methods described below (Jacks et al., 1988). Subjects gave their written consent to the experiments, in accordance with the requirements of the University of Alberta Human Ethics Committee and the Declaration of Helsinki. For wrist movements, the right forearm was strapped to a comfortable horizontal support in a half supinated position. The hand was strapped to an extension of the support, which could pivot freely in the horizontal plane about a fulcrum located under the wrist joint. For the elbow, the arm was stabilized and the forearm was free to pivot on a light horizontal support (Fig. 2). In both cases displacement was monitored with a low-noise optical transducer. Surface electrodes (typically 2 x 3 cm) were used as cathodes to activate the triceps and biceps brachii selectively. These were either pre-gelled adhesive electrodes (Chattanooga Corp.) or moistened pads pressed onto the skin by thin stainless-steel plates. For forearm muscle stimulation the indifferent electrode (anode) consisted of a moistened sponge strip wrapped around the wrist. For arm muscles the indifferent was a large moistened pad attached to the right leg anteriorly over the proximal end of the tibia. (FIG. 2)

Initial isometric adjustments The following setting-up procedures were performed with

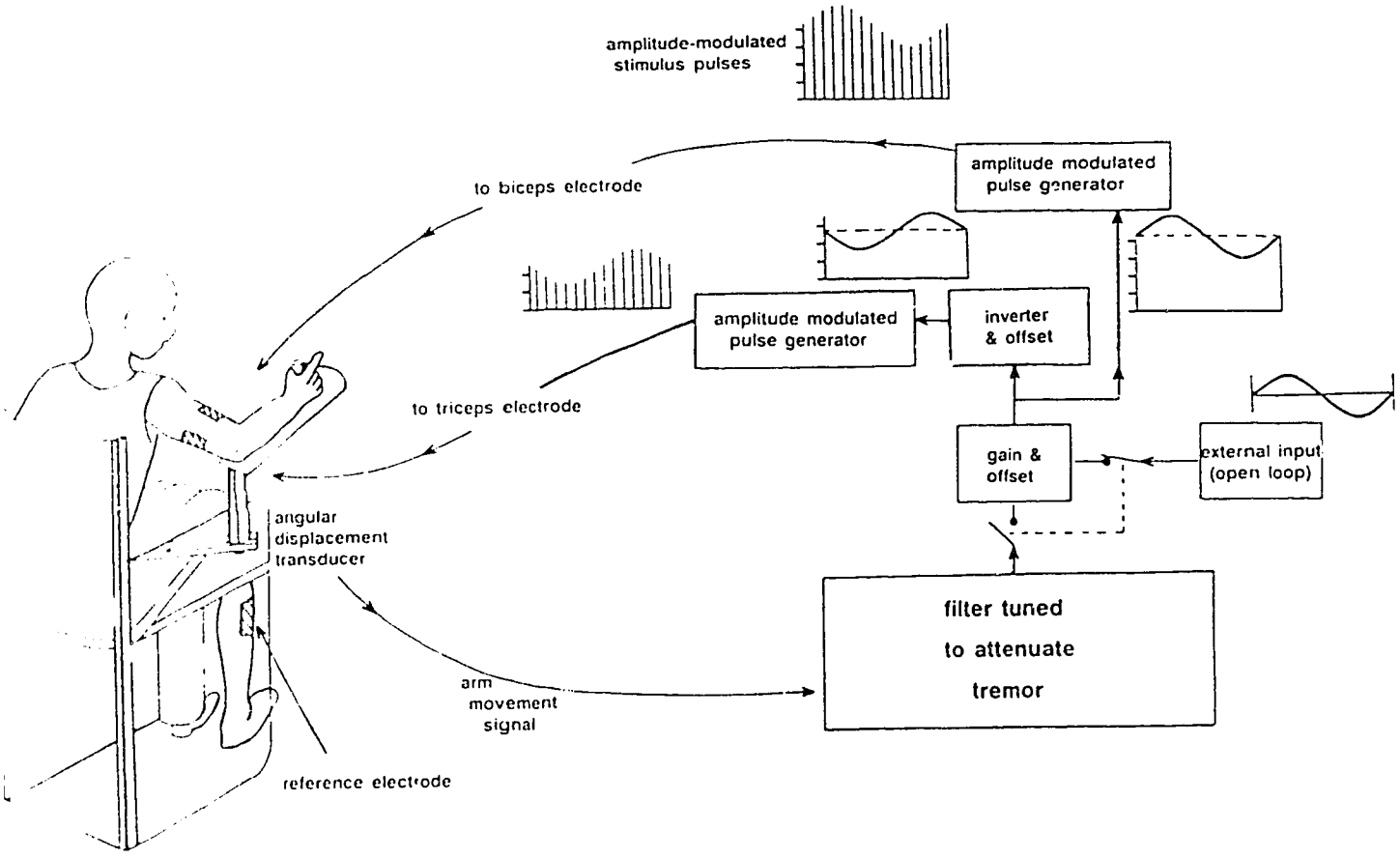

Figure 2. Experimental set-up for forearm movements. Armrest pivots horizontally, displacement signalled by a transducer. Triceps and biceps brachii are selectively stimulated with surface electrodes. Stimulus pulse trains are interleaved, and amplitude-modulated so that as flexor stimulation increases, extensor stimulation decreases. Control is either open-loop (external input: for characterization of frequency response of muscle/load) or closed-loop (controlled by filtered movement signal). Filter is optimally designed so that electrical stimulation is out-of-phase with tremor cycle, opposing and attenuating the tremor, while minimally affecting slower, useful movements.

either flexor stimulation alone or extensor stimulation alone. A rigid force transducer was attached to a wristlet to measure elbow torque (Jacks et al., 1988) or to a bar at the metacarpophalangeal joint to measure wrist torque. The amplitude of the 30/s train of 100 μs stimulus pulses was adjusted in the range 20-100 mA to produce a steady "offset" contraction corresponding to 2.5%, 5% or 10% of maximal voluntary torque. The pulse train was now sinusoidally amplitude-modulated at 1 Hz to produce a sinusoidally-varying torque with a depth of modulation of about $\pm$ 2.5% of maximal voluntary torque, centred about the offset torque. The reason for choosing 2.5% was to ensure that one or the other of the muscles would be actively contracting throughout the tremor cycles, thus ensuring continuous control.

When these adjustments had been made for the flexors and extensors separately, the force transducer was removed, allowing free movement of the extremity. Both channels of stimulation were switched on. Because the flexor and extensor pulse trains were interleaved, there was no interaction between the electric fields of individual pulses, ensuring independence of flexor and extensor activation. Modulation of the two channels was reciprocal (i.e. as flexor stimulation increased, extensor stimulation decreased). Because the stimulus parameters had been adjusted to produce equal flexor and extensor offset torques, the resulting movement was a sinusoid centred around the neutral position (90° for elbow, 180° for wrist). In practice, a slight deviation of the centre position occurred when the two channels were first switched on together. This was due to a slight mismatch between flexor and extensor offset torques, which were readily corrected with small adjustments of the stimulus offset parameters.

Frequency response analysis The subjects' wrist or elbow movements and concomitant

stimulator command signals were recorded on cassette tape (TEAC R61 instrumentation recorder) and some trials were video-taped. Movement responses to sinusoids of constant modulation depth and frequencies ranging from 0.5 Hz to 10 Hz were logged. Subsequently, selected segments of the analogue data were digitised using a Cambridge Electronic Design (CED) 1401 laboratory interface linked to an Olivetti M28 microcomputer. The data were digitised, displayed and printed (Hewlett Packard Laserprinter) with the use of CED "Massavg" software. This allowed us to align individual tremor cycles and collect them together into an average, typically of 10 cycles. In some cases power spectral analysis was performed with CED "Waterfal" software. The amplitude and phase of the movement response was plotted against modulation frequency.

Filter design

With the help of control systems software ("Alcon": see Wood, 1988) linear transfer functions were developed which gave good fits to the frequency response curves for elbow and wrist. Next, treating these transfer functions as part of a feedback loop, a compensating filter was designed and tuned to maximize the open loop gain in the range 2-5 Hz while minimising net phase lag in the 0 - 10 Hz range. The aim was for the closed loop (which includes the muscle/load and the filter) stably to resist 2-5 Hz movements, while responding minimally to slow voluntary movements or high-frequency transducer noise. The filter was realised with an array of linear operational amplifiers built into a purpose-designed prototyping device (see Appendix). Easy access to passive components on the front panel of the device allowed us to fine-tune the filter, and to experiment with additions and deletions of stages.

Closed-loop experiments The system was first evaluated in normal subjects performing

voluntary tasks ranging from slow, goal-directed movements to rapid tremor-like ones. In some experiments a video recording of a moving-bar target was replayed to the subject, the surface of the video screen being just beyond the subject's fingertips. The attenuation of the amplitude of these various classes of movement during short periods of closed loop stimulation of unexpected onset and duration was measured. After some experience with the system a number of trials were conducted on patients with essential tremor, parkinsonian tremor and cerebellar tremor; these are described in chapter III.

Results

Open loop trials

Linear transfer function of the wrist

As stated, the technique relies on accurately controlled electrical stimulation of the tremorogenic muscles, and as such, the first requirement was an accurate description of the way the load-moving muscles respond to smoothly modulated trains of electrical stimulus pulses. Fig. 3 shows the frequency response characteristics of sinusoidal wrist flexion-extension movements in six normal subjects evoked by modulated electrical stimulation as described in the Methods. Separate symbols identify the amplitude and phase of the responses of each subject to command signal frequencies ranging from 1 to 12 Hz. The response amplitudes are expressed in decibels in relation to the response amplitude at 1 Hz. Phase is expressed in relation to the sinusoidal modulating signal. These trials were performed with 5% background (offset) co-contractions (i.e. the sinusoidal movements were elicited by modulating flexor and extensor stimulation about tonic levels which separately produced torques 5% of maximal voluntary torque). The

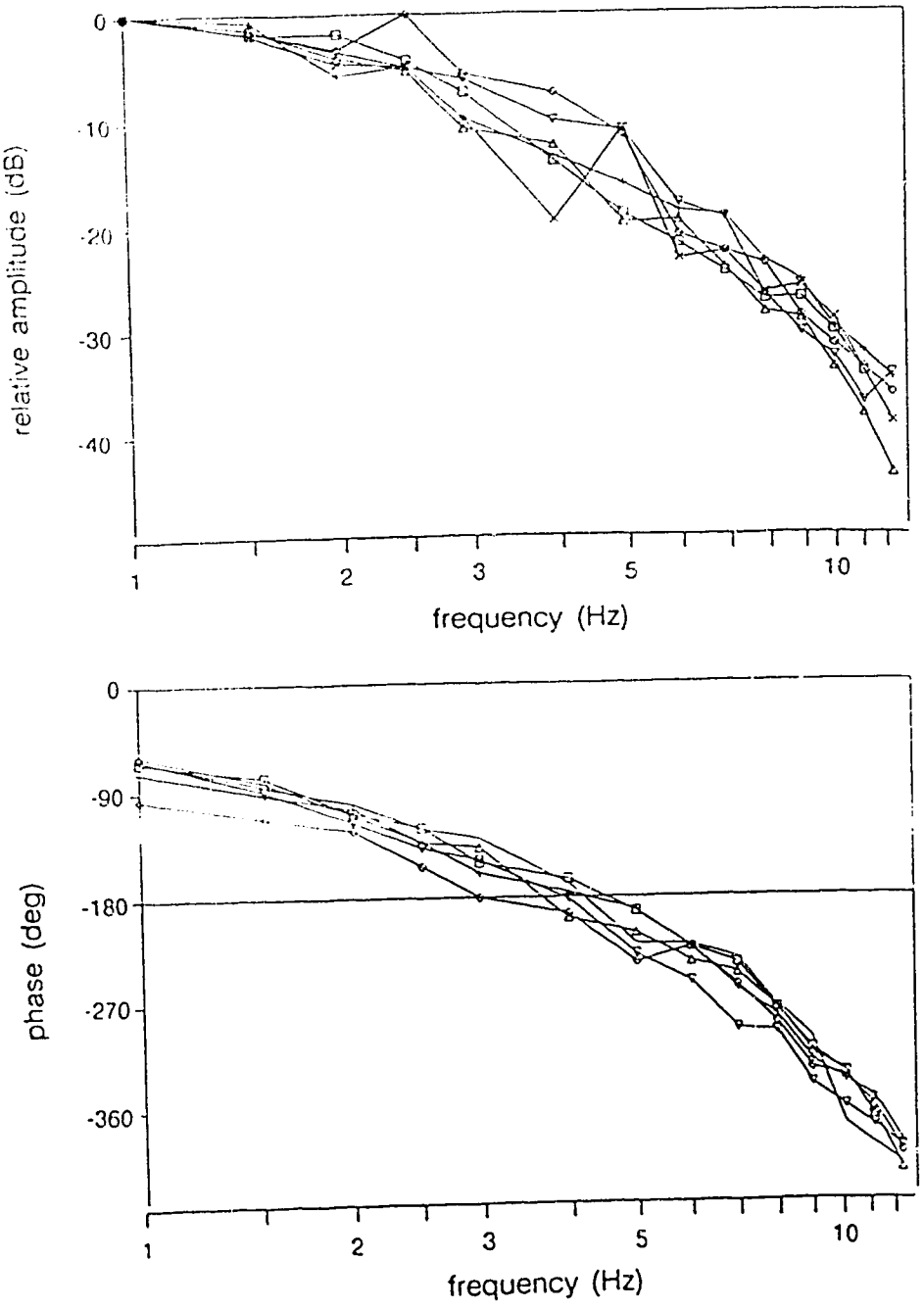

Figure 3. Frequency response characteristics of wrist flexion-extension movements in 6 normal subjects evoked by modulated electrical stimulation. Response amplitudes expressed in dB relative to the response amplitude at 1 Hz. Phase relative to that of the sinusoidal modulating signal. Note low-pass properties, with 3 dB roll-off at about 2 Hz and 180° phase lag at 4 Hz.

response characteristics were similar across subjects, showing low-pass properties, with 3 dB attenuation at about 2 Hz. f_{180}, the frequency at which the phase lag was 180°, lay between 3 and 4 Hz. As will be seen later, the f_{180} parameter has a special significance for closed-loop control, in that if the gain around the loop exceeds 1 at this frequency, positive feedback occurs, and the control system exhibits instability, manifested by oscillation. (FIG. 3)

Next we fitted a linear transfer function to the averaged wrist data of Fig. 3. This was done with a control systems software package, Alcon, which computes and displays Bode plots of functions comprising up to 24 terms. In a large number of trial-and-error iterations a transfer function was developed whose amplitude and phase characteristics are plotted in Fig. 4, and which is described in the frequency domain by the Laplace equation:

$$\frac{K}{(s + 8.5)\,(s + 55)^5} \qquad .....(1)$$

where K is a constant and s is the Laplace operator. (FIG. 4)

At the outset it was not clear whether there would be a unique solution to this curve-fitting problem or not. In the event, a number of transfer functions were found with differing configurations of poles and zeros which gave good fits both to the amplitude and phase data. Furthermore, when these were used in combination with filters in the analysis of closed loop stability to be described below, they led to similar conclusions regarding

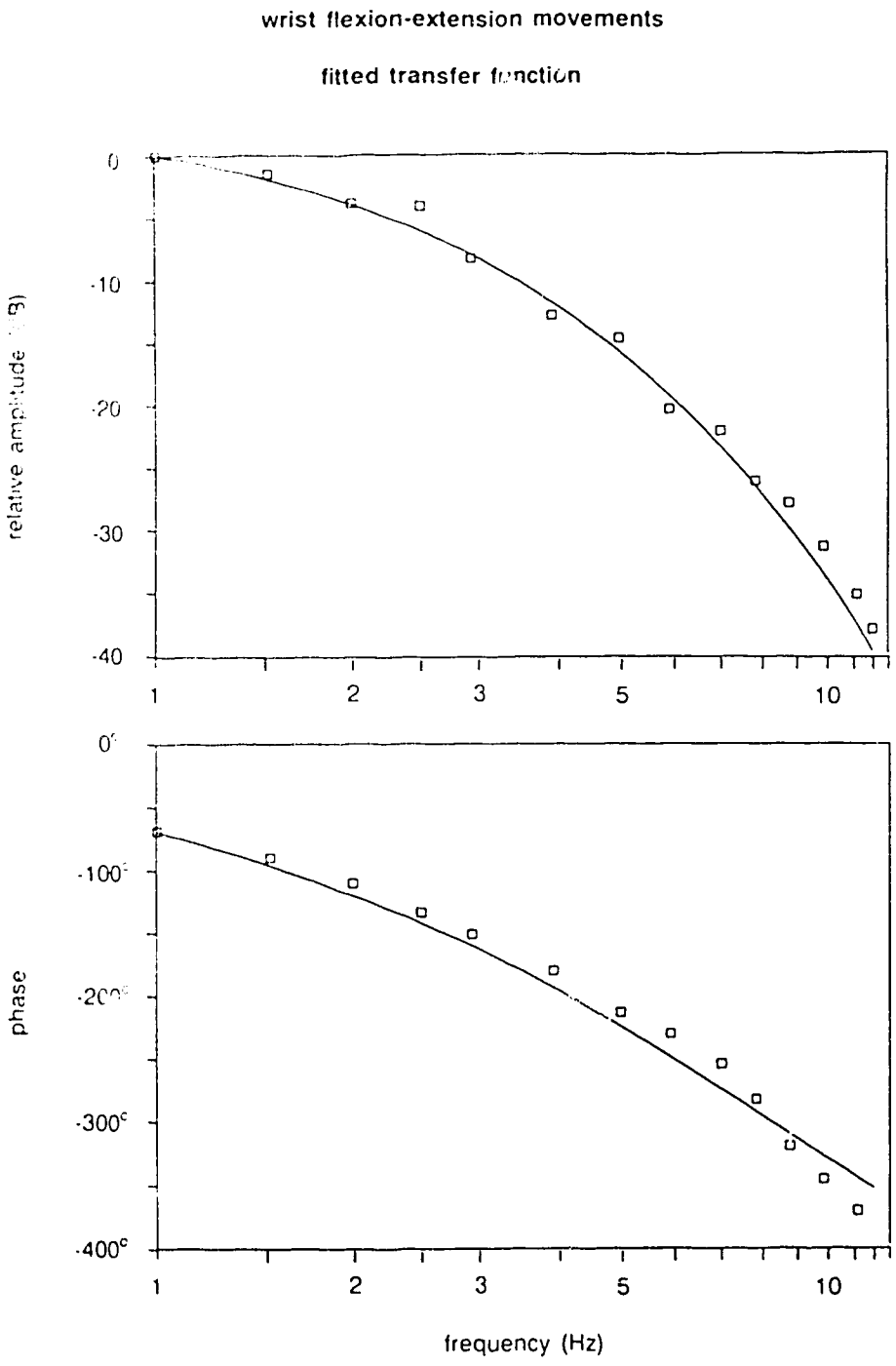

Figure 4. Averaged wrist data of Fig. 3 (squares) with fitted transfer characteristic described in text.

parameters such as f_{180} and gain margin. Thus there is nothing absolute about the transfer functions derived and no attempt was made to a mathematically rigorous optimisation of them. Nonetheless the functions derived in this way appear to be sufficiently representative and accurate for the present application. (FIG. 5)

Linear transfer function of the elbow

A similar procedure was followed for movements about the elbow. Figure 5 shows the averaged data from 6 subjects. In this case we measured the frequency response characteristics for background (offset) torques of 2.5% and 5% of maximal voluntary torque respectively. The fitted transfer function represented in the figure is the following:

$$\frac{K}{(s+12)^4} \quad \ldots\ldots (2)$$

Filter design for closed loop stimulation

Wrist

The next task was to develop filters which, when combined with the above model transfer functions, would result in frequency response curves with sharp peaks at tremor frequencies of 2 - 4 Hz, together with phase shifts consistent with stable closed-loop operation. In the closed loop, the tremor may be viewed as an external perturbation which the loop resists and attenuates (by out-of-phase activation of the selfsame muscles producing the tremor). Intuitively, a notch filter tuned to the tremor frequency seemed the most logical design to try. Figure 6A shows the individual and combined characteristics

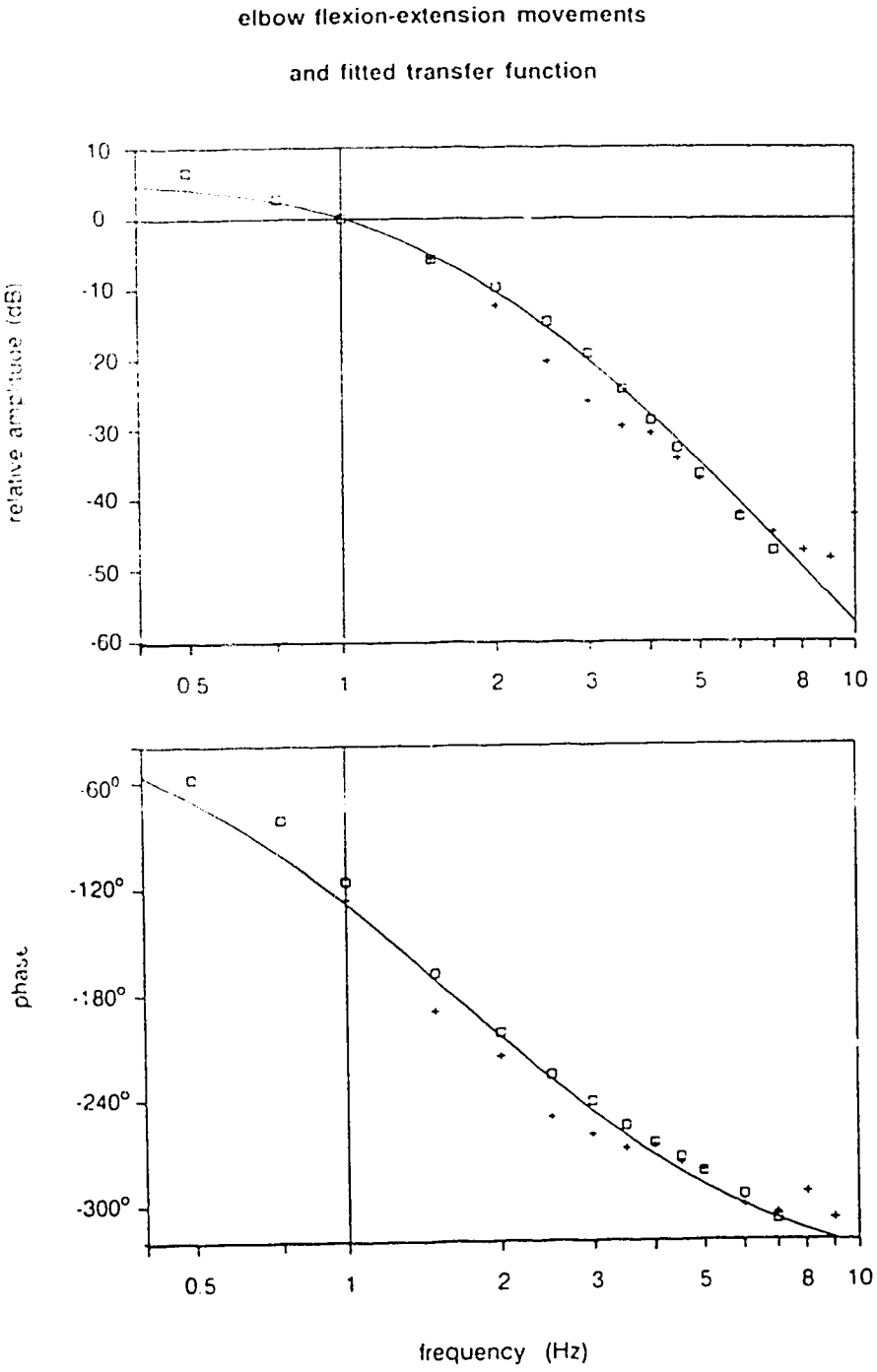

Figure 5. Averaged elbow characteristics with fitted transfer function. Squares: modulation about a 5% background co-contraction, crosses: modulation about a 2.5% background co-contraction.

of the wrist model (equation 1 above) and a 3 Hz notch filter, the transfer function of which was:

$$\frac{K}{(s + 0.5 + j20)^2 (s + 0.5 - j20)^2} \quad \ldots\ldots (3)$$

The amplitude characteristic of the combined (wrist + notch filter) function showed the desired peak at 3 Hz. The gain margin (the difference between peak amplitude and amplitude at f_{180}) was 23 dB. The significance of this is as follows. Instability occurs in a closed feedback loop when the gain around the loop exceeds 1 at f_{180}. In the example of the notch filter characteristic of Fig. 6A, if the amplitude (gain) at f_{180} were raised to 1 (0 dB) the peak amplitude at 3 Hz would rise to 23 dB (13 in absolute terms), i.e. instability would just occur when the gain at 3 Hz was 13 (the gain margin). Thus a loop gain of say 12 should in theory be attainable at 3 Hz without making the system oscillate at f_{180}. Now a negative feedback loop attenuates an external perturbing input by a factor of:

(1 + open loop gain)

(i.e. the response to the perturbation is reduced by this factor compared to the response in the absence of feedback). So with a gain of 12 permissible from a stability point of view, the use of this particular notch filter in the closed loop should in theory have resulted in a 13-fold attenuation of tremor. We implemented the filter with analogue circuitry, and set up a closed loop experiment of the type illustrated in Fig. 2 with a normal subject. Surprisingly, although the subject found it more difficult to produce 3 Hz

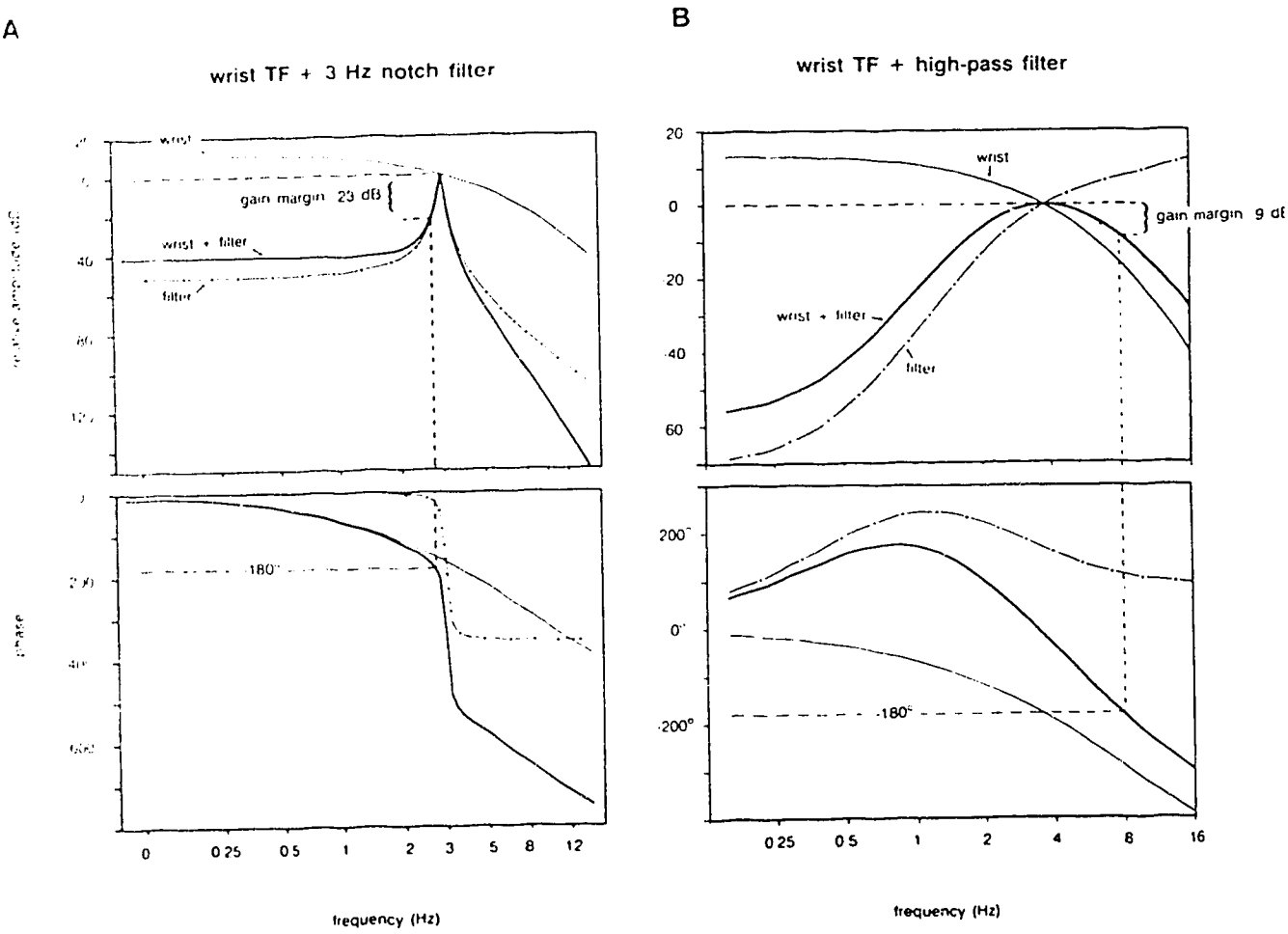

Figure 6. Two filters (A: notch, B: high-pass) designed to cause maximal attenuation of 3-4 Hz tremor, with minimal attenuation of 0.1-1.0 Hz "useful" movements. Thin lines: wrist model (Fig. 4); dash-dot: filter; thick lines: combined characteristics. Amplitudes normalised to 0 dB at peaks of combined characteristics. Relative amplitude at f_{180} (frequency at which net phase lag is 180°) is "gain margin", a measure of potential efficacy of loop in attenuating tremor. Paradoxically, though gain margin was greater in A, overall performance of system B was superior.

tremor-like movements, there were long-lasting after-oscillations which grossly interfered with voluntary movements of 0.5 to 1 Hz frequency content. Indeed any voluntary movements at all gave rise to such after-oscillations. With hindsight, the reason for this is fairly obvious: although the loop incorporating the notch filter does not become completely unstable until the gain at 3 Hz exceeds 13, it is grossly under-damped even at gains as low as 1 or 2. This was confirmed in step responses computed using the Alcon software and in root locus plots which revealed trajectories starting from close to the imaginary axis and slowly approaching it as gain increased. We tried mitigating this by shifting the starting positions of the notch filter poles away from the j-axis to $(s + 2 \pm j20)$, but this merely reduced the gain margin to about 10 dB, without sufficiently damping the system (FIG. 6).

A more satisfactory filter is shown in Fig. 6B. Although the combined wrist + filter transfer function had a less selective bandpass characteristic than the notch filter, and the gain margin for closed-loop operation was only 9 dB, this filter operated well, allowing gains of 2 to 2.5 to be used in patients (3 to 3.5-fold tremor attenuation), without noticeable after oscillations or attenuation of slow voluntary movements. The transfer function of this filter was:

$$\frac{(s + 3.3)^6 (s + 100)^2}{(s + 15)^6 (s + 300)^2}$$

In fact this was a truncated version of the following design, which gave a slightly better gain margin of 11 dB (4-fold tremor attenuation):

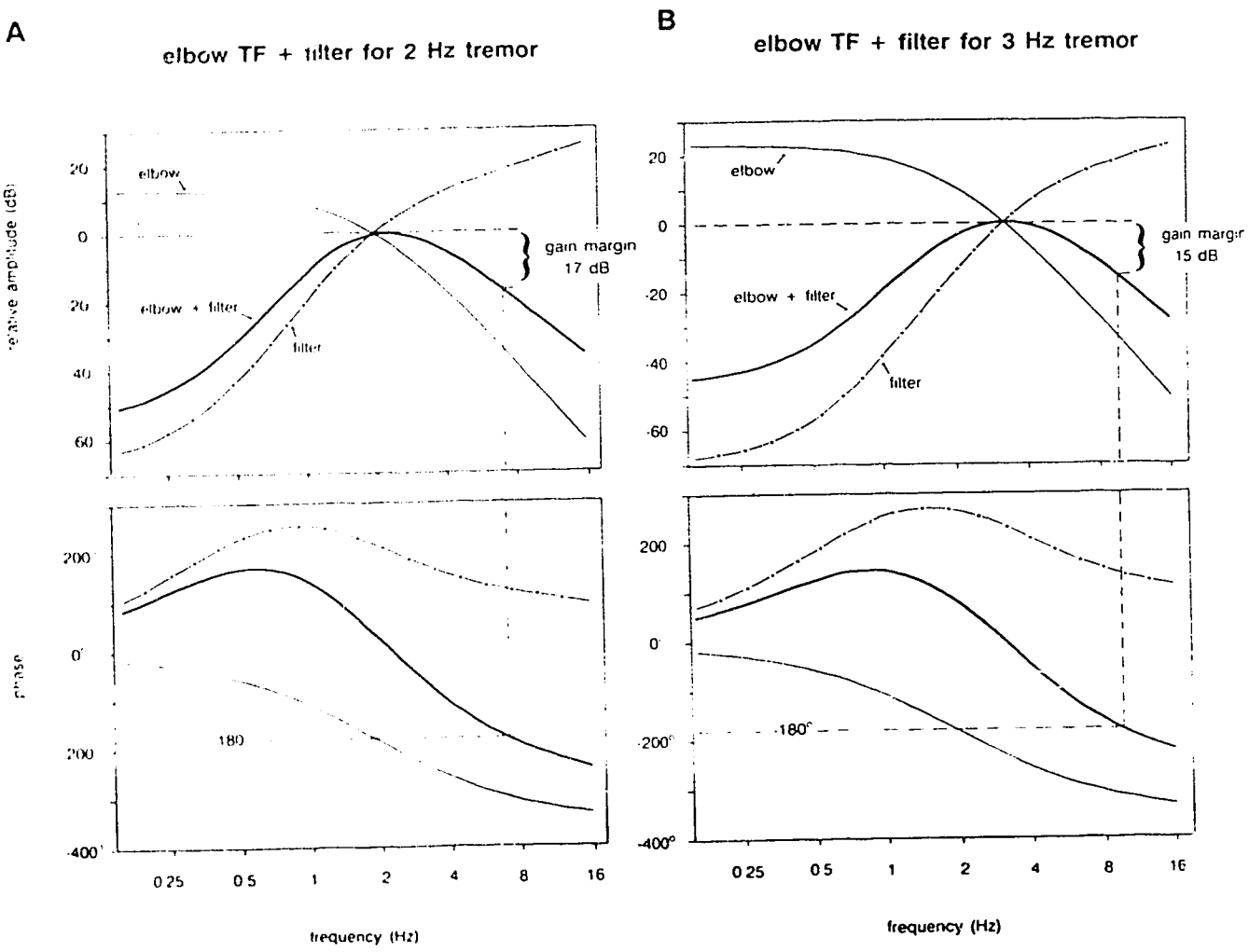

Figure 7. Filters designed to attenuate 2 Hz (A) and 3 Hz (B) tremor about the elbow. Thin lines: elbow model of Fig. 5; dash-dot: filter; thick lines: combined characteristics

$$\frac{(s + 3.3)^6 (s + 100)^4}{(s + 15)^6 (s + 300)^4}$$

However, in closed-loop trials on two normal subjects and two patients, this full version, though very effective at attenuating tremor, tended to produce large high-frequency transients of stimulation which were uncomfortable and at times even painful with the surface electrodes used. Furthermore, stability was less robust than with the truncated version, in that there was a tendency for high-frequency (10-12 Hz) oscillations to develop at certain wrist orientations. Pain is generally less of a problem with intramuscular stimulation, so this design might be suitable for systems based upon implanted electrodes (e.g. Marsolais & Kobetic, 1987; Stein et al., 1990) (FIG. 7).

Filter design for the elbow

Filters were also designed for attenuation of tremor about the elbow. The filters shown in Fig. 7B for 3 Hz tremor were first developed. The gain margin of 15 dB (corresponding to an absolute value of 5.6) would in theory allow a maximal tremor attenuation of 6.6:1, though in practice we found that instability tended to occur above gains of about 3. Again, this was a truncated version of an even more effective filter which offered a closed-loop gain margin of 25 dB, however in trials this had the same drawback of high-frequency transients as the optimal wrist filter. The transfer function describing the 3 Hz truncated design is:

$$\frac{(s + 4)^6 (s + 100)^2}{(s + 21)^6 (s + 310)}$$

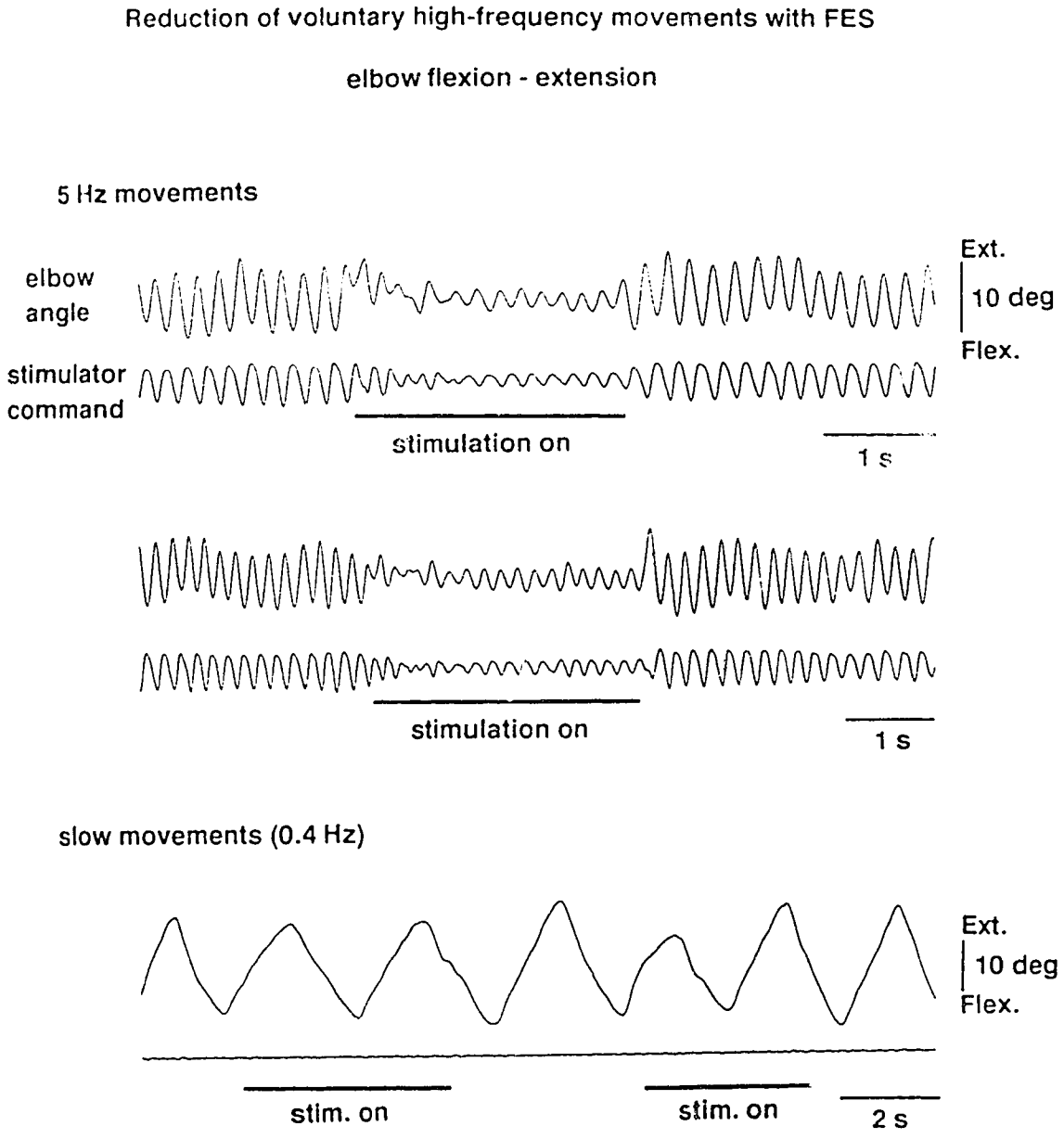

Figure 8. Normal subject performing tremor-like (top) and slow tracking (bottom) movements with and without closed-loop stimulation using the system in Figure 7B (horizontal bars indicate periods when stimulator was on). Tremor was strongly attenuated, while the slow movements (ca. 0.4 Hz) were little affected.

Closed loop trials

Prior to evaluating these systems in patients, we tested and optimised them in normal subjects performing tremor-like and slow tracking movements. Figure 8 shows three such tests of the 3 Hz elbow system with the loop gain adjusted to be about half (-6 dB) that which caused instability (from Fig. 7B the loop gain was therefore 15 dB - 6dB = 9 dB, i.e. an absolute value of 3). The 5 Hz tremor-like movements were attenuated by about 3.5:1, which is close to the expected attenuation of 4:1 for a loop gain of 3. Fig. 8, bottom panel shows that slow (0.4 Hz) tracking movements were only slightly attenuated, which is of course an important requisite of a functionally useful tremor-suppression system (FIG. 8).

As will be seen in the following chapter, the 3 Hz truncated elbow filter worked well in normal subjects mimicking 3 Hz tremor but unsatisfactorily in patients with cerebellar tremor. In reviewing our results, we found that the cerebellar tremors had been of a somewhat lower frequency (1.5 - 2.5 Hz), a 2 Hz truncated design was developed for future work. This is shown in Fig. 7A.

$$\frac{(s + 2.5)^6 (s + 50)}{(s + 12)^6 (s + 150)}$$

Figure 9 shows similar tests of the wrist system. Tremor-like movements were attenuated by about 2:1 for a gain adjusted to 6 dB below instability, and about 3:1 at 3 dB below instability. These attenuations were in line with the corresponding predictions based on the 9 dB gain margin shown in Fig. 6.

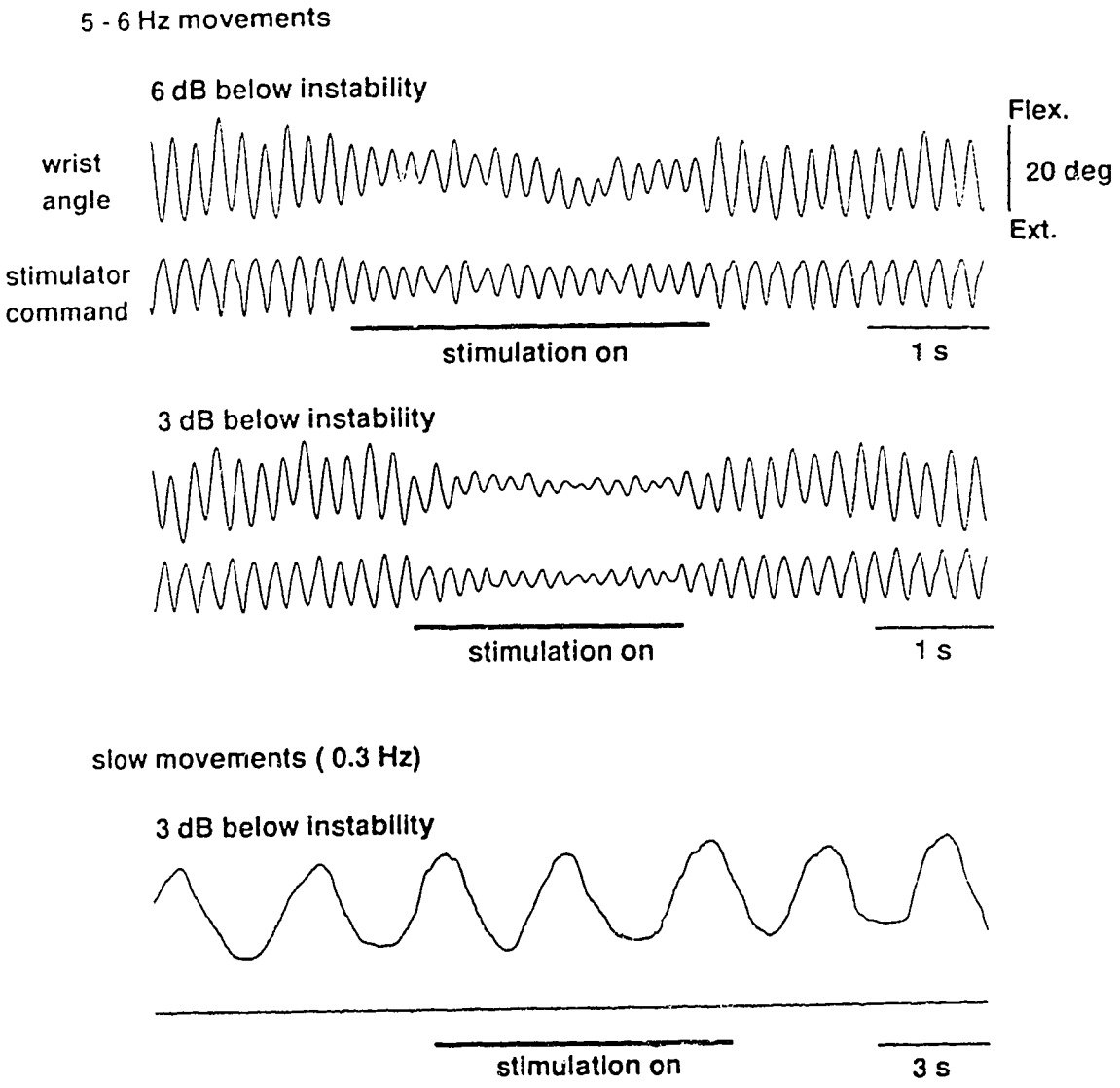

Figure 9. Similar tests to Fig. 8 of the wrist system of Fig. 6B. Tremor was attenuated by about 2:1 for a gain adjusted to 6 dB below instability, and about 3:1 at 3 dB below instability. Slow movements were little affected.

Effect of inertial loads

A system of the type just described would be of little practical use if tremor suppression were reduced, or if instability occurred whenever the patient's hand became inertially loaded. A priori this seemed quite possible in that the dynamic response characteristics of muscle are known to be load-dependent (e.g. Partridge, 1966): large loads could cause changes in the combined frequency characteristic, substantially reducing overall gain at the tremor frequency and destabilising the closed loop. We addressed this issue by first measuring the open-loop frequency responses at wrist and elbow in normal subjects with loads consisting of 50 mm wide strips of lead wrapped around the wrist or proximal phalanges. The weights were selected to cover the range of common household objects. For elbow trials, up to six 0.35 Kg weights were attached concentrically about the wrist (i.e. the net load was increased in 0.35 Kg increments to a maximum of 2.1 Kg). Assuming mean forearm moments of inertia about the elbow of 0.07 kg/m^2 (Peyton, 1986), we calculated that each 0.35 Kg wristlet increased the moment of inertia on average by 20%, the maximal increase therefore being 120%. The frequency response characteristics in Fig. 10A illustrate the main result, that loading in this limited but utilitarian range caused changes in amplitude of maximally 10 dB and in phase of maximally 60°. Larger changes were seen at the wrist, where from one to four of the same 0.35 Kg weights were wrapped around the fingers. From Winter (1979), we estimated the mean moment of inertia of our subjects' hands to be 0.005 Kg m^2, and each weight to add 0.04 Kg m^2. (i.e. 80% increments to a maximum of 320%). At this maximal load, changes of up to 20 dB in amplitude and 120° in phase were recorded. (Fig. 10B).

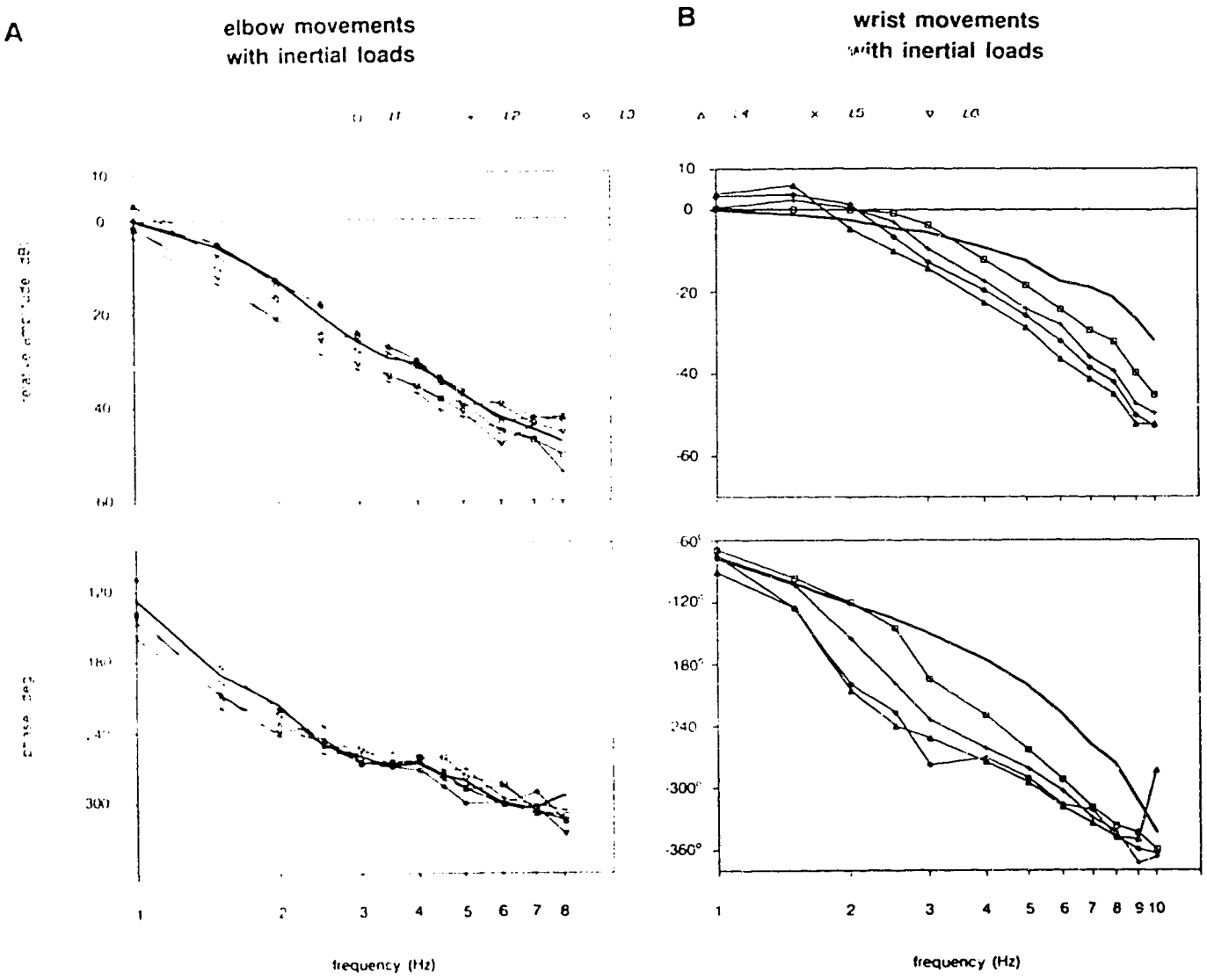

Figure 10. Effect of inertial loading on frequency response of electrically-elicited movements at A) elbow, B) wrist. Load was incremented by fixed amounts (elbow: six increments (L1 - L6) each representing 20% of moment of inertia of forearm; wrist: four increments (L1 - L4) each representing 80% of moment of inertia of hand). Solid lines show no-load responses. Wrist characteristics were significantly altered as load increased.

To see how this heavy loading of the hand might affect closed-loop operation, we combined the worst-case open-loop characteristics of Fig. 10B (4 weights = 1.3 Kg; cubic curve-fit: Supercalc 5 software) with the transfer function of the anti-tremor filter (Fig. 6B). The result, shown in Fig. 11B, is contrasted with the no-load characteristics in Fig. 11A, obtained by combining the no-load plots of Fig. 10B with the same filter transfer function. Two points emerge from the comparison. 1) The amplitude characteristic remains bell-shaped with the heavy load, though the peak is shifted from 4 Hz to 2 Hz. 2) the gain margin with the heavy load is larger than that with no load. This would imply that for a 3 Hz tremor, closed-loop operation would remain stable and effective with heavy loading. We confirmed this in closed-loop trials with gain adjusted to 3 dB below that causing instability of the unloaded hand: addition of the largest load did not cause instability, and tremorous movements, already attenuated by the load itself, were further attenuated by the closed-loop stimulation.

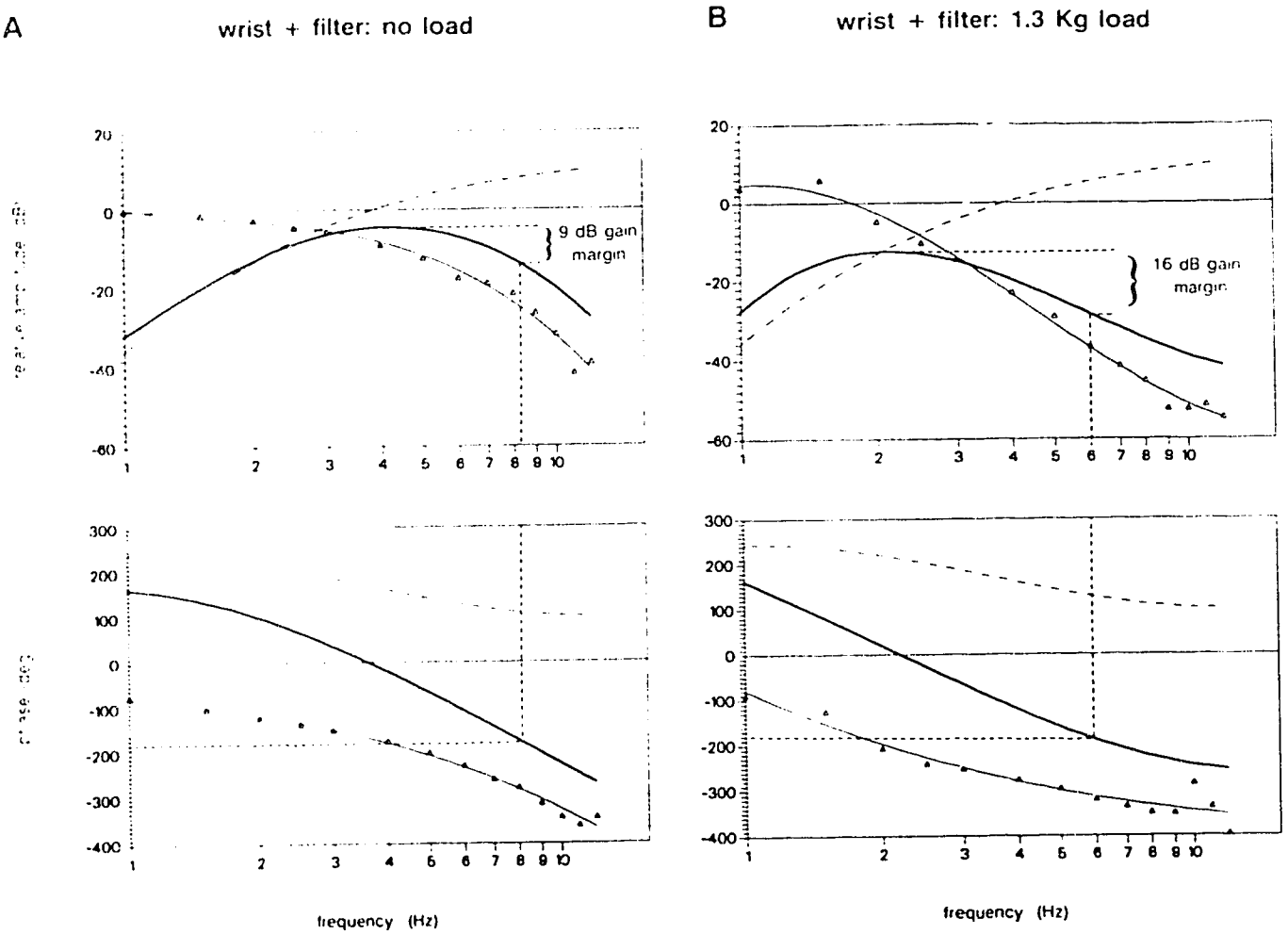

Figure 11. Impact on closed-loop operation of largest load of Fig. 9B. A) triangles, fitted curves: no-load characteristics (from Fig. 9B); dash-dot curves: anti-tremor filter (from Fig. 5B); thick curves: combined response showing peak at 4 Hz. B) triangles, fitted curves: 1.3 Kg load (from Fig. 9B, curve L4); dash-dot curves: anti-tremor filter (from Fig. 5B); thick curves: combined response showing shift of peak to 2 Hz. Curves in B indicate that closed-loop operation remains stable and effective (see text).

CHAPTER III

ATTENUATION OF PATHOLOGICAL TREMORS BY FUNCTIONAL ELECTRICAL STIMULATION: II- METHODOLOGY AND RESULTS IN PATIENTS

Objectives of the study

In the previous chapter a new method was described for selectively attenuating tremor by using closed-loop functional electrical stimulation (FES) to activate the tremorogenic muscles out-of-phase. The technique relies on feedback of a displacement signal to an electronic controller which uses the filtered signal to control muscle stimulation, the closed loop effectively being "tuned" to the tremor frequency. When tested on normal subjects, tremor-like movements were attenuated by up to 70%, whereas slower "useful" movements remained virtually unaffected.

The potential advantage of such a system is that it does not rely on mechanical loading of the extremity (Hewer et al., 1972; Morrice et al., 1987), nor on externally-powered electromechanical devices (Morrice et al., 1987). However, there were various factors which we felt a priori might mitigate against a successful clinical application of the technique.

In the second part of this study the FES technique was evaluated for tremor-suppression

in pathological states. The technical details were already described in the previous chapter. Three groups of patients were investigated, those with essential tremor, parkinsonian tremor and cerebellar tremor associated with multiple sclerosis. In each group tremor was attenuated by significant amounts (essential tremor: 73%, parkinsonian tremor: 62%, cerebellar tremor: 38%). These attenuations were in good accord with predictions based on the dynamic analyses and filter designs derived in the previous chapter. With filters "tuned" to the lower mean tremor frequency encountered in the cerebellar patients, more attenuation was possible in this group as well. In terms of application, we identified a number of practical limitations of the technique in its present form. The most important was that in daily use, only one agonist-antagonist pair of muscles can realistically be controlled. At first sight this restricts the usefulness of the system to the small number of patients with single-joint tremors. However, the addition of mechanical supports may broaden the scope of application.

Patients and Method

Clinical assessment of patients

A total of 24 patients were referred from the University of Alberta Hospital's inpatient neurology unit, outpatient neurology clinics, and multiple sclerosis research clinic. The patients were diagnosed as having three categories of tremor: essential tremor, parkinsonian tremor and cerebellar tremor. All patients were examined clinically by myself and videotaped prior to and during the trial. 3 patients with essential tremor, 5 patients with Parkinson's disease and 5 patients with cerebellar tremor due to multiple sclerosis were selected. The only criterion for selection was a disabling rhythmical tremor involving the wrist (mostly in essential and parkinsonian tremor) and/or the elbow (in cerebellar

tremor). Patients with mild resting or postural tremor not interfering with daily work, and patients responsive to tremor-suppressing medications were excluded, as were two severely depressed patients. One patient with the diagnosis of Parkinson's disease also had postural tremor and had not responded to antiparkinsonian therapy. Another patient diagnosed as having essential tremor also had rest tremor and other minor parkinsonian features. Although medication was discontinued 2-3 days prior to the trial in most of these patients, 3 patients remained on medication throughout. Patients or their guardians gave their written consent to the experiments, in accordance with the requirements of the University of Alberta Human Ethics Committee and the Declaration of Helsinki.

Functional electrical stimulation trials

The experimental arrangement was similar to that described in the previous chapter except for some small simplifications designed to minimise inconvenience to the subjects. For wrist experiments the subject's arm was completely free to move, hand displacement being monitored by a miniature displacement transducer consisting of a compliant elastic band attached to a small cantilever strain gauge. The ends of the gauge, which was stretched across the joint on the palmar side approximately in line with the middle finger, were attached to the skin with double-sided adhesive tape. It is worth noting that the frequency response of this type of gauge is flat to 50 Hz provided that the elastic band has not deteriorated. We found that phase advances due to age-related viscosity in the elastic material alter the open-loop transfer functions described in the previous chapter, and can seriously affect the efficacy of closed-loop stimulation. This problem will be addressed again in the Discussion. For elbow movements patients were seated comfortably in the experimental chair illustrated in Fig. 2 of the previous chapter, their forearm supported

by the pivoting armrest. In this case the transducer monitored the movements of the armrest rather than the subject's forearm, to avoid the problem of muscle mobility (see previous chapter).

Pre-gelled adhesive electrodes (Chattanooga Corp.) or moistened pads were used as cathodes to activate the extensors and flexors selectively. The indifferent electrode (anode) consisted of a moistened sponge strip wrapped around the wrist, or around the ipsilateral leg just below the knee.

Initial parametric adjustments Instead of the rigorous setting-up procedures described in the previous chapter to ensure specific, balanced background forces, in the patient trials the tonic level of stimulation was increased to the flexors and extensors separately until contraction thresholds were just reached. Loop gain was then gradually increased with flexor stimulation alone until instability just occurred (the hand or forearm started oscillating, typically at 7 - 9 Hz, as expected from the f_{180} values derived in the previous chapter). The same was now done with extensor stimulation alone. Next, with concomitant flexor and extensor stimulation (effectively doubling net loop gain) overall gain was reduced until marginal stability was re-attained (brisk taps applied to the hand eliciting a damped oscillation). From this reference point gain was now further reduced by specific amounts (e.g. 6 dB, equivalent to 50%).

Movement trials In patients with resting tremor, the efficacy of tremor-suppression was evaluated in the absence of voluntary movement of the affected limb. In several cases tremor was potentiated prior to switching on the stimulator by distracting the patient with a simple task with the contralateral hand such as knee-patting. Patients were then asked

to track slow movements of the experimenters' hand, or of a moving-bar target on a video screen, the surface of which was just beyond the subject's fingertips. In patients with intention tremor, functional tasks such as attempting to bring a half-filled cup to the mouth were also tested. The attenuation of the amplitude of both tremor and voluntary displacement in these various classes of movement during short periods of closed loop stimulation of unexpected onset and duration was analyzed off-line.

Analysis The subjects' wrist or elbow movements and concomitant stimulator command signals were recorded on cassette tape (TEAC R61 instrumentation recorder) and some trials were video-taped. Selected segments of the analogue data were digitised off-line using a Cambridge Electronic Design (CED) 1401 laboratory interface linked to an Olivetti M28 microcomputer. The data were digitised, displayed and printed (Hewlett Packard Laserprinter) with the use of CED "Massavg" software. Power spectral analysis was performed with CED "Waterfal" software.

Results

Patients tolerated the electrical stimulation very well. After a minute or two of "getting used" to it, eleven of the twelve patients reported little or no discomfort, and felt that long-term use would be acceptable. One patient reported muscle fatigue after a 20 minute stimulation session, and did not feel that this would be acceptable if the system were used daily. Figure 12 serves to illustrate typical results. The patient was a 54 year-old male with familial (essential) wrist tremor of unknown etiology. The filter used in this patient is that illustrated in Fig. 6B of the previous chapter.

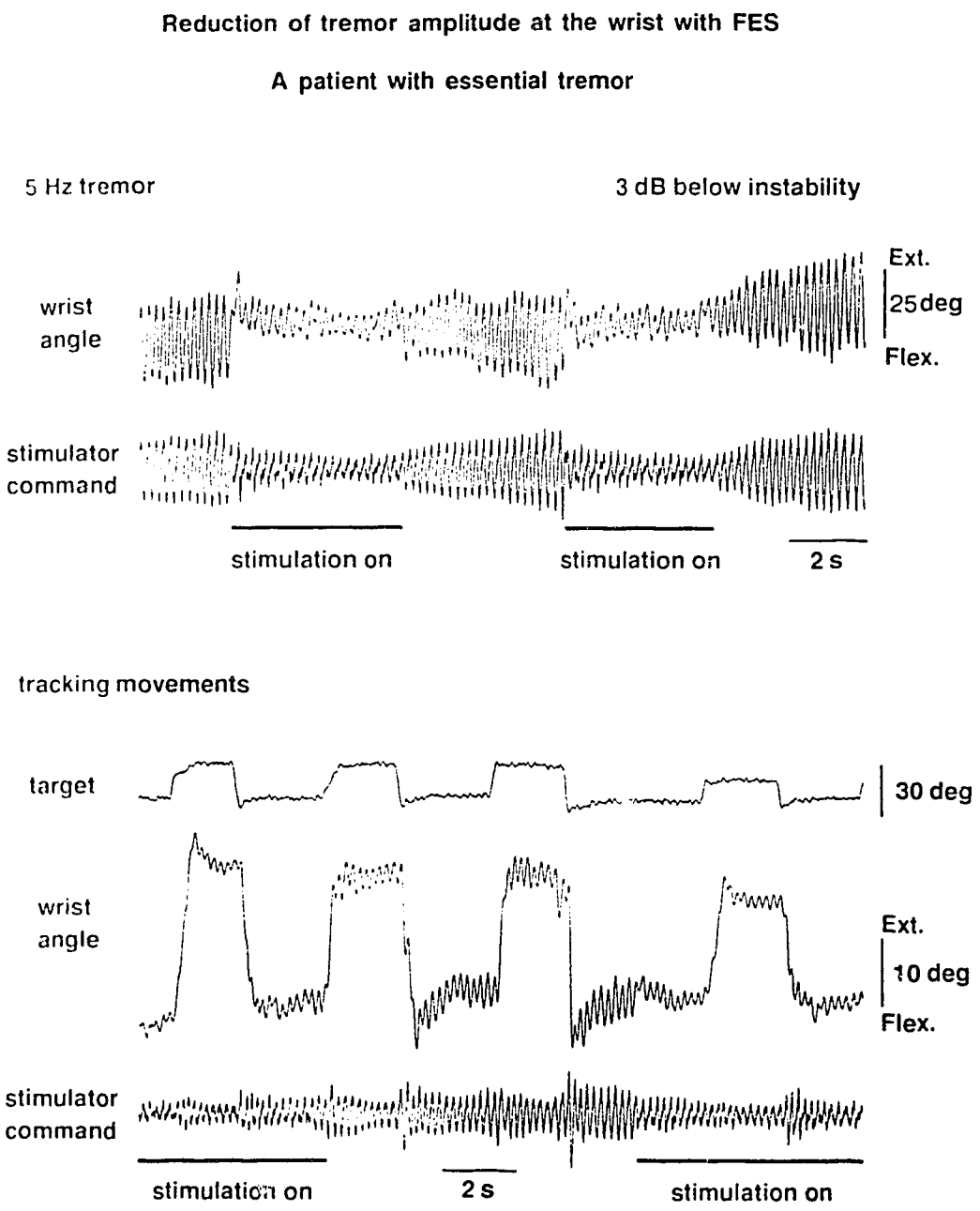

Figure 12. Electrical suppression of tremor in a patient with essential tremor. Top panel shows wrist angle and the stimulator command signal derived from it. Horizontal bars indicate when closed-loop electrical stimulation was present. An immediate and enduring reduction in tremor amplitude is apparent. The lower panel shows that the electrical stimulation did not significantly interfere with voluntary tracking of a slowly-moving target (middle trace) yet the superimposed tremor was attenuated.

At a loop gain of about 6 dB (3 dB below that at which stability was marginal, established as described above in the Methods), tremor was reduced by about 3:1 as anticipated (attenuation = (1 + gain): for details see previous chapter). The patient was able to perform accurate tracking movements during closed-loop stimulation (Fig. 12 bottom panel), and indeed because the superimposed tremor was attenuated, the overall accuracy of tracking was enhanced. (FIG. 12)

A more detailed evaluation of these data was obtained by computing the power spectra of segments of the displacement signal before, during and after stimulation. This form of analysis, done with the "Waterfal" software described in the Methods, is shown in Fig. 13. Panel B shows consecutive spectra computed from 20 overlapping 4 sec. "slices" of the recording in panel A (same patient as in Fig. 12, but a different trial). Panel C shows averages of slices 6-10 ("FES off": solid line) and slices 15-19 ("FES on": dashed line). Several interesting points emerge. First it is quite clear from Fig. 12C that tremor was suppressed during stimulation, the mean power attenuation at the fundamental frequency (3.4 Hz) being 16:1 (equivalent to an amplitude attenuation of 4:1, i.e. 12 dB or 75%). Second, tremor suppression was instantaneous and enduring. Third, the fundamental frequency of tremor was unchanged during stimulation despite the likely disruption of proprioceptive input resulting both from the diminished movement and the direct electrical stimulation of muscle afferents. (FIG. 13)

A similar set of data from a parkinsonian patient is presented in Fig. 14. This patient was a 53 year old woman with a long-standing prominent rest tremor associated with other features of Parkinson's disease. Tremor was mainly observed in the right hand and wrist

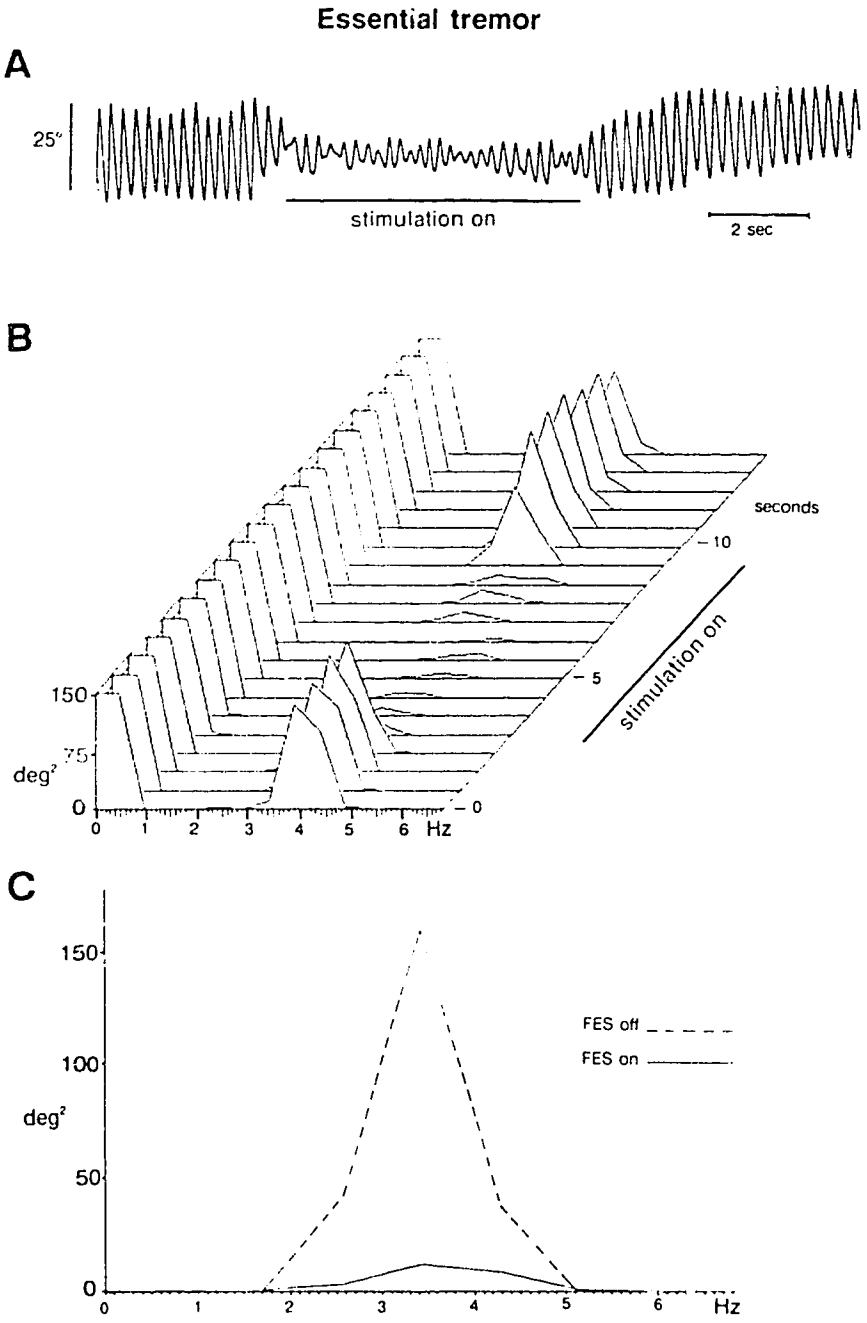

Figure 13. Power spectral analysis of further data from the same patient. The 16 sec. segment of displacement signal (A) was divided into 20 staggered and overlapping "slices" each of 4 sec. duration. The power spectrum of each slice was computed and plotted in a 3-dimensional display (B). Stimulation applies to the middle 9 segments of this display, the 3 - 4 Hz tremor peaks being clearly attenuated. The means of the power spectra with stimulation (slices 6-10) and without stimulation (slices 15-19) are shown in C, revealing a 16:1 attenuation of the 3.4 Hz peak during stimulation.

with significant involvement of the fingers. Her tremor had not responded well to anti-parkinsonian medications. Tremor was suppressed during closed-loop stimulation, the mean power at 3.4 Hz showing 28:1 attenuation (Fig. 14C) equivalent to an amplitude attenuation of 5.3:1, i.e. 14.5 dB or 81%. Again the frequency of the residual tremor was similar to that of the unattenuated tremor. In this patient there was an underlying irregular dysmetria which seemed to be "unmasked" when the tremor was suppressed. This may have been due in part to an interaction with the continuing finger tremor, not suppressed by stimulation. We observed this unmasking effect in all 4 parkinsonian patients. (FIG. 14)

Finally the results from a cerebellar patient with tremor about the elbow are presented in Fig. 15. This was a 32 year old man with long-standing multiple sclerosis. He had clinical evidence of marked abnormalities of the spinal cord and brainstem. Severe intention tremor and ataxia indicated cerebellar involvement. The patient was wheel-chair bound and his arm tremor was such that he was unable to feed himself or hold a cup steadily enough to be functional. None of the standard medications had suppressed the tremor. Heavy inertial loading attenuated the tremor but severely impaired movement and endurance.

The patient tracked a moving bar displayed on a video screen, the target displacement shown in the lower trace of Fig. 15A. Stimulation of elbow flexors and extensors was turned on unexpectedly during this tracking period. Fig. 15C shows that the power content of the tremor was attenuated by 6.2:1, equivalent to an amplitude attenuation of 2.5:1, (8 dB or 60%). The amplitude of the underlying voluntary tracking movements was

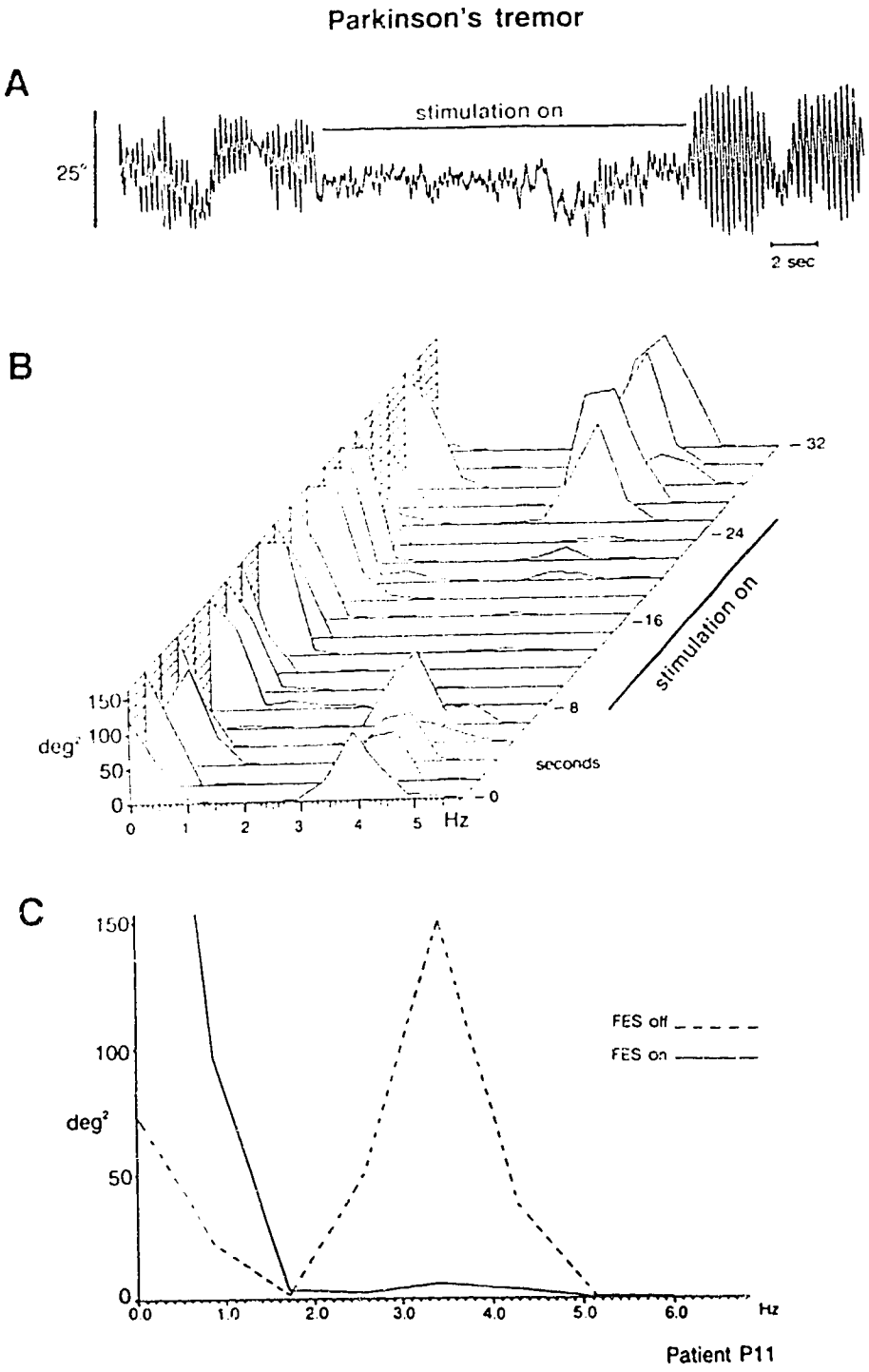

Figure 14. Similar data for a patient with Parkinson's disease. Attenuation of the tremor was associated with the unmasking and slight augmentation of slower irregular movements. Tremor power at 3.4 Hz was attenuated by 28:1 and frequency was unaffected.

not noticeably changed as judged from the displacement record of Fig. 15A. Table 3 indicates that the level of suppression of tremor in this patient was at the upper end of the range in the cerebellar group (mean 38% reduction compared to 61% in parkinsonian tremor and 73% in essential tremor). We only noticed after having tested 5 cerebellar patients that their mean tremor frequency was significantly lower than in the other groups (2.4 Hz cf. 3.7 Hz in essential tremor and 4.6 Hz in parkinsonian tremor). The elbow filter used in these trials was that of Fig. 7B, designed to be maximally effective in the 3-4 Hz range. In one patient with cerebellar tremor (patient number 15), 68% attenuation was obtained with the use of the 2 Hz filter of Fig. 7A of the previous chapter. An interesting feature of the responses in Fig. 15 was the shift in frequency from 2.4 Hz to 2.1 Hz during stimulation. (FIG. 15) (Table 3)

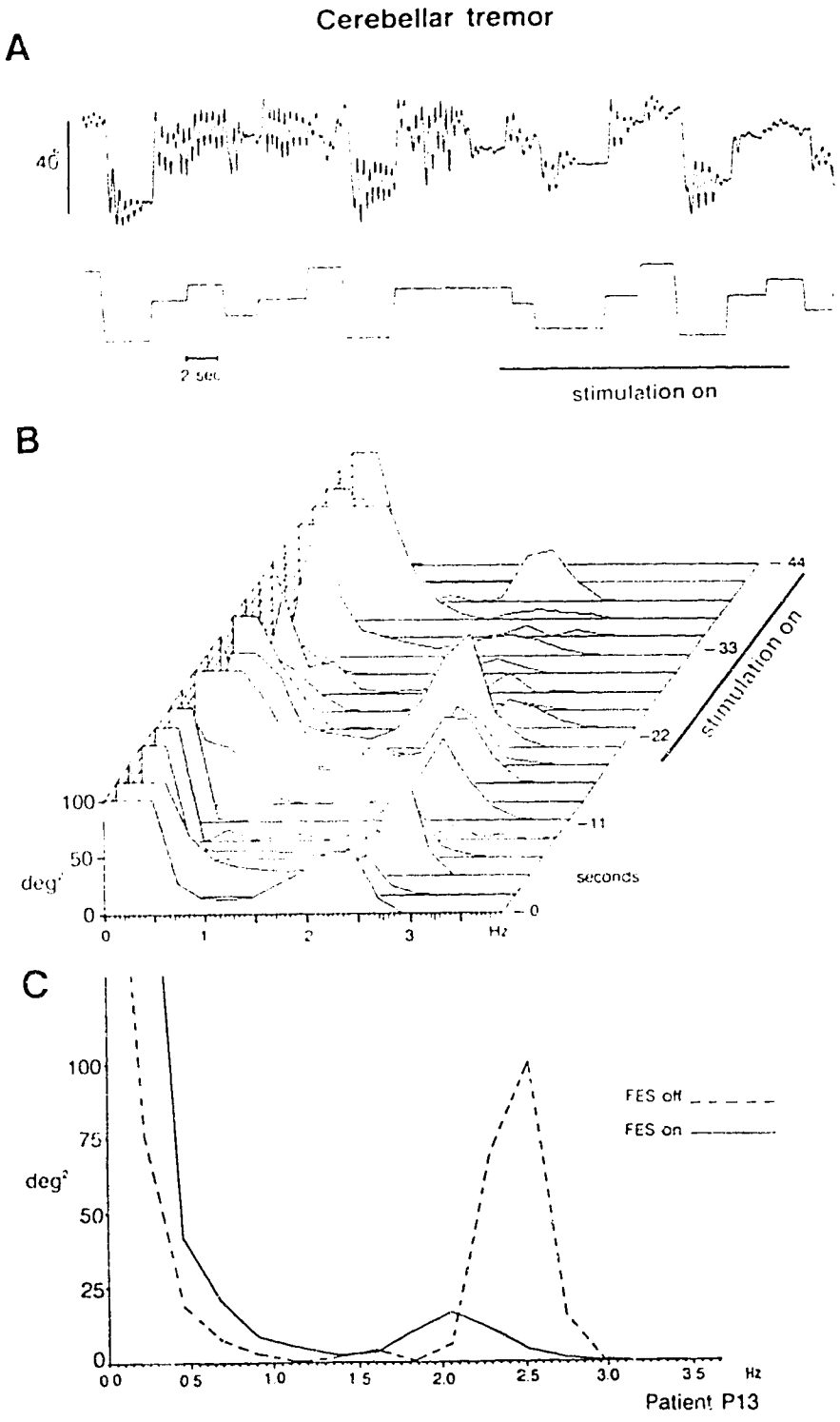

Figure 15. Similar data for a patient with cerebellar tremor associated with multiple sclerosis. In this case the patient was tracking a moving-bar target on a video screen. The tremor peak at 2.5 Hz was attenuated by 6.2:1 and shifted to 2.1 Hz during stimulation.

Table 3. TREMOR ATTENUATION IN PATIENTS USING FES SYSTEM

PATIENT & TREMOR	FREQUENCY stim. off	+SD (Hz) stim on	n	t	signif. p<0.1)	mean % atten.
2 essential	4.5 ±.2	4.6 ±.1	13	1.00	no	72
3 "	2.7 ±.1	2.7 ±.2	9	1.14	no	55
4 "	3.9 ±.05	3.5 ±.2	4	2.38	yes	91
6 Parkinson	4.9 ±.05	5.0 ±.3	11	1.26	no	54
7 "	5.4 ±.3	5.4 ±.3	11	0.45	no	57
10 "	4.4 ±.1	4.3 ±.2	6	1.57	no	69
11 "	4.5 ±.2	4.6 ±.1	13	0.86	no	66
5* cerebellar	2.8 ±.2	2.6 ±.3	5	1.24	no	66
8* "	2.5 -	2.5 -	2	-	-	0
12* "	3.0 ±.2	3.1 ±.4	4	0.32	no	10
13* "	2.0 ±.4	1.6 ±.1	3	1.57	no	50
14* "	1.9 ±.1	2.0 ±.2	9	1.57	no	36
15# "	2.0 -	1.6 -	2	-	-	68

n: number of paired spectra (stim. on vs. off).
t: calculated Student's t value for comparison of means
* 3 Hz filter was used.
# 2 Hz filter was used

CHAPTER IV

DISCUSSION

In this study the technical details of a new method are presented which involve attenuation of pathological tremor with functional electrical stimulation. The basic idea is to stimulate the tremorogenic muscles out-of-phase so as to suppress the tremor, while minimally interfering with useful volitional movements. Our approach was first to measure the frequency-response properties of two pairs of load-moving muscles often involved in pathological tremors: the elbow and wrist flexors and extensors. This was done in normal subjects, and allowed us to fit model transfer functions to the averaged results. Filters were then designed which, when combined with these models in the closed loop, gave bandpass characteristics causing attenuation of 2 - 4 Hz tremor with barely noticeable effects on slower voluntary movement.

Validity of linear analysis

It is often pointed out that the neuromuscular system exhibits non-linear properties, and that linear modelling such as we have used is therefore invalid. Yet we found in our study that predictions regarding gain margins, resonant frequencies and tremor attenuation derived from the linear models were accurate and dependable when evaluated in closed-loop experiments. The most likely explanation of this is that for the relatively small

movements seen at the onset of instability and in tremor, muscle/load properties are in fact adequately described by linear transfer functions, at least to the level of precision required for this type of application. This is not to deny that a non-linear systems approach might provide more accurate or more general models which might enable one to design filters with better closed-loop performance and greater stability margins. Indeed even within the constraints of linear modelling one can not be certain whether the filters used are the best possible filters. The purpose at this stage is to present the general approach and some workable solutions which provide enough tremor suppression to be considered for practical clinical use.

Parametric variation between subjects

At the outset, the question was whether it would be necessary to optimise a filter design for each individual based on his or her particular muscle/load properties. This turned out not to be the case: the inter-individual variation in frequency responses (e.g. Fig. 3) within each group was small enough to allow the same filters to be used successfully on all subjects. Furthermore the relative insensitivity of the system to the variations in muscle/load characteristics illustrated in Fig. 11 was considerably more favourable than expected. On the other hand, it became evident that a filter appropriate for 4 Hz tremor might not attenuate 2 Hz tremor sufficiently. This means that for the best outcome a filter should be chosen from a standard set to suit a particular patient's tremor frequency.

The loading studies revealed an interesting difference between hand and forearm which has implications for normal CNS control of movement. A 1.3 Kg weight attached to the hand attenuated higher-frequency movements more at the wrist than at the elbow. Let

us assume that forearm and hand movements are controlled with closed-loop proprioceptive feedback and that in many individuals stability margins are quite low (Prochazka, & Trend, 1988). A priori, one might suspect that inertial loading would destabilise the hand first because of its larger effect on the overall transfer function. To compensate, the CNS could adaptively adjust the dynamics of central transmission, or it could simply operate the wrist loop at a lower gain to start with (consistent with the greater briskness of tendon jerks in arm vs. forearm muscles). On the other hand, depending on the overall transfer characteristics, loading may in fact make wrist (and elbow) control more stable, as exemplified in Fig. 11.

The scope of this study was to explore the basic feasibility of attenuating tremor with electrical stimulation. A more rigorous analysis of the sensitivity of various closed-loop configurations to parametric variation is now called for, partly because it might lead to better filter designs, and partly for the insight it would no doubt give on the organisation required within the central nervous system to control movement in the face of parametric variation in muscles and their loads.

Limitations

There were three main areas of difficulty and unreliability in suppressing tremor with the systems described above.

1) **Stimulation**. Accurate placement of surface electrodes was required for reproducibility of open-loop responses and for correct operation of the closed loop. In some subjects it was quite difficult to locate appropriate sites. Surface electrodes tend to be somewhat cumbersome, cosmetically unappealing and time-consuming to apply and remove.

Percutaneous intramuscular electrodes (e.g. Mortimer, 1981; Mortimer et al., 1987; Marsolais & Kobetic, 1987; Popovic et al., 1990; Stein et al., 1990) may bypass these difficulties, but introduce some problems of their own. They are invasive and so tend to be reserved for use in severely disabled individuals only. Fully implanted stimulators controlled by percutaneous telemetry (e.g. Waters et al., 1975) may provide viable alternatives in the future but at this stage are only commercially available for stimulation of the common peroneal nerve.

2) **Displacement transduction** It is relatively easy to fit a suitable low-noise, high-resolution transducer to a pivoting armrest or handrest. However, if unrestricted movement of the arm is to be allowed, the task of reliably sensing joint displacement becomes much harder. In some trials, we spanned the elbow or wrist with a miniature displacement transducer consisting of an elastic band attached to a small cantilever strain gauge. The ends of the gauge were attached to the skin with double-sided adhesive tape. This arrangement worked reasonably well, except that instability tended to occur at lower gains than in the stabilised forearm. The reason seemed to be that mobility of the muscle belly over which the transducer was attached caused a modulation of the displacement signal additional to the displacement of the joint. This was not taken into account in the open-loop transfer functions. The result was a high-frequency instability consisting of rapid muscle "bouncing" with little joint displacement, but with discomfort caused by the large rhythmical bursts of electrical stimuli. Goniometric transducers of the type manufactured by Penny and Giles (Blackwood, Gwent, U.K.) might circumvent this problem, in that their attachment is distributed along the extremity, and so their responses are less likely to be distorted by local muscle bulging.

3) **Multiple-joint tremor** The clearest difficulty we see in applying the technique to patient populations relates to the practical difficulties of simultaneously suppressing tremor about more than one joint.

Attenuation of pathological tremor in patients

Several aspects emerge from this pilot study on the possible use of FES in controlling tremor. First and foremost, it was clear that significant attenuation was possible in the three main types of pathological tremor. Patients generally tolerated the electrical stimulation well. The natural waxing and waning of tremor amplitude did not disrupt the performance of the system, nor were the variations in tremor frequency within an individual patient sufficient to degrade tremor suppression. Other than brief startle responses when stimulation was turned on abruptly, the motor consequences of stimulation were consistent with direct muscle activation only, and there were no major components of response indicative of reflexive action. This is not to say that reflexes were absent or unaffected by the intervention (see below), but merely that they did not significantly change the behaviour of the closed loop from that expected from direct stimulation alone. The slow "useful" movements were not significantly affected. The degree of attenuation of small slow movements was proportionally the same as for large slow movements.

The open-loop characteristics of response to electrical stimulation could not be mesured in patients because of their ongoing tremor. The filters used were therefore based on data from normal subjects on the assumption that patients' muscles would respond similarly. This assumption was most likely valid, for the following reasons. In the patients the

threshold of instability was used as the reference point for the setting of loop gain. From the corresponding reference point in normals (e.g. at 8 Hz, Fig. 6B), we could determine the expected loop gain at the tremor frequency for a setting corresponding to say 3 dB below instability. From this followed a prediction of tremor attenuation at this setting if the above assumption were valid. Predictions were accurate to within 3 dB and the conclusion was that the response dynamics of normals were indeed similar to those of the patients we studied. This is not too surprising, since the patients' muscles were generally in good condition, and well exercised by the persistent tremor.

Central or Peripheral mechanisms? As I discussed in the introductory chapter, the general opinion is that parkinsonian, essential and cerebellar tremors are primarily generated by central mechanisms. However, the peripheral mechanisms modify the amplitude of tremor. Interestingly enough, our conclusion is very similar. In two of the three essential tremors, and in all of the parkinsonian tremors, frequency was remarkably constant in the face of the major changes in proprioceptive input likely to result from the movement attenuation and the electrical stimulation of afferents. In the parkinsonian patients, additional irregular involuntary movements were "unmasked" by stimulation. This is most likely due to an interaction with continuing finger tremor, and may be related to the waxing and waning of tremor amplitude seen in Parkinson's disease. The constancy of the fundamental frequency component during stimulation supports the notion that parkinsonian and essential tremors are largely central in origin, and relatively uninfluenced by peripheral input (rev: Marsden, 1984, Freund et al., 1984; but see Lee & Stein, 1981 and Rack & Ross, 1986).

In some trials tremor frequency in cerebellar patients (numbers 5, 13 and 15) changed during stimulation (e.g. Fig. 15), but statistically this was not significant at the $p < 0.1$

level (however note that in patients 13 and 15 only 5 paired comparisons of spectra were available). If this impression is correct that frequency is indeed altered by stimulation in these patients, this would be consistent with a peripheral contribution to this type of tremor. Admittedly there is also the further possibility of a generalised arousal response to electrical stimulation in these patients which might tonically influence an otherwise centrally generated rhythm.

Practical application

While this study showed that in principle FES could provide long-term tremor suppression in patients in whom tremor is not sufficiently reduced by medication, some basic limitations became apparent and a number of practical problems were identified. The main limitation in a system intended for daily use is that with the currently available sensors and electrodes, it is unrealistic to aim to control more than one pair of agonist-antagonist muscles at a time. At first sight this would seem to restrict application to the relatively small number of patients with tremor confined largely to one joint. However, the use of splints and other mechanical supports in conjunction with the present FES system may greatly broaden its scope. For example, in severely incapacitated individuals with multiple sclerosis an arrangement similar to that shown in Fig. 2 is being tested, whereby the forearm is supported on a horizontally-pivoting armrest shaped to enclose the wrist so that pronation-supination tremor is mechanically limited. These simple constraints effectively reduce the task of FES tremor-suppression to a single degree of freedom, namely elbow flexion-extension. With this hybrid system patients with severe tremor who otherwise could not feed themselves, can bring food to their mouths in a controlled way. The armrest assembly is clamped to a high table allowing wheelchair access. Food placed on the table surface is at chin height, and the armrest swings through a 90° arc about 5 cm

above this, allowing the patient to pick up food and move it to his or her mouth. Convenience in use is a major factor in the success of active orthotic devices. For daily use we envisage patients using pre-gelled self-adhesive electrodes which may be worn for up to a week (Chattanooga Corp.). The patient's wheelchair is pushed up to the table, his or her forearm is placed on the armrest, three snap-lock connections are made to the electrodes and the system is turned on.

The further practical problems encountered were as follows:

1) **electrode placement** could vary somewhat between individuals (though not generally from one trial to the next in a given person). In chronic use surface electrodes have a number of drawbacks, and so in patients who benefit in a major way from FES tremor-suppression, percutaneously implanted wire electrodes (e.g. Stein et al., 1990) might provide a more convenient alternative.

2) **Initial gain and offset adjustments** must be set accurately for good tremor attenuation. Though the design of electronically self-calibrating devices is feasible, this would only be worthwhile if the basic technique comes into widespread use. For the present patients or support personnel would have to learn this procedure. Provided that electrode placement and impedances do not vary, the settings for an individual should remain constant for an indefinite period of time. However in practice it will probably be necessary to check them at regular intervals.

3) **The displacement sensors** used in this study could in principle allow free movement of the arm. However in practice we found that they only operated satisfactorily for flexion-extension tremor at the wrist. Although elbow flexion-extension tremor could sometimes be suppressed with the use of one of these transducers, this was generally unsatisfactory

for two main reasons. First tremor about the elbow is often complex, shifting between flexion-extension, pronation-supination and abduction-adduction; control of flexion-extension tremor alone does not bring much functional benefit. Second, muscle bulging distorts the signal monitored by a surface-mounted transducer (see previous chapter). The problem is minor at the wrist but significant at the elbow. Transducers of another design may circumvent this problem.

Patients' opinion about the FES technique

When the patients were asked whether they would be willing to use FES to improve their functional abilities, majority of them responded that the idea of the technique is good. Most patients felt that FES reduced their tremor during the study. However, they felt that the technique was not very practical. If the FES system could be made in a small portable box and easy to carry along, and if they did not have to adjust the electrode location, most of them would use the FES. The positive response was particularly noted in patients with essential tremor.

Bibliography

Agnoli A, Casacchia M, Fazio C et al. (1974). Comparison between therapeutic effects of L-dopa and L-dopa plus dopadecarboxylase inhibitors in Parkinson's disease. In: Yahr MD, ed. Current Concepts in the Treatment of Parkinsonism. New York: Raven Press.

Albe-Fessard D, Arfel G, Guiot G, et al. (1966). Electrophysiological studies of some deep cerebral structures in man. J Neurol Sci 3:37-51.

Allum JHJ, Dietz V, and Freund HJ (1978). Neuronal mechanisms underlying physiological tremor. J Neurophysiol 41: 557-571.

Allum JHJ, and Hulliger M (1982). Presumed reflex responses of human first dorsal interosseous muscle to naturally occurring twitch contractions of physiological tremor. Neurosci lett 28:309-314.

Allum, JHJ (1984). Segmental reflex, muscle mechanical and central mechanisms underlying human physiological tremor. In: Findley LJ, Capildeo R, eds. Movement disorders: Tremor. London: Macmillan, pp 135-155.

Altenburger H (1937). Electrodiagnostik. In: Bumke und Foerster Hb. der Neurologie, vol 3, Berlin:Springer. pp 747-1086

Andrew J (1984). Surgical treatment of tremor. In: Findley LJ, Capildeo R, eds. Movement Disorders: Tremor. London: Macmillan. 1984.

Baker WW, Lalley PM, Conner JD, and Rossi GV (1976). Neuropharmacologic analysis of cholinergic tremor mechanisms in the caudate nucleus. Clin Pharmacol Ther 1:459-473.

Barbeau A (1962). The pathogenesis of Parkinson's disease: a new hypothesis. Can Med Assoc J 87:802-807.

Barbeau A (1969). L-dopa therapy in Parkinson's disease: A critical review of nine years experience. Can Med Assoc J 101:791-800.

Benedikt M (1889). Tremblement avec paralysie croisee du moteur oculaire commun. Bull Med 3:547-548.

Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, and Seitelberger F (1973). Brain dopamine and the syndromes of Parkinson and Huntington: clinical, morphological and neurochemical correlations. J Neurol Sci 20:415-455

Boshes B (1976). Further insight into parkinsonian tremor. In: Birkmeyer W,. Hornykiewicz O, eds. Advances in Parkinsonism. Basel: Roche.

Botterell EH, and Fulton JF (1938). Functional localization in the cerebellum of primates. III. Lesion of hemispheres (neocerebellum). J Comp Neurol 69: 63-87.

Brumlik J, and Yap CB (1970). Normal tremor: A comparative study. Springfield, IL: Charles C Thomas, pp 93.

Caccia MR, Mangoni A (1985). Clonidine in essential tremor: Preliminary observations from an open trial. J Neurol 232:55-57.

Caln DB, Barton K, Beckman J, et al. (1984). Dopamine agonists in PD. Can J Neurol Sci 11:221-224.

Caln DB, Calveria LE, Allen JG (1974). Plasma levodopa and "on-off" effect after chronic treatment of Parkinson's disease. In: McDowell F, Barbeau A, eds. Advances in Neurology, vol 5, Second Canadian-American conference on Parkinson's disease. New York: Raven Press.

Calzetti S, Findley LJ, Gresty MA, et al. (1983). Effect of a single oral dose of propranolol on essential tremor. A double-blind controlled study. Ann Neurol 13:165-171.

Capildeo R, and Findley LJ (1984). Classification of tremor. In: Findley LJ, Capildeo R, eds. Movement Disorders: Tremor. London: Macmillan.

Carrea RME, and Mettler FA (1947). Physiological consequences following extensive removals of the cerebellar cortex and deep cerebellar nuclei and effect of secondary cerebral ablations in the primate. J Comp Neurol 87:169-288.

Charcot JM (1868). Gaz Hop Civ Milit, as cited by Wilson, SAK (1940). Neurology, vol 1, Baltimore:Williams & Wilkins, pp 148.

Cleeves L, Findley LJ, Gresty MA (1987). Assessment of rest tremor in Parkinson's disease. In: Yahr MD, Bergmann KJ, eds. Advances in Neurology, vol 45. New York:Raven Press.

Conner JD, Rossi GV, and Baker WW (1966). Analysis of the tremor induced by injection of cholinergic agents into the caudate nucleus. Int J Neuropharmacol 5:207-216.

Cooper IS (1955). Chemopalledectomy, an investigative technique in geriatric parkinsonians. Science 121:217-18.

Cooper IS (1960). Neurosurgical relief of intention tremor due to cerebellar disease and multiple sclerosis. Arch Phys Med 41:1-4.

Cooper IS (1962). Heredofamilial tremor by chemothalamectomy. Arch Neurol 7:129-131.

Cotzias GC, Van Woert MH, Schiffer LM (1967). Aromatic aminoacids and modification of parkinsonism. N Engl J Med 276:374-378.

Cotzias GC, Papavasiliou PS, Gellen R (1969). Modification of Parkinsonism: Chronic treatment with L-dopa. N Eng J Med 280:337-345.

Critchley E (1949). Observations on essential (heredofamilial) tremor. Brain 72:113-39.

Critchley E (1972). Clinical manifestations of essential tremor. J Neurol Neurosurg Psychiat 35:365-372.

Denny-Brown D (1968). Clinical symptomatology of disease of the basal ganglia. In: Vinken PJ, and Bruyn GW, eds. Handbook of Clinical Neurology, vol 6, Diseases of Basal Ganglia. Amsterdam: North- Holland pp 133-172.

Dejerine J (1914). Semiologie des affections du systeme nerveux (Masson, Paris).

Doshay LJ, and Constable K (1949). Artane therapy for Parkinsonism: preliminary study of results of 117 cases. J AM Med Assoc 140:1317-1322.

Effron AS, Denker PG (1950). A clinical evaluation of certain antihistamines and antispasmodic drugs in Parkinson's disease. JAMA 144:5-8.

Ehringer H, und Hornykiewicz O (1960). Verteilung von Noradrenaline und Dopamine (3 Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. Klin Wschr 38:1236-1239.

Elbe RJ (1986). Physiologic and essential tremor. Neurology 36:225-231.

Elek J, Prochazka A (1989). Attenuation of wrist tremor with closed-loop electrical stimulation of muscles. Journal of Physiology 414, pp 17.

Elsasser G (1941). Erblicher Tremor. Fortschr. Erbpath 5:117-135.

England AC, Schwab RS (1959). Management of Parkinson's disease. Arch Intern Med. 104:439-468.

Fahn S, Libsch LR, and Cutler RW (1971). Monoamines in the human neostriatum: topographic distribution in normals and in Parkinson's disease and their role in akinesia, rigidity, chorea and tremor. J Neurol Sci 14:427-455.

Fahn S (1972). Differential diagnosis of tremors. Med Clin N Am 56:1363-75.

Fahn S (1974). "On-off" phenomenon with levodopa therapy in parkinsonism. Neurology 24:431-441.

Ferrier D, and Turner WA (1894). A record of experiments illustrative of the symptomatology and degenerations following lesions of the cerebellum and its peduncles and related structures in the monkey. Phil Trans R Soc B 185:719-778.

Findley LJ (1988). Tremors. Differential Diagnosis and Pharmacology. In: Jancovic J, and Eduardo T, eds. Parkinson's Disease and Movement Disorders. Baltimore-Munich: Urban & Schwarzenberg.

Findley LJ, Cleeves L, Calzetti S (1984). Action tremor with alternating activity in antagonist muscles. Neurology 34:1618-1619.

Findley LJ, Cleeves L, Calzetti S (1985). Primidone on essential tremor of the hands and head: A double-blind control clinical study. J Neurol Neurosurg Psychiat 48:911-915.

Findley LJ, Gresty MA (1984). Tremor and rhythmical involuntary movements in Parkinson's disease. In: Findley LJ, Capildeo R, eds. Movement Disorders: Tremor. London: Macmillan.

Findley LJ, Gresty MA and Halmagyi GM (1981). Tremor, the cogwheel phenomenon and clonus in Parkinson's disease. J Neurol Neurosurg Psychiat 44:534-46.

Findley LJ, and Salisachs P (1984). Problems in the differential diagnosis of essential tremor. In: Findley LJ, Capildeo R, eds. Movement Disorders: Tremor. London: Macmillan.

Foerster O (1911). Resection of the posterior nerve roots of spinal cord. Lancet 2:76-79.

Foerster O (1936). Symptomatologie der Erkrankungen des Ruckenmarks und seiner Wurzlen. In: Bumke und Foerster Hb. der Neurologie, vol 5, pp 10403. Berlin: Springer.

Freund HJ, Homberg V, Hefter H (1987). In: Bencke R, Conrad B, Marsden CD, eds. Motor disturbances I. Tremor: clinical aspects and treatment. Academic press Ltd., PP 19-40.

Freund HJ, Hefter H, Homberg V, and Reiners K (1984). Determinants of tremor rate. In: Findley LJ, Capildeo R, eds. Movement Disorders: Tremor. London: Macmillan, pp 195-204.

Goldberger ME, and Growdon JH (1973). Pattern of recovery following cerebellar deep nuclear lesions in monkeys. Exp Neurol 39:307-322.

Graham JDP (1945). Static tremor in anxiety states. J Neurol Neurosurg Psychiat 8:57-60.

Greenblatt DJ, Koch-weser J (1974). Adverse reaction to beta-adrenergic blocking drugs-Boston collaborative report. Drugs 7:118-129.

Gresty MA, Findley LJ (1984). Definition, analysis and genesis of tremor. In: Findley LJ, Capildeo R, eds. Movement Disorders: Tremor. London: Macmillan.

Growdon JH, Shahani BT, Young RR (1975). The effect of alcohol on essential tremor. Neurology 25:259-262.

Guiot G, Brion S, Fardeau M, et al. (1960). Dyskinesie volitionnelle d'attitude supprimee par la coagulation thalamocapsulaire. Rev Neurol (Paris) 102:220-229.

Gurfinkel VS, and Osovets SM (1973). Mechanism of generation of oscillations in tremor form of Parkinsonism. Biofizika 18: 731-738.

Hagbarth KE, and Young RR (1979). Participation of stretch reflex in human physiological tremor. Brain 102:509-526.

Hagbarth KE, Wallin G, Lofstedt L, Aquilonius SM (1975). Muscle spindle activity in alternating tremor of parkinsonism and in clonus. J Neurol Neurosurg Psychiat 38:636-641.

Hallet M, Lindsay JW, Dov Adelstein B, et al. (1984). Double-blind trial of isoniazid for severe postural cerebellar tremor in patients with multiple sclerosis. Neurology 34 (suppl I):128.

Halliday AM, and Redfearn JWT (1956). An analysis of the frequencies of finger tremor in healthy subjects. J Physiol 134:600-611.

Halliday AJ, Redfearn JWT (1958). Finger tremor in tabetic patients and its bearing on the mechanism producing the rhythm of physiological tremor. J Neurol Neurosurg Psychiat 21:101-108.

Hewer LR, Cooper R and Morgan MH (1972). An investigation into the value of treating intention tremor by weighting the affected limb. Brain 95:579-590.

Hoefer PFA, and Putnam TJ (1940). Action potentials of muscles in athetosis and sydenham's chorea. Archs Neurol 44:517-531.

Holmes G (1904). On certain tremors in organic cerebral lesions. Brain 27:327-375.

Holmes G (1917). The symptoms of acute cerebellar injuries from gunshot wounds. Brain 40:461-535.

Holmes G (1922). Clinical symptoms of cerebellar disease (The Croonian Lectures). Lancet 1:1177-82, 1231-1237, and 2:59-65, 111-115.

Jacks A., Prochazka A, and Trend P St J (1988) Instability in human forearm movements studied with feedback-controlled electrical stimulation of muscles. J Physiology 402:443-461.

Jankovic J (1986). The clinical spectrum and treatment of tremors. Neuroview 2:1-6.

Jankovic J, and Fahn S (1980). Physiologic and pathologic tremors. Diagnosis, mechanism, and management. Ann Intern Med 93:460-465.

Jasper HH, Bertrand G (1966). Recording from microelectrodes in stereotactic surgery for PD. J Neurology 24:219-221.

Jenner P, and Marsden CD (1984). Neurochemical basis of Parkinson's tremor. In: Findley LJ, Capildeo R, eds. Movement Disorders: Tremor. London: Macmillan.

Joyce GC, and Rack PMH (1974). The effect of load and force on tremor at the normal human elbow joint. J Physiol 240:375-396.

Joyce GC, Rack PMH, and Ross HF (1974). The forces generated at the human elbow joint in response to imposed sinusoidal movements of the forearm. J Physiol (Lond) 240:375-396.

Keenan RE (1970). The Eaton collaborative study of levodopa therapy in parkinsonism: A summary. Neurology 20:46-52.

Klawans HL, Goetz C, Bergen D (1975). Levodopa-induced myoclonus. Arch Neurol 32: 231-234.

Koller WC (1984a). Diagnosis and treatment of tremors. Neurol Clin 2:499-514.

Koller WC (1984b). Pharmacological trials in the treatment of cerebellar tremor. Arch Neurol 41:280-281.

Koller WC (1986). Ineffectiveness of phenoxybenzamine in essential tremor. J Neurol Neurosurg Psychiat 49:222.

Koller WC, Biary N (1984). Effect of alcohol on tremors: comparison with propranolol. Neurology 34:221-222.

Koller WC, Royse VL (1986). Efficacy of primidone in essential tremor. Neurology 36:121-124.

Lalley PM, Rossi GV, and BaKer WW (1970). Analysis of local cholinergic tremor mechanisms following selective neurochemical lesions. Exp Neurol 27:258-275.

Lamarre Y (1975). Tremorogenic mechanisms in primates. In: Meldrum, BS and Marsden CD, eds. Primate models of neurological disorders, Advances in Neurology, vol 10, New York:Raven Press, pp 23-34.

Lamarre Y, and Dumont M (1972). Medical Primatology. In: Goldsmith EI and Moor-Jankowski J, eds. Basel: Karger, pp 274-281.

Lamarre Y, Joffray AJ (1979). Experimental tremor in monkeys: Activity of thalamic and pre-central cortical neurons in the absence of peripheral feedback. In: Poirier LJ, Sourkes TL, Bedard PJ, eds. The extrapyramidal system and its disorders. Adv. Neurol 24: 109-122.

Lance JW, and McLeod JG (1975). A physiological approach to clinical neurology. London: Butterworth.

Lance JW, Schwab RS, and Peterson EA (1963). Action tremor and the cogwheel phenomenon in Parkinson's disease. Brain 86: 95-110.

Lapresle J, Rondot P, Said G (1974). Tremblement idiopathique de repos, d'attitude et d'action. Rev Neurol (Paris) 130:343-348.

Larrson T, and Sjogren T (1960). Essential tremor. A clinical and genetic population study. Acta Psychiat Scand 36: suppl 144, pp 1-176.

Lee RG, Stein RB (1981). Resetting of tremor by mechanical perturbances: A comparison of essential tremor and Parkinsonian tremor. Ann Neurol 10: 523-531.

Lee RG, Tatton WG (1975). Motor responses to sudden limb displacements in primates with specific CNS lesions and in human patients with motor system disorders. Can J Neurol Sci 2:285-293.

Lees AJ, Haddad S, Shaw KM, et al. (1978). Bromocriptine in parkinsonism- A long term study. Arch Neurol 35:503-505.

Lhermitte F, Agid Y, Signoret JL (1978). Onset and end-of-dose levodopa-induced dyskinesias. Arch Neurol 35: 261-263.

Lieberman A, Goldstein M, Liebowitz M, et al. (1981). Treatment of advanced Parkinson's disease with pergolide. Neurology 31:675-682.

Lieberman A, Goldstein M, Gopinathan G, et al (1982). Further studies with pergolide in Parkinson's disease. Neurology 32:1181-84.

Lieberman A, Krupsersmith M, Estey E, et al. (1976). Treatment of Parkinson's disease with bromocriptine. N Eng J Med 295: 1400-1404.

Lieberman A, Krupsersmith M, Neophytides A, et al. (1980). Long term efficacy of bromocriptine in Parkinson's disease. Neurology 30:518-505.

Lindqvist T (1941). Finger tremor and the alpha-waves of the electroencephalogram. Acta Med Scand 108: 581-585.

Lippold OCJ (1970). Oscillation in the stretch reflex arc and the origin of the rhythmical 8-12 c/s component of physiological tremor. J Physiol 206:359-382.

Lippold OCJ, Redfearn JWT, and Vuco J (1957). The rhythmical activity of groups of motor units in the voluntary contraction of muscle. J Physiol 137: 473-487.

Llinas RR (1984). Rebound excitation as the physiological basis for tremor: a biophysical study of the oscillatory properties of mammalian central neurones in vitro. In: Findley LJ, Capildeo R, eds. Movement disorders: Tremor. London: Macmillan, pp 165-182.

Llinas R, Jahnsen H (1982). Electrophysiology of mammalian thalamic neurons in vitro. Nature 297:406-408.

Lloyd KG, Davidson L, and Hornykiewicz O (1975). The neurochemistry of Parkinson's disease: Effect of L-dopa therapy. J Pharmacol Exp Ther 195:453-464.

Mai J, Olsen RB (1981). Depression of essential tremor by alpha-adrenergic blockade. J Neurol Neurosurg Psychiat 44:1171.

Marsden CD (1978). The mechanisms of physiological tremor and their significance for pathological tremor. In: Desmedt JE, ed. Physiological tremor, pathological tremor and clonus. Progress in clinical neurophysiology, vol 5. Basel: Karger.

Marsden CD (1984). Origins of normal and pathological tremor. In: Findley LJ, Capildeo R, eds. Movement Disorders: Tremor. London: Macmillan.

Marsden CD, Foley TH, Owen DAL, and McAllister RG (1967). Peripheral β-adrenergic receptors concerned with tremor. Clin Sci 33:53-65.

Marsden CD, Gimlette TM, McAllister RG, Owen DAL and Miller TN (1968). Effects of β-adrenergic tremor on finger tremor and achilles reflex time in anxious and thyrotoxic patients. Acta Endocrinal 57:353-62.

Marsden CD, Meadows JC and Lowe RD (1969). The influence of noradrenaline, tyramine and activation of sympathetic nerves on physiological tremor in man. Clin Sci 37:243-52.

Marsden CD, Meadows JC, Lange GW, Watson RS (1967). Effect of deafferentation on human physiological tremor. Lancet ii: 700-702.

Marsden CD, Meadows JC, Lang GW, and Watson RS (1969). The role of the ballistocardiac impulse in the genesis of physiological tremor. Brain 92: 647-662.

Marsden CD, Merton PA, and Morton HB (1976b). Stretch reflex and servo action in a variety of human muscles. J Physiol (Lond) 259: 531-560.

Marsden CD, Merton PA, and Morton HB (1976a). Servo action in the human thumb. J Physiol (Lond) 257: 1-44.

Marsden CD, Merton PA, Morton HB, and Adam J (1978). The effect of lesions of the central nervous system on long-latency stretch reflexes in the human thumb. In: Desmedt JE, ed. Cerebral motor control in man: Long loop mechanisms. Progress in clinical neurophysiology, vol 4, Basel: Karger, pp 334-341..

Marshall J (1962). Observations on essential tremor. J Neurol Neurosurg Psychiat 25:122-125.

Marshall J (1968). Clinical symptomatology of disease of the basal ganglia. In: Vinken PJ, and Bruyn GW. eds. Handbook of Clinical Neurology, vol 6, Diseases of Basal Ganglia. Amsterdam: North- Holland, pp 809-825..

Marshall J, and Schnieden H (1966). Effect of adrenaline, noradrenaline, atropine and nicotine on some types of human tremor. J Neurol Neurosurg Psych 19:214-218.

Marshall J, and Walsh EG (1956). Physiological tremor. J Neurol Neurosurg Psychiat 19: 260-267.

Martinez Lage JM, Marti Masso JF, Carrera N, et al. (1974). A single-blind comparative study with the combination of carbidopa and L-dopa in Parkinson's disease treatment. In: Yahr MD, ed. Current Concepts in the Treatment of Parkinsonism. New York: Raven Press.

Matthews PBC, and Muir RB (1980). Comparison of electromyogram spectra with force spectra during human elbow tremor. Journal of Physiology 302: 427-441.

Marsolais EB, And Kobetic R (1987). Implantation techniques and experience with percutaneous intramuscular electrodes in the lower extremities. J Rehab Research 23:1-8.

[illegible] PI, Boulding JE, Gibson WW, and Foulkes RG (1961). Drug-induced [illegible]ramidal reactions. J Am Med Assoc 177:665-670.

Melamed E (1979). Early-morning dystonia: A late side effect of long term levodopa therapy in PD. Arch Neurol 36:308-310.

Merton PA, Morton HB, and Rashbass C (1967). Visual feedback in hand tremor. Nature 216: 583-584.

Meunter MD, Sharpless ND, Tyce SM (1977). Patterns of dystonia ("I-D-I" and "D-I-D") in response to L-dopa therapy for Parkinson's disease. Mayo Clin Proc 52: 163-171.

Meyers R (1940). A surgical procedure for postencephalic tremor with notes on the physiology of the premotor fibers. Arch Neurol Psychiat (Lond) 44:455.

Miller EM, Wiener L (1974). Ro4-4602 and levodopa in the treatment of parkinsonism. Neurology 24:482.

Milner-Brown HS, Stein RB, and Yemm R (1973a). The orderly recruitment of human motor units during voluntary isometric contractions. J Physiol (Lond) 230: 359-370.

Milner-Brown HS, Stein RB, and Yemm R (1973b). The contractile properties of human motor units during voluntary isometric contractions. J Physiol (Lond) 228: 285-306.

Milner-Brown HS, Stein RB, and Lee RG (1975). Synchronization of human motor units: Possible role of exercise and supraspinal reflexes. EEG Clin Neurophysiol 38: 245-254.

Mori S (1975). Entrainment of motor-unit discharges as a neural mechanism of synchronization. J Neurophysiol 38: 859-870.

Morrice BL, Lee RG, Becker WJ, White DG, and Hoffer JA (1987). Viscous loading improves manual tracking accuracy in humans with cerebellar incoordination. Society for Neuroscience Abstracts. 13: 1700.

Mortimer JT (1981). Motor prostheses. In: American Handbook of Physiology II, Section I: Motor control. Edited by VB Brooks. Baltimore : Williams and Wilkins. pp. 155-187.

Mortimer T, Kicher TP, and Daroux M (1987). Intramuscular electrodes - Neural Prosthesis Program, Contract No. 1-NS-4-2396, NIH Washington, D.C.. 1st Progress report, December 1.

Murray TJ (1972). Treatment of essential tremor with propranolol. Can Med Assoc J 107:984-986.

Narabayashi H, and Ohye C (1978). Parkinsonian Tremor and Nucleus Ventralis Intermedius of the Human Thalamus. In: Desmedt JE, ed. Physiological tremor, pathological tremor and clonus. Progress in clinical neurophysiology, vol 5. Basel: Karger.

Narabayashi H, and Ohye C (1980). Importance of microstereoencephalatomy for tremor alleviation. Appl Neurophysiol 43:222-227.

Narabayashi H (1986). Tremor: its generating mechanism and treatment. In: Vinken PJ, Bruyn GW and Klawans HL. eds. Extrapyramidal disorders. Handbook of Clinical Neurology, vol 5, Amsterdam: Elsevier, pp 597-607.

Nausieda PA, Weiner WJ, Klawans HL (1980). Dystonic foot response of parkinsonism. Arch Neurol 37:132-136.

Ohmoto T, Kiskisawa H (1975). L-dopa therapy combined with peripheral decarboxylase inhibitor (MIC-486) in parkinsonism. Folia Psychiat Neurol JPN 29: 1-13.

Ohye C, Bouchard R, Carochelle L, et al. (1970). Effect of dorsal rhizotomy on postural tremor in the monkey. Exp Brain Res 10: 140-150.

Owen DAL, Marsden CD (1965). Effect of adrenergic β-blockade on parkinsonian tremor. Lancet 2:1259-62.

Parkes JD, Delano AG, Marsden CD (1976). Bromocriptine in parkinsonism: long term treatment, dose response, and comparison with levodopa. J Neurol Neurosurg Psychiat 39:1101- 1108.

Parkes JD, Schachter M, Marsden CD, et al. (1981) Lisuride in Parkinsonism. Ann Neurol 9:48-52.

Parkinson J (1817). An essay on the shaking palsy. London: Wittingham & Newland.

Partridge LD (1961). Motor control and myotatic reflex. Am J Phys Med 40:96-103.

Partridge LD (1965). Modifications of neural output signals by muscles: frequency response study. Journal of Applied Physiology 20: 150-156.

Partridge LD (1966). Signal-handling characteristics of load-moving skeletal muscle. American Journal of Physiology 210: 1178-1191.

Partridge LD, Huber J (1967). Factors in the interpretation of the electromyogram based on muscle response to dynamic nerve signals. Am J Physic Med 46:1276-1288.

Peterson EW, Magoun HW, McCulloch WS, and Lindsley DB (1949). Production of postural tremor. J Neurophysiol 12:371-384.

Peyton AJ (1986). Determination of the moment of inertia of limb segments by a simple method. Journal of Biomechanics 19:405-410.

Popovic D, Gordon T, Rafuse V, and Prochazka A (1990). The role of electrode placement for functional electrical stimulation. Annals of Biomedical Engineering, In preparation.

Pollock LJ, Davis L (1930). Muscle tone in parkinsonian states. Arch Neurol Psychiatry 23:303-311.

Price KS, Farley IJ and Hornykiewicz O (1978). Neurochemistry of Parkinson's disease: relation between striatal and limbic dopamine. Adv Biochem Psychopharmacol 19:293-300.

Pringle JWS (1960). Models of muscle. In: Models and analogues in biology. Symp. Soc Expt Biol 14.

Prochazka A, Trend J (1988). Instability in human forearm movements studied with feedback-controlled muscle vibration. J Physiol 402:421-442.

Rack PMH (1978). Mechanical and reflex factors in human tremor. In: Desmedt J.E. (ed) Progress in Clinical Neurophysiology: Physiological Tremor, Pathological Tremor and Clonus. Vol 5, Basel:Karger, pp 17-27.

Rack PMH (1981). Limitations of somatosensory feedback in the control of posture and movement. In: Brooks VB, ed. Handbook of Physiology. The Nervous System, Motor Control, part 1. Baltimore: Williams and Wilkins, pp 229-256.

Rack PMH, Ross HF (1986). The role of reflexes in resting tremor of Parkinson's disease. Brain 107:637-654.

Rack PMH, and Westbury DR (1974). The short range stiffness of active mammalian and its effect on mechanical properties. J Physiol 240:331-350.

Rascol A, Clanet M, Montastruc JL, Delage W, Guiraud-Chaumeil B (1981). L5H tryptophan in the cerebellar syndrome treatment. Biomed 35:112-113.

Redfearn JWT (1957). Frequency analysis of physiological and neurotic tremors. J Neurol Neurosurg Psychiat 20: 302-313.

Rietz RR, Stiles RN (1974). A viscoelastic-mass mechanism as a basis for normal postural tremor. J Appl Physiol 37:(6)852-860.

Rinne Uk, Sonninen V, and Siirtola T (1972). Treatment of Parkinson's disease with L-dopa and Decarboxylase inhibitor. Z Neurol 202:1-20.

Rondot P, and Bathien N (1976). Peripheral factors modulating parkinsonian tremor; in Birkmayer and Hornykiewicz, Advances in Parkinsonism. Basel:Roche, pp 269-276.

Rondot P, and Bathien N (1978). Pathophysiology of Parkinson's tremor. In: Desmedt JE, ed. Progress in Clinical Neurophysiology: Physiological Tremor, Pathological Tremor and Clonus. Vol 5, Basel:Karger, pp 138-149.

Rondot P, JedynaK CP, and Ferrey G (1978). Pathological tremor: Nosological Correlates. In: Desmedt JE, ed. Physiological tremor, pathological tremor and clonus. Progress in clinical neurophysiology, vol 5, Basel: Karger.

Rothwell JC, Kachi T, Thompson PD, Day BL, and Marsden CD (1987). Physiological investigations of parkinsonian rest tremor and benign essential tremor. In: Motor disturbances I, eds. Bencke R, Conrad B, Marsden CD, Academic press Ltd., PP 1-17.

Sabra AF, Hallett M, Sudarsky L, Mullally W (1982). Treatment of action tremor in multiple sclerosis with isoniazid. Neurology 32:912-913.

Sabra AF, Hallett M (1984). Action tremor with alternating activity in antagonist muscles. Neurology 34:151-156.

Salisachs P (1976). Charcot-Marie-Tooth disease associated with essential tremor. J Neurol Sci 28:17-40.

Sander M (1898). Ein pathologisch-anatomischer Beitrag sur Functin des Klein-hirns. Dtsch Z Nervenheil 12:363-383.

Selby G (1968). Parkinson's disease. In: Vinken PJ, and Bruyn GW, eds. Handbook of Clinical Neurology, vol 6, Diseases of Basal Ganglia, Amsterdam:North-Holland, pp 173-211.

Schwab RS, and Leigh D (1949). Parpanit in the treatment of Parkinson's disease. J Am Med Assoc 139:629-634.

Schwab RS, and Young RR (1971). Non-resting tremor in Parkinson's disease. Trans Am Neurol Assoc 96:305-6.

Sevitt I (1971). The effect of adrenergic beta-receptor blocking drugs on tremor. Practitioner 207:677-678.

Shahani BT, and Young RR (1976a). Physiological and pharmacological aids in the differential diagnosis of tremor. J Neurol Neurosurg Psychiat 39:772-783.

Shahani BT, and Young RR (1976b). Asterixis- A disorder of neural mechanisms underlying sustained muscle contraction. In: The motor system- neurophysiology and muscle mechanisms. Amsterdam: Elsevier.

Shahani BT, and Young RR (1978). Action tremors: A clinical and physiological review. In: Desmedt JE, ed. Physiological tremor, pathological tremor and clonus. Progress in clinical neurophysiology, vol 5. Basel: Karger.

Sherrington CS (1925). Notes on temperature after spinal transection with some observations on shivering. J Physiol (Lond) 58:405-423.

Stein RB, Lee RG (1977). Tremor and clonus. In: Brooks, VB. ed. Handbook of Physiology. The nervous system, Motor Control, part 2. Baltimore: Williams and Wilkins, pp 325-343.

Stein RB, Oguztöreli MN (1976a). Tremor and other oscillations in neuromuscular systems. Biology and Cybernetics 22:147-157.

Stein RB, Oguztöreli MN (1976b). Does the velocity sensitivity of muscle spindles stabilize the stretch reflex?. Biology and Cybernetics 23:219-228.

Stein RB, Prochazka A, Popovic D, Edamura M, Llewellyn M, and Davis LA (1990). Technology transfer and development for walking using functional electrical stimulation. In: Advances in External Control of Human Extremities. Edited by D. Popovic. Belgrade: Yugoslav Committee for Electronics and Automation, In Press.

Stephens JA, and Taylor A (1974). The effect of visual feedback on physiological muscle tremor. Electroenceph Clin Neurophysiol 36:457-464.

Stiles RN, Randall JE (1967). Mechanical factors in human tremor frequency. J Appl Physiol 23:324-330.

Struppler A, Erbel F, and Velho F (1978). An overview on the pathophysiology of Parkinsonian and other pathological tremors. In: Desmedt JE, ed. Physiological tremor, pathological tremor and clonus. Progress in clinical neurophysiology, vol 5. Basel: Karger.

Studler JM, Javoy-Agid F, Cesselin F, Legrand JC, and Agid Y (1982). CCK-8-Immunoreactivity distribution in human brain: selective decrease in the substantia nigra from parkinsonian patients. Brain Res 243:176-179.

Sutton GC, and Sykes K (1967a). The effect of withdrawal of visual presentation of errors upon the frequency spectrum of tremor in a manual task. J Physiol 190: 281-293.

Sutton GC, and Sykes K (1967b). The variation in hand tremor with force in healthy subjects. J Physiol 191:699-711.

Taylor A (1962). The significance of grouping of motor unit activity. J Physiol 162: 259-269.

Teravainen H, Caln DB (1980). Action tremor in Parkinson's disease. J Neurol Neurosurg Psych 43: 257-263.

Teravainen H, Fogelholm R, Larssen A (1976). Effect of propranolol on essential tremor. Neurology 26:27-30.

Teychenne PF, Bergsrud D, Elton R, et al. (1982). Bromocriptine: Low-dose therapy in PD. Neurology 32:577-583.

Thompson C, Lang A, Parkes JD, Marsden CD (1984). A double-blind trial of clonazepam in benign essential tremor. Clin Neuropharmacol 7:83-88.

Walsh FMR (1924). Observations on the nature of muscular rigidity of paralysis agitans, and on its relationship to tremor. Brain 47:159.

Waters RL, McNeaL D, and Perry J (1975). Experimental correction of footdrop by electrical stimulation of the peroneal nerve. Journal of Bone and Joint Surgery, 8:1047-1054.

Weiner WJ, and lang AE (1989). Tremor. In: Weiner WJ, and lang AE, eds. Movement Disorders: A comprehensive Survey. Mount Kisco, NY, Futura Publishing Co. Inc.

Winkler GF, Young RR (1971). The control of essential tremor by propranolol. Trans Am Neurol Assoc 96:66-68.

Winkler GF, Young RR (1974a). The control of essential tremor by propranolol. trans Am Neurol Assoc 96:66-68.

Winkler GF, Young RR (1974b). Efficacy of chronic propranolol therapy in action tremors of the familial, senile or essential varieties. N Engl J Med 290:984-988.

Winter DA (1979). Biomechanics of Human Movement. New York: Wiley. pp 151.

Wood RC (1988). Automatic Linear Control System Analysis and Design Software. West Educational Publishing Co.

Young RR (1986). In: Vinken PJ, Bruyn GW and Klawans HL. eds. Extrapyramidal disorders. Handbook of Clinical Neurology, vol 5, Amsterdam: Elsevier, pp 565-581.

Young RR (1987). Summary, part I, Tremor. In: Motor disturbances I, eds. Bencke R, Conrad B, Marsden CD, Academic press Ltd., PP 79-85.

Young RR, and Shahani BT (1979). Single unit behaviour in human muscle afferent and efferent systems. In: Poirier LJ, Soukes TL, Bedard PJ, eds. Advances in Neurology, vol 24. New York: Raven Press.

APPENDIX

Filter circuit

Fig. 16 shows the circuit module we used to generate two pairs of poles and zeroes when realising optimised filters. (FIG. 16)

The transfer function of this circuit is:

$$\frac{(s + z_1)(s + z_2)}{(s + p_1)(s + p_2)}$$

where $z_1 = \frac{1}{R_2C_2}$ $\quad z_2 = \frac{(R_1+R_f)}{R_1R_f(C_1+C_f)}$

and $p_1 = \frac{1}{R_fC_f}$ $\quad p_2 = \frac{(R_2+R_3)}{R_2R_3C_2}$

For example the following part of the transfer function of the filter illustrated in Fig. 5B:

$$\frac{(s + 3.3)^2}{(s + 15)^2}$$

was realised with the following components:

$R_1 =$ 390K $\quad C_1 = 1$ F $\quad R_f =$ 1M $\quad C_f = .068\mu$ F

$R_2 =$ 330K $\quad C_2 = 1$ F $\quad R_3 =$ 82K

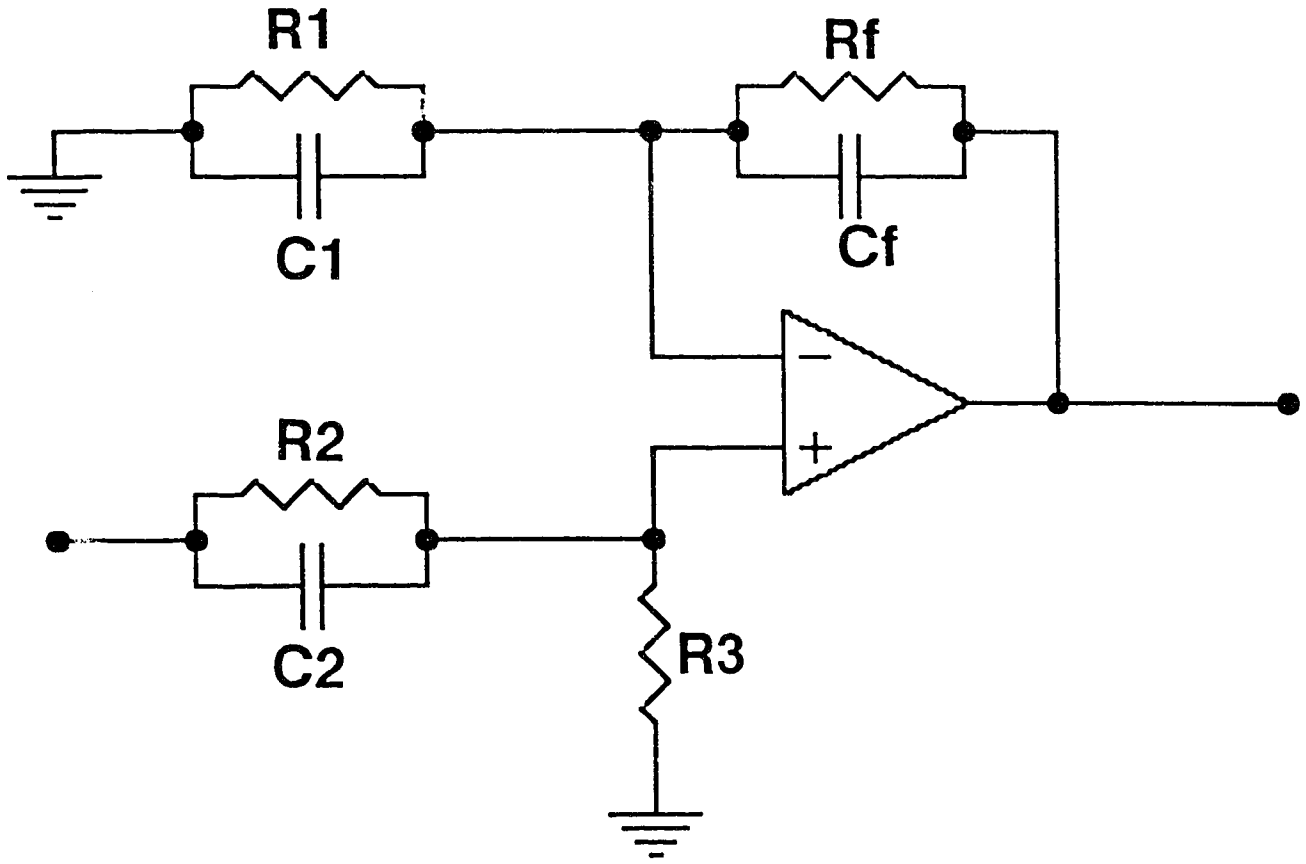

Figure 16. Circuit diagram of filter module.