Electrical stimulation as a therapeutic option to restore eyelid movements in patients with seventh nerve damage

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Abstract

Damage to the seventh nerve is a relatively common clinical problem, the most important consequence of which can be the inability to close the eyelid. The purpose of this study was to investigate whether electrical stimulation could be used to restore eyelid function. Two electrical stimulation regimes were investigated. The first was based on a commercial electrical stimulator and used rectangular pulses (pulse width 200μs, pulse repetition frequency 10 Hz, burst length 5s, applied for 1 hour daily for a period of 3 months) on ten patients. The second regime, (based on 15 ms rectangular pulses applied at a pulse repetition frequency of 10 Hz burst length 5s, applied for one hour daily for a period of three months), was implemented using a programmable stimulator designed specifically for this task and was used on seven patients. Treatment outcome was assessed in terms of maximum displacement and velocity of eyelid movement during blinks compared to normal values, and was measured with a purpose built imaging system.

Key results from this study were that both stimulation methods improved the amplitude of voluntary eyelid closure, but spontaneous eyelid movements were not affected. Eyelid velocities during closure remained below normal values for both stimulation regimes. The observed increases in voluntary closure were attributed to a reduction in stiffness of the eyelid mechanics rather than an improvement in muscle function. Some functional movement (<2 mm) was obtained with the regime based on long pulses in direct response to electrical stimulation, which was not observed with the shorter pulses. The observed function was attributed to stimulation of surviving motoneurons. The regime using shorter pulses was better tolerated by patients because long pulses induced a visual aura and were more uncomfortable.
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Statement of originality

The material in this thesis presented without reference to the work of others is original. The work has been undertaken and the thesis written solely by myself. Some of the material in this thesis is contained in:

A line imaging system for the measurement of eyelid movements. (Gittins J, Martin K and Sheldrick JH) Physiological Measurement 1995, 16, 303-311

also in

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J. Gittins
Chapter 1

1.1 Introduction

Facial paralysis caused by damage to the seventh nerve is one of the most common peripheral nerve injuries (Greer et al., 1974), for which there is no single therapy that satisfactorily deals with all related problems (Otto et al., 1986). The most clinically significant problem facing these patients is the inability to blink (Goren and Clemis, 1979). This study is concerned with the application of transcutaneous electrical stimulation to restore eyelid movement in patients with facial paralysis. It involves the identification of suitable electrical stimulation regimes to treat facial paralysis, the development of equipment to implement such regimes and the development of an eyelid movement measurement system to assess treatment outcome.

Electrical stimulation can affect the human body because of the electrophysiological properties of human cells. It has been used in many applications such as pain relief, control of epileptic seizures and muscle control. The ability to directly control muscles paralysed by nerve damage using a controlled electrical current is of particular interest to researchers involved in the rehabilitation and treatment of paralysed patients. The purpose of electrical stimulation in such cases is to restore some function to them, giving rise to the term Functional Electrical Stimulation. It is primarily used on patients suffering from impairment or disease of the central nervous system e.g. patients with a spinal cord injury or multiple sclerosis. Such patients can be described as having upper motor neurone lesions, but with preserved excitability of the lower motor neurones.

However, some uses of electrical stimulation still attract controversy, especially when used to treat peripherally denervated muscle (also known as a lower motor neurone lesion), as clinical benefits have not been conclusively demonstrated (Belanger, 1991). This study investigates whether or not the atrophic changes arising from peripheral denervation of the muscles controlling the eyelid can be reversed sufficiently to allow the denervated muscle to contract in response to electrical stimulation. If this is found to be possible, it may then become feasible to permanently restore eyelid function with a suitable prosthesis.

Section 1.2 describes some successful applications of electrical stimulation which are then used to justify facial paralysis as a likely area to benefit from electrical stimulation. Section
1.3 highlights the clinical problem of facial paralysis in more detail, together with a description of current therapies employed to control symptoms. This section is used to justify applying electrical stimulation to treat facial palsy on clinical grounds, highlighting the potential benefits to patients.

Section 1.4 summarises the study design, outlining the criteria for patient recruitment, measurements of treatment outcome and implementation of treatment regimes.

1.2 Applications of Electrical Stimulation

1.2.1 Diagnostic applications

For diagnostic purposes, electrical stimulators have been used to test the functional integrity of tendons and nerve pathways. The nerve or muscle under investigation can be stimulated using an appropriate electrical pulse and the resulting contraction observed, or the electrical response of the nerve or muscle measured. For a review see Low and Reed, (1994).

The state of innervation of a given muscle group can be quantified by using electrical pulses of different durations and measuring the amplitude of the pulse required to give a consistent measurable response. Plotting stimulation pulse duration against stimulation pulse amplitude generates a strength/duration curve, which can be used to quantify the state of innervation of a muscle group (Stephens, 1973).

1.2.2 Functional applications.

Prosthetic systems to restore function in paralysed muscle groups have been successfully developed for a wide range of applications including peroneal nerve stimulation for the correction of drop foot (Liberson et al., 1961), standing and walking systems for paraplegics (Krajl and Bajd, 1989) and nerve stimulation for bladder control (Brindley et al., 1982). In all of the above applications, electrical pulses are used to stimulate the peripheral nerve distal to the nerve lesion. The resulting action potential thus generated in the peripheral nerve causes muscular contraction via the normal physiological mechanism (see chapter 2). In such applications, the problem facing investigators is how to optimally control muscle contractions rather than being able to simply induce a contraction.
1.2.3 Therapeutic applications.

Muscle fibres immobilised by paralysis or through mechanical constraints undergo significant changes, the most clinically obvious being muscle atrophy. The rationale for using electrical stimulation for therapeutic purposes is to halt, or reverse, the observed changes in immobilised muscle fibres by imposing activity on them. Such applications of electrical stimulation include muscle strengthening regimes, where disuse atrophy due to limb immobilisation can be reduced or prevented (Gibson et al., 1988).

Previous research has shown the mutual effect that muscle fibres and nerves exert on each other: one cannot exist in its normal condition without the other (Buller et al., 1960). Even though electrical stimulation has been used to successfully treat atrophic muscle when the peripheral nerve is intact, there is no conclusive evidence to show that the same beneficial effects are observed when the same stimulation regimes are used to treat peripherally denervated muscle (Belanger, 1991). The long term beneficial effects of such regimes remain controversial, with research groups using different animal models showing different results, depending on the animal models used. This is discussed in more detail in chapter 3.

Studies claiming successful applications of therapeutic electrical stimulation have recommended that therapy must be used daily, for a reasonably long period of time (six weeks) for beneficial effects to be observed (Farragher, 1987). The facial muscles of expression are relatively small, superficial and easily accessible which makes it feasible to design a stimulation regime which could be implemented on an out-patient basis, satisfying the conditions of regular use without significantly interfering with the daily activities of the patient. If such a regime is successful, it may then be possible to design an implanted system to maintain function, making the regime more convenient and cosmetically acceptable to the patient.
1.3 The clinical problem of facial paralysis

1.3.1 Consequences of facial paralysis

The area chosen for application of electrical stimulation in this study was that of facial paralysis. This normally occurs unilaterally and is caused by damage to the seventh cranial nerve. Typically, the seventh nerve damage results from head trauma (accidents or from surgery to excise life threatening tumours) or viral infections (Otto, 1997). Psychological problems can be caused by the cosmetically disfiguring asymmetric appearance of unilateral facial palsy (Weir et al., 1995). Facial function can be affected leading to difficulties with activities of daily living such as talking, eating and drinking (Weir et al., 1995).

Clinically, the most important consequence of a facial palsy is paralysis of the upper eyelid on the affected side. If the upper eyelid is unable to move over the surface of the cornea, inadequate tear film coverage is maintained. This results in defective wetting of the ocular surface, leading to corneal drying and soreness. If this is left uncontrolled, ulceration can occur, leading to impaired vision (Salerno et al., 1991). The problem can be further exacerbated since tactile sensation on the affected cornea can also be reduced due to damage to the trigeminal nerve, which often accompanies seventh nerve damage (Hanner et al., 1986).

The problem of poor tear distribution associated with eyelid paralysis can be compounded by alteration in the rates of tear production and evaporation which can also accompany damage to the seventh nerve (Stearns, 1992). A reduction in tear production can increase the severity of problems associated with corneal drying. Symptoms can increase in severity during very dry, cold, warm or windy weather conditions when the ability to blink and maintain an adequate tear surface over the cornea becomes more important.

Excessive tear production can cause skin emaciation, where tears continually spill over the lower lid margin and down onto the cheek. The latter situation arises because of an inadequate tear drainage system, which relies on the pumping action of movement of the upper and lower eyelids for normal function (Moses, 1981). Eyelid retraction which sometimes accompanies facial paralysis can enlarge the exposed corneal area, leading to increased levels of evaporation.
Damage or irritation to the ocular surface can arise from the lower eyelid, when the reduction of muscle tone may cause the eyelid margin to rotate inward (entropian), causing the eye lashes to rub against the eye. Similarly, loss of muscle tone in the upper eyelid can cause the lashes of the upper lid to irritate the corneal surface. The eyebrow can droop over the eye which can interfere with vision, or hair from the eyebrow can cause corneal irritation. The mechanical protection from foreign objects or bright light offered to the eye by the upper eyelid is also compromised since there will be no effective blink reflex.

1.3.2 Current therapies to treat eyelid paralysis

Symptoms associated with poor tear distribution include reddening and soreness of the cornea and are often controlled using artificial tear drops or eye ointments. Different ointment preparations offer different degrees of viscosity. More viscous products have a longer lasting effect but at the cost of causing some degree of blurring to vision. It is sometimes necessary to include an antibiotic in the treatment of the eye to replace the anti bacterial component of normal tears. The corneal surface is especially prone to infection if there is continuous irritation.

Management of symptoms using artificial tear preparations can control discomfort relating to dry and irritated eyes, but such regimes do not improve mechanical protection, nor do they improve the cosmetic problems relating to facial asymmetry.

Surgical techniques are commonly used to improve static eyelid position. Procedures include canthoplasties which involve tightening either or both corners of the eye. Tarsorrhaphies can be used to suture the eyelids partially closed, thereby limiting the area of exposed cornea. Such techniques however can be cosmetically disfiguring and may also result in reduced peripheral vision.

Surgical techniques to re-animate the paralysed upper eyelid include the insertion of gold weights into the upper eyelid, which improve eyelid closure by enhancing the effects of gravity on the eyelid. Palpebral springs are an active mechanical prosthesis implanted in the eyelid, designed to oppose the muscle responsible for eyelid elevation. When this muscle is relaxed, eyelid closure is enhanced. Both approaches have been reported to be useful for
cases of mild to moderate paralysis of the upper eyelid, but are not effective in cases of severe paralysis (Levine, 1992).

More complicated surgical procedures include muscle and nerve grafts, which require an experienced neurosurgeon to perform the procedure, are relatively expensive, require a degree of retraining for the individual to use this new functionality and are not always successful (Stearns, 1992). For all but one of the patients recruited to this study, active treatments such as nerve crossovers and muscle grafts to reverse the effects of the facial paralysis were not clinically indicated and had not been offered.

Electrical stimulation may offer an alternative therapy to manage eyelid paralysis. If sufficient function can be restored, adequate tear film coverage, mechanical protection and symmetry between the two eyelids are all problems that would be addressed. Trials of electrical stimulation therapy need not interfere with existing treatments, thus incurring no additional risk to the subject’s condition resulting from this investigation.

In summary, an alternative therapy for chronic facial palsy, based on electrical stimulation, was perceived as a clinically useful area in which to explore the effects of electrical stimulation on peripherally denervated muscle.

1.4 Study Outline

This study is designed to investigate whether the contractile ability of peripherally denervated muscle could be restored in response to electrical stimulation. If sufficient contractile ability can be restored, then it might become possible to permanently restore function using a suitably designed prosthesis. As such, the nature of this study is investigative, in order to identify an appropriate stimulation regime, rather than a direct comparison of a given regime of electrical stimulation as a viable alternative to current therapies.

The investigative nature of the study avoids the commonly cited criticisms of physiotherapeutic applications of electrical stimulation, some of which have led to a degree of notoriety for lack of scientific control over study design (Belanger, 1991). These criticisms have arisen for a variety of reasons, which are now described.

It is technically difficult to design a study with an adequate and meaningful placebo for a control group, because of the sensations produced by electrical stimulation which are typically
described as a 'tingling' or 'pricking' feeling. Identifying matched groups of patients for a comparative study (one group to be given stimulation and the other general advice on the management of their condition) is difficult because typically, patients would differ in the cause, site and severity of the nerve lesion, age and the duration since the onset of nerve injury. Not all of these potentially confounding factors can be accurately determined by clinical observation and all could conceivably effect treatment outcome. The use of cross over trials to compare different regimes of electrical stimulation may not be convincing because the effects of treatment carry-over are not well documented in the literature. This would make it difficult to define end points in treatment and durations between periods of therapy and periods of non-treatment.

Extrapolation of data derived from animal studies to a clinical situation is also not ideal. The literature review in chapter 3 demonstrates that even data on different animals can provide different results depending on the muscle groups studied. In animal studies nerve lesions can be carefully induced and controlled, which as has been described, would not occur in a clinical situation. Also, there is no evidence to suggest that observations made in different animal models can accurately reflect the situation in humans.

In this study, patients were recruited according to the severity of their paralysis as measured with a standard facial palsy grading scale (House and Brackmann, 1985). For inclusion to the study, patients had to have a grade III palsy or worse (chapter 4). The condition of the palsy also had to be defined as chronic, based on the length of time for which no clinical change in facial function had been observed and was set at 12 months. This figure was justified by data available from studies on Bells palsy (Farragher, 1987).

The definition of a chronic palsy condition based on a stable clinical state does not imply that the disease state is stable, which may influence the results from this study. The time scale of changes occurring to muscle fibres as a result of denervation can span several years (Sunderland, 1978). The effect of these changes may depend on the severity, site and cause of the nerve lesion as well as the clinical state of the subject (e.g. age) and is discussed in chapter 3.
Treatment outcomes for facial palsies have previously been based on subjective assessment of facial movements (Farragher, 1987). This study was concerned specifically with the effect on eyelid closure. As such, a system was designed to accurately measure eyelid dynamics for use as a measure of treatment outcome. This system was initially used to measure eyelid movement in normal volunteers, characterising blinks in terms of the maximum displacement and the maximum speed achieved during spontaneous and voluntary blinks. A comparison was made between normal data acquired during this study with data from previous studies using alternative measurement techniques. The normal data were then used to compare with the blink responses of patients over the treatment period, in order to assess the patients response to a given stimulation regime. Specific measurements included a measure of lagophthalmus (a static measurement of the maximum eyelid closure achieved) and dynamic measurements of spontaneous blinks (peak displacement and associated peak velocity). The eyelids’ response to direct electrical stimulation was also assessed using the eyelid movement measuring system.

The design of suitable stimulation regimes was based on previous studies using electrical stimulation on peripheral denervation. The first was based on the stimulation regimes used to treat Bells palsy (Farragher, 1987) except in this case, applied to cases of moderate to severe chronic paralysis. The second regime adopting longer pulse widths than that of Farragher 1987, was based on studies to induce function in denervated quadriceps muscle (Mokrusch and Neundorfer, 1994). It was possible to implement the first regime using commercially available stimulation equipment. The second regime is based around a new stimulator, designed specifically for this study. The new microcontroller based stimulator was designed to offer as wide a range of stimulation parameters as possible. The system is programmable, allowing stimulation regimes to be tailored to individual requirements, whilst maintaining a very simple user interface. The new stimulator also improved control over the study by implementing data logging to allow measurement of patient compliance, and current monitoring to improve standards of dosimetry, neither of which was possible with the available commercial equipment.

The long pulse stimulation regime implemented using the purpose built stimulator was found to induce a visual aura. The stimulation parameters affecting the magnitude of this visual
aura were investigated in this study by recording the visual evoked responses corresponding to the stimulation pulses (chapter 9).

In conclusion, the primary aim of this study was to develop a system to improve eyelid closure in patients with a facial palsy. As part of this study it was necessary to identify and characterise suitable electrical stimulation regimes. A requirement for a portable, versatile stimulator for out-patient use was identified which was not covered by commercial units, therefore the development of a suitable system is included as part of this study. The need for a suitable non-invasive eyelid movement measurement system was also identified. Again, such a system was not currently commercially available, given that high speed cameras were too expensive, and the design and characterisation of a suitable measurement system forms a major part of this work.

The results of the first stimulation regime applied to a group of ten patients and the second regime to a second group of 7 patients are presented in the final part of this thesis.
Chapter 2

Muscle Fibre Classification and the Effects of Denervation

Muscle groups provide the final link in the nervous system to produce functional movement. Different muscle groups have evolved to meet a range of functions. Some are required to produce sustained periods of activity e.g. muscles involved in postural control. Other muscle groups are more suited to producing short bursts of vigorous activity. The properties of a muscle group are determined by the properties and relative proportion of the different muscle fibre types of which it is composed.

The effect of muscle denervation, and the ability to induce functional contraction using electrical stimulation is dependant on factors such as muscle fibre type and duration since the onset of nerve injury. For these reasons, this chapter briefly describes how muscle fibre types have been classified in the literature, followed by a description of the normal mechanism of muscle contraction. The effects of denervation on muscle fibres are then discussed.
Chapter 2: Muscle fibre classification

2.1 Muscle Fibre Classification

The following classification of muscle fibres is commonly reviewed in Totora and Anagnostakos (1990), as is the mechanism for the generation of action potentials to activate muscle fibres. Chapter 2.2 is devoted to the control of contractility of the fibre, which are discussed below.

Muscle fibres are classified into three types according to their diameter and contractile properties, which are composed of proteins called actin and myosin. There are two protein types of myofilaments that differ in diameter and contractile properties. Thin myofilaments, which are made up of actin, are 10 nm in diameter and have contractile properties. Thick myofilaments, which are composed of myosin, are 15 nm in diameter and non-contractile. The contraction of muscle fibres is dependent on the interplay of the thin and thick myofilaments. The thick myofilaments are associated with the dense bodies, which are the z-discs (Z line) and the M line. The thin myofilaments are associated with the Z line and the sarcomere structure.

Figure 2.1 Structure of a muscle fibre

Reproduced from Totora and Anagnostakos, 1990
2.1 Muscle Fibre Classification

2.1.1 Muscle Fibre Structure

The following description of normal muscle fibres is extensively reviewed in Tortora and Anagnostakos (1990), as is the mechanism for the generation of action potentials in nerve cells (section 2.2). A brief description is included for completeness.

Muscle fibres are multinucleate cells which can range from 10 - 100 μm in diameter and can be up to 30 cm in length. Each muscle fibre is composed of myofibrils, which are themselves composed of protein structures called myofilaments arranged in compartments called sarcomeres (figure 2.1). On microscopic examination it is possible to see individual sarcomeres demarcated by bands called Z-lines. There are two distinct types of myofilament, commonly termed thin and thick myofilaments, which are composed of proteins called actin and myosin respectively.

Myofibrils are surrounded by sarcoplasm which contains other structures important to the contraction mechanism including mitochondria (responsible mainly for energy production within the cell), the sarcoplasmic reticulum (important for the control of calcium ions within the cell) and the transverse T system which is important for conducting the action potential that initiates the contraction process.

The structural properties of myofibrils allow cross links to be formed between thin and thick myofilaments through actin/myosin binding sites. In the normal muscle resting state, this is not possible because of the presence of another protein group, the troponin and tropomyosin complex. This effectively covers the actin and myosin binding site, thus inhibiting their interaction until contraction occurs, which is described in section 2.2.

2.1.2 Fibre Classification

Muscle fibres are commonly classed as voluntary or involuntary fibres depending on whether they are made to contract and relax under conscious control or by the autonomic nervous system respectively. Voluntary muscle fibres can be further classified as slow twitch (type I) or fast twitch (type II). This classification is based on the mechanical properties of the fibre. Type I fibres are characterised by long twitch times, small peak contraction forces and are
relatively fatigue resistant. Type II fibres have a shorter contraction time and are capable of producing relatively large forces but tend to fatigue easily.

Biochemically, type I and type II fibres are distinguished by the way that energy for contraction is derived. Slow fibres, (known also as red or phasic fibres), contain myoglobin which acts as a reserve for oxygen. They are generally smaller in cross section than fast fibres, they have a higher capacity for oxidative metabolism, and lower capacity for glycolitic metabolism. The method of energy production used suits the level and type of activity expected from the respective fibre types.

All muscle fibres innervated by the same motor neurone are found to be of the same histochemical type. The motor neurones can be distinguished by their rate of firing. In general slow twitch motor neurones discharge at a rate of between 10 and 20 Hz, while most fast twitch motor neurones fire at a rate of between 30 and 60 Hz.

Although two distinct muscle fibre types have been described, fibre properties are relatively plastic, differentiating into fast or slow types during development depending on their innervation. Buller et al., (1960) demonstrated that by cross innervating a fast twitch fibre to a slow twitch motoneuron, the fast twitch fibre developed slow twitch properties and vice-versa. The same effect has been recorded by imposing activity on normally innervated muscle using electrical stimulation, whereby muscle fibres can be trained to adopt fast or slow twitch characteristics (Salmons and Vrbova, 1969). This property of plasticity has implications for choosing a suitable stimulation frequency as discussed in chapter 3.
Figure 2.2a Response of fast twitch and slow twitch fibres to a single stimulus

Figure 2.2b Diagram representing temporal summation of twitches resulting in tetany.

Both illustrations were reproduced from Keynes and Aidley, 1991
2.2 Muscle Contraction: The normal physiological mechanism.

Skeletal muscle groups can be made to contract under conscious control. The signal for contraction originates in the motor cortex of the brain, passes down through the spinal cord, the peripheral nerve and through to the neuromuscular junction. The signal then spreads through the muscle fibre via the transverse tubular T system, causing the muscle to contract.

Contraction at the level of the neuromuscular junction is initiated by the release of a neuromuscular transmitter (acetylcholine), from the synaptic bulbs at the end of the motor nerve following electrical excitation. The muscle fibre membrane has acetylcholine receptors in the region of the nerve endings (the motor end plate). The action of the acetylcholine on the receptors causes the muscle cell membrane to depolarise (i.e. channels open in the cell membrane which allow sodium ions to pass into the cell). Depolarisation of the muscle fibre results in the release of calcium ions from the sarcoplasmic reticulum of the muscle cell. The calcium ions interact with the protein troponin which itself is wrapped around the actin myofibre, resulting in exposure of the actin/myosin binding site, thus allowing the actin and the myosin to interact together. A mechanical analogy of this mechanism has been made with a rowing boat - the links created between the actin and myosin effectively acting as the oars on the boat. A poorly understood molecular mechanism occurs, which effectively causes rotation of the actin molecule, which in turn slides the myofilaments across each other. The analogy with the boat is that the actin is effectively rowing across the myosin. This effectively shortens the distance between adjacent z lines, causing contraction of the muscle fibre. The calcium ions are then transported back into the sarcoplasmic reticulum to await the next depolarising pulse.

2.2.1 Types of Muscle Contraction

When a single high intensity stimulus is applied to a muscle fibre arranged for isometric recording, there is a rapid increase in tension which then decays away. This is known as a twitch response, the actual duration of which depends on the type of muscle fibre involved. Contraction of the muscle fibre occurs as an all or nothing response, requiring a stimulus of a given threshold (chapter 3). Figure 2.2a shows the response of fast and slow muscle fibres to a single stimulus. There is a period of approximately 10 ms between the onset of the stimulation and the start of contraction, which has been attributed to the transport time of calcium ions from the sarcoplasmic reticulum acting on the troponin/tropomyosin complex.
The period of contraction then normally lasts for up to 50 ms and the period of relaxation a further 150 ms, depending on the fibre type.

After a fibre has received a stimulus and contracted, it is not normally possible to stimulate it again immediately as the membrane becomes less excitable. The period of reduced excitability is known as the refractory period of the muscle which is typically 0.4 - 1 ms.

Temporal summation of the contractile force generated by a single twitch can be achieved by applying a train of stimuli. If the second stimuli arrives after the refractory period but before the tension in the muscle fibre has reduced to zero, the peak tension in the second contraction will be greater than that observed during the first. This is termed tetanic contraction. Most muscle group contractions are short term tetanic contractions. Figure 2.2b illustrates the effect of tetany. Curves a through d show the effect of increasing the stimulation frequency, causing tetanic contraction.

2.2.2 Contraction Control

A motor-neuron, together with all the muscle fibres that it innervates is referred to as a motor unit. The number of fibres that are innervated by a single neuron depends on the function of the muscle involved. Muscle groups requiring a high level of control such as the oculomotor muscles, have a relatively small number of fibres innervated by a single motor neuron. Muscles designed for gross movements such as the quadriceps of the legs will have a large number of fibres innervated by a single motor-neuron.

A particular muscle group will be composed of many motor neurons, firing asynchronously. The strength of contraction is controlled by the number of fibres recruited at any one time and the firing frequency of individual motor neurones. As well as controlling the strength of contraction, this mechanism also prolongs the time before muscle fatigue sets in, as fibres can be recruited in rotation. The order of recruitment is such that smaller diameter motor neurones tend to be recruited first, larger fibres are recruited as tension increases. Since fibre diameter is directly related to the maximum strength of contraction possible, this mechanism enables fine control to be realised at low contraction strengths.
Chapter 2 : Effect of denervation

2.3 Effect of Denervation on Muscle fibres

There is a complex interaction between the condition of a muscle group, its constituent muscle fibres, the motor neurons innervating it and the effect of externally imposed activity using electrical stimulation. Studies investigating atrophic effects during limb immobilisation when the neural system remains intact, have shown that maintenance of muscle fibre properties depends on activity of both muscle fibres and their motorneurons (Gibson et al., 1988). However, studies investigating peripheral denervation have shown that imposed activity using electrical stimulation cannot completely halt or reverse all changes occurring as a result of peripheral denervation. For a review see Belanger (1991). This observation led to the suggestion of a nourishing or 'trophic' effect occurring between nerve and muscle structures, although the exact nature of this effect remains undefined. (Guth, 1968).

The most obvious clinical consequence of disruption to the motor innervation of a given muscle group is the immediate loss of voluntary and reflex use of the muscle. This is followed by atrophy or 'wasting' of the muscle over the following weeks. As well as the obvious clinical observations, denervated muscle fibres have been shown to undergo biochemical, mechanical, electrical and morphological changes which depend on the duration since nerve injury and the fibre type. The following sections discuss these changes.

2.3.1 Muscle Fibre Atrophy

Atrophy is a wasting away or shrinking of the muscle and has been observed in both immobilised and denervated muscle (Gibson et al., 1988). The effects of atrophy have been quantified by excising and weighing denervated muscle, measuring fibre diameters using microscopic techniques (Kanaya and Tajima, 1992) and by using histochemical staining techniques (Romanul, 1965). Loss of muscle bulk has been attributed to a reduction in fibre cross sectional area rather than to fibre degeneration (Finkelstein et al., 1993), although the latter has been observed in infected and long term denervated muscles (Anzil and Wernig, 1989). In controlled conditions, complete degeneration of muscle fibres was not observed for at least 3 years following the induction of a nerve lesion (Anzil and Wernig, 1989), whilst facial muscle fibres have been observed 20-30 years following nerve injury (Conley et al., 1974).
Stonnington and Engle (1973) showed that sciatic nerve section in adult rats resulted in similar percentage weight loss and decrease in fibre diameter in both fast gastrocnemius muscle and slow soleus muscle. A reduction to 3% of control values was recorded in muscle fibre diameter. Mokrusch et al. (1990) showed that in rabbit fast muscle (flexor digitorum sublimis), the effect of atrophy was greater in type II (fast) fibres than in type I (slow) fibres. Reasons for differences between studies have been attributed to the different fibre type composition of the muscle group under investigation (Mokrusch et al., 1990), metabolic differences between muscles of different animals (Frostick, 1995) and the time after denervation after which the measurements have been made (Engle and Stonnington, 1974). These results highlight the difficulty of comparing experimental results between studies and casts doubt on the suitability of extrapolating such results to a clinical situation.

2.3.2 Morphological Changes.

Mitochondria are the cellular elements largely responsible for energy production. Slow muscle fibres have more mitochondria than fast fibres (Stonnington and Engle, 1973). On denervation, after a transient increase in relative mitochondrial area, denervated soleus muscle (predominantly slow fibres) shows a reduction in overall area with a change in distribution throughout the fibre with the appearance of clusters of mitochondrial elements (Stonnington and Engle, 1973).

The sarcotubular system (responsible for calcium transport) proliferates in response to denervation within a few days (Engle and Stonnington, 1974), followed by a reduction in sarcotubular area in both fibre types. Changes to both energy producing and calcium transport systems have implications for the successful application of electrical stimulation. It is important for the cell to be able to produce the energy for contraction while calcium transport is of importance during the contraction process.

2.3.3 Fibre Type changes.

As described in Section 2.2, the firing properties of the motor neuron dictate the properties of the muscle fibre. On denervation, the neuronal influence disappears, leading to de-differentiation of fast fibre types to predominantly slow twitch characteristics (Kuno et al., 1974).
Chapter 2 : Effect of denervation

2.3.4 Acetylcholine hypersensitivity.

Acetylcholine receptors, which are normally present only in the motor end plate region, proliferate in response to denervation and become distributed over the entire length of the muscle fibre membrane (Axelsonn and Thesleff, 1957). This can lead to increased sensitivity of denervated muscle to acetylcholine. The proteins controlling acetylcholine receptors have been linked to the expression of regulating proteins connected with the development of muscle fibre type i.e. fast or slow twitch fibres (Koningsberg, 1963). The fibre type will affect the optimum frequency of electrical stimulation for producing tetanic contraction (section 2.2.1). Such changes are reported to begin between 8 and 12 hours after nerve division, depending on the length of the nerve stump (Miledi and Slater, 1970). Axelsonn and Thesleff (1957) described equal chemical sensitivity of the entire length of excised cat muscle occurring 2 weeks after denervation.

2.3.4 Membrane changes

Following denervation, the resting potential of the muscle fibre membranes falls (becomes less negative) and the trans-membrane resistance increases, effectively decreasing cell excitability. The fall in membrane potential has been reported to occur within two days of denervation (Redfern and Thesleff, 1955), although a dependence on the length of the nerve stump has been noted (Slater, 1966). The fall in membrane potential has been attributed to alterations in Na\(^+\) and K\(^+\) conductivity and to changes in the property of the Na\(^+\)/K\(^+\) pump (Creese et al., 1968). Changes in the conductance of Cl\(^-\) ions have also been implicated (Camerino and Bryant, 1976). The denervated endplate membrane develops pacemaker characteristics which has been proposed as an explanation for the appearance of fibrillation potentials over the surface of denervated muscle (Bray et al., 1976).

2.3.5 Changes in Contractile Ability.

Functional characteristics of denervated muscle change rapidly with respect to both the maximum contraction force that can be developed and the rate of force development, these changes occurring as early as 2-6 days post-denervation (Finol et al., 1981). Immediately following denervation, the force that can be developed in response to a single supra-maximal stimulus changes little, but the response to tetanic stimuli decreases (Finol et al., 1981). This process occurs in both fast and slow muscle fibres, although the changes in the fast fibres are
reported to be greater than in slow fibres (Gunderson, 1985). At later stages of denervation, tetanic tension falls in both fast and slow muscle by up to 80 - 90% with denervated slow muscles tending to show greater losses earlier (Schmalbruch et al., 1991).

A reduction in contractile force precedes atrophy after denervation. Also, contractile force reduces in denervation of the hemidiaphragm in the rat which actually undergoes hypertrophy (Gutmann et al., 1966). These two factors indicate that muscle fibre atrophy is not solely responsible for the observed reduction in contractile force. The loss of contractile ability has been attributed to the disruption of muscle fibre structure. Generation of force is confined to the few fibres that retain contractile filaments and a sarcoplasmic reticular system of sufficient complexity to allow force generation (Schmalbruch et al., 1991).

2.3.6 Biochemical Changes

Hajck et al., (1964) suggested that enzyme activation is responsible for the processes leading to atrophy, although the exact role of such enzymes remains unclear. Atrophy has also been attributed to decreased protein synthesis (Goldspink, 1976).

Energy production is also related to glycogen content within a fibre. Denervation produces a rapid reduction in glycogen content in rat hind limb muscles (Burent et al., 1984). Denervation also produces changes in insulin handling, again affecting energy production. Insulin resistance is evident within 24 hours of denervation and reaches a maximum after approximately 3 days (Smith and Lawrence, 1985, Davis and Karl, 1988).

2.3.7 Conclusion

There are many changes affecting denervated muscle which can affect the ability of a muscle fibre to contract in response to electrical stimulation, occurring over time scales ranging from several hours to several years. Clinically, the most obvious are the absence of voluntary muscle contraction and muscle fibre atrophy.

The following chapter reviews the use of electrical stimulation to impose activity on denervated fibres which can reverse some of these changes, however, the neuronal influence necessary to restore all fibre properties will not be available in cases of chronic peripheral denervation. This has led some investigators to believe that stimulation applied in such cases is of limited value, but the following chapter reviews investigations where beneficial effects have been observed.
Chapter 3

Mechanisms for Electrical Stimulation of Excitable Membranes

This chapter discusses the properties of excitable membranes and the mechanisms by which electrical stimulation has a physiological effect. This is followed by a description of the electrical parameters that must be controlled to adequately define a given stimulation regime.

The characteristics of facial muscles are then introduced leading to a description of the implications for using electrical stimulation to induce eyelid movement. Previous animal studies which have been used to demonstrate the feasibility of using electrical stimulation to induce eyelid movement in acute facial paralysis are then described.

In this study, electrical stimulation is to be applied to conditions of chronic paralysis, where the effects of muscle atrophy must be reversed, before significant function can be induced. A review of studies showing beneficial effects on denervated muscle is given, leading to a description of two potential stimulation regimes to be used in this study.
Chapter 3: Mechanisms of electrical stimulation

3.1 Electrical properties of excitable membranes.

For voluntary muscle control, electrical signals are generated in the motor cortex of the brain and pass along nerves to the muscles fibres that they innervate. The method of transmission of the signal occurs via an electrical ‘action potential’ which is generated as an all or nothing response to a given stimulus. The following sections outline how the chemical and electrical properties of the cell membranes allow this mechanism to work, which leads to a discussion of how electrical stimulation can be used to bypass the normal control mechanism and generate action potentials. For a full description, see Tortora and Anagnostakos (1990), Bagshaw (1993).

A potential difference exists across both nerve and muscle membranes which depends on the ionic conductance through the cell membrane (causing electrical gradients) and the relative permeability of the membrane to the ions present (causing chemical gradients). For nerve cells, the ions involved are mainly sodium, potassium and chloride. As well as the effect of the chemical and electrical gradients that can exist across a membrane, the cell also has an active electrogenic pump mechanism. On average, 2 potassium ions are transported into the cell for every 3 sodium ions transported out of the cell. The effects of diffusion and the pump mechanism interact to give a resting trans-membrane potential of approximately -80 mV. The ion conductances are not fixed but are themselves dependant on the magnitude of the membrane potential and time. It is the time and voltage dependence of these ionic conductances which directly affects membrane excitability and the ability to generate an action potential.

3.2 Generation of an action potential.

A nerve conducts an electrical impulse because of a change in the electrical properties of the cell membrane. When a stimulus is applied to a membrane, the voltage sensitive sodium channels in the membrane open, resulting in a transient increase in sodium ion conductance. Sodium ions diffuse into the cell, effectively changing the potential difference across the cell from approximately -80 mV to +30 mV. At this point, sodium channels close and potassium channels within the membrane open causing potassium ions to diffuse out of the cell, thus returning the membrane to its resting potential (repolarisation). The change in the electric field at one point of the fibre then effectively acts as the trigger for adjacent areas of the membrane, thus propagating the action potential along the fibre.
Chapter 3: Mechanisms of electrical stimulation

Figure 3.1 Diagram of Strength Duration curves for normal (A) and denervated muscle (B)

Modified from Low and Reed, 1994b
Although this description has been made for a typical nerve fibre, the same principle can be applied to muscle fibres, although there are some differences in the ions involved. For example, a significant component of the action potential generated by a typical muscle fibre is caused by the transport of calcium ions across its membrane. Experimental evidence indicates that the different mechanisms involved in direct electrical stimulation of muscle fibres make them more difficult to excite than nerve fibres (for a review see Belanger, 1991).

3.3 Mechanism of Electrical Stimulation

Electrical stimulation causes a movement of ions within tissue. The resulting electrical field developed within the tissue disturbs the ionic balance across excitable membranes, resulting in membrane depolarisation. For intact nervous tissue, this can result in the development of an action potential, which can then propagate along the nerve in the manner described in section 3.2. In this way, electrical stimulation of a peripheral nerve can be used to control the muscle fibres that it innervates.

Smaller diameter nerve fibres require more charge to generate an action potential. This is related to the passive electrical properties of the nerve fibres. Larger diameter fibres exhibit a lower effective resistance and increased capacitance compared to smaller diameter fibres. (Nicholls et al., 1992). The practical consequence of this when using electrical stimulation is that the order of recruitment is reversed from that occurring naturally, with larger diameter fibres being recruited more easily than smaller fibres.

Experimental data has shown that an action potential will only be generated when the stimulating pulse has a minimum charge (Lapique, 1907). The consequence of this is that the amplitude of the stimulating pulse required to initiate an action potential in nerve fibres is greater for shorter pulses than for longer pulses, for fibres of a given diameter. However, a certain minimum current, known as the rheobase current, is needed to trigger an action potential when using very long pulse lengths. Experimentally derived data takes the form illustrated in figure 3.1. This is known as a strength-duration (SD) curve.

The shape of this curve is different for nerve fibres, normally innervated and denervated muscle fibres. The characteristic curves in figure 3.1 show that normally innervated muscle fibres can typically be excited using pulses of 100-300 \( \mu \text{s} \) duration. Denervated muscle
fibres are significantly more difficult to excite and require pulses greater than 10 ms in
duration (Mokrusch and Neundorfer, 1994).

3.4 Stimulation Parameters

In the past, stimulation regimes have been gifted with names such as faradic stimulation,
galvanic stimulation, diadynamic stimulation and eutrophic stimulation. The only differences
between these regimes are the electrical parameters used to define the stimulating pulses. The
following section details all of the electrical parameters that must be used to adequately
define a given stimulation regime.

The definition of a given regime should include a description of the pulse shape used. The
most commonly used shape is a rectangular pulse, although triangular, trapezoidal and
sinusoidal shapes have also been used (for a review see, Low and Reed, 1994). An important
aspect of the pulse shape is its rise time. A slowly changing potential applied to nervous
tissue allows accommodation of the membrane potential to the applied stimulus. It has been
claimed that triangular pulses can selectively stimulate muscle fibres over nervous tissue,
since muscle fibres are less able to accommodate to the changing potential. This claim has
been shown to be difficult to prove in practice (for a review see Belanger, 1991).

Monophasic pulses have been associated with electrochemical effects due to their inherent dc
component, which can be reduced using biphasic pulses (Low and Reed, 1994).

Other characteristics of a given stimulation regime include the pulse width, the pulse
repetition frequency and the duration for which the stimulation is applied. The frequency at
which pulses are applied (pulse repetition frequency) will affect the response of the tissue.
Pulses presented at a relatively low frequency (<5 Hz) will result in a series of muscle
twitches, but higher frequencies can result in temporal integration of individual twitches
leading to a state of sustained contraction (tetany). The actual frequency at which tetany
occurs will depend on the fibre type. It could be as low as 10 Hz for slow twitch muscle,
rising to 20-30 Hz for fast twitch fibres.

The pulse width has been associated with the relative comfort of a given regime (Low and
Reed, 1994). Longer pulses are associated with stimulation of skin receptors giving a
stinging sensation. The use of shorter pulses is consistent with improved capacitive coupling
across the relatively high resistance skin barrier (section 3.6). Lastly, the stimulation regime
should include a statement describing the electrode type and size, which will influence the effective load impedance and the current density (section 3.6).

### 3.5 Potential Distribution

The electric field distribution within a semi-infinite homogenous conductive medium due to a circular electrode with an intervening skin layer has been analysed by Rattay, 1988. It was shown that the solution of the Laplace equation for electrical potentials showing axial symmetry is of the form:

$$V(r,z) = \int_{0}^{\infty} A(k) e^{-k|z|} J_0(kr) dk$$

where $k$ = bessel function parameter with dimensions of inverse length

$r$ = distance from the axis of the electrode

$z$ = depth under the electrode

$V_0$ = electrode surface potential

$V(r,z)$ = potential at depth z, radius r

with the Bessel function $J_0$ and $A(k)$ chosen to satisfy suitable boundary conditions. In this case these are:

$V = V_0$ for $z = 0, r \leq a$

$$\frac{\partial V}{\partial z} = 0 \text{ for } z = 0, r > a$$

$V \rightarrow 0$ for $r \rightarrow \infty, z \rightarrow -\infty, a = \text{electrode radius}$

The following analytical solution has been shown to hold for this situation.

$$V(r,z) = \frac{2V_0}{\pi} \arcsin \left( \frac{2a}{\sqrt{(r-a)^2 + z^2} + \sqrt{(r+a)^2 + z^2}} \right)$$  \hspace{1cm} (1)

The potential distribution $V(r,z)$ was calculated using MATLAB according to (1) and is shown at $z = -a/2$ and $z = -a/10$ in figure 3.2a with a electrode diameter of 0.01 m. The potential distribution can be seen to fall with increasing $z$, for $r < a$. Also, there is a rapid fall in potential in the region $r > a$. Rattay, (1988) showed by analysis of an electrical circuit
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Figure 3.2a (upper) shows the relative potential distribution from a circular electrode of radius $a$.

Figure 3.b (lower) shows the activating function for this electrode.
analogue of a myelinated fibre that the response of a fibre to the extracellular potential is
determined by the second derivative of the extracellular potential distribution, which has been
termed the activating function. Performing a numerical differentiation on the data in figure
3.2a gives the activating function which is shown in figure 3.2b. The figure illustrates the
effect of depth on the activating function, which is seen to diminish in amplitude with
increasing z. The activating function also shows a maximum in the region of r = a, where the
changes in the potential distribution are greatest i.e. stimulation is most effective beneath the
perimeter of the electrode. As the activating function decreases with depth, larger electrode
potentials are required to activate deeper fibres. Increasing the pulse duration however, will
not alter the effective depth of penetration, but can affect fibre recruitment, affecting fibres of
smaller diameter.

This analysis serves to illustrate that the site of the electrode is important for adequate
stimulation. Figure 3.2a illustrates that the potential falls off rapidly in the region r > a,
implying that to directly stimulate muscle fibres, the electrode must be placed directly over
the target muscle.

3.6 Effect of the Skin Barrier on Electrical Stimulation Regimes.

Stimulator outputs are often quoted in terms of current into a resistive load. This is not ideal,
as the outer surface of the skin is relatively non-conductive and its dielectric properties and
thinness result in capacitive coupling between an electrode and the underlying tissues. Some
ions however, can traverse the skin through paracellular pathways (hair follicles, sweat ducts
etc.)

Contact impedance of the electrode interface has been investigated with respect to systems
designed for electrical impedance tomography (MacAdams et al., 1996) as well as for
stimulation regimes (Nolan, 1991). The impedance loci of the epidermal layer of the skin and
underlying tissues have shown that the electrode/electrolyte components dominate at low
frequencies, the impedance of the skin dominates at mid frequencies (1 - 10 kHz) and the
impedance of the underlying tissues dominate at higher frequencies (100 kHz - 10 MHz)
(Prausnitz, 1996). A commonly used skin model to represent skin impedance is given by a
resistor (Rs) in series with a parallel combination of a resistor (Rsc) and a capacitor (Csc).
Representative values for these components are $R_s = 100-200 \, \Omega \text{cm}^2$, $R_{sc} = 10^{-10} \, \Omega \text{cm}^2$, $C_{sc} = 1\, -50 \, \text{nFcm}^{-2}$.

Skin capacitance and conductance have been shown to be proportional to area, therefore, actual values will depend on the geometry of the electrodes used. In practice, the figures shown above are not fixed but exhibit non-linear properties which depend on the applied stimulus. These have been shown to be a function of applied voltage, rather than applied current or power density (for a review see Prausnitz, 1996). The duration of current flow has also been shown to have an effect. Over a short time scale (of the order of microseconds to milliseconds) rapid drops in resistivity have been observed (Prausnitz et al., 1993). Gradual reductions in resistance have been observed over time scales of the order of seconds to hours (Pikal and Shah, 1991). The magnitudes of the changes are generally small for small applied voltages, increasing for higher voltages (~100 V). Skin properties can also depend on a number of environmental conditions such as the degree of skin hydration, temperature and time of the year.

This section shows that characterising the output of a stimulator into a simple resistive load is of limited value. To fully define a given stimulation regime and to maintain adequate dosimetry, it would be beneficial to monitor the delivered current/voltage waveforms from a given stimulator.

### 3.7 Determining optimum stimulation parameters for the stimulation of eyelid movement in normal volunteers.

Many applications using functional electrical stimulation require a graded response from the target muscle to offer some degree of control over the strength and speed of contraction e.g. standing and walking systems for paraplegics (Krajl and Bajd, 1989). When stimulation is applied transcutaneously, there are three main problems relating to adequate control. The first relates to the specificity of the stimulus. It is almost inevitable that the resulting electric field in the tissue will affect muscle and nerves adjacent to the target tissues. Also, the order of fibre recruitment changes during electrical stimulation. Larger fibres will be recruited before smaller ones, reversing the normal physiological recruitment pattern, making strength of contraction more difficult to control. The third problem relates to the synchronous nature of fibre recruitment, which will tend to result in muscle fatigue occurring sooner.
Chapter 3: Therapeutic regimes to treat denervated muscle

It is important for many applications of Functional Electrical Stimulation such as standing and walking systems to produce a graded muscle response since failure to do so would have safety implications relating to balance and stability. Although normal spontaneous blinking does exhibit some degree of graded response (i.e. not all blinks result in full eyelid closure), the safety implications of having an all or nothing spontaneous blink response are minimal. However, a prosthetic device to restore eyelid function may have to be capable of producing a graded response to maintain facial symmetry, otherwise the cosmetic result may not be acceptable to the patient. Increased levels of fatigue within the stimulated muscle should not present a problem since contraction is not necessarily sustained: only very brief activations of the orbicularis oculi muscle fibres are required on an intermittent basis, although producing sustained tonic activity to close the eyes during sleep may prove difficult.

Facial muscles are predominantly slow twitch in nature, although the orbicularis oculi (responsible for eyelid closure) has a large proportion of fast twitch fibres with firing frequencies up to 100 Hz having been previously detected (Gordon, 1951). This implies that eyelid closure will be optimally achieved via a relatively high frequency stimulation regime. Chapter 5 shows that in normals, this is true. However, the changes that occur in denervated muscle alter the mechanical properties of the muscle, resulting in the adoption of slow twitch characteristics (chapter 2), so that high frequency stimulation may not be an optimum regime for inducing functional movement in such cases. Regimes designed to stimulate denervated muscle are discussed in section 3.9

3.8 Previous work to restore eyelid movement in acute facial paralysis

Animal models have been used previously to demonstrate the feasibility of re-animating paralysed facial muscles using electrical stimulation. Tobey and Sutton (1978) used implanted electrodes in a rabbit model to maintain functional eyelid movement for a period of 5 months after paralysis had been surgically induced. The stimulation regime consisted of a single 200 ms pulse with an applied voltage of 3 - 5 V. If a typical tissue resistance of 300 Ω is assumed, this translates to a peak current of approximately 10 mA. It was observed that higher stimulation levels induced significant synkinesis into facial movements. This was attributed to spill over of the stimulating pulse to adjacent muscles. The conclusions from this study was that maintenance of eyelid movement was possible after denervation.
Otto et al., (1986) used a canine model and also showed that a symmetrical blink could be induced in the paralysed eyelid using electrical stimulation. This study used a signal derived from the Electromyograph (EMG) on the contra lateral side to trigger a stimulator. The stimulus was applied via electrodes implanted into the orbicularis oculi three months after the onset of paralysis. No indication is given as to the stimulus parameters used or the length of time for which the stimulation was applied, but it was reported that the dogs tolerated the stimulus regime very well. The conclusion from this work was also that maintenance of eyelid function was possible.

Salerno and Bleicher, (1991) also used a canine model. Two aspects of electrical stimulation were investigated.

1. The feasibility of restoring denervated orbicularis oculi muscle function by electrical stimulation.

2. The possibility of reversing the denervation changes in the orbicularis oculi using electrical stimulation.

Unilateral nerve paralysis was induced in 8 dogs. The stimulation regime was applied via implanted electrodes. In this case, the stimulation wave form to induce eyelid closure consisted of single 80 ms pulses with a stimulation current of 11-13 mA. The stimulation regime to reverse denervation changes consisted of 5ms pulses applied at 0.5 Hz for 40 minutes a day. Eyelid function was maintained for a period of 75 days post denervation. This study showed that the function of denervated orbicularis oculi muscle was maintained using this regime. They also showed that applying a daily regime of electrotherapy only reduced the pulse strength required to induce functional movement in treated muscles compared to denervated non-treated muscle for a period of thirty days, after which thresholds for treated and non-treated muscles became similar. However, full contraction could still be achieved after a period of seventy five days.

More recently, Oestricher et al., (1995) discussed the restoration of eyelid function with respect to a rabbit model. Multiple implanted electrodes were used and eyelid function was maintained for a period of 1 month. They reported that contraction strength could be adjusted by varying pulse amplitude, duration and by frequency modulation, but no details were given of the stimulation regime used, nor were details given as to the length of time that adequate
function could be maintained. They reported no tissue damage resulting from the electrical stimulation and concluded that restoration of eyelid function was possible using electrical stimulation.

The animal studies described above are highly relevant to this study as they show the feasibility of restoring function to denervated muscles using electrical stimulation. All the above studies employed implanted electrodes in cases of acute peripheral denervation of facial muscles. They have used long pulses (tens of milliseconds) applied at relatively high current levels (typically >10 mA peak). They have all described successful stimulation of the orbicularis oculi muscle with levels of stimulation that appeared to be tolerable. With the application of technology, such as RF coupled implanted stimulators (Loeb et al., 1991), it should therefore be possible to design a system to maintain eyelid function. However, several important questions remain unanswered. There is no conclusive evidence that human muscles will react in the same way as the animal models, also, there is no evidence relating to the long term condition of the muscle fibres and its response to chronic stimulation. It is not clear that the muscle will maintain properties such that electrical stimulation will continue to work over an extended period of time. There is no mention of the potential effects of chronic electrical stimulation on adjacent structures such as the oculomotor muscles and the visual system. The problems relating to long term denervation remain unanswered: there is no indication offered as to whether electrical stimulation can reverse the effects of muscle atrophy to restore contractile ability in muscle fibres after a prolonged period of denervation prior to starting stimulation. From a practical viewpoint, the above studies do not comment on whether such aggressive stimulation regimes are likely to be tolerated in humans, nor do they comment on the effect of non-symmetry or synkinesis which could affect the cosmetic acceptability. These criticisms indicate that more work on humans was required using transcutaneous stimulators, before implanting electrodes into humans could be justified.

For this reason, the investigation of transcutaneous stimulation regimes to recover function in chronically denervated muscle was identified as an important step towards the development of an implantable system. For a therapeutic regime to be useful in cases of peripheral denervation when re-innervation is unlikely, it must be possible to permanently maintain adequate contractile ability within the muscle group so that the muscle fibres can be made to contract directly using electrical stimulation, giving the opportunity to restore function permanently using a suitable prosthesis.
3.9 Therapeutic Regimes to treat peripherally denervated muscle.

Section 3.8 reviewed stimulation regimes designed to induce functional movement in cases of acute peripheral denervation of the facial nerve, none of which addressed the issue of restoring the contractile ability of muscle fibres using electrical stimulation in chronic cases. The effects of denervation on muscle fibres have been discussed in chapter 2 and include changes to electrical, structural and biochemical properties. The rationale for using electrical stimulation in such cases is that imposed muscle activity can reverse some of the changed muscle fibre properties resulting from denervation. The evidence from the literature to support this hypothesis is not conclusive (Belanger, 1991). However, the wide range of muscle types investigated coupled with the range of stimulating regimes used makes direct comparisons between studies difficult (Belanger 1991, Davis 1983). The following review of the literature highlights several studies that have shown beneficial effects of electrical stimulation and also indicates conflicting results that have arisen when using different experimental conditions.

3.9.1 Animal Studies

Westgaard (1974) investigated the effect of direct electrical stimulation on the passive electrical properties (membrane resistance and capacitance) of denervated soleus muscle in the rat. This muscle group is characterised by a relatively low proportion of slow twitch muscle fibres (approximately 10%) compared to fast twitch fibres. A stimulation regime based on rectangular pulses with a pulse width of 2.5 ms was used, applied with a pulse repetition frequency of 10 Hz. Pulses were applied in bursts of 8 s with a 12 s interval between bursts. It was observed that this regime of stimulation was able to reverse the observed changes to fibre membrane resistance and capacitance. The changes in resting membrane potential were also reversed as a result of the stimulation regime. Chapter 2 indicated that the electrical properties of the fibre membrane will influence its excitability in response to electrical stimulation. This study failed to show any effect of the stimulation regime on reduced muscle fibre diameters resulting from muscle atrophy.

Kanaya and Tajima, (1992) investigated the influence of electrical stimulation on the tibialis muscle after severing the peroneal nerve in rats. Electrical stimulation was applied via rectangular pulses with a pulse width of 100 ms, at a pulse repetition frequency of 2 Hz. After 12 weeks the muscle failed to respond to electrical stimulation, although up to this point
Chapter 3: Therapeutic regimes to treat denervated muscle

this regime of stimulation had retarded denervation atrophy. No effect was observed on the electrophysiological properties of the fibre membrane.

Girlanda et al., (1982) showed that electrotherapy increased weight loss in type 1 fibres compared to non treated controls, but reduced weight loss in type II fibres using a regime of 10 mA pulses, 400 ms in duration applied at a frequency of 0.6 Hz, twice a day for 5 minutes in each stimulation period.

Hennig and Lomo (1987) investigated the effect of a regime consisting of 0.2 ms pulses applied at a frequency of 100 Hz on fast and slow fibre types. The stimulation was applied via implanted electrodes. This study showed that stimulation, starting several months after denervation, increased the tetanic tension (a measure of the contractile ability of the muscle fibre) 37 times in the fast muscle fibres and 8 times in slow fibres, compared to non-stimulated controls.

The increased distribution of acetylcholine receptors from the motor end plate to cover most of the muscle fibre is a well documented effect of denervation (Axelsonn and Thesleff, 1957). The reversal of these changes following electrical stimulation is also well documented. Other biochemical changes, such as the loss of oxidative enzymes in denervated muscle have been shown to be reduced in guinea pigs as a result of daily electrical stimulation (0.8 ms rectangular pulses, frequency 10 Hz, 1 s on 1 s off applied 8 - 9 hrs per day). (Nemeth, 1982)

These studies illustrate the difficulties in comparing results from the literature relating the effects of electrical stimulation on denervated muscle. Kanaya and Tajima, (1992) found no response on Extensor Digitorum Longus (EDL) muscle after 3 months, whereas Hennig and Lomo (1987) found that some function could be recovered after a period of 4 months. A possible explanation for the discrepancy in these observations may lie in the stimulation regime used coupled with the predominant fibre type used in each study. Hennig and Lomo (1987) used a relatively high frequency regime and showed a beneficial effect on fast twitch fibres, whereas Kanaya and Tajima (1992) used a low frequency regime on predominantly fast twitch fibres and recorded no appreciable effects after a period of 12 weeks. Fast twitch muscle fibres will have a higher characteristic firing frequency than slow twitch fibres (chapter 2) which may account for the improved results, since the stimulation regime is similar to the observed natural firing frequency. The results of Kanaya and Tajima, 1992 (no
effect on muscle atrophy using electrical stimulation) and Girlanda et al., 1982 (reduction in type II fibre atrophy) are also contradictory with the latter study showing beneficial results on fast twitch fibres using low frequency stimulation. As well as difficulties in comparing studies using different regimes and muscles, the physical preparation of the study may also have an influence. For example, severing the nerve very close to the muscle is likely to produce recordable changes more quickly. Hence, a relatively long nerve stump may maintain the motor unit in a more stimulable condition for a longer period of time which may be attributable to the trophic effect of nerve on muscles (Arancio et al., 1992))

All the studies mentioned thus far have been relatively well controlled animal studies where total denervation of the studied muscle group can be ensured. The clinical situation is often more complex. Denervation may not be total: there may be several surviving motor units which cannot be detected using routine clinical testing. Extrapolating results from animal studies to the clinical situation may have to account for partial denervation, differences in the proportions of fast and slow twitch muscles and metabolic differences between the animal models compared to humans. The relative effect of these differences are not documented in the literature.

3.9.2 Clinical Studies

The following section discusses the application of electrical stimulation to clinical conditions of muscle denervation and the treatment of facial paralysis.

Electrical stimulation has been used to treat Bells palsy, a specific cause of facial paralysis. The rationale for such treatment is to maintain normal fibre properties for as long as it takes for the nerve to recover. The aetiology of Bells palsy is such that 80% of patients will improve spontaneously, normally within a period of 3 months. Anecdotal and case study evidence (Shrode 1993, Frach et al., 1992) has inferred that stimulation aids recovery in Bells palsy, although such studies have not been controlled in that the patients used may have belonged to the group that would have experienced spontaneous recovery.

Kidd et al., (1989) showed that significant improvements in functional ability and endurance were achieved on denervated wrist muscles when the stimulation regime mimicked the natural firing frequency of that muscle group. In this study, the frequencies of the Motor Unit Action Potentials (MUAPs) were recorded from normal muscle groups and analysed to
determine the natural firing frequency. The rationale for this work was that electrical activity in the motor unit co-operates in maintaining the biochemical and structural properties of the muscle fibres. Reproducing this ‘natural’ firing frequency using electrical stimulation would encourage restoration of normal structure and function in denervated muscle fibres. This type of patterned stimulation has been termed eutrophic stimulation. Oldham and Stanley (1989) compared two stimulation regimes on atrophied muscle in the rheumatic arthritic hand and found that the regime based on the natural firing frequency was more effective than a uniform pattern of electrical stimulation, even though the mean frequencies were the same. Of course, this study is dealing with atrophied, not denervated, muscle.

Farragher (1987) studied 40 patients with Bells palsy using eutrophic stimulation. The natural firing frequency was determined from electromyograph recordings, made while performing specific facial movements. The optimum firing frequency was determined to be 7.5 Hz for stimulation of the orbicularis oculi. This appears to be low compared to the measured firing frequency of orbicularis oculi function during contraction (typically 50 Hz, Gordon 1951). Farragher (1987) argued that the facial muscles are predominantly postural in function and therefore consist of slow twitch fibres. The criteria for patient recruitment was that there had been no significant recovery for at least 12 months since the onset of the palsy. The mean duration between the onset of palsy and treatment was 74 months. Assessments were carried out at six week intervals for a period of approximately 6 months. Treatment was performed (7.5 Hz, 80μs, up to 18V) for an average of 3 hours daily. Eyelid movements were included only as part of an overall facial movement assessment, therefore it was possible that beneficial results were reported without significant improvement to eyelid function. Farragher (1987) claimed beneficial results were achieved by stimulation of surviving motor neurones, rather than direct stimulation of denervated muscle. This work represents one of the regimes identified for use in this study.

An alternative approach to the treatment of peripherally denervated muscle was adopted by Mokrusch and Neundorfer (1994), who used a regime based on long duration pulses. The use of long pulses may be justified by considering strength duration curves for denervated muscle. Section 3.1 has already explained that such curves are used in electrophysiological studies to characterise the excitability of neuromuscular systems. Denervated muscle shows a shift in the SD curve compared to normally innervated muscle, inferring that denervated
Chapter 3: Therapeutic regimes to treat denervated muscle

muscle is more difficult to electrically excite. Also, the twitch times for denervated muscle become extended (Finol et al., 1981), implying that the muscle fibres take longer to reach their maximum contractile force. The twitch time will also be related to the effective tetanic fusion frequency, which will be lowered, following the extension of twitch times. Low frequency (10 Hz), long pulses (>10 ms) may offer a suitable stimulation regime for stimulating denervated facial muscle. Mokrusch and Neundorfer (1994) measured an increase of 50% in the maximum force that can be induced in peripherally denervated quadriceps muscle using this regime. The use of low frequency, long duration pulses represents the second regime identified for use in this study.

3.10 Skin preparation and electrode choice

A given stimulation regime can only be successful if it is used with high levels of patient compliance. In practical terms, this means making the stimulation regime as comfortable as possible with an easy set up method. Many different electrode types have been used with previous TENS (Transcutaneous Electrical Nerve Stimulators) systems. Earlier electrodes were manufactured from silicone rubber impregnated with carbon. Other types include single use pre-gelled electrodes, re-useable pre gelled electrodes and cloth based electrodes soaked in water. For this study, re-usable pre-gelled self adhesive electrodes were considered appropriate since they are simple to apply and readily adapted to facial contours. Other commonly used electrode types including carbon pads and metal electrodes were considered unsuitable because of their rigidity.

As well as factors of convenience, the electrode type coupled with methods of skin preparation will affect the impedance of the electrode/skin interface. Nolan (1991) compared 25 electrode types for use in a stimulation regime commonly used for pain relief (10 mA, 200 μs pulses applied at a PRF of 85 Hz). Pre-gelled electrodes similar to those used in this study were shown to have an electrode/skin impedance of the order of 5 kΩ, depending on the quality of skin preparation. Although other electrode types could offer lower impedances, giving more effective coupling to the underlying tissues, it was felt that they would be cumbersome to use in a home environment.

MacAdams et al. (1996) discussed methods by which skin/electrode impedances could be minimised. It was concluded that aggressive skin preparations such as rubbing the electrode site with abrasive paste prior to application did result in a significant reduction in electrode
skin impedance, although this was not quantified. However, such aggressive techniques can lead to increased risks of skin irritation when stimulation is applied over a prolonged period. Furthermore, aggressive skin abrasion could lead to small areas of increased current density which would be consistent with more painful stimulation. The use of alcohol wipes to degrease skin before electrode application was criticised for its tendency to de-hydrate the skin, leading to slightly elevated initial impedances (MacAdams et al., 1996).

Patients participating in this study were instructed to thoroughly wash and dry their face before application of 1" PAL electrodes to the medial and lateral canthi of the affected eye. The electrode positions used represent a compromise between ease of application and the ideal electrode location, which would be directly over the muscle fibres responsible for spontaneous blinking. The following chapter will show that the fibres responsible for spontaneous blinking lie within the eyelid itself, whereas the orbital fibres are used for movements such as screwing the eyelids tightly closed.

In summary, two potential stimulation regimes have been identified. Farragher (1987) has advocated eutrophic stimulation for the treatment of Bells palsy. It seems reasonable to extend this work to the patient group described in this study. The treatment regime has been well characterised and commercial stimulators are available which are designed for this application.

Mokrusch and Neundorfer (1994) have identified a stimulation regime which is optimised for the treatment of denervated muscle. However, commercial equipment is not available to implement this regime on an out patient basis and the treatment has not been characterised for use on facial palsy. Chapter 8 gives a technical description of a stimulator designed to implement this treatment regime and Chapter 7 characterises the regime on normal volunteers. The results from both treatment regimes on facial palsy volunteers are presented in chapter 10.
Chapter 4

Facial Nerve and Muscle Anatomy

This chapter describes the anatomy of the seventh nerve and classifies different types of peripheral nerve injury. The concept of facial nerve grading systems is then introduced, which is an important factor influencing patient selection in this study.
4.1 Muscles of Facial expression

Facial paralysis occurring through trauma, injury or through other mechanisms such as Bells palsy tend to occur unilaterally. The most important clinical consequence of facial paralysis is the inability to blink and maintain adequate protection for the surface of the cornea (Salerno et al., 1991). Since this aspect is the main area of study, it is discussed more fully in chapter 5. This chapter discusses the effect of seventh nerve damage on the other facial muscles of expression, the effects of damage on individuals and grading systems used to define the degree of paralysis.

Facial muscles are concerned primarily with the opening and closing of the eyelids and compressing and relaxing the cheeks and lips. Differences in facial expression between individuals arise from the relative strength and direction of different muscles from their point of origin to their point of insertion. The facial muscles have an intimate relationship with overlying superficial fascia. They are capable of a fine degree of control coupled with a wide range of contraction strength. These factors result in an almost infinite range of facial expression capable of conveying emotion and feelings.

Facial paralysis can result in severe cosmetic and psychological consequences in an individual. This can lead to problems of low self esteem, anxiety, depression and restricted social contact (Weir et al., 1995). Functionally, patients can experience problems with the affected eye, problems with eating, coupled with drooling, due to the relaxed state of the cheek and can experience difficulty with speech. Pensak et al., (1986), in a study of patients undergoing anastomosis to improve facial palsy secondary to tumour excision, showed that 23% of patients described a change in their social life following the palsy, and 21% described an effect on their business life.

4.2 Anatomy of the Seventh Nerve.

For a full description of facial nerve anatomy, see May (1986).

The facial nerve has two motor (efferent) components. The greater part of these two components is composed of motor nerves to the muscles of facial expression. It also carries secretomotor fibres for the submandibular and sublingual salivary glands and the lacrimal gland. The motor pathway for the facial muscle begins in the region of the motor cortex for the face (central fissure in the precentral gyrus). Fibres from the cortical cells pass through to the motor nucleus in the pons. Many of the fibres cross the midline synapse and reach the
Figure 4.1 Illustrating pathways of the seventh nerve in the face
contra lateral motor nucleus. Some descend without crossing to innervate the sub nuclei responsible for the periorbital and frontalis muscles. These sub nuclei have an ipsilateral and a contra lateral cortical innervation. The sub nuclei for the lower half of the face have contra lateral innervation only. The situation is complicated by other cortical areas associated with the regulation of emotional movements of the face which contain synaptic junctions in the hypothalamus, basal ganglia and mid brain tegmentum. Hence it is possible for facial expressions, such as pursing the lips whilst concentrating, to exist in people with a supra nuclear facial palsy.

The cells of the motor nucleus lie in the lower third of the pons deep in the reticular formation. The cells are arranged in small groups to form sub nuclei which innervate the muscles supplied by an individual nerve branch. The bilateral innervation present in the motor nucleus means that voluntary control of muscles in the upper face are retained in upper motor neurone facial paralysis.

The facial nerve emerges from the brain stem and courses along the cerebellopontine angle together with the vestibulo-acoustic nerves before running superiorly along the roof of the internal auditory canal. The facial nerve then enters the Fallopian canal before leaving it at the stylomastoid foramen where it runs anteriorly through the parotid gland. From here, the facial nerve bifurcates into an upper and lower division after which many small nerve filaments are formed which innervate the facial muscles.

Interruption of the pathway from the brain to the motor receptors in each muscle group can cause paralysis or affect the co-ordination of facial movements. This damage could occur in the cerebral cortex, the motor pathways in the brain, the facial nucleus, the facial nerve in the cranium, the temporal canal or in the face itself. Figure 4.1 illustrates the typical pathways followed by the facial nerve in the face, which separates into branches controlling different parts of the face. The branch of the seventh nerve affecting eyelid control is the temporal branch and follows a pathway from behind the ear into the orbital region of the eyelid.

Clinically, paralysis can be divided into two major categories, depending on the position of the nerve lesion. Lesions distal to the facial nucleus are classified as upper motor neuron lesions. Lesions proximal to the nucleus are termed lower motor neuron lesions and are typified by involvement of all facial muscles ipsilaterally, affecting both voluntary and reflex...
Chapter 4: Facial muscle and nerve anatomy

movements. Patients recruited to this study have a lower motor neuron lesion, therefore have no voluntary or reflex control over their affected facial muscles.

4.3 Types of Nerve Damage

The following brief descriptions are fully reviewed by Sunderland (1978).

4.3.1 First degree injury

This type of injury can be caused by twisting or compression. The Schwann sheath, myelin layer, endoperium and axon remain intact and sarcoplasmic transport routes are still viable. Recovery from such an injury usually takes place within three weeks without medical intervention, and recovery is usually complete. As such, patients with this type of nerve injury were not included in this study.

4.3.2 Second degree injury

The nerve axon is compressed by indentation, twisting or distortion and continuity is compromised. The loss of continuity causes degeneration of the axon distal to the injury, resulting in biochemical and histological changes to the target muscle (described in chapter 3). The proximal segment of the axon can act as a conduit, allowing axon regeneration. Recovery is normally apparent after 3 - 8 weeks, although some residual weakness may remain. Again, subjects with this type of injury were not included in the study.

4.3.3 Third degree injury

This is used to describe nerve injury with greater distortion than that occurring in first or second degree injury. Degeneration of the fibre can occur. During regeneration, the axon sprouts are able to enter any endoneurial tube available. This can lead to inappropriate gross muscle movements, called synkinesis. Such injuries can exhibit recovery after 3 - 4 months, but do not exhibit full recovery and residual synkinesis may remain.

4.3.4 Fourth degree injury

This is defined as disruption of the perineurium surrounding nerve fascicles with preservation of the nerve sheath. The perineurium no longer confines regenerating axon sprouts to the appropriate fascicle. The axon can then be lost in neuroma formation or can regenerate into a distal endoneurial tube with an adjacent fascicle. This can reduce innervation to the original end plate, resulting in a diminished maximal muscle contraction. Such injuries can take up to
12 months to exhibit recovery, although there will certainly be some degree of residual weakness.

4.3.5 Fifth Degree injury

This term is used to describe an injury where the entire nerve trunk has been disrupted. Again, degeneration and subsequent regeneration can occur but the correct re-innervation of appropriate motor end plates is unlikely. Synkinesis can occur coupled with a large degree of residual weakness.

4.4 Facial Palsy Grading Scales.

The scheme most commonly accepted by the international community to assess the degree of facial paralysis after seventh nerve injury is that proposed by House and Brackmann, (1985). Table 4.1 describes this classification scheme.

In practice, assessment schemes such as these are subjective and can only act as a guide. Conditions where patients present with a total paralysis are quite rare. All subjects recruited to this study had some degree of residual function and some remaining muscle tone. For recruitment to the study, patients had to have had at least a grade III palsy present for at least 12 months. In terms of the description of nerve injury reviewed in the previous section, these selection criteria indicate that the subject had suffered at least a third degree nerve injury.

Since most patients in this study suffered seventh nerve damage following excision of an acoustic neuroma, the most common injury site was within the temporal canal.
<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>normal</td>
</tr>
<tr>
<td>II</td>
<td>rest</td>
</tr>
<tr>
<td>mild dysfunction</td>
<td>normal symmetry</td>
</tr>
<tr>
<td></td>
<td>motion</td>
</tr>
<tr>
<td></td>
<td>face: moderate to good</td>
</tr>
<tr>
<td></td>
<td>eye: closure possible</td>
</tr>
<tr>
<td>III</td>
<td>rest</td>
</tr>
<tr>
<td>moderate dysfunction</td>
<td>obvious asymmetry, noticeable synkinesis</td>
</tr>
<tr>
<td></td>
<td>motion</td>
</tr>
<tr>
<td></td>
<td>eye: closure with effort</td>
</tr>
<tr>
<td></td>
<td>forehead: slight to moderate movement</td>
</tr>
<tr>
<td></td>
<td>mouth: remains poor with maximal effort</td>
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<tr>
<td>IV</td>
<td>rest</td>
</tr>
<tr>
<td>moderate to severe</td>
<td>asymmetry, disfigurement</td>
</tr>
<tr>
<td>dysfunction</td>
<td>motion</td>
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<tr>
<td></td>
<td>forehead none</td>
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<tr>
<td></td>
<td>eye incomplete closure</td>
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<td></td>
<td>mouth asymmetry even with maximal effort</td>
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<tr>
<td>V</td>
<td>rest</td>
</tr>
<tr>
<td>Severe dysfunction</td>
<td>asymmetry</td>
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<tr>
<td></td>
<td>motion</td>
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<tr>
<td></td>
<td>forehead none</td>
</tr>
<tr>
<td></td>
<td>eye incomplete</td>
</tr>
<tr>
<td></td>
<td>mouth slight movement</td>
</tr>
<tr>
<td>VI</td>
<td>total paralysis</td>
</tr>
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Table 4.1 The House Brackmann facial palsy grading scale.
Chapter 5

Eyelid Movement

Chapter 1 described the effect of seventh nerve palsy on the muscles of facial expression. Eyelid paralysis was cited as the most important consequence from a clinical perspective. The following chapter describes the physiological mechanisms underlying eyelid movements, including a description of the motor mechanism controlling upper eyelid position. The role of eyelids in protecting and maintaining the condition of the ocular surface is then discussed, which includes a description of different categories of eyelid movement. A description of the parameters commonly used to characterise normal eyelid movements is given, followed by a description of the effect of facial paralysis on eyelid movement.
Figure 5.1 Anatomy of the eyelid motor system
Chapter 5: Eyelid movement

5.1 The eyelid motor system

The motor system of the eyelids consists of the levator palpebrae superioris (LPS), the orbicularis oculi (OOc) and Mullers muscle. The relative positions of these muscles are illustrated in figure 5.1, with the OOc positioned anterior to the levator muscle. Mullers muscle lies posterior to the levator muscle and is not shown in this figure. The levator muscle is innervated by the fifth cranial nerve, Mullers muscle by the sympathetic nervous system and the OOc by the seventh cranial nerve. Tonic activity in the LPS is responsible for eyelid elevation. Mullers muscle plays a role in adjusting the width of the palpebral fissure (the maximum distance between the upper and lower eyelid margins). Contraction of the OOc is responsible for eyelid closure. The OOc has been described as having three separate components, termed the pre-septal, pre-tarsal and orbital components (Moses, 1981). The preseptal and pretarsal sections normally contract for spontaneous and reflex blinking. The orbital section is used during forceful eye closure and for protective acts such as screwing the eyes closed in bright light.

Patients presenting with a facial palsy have damage to the seventh cranial nerve, thus it is the control over the OOc and the ability to close the eyes which is compromised.

5.2 A description of eyelid movements

The eyelids provide the mechanical component involved in protection of the corneal surface. The motor system controlling the position of the eyelid can be summarised as having five major roles.

1. Spontaneous (or periodic), reflex and voluntary blinking.
2. Elevation of the eyelid during normal waking.
3. Voluntary eye closure and eye opening.
4. Involuntary adjustment of the eyelid position to match the vertical globe position (saccadic eyelid movement).
5. Firm eye closure in acts such as sneezing

This study is primarily concerned with the effects of facial paralysis on blinking. However, the above eyelid movements are also relevant to the study and are described in the following sections.
5.2.1 Blinking

A blink can be described as a brief closing of the palpebral orifice. The upper eyelid moves downwards, closing from the lateral to the medial canthus towards the lower eyelid in an almost zipper-like fashion (Moses, 1981). The lower eyelid provides only a very small contribution to eye closure, and moves nasally and upwards (Moses, 1981). A blink is normally a bilateral event, with a high degree of conjucacy occurring between the two upper lids (Stava et al., 1994). In all types of blinks, when the eyelid closes, there is a brief, abrupt, inhibition of tonic LPS activity, before a burst activation of Ooc motoneurons resulting in downwards movement of the upper eyelid. Eyelid re-opening is caused by decay of Ooc activity and the onset of tonic LPS activity to its prior level, without overshoot (Evinger et al., 1991, Schmidtke and Buttner-Ennever, 1992). The period of inhibition of the LPS normally precedes and outlasts Ooc activation by approximately 10 ms (Schmidtke and Buttner-Ennever 1992).

5.2.2 Reflex Blinks.

Reflex blinks provide the mechanism for mechanical protection of the cornea and are caused by tactile, auditory or visual stimuli. For example, an object touching the cornea or eyelashes will cause a reflex blink as will a sudden movement of an object towards the cornea. A loud noise will also elicit a reflex blink. A typical blink downphase will last approximately 90 ms. The whole blink sequence typically takes 300 ms (Evinger et al., 1991).

5.2.3 Spontaneous Blinking

As well as acting as a mechanical protective barrier, the purpose of the eyelids is to maintain a tear film over the surface of the cornea. This is normally achieved via the act of spontaneous blinking. The rate of blinking, or the inter blink interval, varies between individuals but typically occurs at a rate of 14 blinks/minute (Schmidtke and Buttner-Ennever, 1992). The blink rate of an individual will normally remain relatively constant provided the external environment remains constant. Environmental conditions that can affect blink rate include low humidity and windy conditions which result in elevated levels of tear evaporation and an increased rate of blinking. Different blinking patterns have also been associated with the cognitive state of an individual such as excitement or fatigue (Tsubota et al., 1996), psychological conditions such as schizophrenia (Stevens, 1978) and central acting dopamine levels (MacClean et al., 1985).
The trigger for a spontaneous blink is not fully understood. Several ideas have been suggested, including a signal from the visual system (Gordon, 1951) or from receptors on the corneal surface. However, anaesthetising the cornea does not result in a significant change in blink rate. Also, the rate of blinking is not significantly altered in blind people (Moses, 1981).

5.2.4 Voluntary Blinking

A voluntary blink can be made in normal humans. Voluntary blinks tend to have larger amplitudes than a typical spontaneous blink (Evinger et al., 1991). In this study, reference is made to the term 'forced eye closure', which is an extension to the meaning of a voluntary blink and refers to the ability to close both eyes under voluntary control. The difference between forced eye closure and a voluntary blink is related to the duration of the eyelid movement, typically 300 ms for a normal voluntary blink (Evinger et al., 1991) and up to 1.4s for forced eye closure.

5.2.5 Eyelid Elevation

Eyelid elevation is performed by tonic activity in the LPS. A close relationship exists between levels of alertness and LPS activity. Fatigue causes the upper eyelid to lower involuntarily; it becomes impossible to maintain eyelid elevation at high fatigue levels.

5.2.6 Voluntary Eyelid Control

Voluntary eye closure and inhibition of the LPS affects both eyelids synchronously. It is not possible to effect voluntary unilateral control over the eyelids i.e. winking will always involve the contra-lateral side.

5.2.7 Involuntary adjustment of eyelid position

The position of the eyelid, in normal humans, is affected by the position of the globe. If gaze is directed upwards, there is an associated movement of the eyelids upward. Similarly, when an individual gazes downwards, the upper eyelid tracks downwards also. This is termed saccadic movement of the eyelid. The characteristic burst of OOc activity associated with the blink down phase is generally not observed during downward eyelid movement during saccades. Some studies have shown the OOc to be inactive during such movements (Evinger et al., 1991, Guitton et al., 1991), although other studies have observed some OOc activity for larger saccadic movements (Gordon 1951) and it has been suggested that a brief contraction
of the OOc may have been overlooked (Becker and Fuchs, 1988). Kinematic saccadic data on patients with seventh nerve palsy show similar values to normal controls (Tsubota et al., 1996), again suggesting that the role of the OOc in such movements is minimal. Evinger et al., (1991) have explained this similarity by attributing the driving forces for downward lid saccades to the mechanical linkage caused by the fascia that connects to the superior rectus muscle (controlling globe position) and the LPS and the interaction between the LPS and the superior transverse (Whitnalls) ligament. This is shown in figure 5.1a. During eyelid elevation, the LPS pulls on the ligament and the forces generated by the LPS will be balanced by the downward stretch force generated by the ligament. When the LPS relaxes, the passive force generated by the ligament can cause downwards movement of the eyelid. Evinger et al., (1991) also proposed that some downwards force can be caused by the tone of the OOc muscle. Stretching this muscle by eyelid elevation and activity in the LPS must generate some downwards force when the LPS is inhibited.

5.2.8 Forceful eyelid closure

Forceful eye closure is generated by reciprocal activity of the OOc and the LPS, however, unlike spontaneous blinking, the orbital portion of the OOc is used as well as the palpebral portion.

In conclusion, the main motor force controlling eyelid movements are derived from reciprocal activity of the OOc and the LPS. However, mechanical linkages and the elastic properties of the eyelid system also have an effect on eyelid dynamics. The following section describes the parameters used to characterise eyelid movements and indicates how electromyograph (EMG) studies have been used in conjunction with studies on eyelid movement to elucidate further the motor mechanisms involved.

5.3 Measurement of eyelid movement

The position of the eyelid relative to the globe, and eyelid motility in general, have been analysed for assessing ptosis, third and seventh nerve palsies, myasthenia gravis, Graves disease and Parinauds syndrome (Guitton et al., 1991). Blinks have also been assessed in
Chapter 5: Eyelid movement

Figure 5.2a Data reproduced from Guitton et al., 1991. Reflex, voluntary and spontaneous blink main sequence data for 9 normal volunteers. Each point represents at least 6 blinks. The vertical bars represent one standard deviation.

Figure 5.2 b Data reproduced from Evinger et al., 1991. Each point represents ten blinks from 9 volunteers for voluntary, spontaneous and reflex blinks. This data shows differences in the blink main sequences derived from the three types of blink movement.
terms of inter blink frequency for conditions of dry eye (Tsubota et al., 1996), for monitoring
fatigue levels and the cognitive state of the individual (Schmidtke and Buttner-Ennever,
1992) and with relevance to central dopamine levels (MacClean et al., 1985).

5.3.1 Characterisation of blink movements

This section describes parameters commonly used to characterise eyelid movements.
Methods used to measure these parameters are discussed in more detail in the chapter 6.

Blinks have been characterised in terms of both inter-blink intervals and in the dynamics of
individual blinks. Eyelid movement has been quantified in terms of both angular
displacement (Evinger et al., 1991, Sibony et al., 1991), and vertical linear motion (Guitton et
al., 1991).

Gordon (1951) measured the extent of eyelid movement (the peak upper eyelid displacement)
and the time taken from the onset of the blink until the point of maximum eyelid
displacement. More recent studies have characterised eyelid movement in terms of the peak
eyelid displacement and the maximum velocity attained by the eyelid. The relative merits of
the different measuring systems are reviewed in chapter 6.

It has been established that larger eyelid displacements during a blink are associated with
higher peak velocities during both the down-phase and the up-phase (Evinger et al., 1991,
Guitton et al., 1991, Niida et al., 1987). It has also been observed that the blink down-phase
achieves higher peak velocities than the up-phase (Evinger et al., 1991, Guitton et al., 1991,
Niida et al., 1987). Measurements are typically displayed as a graph of peak velocity versus
maximum displacement, for a series of blinks of different amplitudes. A linear regression fit
applied to the resulting data is commonly referred to as the main sequence relationship
(Evinger et al., 1991, Guitton et al., 1991, Niida et al., 1987). This has been used for
characterising normal blinks (Evinger et al., 1991, Guitton et al., 1991), for investigating age
related changes to blink parameters (San et al., 1997) and for characterising eyelid
movements in facial paralysis (Sibony et al., 1991, Huffman et al., 1996). For normal blinks,
the main sequence relationship is linear over the range of blinks commonly observed (0-12
mm), although there is disagreement regarding the best fit linear regression coefficients
(chapter 7).

Guitton et al., (1991) used a search coil technique (described in chapter 6) to measure eyelid
movements and described a typical spontaneous blink as having an amplitude of 10 mm, a
peak down-phase velocity of 340 mm/s and a peak up-phase velocity of 140 mm/s. They also showed no significant differences in the dynamics of voluntary, reflex and spontaneous blinks. The actual data is shown in figure 5.2a representing spontaneous, reflex and voluntary blinks. Each point represents a mean of between 6 and 32 blinks derived from 9 normal volunteers. The vertical bars on each point indicate one standard deviation, which indicates the high variability associated with blink measurement. This is discussed further in chapter 7. Evinger et al., (1991) also using a search coil technique, noted velocity differences between electrically evoked reflex blinks, voluntary blinks and spontaneous blinks. Peak velocities during reflex blinks were higher than those occurring during equal size voluntary blinks. Spontaneous blinks were recorded as having the lowest peak velocities. These data (presented in terms of angular rotation) are reproduced in figure 5.2b. In this case, each point represents an average of at least ten blinks from 9 normal volunteers. Evinger et al., (1991) explained these results with reference to EMG recordings made simultaneously with the eyelid movement recordings. These showed that reflex blinks are associated with simultaneous discharge of many OOc motor units involving septal and orbital portions of the OOc. Spontaneous blinks were shown to have a gradual onset of OOc activity involving only the septal OOc portion.

Evinger et al., (1991) showed the speed of downward lid saccades to be consistent with a passive movement mechanism, with peak velocities lower than those achieved during normal blinking. Upward saccadic movement was attributed to a pulse step discharge of the LPS muscle. No significant differences between peak velocities in upward movement of blinks and saccades were recorded. However, Niida et al., (1987) showed that upwards saccadic movements (typically 60 mm/s) were quicker than upwards movement during blinking (typically 50 mm/s), which was attributed to mechanical linkage between the globe and the eyelid.

5.3.2 Eyelid Movements in Facial Paralysis

Sibony et al., (1991) studied the eyelid movements of patients with unilateral facial paralysis using a search coil technique. They recorded a reduction in peak velocity and maximum displacement of the eyelid. The main sequence relationship for the blink down-phase was described as a slow saturating power function as opposed to the linear relationship observed in normal volunteers. They also reported that the contra lateral normal lid exhibited signs of
hyperactivity, leading to increased velocities during the blink down-phase. Huffmann et al., (1996) studied the eyelid movements of patients with recovering facial palsy, again using a search coil technique. In agreement with Sibony et al., (1991), they established that peak velocities and amplitudes during spontaneous blinks were reduced by approximately 30% compared to the contra lateral side. They also recorded elevated peak velocities on the normal side and attributed this to increased OOC motor output. This was termed adaptive gain. However, for severe paralysis, adaptive gain was not observed. They suggested that OOC activity must exceed a certain threshold on the affected side before adaptation could occur.

Peak velocities during the blink up-phase in palsied patients have also been reported to be lower than normal values (Sibony et al., 1991, Huffmann et al., 1996), although the differences are not as great as during blink down-phase. No significant differences were observed in peak amplitudes and velocities of vertical eye saccades, although they reported the paretic eyelid to lag behind the normal eyelid. Using the contralateral lid as a control, it was observed that peak amplitudes and velocities were lower on the affected side even though values lay within normal limits.

In summary, although all studies are in agreement about general comments that can be made about blink metrics, such as larger displacements being associated with higher velocities, the exact relationship between these two parameters varies between studies (chapter 7). This may be attributable to the different measurement techniques used or to the experimental protocol where measurement techniques are similar. For example, some workers have commented that it is difficult to determine which blinks are truly spontaneous when subjects know that they are being monitored, making accurate comparisons between voluntary and spontaneous blinks difficult. However, measurements of amplitude and temporal characteristics of eyelid movements have been shown to reflect changes occurring as a result of facial paralysis (Huffman et al., 1996). Repeated measurements made over time should allow the progress of therapies designed to improve eyelid closure to be monitored.
A New Method for Measuring Eyelid Movement

Previous methods of measuring and characterising eyelid movements are reviewed, leading to justification for the development of a new measurement technique. The new technique is designed around a high speed imaging system and can produce graphs of upper eyelid displacement versus time and velocity versus time, after analysing the image data off-line. These graphs can be used to characterise eyelid movements in terms of peak amplitude and peak velocity. Using a range of blink amplitudes, it is possible to generate the 'main sequence' description of eyelid metrics, allowing results from this measurement technique to be compared directly with results derived from alternative methods, such as the commonly used search coil technique.
6.1 Introduction

The condition of a muscle fibre and the effects of denervation can be characterised in many ways including measurement of fibre diameter, membrane potential, the organisation of the contractile apparatus and the mean weight of the muscle group (Chapter 2). However, it is not practical to measure such parameters in a routine clinical environment. Furthermore, measurement of these parameters would not directly give any information as to the ability of the muscle to contract and produce functional movement in response to electrical stimulation. Hence, it was necessary to measure eyelid movement accurately, relating these data to the condition of the muscle fibre and its response to treatment with electrical stimulation (Gittins et al., 1999).

Eyelid movements have previously been characterised using a variety of measurement techniques. Gordon (1951) used a steel ball bearing mounted on the eyelid to reflect light onto moving photographic paper. Other early systems used a mechanical lever fixed to the eyelid to drive a measuring system, e.g. a potentiometer (Kennard and Glaser 1964). More recent techniques include the use of a Hall effect sensor mounted on the lower lid and a magnet on the upper lid (Hamiel et al., 1994), but most studies have used a search coil mounted onto the eyelid and measured the voltage induced in a second coil close to the eyelid when both are subject to an alternating magnetic field (Evinger et al., 1991, Guitton et al., 1991, Huffmann et al., 1996). As in all methods involving physical contact with the eyelid, this measurement technique could influence eyelid motion and is cumbersome to use as part of a routine clinical assessment. Non-contact optical techniques include systems based on a standard video format (Niida et al., 1987), but are limited by their poor temporal resolution. For this technique, eyelid movement was expressed in terms of the area of the exposed eyelid, which was then calibrated in terms of eyelid displacement. High speed video systems have been used (Hung et al., 1978), but their application is limited by their relatively high cost (a typical high speed camera may cost £10,000).

Optical methods of measurement have the advantage of not being in contact with the eyelid, thus avoiding modification of the eyelids' movement by physical interference. Such systems would also have the advantage of being easily used in a routine clinic. However, the success
Figure 6.1 Circuit diagram of I-Scan board (reproduced from the data sheet)
of such systems would depend on overcoming the limitations of temporal resolution and cost. Consequently, a measurement system based on a low cost, high speed line scan camera was developed as part of this study (Gittins et al., 1995).

6.2 The Line Scan System

6.2.1 System Overview

The imaging device consists of a 256 element Charge Coupled Device (CCD) linear array. When an image of the eye and eyelids is focused onto the CCD array (Loral Fairchild CCD 111), using a standard f/2, 48 mm focal length camera lens, electric charge accumulates on each element at a rate determined by the wavelength and intensity of the incident light. The array responds to radiation of wavelengths ranging from 200 - 1000 nm with a peak response around 830 nm. The difference in reflectivity or contrast that exists between skin and the corneal surface results in a corresponding charge profile within the CCD array. The charge on each element is converted to a voltage level as it is clocked sequentially out of the array, giving a line image of the eye from which the position of the eyelid margins can be determined. By acquiring a sequence of reflectance profiles during eyelid movement, it is then possible to determine the position of the eyelid margin through the blink sequence, from which a graph of upper eyelid displacement versus time can be derived. These data can then be used to determine a velocity versus time profile by differentiating the displacement data set with respect to time.

6.2.2 Hardware Design

A commercially produced circuit board (I-Scan, Optimum Vision PLC) which contained the CCD array and all the necessary scanning circuits was used to generated line image signals. The circuit for this camera board is reproduced in figure 6.1. In normal operation, the CCD array accumulates charge in each of the 256 elements for an exposure period determined by the monostable U4. This period can be altered via R6. After this exposure period, the charge on each CCD element is transferred serially along the array to the output using a biphasic clock (θ1 and θ2). The resulting analog signal is made available from the CCD array via transistor Q1. The array also requires a reset pulse to be applied to the output line after the...
Figure 6.2 Illustrates the important timing signals generated by the I—Scan board (master clock Θr, line pulse and element data) and the signals derived by the measurement system control logic

Figure 6.3 Block diagram of the line scan system
analog signal from each element has been clocked out (θr). The line scan camera board derives all the required pulses (exposure pulse, θ1, θ2 and θr) from a single master clock. The overall serial transfer rate is therefore controlled by the master clock frequency, which can be adjusted via potentiometer R1 (range 1 MHz - 4 MHz), although the actual data rate is half the master clock rate because of the biphasic clocking action previously described. The raw data from the line scan camera thus consists of blocks of data (lines) each comprising 256 elements. The effective line acquisition frequency is determined by the exposure period and can be adjusted via R6 through a range of 200 Hz - 1000 Hz. The timing relationships for the scan control is shown in figure 6.2.

For this application, the line acquisition frequency was set to 400 Hz, giving a minimum time resolution of 2.5 ms. The frequency of the master clock was set to its minimum value of 1 MHz, giving a serial data rate from the camera board of 500 kHz. This serial data rate was too high to be easily interfaced to a PC without using a relatively expensive dedicated analog I/O card. For this reason, a system was designed to acquire the line scan data to memory external to the PC, before transferring the acquired data to the PC for subsequent analysis.

6.2.3 The Line Scan Acquisition System

The main elements comprising the line scan system can be identified with reference to figure 6.3. The serial analog signal from the line scan board is amplified (a.c. coupled amplifier block) and digitised (a-d converter block). The resulting digital data is then stored via a latch into the line scan system memory. When data acquisition is complete, data from the memory is transferred to the PC via the parallel port interface for subsequent analysis. Data direction is controlled via the control logic and the latch. The memory is addressed via two 8 bit counters, which are clocked by signals derived from the line scan system and the control logic during data acquisition, or directly by the PC when data is being transferred.

6.2.4 Buffer Memory Organisation

The buffer memory in the line scan system is organised into 256 blocks each containing 256 elements i.e. each block contains one line of data. An 8 bit counter synchronised to the master clock is used to address consecutive element positions in the memory and a second 8 bit
Figure 6.4 Effect of movement on signal to noise and contrast
counter synchronised to the line rate pulse is used to address consecutive memory blocks. Data can be acquired in two modes. In the first mode data is acquired continuously, with the memory acting as a circular buffer. With a line rate of 400 Hz, and the ability to store 256 lines, the memory is capable of storing approximately 0.65 seconds of line information. When the memory becomes full, old data is overwritten. In the second mode of operation, data is acquired in response to a given stimulus. When the memory is full, data acquisition ceases.

To extend the effective storage time of the system, a selectable divide by 2, or divide by 4 circuit acting on the clock incrementing the line memory counter is available to reduce the line counter clocking frequency to 200 Hz or 100 Hz respectively. When these are used, although line data is effectively acquired at 400 Hz, only one in two, or one in four lines are actually stored, extending the acquisition time without affecting signal to noise ratio and contrast. Although the acquisition period could have been extended by lowering the line acquisition rate, this solution would have affected the signal to noise ratio by altering the time available for charge to accumulate on the CCD elements. This appears to be favourable, since lowering the line acquisition rate will increase time available to acquire charge and improve signal to noise ratio. However, lowering the line acquisition rate will cause blurring when imaging a moving structure. Figure 6.4 illustrates this point. When imaging a static black to white transition (6.4a), the largest signal will be accumulated on element 3 as the white area entirely covers this element. Changing the line acquisition time in this case will generate larger signals, improving the contrast between the black and white areas on the image. Figure 6.4b illustrates a black to white transition moving at a constant velocity. In this case, during the acquisition period, the white area will contribute signals to elements 2,3,4,5,6 and 7, reducing the contrast between the black and white areas and making it more difficult to determine the position of the white area. Decreasing the line acquisition frequency will make this situation worse.

Figure 6.4c illustrates the situation where the object is accelerating. During the acquisition period, the largest signal will be accumulated on element 2, with decreasing contributions to subsequent elements, as the object is accelerating. Again, using low line acquisition frequencies, the image may become more difficult to interpret correctly because of this effect. In such circumstances, reducing the line memory counter clock rate to 200 Hz, via the divide
circuitry described previously, increases acquisition time by storing only one in two, or one in four line images without affecting signal to noise ratio and contrast.

6.2.5 Control Logic and Memory Clock Generation

The operating mode of the linescan system (i.e. data acquisition mode or data transfer mode to the host PC) is defined by the control logic, which is in turn controlled via the host PC through the parallel port interface. This logic also conditions the available clocks from the camera board to the requirements of the other components comprising the line scan system. These include the memory element counter clock, the memory line counter clock, the analog to digital converter clock, and a clock to strobe the memory read/write (r/w) control line. The element memory counter and the line memory counter clocks are either derived from the camera board or generated directly by the PC, according to whether data is being acquired or transferred respectively.

Figure 6.2 illustrates the timing signals generated by the camera board which are used by the line scan acquisition system (master clock, exposure pulse and $\theta_r$). The clocks derived from these by the control logic are also shown. The derived clocks are the element memory clock (used to address the memory locations for each data element of the CCD array), the a/d clock which is a balanced clock necessary to drive the analog to digital converter and the memory r / w line. Figure 6.2 also illustrates the temporal relationship of the actual CCD data with the clock pulses. The position of valid data is illustrated by the numbers 1 and 256 under the respective elements of the CCD array.

6.2.6 Clock conditioning

The master clock from the camera board cannot be used directly to increment the element memory counter since the CCD elements are clocked out using a biphasic action which results in a data rate which is half the clock rate. Also, the master clock is a free running oscillator. Hence, between each line pulse, after the first 256 element values have been used to fill the memory with valid data, the memory would be overwritten with invalid data until the next
line interval pulse. Figure 6.5 illustrates the control logic designed to overcome this problem. The control logic combines the master clock with the $\theta_r$ using AND1 to generate the element memory clock, which will then be synchronised to element data. The division of the clock into 256 pulse bursts to avoid memory overwriting is achieved via RS1. Element memory counter clock pulses are then enabled via the flip flop and the control gates AND2, AND3, OR1 when the line rate pulse is received (which is also used to reset the element counter via OR2). The element memory counter is then clocked until it generates a carry out signal (active low) which is used to reset flip-flop RS1 and disable the transmission of further pulses through to the counter until the next line rate pulse arrives. The resulting element memory clock is illustrated in figure 6.2. With reference to figure 6.2, it should be noted that this solution fills the first 10 memory locations with redundant data. This was considered to be an acceptable compromise given the extra circuit complexity that would be needed to overcome this situation.

The line memory counter is derived using a similar scheme to the above. In this case, the line pulse sets RS2. The line pulse is also used to clock the memory line counter via AND4, monostable and OR4. The monostable was required to stretch the line rate pulse as this was too short for reliable clocking of the counter. Again, the carry out signal from the line memory counter is used to reset RS2. This feature is used to implement the function of acquisition to a given stimulus which will then cease after 256 line images have been stored. Continuous acquisition occurs when the acquisition enable line from the PC interface is high, forcing line pulses through AND4 via OR4. With a line counter clock rate of 400 Hz, the memory can store up to 0.6 seconds of line information. A normal typical spontaneous blink takes 300 ms, thus it is easily possible to contain a complete blink sequence within the line scan memory. In certain circumstances, such as imaging the relatively slow eyelid movements occurring during voluntary eye closure of palsied patients (chapter 9), it was found that 0.8 s was sometimes not long enough to adequately image the whole eyelid movement cycle, thus the selectable divide circuitry was included (section 6.2.4) to extend the effective acquisition period.

The element memory counter can also be clocked under the direct control of the PC via OR1 and the pc element clock rather than through the camera board timing signals. The line memory counter can similarly be directly controlled via OR4 and the PC line clock. The
counters can be reset from the PC via OR2 for the element counter and directly for the line counter. The memory r / w line can also be controlled by the PC or by the master clock via OR5. Direct PC control facilitates data transfer from the line scan system to the the PC (section 6.2.8).

6.2.7 Analog to Digital Conversion

The serial data from the camera board is terminated with a 75Ω resistor to optimise the frequency response. The signal is then buffered and amplified using a gain of approximately 10. The AD829 video amplifier used for this purpose has low noise (3nV/√Hz) and a gain bandwidth product of 75 MHz, which is adequate for this application. Analog to Digital conversion (A/D) is provided by an MP7684 which can support a sampling rate of up to 20 MHz with 8 bit resolution. The A/D converter requires a balanced clock for correct operation, which is derived directly from the master clock. The converter samples the input on the low phase of the pulse, and conversion is carried out on the high phase. The r / w control of the memory chip is also derived from the master clock, but is inverted and delayed. Data are placed into memory on the following low level transition of the r / w line. The line counter is incremented by the following rising edge of the element clock. Figure 6.2 shows the temporal relationships between these pulses.

6.2.8 PC Interface

Data is transferred between the external buffer memory of the line scan system to the host PC via the parallel port on the PC. This solution eliminates the need for a dedicated I/O card within the host PC. The 24 pin parallel printer port on an IBM compatible PC has 12 output and 5 input lines, configured as one 8 bit output port, one 4 bit output port and one 5 bit input port. The location of these ports in an IBM compatible PC memory map are shown in table 6.1.
TABLE 6.1 Location of the printer port addresses in an IBM compatible PC.

Care must be exercised in using ports 37AH and 379H since some inputs/outputs are inverted.

Tables 6.2 and 6.3 indicate the logic state on the 24 pin connector compared to the logic state in the port for ports 379H and 37AH

<table>
<thead>
<tr>
<th>Connector pin number</th>
<th>Function</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,14,16,17</td>
<td>output</td>
<td>37AH</td>
</tr>
<tr>
<td>2(LSB)-9(MSB)</td>
<td>output</td>
<td>378H</td>
</tr>
<tr>
<td>10,11,12,13,15</td>
<td>input</td>
<td>379H</td>
</tr>
<tr>
<td>18-25</td>
<td>ground</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>port</th>
<th>7</th>
<th>6</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>direction</th>
<th>logic level</th>
<th>pin</th>
</tr>
</thead>
<tbody>
<tr>
<td>379</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>in</td>
<td>Q</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td>in</td>
<td>Q</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>in</td>
<td>Q</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*</td>
<td></td>
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<td></td>
<td>in</td>
<td>Q</td>
<td>13</td>
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<td>*</td>
<td></td>
<td></td>
<td>in</td>
<td>Q</td>
<td>15</td>
</tr>
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<td></td>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
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<td></td>
<td></td>
<td>in</td>
<td>Q</td>
<td>not used</td>
</tr>
</tbody>
</table>

TABLE 6.2 Defines the logic level read by the PC from port 379 when a logic Q is presented to its input. This port was used for reading data from the line scan system to the PC.
TABLE 6.3 Defines the logic level output by the PC from port 37A when a logic Q is written to the port. This port was used for controlling the decoder on the line scan system.

6.2.9 Controlling the line scan system

Figure 6.6 (overleaf) illustrates the PC interface. Port 378H can be used to send data directly to latch 1. The data is then clocked to the output of this latch using a 3-8 line decoder which is controlled via port 37AH. The decoder is enabled by setting pin 1 of the parallel port high. The output line defined by the logic levels on pins 14,16,17 is then driven low. To transfer data on port 378H through the output latch the appropriate decoder line (0) must be selected, then de-selected, effectively clocking the latch. To drive line 0 of the decoder low, 0001 must be output from port 37AH. The least significant bit enables the decoder, the other three bits represent the address inputs to the decoder and define the line to be driven low.

Reference to table 6.3 shows that to output 0001 to the output port 37AH, it is necessary to send 1010, since bits 0, 1 and 3 are inverted. The selected control line is then forced high again by deselecting the decoder.

The control functions in the line scan system, such as enabling data acquisition, or clocking the memory counters via the PC are achieved by writing an appropriate control word to port
Figure 6.6 Illustration of PC interface logic
378H and clocking it through the latch using port 37AH as described above.

Reading data via port 379H requires the incoming byte to be manipulated into two four bit nibbles, since there are only four input lines available. Latch 3 takes the 8 bit data from the line scan system, presenting it to the inputs of latch 2 which acts as a buffer to rearrange the 8 bit input data into two four bit nibbles.

For example, to read data into port 379H, latch 3 must be clocked to transfer the 8 bit word from its input pins to the input pins of latch 2. This is achieved in a similar manner to clocking the output data, described in the previous section. In this case, line 2 of the decoder must be driven low, then high. The two nibbles are read in consecutively by driving the appropriate enable lines (g1, g2) low using the appropriate output from the decoder. Since the data is read into the most significant bits of port 379H, the upper nibble can be used without further processing. To record the correct value of the low nibble, the contents of the port must be divided by 16. The two results are then added together to restore the original 8 bit word. Using the parallel printer port in this manner restricts the speed at which data can be transferred between the line scan system and the host PC, but does not affect the acquisition speed of the line scan system.

6.3 Software

6.3.1 Acquisition Software

The acquisition software is written in Microsoft QBasic and was developed on an IBM compatible 486 machine. The software has two main functions. It controls the operation of the line scan system, starting and stopping data acquisition. It also provides a real time display of the line image to allow the camera to be focused and aligned correctly onto the eyelid.

6.3.2 Real time display.

This mode is primarily used to ensure correct patient alignment. The control lines to the line scan system are set for data acquisition. When the PC is ready to transfer and display a line, data acquisition is suspended and the counters in the linescan system are reset. One line of
Figure 6.7 Illustrating the control flow for the real time display
information is then transferred from memory block 0. The counters are then reset once more and data acquisition restarts in the line scan system while the software displays the last acquired line. During the time taken for the PC to process the previous data and prepare the screen for display, line memory block 0 will have acquired a fresh line. The control sequence is displayed in figure 6.7. Thus, display and acquisition are not synchronised, and the time interval between consecutive displayed lines may not be constant. However, using a 486 equivalent machine, approximately 1 in 3 lines are displayed, which is sufficient for the purpose of aligning and focusing the line scan system.

The apparent stability of the display is improved by implementing video paging into the software. Effectively two pages are used, one of which is the currently displayed page, whilst the second is used to write currently acquired video data. On each pass of the main program loop, the currently displayed page is toggled with the page used for preparation. In this way, plotting of data into video memory, which is relatively slow and visually annoying, is made invisible to the user.

6.3.3 Acquisition Mode.

In this mode, the PC enables the line scan system to acquire data and fill the buffer memory. As already described, the memory is filled in a circular fashion: data is continually rewritten and the memory contains the last 1.7 seconds of line information (for a 200 Hz acquisition). During acquisition, the real time display is suspended allowing acquisition at the full line rate. The PC used for development was limited to a data rate of 32 kHz through the parallel port for reliable data transfer. Effectively, 512 nibbles must be transferred, imposing a minimum transfer time of 15 ms per line, based on a maximum data rate of 32 kHz. A line rate of 200 Hz imposes a 4 ms interval in between lines, so unless the bottleneck of the parallel port can be avoided and data transfer speeded up, the real time display cannot be maintained during data acquisition at the required line rate.

6.3.3.1 Manual Control

The acquisition can be stopped by the operator under keyboard control, after a blink event has been observed. The disadvantage of this acquisition mode is that the operator must be quick to stop data acquisition immediately after the blink event as data can be overwritten.
6.3.3.2 Automatic Control

As previously described, the line scan system can be configured to acquire data in response to a given event, such as a flash of light or a blink response to electrical stimulation. In this mode, data acquisition commences in response to the trigger event and ceases automatically when the memory is full. This mode gives the advantage of making the acquisition simpler for the operator, as it is no longer necessary to stop the data acquisition, before data is overwritten.

6.3.3.3 Data Transfer

After acquisition, data are subsequently transferred across to the PC via the parallel printer port. Using a Pentium 100 MHz PC, the data transfer takes as little as 5 seconds, but on an 386 compatible machine, this process can take up to 30 seconds. This data is stored in binary format to a file of the user's choice for subsequent analysis. It may be the case that using a higher specification PC with more processing speed, the real time display could be maintained whilst performing full speed acquisition, although the bottleneck is likely to be the data transfer rate through the parallel printer port.

6.4 Imaging Performance

6.4.1 Temporal Resolution.

The temporal resolution of the line imaging system is determined by the line acquisition rate. The maximum acquisition rate can be adjusted via a trim potentiometer on the CCD camera board. Increasing the line rate reduces the integration time for the CCD elements, reducing the signal-to-noise ratio within the system as previously described. Increasing the temporal resolution also increases the amount of memory needed to store a complete blink sequence.

A line acquisition rate of 400 Hz (corresponding to a temporal resolution of 2.5 ms) was used to give adequate temporal resolution for normal blinks given that a typical blink takes approximately 90 ms (Evinger et al., 1991). This could be reduced to 200 Hz using clock division to image the relatively slow eyelid movements associated with facial paralysis, when temporal resolution is not as important. Thus, the versatile control offered by this measurement system allows the hardware to be configured for a wide range of situations. For imaging normal blinks, the temporal resolution can be increased, while the slower eyelid
movements can be imaged using the same memory requirements by reducing the line acquisition rate.

6.4.2 Dynamic Range and Signal to Noise Ratio.

The dynamic range of the CCD array was estimated from measurements of saturation voltage and RMS electronic noise level at its output as 42 dB. The A-D converter digitises to 8 bits giving a dynamic range of 48 dB. Typical signal levels from white skin, dark skin, blue iris and brown iris were, respectively, 320 mV, 220 mV, 240 mV and 100 mV. With an RMS noise level of 4 mV, the resulting signal-to-noise ratios were in the range 28 dB to 38 dB. Hence the system is capable of processing the normal range of signals without loss of dynamic range.

6.4.3 Spatial Resolution

The palpebral fissure is typically 10 mm at its widest point. The magnification of the optics of the line imaging system was set so that the length of the 256 element array in the image plane corresponded to a length of approximately 20 mm in the object plane. This allowed for subjects with larger than average palpebral fissures and for variations in subject positions. The element pitch of the CCD array thus corresponded to approximately 0.078 mm in the object plane. Figure 6.8 (overleaf) shows one line of information corresponding to an image of a white ruler with 1mm black gradations. A black to white transition covered four elements of the CCD array indicating that the spatial resolution of the system was limited by the optics to approximately 0.3 mm, although in practice, figure 6.8 shows that the position of a black gradation can be determined to within two pixels or approximately 0.15 mm.
6.5 Analysis Software

6.5.1 Manual Eyelid Tracking

The analysis software was developed as a visual BASIC application on an IBM Pentium P100 system. The function of this software was to take the raw line image data and process it to generate displacement versus time and velocity versus time graphs.

The software takes the line image data acquired as described in section 6.4 and stores it in a 256 x 256 element array within the PC, corresponding to 256 lines of information each containing 256 elements.

The data set can then be displayed as cine-loop, with each line image displayed consecutively. This is useful to establish the start point of the blink in the array. It also enables the operator to visualise the whole data set and identify an appropriate feature in the line image which can easily be tracked through the blink sequence. Figure 6.9 illustrates a sequence of line images acquired from a moving eyelid. The cine loop display is useful because the operator can dynamically visualise the whole blink sequence in slow motion. The next stage in the analysis is for the operator to display each line image in turn, and mark the tracked feature using a cursor. The software automatically records the position of the cursor and the frame number. Thus, in this mode, the system depends on the ability of the user to identify an
Figure 6.9 Showing line images corresponding to different eyelid positions
Figure 6.10a (upper) showing a typical corneal profile with feature enhancement. Figure 6.10b (lower) showing a sequence of line images displayed as a grey scale image.
appropriate feature in the image corresponding to the eyelid margin. This feature must remain constant over the blink sequence for accurate determination of eyelid margin position to be maintained.

6.5.2 Feature Enhancement

In practice, it is sometimes difficult to identify an appropriate feature. For example, a distinct edge arising from the contrast that exists between the eyelid margin and the corneal surface when the eye is open can be lost when the eye is closed. For some skin and iris colour combinations, such as dark skin and brown eyes, the position of the upper and lower eyelid margins can be difficult to determine. Also, when examining facial palsy patients, with minimal upper eyelid movement, Bells phenomenon, which is the upward rotation of the globe during blink can cause misinterpretation of the image. The white sclera can sometimes appear as upwards movement of the lower lid margin. Using cosmetic face paint or make up to highlight the eyelid margins can be beneficial in such circumstances. Figure 6.10a shows a line image with a black trough painted onto the eyelid. The trough corresponding to the black make up is clearly visible. Although the feature to be tracked will not then be the true eyelid margin when tracking the painted feature, it is the relative motion of the upper eyelid rather than the absolute position which is important for this application.

Figure 6.10b shows this data set with the relative element values converted to a grey scale. The trough corresponding to the black make up can be seen to move down and back up through the blink sequence. This example also illustrates some difficulties involved in image interpretation. As the upper lid moves towards the lower lid, the relative signal from the lower eyelid margin becomes reduced, which may be interpreted as movement of the lower lid. This change in signal is actually caused by shadowing of the lower eyelid margin by the upper eyelashes.

In summary, some care must be taken during image analysis to determine the true eyelid margin. In practice, ambiguities can be resolved using make-up to provide consistent features in the image. Once the eyelid margin has been tracked through the complete blink sequence, the software can use calibration figures relating object size and image size, together with the knowledge of the time interval between each line image to generate a graph of upper eyelid
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Figure 6.11a Error estimation due to image interpretation based on five volunteers
Figure 6.11b Revised data set with observer m3 removed.
displacement versus time. The velocity versus time relationship can then be determined by differentiating the displacement data with respect to time.

6.5.3 **Error Estimation - system hardware**

Uncertainties in the measurement of eyelid displacement versus time will be determined by the accuracy to which the true inter-frame interval can be determined, the spatial resolution of the system, the accuracy of the calibration figure between object size and image size and in interpretation of the image to identify the eyelid margins.

The line acquisition frequency was set using an oscilloscope to approximately 400 Hz. Before using the system, a calibrated frequency counter was used to accurately determine line acquisition frequency. Checking the actual frequency before use reduces inaccuracies introduced to the measurement resulting from long term drift of the line acquisition frequency. The accuracy of this measurement was assessed as ± 0.01%. The spatial resolution for a static image has been assessed as 0.15 mm.

6.5.4 **Error estimation resulting from image interpretation**

The uncertainties in eyelid displacement measurements due to image interpretation were also assessed.

To perform this assessment, a complete data set derived from a spontaneous blink on a normal volunteer was analysed by 5 people who were unacquainted with this measurement technique. They were instructed to place a cursor on a consistent feature on consecutive images. In this manner, five independent assessments of upper eyelid position were made on each line image. An average eyelid margin position was calculated for each line image and the difference between the measurement made by each individual and the average calculated from all 5 individuals was plotted against this average value for each line image. The results shown in figure 6.11a illustrate that, with the exception of one operator, agreement was within approximately 2 pixels over the blink sequence. The mean difference was 0.05 pixels with a standard deviation of 1.04 pixels. The relatively poor performance of one operator could be attributed to the feature which was tracked. Four operators chose the position of maximum gradient on the leading edge of the trough, whereas this operator chose the turning point at the top of the leading edge, which was not as easy to track. Figure 6.11b shows the previous data set with this operator excluded. Agreement is within approximately 1.5 pixels.
(mean 0.01 pixels, standard deviation 0.6.), which is within the specified spatial resolution of the system (2 pixels). Another feature of this data set is that observers tended either to be biased low or high compared to the average value, but with errors within the spatial resolution of the system.

In conclusion, it was possible to interpret the image and consistently mark the position of the upper eyelid with an error less than the assessed spatial resolution of the system, provided an appropriate and consistent feature is used.

6.5.5 Automatic Tracking

Manual tracking of eyelid position was time consuming and tedious, which could possibly cause a degradation in measurement accuracy with increasing operator fatigue. The previous section also showed that the choice of feature to be tracked may also influence results. For this reason, an algorithm was developed to automatically track the upper eyelid position. The advantages of automating the analysis include time saving, less operator fatigue and more consistent results.

For this algorithm to be used, it was necessary to specify a region of interest (ROI) encompassing the position of the upper eyelid or the feature in the image to be tracked. The ROI is identified using two vertical cursors, which can be positioned to the nearest element. The data within the two cursors is then used as a template by the software to track the eyelid position on subsequent line images. Figure 6.12 illustrates the ROI marked on an eyelid profile.
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Average of All observations versus Auto Observation-Average

![Graph showing the comparison between average observations and auto-averaged observations.](image)

Figure 6.13

Effect of changing ROI width on algorithm performance

![Graph showing the effect of changing ROI width on algorithm performance.](image)

Figure 6.14

Figure 6.13 Error estimation from using the automatic tracking algorithm

Figure 6.14 Effect on changing the ROI on the tracking algorithm
The position of best fit of the template is established automatically by sliding the template along the data from each frame and performing an element by element subtraction of the template from the data set. A running total of the differences between elements in the template and the data set is maintained. The position of the lowest running total is taken as the position of best fit of the template within each video frame. The position data is made available to the investigator in a text file, which can be further analysed and displayed using any suitable software package. For the purposes of this study, MATLAB was used for data display. One major feature of the algorithm is that the shape of the ROI is not important, unlike algorithms based on specific features such as edges or areas of steep gradient. The data set required no further processing, whereas algorithms using feature enhancement, such as differentiation to highlight further areas of steeper gradient such as those occurring on the eyelid margin might result in more complex code without additional benefit.

6.5.6 **Algorithm Performance.**

The data set analysed previously by the four consistent individuals was analysed using this algorithm. Again, the average of all analysed data sets was taken and figure 6.13 shows the difference between the position recorded by the algorithm and the average value for each line image plotted against the average value. This figure shows that agreement is very good (mean difference = -0.23, standard deviation 0.41 pixels) for small displacements (<60 pixels). Performance worsens at higher displacements, with evidence of a systematic underestimation of eyelid position, although agreement is still within the specified spatial resolution of the system. It can be observed that the algorithm does not systematically under or over estimate position for smaller displacements (<60 pixels). This can be compared to the manual tracking data (figure 6.11), which was observed to show a bias within each operator to either underestimate or overestimate eyelid position.

The effect of changing the width of the ROI from 2 pixels to 10 pixels, centered on a consistent image feature can be seen in figure 6.14. Again, the difference between estimates of eyelid position for each ROI and an average of all estimates is plotted against the average value. Again, agreement is within 2 pixels and there is no evidence that changing the width of the ROI changes the estimate of eyelid position, provided the ROI encompasses a consistent feature.
6.5.7 Velocity Estimation

The velocity versus time data was derived by differentiating the displacement versus time data. To reduce noise, a low pass filter algorithm (cut off 90 Hz) was applied to the displacement data before differentiation. Evinger et al., (1991) observed no significant frequency component greater than 90 Hz in a normal blink, justifying filtering with this cutoff frequency. The main source of the noise appeared to be due to timing 'jitter' when displacement data was offset by one pixel between adjacent frames, leading to the tracking algorithm 'hunting' between two adjacent pixels on consecutive frames at very low velocities. The filter was implemented using a zero phase butterworth digital filter derived from MATLAB, which was chosen because of its flat pass band characteristic. The MATLAB function buttord was used to design a filter with a maximum of 0.1 dB attenuation up to the pass band (90 Hz) corner frequency, rolling off to at least 30 dB at the stop band corner frequency (95 Hz). The MATLAB function filtfilt implements zero phase filtering by reversing the filtered sequence after filtering in the forward direction and running it back through the filter. Zero phase filtering was important to maintain the correct position of the velocity profile relative to the displacement profile.

6.6 Summary

In summary, different measurement methods have relative advantages and disadvantages. Techniques based on angular displacement of the eyelid, such as the search coil technique, must make assumptions about the geometry of the globe and the relationship of the eyelid to the globe. Workers basing techniques on measuring linear vertical motion must also approximate the true trajectory of the eyelid to vertical motion, which may introduce a systematic error into the measuring system.

Since eyelid motion has been described as a zipper like action (Moses, 1981), perhaps the technique of measuring exposed corneal area warrants further investigation especially with regard to studies of dry eye where the tear film distribution over the cornea is more important than the protective role of the eyelid.

For the purposes of this study, characterising eyelid movements with respect to vertical linear motion reflected the ability of the O0C muscle to contract and close the eye. Deriving the
main sequence relationship between peak velocities and displacements also allowed data from this study to be compared directly to that from previous studies.

This chapter has described the design of a line scan system for measuring eyelid movements. The line scan system provides a non contact method of measuring eyelid dynamics with adequate spatial (approximately 0.15 mm) and temporal resolution (5 ms). The following chapter will examine data acquired from normal volunteers and compare the data acquired from previous studies with the normal data derived in this study.
Chapter 7

Normal Eyelid Movement Data

This chapter examines the main sequence data derived from voluntary, spontaneous and electrically stimulated blinks in normal volunteers and compares these data to normal data derived from previous studies using alternative eyelid movement measurement techniques. Possible reasons for differences between the three types of blink are discussed. Differences in eyelid movement data between studies are also highlighted and discussed.
7.1 Introduction

A technical description of the line scan system designed to measure the amplitude and velocity of upper eyelid movements was given in chapter 6. In summary, this system can measure upper eyelid movement with a spatial resolution of 0.15 mm (section 6.4.3) and a temporal resolution of 2.5 ms (section 6.4.1). There has been a range of other measurement techniques used in previous studies, which were also discussed briefly in the previous chapter.

Eyelid movements have been previously characterised by plotting a graph of peak velocity versus corresponding maximum eyelid displacement, for a range of eyelid displacements. This has been termed the blink main sequence and has been shown to be linear over the normal range of observed blink amplitudes (2 - 10 mm) (Evinger et al., 1991). Data presented in this manner have consistently shown that larger amplitude blinks are associated with higher velocities, for both blink down phase and blink up phase, with up-phase periods exhibiting lower peak velocities than the down-phase. However, the exact relationship between peak displacement and corresponding peak velocity does differ between studies, depending on the measurement technique and the experimental protocol followed. For this reason, normal eyelid movement data for the line scan system was obtained from normal volunteers. This was presented as peak velocity versus maximum displacement and compared to data derived from previous studies. The purpose of this chapter is twofold. In the first instance, it was necessary to show that results derived from the line scan system were comparable to previously published work. Also, establishing a database of normal blink measurements would allow comparison of eyelid movement parameters in patients presenting with a facial palsy to be compared with a normal range using the same measurement technique and protocol. This would allow the progress of therapy to be monitored as well as simply classifying eyelid movements as normal or abnormal.

Previous studies have shown that the linear relationship between peak velocity and peak displacement of the eyelid during normal blinks exhibits a degree of variability, which appears as scatter of the data around the regression line. In previous studies, the source of this variability is unclear. In addition to variability arising from the measurement technique and the experimental protocol followed, variability may exist in a set of pooled data arising from inter and intra subject variability. Figure 7.1a illustrates the situation where individuals
Figure 7.1a

Figure 7.1b
Figure 7.2 Photograph illustrating operation of the line scan system
may generate blink main sequence data with a high degree of correlation, but with large differences between individuals. If a single regression line is fitted to the pooled data, a large degree of scatter and poor correlation may be indicated, even though the main sequence relationships for individuals are highly correlated. This corresponds to a situation of low intra subject variability but high inter subject variability. Alternatively, the data could follow the pattern illustrated in figure 7.1b where the individual main sequence relationships are not highly correlated, but main sequence relationships from different individuals are very similar, corresponding to a situation of low inter subject variability and high intra subject variability.

It was hypothesised that the regression line derived from pooled normal data could be used as a predictor of normal blink parameters. If, however, the model of figure 7.1a was found to more accurately reflect the true situation, but a regression line based on the pooled data was used, then an unnecessarily wide range on the velocity associated with a given displacement may be set. This may lead to an insensitive test for a normal blink. A more appropriate measure of treatment progress in such a case may be to directly compare the affected eyelid movement in a given patient with the contralateral side, given the highly conjugate nature of blinks (Huffman et. al., 1996). If however, the situation in figure 7.1b was applicable, then comparison of a patients’ measurements to a pooled set of data would be justified. To analyse inter and intra subject variability, and to acquire normal data, five consecutive blinks were recorded in each of thirty individuals (age 22-46). Fifteen blinks were then recorded from four volunteers over a range of blink amplitudes. The analysis is described in section 7.3.

7.2 Acquiring Data

7.2.1 Spontaneous and voluntary blinks

The subject's head was stabilised using a chin/head rest (see figure 7.2). The height of the chin rest can be adjusted using a thumbwheel to allow vertical alignment. The lens system could be moved on a sliding table to adjust position in the horizontal plane. The position of the lens could also be adjusted to ensure that the target was positioned in the focal plane of the lens. Correct positioning was aided by two Light Emitting Diodes (LEDs). The LEDs were mounted above and below the imaging lens. The beam directions from the LEDs had previously been adjusted so that their point of intersection coincided with centre of the focal plane of the imaging lens. The subject was asked to fixate their gaze onto the centre of the
Figure 7.3 Profile of a normal spontaneous blink
The upper trace shows upper eyelid displacement versus time. The lower trace shows the corresponding velocity versus time profile.
Normal data derived from line scan system compared to published data

Line scan: $20.23 + 22.135 \times \text{displacement}$

Evinger: $31.7 + 21.4 \times \text{displacement}$

Figure 7.4a

Normal data from the line scan system compared to published data

line scan: $16.87 + 9.854 \times \text{x}$

Evinger: $-5.87 + 13.5 \times \text{x}$

Figure 7.4b

Figure 7.4 Main sequence slopes from Evinger et al., (1991), compared to data acquired using the line scan system for normal volunteers.

Figure 7.4a is for the blink down phase

Figure 7.4b is for the blink up phase
Chapter 7: Normal Data

lens to ensure reproducibility of the eyelid starting position. Since subjects were aware of the purpose of the investigation, data was captured in response to either a spontaneous or voluntary blink, with no distinction being made between the two movements. Recordings were made under fixed illumination conditions and at approximately the same time of day to minimise measurement variability arising from external factors. Temperature and humidity could not be controlled but were relatively constant.

7.2.2 Electrically Stimulated Blinks.

PAL™ electrodes were placed on the medial and lateral canthi of the eye, following the protocol described in chapter 3. Electrical pulses were delivered using the stimulator described in chapter 8. The stimulation regime was based on a 0.5 s pulse train comprising 200 μs rectangular biphasic pulses, delivered at consecutive pulse repetition frequencies of 5, 10, 20 and 50 Hz, with an amplitude of 20 V.

7.3 Results

7.3.1 Profile of a typical spontaneous blink

Figure 7.3 (upper) shows the upper eyelid displacement vs. time curve obtained from the line scan imaging system for a normal spontaneous blink. The corresponding velocity vs. time relationship is shown in figure 7.3 (lower). The displacement curve shows rapid closure of the upper lid. The peak displacement is reached after a period of approximately 90 ms, with the upper eyelid reaching a peak velocity of approximately 200 mm/s. The velocity trace shows that initial movement of the eyelid is relatively slow, the peak velocity is not attained until approximately midway between the onset of the blink and point of maximum displacement. The closing or down phase is followed by a longer upwards phase (approximately 350 ms) in which the peak velocity is lower (approximately 85 mm/s).

7.3.2 Normal blink main sequence data (down phase)

The pooled data derived from the thirty normal volunteers is shown in figure 7.4. The variability of blink main sequence data observed in this study is consistent with previous studies (Evinger et al., 1991, Guitton et al., 1991), as is the positive correlation between peak velocity and blink amplitude. Also, peak velocities during blink down phase are greater than
corresponding up-phase velocities. Linear regression analysis of the peak eyelid velocity (Y mm/s) and maximum eyelid displacement (X mm) data gave the following relationship:

\[
\begin{align*}
Y &= 22.235X + 20.23 & \text{down phase} \\
Y &= 10.8X + 13.7 & \text{up phase}
\end{align*}
\]

This can be compared to the data of Evinger et al., (1991):

\[
\begin{align*}
Y &= 21.4X+31.7 & \text{down phase} \\
Y &= 13.5X - 5.87 & \text{up phase}
\end{align*}
\]

The 95% confidence limits for the position of the linear regression line in this study are also shown in figure 7.4. For the blink downphase, the line given by Evinger et al. (1991), is shown to lie within the 95% confidence interval for the regression line derived from this study. This is not the case for the blink up phase data, with the line from Evinger falling outside the 95% confidence limits for this line, but agreement is reasonable within the most common range of blink data (4mm-8mm).

The blink amplitudes from the thirty normal volunteers ranged from 2mm -12 mm, although not all volunteers contributed data over the whole range i.e. some individuals data was clustered around the higher blink amplitudes. For this reason, the analysis to establish whether pooled data was appropriate was performed on the blink downphase data using fifteen blinks from four volunteers, recorded for a wide range of blink amplitudes from each individual.

7.4 Analysis of Inter and Intra Subject Variability.

Following the arguments presented in section 7.1, if the main sequence relationships between subjects are similar, a single linear regression may be fitted to pooled data from a random sample of individuals. Alternatively, if the relationships are completely different, then it may be necessary to fit separate regression lines to each set of data from each individual. In between these two extremes, an appropriate model may be to assume that the gradients of individual regression lines are different, but the intercepts coincide. An alternative model may assume that the intercepts are different, but the gradients are the same. The latter would imply that the relationship between velocity and displacement between individuals are the same but ‘base-line’ values are different between groups. To establish which was the
simplest appropriate model, a single regression line was fitted to the pooled data which represents the simplest model, five parallel lines were then fitted, and separate lines were fitted to each data set without the constraint of parallel lines. Following Krzanowski (1998), the analysis then uses an F test on the ‘extra sum of squares’ produced when moving from the simplest model to the more complicated models.

Analysis of the regression sum of squares and the residual sum of squares is summarised in the following ANOVA table, where:

\[ S_{sr} = \text{regression sum of squares from pooled data regression} \]
\[ S_{sel} = \text{residual sum of squares from pooled regression} \]
\[ S_{se2} = \text{residual sum of squares from parallel lines model} \]
\[ S_{se3} = \text{residual sum of squares from separate regressions model} \]
\[ k = \text{degrees of freedom} \]
\[ M_{Sr} = \frac{S_{sr}}{k} \]
\[ M_{Sp} = \frac{(S_{sel} - S_{se2})}{k} \]
\[ M_{Ss} = \frac{(S_{se2} - S_{se3})}{k} \]
\[ M_{Se} = \frac{S_{se3}}{k} \]

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>Sum of Squares</th>
<th>Degrees of Freedom</th>
<th>Mean Square</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Line</td>
<td>184636</td>
<td>1</td>
<td>MSr=184636</td>
<td>F1=MSr/MSe= 108.35</td>
</tr>
<tr>
<td>Parallel line</td>
<td>13731</td>
<td>3</td>
<td>MSp=4577</td>
<td>F2=MSp/MSe= 2.68</td>
</tr>
<tr>
<td>given single</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Separate line</td>
<td>1018</td>
<td>3</td>
<td>MSs=339</td>
<td>F3=MSs/MSe= 0.19</td>
</tr>
<tr>
<td>given parallel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual</td>
<td>88615</td>
<td>52</td>
<td>MSe=1704</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>59</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F1 is significant at the 95% level, so there is strong evidence of the increase in eyelid velocity with increasing displacement. F2 is only just significant at the 95% level indicating that parallel lines may provide improvement over the single line model. In other words, this analysis shows evidence that the linear relationship between displacement and velocity is similar between subjects, but there may be a base value difference. F3 is not significant at the
Figure 7.5a 95% confidence ellipse for blink down phase
Figure 7.5b 95% confidence ellipse for the blink up phase
Figure 7.6 Effect of increasing frequency of electrical stimulation on a normal volunteer. In each case the upper trace is the displacement vs. time profile. The lower trace is velocity vs. time.
95% level indicating that there is no improvement achieved by fitting individual regression lines to each set of data.

As far as this study is concerned, the above results show that it is valid to pool data from a sample of individuals to estimate the main sequence gradient for the normal population, although the marginal significance of F2 indicates that the intercept may be of importance between individuals. Given that the emphasis in this study is to improve eyelid closure in patients with a facial palsy, an assessment of an individual is likely to result in a series of data points clustered around their particular maximum possible displacement, which is very likely to be in the lower range of the normal data. The clustering of the data coupled with the limited amplitude range will mean that generating regression equations based on a limited data range may not be as useful as averaging the observations made in a given assessment and comparing this to the normal range of main sequence data. Thus, this approach still requires a judgement to be made as to whether the data derived from a single assessment lies within normal limits. The software package Statistica can be used to generate an ellipse superimposed on the normal regression line. The shape of the ellipse can be adjusted by altering the probability that the data points will lie within the ellipse. For this study, an ellipse corresponding to a 95% probability of enclosing the data was specified. The data acquired from the patient can then be plotted onto the normal blink sequence graph to see whether or not it lies within the ellipse. Figure 7.5 shows the 95% confidence ellipse superimposed onto the main sequence data for the blink downphase (upper) and blink upphase (lower).

7.5 Electrically Stimulated Blinks

For relatively small (<35 V), narrow (<200 μs) stimulating pulses applied at a relatively low pulse repetition frequency (<10 Hz), a series of eyelid twitches is observed. As the stimulating frequency is increased, then temporal summation of individual muscle twitches occurs (chapter 2), resulting in full eyelid closure. This was measured using the line scan system. The results are shown in figures 7.6a-e. Electrical stimulation was applied using the skin preparation techniques and electrode positions described in chapter 2. The stimulation regime consisted of 200 μs monophasic pulses, applied with pulse repetition frequencies shown in the figure captions.
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The figures clearly show the increasing degree of tetany as the pulse repetition frequency is increased. In consecutive diagrams, the effective maximum displacement is increased as the temporal interval between stimulating pulses reduces. The muscle fibres are unable to relax fully between pulses and individual muscle contractions merge together to produce a sustained contraction, which is evident for stimulation frequencies greater than 25 Hz. This suggests that the optimum frequency for producing eyelid closure should be around 25 Hz, but this does not take into account the changes accompanying muscle denervation. Such changes cause the twitch times of muscle fibres to be extended (chapter 4), thus altering the frequency at which sustained contraction occurs. This is further discussed in chapter 10.

If the morphology of the displacement profile in figure 7.6e is compared to that of the normal spontaneous blink (figure 7.3), it is apparent that the gradual onset, steeper midphase, followed by slowing as the eyelid reaches maximum displacement is replaced by a more linear closing profile. This may arise because a smaller number of fibres are activated continuously using electrical stimulation, the strength of contraction being controlled solely by the frequency of electrical stimulation, whereas for the normal spontaneous blink, there is gradual recruitment of more muscle fibres.

If longer (e.g. 10 ms) low amplitude (<10 V) pulses are used, the responses when applied to normal volunteers are very similar to those described above i.e. a series of twitches is observed. If, however, larger amplitude (e.g. 20 V) pulses are used, eyelid closure can be attained using a single pulse. This is not pursued in this study because this type of response may be due to the generation of a reflex blink secondary to pain or involvement of the trigeminal nerve.
7.6 Summary

The line scan system has the capability to measure eyelid dynamics efficiently and easily in a routine clinical environment. Results obtained during this study have been comparable with results achieved in previous studies using alternative measuring systems such as the search coil technique (Guitton et al., 1991, Evinger et al., 1991). General comments made about the main sequence relationship such as large amplitude blinks having higher peak velocities are in agreement, although the exact relationship between peak velocity and peak displacement does differ between studies. However, the data derived from Evinger et al., (1991) was found to lie within the 95% confidence intervals of the normal data measured in this study.

The high total variability in main sequence data derived from different normal subjects may account for the differences observed between studies. This variability may reflect factors which are difficult to control, such as the mental state of the subject (alert, tired, nervous etc.). The experimental method used could also affect results, especially where an attempt is made to distinguish between voluntary and spontaneous blinking, as it is difficult to determine the occurrence of a truly spontaneous blink when the subject is anticipating the measurement. No distinction between spontaneous and voluntary blinks was made during the acquisition of normal data in this study. Some studies artificially induce different amplitude blinks by altering the starting position of the eyelid (Guitton et al., 1991) which may affect eyelid dynamics. In this study, all blinks were measured from the same eyelid starting position. An improvement to this experimental method could be made by monitoring the orbicularis EMG during the blink, to differentiate between voluntary blinks which use the orbital section of the OOC and spontaneous blinking which generally involves only the palpebral section (Schmidtke and Buttner-Ennever, 1992).

Establishing a main sequence relationship for normal volunteers to act as a predictor of velocity for a given eyelid displacement provides normative data against which the eyelid movements of subjects with a facial palsy can be compared. The large degree of variability observed in normal blink main sequence measurements means that comparisons of velocity estimates must be interpreted carefully. For this study, the criteria for an abnormal response was set using a 95% confidence ellipse around data derived from a normal population of 30...
volunteers. It was hypothesised that comparisons between data from patients and normal values could be used to monitor therapy progress, which will be discussed in chapter 10.
Chapter 8

Technical Description and Characterisation of the Stimulators

A brief description of the commercial stimulator used to implement the narrow (200 µs) pulse regime described in chapter 3 is given. The output characteristics of this device are described. A technical description of a new stimulator designed specifically to implement the long pulse regime, also described in chapter 3, is also given. The relative advantages of this design over the commercially available stimulators are highlighted.
8.1 General Stimulator Characteristics

Commercial electrical stimulators offer a range of wave shapes and stimulation parameters. Examples of available waveshapes include biphasic rectangular pulses, compensated monophasic pulses, monophasic pulses and triangular pulses. Highly specified electrical stimulators for use in physiotherapy departments offer a wide range of such output possibilities, but their relative cost, complexity and size make them unsuitable for use in a home environment. Most units designed for home use offer a fixed output waveshape but include the facility to modify some of the electrical parameters defining the stimulation regime e.g. pulse width and pulse repetition frequency. All have the ability to control the magnitude of the output pulse. Common uses include nerve stimulation to control pain rather than for muscle activation and control. As such, units designed for home use offer a limited range of pulse widths, typically less than 300μs.

The type of output circuit used influences the description of the stimulating waveforms, which are commonly characterised as having constant voltage or constant current outputs. An ideal constant voltage stimulator will maintain an output voltage irrespective of the electrode impedance (limited by the maximum current output capability), whereas an ideal constant current stimulator will maintain a set current independent of the load impedance within the voltage compliance range of the unit. In practice, the constant voltage or current characteristics will be maintained over a limited load range.

The advantage of using a constant current output is that the total charge delivered to the tissue will remain constant irrespective of impedance offered by the electrodes and tissue, within the voltage compliance range of the stimulator. However, if the effective electrode/skin contact area is reduced, which can occur as electrodes 'dry out', a constant current approach may result in areas with a high current density possibly leading to discomfort and tissue damage. Constant voltage stimulators therefore may offer a safer form of stimulation when used without direct supervision.

In practice, most experimental and commercial portable muscle stimulators incorporate some form of step-up transformer coupling to generate the required voltage levels from a low voltage power supply such as batteries. The interaction between the transformer coupled
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Figure 8.1 Transformer equivalent circuit
output stage and the mainly capacitive electrode load will result in distortion of the
current/voltage pulse delivered to the tissue. A simplified equivalent circuit for a transformer
is shown in figure 8.1a (Grossner, 1983). Considering the rising edge of a square pulse
applied to the transformer, the reactance of Lp, the primary inductance, is large compared to
the parallel reactance of C, the primary capacitance, so for the purposes of simplifying the
equivalent circuit during the rising edge period, Lp can be ignored. This simplifies the
equivalent circuit to that shown in figure 8.1b. The solution to the equations describing this
circuit can be solved to show that the rise time response follows that of a typical second order
system, the characteristics of which depend on the damping factor of the circuit, which, in
turn, depends on Rp, the lumped primary resistance, Rs the lumped secondary resistance, C,
and the leakage inductance L1 (Grossner, 1983). The flat top portion of the pulse can be
modelled by a low frequency equivalent circuit which is obtained from the equivalent circuit
(a) by neglecting the leakage inductance and shunt capacitance (figure 8.1c). The output
pulse will be tilted down and the amount of tilt will depend on the pulse width and the
primary inductance of the transformer, Lp.

8.2 The Portable Transcutaneous Electrical Nerve Stimulator (TENS) Unit

8.2.1 User Controls

This section describes the characteristics of the commercial TENS unit (Model 120 Z, I.T.O.
Company, Japan) used to implement the narrow (200 ps) therapeutic regime. The description
includes the output characteristics measured with respect to a defined resistive load and when
applied to the medial and lateral canthi of the eye using PAL™ electrodes.

The manufacturer describe the output as a compensated monophasic waveshape. Pulse width
could be adjusted over a range of 10 - 300 μs and pulse repetition frequency could be
adjusted over a range of 1 - 300 Hz. Amplitude could be controlled through a range of 0 - 5
mA when applied to a load of 1kΩ. All the controls were operated via thumbwheels, which
could be locked into position. The unit could be used in two modes described as 'continuous'
or burst mode selected via a slide switch. In continuous mode, pulses were applied
continuously at
Figure 8.2a TENS unit output voltage waveform when applied to a resistive load
Figure 8.2b TENS unit output voltage waveform when applied to the medial and lateral canthi using PAL electrodes
Figure 8.3a Output voltage and current from the TENS unit when applied to a varying resistive load

Figure 8.3b Power delivered to a resistive load using the TENS unit
the set PRF. In burst mode, pulses were generated at the prescribed PRF with a duty cycle of 2 s on and 1 s off.

8.2.2 Measurement of the output characteristics

To measure the output characteristics of the TENS unit, the output was connected to a resistive load. The pulse width of the TENS unit was set to 200 µs and pulse repetition frequency was set to 10 Hz, matching the narrow pulse parameters used in this study. The resulting voltage waveform generated across a 10kΩ load was recorded using a digital oscilloscope with cursor measuring facilities and is shown in Figure 8.2a. For comparison, the voltage waveshape recorded from the electrodes when the output of the TENS unit was applied to the medial and lateral canthi of the eye using PAL electrodes is shown in figure 8.2b.

The peak positive output voltage was measured with reference to ground (0 V) and was recorded as a function of load resistance (range 0.5 - 50 kΩ). Peak output current was calculated as peak output voltage/ load resistance. Both the current and voltage versus load resistance characteristics are shown in figure 8.3a. The power delivered to the load was measured by multiplying together the values of current and voltage at each value of load resistance. The resulting data are shown in figure 8.3b.

8.2.3 Discussion

Figure 8.2a illustrates a typical pulse delivered into a 10 kΩ load and is described by the manufacturers as a compensated monophasic waveform. The pulse shape shown in figure 8.2a shows that with a load resistance of 10 kΩ, the response is typical of an underdamped system, showing some overshoot and oscillatory behaviour in the region of the peak positive voltage. Following the discussion in section 8.1, the small amount of tilt (approximately 2%) shows that the pulse width is relatively small compared to the time constant of the RL circuit.

Considering the morphology of the output waveform when applied to skin (figure 8.2b), the ringing, or underdamped response has become damped, especially when the voltage is relaxing back to zero on the trailing edge of the pulse. This can be explained by considering the capacitive component of the load when electrodes are applied to skin, resulting from the
Figure 8.4a TENS unit output waveform delivered to skin using PAL electrodes
Figure 8.4b TENS unit output waveform delivered to a load consisting of a resistor and a parallel capacitor
interaction of the relatively good conduction properties offered by the electrodes and the underlying tissue separated by the relatively poor conducting properties of skin. Typically, this capacitance is of the order of 0.025 μF (Prausnitz, 1995). For a 200μs pulse, the reactance offered by this capacitance is low (of the order of 1kΩ). The resistive component of the load will be reduced by the shunting effect of the electrode/skin capacitance thus increasing the damping factor for the circuit. However, the increased damping has not significantly altered the pulse rise time, which has already been discussed as being an important parameter for nerve and muscle stimulation (chapter 3). This anomaly between the shape of the leading and trailing edges of the pulse may be due to an asymmetric drive circuit, or due to saturation in the transformer, although the exact details of this were unavailable. A simple equivalent circuit of a 10kΩ resistance with a parallel capacitance of 0.033μF was used as a model to confirm this explanation. Figure 8.4a shows the voltage waveform when applied to skin while figure 8.4b shows the voltage waveform when applied to the simple resistor/capacitor model. The morphology of both waveforms are similar. The underdamped response observed when the TENS unit is applied to a purely resistive load has been changed by adding the parallel capacitor, to a response more typical of a TENS unit applied to skin.

A constant current circuit would present a large output impedance compared to the load whereas a constant voltage circuit would present a low impedance compared to the load. Considering now the results shown in figure 8.3a, which shows output current and voltage plotted as a function of load resistance, the output current is observed to rise sharply as the output voltage falls, when the resistive load is less than approximately 8 kΩ. At resistive loads greater than approximately 30 kΩ, the unit is reaching the limit of its voltage compliance. The Thevenin equivalent series impedance of the transformer secondary can be approximated by dividing the open circuit voltage by the short circuit current in figure 8.3a, giving approximately 1.3 kΩ. This can be compared to a typically expected skin impedance of 5 - 10 kΩ for this electrode type (Nelson et al., 1980), which is not significantly different from the characteristic output impedance. Thus the output impedance from this transformer does not offer particularly good constant voltage or constant current characteristics. According to standard circuit theory, maximum power will be transferred to the load when the load impedance equals the source impedance. Figure 8.3b shows power delivered to
resistive load as a function of the load resistance. At 5-10 kΩ power delivery is approximately 40% of that delivered to a matched load of approximately 1.3 kΩ.

In summary, this TENS unit can deliver pulses capable of stimulating nervous tissue. Some output characteristics can be controlled (amplitude, pulse width and pulse repetition frequency) but the waveshape is fixed. The unit is not capable of generating the long (>10 ms) pulses suitable for stimulating denervated muscle, nor does the method of user parameter control allow auditing of compliance with the prescribed treatment. The transformer coupled output results in some distortion of the output waveform and relatively inefficient power transfer, but the effect of the interaction between the output circuit and skin on important parameters such as the pulse rise time (chapter 3) is not significant.
8.3 Technical description of the new long pulse stimulator

8.3.1 Introduction

This section details the design of a new stimulator for use by outpatients, which offers several advantages over currently available commercial stimulators. These advantages are discussed in the following section.

The stimulator designed for this study is programmable, the range of stimulating waveforms being limited by the frequency response of the output transformer and the clock frequency of the microcontroller around which it is designed. It is capable of mimicking the output waveforms associated with commonly used tens units, providing programmable pulse widths, pulse repetition frequencies, duty cycles and maximum amplitudes. It can also be programmed to deliver the longer pulses (>10 ms) required for stimulation of denervated muscle. The advantage over commercial TENS type units is that this unit can be pre-programmed with parameters determined for each patient according to their needs, thus eliminating the need for the patient to set and control the electrical output characteristics. This feature limits the uncertainty surrounding the use of the unit outside of a clinical environment, where inappropriate parameters could inadvertently be set. Since the unit is programmable, it also becomes feasible to develop alternative stimulation regimes or adjust stimulation parameters to suit patients over time, as their clinical condition changes.

As well as being programmable, this stimulator can log the date and duration of use. This permits measures of patient compliance towards a given stimulation regime. The facility for data logging to measure compliance, coupled with the use of current monitoring, could make the unit suitable for other applications, apart from that detailed in this study, that would benefit from improved dosimetry of a given stimulation regime. Applications such as pain relief, muscle re-education and muscle strengthening which rely on subjects using stimulators out of a controlled clinical environment may benefit from allowing more accurate studies of electrical dose versus clinical effect to be made.
One of the main advantages of this stimulator is the simplicity of the user interface. The clinician can pre-program the device with all the required parameters for a given subject by communicating via a serial link to a host PC running the programming software. All that is required from the subject for normal operation is to switch the unit on and off. The stimulus amplitude is controlled by an automatic soft start, incrementing the output from zero in steps of approximately 0.5 V until the pre-programmed maximum level is reached.

The unit is programmed while in a service mode and connected to the host PC via a serial port. The service mode is entered by simultaneously depressing a hidden front panel switch and activating an internal reed switch with a magnet held near to the front panel. The combination of reed switch and the hidden switch makes it very unlikely that the service mode could be selected accidentally, while in normal operation. When in service mode, the on/off switch is disabled and the unit will wait in an endless loop until a character sent by the host PC is registered by the stimulator. When this start character has been received, the unit automatically sends out its logged data to the PC and then receives the data defining the stimulation regime from the PC. Alternatively, the unit can be restored from service mode to normal operation by resetting the unit via the reed switch, without re-programming.

8.3.2 System Overview

The stimulator design is based around a 88K014 micro controller (NEC, Japan). It was specified with on-board RAM (1K) and ROM (32K), 60 programmable I/O ports, an 8 channel analogue to digital converter and 3 programmable timers. The chip runs at a maximum clock frequency of 10 MHz, which can be divided to a lower frequency using a control register. Alternatively, a second 32 kHz sub-oscillator can be used, which reduces current consumption from a nominal 5 mA to 30 μA. Its electrical specification was such that operation could be maintained with its supply voltage as low as 2.5 V. This low minimum operating voltage, coupled with low power consumption, made this device ideal for use in a portable battery operated system, where reduction of total power consumption to prolong battery life is important. A low-cost (£300) evaluation system for the device was available, which included an emulator and debugging software, aiding application development. Figure 8.5 (overleaf) illustrates a block diagram of the stimulator.
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Figure 8.5 Block diagram of the programmable stimulator
The 32K ROM on board the microcontroller is used to store the controlling software, while the 1K RAM is used to store the data defining the stimulating wave form and the logged time data. The limited amount of RAM restricts the complexity of the stimulating wave form and the amount of data that can be logged, but was sufficient for this application. The user interface comprises three Light Emitting Diodes (LEDs) to represent machine status, and three switches to control the stimulator, all of which are shown connected to the I/O ports on the block diagram. The user controls have been described, and consist of a simple push button to switch the unit on and off, and a separate, hidden push button and reed switch to control the operating mode of the unit, again interfaced to the microcontroller via its I/O ports.

In operation, a digital representation of the stimulating waveform held within the microcontroller is presented to a digital to analogue converter (D/A), before being power amplified and coupled through to the subject via a step-up transformer.

The output from the power amplifier to the transformer is enabled via a monostable, which must be triggered by the microcontroller before each pulse train delivery, adding an extra safety element into the design. It also helps to reduce power consumption of the system by reducing the quiescent current of the power amplifier from 10 mA to 2 mA when disabled.

The block diagram also illustrates the Real Time Clock (RTC) interfaced directly to the microcontroller. This was used to implement time keeping duties for data logging independently from the microcontroller. The following sections describe the stimulator hardware in more detail.

8.3.3 Power Regulation

The main power supply was provided by 4 AA cells. This was regulated down to 5 V using a MAXIM 665 regulator which offers a very low dropout voltage (100 mV). It also provided low battery level indication, which was directly interfaced to the microcontroller. The controlling software monitored this input, disabling pulse output during low battery conditions. A dc-dc converter was used to generate a -5 V rail for the power output stage.
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Figure 8.6 Block circuit diagram of the new programmable stimulator

Output transformer
1:7 turns ratio
frequency response (-1dB) 50Hz -18 kHz
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An internal battery back up was provided to maintain power to the microcontroller during main battery change over to ensure integrity of the programmed stimulating regime and the logged time data.

8.3.4 Power output stage.

The output circuit of the stimulator is shown in more detail in Figure 8.6. The current output from the A/D converter is converted to a voltage by IC5. The output from this chip is then used to drive the power op amp stage. The power op amp (TDA 2301) offers a high output drive capability coupled with a wide full power band width (1 A 10 MHz). The op amp can also be driven into a high impedance state via two control lines which can reduce the quiescent power consumption from 10 mA to 2 mA. The output from the power op amp is used to directly drive a transformer. The transformer serves two functions.

i). It provides a step up in voltage to the patient leads.

ii). It isolates the patient from any dc current which may flow under fault conditions.

8.3.5 Implementation of data logging

Time and date logging could have been implemented purely with the micro controller, however, this would have increased the complexity of the controlling software. Also, it would not have been possible to put the micro controller into a very low power sleep mode, if it was responsible for time keeping. For these reasons, it was decided to use a dedicated real time clock integrated circuit for time keeping duties. Although this solution increased chip count, power consumption was minimised because the RTC was implemented with CMOS architecture, giving it very low power consumption (30 µA compared to 5 mA for the microcontroller in a normal, non sleep, mode). It was also able to directly interface to an 8 bit port of the micro controller.

The internal architecture of the RTC was based on 3 control registers and 10 data registers, each of which were 4 bits wide, that stored the time information. The limited available RAM meant that only the registers containing the date, hours and minutes were recorded, each time the stimulator was switched off. At switch on, the hours and minutes registers were set to 0.
In this manner, each time the unit was switched off, a record was made of the date and the duration for which the stimulator had been switched on.

The storage of each register of the RTC in separate memory locations of the micro controller would also have been wasteful in terms of memory utilisation since the width of the RTC registers was 4 bits compared to the width of the micro controller data bus (8 bits). For this reason the software compressed two RTC registers into 1 byte, which was then stored in the micro controller RAM. Thus, the logged data required a total of 3 bytes to store the required 6 registers (1 minute, 10 minute, 1 hour, 10 hour, 1 day, 10 day). A total of 256 bytes was allocated for time data storage giving a maximum number of logged data events as 85. This was considered adequate given that the stimulation regime was defined as a single treatment applied daily over a 3 week period between assessments, requiring a minimum of 21 logged events to store the required data.

8.3.6 Current monitoring

Current monitoring is implemented via ICs 7, 8, 9 (figure 8.6). One lead from the output transformer is used as a primary winding on a ferrite ring (Philips 4330-030-37930). The output from the secondary winding of the ferrite ring is amplified via IC7. The amplified signal is passed through a peak hold circuit (IC8, 9). The output from the peak hold circuit is presented to the A/D channel of the micro controller. The output from this circuit is proportional to the current flowing in the patient side of the output transformer. The software then reads this port after each pulse delivery and takes action according to the maximum and minimum thresholds which have been pre-programmed as part of the stimulation regime from the PC.

This implementation ensures that the electrical isolation provided by the output transformer to the patient electrodes is not compromised by the current measuring circuitry.
8.3.7 Safety features

This system offers several features to protect the user should corruption of the software or the programmed stimulation regime occur.

8.3.7.1 Checksum

The waveform data is subject to a parity check before each pulse delivery. A software routine establishes the number of bits set to 1 in the data. This total is compared to a value which has been downloaded from the PC when the unit is programmed. Although it is possible that this method may not flag corrupted data for two balancing errors (e.g. a bit corrupted from 1 to 0 in one word, and 0 to 1 in another), it does provide protection against single bit errors, and errors where multiple corruptions have occurred, where error balancing would be unlikely.

8.3.7.2 Hardware watchdog

A hardware watchdog is started immediately on power up. The watch dog timer must be periodically set by the software (disabled when the unit has entered sleep mode) otherwise the unit is designed to lock up. This protects against inadvertent software loops that may keep the unit functioning incorrectly.

8.3.7.3 Hardware power strobe

The output enable pin to the power op amp is controlled via a monostable which is, in turn, controlled using an ac coupled signal from the micro controller. The software must correctly set and reset this signal to enable the monostable, which occurs before each pulse delivery sequence. The action of the monostable ensures that the output op-amp is only enabled during the correct sequence of pulse delivery.

8.3.8 Defining the stimulation regime

Chapter 3 has already described the parameters used to define a given stimulation regime. These include the pulse shape and amplitude, inter pulse interval, the number of pulses to be included in a burst of stimulation (if appropriate) and stimulation duration. All of these parameters must be independently controllable for the unit to be fully programmable.
8.3.8.1 Pulse shape definition

The pulse-shape is generated by a series of 8-bit integers defining the amplitude of the pulse at a given point, together with a series of corresponding 8-bit integers defining the time duration for which each amplitude integer is valid. An example is illustrated in figure 8.7. For this example, the pulse shape consists of a monophasic 'stair case' shape. A relative amplitude of 0 is maintained for 2 time units, 10 is maintained for 2 time units, 20 is maintained for 5 units and 30 is maintained for 6 units.

![Figure 8.7 Method Used to define stimulation wave shape](image)

8.3.8.2 Implementation

The 8 bit integer defining the pulse amplitude is made available as an 8 bit word to port 3 of the microcontroller. It is converted to an analogue signal using a D/A converter configured so that 0 represents -5 V, 128 represents 0 V and 256 represents +5 V. The 8 bit integer defining amplitude duration is loaded into one of the timer control registers (rt1) of the microcontroller, which is set up to decrement the loaded integer to 0 at a clock frequency of 40 kHz. Thus, the unit has a time resolution of 25 μs and a maximum time interval of 6.4 ms. Durations longer than 6.4 ms are defined using consecutive pulse shape elements with the same amplitude.

The limitation of this approach relates to the amount of memory required, when pulse shapes requiring a large number of points for accurate definition are used e.g. sinusoidal pulse
Figure 8.8 a Main Software loop
Figure 8.8 b Data preparation routine
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Figure 8.8 c User generated Interrupt
Figure 8.8 Waveout routine
shapes. For this application, the number of discrete points defining a given wave form was limited to 128.

As well as defining the pulse shape, the definition of the stimulating regime also includes the inter pulse interval, the number of pulses to be included in each pulse train and the time interval separating each train of pulses.

It should be noted that at each switch on, the unit performs a soft start i.e. the stimulating pulse is amplitude limited, with the amplitude limit being raised on each pulse train delivery. This can result in clipping of the pulse shape until the normal operating level is reached. For example, considering the stair wave waveform, the third step would not be apparent in the delivered waveform until the maximum allowable amplitude had exceeded thirty units. The software could be altered to implement the soft start using a scaling technique rather than clipping, but for rectangular pulses as used in this study, there would be no difference.

8.3.8.3 Communications

The stimulator is programmed via the serial port of a host PC, which also reads the logged usage data. The communications protocol used a data rate of 2400 Baud, with 8 data bits and one stop bit. Data integrity was ensured by echoing received data back to the sending unit. In practice, a typical data transfer takes approximately 10 s, the exact duration depending on the complexity of the stimulating wave form and the amount of logged data.

8.3.9 Software description

Figures 8.8 a illustrates the stimulator software control loop, which is entered on power up, or on receiving a reset signal from the reed switch. In response to either of these conditions, the microcontroller performs register initialisation which includes setting the clock frequency, defining ports as inputs/outputs, initialising the watchdog, setting up timer interrupts etc. The software then examines the I/O port corresponding to the hidden switch (mode select) which selects the stimulation code used during normal operation, or the service code.

8.3.9.1 Stimulation code

On entering the stimulation code, the software performs the checksum routine. If an error is detected, the unit locks up and will require re-programming. The unit then enters the data
preparation routine which has its control flow illustrated in 8.8b. The purpose of this routine is to allow a 'soft start'. The amplitude of the stimulating waveform is compared to the current allowable maximum amplitude. If the amplitude is greater than the current maximum, it is given the value of the current maximum. The maximum allowable value is then incremented.

After returning from the data preparation routine, the software then moves in to a routine which prepares the unit to enter a low power sleep mode (call stop), unless the stimulation enable flag is set. When entering the sleep mode, the main clock is switched off and the sub-oscillator is used, reducing power consumption.

Switching the unit on or off is performed using a single button. When this is pressed, the software responds by toggling the stimulation enable flag. The control flow is illustrated in figure 8.8c. Pressing this button generates a non-maskable interrupt. The sub-routine servicing this interrupt looks at the stimulation enable flag. If it is set (i.e. the stimulator is currently on and needs to be switched off), the LEDs are switched off. The RTC data is stored and the stimulation enable flag is reset. If the flag is not set (i.e. the stimulator needs to be switched on), the RTC is reset, the current maximum amplitude is reset to 0 and the stimulation enable flag is set. The LEDs are set to indicate normal operation.

If the stimulation flag is set before the low power sleep mode is entered, the waveout routine is called. The software flow is shown in figure 8.8d. This routine resets the current monitor signal, and sets the monostable enable. The waveform is then delivered according to the stored data, after setting the appropriate LEDs. The instantaneous amplitude of the waveform is presented to the D/A converter and the corresponding amplitude duration is loaded into the timer register, which automatically starts to decrement. When the timer generates an interrupt on reaching zero, the next amplitude and duration are acted on, until the entire pulse sequence has been completed. On completion of the pulse train, the current value of the A/D converter is read and compared to the predicted value. If it is too low or too high, then the unit switches off, corresponding to a situation of under or over current.
8.3.9.2 Stimulator interface software

The interface between the programmable stimulator and the host PC was provided via the host PC serial port, which was controlled in turn using a Windows based application written in Visual C++. As well as providing the serial link, the software provided the method of defining stimulation parameters, which include:

- wave shape
- number of pulses in each burst
- pulse repetition frequency
- inter pulse train interval
- current monitor thresholds

The software also provided the facility of reading and storing logged time data from the stimulator. A typical window showing the application is shown in figure 8.9. The currently defined pulse shape is shown, together with the dialogue box used to define the waveshape. The dialogue box also requires information for the current monitoring threshold, the number of pulses in the train and the inter train interval. Check boxes are used to define the pulse shapes. This version has pre-defined shapes of rectangular triangular and sawtooth. More complex waveshapes can be defined using the method described in section 8.3.8.1. A data array representing the defined waveform is generated automatically by the software, ready to be downloaded to the stimulator.
8.3.9.3 Serial link

Selecting the comms option on the main menu brings up a dialogue box, on which the serial link protocol can be defined, which need not be changed from the default settings. Clicking OK on the dialogue box opens the serial comms port and an arbitrary character is sent to the stimulator. If this is not echoed back within approximately 1 second, then a Pop up box reporting a serial link fault is generated. When a successful link has been established, the stimulator sends all the logged data to the host PC. When this is completed, the host PC sends the stimulation regime data to the stimulator.

8.3.9.4 Logged data

A summary of the logged data can be displayed on screen, or alternatively, the raw data can be transferred via the clipboard for further analysis and display in a package such as Excel.
Figure 8.10 Photograph of a completed stimulator
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Figure 8.11a Output voltage vs. time into a 10kΩ load for the programmable stimulator
Figure 8.11b Output voltage vs. time applied to skin for the programmable stimulator
8.3.10 Output circuit performance characteristics

A completed stimulator is shown in figure 8.10. The performance of the output circuit was characterised with respect to the pulse regime proposed in chapter 3. A rectangular biphasic stimulating pulse (pulse phase duration 15 ms) was pre-programmed into the unit and the output was connected to a resistive load, which could be varied over a range of 500Ω - 100 kΩ. The peak positive output voltage measured with reference to ground (0 V) was recorded as a function of load resistance (range 0.5-50 kΩ). Peak output current was calculated as peak output voltage / load resistance. The power delivered to the load was calculated by multiplying together the values of current and voltage at each value of load resistance.

The performance of the current measuring subcircuit was characterised during final testing by measuring the output voltage from IC6 in response to changes to the delivered current during stimulation.

8.3.11 Results and discussion

8.3.11.1 Output circuit

A typical voltage waveform with a resistive load of 10kΩ is shown in figure 8.11a. A typical response when applied to skin is shown in figure 8.11b. As previously stated the frequency response of the transformer determines the range of output pulse shapes that can be generated without excessive distortion. The low frequency response of the transformer limits the maximum pulse duration that can be used. In practice, the maximum phase duration defined for therapeutic regimes in this study was 15 ms.

Figure 8.11a shows that when applied to a purely resistive load (10 kΩ) using a pulse width of 15 ms, there is approximately 20% droop caused by the finite primary inductance. This droop could be reduced by increasing the primary inductance, however, this would mean a more bulky transformer, affecting the portability of the unit.

The morphology of the waveform applied to skin via 1" diameter PAL electrodes is similar to that applied to a resistive load. There is some evidence of increased damping causing a softening of the waveform turning points, but the overall effect on the waveshape is not as great as that observed when comparing waveforms from the TENS units applied to skin. This
Figure 8.12 Output voltage from the current monitor sub-circuit over a typical range of delivered current.
Figure 8.13a Output voltage and current into a varying load for the programmable stimulator

Figure 8.13b Output power into a varying load for the programmable stimulator
can be explained by considering the shunt impedance offered by the skin capacitance to a 15 ms pulse (approximately 10 kΩ) compared to the 1kΩ impedance offered when using 200 μs pulses. The effect on the damping factor will not be as great.

The waveshape appears asymmetric around 0 V caused by the pulse droop. This implies that the positive and negative phases are delivering an unequal charge. However, transformers cannot pass dc which would be the implication of unequal positive and negative phases.

Charge balancing is achieved by a shift in the base line position between each pulse in the train of pulses. The implications of this observation is that over one biphasic pulse (a period of 30 ms) there will be a net charge of approximately 0.8 mC delivered, although over the whole pulse train this will be zero. It is unlikely that this charge delivered over time scales of the order of milliseconds would result in skin damage (Low and Reed, 1994). In order to achieve charge balance between pulses it would be necessary to extend the period between each pulse. This would be impractical when the system is being used to apply stimulating regimes where tetanic muscle contractions are required.

8.3.11.2 Current monitor

Figure 8.12 shows the voltage output of the current monitor versus delivered current.

In practice the dynamic range of this subcircuit, although adequate for this application, is limited by the maximum voltage swing of the 7611 amplifier and the noise coupled into the measuring circuit with no load, due to the close proximity of the ferrite ring to the transformer. The output characteristic shown in figure 8.12 show that for higher currents (>3mA), the sub-circuit output is very close to the 7611 integrated circuits' saturation voltage (4.2 V). The calibration of the current monitor could be adjusted if required, by altering the number of turns on the ferrite ring.

8.3.11.3 Output current and voltage as a function of load resistance.

Figures 8.13a shows the output current and voltage as a function of load resistance. The output current is observed to rise sharply as the output voltage falls, when the resistive load is less than approximately 8 kΩ. At resistive loads greater than approximately 24 kΩ, the unit is reaching the limit of its voltage compliance. The Thevenin equivalent series impedance of
the transformer secondary can be approximated by dividing the open circuit voltage by the
short circuit current in figure 8.2a, giving approximately 5 kΩ. This can be compared to a
typically expected skin impedance of 5 - 10 kΩ for this electrode type (Nolan, 1991), which
is not significantly different from the characteristic output impedance. According to standard
circuit theory, maximum power will be transferred to the load when the load impedance
equals the source impedance. Figure 8.13b shows power delivered to resistive load as a
function of the load resistance. Maximum power is delivered with a load resistance of
approximately 6-7kΩ, which is achievable using these electrodes. This can be contrasted to
the situation with the TENS unit, where the characteristic impedance of the output circuit was
approximately 1.3 kΩ, a figure for electrode impedance which is unlikely to be achieved
using these electrodes.

8.4 Laboratory version of the stimulator

A version of this stimulator was built that used exactly the same output stages as described
for the portable unit (ICs 4-6, illustrated in figure 8.6), but in this case, the D-A converter was
controlled by a PC. The interface to the PC was provided via the parallel printer port using a
very similar interface circuit as described for the line scan imaging system (chapter 6). This
allowed direct control over the output parameters. For example, using this version of the
stimulator, it was not necessary to use a ‘soft start’.

The output port of the PC interface could be used to provide a TTL compatible pulse, which
could be used, for example, as a trigger for the line scan imaging system or as a trigger for
signal averaging equipment. The latter facility was used to investigate the effect of
stimulation parameters on the visual aura (chapter 9).

8.5 Conclusion

In summary, the new portable stimulator offers several advantages over commercially
available units. It offers a very simple user interface, with all stimulation parameters pre-
programmed. It can produce a wide range of stimulation regimes, monitoring patient
compliance towards different regimes. Extensive software error checking and current
monitoring make the unit safe to use in a home environment.
Chapter 9

The effect of stimulation on adjacent nervous tissue.

Electrical stimulation applied via transcutaneous electrodes provides a non-specific stimulus which is difficult to localise with any precision, potentially leading to unwanted 'spillover' stimulation of adjacent structures.

Nervous structures in the area close to the electrode positions used in this study include other facial muscles, pain receptors on the skin surface, and components of the visual system including the retina and the optic nerve.

Muscle groups prone to 'spillover' stimulation include other muscles of facial expression (frontalis and corrugator), muscles controlling the position of the eyelid (levator palpebrae superioris and Mullers muscle) and the oculomotor muscles (rectus and oblique muscles). Stimulation of facial muscles could lead to synkinetic facial movements which would be cosmetically unacceptable. Stimulation of the levator and Mullers muscle may mask improvements in eye closure through eyelid elevation. Stimulation of the oculomotor muscles could affect vision by interfering with globe position. These effects are discussed in section 9.1.

Electrical stimulation using electrodes positioned close to the orbital region, and pulse durations greater than 5ms, has been shown to generate an evoked neural response from the visual cortex. This response has previously been used to determine retino-cortical conduction times (Potts et al., 1968) and has been suggested as a clinical tool to investigate the visual pathway, by-passing receptor segments and nuclei of the retina (Potts and Inoue, 1970). This visual response to electrical stimulation was perceived as a disadvantage in the present study since it might influence patient compliance and impose restrictions on using the stimulator (e.g. interference when reading or watching television). This is discussed in section 9.2.
9.1 Stimulation of Adjacent Muscle Groups

9.1.1 Stimulation of facial muscles

The introduction to this chapter highlighted several muscle groups vulnerable to 'spill over' stimulation, when stimulation is applied via electrodes on the medial and lateral canthi of the eye. These include muscles influencing facial expression, the oculomotor muscles controlling globe position, and the levator muscle which controls eyelid elevation. Such effects are difficult to predict and will depend to some extent on the specific anatomy of nerves in a given patient and the clinical condition of the subject. For example, in patients suffering from an incomplete seventh nerve lesion, the nerve segment to the orbicularis oculi may not be intact but the segment to the lower part of the face may be intact. Stimulation applied using electrodes near the orbit may cause the intact nerve segment to depolarise, causing contraction in the lower part of the face.

Stimulation of other facial muscles was considered to be unacceptable since the induction of synkinetic movements is not desirable. Synkinetic movements add to facial asymmetry which can be cosmetically disfiguring. Electrical stimulation has previously been associated with the induction of permanent synkinetic movements which has been noted as an undesirable consequence of stimulation (Fitzgerald, 1993). Such claims have since been refuted and the induction of synkinetic movements has been attributed to incorrect re-innervation of the target muscle (Baker et al., 1994).

However, as well as the issue of aberrant re-innervation, there was a possibility of behavioural conditioning. Stimulation of other muscles whilst attempting eyelid closure may result in learning of this behavioural pattern, resulting in the subject attempting to recruit other muscles to aid closure. A common example is raising the angle of the mouth when attempting to achieve eyelid closure. When patients were assessed, video recordings were used during periods of electrical stimulation. These were examined qualitatively after the stimulation session for any synkinetic movements. There was no sign in any of the patients included in this study of synkinetic movements caused by electrical stimulation.
9.1.2 Stimulation of the ocular motor muscles

The oculomotor muscles are responsible for globe positioning. If stimulation of these muscles was to occur, there could be the potential of interference with vision as gaze position changed in response to electrical stimulation. This could be disturbing to the subject and potentially limit application of the stimulation regime. However, even at higher levels of stimulation no effect on globe position was observed.

9.1.3 Stimulation of the levator muscle

Chapter 4 has described the major role of the levator muscle as assisting in eyelid elevation. If significant levator stimulation was to occur then improvements made to eyelid closure would be masked by eyelid elevation. In practice, both in normals and in palsied patients, no eyelid elevation was observed.
9.2 The visual response

9.2.1 Introduction

Mechanical force, magnetic fields, X-rays and electrical pulses have all been known to produce the sensation of light, which has been termed 'phosphene'. This has been characterised using electrical pulses applied directly to the eye via a corneal contact lens electrode. (Potts et al., 1968)

This study demonstrated that electrical stimulation using long duration (>10 ms) rectangular biphasic pulses applied using electrodes placed on the medial and lateral canthi of the eye, also produces a visual aura associated with each stimulating pulse. Stimulation at a relatively low frequency (of the order of 1 Hz), produced a sensation of individual flashes. At higher pulse repetition frequencies the sensation of a flicker was obtained. This was perceived as an unwanted side effect of the stimulation regime, possibly reducing patient compliance.

The visual aura causes an evoked potential which can be recorded on the occipital scalp region using an appropriate recording protocol. An evoked potential can be characterised by its morphology, amplitude and latency, which is the time interval between presentation of the stimulus and its response (i.e. a measure of the retino-cortical transmission time). The present study was designed to investigate whether varying the temporal characteristics of the stimulating waveform could reduce or eliminate the visual response.

By varying the temporal characteristics of long duration electrical stimuli, Potts et al., (1968) concluded that the critical factor in producing the visual aura was the rate of change of the applied voltage. Latency measurements of the cortical response indicated three significant features.

1. For a rectangular pulse shape, the response appeared to be triggered by the leading edge of the applied pulse.

2. A minimum rectangular pulse width of 2 ms was required below which a visual response could not be recorded.

3. For a 'sawtooth' waveform, the rapid falling edge appeared to trigger the response as opposed to the shallow rising leading edge.
9.2.2 Hypotheses for reduction of the visual aura

Two hypotheses were proposed for the reduction or elimination of the visual aura associated with long pulse width electrical stimulation around the orbital region. The first is based on the observation by Potts et al., (1968) that a rapid transition in the applied pulse was required to generate a cortical response. If the rapid transition was removed from the stimulating pulse (e.g. by the use of a pyramidal waveshape), then the long pulses required for the stimulation of denervated muscle would still be present, but the visual aura might be attenuated or eliminated. This hypothesis makes the assumption that the rapid change in applied potential is solely responsible for the aura. Pyramidal or trapezoidal shaped pulses have been used to treat denervated muscle in other physiotherapeutic applications (for a review see Low and Reed, 1994), thereby further justifying their potential use in this study.

The second hypothesis is based on the observation that a minimum pulse width is required to generate a cortical response. Modulating the long duration pulse into a series of monophasic short pulses may reduce or eliminate the electrically evoked visual response, since the nervous structures responsible for generating the aura would have the chance to 'discharge' between each component of the modulated waveform.

Data for the efficacy of a modulated pulse for inducing contractions in denervated muscle is not available in the literature. However, the review in chapter 2 suggested that muscle fibre membrane properties change after denervation so that the fibre membrane would not be able to recover its resting state after each component of the modulated pulse, and the overall effect would be similar to a 10 ms rectangular pulse of equivalent average charge, thereby justifying their use.

9.2.3 Methods

9.2.3.1 Subjects

One normal volunteer was recruited to this part of the study for response recording (male, aged 31). Subjective assessments were made on four other volunteers to confirm the existence of the visual aura.

9.2.3.2 Stimulation and recording equipment

The electrical stimulation pulses were provided by the laboratory based stimulator described in chapter 8. PAL™ electrodes were applied to the medial and lateral canthus of the eye, after
Voltage (V)

Chapter 9: Visual aura

Stimulus number
1 10 ms, 20V rectangular biphasic
2 10 ms, 20V rectangular monophasic
3 10 ms, 7 ms, 3 ms, 1.5ms, 300us 20V monophasic rectangular pulses
4 10 ms 20V monophasic modulated pulses (mark space ratio ranging from 6%-50%)
5 10ms 10V rectangular monophasic
6 10 ms 20V sawtooth
7 20 ms 10V pyramidal

Figure 9.1

Representation of the waveshapes used during stimulation including their temporal characteristics
the skin had been washed with water and dried according to the stimulation regime previously described (chapter 3). Both monophasic and biphasic rectangular stimulation pulses were used. Monophasic pulses were used so that the results could be compared with those of Potts et al., (1968). Biphasic pulses were used, as these were typical of waveshapes used as part of the therapeutic stimulation regime defined for this study (chapter 3). Biphasic pulses were also found to reduce the stimulation artefact on the recording electrodes compared to a similar amplitude and duration monophasic stimulating pulse. (The stimulus artefact is caused by the recording electrodes picking up the electric field generated by the stimulating pulse. The physical separation of the electrodes around the skull means that the electric field will not be the same under each electrode, thus differential amplification will cause a stimulation pulse artefact). Figure 9.1 illustrates the waveshapes and the temporal characteristics of the stimulating pulses used in this study. All stimulation pulses were applied at a frequency of 1 Hz.

The visual evoked cortical response was recorded using Ag/AgCl electrodes attached at scalp positions 2.5 cm and 6 cm above the inion, on the nasion / inion midline. A ground electrode was placed on the midline equidistant between the two recording electrodes. Electrode impedances were kept below 10 kΩ and within 3 kΩ of each other by first preparing the skin with Omniprep™. Electrode attachment was achieved using a adhesive/conductive paste (Elefix ™). A signal processor (model Spirit, manufactured by Nicolet, America) was used to record and average approximately 10 responses per recording. The external trigger on the signal averager was enabled using a TTL compatible pulse from the PC interface. The trigger pulse was sent immediately prior to delivery of the stimulating pulse. The incoming signal was filtered before averaging (bandpass of 0.1 - 70 Hz.). A post stimulus delay of 40 ms was used to minimise contamination from stimulus artefact. The subsequent 200 ms were recorded for averaging. The subject wore blackened goggles to eliminate ambient light. Signal contamination from α rhythm was minimised by instructing the subject to keep their eyes open and perform mental arithmetic tasks. (α rhythm is a relatively large amplitude signal with a frequency of approximately 10 Hz, generated in the occipital region of the brain when in a relaxed state.) To reduce stimulation artefact further on monophasic stimulating waveforms, repeat responses were recorded with the polarity of the stimulating electrodes reversed between each recording. The responses for both polarities were then summed off-
Figure 9.2
Cortical response to 10 ms rectangular biphasic pulses
1, 2 and 3, 4 are recorded with the polarity of the stimulating electrodes reversed
Trace 5 shows the cortical response to a monophasic 10 ms rectangular pulse
line. The components of the response corresponding to the stimulation artefact on each recording were opposite in phase and therefore reduced on the final summation.

9.2.4 Results and discussion

Evoked potentials generated in response to stimulating pulses of type 1 were used to demonstrate that a repeatable response could be recorded. Stimulating waveform type 2 was used to compare responses derived from monophasic waveforms to those achieved from biphasic stimulating pulses (1). Series 3 was used to investigate the effect of pulse width on the evoked response, while series 4 was used to investigate the effect of mark/space ratio on the evoked responses. Responses from types 4 and 5 were used to compare the relative effect of the 50% mark space ratio pulse compared to a rectangular pulse of equivalent average charge. Finally, evoked potentials derived from pulse type 6 were compared to those from type 7 to investigate whether elimination of the rapid transitional component of the stimulating pulse eliminated the evoked response. The duration of the pyramidal waveshape type 7 was increased with respect to the sawtooth waveform (6) to keep the rate of change of the leading slopes equivalent, although the total charge delivered by the pyramidal pulse was greater.

9.2.4.1 Biphasic pulses vs. monophasic pulses

Figure 9.2 (1-4) indicates typical responses from 20 V, 10 ms rectangular biphasic pulses, as used in the stimulation therapy regime of this study (chapter 3). Each trace represents the average of approximately 10 responses. Recordings 1 and 2 are the responses of one stimulation polarity (biphasic stimulating pulses), whilst 3 and 4 represent the responses from the reversed polarity. Within the region up to 40 ms from the origin, the antiphase responses can be observed, corresponding to the stimulus artefact. The large trough located at approximately 100 ms shows a consistent cortical response.

Examination of figure 9.2 traces 1-4, indicates that the evoked responses show considerable waveform variability in terms of amplitude and latency for repeated responses to the same stimuli. The response trough is also quite broad in appearance, limiting the accuracy of latency measurement. In practice, attempting to resolve latency changes of less than 10-15 ms would not be possible using the biphasic stimulation pulses used in this study. The evoked response derived from the 20V, 10 ms monophasic pulse however, has a well defined
Figure 9.3
Cortical response to monophasic rectangular pulses of increasing width

<table>
<thead>
<tr>
<th>Trace</th>
<th>Stimulating Pulse Width</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3 ms</td>
</tr>
<tr>
<td>2</td>
<td>1.5 ms</td>
</tr>
<tr>
<td>3</td>
<td>2.5 ms</td>
</tr>
<tr>
<td>4</td>
<td>5.0 ms</td>
</tr>
<tr>
<td>5</td>
<td>10 ms</td>
</tr>
<tr>
<td>6</td>
<td>20 ms</td>
</tr>
<tr>
<td>7</td>
<td>30 ms</td>
</tr>
</tbody>
</table>
peak (trace 5). Potts et al., (1968) also achieved well defined peaks from which it was possible to determine estimates of amplitude and latency. There are two possible explanations for the observed difference in response morphology, both of which are related to the stimulation protocol used. The first concerns the site of the stimulation electrodes. Potts et al., (1968) used a corneal contact lens electrode, which they reported to give a stronger more diffuse flash compared to the localised peripheral response achieved when using skin electrodes. In clinical practice, cortical responses to weak or localised light flash stimuli are associated with increased variability in measured amplitude and latencies, compared to bright/diffuse flashes (Connolly et al., 1982). The broadness of the waveform trough in the present study could be related to this factor, or directly attributable to the biphasic stimulus waveform. The broad peaks observed in this study may be a composite of the cortical responses to both the positive and negative phases of the stimulating pulse, which, for a 20 ms pulse will be temporally separated by a maximum of 20 ms. The larger, sharper peak observed for responses to monophasic stimulating pulses in the study of Potts et al., (1968) can similarly be explained by temporal addition of two waveforms (derived from the leading and trailing edges), occurring so closely together that they cannot be resolved.

9.2.4.2 Effect of increasing pulse width

The series of waveforms shown in figure 9.3 illustrate the effect of an increasing pulse width on the cortical evoked potential. The perceived flash increases in strength, which is reflected in the increased amplitude of the evoked response. At 300 μs (trace 1) there was no perceived flash, although there is evidence of a very small cortical response. Trace 5 shows the largest amplitude, corresponding to a 10 ms pulse. Traces 6 and 7 are reduced in amplitude although there was little difference in the perceived visual aura. This may be attributable to a similar effect as seen during biphasic stimulation, where two distinct flashes (triggered by the leading and trailing edges of the long pulses) interfere with each other.

9.2.4.3 Effect of increasing mark space ratio in a modulated waveform

As previously described, the hypothesis for this part of the investigation is that modulating a 10 ms pulse into a series of 300 μs pulses would reduce the cortical response, since a cortical response cannot be recorded when using a single 300 μs monophasic stimulating pulse. Effectively, the nervous structures generating the response will 'discharge' between each
Figure 9.4
Cortical response to rectangular modulated pulses

<table>
<thead>
<tr>
<th>Trace</th>
<th>Mark Space Ratio %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
</tr>
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<td>5</td>
<td>18</td>
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<td>6</td>
<td>21</td>
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<td>7</td>
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<td>8</td>
<td>27</td>
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<td>9</td>
<td>30</td>
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<td>10</td>
<td>35</td>
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<td>11</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
</tr>
</tbody>
</table>
Figure 9.5
Cortical responses to modulated rectangular modulated pulses (1) and a rectangular monophasic pulse (2)
Figure 9.6
Cortical responses to pyramidal monophasic stimulating pulse (1) and a sawtooth monophasic pulse (2)
monophasic 300μs component contained within the modulated pulse, before the effective threshold to generate a cortical response is reached.

The series of waveforms shown in figure 9.4 illustrate the effect of changing the mark space ratio in a range of 6% - 50% over the 10 ms period. The duration of the mark was maintained at 300 μs, which has already been shown not to produce a visual aura.

Increasing the mark space ratio produced a corresponding increase in the magnitude of the visual aura and the evoked potential.

9.2.4.4 Rectangular square wave compared to modulated square wave.

Figure 9.5, trace 1 represents the response to a 20 V, 10 ms modulated rectangular stimulating pulse wave, with 50% mark (300 μs) space ratio. Figure 9.5 trace 2 shows the response to a 10 V, 10 ms conventional biphasic rectangular pulse. The peak voltage of the modulated pulse was twice that of the conventional pulse in order to balance the total charge. The latencies of the responses are very similar while the amplitude of the 50% mark space ratio modulated pulse response (1) is slightly greater than the non-modulated response (2). These differences may not be significant, given the variability in cortical responses observed using biphasic pulses. The conclusion from these observations is that the cortical response could be initiated either by the rapid transition of the leading edges of both modulated and rectangular waveshapes or related to the average charge delivered over the 10 ms period. If the average charge is important, it is evident that significant discharge of the nervous structure causing the response does not occur between the monophasic pulses at higher mark space ratios. If lower mark space ratios are used, the perceived visual aura and the evoked potential are reduced, but the average current delivered over the 10 ms period will also be greatly reduced, reducing the effect of the stimulation regime on denervated muscle.

9.2.4.5 Sawtooth response compared to the pyramidal response.

Potts et al., (1968) showed that the latency of the cortical response to a sawtooth pulse was related to the duration of that pulse. It was concluded that the rapid transitional segment of the stimulating wave initiated the cortical response. Figure 9.6 shows that eliminating the rapid transitional edge by using a pyramidal waveshape, with the temporal characteristics defined in this study, does not eliminate the evoked response. The response to the pyramidal
waveshape is very similar with respect to both amplitude and latency compared to the sawtooth pulse responses.

This observation implies that the response could be related to the total charge delivered by the stimulating pulse rather than by the presence of a rapidly changing edge. This argument is further strengthened by the observation by Potts et al., (1968) that a minimum pulse width is required before a response is generated. However, it is unlikely that this is the full explanation. Potts et al., (1968) showed that increasing the duration of the sawtooth waveform, whilst maintaining the amplitude, resulted in a proportional increase in the latency of the response. If the response was initiated by charge only, the change in latency would not be expected to follow the change in position of the rapid edge directly, but would correspond to the change in time for equal charge to be delivered by the two waveforms.

The response therefore appears to be linked to the total charge delivered plus another component of the waveform. This may be large rates of change of the applied voltage, turning points in the waveform after sufficient charge has been injected into the system, or the point of transition from a positive to a negative stimulus.

Reducing the gradients of the leading and trailing edges of the pyramidal waveform may still eliminate or reduce the visual response. This would increase the effective duration of the stimulating pulse for a given amplitude. Longer pulses (>100 ms), although consistent with previously used therapies to treat denervated muscle are associated with more painful stimulation and would reduce patient compliance in this study. It would be difficult to record responses from such pulses since the stimulating artefact will run into the temporal position of the evoked response.

9.2.6 Conclusion

It is possible to objectively characterise the subjective visual sensation perceived when using long duration (10 ms) pulses, by non-invasive measurement of the evoked potential generated in the occipital cortex of the brain. The observations from this study and that of Potts et al., (1968) indicate that the response to the electrical stimulating pulses is complex. It is difficult to identify the specific component responsible, although the total charge delivered over a defined time period does appear to be a significant factor, along with rapid transitional edges or turning points in the waveform. It may be that a combination of factors is necessary to
evoke a response. Altering the temporal characteristics of long duration pulses does not appear to reduce the visual aura if the total delivered charge remains unchanged, therefore it appears that it is not possible to design a therapeutic regime for treating denervated muscle around the orbital area based on stimulation with long pulses, without obtaining a visual response.

The literature does not suggest that generating a visual aura is harmful in any way, therefore there are no safety implications in using this stimulation regime to treat denervated muscle. However, clinical application of this technique may be limited if subjects find the visual aura disturbing. It is unlikely that the magnitude of the perceived flash would seriously interfere with daily activities such as reading or watching television, although this may depend on individual circumstances. It may be prudent to advise against using this type of stimulation if there is a history of epilepsy within the patient.

In summary, generating a visual aura appears to be an unavoidable side effect of electrical stimulation around the orbital area using long duration pulses, although clinical application of this technique should not be limited provided appropriate advice and warnings are given to the subject.
Chapter 10

Patient Responses to TENS and Long Pulse Electrical Stimulation Regimes

This chapter details the results from the two regimes of electrical stimulation used in this study, which have been described in chapter 3. Measurements of eyelid displacement indicated that both therapeutic regimes were successful in increasing the range of voluntary eyelid closure in patients with at least a grade III facial palsy (House-Brackmann). No significant improvement in the amplitude of spontaneous blinks was observed. Dynamic measurements indicated that the peak velocity of upper eyelid movements did not increase as a result of either treatment regime.

Application of electrical stimulation to restore function gave no response using the narrow pulse stimulation regime whereas movement was observed in both upper and lower eyelids during long pulse stimulation in four out of seven patients.
10.1 Recruitment

Ethical committee approval was obtained to measure the responses of facial palsy volunteers to courses of treatment using electrical stimulation. Informed written consent was obtained in each case.

Ten patients (9 male, 1 female) with a chronic seventh nerve palsy were recruited to use the TENS stimulation regime. Eight were post acoustic neuroma resection with a Grade III facial palsy (House Brackmann) or worse. One patient suffered a facial palsy as a result of a road traffic accident (Grade III House Brackmann). One subject had a facial palsy associated with Ramsay Hunt Syndrome (Grade IV House Brackmann). Two subjects had a previous tarsorrhaphy. The mean time from nerve injury to treatment was 24 months, although one patient had a palsy for 144 months before treatment. The mean age of the subjects was 57 years (range 36 to 76 years).

A separate group of 10 patients were recruited to use the long pulse stimulators. Of these, two patients withdrew from the study after a period of two weeks, claiming that the regime increased facial pain and were not included in these results. One person refused stimulation after being made aware of the visual aura side effect. All seven patients participating in the study suffered a facial palsy following surgery for acoustic neuroma resection (6 male, 1 female, age range 31-76 years, mean 53 years). The period from nerve injury to treatment with electrical stimulation ranged from 2 years to 10 years with a mean of 2 years 5 months.

Five normal volunteers (4 male, 1 female, age range 23-34) were used to assess normal tolerance levels to both stimulation regimes. The purpose of this exercise was twofold. Patients that could tolerate only low amplitude stimulation would not be included in the study. This level was defined as the minimum necessary to produce functional movement in normal volunteers. The second reason was to set a maximum stimulation level based on the tolerance of normal volunteers. It was possible that patients presenting with facial palsy could have trigeminal nerve involvement accompanying the seventh nerve damage, affecting skin sensation. This could lead to patients inadvertently setting stimulation parameters that could potentially cause skin damage or irritation, when using the TENS units.
Chapter 10 Electrical stimulation regime results.

10.2 Patient treatment methods

10.2.1 TENS stimulation

The stimulation regime was implemented using transcutaneous electrical nerve stimulators (TENS Unit, Model 120Z, I.T.O. Company Ltd.). The output from the stimulators was described by the manufacturers as constant voltage with a compensated monophasic pulse shape. Chapter 8 has characterised the stimulator. The stimulation pulses were delivered via one inch diameter PAL™ re-useable electrodes which were placed as near as possible to the medial and lateral canthi of the eye, after washing and drying the contact area.

Patients were instructed to use the electrical stimulator for approximately one hour daily. The pulse frequency and width were set to 10 Hz and 200 μs respectively, consistent with values used in previous studies using therapeutic electrical stimulation on seventh nerve palsies (Farragher, 1987). The duty cycle of the treatment was 2 seconds on 1 seconds off. Patients were instructed to use a level of stimulation in the range 3 - 4 on the thumbwheel, corresponding to a peak output voltage of approximately 18 V (section 10.4), which was consistent with comfortable levels in normal volunteers. They were asked to record the level of stimulation used and the duration for which stimulation was applied.

10.2.2 Long pulse stimulation

This regime was implemented using the new programmable stimulator described in chapter 8. The rational for this regime has been discussed in chapter 3. To recap, strength/duration curves for denervated muscle suggest that long pulses (>10 ms) may be necessary to cause contraction of denervated muscle fibres. Chapter 9 has reported that electrical stimulation using long pulses around the orbit of the eye causes a visual aura. All patients were informed of this side effect.

Patients were again instructed to use the stimulator for approximately 1 hour daily. The pulse repetition frequency was programmed to be 10 Hz and a biphasic pulse was used with a phase duration of 15 ms. A five second interval was maintained between pulse trains, which consisted of 5 pulses. The maximum stimulation level was set to approximately 16 V, which was consistent with comfortable levels in normal volunteers (section 10.4.2). Again, patients were instructed to record the duration of each stimulation session.
10.3 Patient assessment methods

Experience showed that many patients were initially apprehensive about using electrical stimulation, therefore initial stimulation levels were kept low for the first week of treatment. After the initial period of one week, patients were assessed to ensure compliance with the given instructions, after which stimulation levels were increased to ‘comfortable’ levels. Patients were subsequently assessed at 4 weekly intervals. At each assessment, patients were asked to put on the electrodes and switch on the stimulator, to ensure continuing compliance with the given instructions. Eyelid movements were recorded using the line scan system for spontaneous blinks and voluntary eye closure. For the latter, patients were asked to close the eye as much as possible whilst maintaining facial symmetry. Each recording was characterised by measuring the peak displacement and maximum velocity. For each assessment, an average of three maximum eyelid displacements and associated peak velocities were used. A measure of lagophthalmus was made using a ruler to measure the residual palpebral fissure on forced closure, as an additional measure to the line scan system. Responses to functional electrical stimulation required higher stimulation levels. These were not attempted until after one month of treatment, when the patients’ confidence in using electrical stimulation had increased. These responses were also assessed using the line scan system.

Facial movements were recorded on video tape before and during treatment. The video tapes were examined qualitatively for signs of increased synkinesis by comparing movements between the normal and affected sides. Specific movements made in the comparison included raising the eyebrows, smiling, puffing out the cheeks and baring the teeth.

10.4 Normal stimulation levels

10.4.1 TENS stimulation

This section was designed to establish stimulation amplitudes that normal subjects found tolerable with respect to levels of discomfort caused by the stimulation regime. PAL™ electrodes were placed on the normal volunteers as described in chapter 3. The volunteers were instructed to respond according to the following criteria as the examiner slowly turned the stimulation levels up. After each response was given, the stimulator level was turned down, before resuming to find the next level. Each volunteer was asked to respond when they
became aware of the stimulation sensation (1). They were then asked to respond to a comfortable level, which was defined as a level at which they would be happy to use for an extended period (2). They were then asked to respond when the stimulation could only be tolerated for a brief period (3). Finally, they were asked to respond when the stimulation sensation could not be tolerated (4). The mean and standard deviations of the peak voltage (measured with respect to 0 V) measured across the electrodes during stimulation is indicated, when the appropriate response was given.

1. Initial awareness or sensation (10V ± 3 V)
2. Comfortable levels (18 V ± 2V)
3. Tolerable levels (25 V ± 5 V)
4. Intolerable levels (30 V ± 8 V)

10.4.2 Long pulse stimulation

The programmable stimulator was loaded with the same stimulation program to be used on the patients (section 10.2.2). Again, the volunteers were prepared in the same manner as the patients, with PAL™ electrodes positioned on the medial and lateral canthi of the eye. They were asked to respond to the same categories as before. Again, the peak voltage across the electrodes measured with respect to 0 V was recorded for each response. Each value is quoted with a mean and standard deviation:

1. Initial awareness or sensation (5 V ± 2.5V)
2. Comfortable levels (10V ± 2V)
3. Tolerable Levels (20 V ± 3.5 V)
4. Intolerable levels (24 ± 5V)

Subjects were aware of the increasing magnitude of the visual aura with increasing stimulation levels, but the limiting factor when using this stimulation regime was attributed to pain, rather than discomfort due to the visual aura.
10.5 Eyelid displacement measurements after treatment with TENS units

10.5.1 Voluntary eye closure

Treatment of paretic eyelids using this regime of electrical stimulation therapy was successful in increasing the range of voluntary movement. Table 10.1 lists the maximum eyelid displacements during voluntary eye closure before and after the course of treatment for seven patients (the line scan imaging system was not available at the start of treatment of the first 3

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Grade (House Brackmann)</th>
<th>Pre treatment displacement (mm)</th>
<th>post treatment displacement (mm)</th>
<th>Difference (mm)</th>
<th>p-value (t test paired for means)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>III</td>
<td>2.6±0.1</td>
<td>4.3±0.4</td>
<td>1.7</td>
<td>0.018</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>IV</td>
<td>4.2±0.1</td>
<td>6.6±0.1</td>
<td>2.4</td>
<td>0.005</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>III</td>
<td>0.5±0.02</td>
<td>4.6±0.03</td>
<td>4.1</td>
<td>0.002</td>
</tr>
<tr>
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<td>67</td>
<td>III</td>
<td>3.1±0.4</td>
<td>4.5±2.6</td>
<td>1.4</td>
<td>0.131</td>
</tr>
<tr>
<td>5</td>
<td>73</td>
<td>IV</td>
<td>2.7±0.05</td>
<td>6.1±0.05</td>
<td>3.4</td>
<td>0.002</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>V</td>
<td>1.4±0.1</td>
<td>3.38±0.08</td>
<td>2.0</td>
<td>0.003</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>IV</td>
<td>4.7±0.45</td>
<td>4.7±0.05</td>
<td>0</td>
<td>0.442</td>
</tr>
</tbody>
</table>

Table 10.1 Upper eyelid displacement initially and after three months treatment using the TENS unit during voluntary closure.

Increases in eyelid displacement ranged from 1.4 mm to 4.1 mm with a mean value of 2.5 mm. Time to peak closure ranged from 0.4s to 1.8s with a mean of 0.9s. A one sided paired t test was performed on the eyelid displacement data derived from the line scan system for each of the 7 patients. Four out of 7 patients showed a significant improvement in the range of movement (p < 0.005). Two cases were significant at the 2% level. Patient 7, with an existing tarsorrhaphy, showed no difference pre and post treatment. The observed differences in the 7 patients overall were significant at the 5% level. Extending the treatment period beyond three months gave no further benefit to any of the patients recruited to this part of the study.

Multiple regression analysis was used to test whether either the initial amount of movement or the facial palsy scale could be used as an indicator of likeliness to benefit from treatment i.e. the degree of improvement in voluntary closure achieved. An F test based on the
regression and residual mean squares showed that the overall relationship between the predictor variables (palsy grade and initial movement) and the outcome (improvement) was not significant at the 95% level (p = 0.258).

10.5.2 Lagophthalmus

Lagophthalmus measurements using a ruler were carried out for all 10 patients over the treatment period and the measurements are listed in Table 10.2. Eight subjects have shown a reduction in lagophthalmus (mean 2.9 mm, range 0 to 6 mm) including two subjects that improved sufficiently to record no lagophthalmus. A one sided t test on the measurements for all ten patients showed that the observed differences were significant at the 95% level. Patients 7 and 9 who showed no reduction in lagophthalmus after treatment had existing tarsorrhaphies.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Grade</th>
<th>Pre treatment Lagophthalmus (mm)</th>
<th>Post treatment Lagophthalmus (mm)</th>
<th>Difference (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>III</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
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<td>74</td>
<td>IV</td>
<td>6</td>
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<td>4</td>
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<td>III</td>
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<td>6</td>
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<td>III</td>
<td>4</td>
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<td>1.5</td>
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<tr>
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<td>IV</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>V</td>
<td>5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>7†</td>
<td>48</td>
<td>IV</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>8‡</td>
<td>36</td>
<td>III</td>
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</tr>
<tr>
<td>9†</td>
<td>76</td>
<td>VI</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>33</td>
<td>V</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 10.2 Lagophthalmus measured initially and after three months treatment
*indicates patients with Ramsay Hunt Syndrome
†indicates patients with tarsorrhaphy
‡indicates patient with paralysis secondary to an RTA

10.5.3 Spontaneous eyelid movement.

Table 10.3 indicates the maximum recorded spontaneous eyelid displacements before and after treatment for the 7 patients for which the line scan system was available. Measurements in four subjects showed a very small increase in displacement (<0.8 mm), whereas the other
Chapter 10: Electrical stimulation regime results

Figure 10.1a (upper trace) Displacement vs. time for a normal spontaneous blink.

Figure 10.1b (lower trace) Velocity vs. time for a normal spontaneous blink.

Figure 10.2a (upper trace) Displacement vs. time for a voluntary blink in a palsied patient.

Figure 10.2b (lower trace) Velocity vs. time for a voluntary blink in a palsied patient.

Figure 10.3a (upper) Displacement vs. time for a spontaneous eyelid movement in a palsied patient.

Figure 10.3b (lower) Velocity vs. time for a spontaneous movement in a palsied patient.
three show a marginal decrease (<0.5 mm). A one sided t test on the differences showed that the observed changes were not significant.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre treatment displacement (mm)</th>
<th>Post treatment displacement (mm)</th>
<th>p value (t test paired for means)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>1.9</td>
<td>0.44</td>
</tr>
<tr>
<td>2</td>
<td>1.8</td>
<td>2.5</td>
<td>0.15</td>
</tr>
<tr>
<td>3</td>
<td>1.7</td>
<td>1.5</td>
<td>0.35</td>
</tr>
<tr>
<td>4</td>
<td>2.4</td>
<td>2.2</td>
<td>0.21</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>2.6</td>
<td>0.31</td>
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<tr>
<td>6</td>
<td>1.5</td>
<td>1.7</td>
<td>0.26</td>
</tr>
<tr>
<td>7</td>
<td>2.2</td>
<td>1.8</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Table 10.3 Upper eyelid displacement initially and after three months treatment using the TENS units during spontaneous blinking.

10.6 Dynamic eyelid measurements after treatment with the TENS units

Figure 10.1a shows the upper eyelid displacement vs. time curve obtained from the line scan imaging system for a normal spontaneous blink. The corresponding velocity vs. time relationship is shown in figure 10.1b. The displacement curve shows rapid closure of the upper lid followed by a longer upwards phase in which peak velocities are lower. Figure 10.2a shows a typical upper eyelid displacement response for voluntary closure in a palsied patient following treatment, for comparison. The displacement trace shows good eyelid movement in terms of distance moved, although the down phase movement is much slower than in a normal blink sequence. The time to peak closure is approximately twice that observed during normal blinks. The response also shows a plateau separating the closing and opening phases. This indicates the subject is attempting to hold the eye closed for longer than during a spontaneous blink. The lid velocity (shown in figure 10.2b) in the opening phase is similar to that in the closing phase.

Figure 10.3a shows the largest spontaneous response obtained in the same subject. Although the movement is similar in form to that illustrated in figure 10.1 for a normal blink, the maximum displacement is small.

Figure 10.4a shows the 95% confidence ellipse for normal volunteers. The measurements made for the seven patients during their first assessment are also shown, as are the measurements made at the end of their respective treatment periods. Each point
Normal 95% confidence ellipse for the blink down phase
Patient data is shown before and after treatment
TENS stimulation

Figure 10.4a

Comparison of main sequence lines for normals and palsied patients
Blink down phase
TENS stimulation

Figure 10.4b

Figure 10.4a Showing 95% confidence ellipse for normal data with patient data from initial assessments and after a treatment period of three months (blink downphase)
Figure 10.4b Main sequence data for normals and for patients during their treatment periods (blink downphase)
Chapter 10: Electrical stimulation regime results

Normal 95% confidence ellipse for the blink upphase
Patient data is shown before and after treatment

TENS stimulation

---

Figure 10.5a

Comparison of main sequence lines for normals and palsied patients
Blink up phase
TENS stimulation

---

Figure 10.5b

Figure 10.5a Showing 95% confidence ellipse for normal data with patient data from initial assessments and after a treatment period of three months (blink upphase)

Figure 10.5b Main sequence data for normals and for patients during their treatment periods (blink upphase)
represents an average of three blinks. All of the patient data points for the start of treatment lie at the very edge of the confidence ellipse, with low amplitudes and velocities. The data for the end of treatment shows that where voluntary displacement has improved to provide reasonably good closure (>5 mm), the corresponding values for velocity remain very low, thus, these data points lie outside of the 95% confidence ellipse.

Figure 10.4b shows the main sequence data for normal volunteers and palsied patients for the blink downphase, based on data acquired for all seven patients over all of their treatment periods. For both normal and palsied patient data, maximum displacement measurements were banded into 0.5 mm intervals and the mean displacement and velocity was calculated for each interval. The error bars represent the standard deviation around the mean velocity for each interval. Each interval used data from at least 5 blinks.

Paretic eyelid velocities for a given amplitude of movement are significantly lower than for normals and the populations of data points for the two groups are well separated. The regression equations for downward paretic eyelid movements were evaluated as:

\[ Y = 5.7X + 6.2 \]

compared to the regression line derived from normal volunteers:

\[ Y = 21.4X + 31.7 \]

where \( Y \) = peak velocity (mm/s) and \( X \) = maximum eyelid displacement (mm).

Figure 10.5a compares the 95% confidence ellipse for normal volunteers to data derived for the palsied patients during the blink up-phase. The data points for both before and after treatment lie well within the normal range, except for one patient exhibiting very poor voluntary movement. Figure 10.5b shows the main sequence data for the blink up-phase based on data acquired for all seven patients over all of their treatment periods. The regression equation for upward movements in paretic eyelids was evaluated as:

\[ Y = 4.4X + 31.7 \]

compared to the regression line derived from normal volunteers:

\[ Y = 10.8X + 13.7 \]

where \( Y \) = peak velocity (mm/s) and \( X \) = maximum eyelid displacement (mm).

Comparison of main sequence data during upward movement in normal and paretic lids show the data points from the two populations are not well separated. These data indicate that upward eyelid movements in paretic lids are similar to that of normals.
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10.7 Functional effect of TENS stimulation

The stimulation amplitudes used during functional electrical stimulation were raised from levels described as comfortable, to levels described as tolerable. For the TENS regime, this corresponded to a stimulation amplitude of up to 25 V (section 10.4.1).

Application of this therapeutic regime on normal volunteers results in a series of eyelid twitches. Strong contraction of the OOC and full eyelid closure could be obtained in normals by increasing the stimulation frequency to approximately 40 Hz (shown in figure 7.6, chapter 7). Neither of these regimes produced detectable contraction of the OOC in any of the palsied patients throughout their treatment periods.

10.8 Further observations using the TENS units

In addition to the increased voluntary eyelid movement, some beneficial side effects of the TENS stimulation were reported by patients. Four patients reported using less ointment than before treatment. One patient reported occasional slightly increased watering of the eye during stimulation, increasing ocular comfort, which returned to normal after each stimulation session. This was not reported to be secondary to pain or discomfort during stimulation.

Qualitative analysis of facial movements such as smiling, eyebrow movement and puffing out the cheeks showed no change during the treatment period.
Chapter 10 Electrical stimulation regime results.

10.9 Long pulse stimulation

10.9.1 Voluntary eye closure after treatment with long pulse stimulation

Table 10.4

<table>
<thead>
<tr>
<th>Patient</th>
<th>Palsy Grade</th>
<th>Initial Displacement (mm)</th>
<th>Final Displacement (mm)</th>
<th>Improvement (mm)</th>
<th>Average daily stimulation (mins)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>III</td>
<td>1.2±0.7</td>
<td>7.1±0.3</td>
<td>5.9</td>
<td>36±15</td>
<td>0.0018</td>
</tr>
<tr>
<td>2</td>
<td>IV</td>
<td>4.26±0.2</td>
<td>4.8±0.2</td>
<td>0.54</td>
<td>56±10</td>
<td>0.09</td>
</tr>
<tr>
<td>3</td>
<td>IV</td>
<td>1.08±0.2</td>
<td>4.04±0.3</td>
<td>2.96</td>
<td>20±12</td>
<td>0.0004</td>
</tr>
<tr>
<td>4</td>
<td>III</td>
<td>4.56±0.8</td>
<td>4.2±0.3</td>
<td>-0.36</td>
<td>26±15</td>
<td>0.32</td>
</tr>
<tr>
<td>5</td>
<td>V</td>
<td>2.34±0.7</td>
<td>2.5±0.3</td>
<td>0.16</td>
<td>52±17</td>
<td>0.446</td>
</tr>
<tr>
<td>6</td>
<td>IV</td>
<td>2.7±0.4</td>
<td>6.7±0.7</td>
<td>4.0</td>
<td>62±12</td>
<td>0.001</td>
</tr>
<tr>
<td>7</td>
<td>III</td>
<td>1.6±0.2</td>
<td>4.8±0.4</td>
<td>3.2</td>
<td>48±19</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table 10.4 shows that 4 out of 7 patients achieved significant improvement in voluntary eyelid closure (p < 0.02) after 3 months treatment using the long pulse stimulation regime. The improvements ranged from 2.96 mm to 5.9 mm. One patient showed a reduction in displacement, but this result was not statistically significant. The figures for average daily stimulation indicate that patient compliance with the regime was reasonable given that these figures represent average daily stimulation over a three month period, and patients were instructed to use the stimulator for one hour.

10.9.2 Spontaneous blink response after treatment with long pulse stimulation

Table 10.5 shows the results for spontaneous eyelid closure before and after treatment with long duration pulses. The results are similar to the TENS regime in that any improvements are very small (0.1 mm) and are not statistically significant.
Chapter 10 Electrical stimulation regime results.

<table>
<thead>
<tr>
<th>patient</th>
<th>Pre-treatment displacement (mm)</th>
<th>Post treatment displacement (mm)</th>
<th>improvement (mm)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.3</td>
<td>2.4</td>
<td>0.1</td>
<td>0.26</td>
</tr>
<tr>
<td>2</td>
<td>1.8</td>
<td>1.5</td>
<td>-0.3</td>
<td>0.22</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>1.6</td>
<td>0.1</td>
<td>0.27</td>
</tr>
<tr>
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<td>2.1</td>
<td>2.03</td>
<td>-0.07</td>
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</tr>
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<td>2.06</td>
<td>2.13</td>
<td>0.07</td>
<td>0.37</td>
</tr>
<tr>
<td>6</td>
<td>1.9</td>
<td>2.0</td>
<td>0.1</td>
<td>0.46</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>1.6</td>
<td>0.1</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Table 10.5

Upper eyelid displacement initially and after treatment using long pulse stimulation during spontaneous closure.

10.10 Dynamic eyelid measurements after treatment with long pulse stimulation

The 95% confidence ellipse for normal data is shown in figure 10.6a (overleaf). The data for all seven patients at the beginning and end of treatments are shown also. The results are similar to those achieved using the TENS units in that the data points lie very close to the edge of the ellipse. As improvements in displacements are made, there is no significant improvement in the maximum velocity achieved, causing the data points to move further out of the 95% confidence ellipse. The main sequence slope for all the blink down phase data for normal and paretic eyelids after a course of long pulse therapeutic electrical stimulation is shown in figure 10.6b. Again, the data points shown are from all patients with each point representing at least five blinks. The voluntary movements of paretic eyelids are similar to those following treatment with commercial units i.e. the movements are significantly slower than eyelid movements in normal volunteers. Linear regression analysis of this data gives:

\[ Y = 4.1X + 19, \] which is very similar to that shown for the TENS stimulation results:

\[ Y = 5.7X + 6.2 \]

Figure 10.7a shows the results from measurement of the blink up-phase. This figure shows that the blink up-phase results lie within the 95% confidence ellipse for normal data for both pre and post treatment results. Once again, comparison of the blink main sequence regression lines (figure 10.7b) for all the patient data acquired for this part of the study to the normal blink main sequence line shows that data from both populations are not well separated and the blink up phase movements are similar to normal values.
Chapter 10: Electrical stimulation regime results

Normal 95% confidence ellipse for the blink down phase
Patient data is shown before and after treatment
long pulse stimulation

![Normal 95% confidence ellipse for the blink down phase]

Comparison of main sequence lines for normals and palsie patients
Blink down phase
Long pulse stimulation

![Comparison of main sequence lines for normals and palsie patients]

Figure 10.6a Showing 95% confidence ellipse for normal data with patient data from initial assessments and after a treatment period of three months (blink down-phase)

Figure 10.6b Main sequence data for normals and for patients during their treatment periods (blink downphase)
Chapter 10: Electrical stimulation regime results

Normal 95% confidence ellipse for blink up phase
Patient data is shown before and after treatment
long pulse stimulation

Figure 10.7a Showing 95% confidence ellipse for normal data with patient data from initial assessments and after a treatment period of three months (blink upphase)

Figure 10.7b Main sequence data for normals and for patients during their treatment periods (blink upphase)
10.11 Effect of functional electrical stimulation using long pulses.

Although voluntary and spontaneous movements following treatment using long pulse stimulation were essentially similar to those following treatment using commercial stimulators, the functional response to long pulse stimulation was different. Again, stimulation levels were increased to ‘tolerable’ (section 10.4.2), which for this regime corresponded to a peak output voltage of approximately 20 V. Functional movement was obtained in four out of seven patients after treatment with long pulse stimulation, which was not observed in patients treated with the commercial stimulators. The response was consistently observed in the lower part of the orbicularis oculi (i.e. the lower eyelid) with the strongest contraction occurring between the two electrodes. The site of the response was unfortunate as contraction of the lower orbicularis does not contribute greatly to eyelid closure. The maximum amplitudes of the upper eyelid movements in the four patients to respond to functional stimulation were very similar (mean 1.7 mm, standard deviation 0.15 mm). Figure 10.8 illustrates a typical response. This graph shows upper eyelid displacement versus time. The temporal positions of the peaks, separated by approximately 100 ms show that the eyelid is moving in direct response to each stimulating pulse, which are applied at a pulse repetition frequency of 10 Hz.

![Figure 10.8 Typical twitch response of upper eyelid to functional electrical stimulation after three months of therapeutic stimulation](image)

Inspection of Table 10.4 indicates that the patients most likely to respond to functional electrical stimulation are also the ones exhibiting the greatest improvements to voluntary closure (patients 1,3,6,7). Good initial displacement does not appear to be a good indicator of a likelihood to respond to stimulation, as the two patients with the greatest initial
displacement (patients 2, 4) did not show a response. Again, showing a similar trend to that observed for the TENS results, the facial palsy grading scale appears to be a poor indicator e.g. patient 4 (grade III) did not respond, while patients 3 and 6 (grade IV) did respond.

Increasing the levels of stimulation from ‘comfortable’ to ‘tolerable’ did not reduce patient compliance due to an increased visual aura.

10.12 Discussion

10.12.1 Stimulation regime acceptability

Stimulation of normal volunteers showed that levels of stimulation associated with sensation did not vary much between individuals. However, levels associated with painful stimulation did vary more between individuals, which simply reflects how the perception of pain varies between individuals. However, complete eyelid closure was obtained in all normal individuals with levels of stimulation described as tolerable for both stimulation regimes. It is interesting to note that levels of stimulation using the long pulse stimulator with skin electrodes which have been described as intolerable lie below the values reported in previous studies using implanted electrodes in dogs and rabbits (chapter 3), suggesting that what may be regarded as tolerable in an animal study may not be clinically acceptable, although implanted electrodes may eliminate the discomfort due to stimulation of pain receptors in the skin. Generation of a visual aura has not been reported in any of the previous animal studies. It could be that this possibility has been overlooked, or again, the use of implanted electrodes may reduce the effect of the visual aura by localising the electric field resulting from the stimulation regime more effectively.

10.12.2 Improvements to voluntary closure.

The motor response of the eyelid system has been described in chapter 5. To recap, the upper eyelid position is controlled by the levator palpebrae superioris (LPS) which keeps the upper lid open and is innervated by the third cranial nerve. Its action is augmented by the Mullers muscle and the frontalis muscle which are innervated by the sympathetic nervous system and the seventh cranial nerve respectively. The orbicularis oculi (OOc) is responsible for eyelid closure and is innervated by the seventh cranial nerve. The palpebral portion is associated with spontaneous eyelid movement and the orbital portion is used during movements such as
screwing the eyes up for protection. Electromyographic (EMG) studies have shown that eyelid position is maintained by tonic activity within the LPS muscle. Downward motion of the eyelid during a spontaneous blink is caused by cessation of LPS activity before contraction of the OOc. The eyelid is then raised by cessation of OOc activity and the onset of LPS activity. For voluntary eye closure, OOc activity precedes LPS inhibition.

Downward voluntary movement of paretic eyelids might be expected to give complete closure, as there is no LPS activity holding the eyelid up. However, chronic severe seventh nerve paralysis results in very limited voluntary and spontaneous eyelid movement. This has been attributed to stiffening and contracture of the LPS arising from the lack of tonic OOc activity. Changes to OOc fibres might also contribute to a reduction in elasticity of the eyelid structure.

The improvements seen in voluntary closure in this study due to electrical stimulation might be explained either by restoration of the OOc muscles' ability to contract or to a reduction in the stiffness of the eyelid structure which opposes eyelid movement. Recovery of function due to reinnervation of the OOc muscle is unlikely. This is consistent with our observation that displacements and velocities in spontaneous blinks were not improved. During voluntary closure, the LPS is switched off and the eyelid allowed to relax downwards. This movement is likely to be assisted by residual motor forces present in both the palpebral and orbital regions of the OOc. The movement is slow and maximum closure is achieved in a time of the order of 0.9 s. During spontaneous blinks, residual motor forces present only in the palpebral part of the OOc are expected to be involved and the duration of reciprocal LPS and OOc activity is of the order of 50 - 100 ms. Hence spontaneous blink amplitudes are relatively small in paretic eyelids. It is most likely that improvements seen in voluntary closure following treatment with electrical stimulation were due to reductions in stiffness of the LPS and OOc muscles which allowed the eyelid to respond more freely to residual motor and elastic forces present during downward eyelid movement. The lack of response to treatment in the two subjects with an existing tarsorrhaphy may be attributable to the effect of surgical intervention on the mechanics of eyelid movement, which may cause increased stiffness and a reduction in elasticity of the eyelid closure mechanism (Gittins et al., 1999).

The proposed explanation for the observed improvements in most patients may appear inconsistent with the observation that denervated lid saccades, which depend on elasticity
within the eyelid and a reduction in LPS activity shows only a small reduction in
displacement and peak velocity due to seventh nerve palsy (Sibony et al., 1991). However,
the difference in the range of the two types of movement can be attributed to mechanical
linkage between the superior rectus muscle (SR) and the LPS described in chapter 3.
Whereas this link assists downward saccadic movement as the SR relaxes, it may hinder
voluntary eye closure since the latter is accompanied by upward rotation of the eyeball (Bells'
phenomenon) and contraction of the SR.

10.12.3 Dynamic measurements

The dynamic blink measurements showed that improvements to eyelid displacement during
voluntary closure were not accompanied by a significant increase in blink velocity. The 95%
confidence intervals for normal blink data were not particularly good indicators of
abnormality, since small eyelid movements in normals are associated with lower peak
velocities. However, as displacements improved as a result of the treatment regime, the
resulting data points were observed to move further away from the 95% confidence interval,
highlighting the lack of improvement in peak velocity.

The slowness of voluntary eyelid closure following treatment coupled with the lack of
improvement in spontaneous blink response means that a blink reflex suitable for maintaining
physical protection to the cornea will not be recovered by either stimulation regime, despite
the observed improvements in voluntary eyelid closure, implying that current clinical practice
for protecting the cornea should still be followed.

10.12.4 Functional response.

The observation of functional response in some patients following treatment using the long
pulse regime was very encouraging although the position of the response in region of the
lower orbicularis oculi may indicate that electrodes placed on the medial and lateral canthi of
the eye is not optimum for stimulating the part of the orbicularis responsible for movement of
the upper eyelid. The twitch response observed using this regime suggests still that
denervated muscle is not being stimulated, rather the twitches are resulting from stimulation
of surviving motor neurones. This would be consistent with the observation that not all
patients have benefited. The fact that functional response could be achieved using long
pulses and not the TENS regime may be attributable to the greatly increased charge delivered
by the long pulse regime compared to that of the TENS regime, thus recruiting more surviving motor neurones.

Future work may include increasing the stimulation frequency to cause tetanic muscle contraction in the surviving motoneurons as described in chapter 2.

Factors limiting this stimulation regime include discomfort and generation of a visual aura. The visual aura was described by two patients as annoying, and caused one patient to withdraw from the study. Chapter 3 showed an analysis of a circular electrode and indicated that the maximum effect would occur around the perimeter of the electrode. The geometry and sensitive nature of the orbital region makes it difficult to optimise the electrode site, which is further limited by the constraint of electrode size. Electrodes must remain large enough to maintain levels of current density consistent with comfort, whilst being small enough to be placed in suitable positions.

10.13 Conclusion

A total of twenty patients have been assessed as part of this study. Of these, ten patients used a commercial stimulator for approximately three months and improvements in voluntary closure were observed in seven. The TENS stimulation protocol did not give detectable contractions in the orbicularis oculi.

Seven patients have completed a regime based on long pulse stimulation of which four showed improvements in voluntary closure. The main advantage of using such a regime was that some functional movement was observed. Four patients are currently using the long pulse regime. Two patients dropped out of the study when using the long pulse stimulation which probably reflects an increased degree of discomfort compared to using the commercial regime.

However, other benefits were achieved apart from the improvement in voluntary closure. All patients participating in the study were very keen to use the stimulators. They appeared happy to receive active treatment for a condition that they felt had been neglected, which may have psychological benefit (Murray, 1992). Patients reported the face to feel less 'woody' after stimulation. Such effects may be attributable to a physiotherapeutic action of using a stimulator and attempting to use the affected side of the face to a greater degree. Other
subjective benefits were reported including a reduction in the amount of artificial tear preparations used and increased ocular comfort.

The project plan in the original Trent Research Scheme Grant Application included proposals for the development of an implantable stimulator to give permanent restoration of eyelid movements. However, in view of the unexpected difficulties experienced in eliciting functional responses to electrical stimulation in our patients, it has been necessary to concentrate on developing improved therapeutic regimes. Only when substantial functional movement of the paretic upper eyelid has been demonstrated by transcutaneous electrical stimulation will progression to an implanted system be justified.

There is already some evidence to show that this objective may be achievable as some functional movement has been observed in some cases. Some of the problems inherent with a transcutaneous regime such as poor electrode geometry and stimulation of pain receptors in the skin may be eliminated using an implanted system. The results of this study indicate that not all patients may benefit, but using a therapeutic regime as detailed in this study may be able to identify patients likely to benefit. It may also be useful to offer stimulation in acute cases of peripheral denervation, before significant muscle atrophy has occurred, a question which this study has not attempted to answer.
Chapter 11

Conclusions and Future Work

11.1 Overview

This study was designed to investigate whether or not function could be obtained in peripherally denervated muscle in response to direct electrical stimulation. The area chosen for application of this technique was stimulation of the orbicularis oculi muscle responsible for eyelid closure. This particular application was chosen because peripheral damage to the seventh nerve controlling the orbicularis oculi is relatively common, and the inability to close the eyelid represents a significant clinical problem. If movement of the upper eyelid could be achieved in direct response to electrical stimulation it could then become feasible to design an implantable stimulator to permanently restore eyelid function.

A literature review indicated that stimulation of denervated muscle is controversial, with clinical benefits to patients not being demonstrated in all studies. Animal studies have also provided conflicting evidence and the process of extrapolating data derived from animal studies to clinical situations also attracts controversy.

A review of nerve and muscle physiology has shown that nerve and muscle have a mutual dependence on each other. Activity of muscle fibres also plays a role in maintaining and regulating muscle fibre properties but activity imposed using electrical stimulation cannot maintain all fibre properties in the presence of denervation. Consequently, denervated muscle will always show physiological differences from normally innervated muscle. The question is whether the ability to contract in response to electrical stimulation remains or can be recovered. Early experiments in this study indicated that functional response could not be achieved in response to electrical stimulation using protocols that could achieve strong eyelid closure in normal volunteers, leading to the conclusion that it would be necessary to employ electrical stimulation as a therapy to restore some of the normal properties of the atrophied muscle to allow contraction to occur.

Changes to muscle fibre properties caused by denervation have been characterised in terms of passive electrical properties associated with the muscle fibre membrane (capacitance, resistance and potential difference), the structure of the contractile apparatus, muscle fibre diameter and histochemical changes. In a routine clinical environment, it would not be
possible to record all such changes. Consequently, the clinical effect of the electrical stimulation regimes used in this study was measured by recording functional recovery. To perform this analysis, a novel imaging system based on a high speed line scan camera was designed to measure the speed and magnitude of upper eyelid movements.

11.2 Improvements to the imaging system

The imaging system provided the advantages of a non-invasive measurement technique compared to previous methods which could potentially interfere with eyelid movement. The system provided adequate spatial and temporal resolution, and was easy to use in a clinical environment. Eyelid dynamics measured on normal volunteers indicated that results using this system were comparable to those derived from alternative techniques in previous studies. The normal data from this study was used as a comparison with data derived from palsied patients to assess treatment progress.

Further development of this system would involve an alternative lighting source to the halogen bulbs presently used. An infra red based system may be more comfortable to the patients and provide improved contrast between skin and the corneal surface. Automatic sensing and recording of eyelid movements might also be an advantage, rather than an operator controlling data acquisition by observation of eyelid movements. Disadvantages with this system include measurements made on patients presenting with eyebrow ptosis, causing the eyebrow to effectively obscure the eyelid.

As CCD array technology improves, and the cost of higher specification PCs and data acquisition cards reduces, it may become possible to directly interface the imaging system to the PC. This would allow the operator to take advantage of the available storage media in the PC, increasing system flexibility. For example, it may then become possible to analyse a series of consecutive blinks. The use of CCD arrays capable of colour imaging may improve contrast in some cases.

Further research of eyelid movements in patients with facial palsy may be made by studying the response of the unaffected eyelid simultaneously with the affected side. Obviously, two imaging arrays would be required, increasing the complexity of the system.
11.3 Improvements to the stimulation regime

Electrical stimulation was applied using two modalities. The first was based on a commercially available TENS unit, the stimulating protocols used were based on previous studies using electrical stimulation to aid recovery in cases of Bells palsy. The second regime was implemented using a stimulator designed as part of this study. This stimulator offered several advantages over the commercially available unit including a very simple user interface, pre-programmable stimulation regimes, data logging, current monitoring and a wide range of stimulating pulse options including the ability to control amplitude, pulse repetition frequency, pulse shape and pulse width. Further development of the stimulator may include increasing the output voltage range when using a narrow pulse (< 1ms) regime.

The low frequency response of the transformer was adequate when using pulses <15 ms in duration but for applications requiring longer pulses an alternative design would be required. The current monitor was calibrated for rectangular pulses. If alternative pulse shapes were used it may be necessary to modify the current monitor calibration accordingly.

The stimulation regime using the TENS units was well tolerated by all patients who took part in this trial, with all patients recruited completing the study. However, the regime using 15 ms pulses was not so well tolerated, with two people dropping out of the study because they described the stimulation as being too uncomfortable. The range of amplitudes tolerated by patients during long pulse stimulation therapy was greater than the range using the TENS units.

There were no reported side effects from using the TENS units, whereas long pulse stimulation resulted in the generation of a visual aura as well as the increased amount of skin sensation, which some patients found disturbing. It was not possible to eliminate this visual aura by varying the temporal properties of the stimulation regime, whilst maintaining a regime suitable for stimulating denervated muscle. Future work to further characterise this response and the mechanism from which it arises may be justifiable. This may lead to elimination of the response or to the identification of alternative applications utilising the resulting visual aura and evoked response.

An analysis of the electric field geometry arising in tissue using transcutaneous electrodes indicated that electrode placement may not yet be optimal, but the physical constraints imposed by the surface geometry around the eye and the electrode type used limited the
available options. Future work may show that improved electrode type and positioning could improve on the encouraging results already observed. Some of the problems inherent with a transcutaneous stimulation regime such as poor electrode geometry and stimulation of surface skin and pain receptors may be eliminated using an implanted system, the design of which could be included in future work. However, this study has shown that many of the successful regimes using implanted electrodes on animal models may not be well tolerated in humans because of the visual aura. It also remains to be seen whether implanted electrodes would totally eliminate the discomfort associated with long electrical stimulation pulses in this application.

11.4 Results

The key results from the analysis of patient data using the imaging system were that both the amplitude and velocity of eyelid movements were reduced in patients presenting with seventh nerve paralysis. Both stimulation regimes improved the magnitude of eyelid displacement during voluntary eyelid closure, while the peak velocities achieved during such movements remained below normal values. Such results were normally achieved during a treatment period of three months with electrical stimulation applied for one hour daily. The dynamics of spontaneous blinks remained unchanged during the same period. An explanation of an improved passive eyelid closing mechanism was postulated to explain these results.

There was no functional response in direct response to stimulation with the TENS units, whereas a contraction was observed in the region of the lower orbicularis oculi and approximately 1.5 mm movement in the upper eyelid was observed in response to long pulse duration stimulation. The observed contraction was attributed to surviving motoneurons rather than to direct stimulation of denervated muscle fibres.

This study has shown that not all patients benefit from electrical stimulation in chronic facial palsy. This may be related to clinical factors such as the presence of surviving motoneurons within the orbicularis oculi, age and duration since nerve injury. In the future, it may be useful to offer stimulation in acute cases of facial palsy with a poor prognosis for adequate recovery, before significant muscle atrophy can occur, to see whether function can be maintained in such cases.
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