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**"Quantitative Studies of Eye Movement Generation:
Biomechanics and Neural Control"**

by

Kerstin Pfann

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Bioengineering

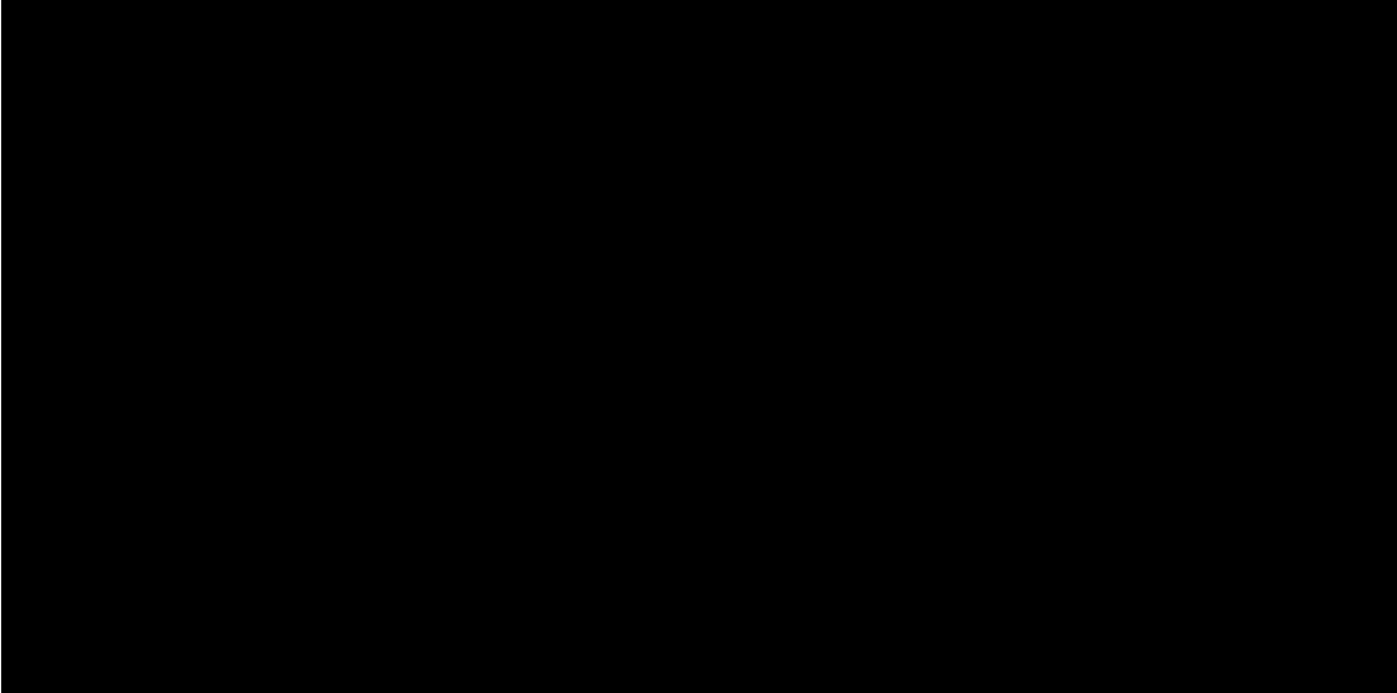
in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA

San Francisco /Berkeley



**Quantitative Studies of Eye Movement Generation:
Biomechanics and Neural Control**

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Kerstin Pfann

Abstract

Quantitative Studies of Eye Movement Generation: Biomechanics and Neural Control

by

Kerstin Pfann

Doctor of Philosophy in Bioengineering

**University of California, Berkeley
University of California, San Francisco**

Professor E. L. Keller, Chair

The oculomotor control system is interesting to many investigators because it is robust and adaptable. Two common approaches to studying neuromuscular control exist: examining the mechanical properties and inferring the control signals or directly recording neural control signals. In this study, the mechanics of a monkey's oculomotor system were studied by measuring eye position and muscle forces (with chronically implanted force transducers on the medial and lateral recti) during horizontal saccadic eye movements. The agonist and antagonist force profiles were stereotyped and qualitatively symmetric, which was surprising given the asymmetry in the force-velocity relationship. Simulations with currently accepted models of the saccadic system did not predict the measured force profiles; this motivated a closer

study of these models. Two types of models were developed for extraocular muscle. A modified Hill-type model, which is based on functional components of steady-state, macroscopic muscle properties, was studied because it was simple and commonly used in modelling muscle systems. A distribution moment model, which is based on the cross-bridge mechanism of contraction, was studied because it was closely tied to the physiology and better represented transient muscle properties. The modelling yielded insights that suggest different fiber types within extraocular muscle may dominant muscle properties depending on the innervation (and recruitment order). In addition, an orbital model was derived from the data. An additional experiment measured the step response of the orbital mechanics in an anesthetized monkey. These mechanics in the alert, behaving monkey were not the same as those in the anesthetized monkey, which suggests the role of the vertical and oblique extraocular muscle is important even in the horizontal saccadic system.

In addition to studying the peripheral aspect of the oculomotor control system, an experiment that studies the central control was presented. The effect of electrical microstimulation in dorsal lateral pontine nucleus on smooth pursuit eye movements is studied. Stimulation during open and closed-loop pursuit produced different effects demonstrating that visual feedback is functional during stimulation in DLPN. Moreover, to understand the range of effects observed, the distributed nature of the system must be considered.

Approved: Edward L. Keller

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Introduction and Overview

1. General Introduction and Motivation

The primate nervous system has a tremendous capacity to monitor, process, and integrate sensory information and to elicit behaviors that result in effective interactions with the environment. As a controller, the nervous system is simultaneously flexible and robust. It's ability to adapt allows the body to function effectively in changing or unusual environments. Parallel processing reduces processing time and enhances robustness to component failure (e.g., loss of neurons). Consequently, studying this biological control system can lead to new control methodologies that enhance performance of engineered systems.

The oculomotor system exhibits many characteristics that would be useful in engineered systems. Most notably, the system adapts readily to developmental changes as well as changes required by many experimental paradigms.

In addition, this system is relatively simple to study. It has a simple structure and is accessible to measurement. Because the system has evolved in stages, in conjunction with the evolution of the visual system as a whole, separate neural pathways have developed to control different types of eye movements; yet they all produce eye movements using the same mechanical structure (eyeball, extraocular muscles, and other orbital contents). As a result, the control of different types of eye movements can be studied somewhat independently.

The optics of the eye focus light on the photoreceptor layer of the retina, resulting in electrochemical signals in the outer segments of the photoreceptors. These signals are processed through the cellular layers of the retina, resulting in action potentials in the ganglion cell layer. These action potentials carry information into the central nervous system (CNS). The effective use of vision depends, in part, on the ability to control gaze (where the eyes are pointed in space). Primates have several oculomotor subsystems that control particular tasks: a) the vestibulo-ocular reflex (VOR) stabilizes retinal images during head movements, b) the smooth pursuit system tracks slowly moving objects, c) the optokinetic system stabilizes the eye with respect to full-field motion, d) the saccadic system rapidly changes the point of fixation, and e) the vergence system aligns the visual axes of the eyes to targets at different distances. The VOR is phylogenetically the oldest oculomotor subsystem; even the most primitive visual system is improved when an image is stabilized during head movements. (For example, the rabbit has a VOR but no voluntary saccadic system.) In contrast, saccadic and pursuit eye movements were not advantageous until the retina developed into a central region of high acuity (the fovea) and a peripheral region of low acuity. With this organization, the image of an object could be closely examined when moved to or maintained on the fovea; saccades and pursuit movements provide a method for accomplishing these tasks.

As a result of these evolutionary improvements, humans have come to rely heavily on visual perception, so eye movement disorders can be quite debilitating. Consequently, there are also medical reasons for studying the oculomotor system. The

more we understand about the oculomotor system, the more we may be able to improve diagnosis and treatment of eye movement disorders.

The task of understanding control of movements can be divided into two basic parts: (1) understanding the mechanical properties of the plant (in this case the eye, surrounding tissue, and musculature) and (2) the neural control. By studying the biomechanical properties of the system, we hope to understand the control requirements for it. If we know the goal of the movement and the dynamical properties of the system, we can infer the neural control signals that can accomplish that movement. It also suggests limitations of movements. In addition, understanding the neural and mechanical properties of the system can help distinguish whether a movement disorder is neurally or mechanically based.

Another method used to study neural control is to directly record neural firing patterns from regions of the brain thought to be involved in the movement of interest. With this approach, one hopes to correlate firing patterns with aspects of the movement. Perturbations can then be applied by stimulating or lesioning small or large areas within the region of interest, and the effects of the perturbation on the resulting movement can be studied. By combining the results of similar physiological studies from different regions of the brain with anatomical studies that link the regions, one can begin to develop a picture of how the signals are interacting. At first, this direct method may appear to be the best approach; however, the structure of the brain is so complicated, with signals from many regions interacting at many levels, that it is difficult to understand the processing with this method alone.

2. Overview

This thesis will focus on the mechanics of eye movements (Chapters 2-6) but will touch on central control in Chapter 7. In studying the mechanics of eye movements, I take advantage of the high velocity eye movements that are commonly made, saccades, which bring to light many of the mechanical properties of the system. In addition, several studies of the steady-state macroscopic properties of extraocular muscle, as well as studies of the firing patterns of ocular motoneurons during saccades, are used. This work is extended by recording individual muscle forces in a monkey with chronically implanted force transducers during saccadic eye movements. The results are used to model extraocular muscle and the horizontal saccadic system. In addition, a specific example of directly studying the neural control of eye movements will be presented. In this latter study, the role of dorsolateral pontine nucleus (DLPN) in controlling smooth pursuit will be explored by electrically stimulating in DLPN with a microelectrode during pursuit movements.

This chapter will cover the fundamental background material underlying the work in the other chapters, mostly Chapters 2-6. The structure of the eye movement system will be presented, followed by a brief description of some of the technology used to study the oculomotor system. Since the main focus of this thesis is the mechanics of eye movements, the structure and function of skeletal muscle in general and extraocular muscle in particular will be discussed at macroscopic and microscopic levels. In addition, general models of muscle at both these levels will be discussed.

Chapters 2-6 will focus on the dynamics of saccadic eye movements. In Chapter 2, eye position, velocity, and muscle force profiles recorded in a monkey during saccadic eye movements will be presented and discussed. In Chapter 3, the traditional models of the horizontal saccadic system are discussed with respect to the new data. For the most part, these models were derived from steady-state, macroscopic muscle properties, and the model discussed in detail can generate realistic position, velocity, and acceleration profiles. In Chapter 4, the abilities of a phenomenological muscle model and a muscle model based on the molecular mechanism of contraction to represent the properties of extraocular muscle during saccadic eye movements will be compared. The approach I will take is to calculate and compare the muscle activations necessary for each model to generate the position and force profiles recorded in the monkey. In Chapter 5, a more representative model of the orbital mechanics is developed, and the two types of muscle models are combined with the model of the orbital mechanics. Finally, the improved model's sensitivity to parameter modifications will be presented. Chapter 6 will be a general discussion about the research presented.

Finally, in Chapter 7, an example of an experiment that attempts to explore the control hierarchy generating eye movements (in this case, smooth pursuit eye movements) will be presented. The goal is to bring to light some of the difficulties in studying central neural control that are not as apparent when trying to infer peripheral (motoneuron) neural control based on the mechanical properties of the controlled system.

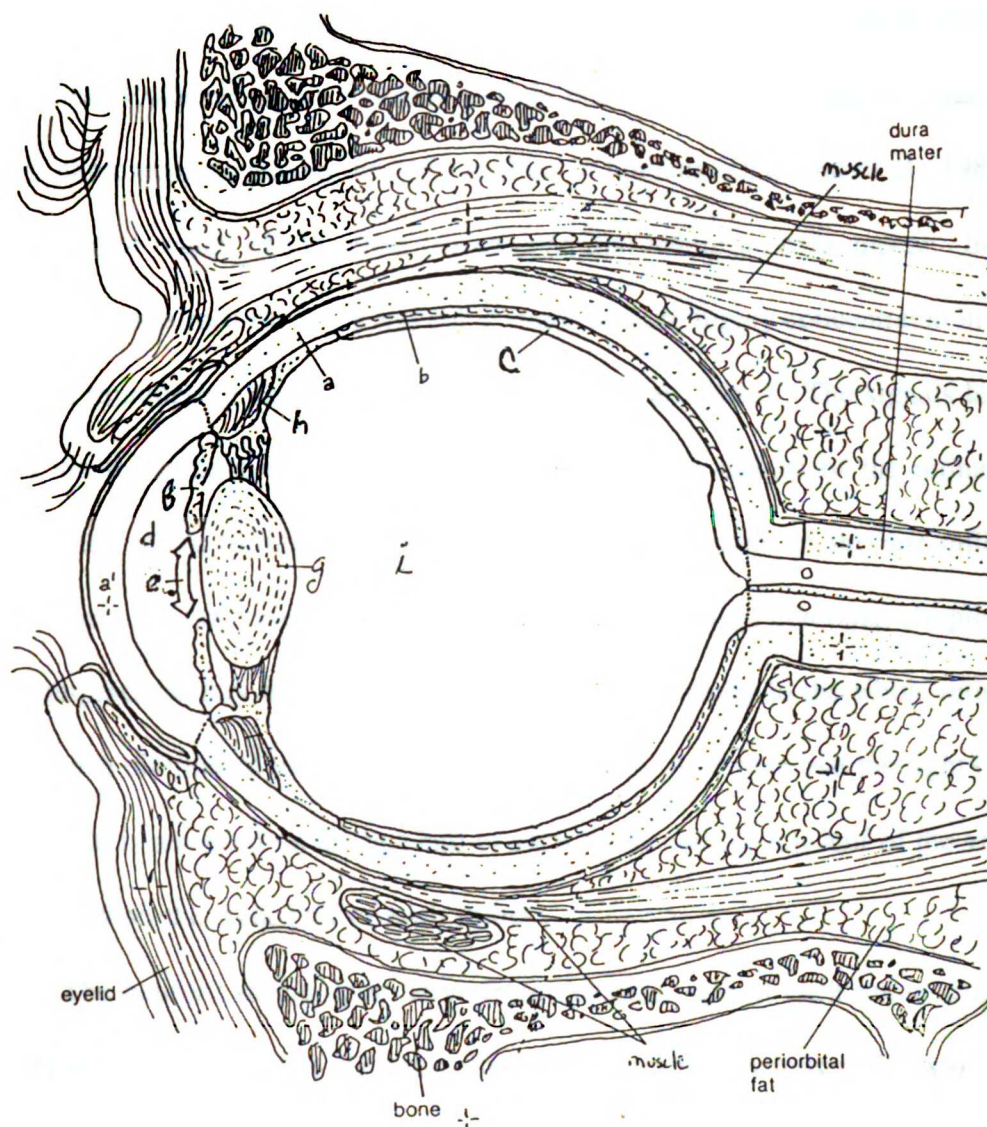
3. Background

3.1 Description of the Oculomotor System

Extraction of information from ambient light begins in the eye. The amount of light entering the eye is adjusted by modulating the size of the pupil; the light rays are refracted to focus on the retina by modulating the radius of curvature of the lens. The array of photoreceptors, making up one layer of the retina, transduces light into electrochemical signals and, with subsequent retinal processing, performs the early stages of extracting visual information from ambient light.

The eye (see Fig. 1.1) consists of a protective shell of collagenous connective-tissue fibers that is mostly white (sclera) but is transparent in front (cornea). The inside of the sclera is lined with a highly pigmented layer upon which the retina lies; the pigmentation absorbs light, and, thereby, prevents scattering. Light entering the eye is refracted by the convex cornea and then passes through the anterior chamber which is filled with a watery liquid. The light then passes through an aperture (pupil) whose size is modulated by a disk-like structure with smooth muscle (iris). Next, the light passes through the lens, which is an elastic structure whose convexity increases when the ciliary muscle contracts. Finally, the light travels through a gel of water and mucoprotein (vitreous humor) to the retina.

The retina consists of three basic layers: photoreceptors, bipolar cells, ganglion cells. Horizontal connections within these layers are provided by horizontal and

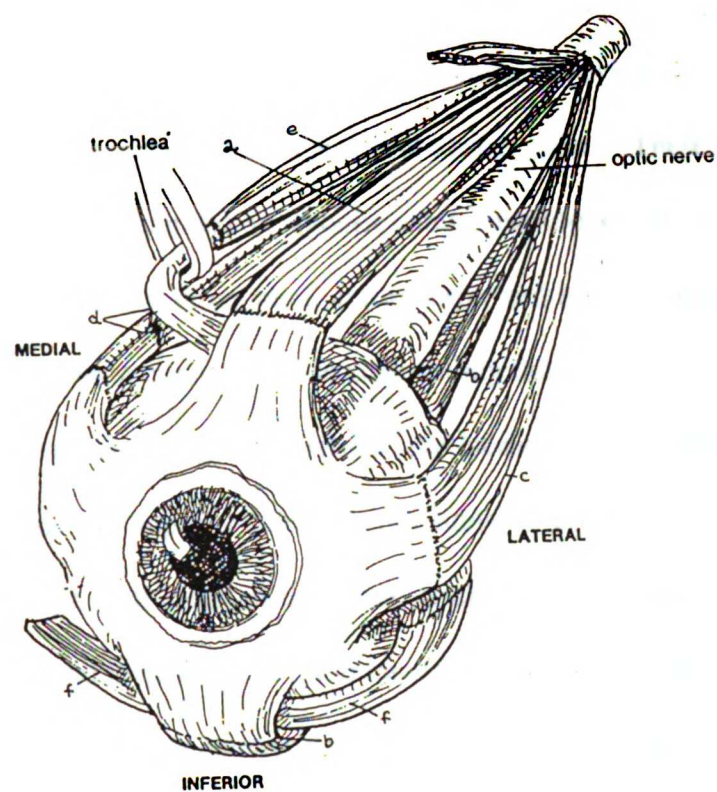


The Eye. The schematic shows: sclera, a; cornea, a'; pigment layer, b; retina, c; anterior chamber, d; pupil, e; iris, f; lens, g; ciliary muscle, h; and the vitreous humor, i. (The figure was slightly modified from Kapit & Elson, 1977, plate 137.)

Figure 1.1

amacrine cells. The first layer of the retina consists of two types of photoreceptor: rods and cones. Rods are highly sensitive to light but insensitive to color and make up most of the photoreceptor population (100 million in humans; Diamond et al., 1985) except in the central region of the retina (fovea centralis) where no rods appear. In contrast, cones are specialized for acute and color vision and are highly concentrated in the fovea centralis (numbering about 7 million; Diamond et al., 1985). The signals leaving the retina via the ganglion cell axons run along the inner surface of the retina and exit through the sclera forming the optic nerve. Ninety percent of the one million optic nerve fibers are concerned with information from the fovea centralis. Implicit in this is the impracticability of extending the region of high acuity to the whole retina, which would have eliminated the need for eye movements. Also note that the right half of the visual field is recorded on the left half of each retina and the left half of the visual field is recorded on the right half of each retina.

The neurons in the optic nerve from the nasal side of each retina cross over to the opposite hemisphere at the optic chiasm and join the uncrossed fibers on the other side forming the optic tract. This crossover combines all the signals from the left visual field in the right optic tract and vice versa. The optic tract projects primarily to the lateral geniculate which, in turn projects primarily to the visual cortex, where a spatial map of the retinal image is reconstructed. From here, the visual information is processed in many ways, in many different areas of the brain resulting in our visual perception of the world as well as generating commands to drive eye movements.



Extraocular Muscles. The schematic shows: superior rectus, a; inferior rectus, b; lateral rectus, c; medial rectus, d; superior oblique, e; and inferior oblique, f. (The figure was slightly modified from Kapit & Elson, 1977, plate 139.)

Figure 1.2

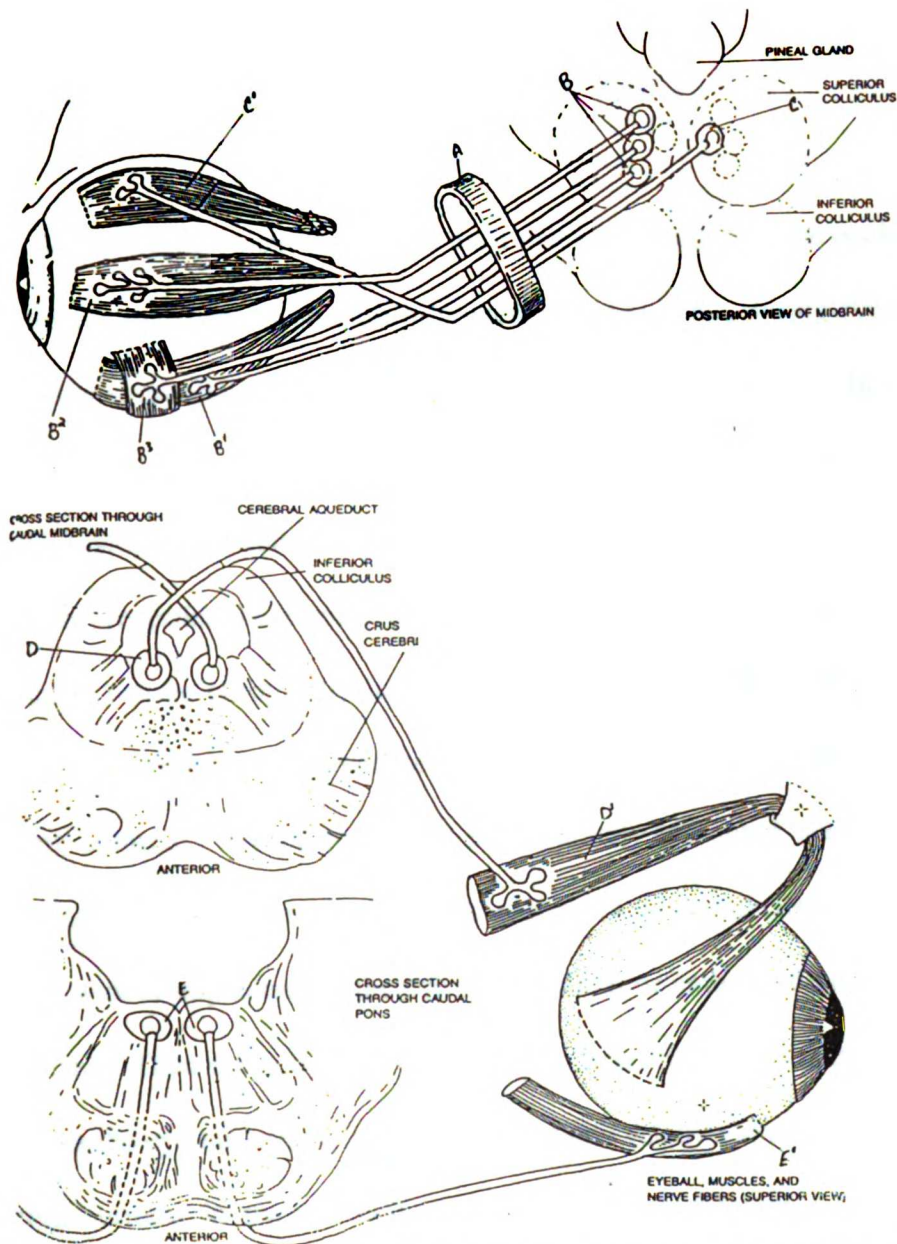
3.2 Biomechanical Structure of Oculomotor System

Six extraocular muscles (see Fig. 1.2) produce the eye movements of each eye (Moses, 1970), which moves like a ball-and-socket joint. These extrinsic skeletal muscles are arranged (roughly) in agonist-antagonist (opposing) pairs: medial and lateral recti, superior and inferior recti, and superior and inferior obliques. The rectus muscles originate from a circular tendon surrounding the optic nerve (annulus of Zinn), while the inferior oblique originates behind the lacrimal fossa (part of the bony orbit of the nose) and the superior oblique functionally originates at the trochlea (a cartilaginous pulley). All insert in the sclera at different locations.

The action and interaction of the extraocular muscles are complicated. However, if the study is restricted to movements in the horizontal plane containing primary position (eye pointing straight forward), then the system is greatly simplified. These movements are predominantly controlled by the medial and lateral recti acting in a push-pull relationship.

The eye and muscles sit in a fatty tissue surrounded by a bony orbit that limits the range of motion to 45-50 deg each way from primary (central) position. In the context of the horizontal saccadic system, the orbit refers to the eyeball, vertical and oblique extraocular muscles, nerves, fascial connective tissue, and orbital fat, all of which affect the dynamics of eye movements.

By processing visual and motor information, the central nervous system generates input commands to the eye muscles in terms of neural firing patterns. Although, many neurons activate a given muscle, a single neuron innervates fibers in only one of the six, so different commands can be sent to each muscle. Through complicated chemical reactions, active neurons cause muscles to contract; inactive neurons allow muscles to relax. The firing pattern across the neurons determines the extent, direction, and speed of the eye movement, just as the angle of the accelerator pedal and the rotation of the steering wheel determine the movement of a car. Different portions of the oculomotor (III) nerve innervate the ipsilateral medial rectus, inferior rectus, and inferior oblique, and contralateral superior rectus while the trochlear (IV) nerve innervates the contralateral superior oblique and the abducens (VI) nerve innervates the ipsilateral lateral rectus (see Fig. 1.3). In addition, the abducens nucleus contains interneurons whose axons cross the midline and project via the medial longitudinal fasciculus to the medial rectus region of the oculomotor nucleus. This connection is presumably essential to conjugate eye movements because it ensures that the ipsilateral lateral rectus and contralateral medial rectus are innervated roughly simultaneously, thereby driving both eyes in the same horizontal direction. This feature is called Hering's law, and it is taken advantage of in certain experiments (e.g., see section 3.6.1.)



Innervation of the Extraocular Muscles. The top schematic shows the III nerve (A) innervation. The lateral portion of the oculomotor nuclei (B) innervates the ipsilateral inferior rectus (B¹), medial rectus (B²), and inferior oblique (B³). The medial portion of the oculomotor nuclei (C) innervates the contralateral superior rectus (C¹). The bottom schematic shows the IV (D) and VI, abducens (E) nerve innervation. The IV nerve innervates the contralateral superior oblique (D¹), and the VI nerve innervates the ipsilateral lateral rectus (E¹). (The figures were slightly modified from Diamond et al., 1985, plates 6-9 and 6-10.)

Figure 1.3

3.3 Measurement Techniques for Eye Movement Studies

Many measurement techniques exist that aid in studies of the oculomotor system. In contrast to experiments on most biological motor systems, during eye movements the neural inputs, muscle forces, and eye positions can be measured. In experiments on alert monkeys or other animals, microelectrodes are used to record the firing patterns of individual neurons during different movements. Until recently, most measurements of muscle properties were made using detached muscles. Now, however, small force transducers can be chronically implanted in eye muscles (Miller & Robins, 1992), so force measurements can be recorded during voluntary eye movements in fully alert, behaving animals. Eye positions can be accurately measured using several different devices, the most common of which is a magnetic search coil (Robinson, 1963). (First, a coil of wire is implanted on the eye of an animal or embedded on a soft contact lens for humans. Then the subject is placed inside large field coils that generate magnetic fields. As the eye moves, the angle of the eye coil relative to the magnetic field varies, inducing currents in the eye coil to vary, thereby specifying eye position.) Taken together, these measurements generate a representation of the input/output relationship of the peripheral part of the oculomotor system.

3.4 Skeletal Muscle

3.4.1 General Structure

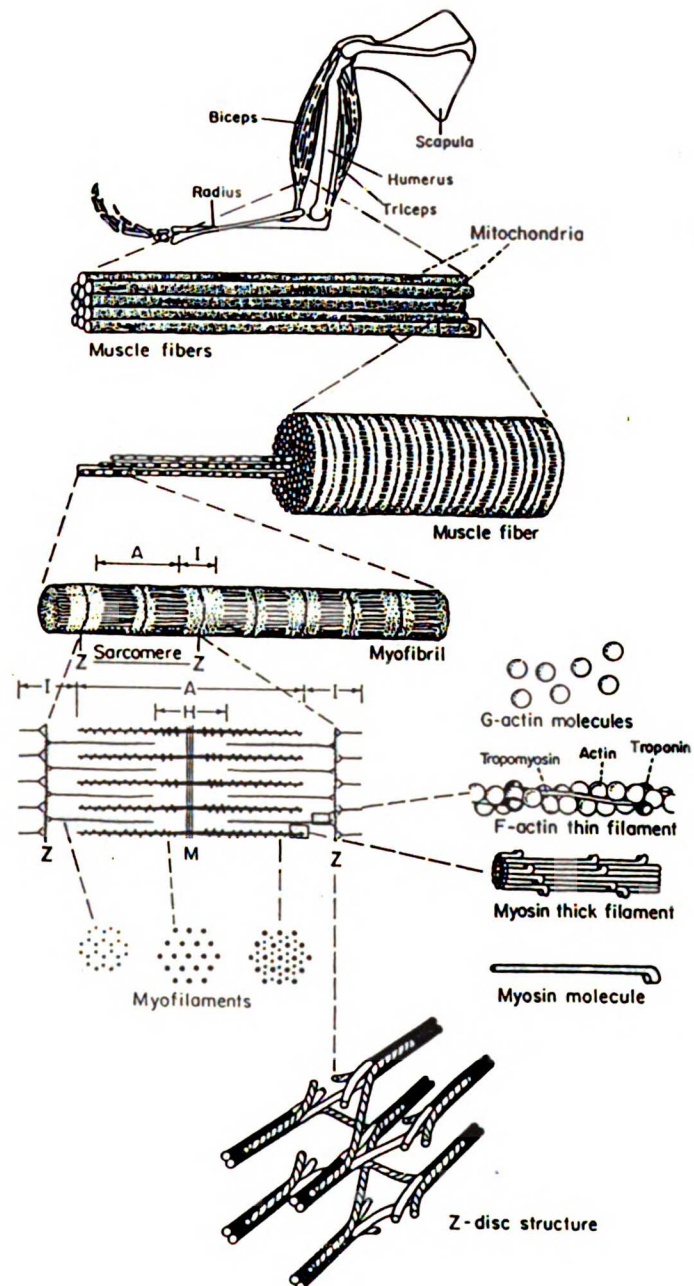
Skeletal muscle is composed of muscle fibers, which may run parallel to the long axis of the muscle (parallel) or obliquely to it (pennate). The fibers attach to connective tissue, tendon, which attaches the muscle to the bone. In general, pennate muscles generate more power than parallel muscles equal in volume because the structure allows more fibers to operate in parallel; at the same time, however, they tend to have a slower velocity of shortening because each fiber is shorter, and, therefore, has a shorter working stroke (McMahon, 1984). Consequently, the structure of the muscle depends on the job it must perform in the body.

Similarly, muscles are composed of different fiber types, each of which best performs a particular function; therefore, the distribution of fiber types also dictates the type of function a muscle can perform. At the simplest level, fiber types can be described by two categories: fast and slow. Fast fibers can generate a lot of force but generally fatigue rapidly and are, therefore, best for generating fast, brief movements. When stimulated, they contract and relax rapidly. In contrast, slow fibers contract and relax slowly and are resistant to fatigue; therefore, they are best for maintaining contraction. In addition, they are usually smaller in diameter and generate less force. Muscles generally contain different ratios of slow/fast fibers depending on their function.

Muscle contraction is controlled by motoneuron innervation, and the smallest functional unit that can be controlled by the nervous system is the motor unit, which consists of a single motoneuron and all the muscle fibers it innervates. A single ocular motoneuron, for example, only innervates a few fibers. (In humans the abducens nerve contains 3500-5000 motoneurons, Mühlendyck, 1978, and it innervates about 35,000 fibers in the lateral rectus, Kato, 1938). The fewer fibers innervated by each neuron the finer are the gradations in force that the system can control. These gradations in force are controlled by recruitment of motor units and by rate coding in the firing pattern of individual motoneurons. Moreover, in the motoneuron pools of the spinal cord, recruitment of motor units is described by Henneman's size principle (Henneman et. al., 1965), i.e., the smaller, slower conducting neurons are recruited earlier while the larger, faster conducting neurons are recruited later. In addition, the motor units associated with smaller neurons generally generate less force than those associated with larger neurons. Whether or not this principle applies to extraocular muscle is still an open question.

3.4.2 Microscopic Structure, Function, and Mechanism of Contraction: Sarcomere

The sarcomere is the functional unit of a muscle. Sarcomeres are mechanically linked in series to form myofibrils, which, in turn, combine with other myofibrils in parallel to form muscle fibers. The sarcomere contains parallel chains of actin and myosin fibers, which drive muscle contraction. Figure 1.4 shows a schematic of a

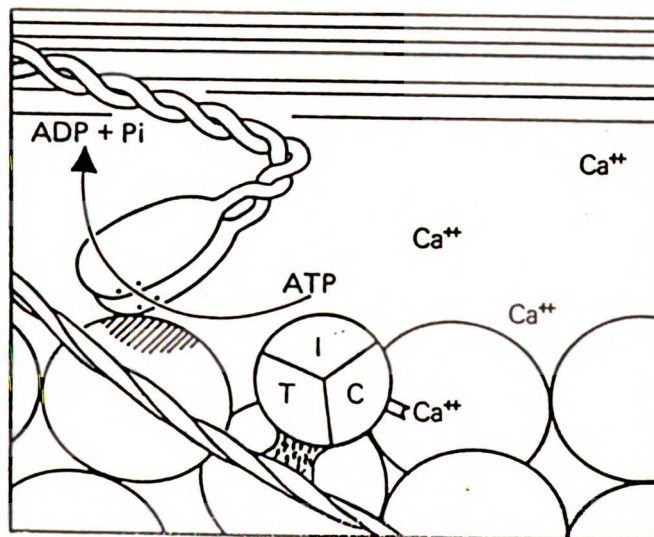
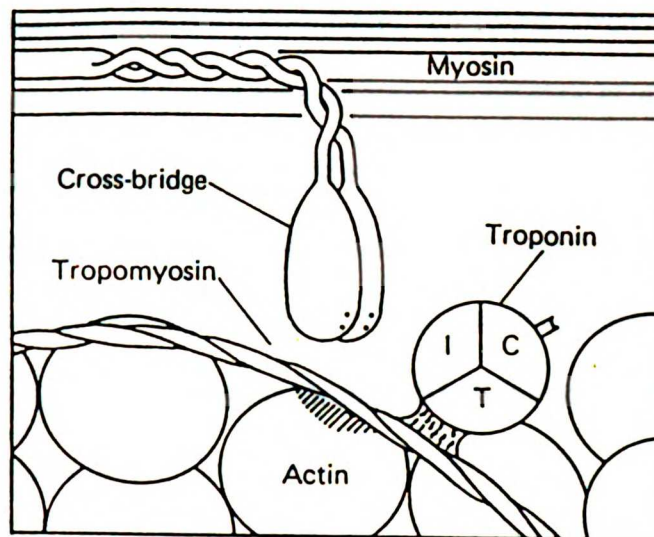


Structure of Skeletal Muscle. Muscles are composed of muscle fibers, each of which consists of a bundle of myofibrils. Myofibrils consist of a series of sarcomeres attached at the Z-discs. Sarcomeres are composed of thick myosin filaments and thin actin filaments. Cross-bridges can form in the region in which these fiber types overlap. (From McMahon, 1984, p.

56.)
Figure 1.4

sarcomere. Sarcomeres join together at the Z-disc. The thick lines represent myosin filaments and the thin lines represent actin filaments. The sarcomere generates force by forming cross-bridges between the actin protein and myosin protein heads that stick out from the myosin filament; it shortens by sliding the actin and myosin fibers across one another as a result of a conformational change in the myosin head, thereby increasing the fiber overlap as illustrated in Fig. 1.4. Integral to the activation of the cross-bridges are the surrounding membrane systems: the sarcoplasmic reticulum and the transverse tubular system (T-system).

Sarcomere activation is generated by a complex process. When an action potential reaches the terminal of the neuron, the motoneuron releases neurotransmitter into the synaptic cleft. The transmitter diffuses across the cleft and interacts with receptors in the endplate region, which causes changes in the membrane conductance to particular ions resulting in the depolarization of the postsynaptic potential. (The depolarization is ended by enzymatic breakdown of the neurotransmitter in the cleft). If the depolarization is greater than a threshold, a muscle action potential is triggered. The action potential travels down the transverse tubules. Following depolarization of the T-tubules, calcium is rapidly released into the myofibrillar space. Calcium then binds reversibly with troponin, which releases the actin binding site from inhibition (see Fig. 1.5), thereby allowing the formation of the actin-myosin cross-bridge. ATP is necessary to detach the cross-bridge. While the calcium concentration remains high, cross-bridges can continuously cycle between the attached and detached states. However, a calcium pump acts to lower the concentration of free calcium, which results



Schematic of Cross-bridge Formation. The actin binding site is inhibited from binding with the unattached cross-bridge (top). When calcium ions (Ca^{++}) bind with troponin, the inhibition is released and actin can bind to form an attached cross-bridge. ATP is needed to break the bond. (From Ganong, 1975.)

Figure 1.5

in calcium detaching from troponin, thereby reestablishing inhibition of the actin sites and preventing further cross-bridge formation. Of course, even at rest, these processes are in a dynamic state of equilibrium, but the probability of a cross-bridge forming depends on the probability of the actin site being released from inhibition, and this, in turn, depends on the concentration of free calcium.

3.5 Extraocular Muscle: Structure, Motor Unit Properties, and Motoneuron Firing Patterns

Extraocular muscle fibers run parallel to the long axis of the muscle; large fibers tend to be the entire length of the muscle while the small fibers tend to be shorter (Alvarado & van Horn, 1975). Five different fiber types that vary in diameter, type of innervation, amount of sarcoplasmic reticulum, and amount of mitochondria have been identified (Alvarado & van Horn, 1975). In general, the smaller, slow fibers are concentrated near the outside surface of the muscle (orbital layer; 100 μ m-200 μ m thick) and the larger, fast fibers are concentrated in the core of the muscle next to the globe (global zone) with an intermediate zone of mixed cell types separating them. Although the orbital layer contains 30-50% of the number of cells in the muscle, it only accounts for 10-20% of the total cross-sectional area (Alvarado & van Horn, 1975).

Extraocular muscle has one of the fastest times to peak contraction of all mammalian muscle (7.5-10 msec verses 25 msec in the fastest hind-limb muscle). (For review of extraocular motor units see Lennerstrand, 1975.) The fast motor units are

composed of twitch fibers and are singly innervated by large, fast conducting nerve fibers and conduct impulses. Because the large nerve fibers are more easily isolated, these motor units have been more readily studied than the slow motor units. Individual large fibers have a contraction time of 5-8 msec and a half-decay time of 7 msec; the fusion frequency and frequency at which maximum force is reached is about 350-450 pulses/s; further increases in stimulation frequency up to 800 pulses/s increased the rate of rise in force, but not the maximum force (similar to the muscle as a whole; Fuchs & Luschei, 1971). Surprisingly, many of these fast motor units are fatigue resistant. Although it has not been experimentally verified, it is generally believed that fast motor units consist of the larger muscle fibers in the global layer.

Surprisingly, given the fast contraction time, extraocular muscle exhibits a long-lasting, tonic contraction when exposed to acetylcholine, similar to the behavior of slow, non-twitch fibers in amphibian and avian muscle. This establishes the existence of a separate slow component of extraocular muscle. The slow motor units are multiply innervated by smaller, slower conducting neurons. At least some of the slow motor units are twitch units with contraction times about 25 msec. Fusion frequency is probably under 50 pulses/s, but maximum force continues to increase until input exceeds 200 pulses/s. Since the fibers in the orbital layer are small, rich in mitochondria etc., properties thought to be suited for tonic activity, they are believed to form a significant portion of the slow component; however, this has not been experimentally verified.

The existence of both slow and fast components of extraocular muscle seems to be ideal for establishing a division of labor. For example, the slow motor units would

be responsible for tonic activity such as holding the eye at fixation, while the fast motor units would be responsible for rapidly moving the eye during saccades. However, all units seem to be involved in saccades and motor unit recruitment seems to depend strictly on eye position and movement velocity (Robinson, 1970)

Single ocular motoneuron firing patterns from abducens and oculomotor nuclei have been well studied in alert monkeys during fixation at different eye positions and during saccades (e.g., Robinson, 1970, Fuchs & Luschei, 1970, Schiller, 1970). The basic firing pattern during a saccade can be described as a pulse-step or pause-step (Robinson, 1970) depending on whether the innervated muscle is the agonist or antagonist. A more accurate description is pulse-slide-step (pause-slide-step) (Goldstein & Robinson, 1986), where the pulse is a high frequency burst thought to enable the highly damped oculomotor system to move rapidly, the slide is a smooth transition in rate at the end of the pulse, and the step is the change in tonic firing rate necessary to hold the eye in its new fixation position.

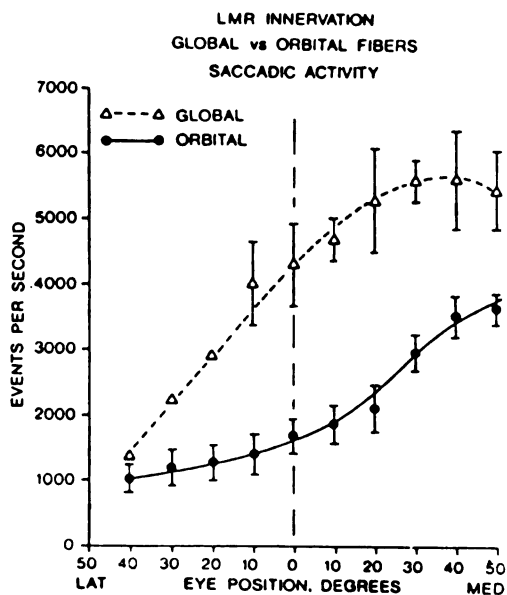
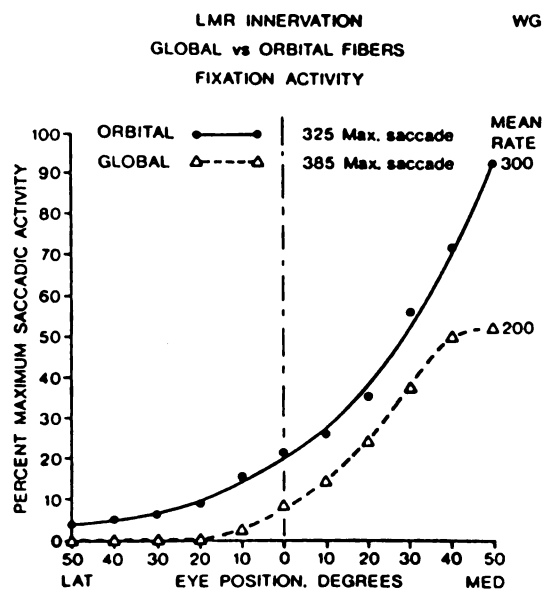
For each motoneuron, a relationship between fixation position and firing rate can be established. (For the purposes of the subsequent explanation a motoneuron's "on" direction refers to a movement in the direction of pull of the muscle it innervates; the "off" direction is in the opposite direction.) A typical motoneuron doesn't fire if the eye is far in the "off" direction. As the eye moves in the "on" direction, a threshold (θ) is reached at which point the motoneuron begins to fire. As the eye continues to move further in the "on" direction, the firing rate increases linearly (with a slope k). The thresholds range from -60 deg (i.e., 60 deg in the "off" direction) to 20 or 25 degrees

in the "on" direction, with 79% of the units already recruited by primary position, and the slopes of the rate-position relationships (k) vary from 1.1-14.5 spikes/s/deg in monkey; moreover, higher thresholds are correlated with higher slopes (Keller, 1981). There are no experimentally verified links between threshold, slope and fiber type, but a relationship consistent with expected function of motor unit types would be that low threshold, slope units are the slow motor units (but see, Shall & Goldberg, 1992).

Similarly, burst (pulse) firing patterns of motoneurons during saccades can be characterized. Nearly all motoneurons are active during saccades in the innervated muscle's "on" direction. Burst frequency appears to be correlated with peak saccadic velocity, and burst duration is correlated with saccade duration. (For review see Keller, 1981.) Moreover, the peak firing rates are in the range of firing frequencies shown to produce the maximum rate of rise in force in both motor units and whole extraocular muscle (review Lennerstrand, 1975). Another study (Goldstein & Robinson, 1992) shows that burst frequency and duration are position dependent; if a saccade is completed without crossing a motoneuron's position threshold, the burst duration during the saccade is often shorter than during the same size saccade further into the "on" region, after the unit has been recruited during fixation. In addition, although the burst rate increases for similar saccades initiated from positions further in the "on" direction, the change in firing rate (relative to steady-state firing rate) actually decreases beyond a certain eye position.

The relationship between single ocular motoneuron firing patterns and subsequent force development in extraocular muscle is a complicated issue. Simultaneous EMG

recordings from both orbital and global fibers suggest some answers (Scott & Collins, 1973, Collins, 1975). A needle with an array of ten pairs of bipolar electrodes (500 μ m apart, recording radius of approximately 25 μ m) was inserted at a 30 deg angle into the extraocular muscle. The needle was inserted until the electrode pair nearest the tip was silent, thereby ensuring that the electrode pairs nearest it were recording from the large, global fibers. At the same time, the small angle ensured that at least two electrodes pairs recorded from orbital fibers. Figure 1.6 shows the activity of the two types of fibers during fixation and saccades. During fixation, the orbital fibers are active over the entire range of positions, and they become more active as the eye moves more into the muscle's "on" direction. On the other hand, the global fibers are inactive in the muscle's "off" direction during fixation; they become active as the eye moves into the "on" region, and the activity saturates at about half the maximum activity during saccades. In contrast, during saccades, the global fibers are more active than the orbital fibers. This is the best evidence to draw connections amongst the low threshold, low slope of rate-position relationship motoneurons, the slow fibers, and tonic activity and amongst the high threshold, high slope motoneurons, the fast fibers, and the large force, phasic activity.



Activity of Orbital and Global Fibers During Saccades and Fixation.

(a) Peak activity of the orbital (solid, circles) and global (dash, triangle) fibers during 10-degree "on" saccades. (b) Relative contributions of orbital (solid, circles) and global (dash, triangle) fibers to fixation. (From Collins, 1975, pp 156 and 150.)

Figure 1.6

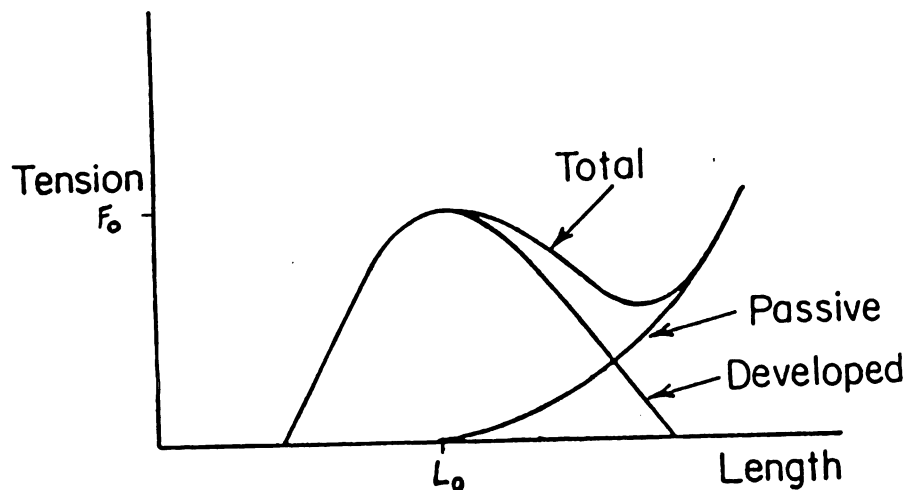
3.6 Muscle Mechanics

Muscle mechanics have been commonly studied along two basic paths. The first involves examining functional components contributing to the behavior of the whole muscle. This approach has led to the development of phenomenological models based mostly on studies of steady-state, macroscopic muscle properties. The second involves examining the mechanism of contraction at the microscopic level. This approach has led to models of the kinetics of the processes within a sarcomere; the whole muscle properties are generally derived by assuming that all other sarcomeres in the muscle are the same. The development of each type of model will be discussed in subsequent sections, but first some of the basic properties of macroscopic muscle will be described.

3.6.1 Macroscopic Muscle Properties

Isometric (constant length) studies of muscle demonstrate the basic relationship between stimulation and force development. When a single, electrical impulse of large enough magnitude is applied to an isometric muscle, force begins to rise, reaches a peak, and then decays; this response is commonly referred to as a twitch. If two electrical impulses, separated by a long enough interval, are applied, then two separate twitches are generated. However, if the second impulse is applied before the first twitch has completely decayed, then the second twitch reaches a higher peak force than the first.

If a train of electrical impulses are applied at a high enough frequency, a maximum level of force is reached and maintained, called tetanus.



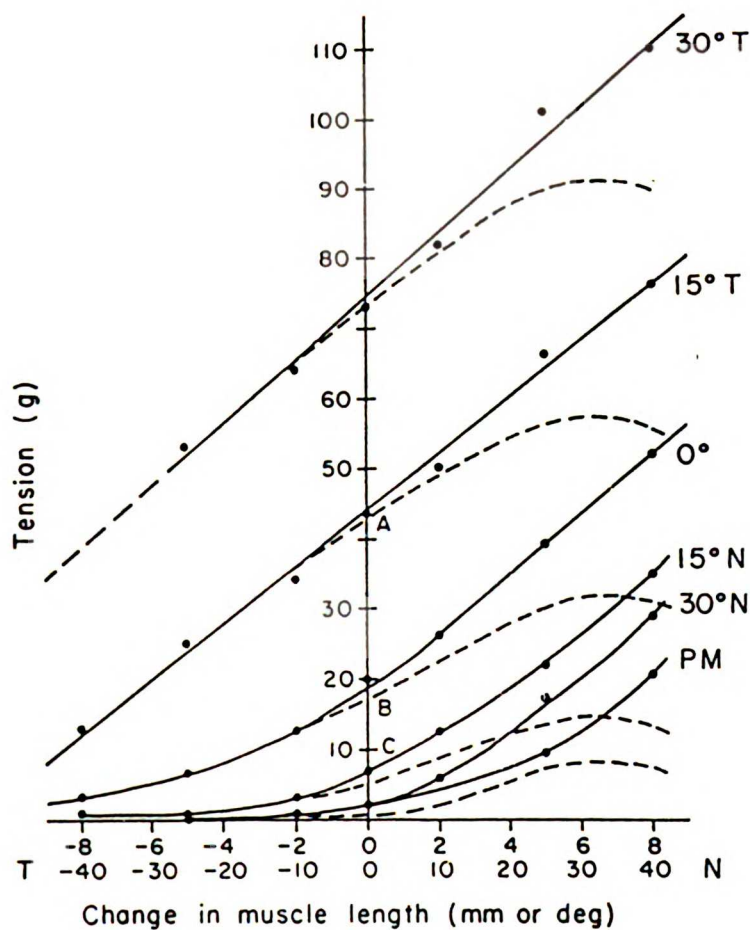
Total, Active and Passive Force in Muscle. The maximum total force developed by a muscle, the passive force, and the active force (total-passive) are all functions of muscle length. The maximum active force is F_0 and the length at which maximum active force is reached is L_0 . (Modified from McMahon, 1984, p.11.)

Figure 1.7

Muscle length has a significant affect on the force that can be developed in both passive and active muscle (see Fig. 1.7). As a passive muscle is stretched beyond a threshold length, it becomes more and more stiff, resulting in a non-linear passive force-length relationship (Fig. 1.7). This is thought to result from stretching the connective tissue within the muscle. The active length-tension relation can be determined by stimulating the muscle at different levels and subtracting the passive muscle force at

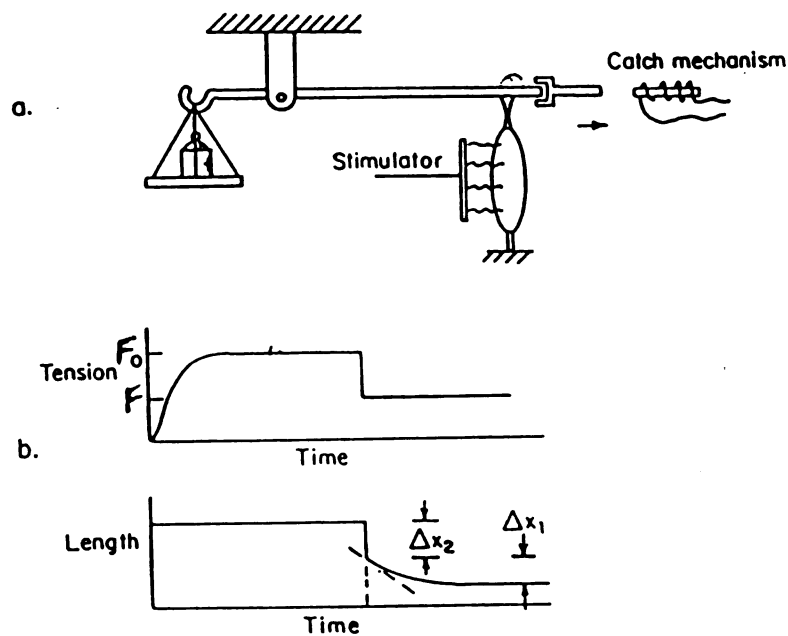
each length from the total muscle force. Figure 1.7 shows the total, active, and passive length-tension relations in a typical skeletal muscle. The active force at tetanus varies with muscle length; F_0 refers to the maximum active force of a muscle, and L_0 refers to the length at which maximum tetanus is achieved.

Figure 1.8 shows the total (solid) and active (dash) length-tension relation in human extraocular muscle for several levels of innervation. The length-tension relation shown was measured in the lateral rectus (LR) during surgery. The data is plotted in terms of muscle length and equivalent degrees of eye rotation (about the vertical axis) relative to primary position (i.e., zero degrees represents the subject looking straight ahead). In addition, the experimental paradigm took advantage of Herings law of innervation (see Section 3.2) to vary the level of muscle activation. Since the LR of the operated eye and the medial rectus (MR) of the unoperated eye receive coordinated inputs to yoke the two eyes together at a given fixation position, the subject is asked to fixate the unoperated eye at various positions while the LR of the operated eye is stretched to different lengths. By varying the fixation position of the unoperated eye, the input to the LR in the operated eye is varied. For a particular level of innervation, as the muscle length increases, the maximum active force developed increases until the muscle is stretched to its length when the eye is rotated 25 deg from primary position away from its direction of pull. At this point the active force begins to level off and then begins to drop. The positive slope of the active length-tension relation is thought to result from an increasing actin/myosin filament overlap, which brings an increasing number of actin sites within range of myosin heads so more cross-bridges can be



Length-Tension Curves for Human Extraocular Muscle (Lateral Rectus). The solid lines show total muscle tension as a function of length for a variety of levels of innervation. Change in muscle length is relative to primary position and is given in millimeters (top row) and equivalent degrees of eye rotation (bottom row). The curves were determined when the muscle was detached during surgery. Each curve shows the length-tension relation for a particular level of innervation determined by the deviation from primary position of the unoperated eye, taking advantage of reciprocal innervation. The passive muscle tension curve is labelled "PM". The dashed curves are the active length-tension relations calculated by subtracting the passive muscle tension from the total muscle tension. (From Robinson et al., 1969, p.550)

Figure 1.8



Quick Release Experiment. (a) shows the apparatus. A catch mechanism holds the muscle isometrically while the muscle is stimulated to tetanus (F_0). When the catch is released, the force of the weight in the pan (F) is applied to the muscle. (b) shows the muscle force and length during the experiment. The muscle is stimulated tetanically and, while maintaining stimulation, the catch is released and the new force is applied. When the catch is released, the muscle changes length rapidly by an amount represented by Δx_2 , which is proportional to the change in force ($\Delta F = F_0 - F$). (Modified slightly from McMahon, 1984 p. 11.)

Figure 1.9

formed. In addition, at any particular length, the higher the innervation, the higher the muscle force.

Quick release experiments demonstrated some other muscle properties (Fig. 1.9). The basic experiment consists of a muscle that is initially held isometrically and stimulated. Then, the force holding the muscle is suddenly reduced to a new level and the resulting change in muscle length is recorded. The response of the muscle to this step change in force ($\Delta F = F_0 - F_f$) was an instantaneous change in length followed by a continuous change in length at a particular initial velocity. Finally, the experiment was repeated while varying the final force (F_f) and, consequently, the step change in force (ΔF). The instantaneous change in length was found to vary linearly with the magnitude of the change in force ($k \cdot \Delta L = \Delta F$), which is the same characteristic as a linear spring.

On the other hand, the velocity of shortening, following the instantaneous change in length, varied non-linearly with the magnitude of the force. When the force-velocity data was plotted it was found to be well described by a hyperbola with asymptotes based on physiological parameters, which relate the maintenance heat generated during a maximum isometric contraction to F_0 , isometric force, and V_{max} , maximum velocity of shortening (Hill, 1938):

$$(F + a_H)(V + b_H) = (F_0 + a_H)b_H$$

F , force

F_0 , isometric force at tetanus

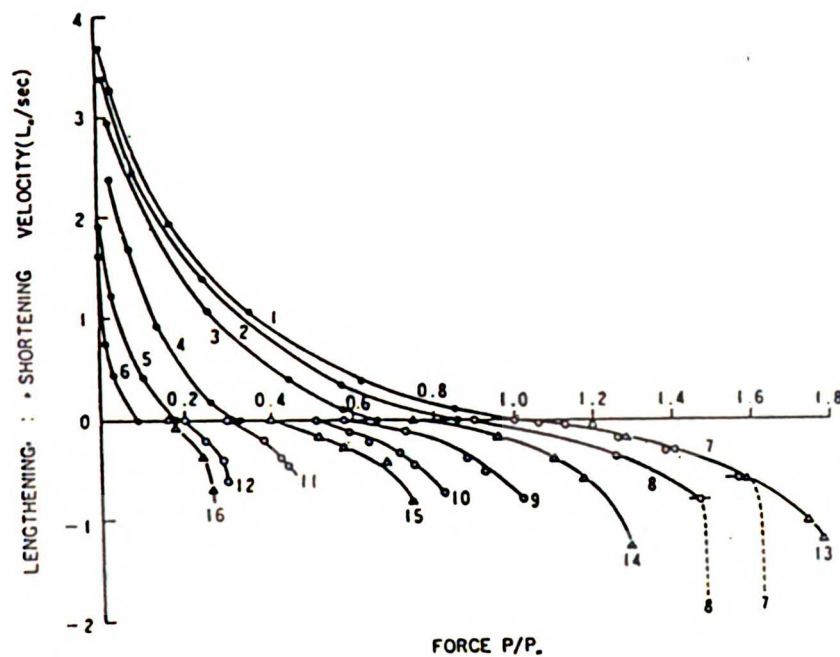
V , velocity

$a_H = F_0/4$, constant partially characterizing the force-velocity
relationship of shortening muscle [force]

$b_H = V_{\max}/4$, constant partially characterizing the force-velocity
relationship of shortening muscle [velocity]

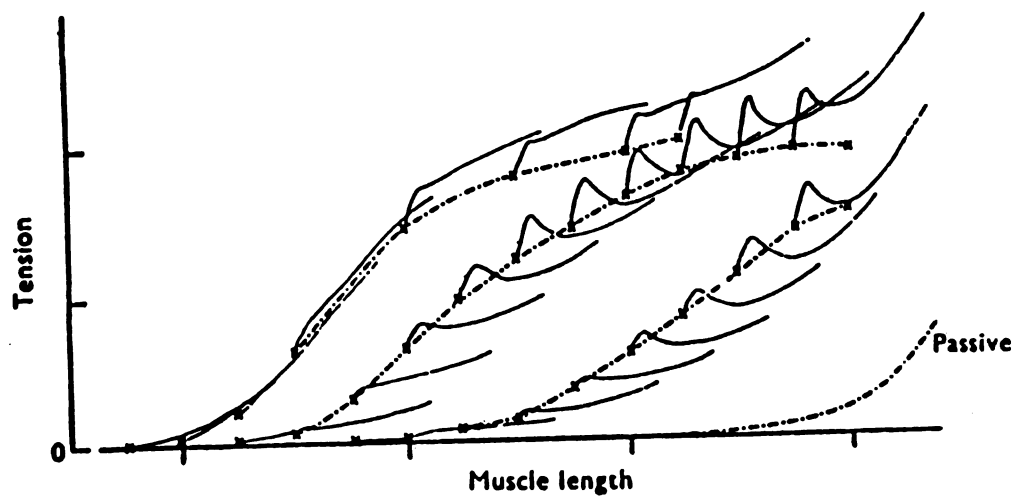
$a_H b_H$, approximately equivalent to the rate of maintenance heat
production, which is the rate heat is released during
steady-state isometric contraction at L_0

Of course, this experiment only yields data for one level of stimulation, so the relationship had to be established (or estimated) for each level of innervation, resulting in a family of characteristic curves. Figure 1.10 shows the force-velocity relation for partially and fully innervated muscle, both shortening and lengthening. The lengthening portion of the curve was determined by sampling force at a particular time after the step change in force occurred. Therefore, it does not include the transient behavior actually observed (see Fig. 1.11). In fact, no steady-state force-velocity relationship exists for lengthening muscle; isovelocity experiments lead to different estimates of the lengthening force-velocity relationship than do isoforce experiments.



Force-Velocity Relationship for Full and Partial Activation. The force-velocity relation from frog sartorius is shown for both shortening and lengthening. (From Akazawa, 1974.)

Figure 1.10



Transient Behavior in Force-Velocity Relationship for Lengthening Muscle. The four base level curves show isometric force at different levels of activation (increasing activation from right to left). The solid curves show the tensions measured during isovelocity stretches. Note that they often exhibit yielding. (From Joyce et al., 1969.)

Figure 1.11

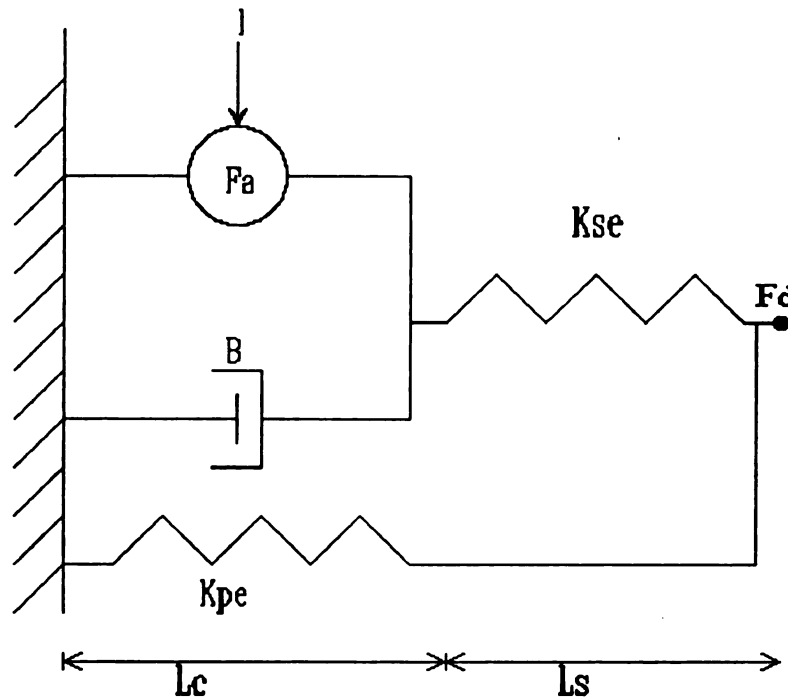
3.7 Muscle Models

3.7.1 Phenomenological Model

Because muscles are biological actuators, the simplest muscle model is a pure force generator, but this doesn't reflect the dynamics of muscle contraction and relaxation. Muscle viscosity and elasticity affects how much force dissipates and how much acts on the joint being considered, and these properties are fairly complicated. A.V. Hill (Hill, 1938) was the first to present a lumped-parameter, mechanical circuit model to represent the mechanics and energetics of shortening muscle. In mechanical circuits, springs represent relationships between force and length, dashpots represent relationships between force and velocity, and inertial elements represent relationships between force and acceleration.

Figure 1.12 shows the structure of this model, which consists of a spring (K_{pe}) in parallel with a series combination of a contractile element and a spring (K_{se}). The contractile component is the force generator which not only depends on the level of activation (F_a) but also on the velocity of shortening, which is represented by the non-linear dashpot (B). (The hyperbola used to describe the force-velocity relation of shortening muscle at tetanus is usually assumed to scale by activation. In addition, a quasi-steady-state assumption must be made, i.e., as the innervation changes, the muscle properties vary smoothly as their representation moves from one innervation curve to

the next.) Finally, the contractile component is connected to the series elasticity (K_{se}) shown to be a necessary component by the quick release experiments; the spring must be in series with the contractile component to enable the muscle to exhibit an



Hill Model of Muscle. The contractile component consists of a force generator, F_a , in parallel with a non-linear dashpot, B , that represents the force-velocity relationship. The contractile component is in series with a spring, K_{se} , that represents the series elasticity explaining the quick release experiments. And the whole combination is in parallel with a spring, K_{pe} . The total muscle length is divided into two functional components, L_s and L_c . Innervation, I , is the input.

Figure 1.12

instantaneous change in length in response to a step change in force.

Variations of the Hill model are used to represent many muscles. The mechanical circuit model of macroscopic properties is appealing because the parameters

can be measured relatively easily and because the structure gives insight into the behavior of the muscle during movement. On the other hand, no connection is made with the underlying mechanism of contraction, which is not a problem on a functional level but is a little disconcerting just the same. Moreover, it does not represent known transient properties of lengthening muscle, which could be a problem especially in high velocity movements.

3.7.2 Mechanistic Model

A second approach to modelling the mechanics of force development is to model the mechanism of contraction, or cross-bridge formation and detachment. In this case, the muscle is assumed to consist of a large number of identical sarcomeres, so the macroscopic muscle characteristics can be directly determined from the model of a single sarcomere.

A cross-bridge model for the dynamics of muscle contraction, developed by A. F. Huxley, is shown in Fig. 1.13. Each of the large number of cross-bridges in a muscle is represented by a spring, and the force generated by each cross-bridge is proportional to the length of the spring (x). A change in muscle length is generated by the movement of the myosin heads in a cross-bridge which forces the myosin and actin fibers to slide past each other in opposite directions. If, at a given moment, the distribution of bond lengths, or spring lengths, (n) is known, then the total force generated by the muscle can be calculated. In a simple two-state model with a constant

level of innervation, we only need to know the rate of bond attachment (f) and detachment (g) to write a partial differential equation describing the rate of change of the bond distribution:

$$\frac{\partial n(x,t)}{\partial t} - v(t) \frac{\partial n(x,t)}{\partial x} = f(x)(1 - n(x,t)) - g(x)n(x,t)$$

$n(x,t)$, bond distribution; $0 < n < 1$

$v(t)$, velocity of shortening

$f(x)$, rate of bond attachment

$g(x)$, rate of bond detachment

Zahalak suggested an approximation which makes the simulation of these equations computationally tractable (Zahalak, 1980). First he noted that this partial differential equation can be rewritten as an infinite series of ordinary differential equations of the moments of the distribution. Then he noted that if the shape of the function describing the bond distribution is known *a priori* and if the function is completely described by a finite number of its moments, then the system can be expressed as a finite series of coupled, first-order, differential equations. He assumed the bond distribution was Gaussian, in which case the dynamics can be expressed with three differential equations (because the first three moments completely define a Gaussian distribution). Conveniently, the macroscopic muscle properties of interest are functions of these low order moments. Zahalak's model is called the distributed moment (DM) model.

Define:

$$M_{\lambda} \doteq \int_{-\infty}^{\infty} x^{\lambda} n(x,t) dx$$

$$b_{\lambda} \doteq \int_{-\infty}^{\infty} x^{\lambda} f(x) dx$$

Infinite series of differential equations:

$$\frac{dM_{\lambda}}{dt} + \lambda v(t) M_{\lambda-1} = b_{\lambda} - \int_{-\infty}^{\infty} x^{\lambda} [f(x) + g(x)] n(x,t) dx, \quad \lambda = 0, 1, 2, \dots$$

where:

$$n(x,t) \doteq \frac{M_0(t)}{\sqrt{2\pi}\sigma(t)} e^{-\frac{[x-\mu(t)]^2}{2\sigma^2(t)}}$$

$$\mu(t) = \frac{M_1(t)}{M_0(t)}, \quad \sigma(t) = \left[\frac{M_2(t)}{M_0(t)} - \left(\frac{M_1(t)}{M_0(t)} \right)^2 \right]^{1/2}$$

$$\frac{dM_0}{dt} = b_0 - F_0(M_0, M_1, M_2)$$

$$\frac{dM_1}{dt} = b_1 - F_1(M_0, M_1, M_2) - v(t) M_0$$

$$\frac{dM_2}{dt} = b_2 - F_2(M_0, M_1, M_2) - 2v(t) M_1$$

$n(x,t)$, bond distribution function

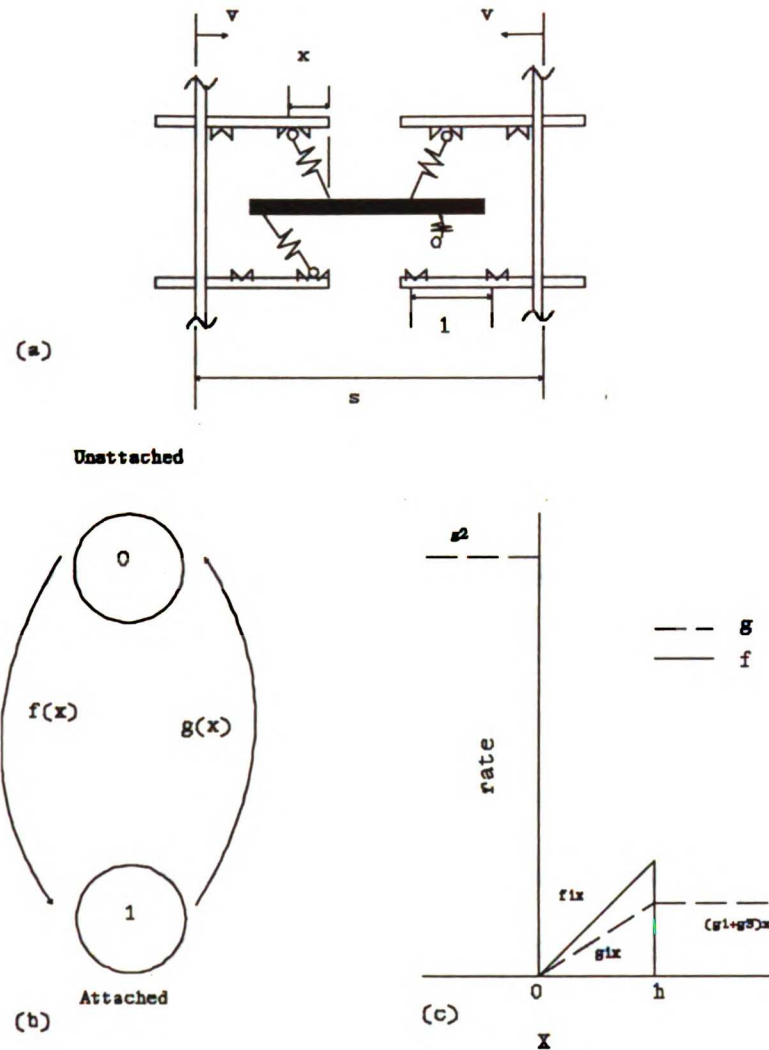
M_{λ} , λ th moment of the bond distribution function

b_{λ} , λ th moment of the rate of attachment function

$f(x)$, $g(x)$, rate of attachment and detachment functions

$v(t)$, velocity of shortening

$F_{\lambda}, \lambda=0,1,2$ λ th moment of the function $(f+g)*n$



Schematic of the Cross-bridge Model of Muscle Contraction. (a) shows a schematic of cross-bridges in a sarcomere. A myosin filament is represented by the thick line and actin filaments are represented by the thin lines. Cross-bridge sites are represented by balls attached to the myosin filament by springs. Actin sites are represented by two triangles. The figure shows both attached and unattached cross-bridges. " x " reflects the length of an attached spring; " v " is the velocity; " l " is the distance between actin sites; and " s " is the sarcomere length. (b) shows the two-state model of cross-bridge formation, and (c) shows the rates of attachment and detachment as a function of " x ".

Figure 1.13

The advantages and disadvantages of this model are the reverse of those for the first model. Here, the steady-state muscle properties are different from the dynamic ones, more like real muscle. For example, this model exhibits yielding in lengthening muscle. Unfortunately, whole-muscle properties are emergent properties of the model rather than direct parameters, so this model is not at the same intuitive level as the first one. In addition, the rate parameters are not experimentally measurable at this time and must be derived from other muscle properties. The derivation of the parameters for a DM model of extraocular muscle will be discussed in Chapter 4.

4. Summary

This chapter was meant to provide a general introduction to the work presented in this dissertation. First, I discussed general interests that led to my pursuing this project. Second, I discussed the basic organization of the work presented. And, finally, I discussed the basic background material underlying the work presented in the following chapters.

Eye Position and Muscle Force Profiles During Monkey Horizontal Saccadic Eye Movements

1. Introduction

The horizontal saccadic eye movement system has been a frequent subject of motor control studies. It is both more simple and more accessible to measurements than most other motor systems. The control of eye movements is not complicated by the need to control the dynamical interactions of multiple links, which is characteristic of naturally occurring musculoskeletal movements. Moreover, there are no large dynamical load changes to overcome during the course of a movement. In addition, the study is further simplified by restricting it to the subsystem generating eye movements in the horizontal plane through primary position. This subsystem is dominated by the action of two muscles, medial and lateral recti, that apply torques in opposite directions. Consequently, the geometry of the muscles' lines of action, which change with eye position in unrestricted movements, does not need to be considered. Another simplification over musculoskeletal movements is that the eye movement system does not have a stretch reflex that might interact with the central control during rapid movements like saccades (Keller, 1981).

In addition, the eye movement system is more accessible to measurements because the entire system is contained within the cranium. With present technology, eye

position can be accurately measured with several techniques, the firing patterns of individual ocular motoneurons can be recorded with microelectrodes, and, now, the muscle forces can be measured with chronically implanted force transducers, all during physiologic eye movements. In contrast, in most musculoskeletal movements electromyograms, not motoneuron firing patterns and muscle force, are used to measure muscle activity. Using the aforementioned techniques along with others, five different types of eye movements have been identified, as well as the single-unit firing patterns of ocular motoneurons during these movements. Moreover, many of the steady-state, macroscopic properties of extraocular muscle have been measured in humans (for review see Robinson, 1971) and other mammals (cat: Robinson, 1964, Collins, 1971, Barmack et al., 1971; monkey: Fuchs & Luschei, 1971; rat: Close & Luff, 1974).

In studying this system, we also take advantage of the fact that we naturally make high velocity eye movements, saccades. The high velocities and accelerations generated during saccadic eye movements serve to accentuate the mechanical characteristics of the system. Saccades are very stereotyped, high velocity movements which function to change the visual fixation point. They show characteristic relationships (called the main sequence, Bahill et al., 1975) between peak velocity and saccade magnitude and between duration and saccade magnitude (Bahill et al., 1975, Fuchs, 1967). In general, saccade duration increases nearly linearly with magnitude, while peak velocity initially increases with magnitude but shows a soft saturation for saccades larger than 20 degrees in both humans and monkeys. Not surprisingly, recordings of ocular motoneurons show a stereotypical pattern of discharge for saccades.

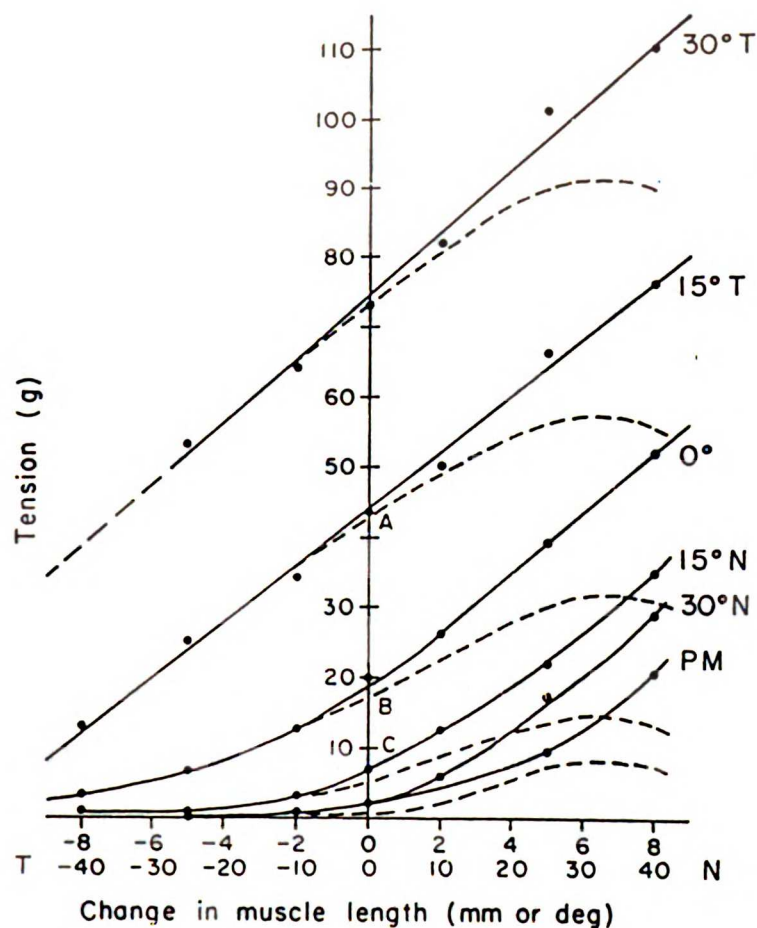


Figure 2.1. Active and Passive Length-tension Relationships in Human

Extraocular Muscle.

The solid lines show total muscle force as a function of length for a variety of levels of innervation. Change in muscle length is relative to primary position and is given in millimeters (top row) and equivalent degrees of eye rotation (bottom row). The curves were determined when the muscle was detached during surgery. Each curve shows the length-tension relation for a particular level of innervation determined by the deviation from primary position of the unoperated eye, taking advantage of Hering's law. The passive muscle force curve is labelled "PM". The dashed curves are the active length-tension relations calculated by subtracting the passive muscle force from the total muscle force. (Source: Robinson et al., 1969)

Agonist inputs consist of a high frequency burst followed by a gradual decline to a new steady-state firing rate, slightly higher than the rate prior to the saccade (pulse-slide-step pattern) (Goldstein et al., 1989). The pulse of neural activity drives the system at high velocities, while a much smaller change in innervation holds the eye in the new steady-state position. At the same time, the antagonist input consists of a pause in discharge followed by an increase to a new, but lower than the initial, steady-state firing rate (pause-slide-step pattern) (Goldstein & Robinson, 1986).

A closer examination of saccade kinematics reveals several asymmetries most notably a temporal/nasal asymmetry. Some controversy exists about which direction is faster. Eye position recordings using an infrared reflection technique (e.g., Fricker & Sanders, 1975) or an eye coil technique (e.g., Robinson, 1964) suggest temporal saccades have higher peak velocities for a given saccade size. In contrast, EOG (electrooculogram) measurements suggest nasal saccades have a higher peak velocity (e.g., Boghen et al., 1974); however, evidence exists that suggests EOG measurements may not be accurate (Hepp et al., 1989). Asymmetries may result from differences in the medial and lateral recti properties, in innervation, or in asymmetric orbital mechanics. To begin to

distinguish the causes, some basic macroscopic, extraocular muscle properties must be understood. The passive and active length-tension relationships have been measured in humans (Robinson et al., 1969, Collins et al., 1981, Collins et al., 1975, Collins, 1975) and other animals (cat: Robinson, 1964, Collins, 1971, monkey: Fuchs & Luschei,

1971). Fig. 2.1 shows a plot of the passive force, total force, and active force recorded from a human lateral rectus (LR). In passive extraocular muscle, as the muscle is stretched it becomes stiffer; when the eye is in primary position the passive force is small, but it increases nonlinearly as the muscle is stretched beyond this position (curve labelled PM). In addition, the length-tension relationship for active muscle (total force minus passive force; dashed curves) has been measured for several levels of innervation. Starting at the shortest physiological muscle length, for a particular level of innervation, active force increases as muscle length increases until the eye is 25 to 30 degrees beyond primary position. At this length, the active force saturates and further extension would be accompanied by a decrease in active force. This length-tension relationship is believed to be a result of sarcomere length and the number of possible cross-bridges that could be formed at a given length. Some evidence exists suggesting that the medial rectus (MR) generates higher forces at analogous positions and innervation levels (Collins et al., 1981). However, other evidence suggest the two muscles are very similar (e.g., Collins, 1975).

In this chapter, the experimental methods are described first, including the chronic implantation of force transducers, which allows individual muscle forces to be measured during physiologic eye movements in the intact orbit. Next, results of eye and force trajectories measured during saccades of different sizes, initial positions, and directions are presented. Finally, the data is discussed in relation to expectations based on our present understanding of eye movements.

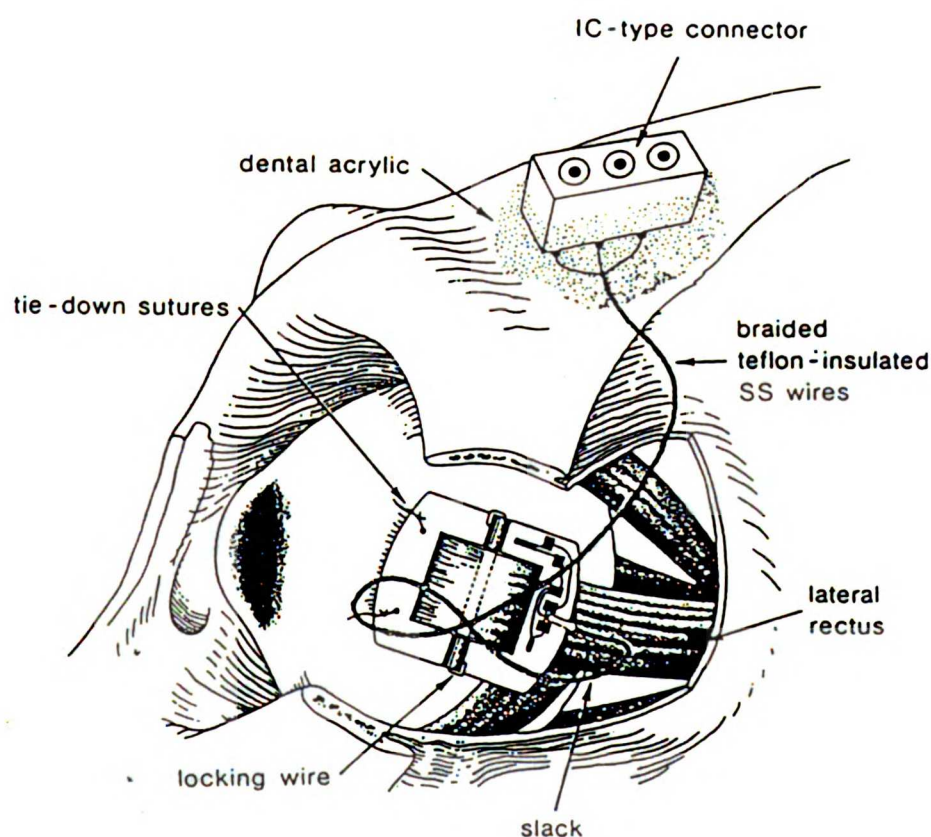
2. Methods

One adult male *Macaca fascicularis* was prepared for this study by the chronic implantation of several devices. Care and use of the animal followed the procedures of the ARVO Resolution on the Use of Animals in Research. The monkey was implanted with a coil of Teflon-coated stainless steel wire mounted under the conjunctiva of the left eye (Judge et al., 1980) to record eye movements using the search coil method (Robinson, 1963). A head restraint was implanted to allow immobilization of the head with respect to the magnetic fields during subsequent experimental sessions. The restraint was fixed in place on the calvaria with dental acrylic cement.

After recovery and prior to implantation of the force transducers, the monkey was trained to make saccades to lighted LED's selected randomly from a grid array. An array of 25 LED's was used consisting of five rows with LED's spaced at 10 degree intervals ranging from ± 20 degrees from primary position.

After training (which will be described subsequently) a buckle force transducer was implanted on the left LR, and 4.5 months later one was implanted on the left MR. Fig. 2.2 shows a drawing of an implanted force transducer on the LR. The force transducers were temperature compensated strain gauges in a Wheatstone bridge circuit (Miller & Robins, 1992). To implant the transducer, the muscle was exposed. With the cross-tube removed, the transducer was placed on the muscle. Then, the cross-tube was inserted on the transducer underneath the muscle. As a result, the muscle threaded up through the transducer frame, over the cross-tube, and back down underneath the frame

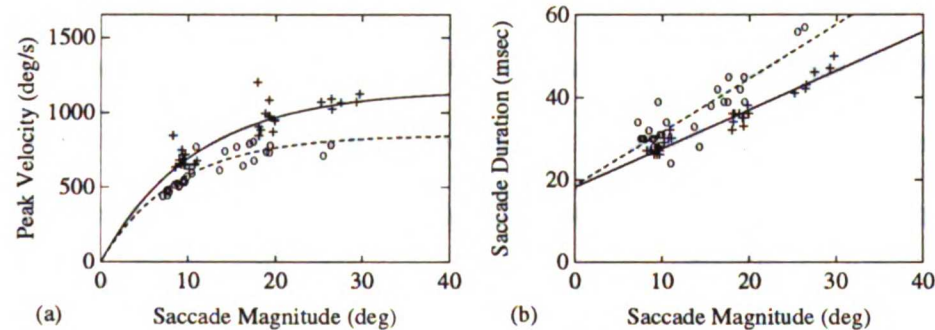
without ever being detached. The transducer was sutured to the muscle to prevent rotation. The signal leads led out of the orbit under the skin and exited through a connector attached to an acrylic cap. The globe was rotated to ensure the leads were not limiting motion.



Force Transducer Implanted on LR
Figure 2.2

All surgeries were performed under sodium pentobarbital anesthesia and sterile conditions. Analgesics and antibiotics were given during post-surgical recovery period.

After the monkey recovered, muscle forces and eye position were measured during saccades and were sampled at 1000 Hz. The trials were sorted, and successful trials of horizontal saccades were examined. Eye position records were smoothed and digitally differentiated. Force records were scaled as a percentage of the total range



Main Sequence. Peak velocity (a) and saccade duration (b) are plotted as functions of saccade size. The plus (+) marks temporal saccades and the circle (o) marks nasal saccades. The solid lines are the result of curve fitting.

Figure 2.3

observed in each muscle during the session; the range and distribution of movements were similar across sessions. (Data from four consecutive sessions was chosen to minimize effects of possible slow changes in force transducer sensitivity.)

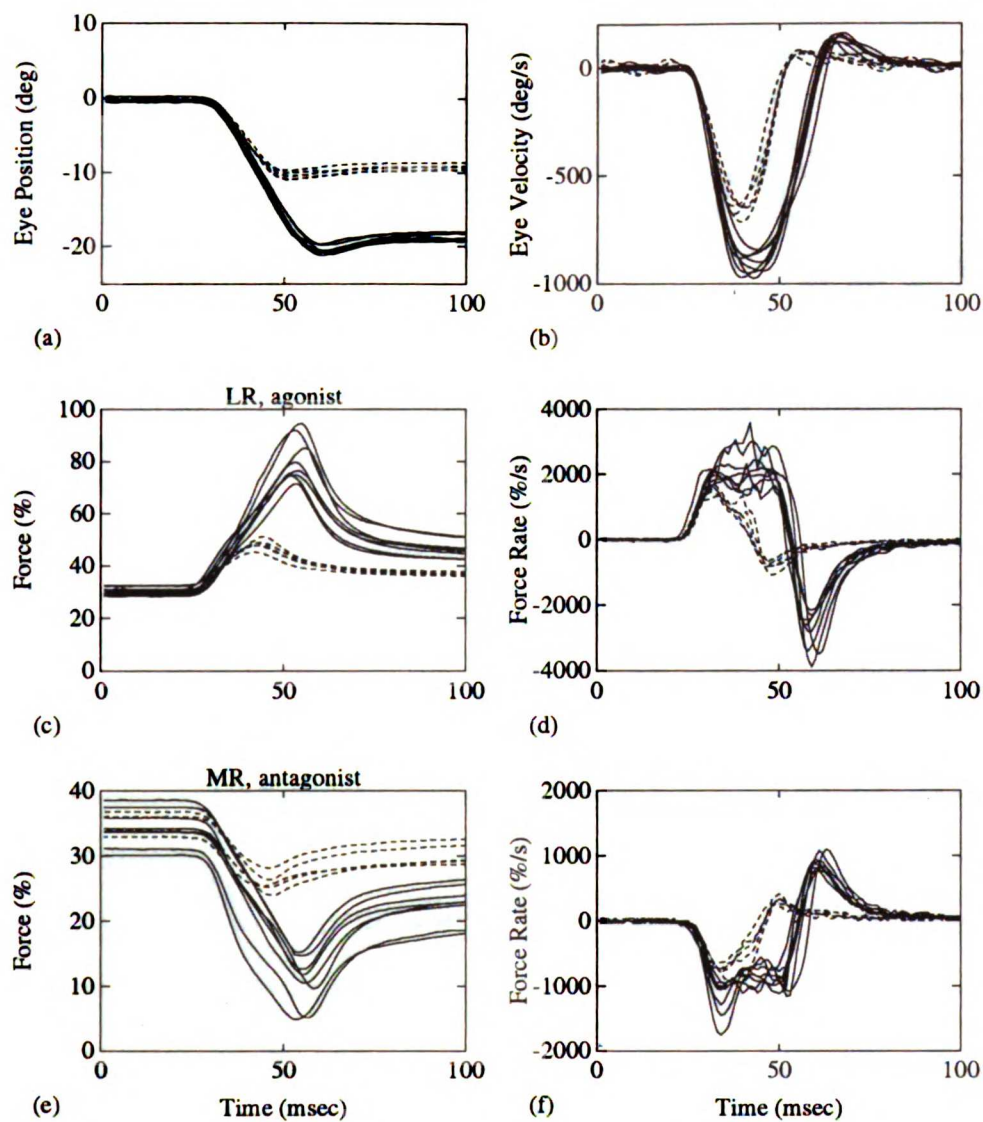
When one of the transducers failed, the monkey was euthanized with an overdose of pentobarbital, and the transducers were excised.

The traces presented in "Results" are single, unaveraged trials. Raw data is shown to exhibit the degree of reproducibility. Also, eye position was recorded relative to primary position, with the convention that positive values represent nasal positions and negative values represent temporal positions.

3. Results

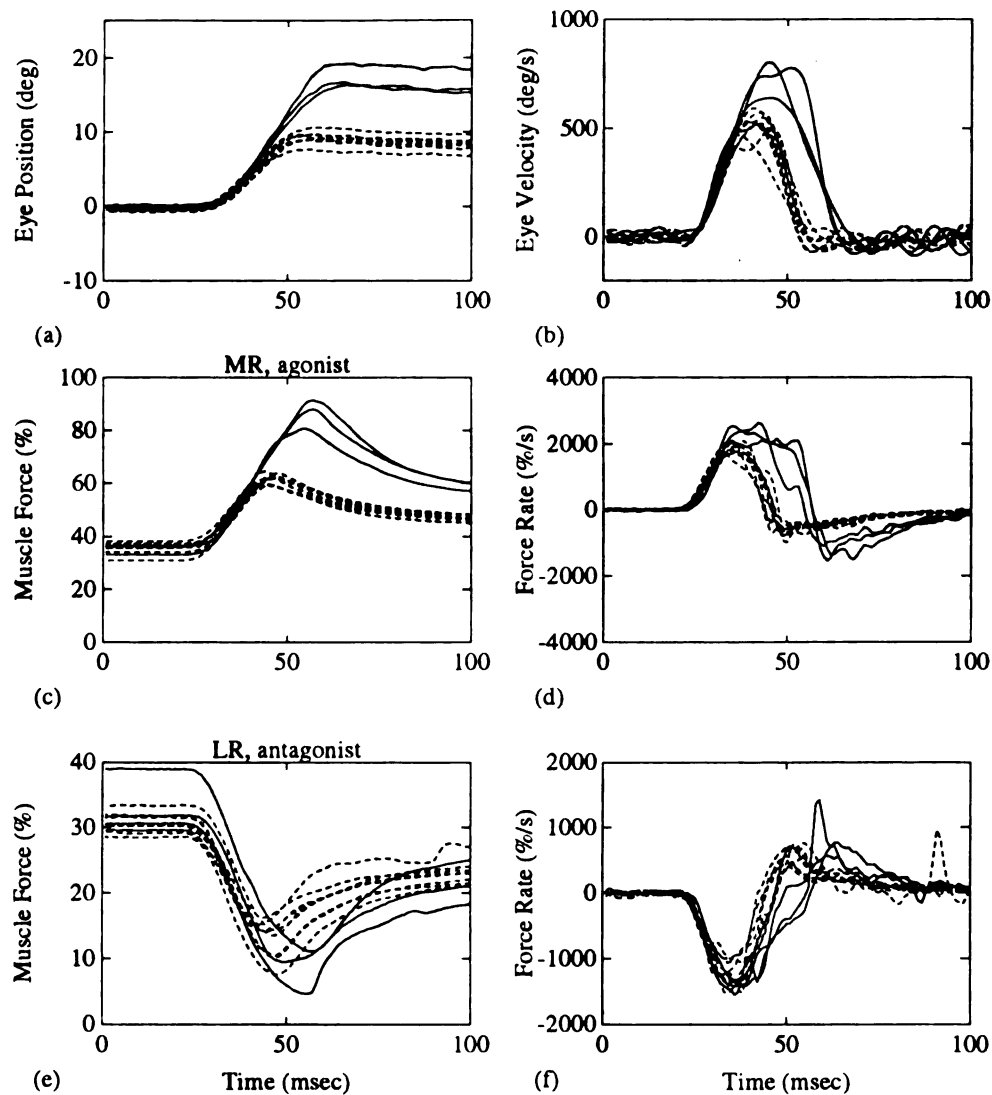
As shown in Fig. 2.3, kinematic data is consistent with the expected main sequence plots. The figure shows that peak velocity increases and then saturates as a function of saccade magnitude (a) and that saccade duration increases as a function of saccade magnitude (b). The curves show the least squares fit for each relationship, with temporal saccades (plus (+) marks saccades, solid curves) distinguished from nasal saccades (circle (o) marks nasal saccades, dash curves). In addition, a temporal/nasal asymmetry is apparent with nasal, or rightward, saccades slower and longer in duration than comparable temporal, or leftward, saccades. The following equations describe the least squares fit to the data:

$$\begin{aligned} \text{Temporal: } & \text{Peak Vel} = 1160(1 - e^{-.10 \cdot \text{Mag}}) \\ & \text{Dur} = .94 \cdot \text{Mag} + 18.2 \\ \text{Nasal: } & \text{Peak Vel} = 840(1 - e^{-.114 \cdot \text{Mag}}) \\ & \text{Dur} = 1.3 \cdot \text{Mag} + 18.7 \end{aligned}$$



Basic Saccade Profiles: 10- and 20-Degree Temporal Saccades Initiated from Primary Position. Eye position (a) and velocity (b), agonist (L) force (c) and force rate (d), and antagonist (MR) force (e) and force rate (f) profiles recorded during 10- (dash) and 20-degree (solid) saccades. Each line represents an individual trial.

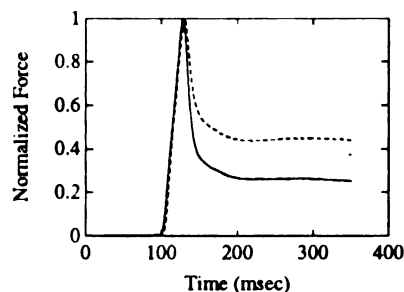
Figure 2.4



Basic Saccade Profiles: 10- and 20-Degree Nasal Saccades Initiated from Primary Position. Eye position (a) and velocity (b), agonist (MR) force (c) and force rate (d), and antagonist (LR) force (e) and force rate (f) profiles recorded during 10- (dash) and 20-degree (solid) saccades. Each line represents an individual trial.

Figure 2.5

Figs. 2.4 and 2.5 show eye position and velocity and muscle force profiles for 10- (dashed lines) and 20-degree (solid lines) saccades initiated from primary position. As expected, 20-degree saccades have a higher peak velocity and longer duration than the 10-degree saccades (Figs. 2.4a,b, 2.5a,b). Agonist (LR, Fig. 2.4c; MR, Fig. 2.5c) and antagonist (MR, Fig. 2.4e; LR, Fig. 2.5e) force profiles are qualitatively symmetric (also see Fig. 2.6). Note that, as a result of this symmetry, the net torque profile applied to the globe would follow the same pattern as the individual muscle force profile (see Chapter 5 for torque profiles). In addition, note that the peak agonist muscle force occurs between the times at which peak eye velocity and peak change in eye position are reached. As seen in Fig. 2.4, during temporal saccades the rate of change of force

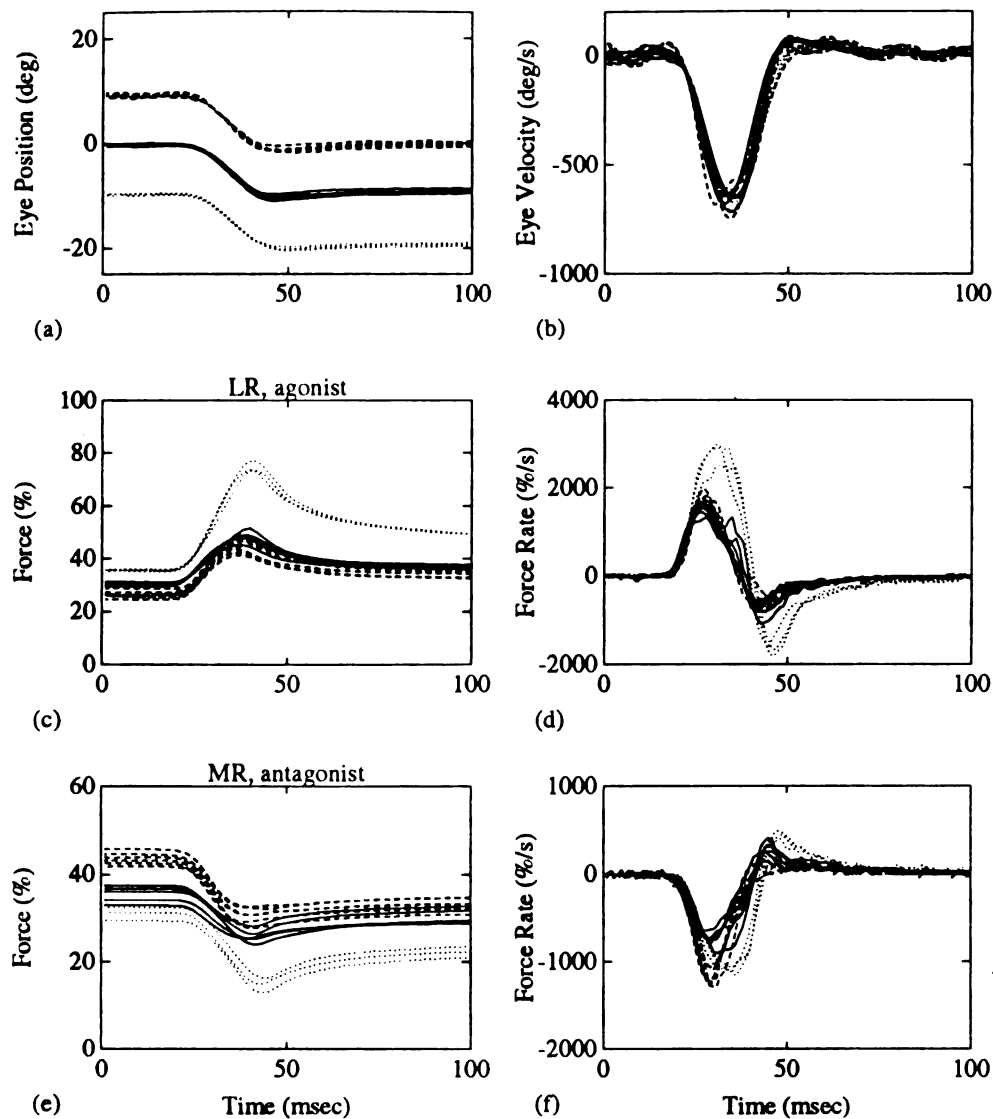


Normalized agonist and antagonist force profiles for a 20-degree saccade. The normalized agonist (solid) and antagonist (dash) force profiles are shown to show the qualitative symmetry in shape.

Figure 2.6

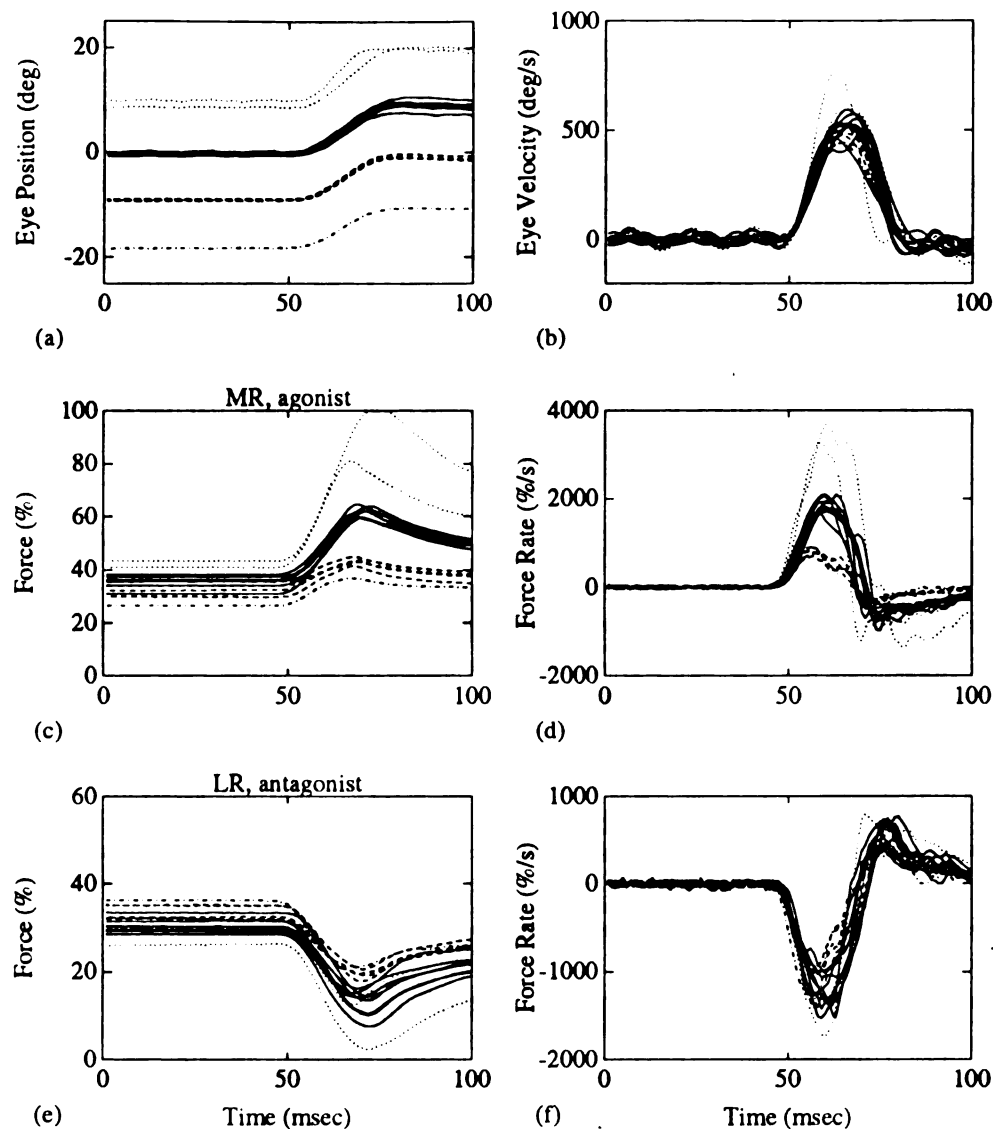
has an initial rapid increase (LR; Fig. 2.4d) or decrease (MR; Fig. 2.4f). During 20-degree saccades, the initial phase is followed by a plateau phase (constant rate). The next phase shows a rapid reversal in force-rate, which drives it to a negative (LR) or positive (MR) peak; the magnitude of the this reversal peak is greater and occurs later than in 10-degree saccades.

Fig. 2.5 shows nasal saccades. Eye position and velocity profiles are similar but not exactly symmetrical to those during temporal saccades (e.g., compare 2.4b & 2.5b), demonstrating the aforementioned directional asymmetry. As during temporal saccades, the agonist (MR) force-rate during 20-degree nasal saccades has a plateau phase (Fig. 2.5d). However, the antagonist (LR) force-rate does not have a comparable plateau phase, although it does decrease more slowly and reaches its peak reversal rate at a later time than during 10-degree saccades (Fig. 2.5f).



Effect of Initial Position on Saccade Profiles: 10-Degree Temporal Saccades Initiated from a Variety of Initial Positions. Eye position (a) and velocity (b), agonist (LR) force (c) and force rate (d), and antagonist (MR) force (e) and force rate (f) profiles during 10-degree saccades. The saccades were initiated from several different initial positions: 10 degrees nasal (dash), primary position (solid), and 10 degrees temporal (dot). Each line represents an individual trial.

Figure 2.7



Effect of Initial Position on Saccade Profiles: 10-Degree Nasal Saccades Initiated from a Variety of Initial Positions. Eye position (a) and velocity (b), agonist (MR) force (c) and force rate (d), and antagonist (LR) force (e) and force rate (f) profiles recorded during 10-degree saccades. The saccades were initiated from several different initial positions: 20 degrees temporal (dot-dash), 10 degrees temporal (dash), primary position (solid), and 10 degrees nasal (dot). Each line represents an individual trial.

Figure 2.8

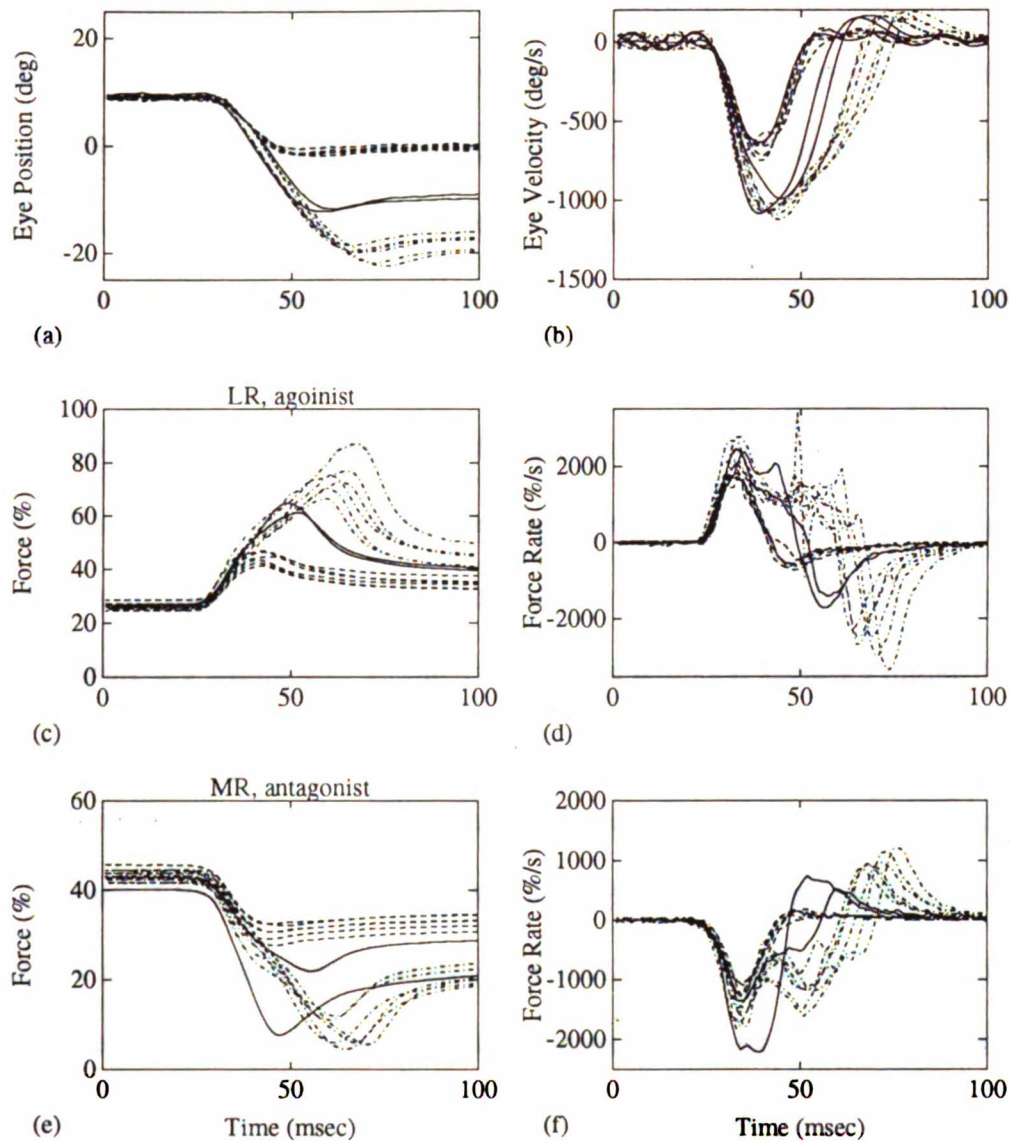
Figures 2.7 and 2.8 show the effect of initial position on saccade kinematics and force profiles. In general, the kinematics were not initial position dependent while the force profiles were position dependent or, more precisely, muscle length dependent. The following table is meant to help with the subsequent discussion by clarifying the muscles' relative lengths at different eye positions:

Fig. 2.7 shows eye kinematic and force profiles recorded during 10-degree temporal saccades initiated from different positions (LR agonist), and Fig. 2.8 shows similar profiles from 10-degree nasal saccades (MR agonist). The velocity profiles are similar

Table I. Relative muscle length as a function of eye position.

	Nasal	Primary Position	Temporal
Lateral Rectus	Long	Medium	Short
Medial Rectus	Short	Medium	Long

for all the temporal saccades (Fig. 2.7b). The agonist (LR) force profiles look like shifted versions of each other except during the saccades initiated from a shortened length, i.e., -10 degrees (Fig. 2.7c; dot). This is emphasized in the agonist force-rate records, which are nearly identical except during the saccades initiated from a shortened length (Fig. 2.7c; dot); these exhibit a higher peak force-rate and higher reversal peak than the other saccades. The antagonist (MR) force profiles show some variation with initial position (Fig. 2.7e). In addition to a general position dependent shift, the change in agonist force during the saccade is smallest for saccades initiated from primary



Effect of Saccade Magnitude on the Profiles: 10-, 20-, and 30-Degree Temporal Saccades Initiated from 10 Degrees Nasal. Eye position (a) and velocity (b), agonist (LR) force (c) and force rate (d), and antagonist (MR) force (e) and force rate (f) profiles recorded during temporal saccades of varying sizes initiated from the same position are shown: 10-degree (dash), 20-degree (solid), and 30-degree (dot-dash). Each line represents an individual trial.

Figure 2.9

position, resulting in a lower peak force-rate (Fig. 2.5e; solid).

During nasal saccades (Fig. 2.8), the velocity profiles are similar except for one of the two saccades initiated from 10 degrees (Fig. 2.8b). (Unfortunately, we cannot determine which of the two is more representative.) The agonist (MR) force-rate records (Fig. 2.8d) are similar for saccades initiated from -20 (dot-dash) and -10 degrees (dash), the force-rates are higher for saccades initiated from 0 degrees (solid), and they are even higher for those initiated from 10 degrees (dot). On the other hand, the antagonist (LR) force-rates are similar for all the nasal saccades with only a slight increase in maximum force-rate when the muscle is more stretched at saccade initiation (Fig. 2.8f). As the muscle length decreases beyond a threshold, the muscle generates more force during the same size saccade.

Figure 2.9 shows 10-, 20-, and 30- degree temporal saccades initiated from 10 degrees nasal. First, notice that the peak velocity for 20- and 30-degree saccades is about the same (Fig. 2.9b), i.e., peak velocity has saturated. Second, compare the agonist force (LR) and force-rate profiles (Fig. 2.9c,d respectively) with those recorded during 10- and 20-degree temporal saccades from 0 degrees (Fig. 2.4c,d). Although the agonist force-rate during 20-degree saccades does not actually plateau, it does show an extended period of positive force-rate; In addition, it does plateau during 30-degree saccades; however, it does not plateau at its peak rate. Instead, the force-rate peaks, begins to drop and then plateaus. In contrast, the force-rate plateaus at its peak during large saccades initiated from primary position (0 degrees). Therefore, the shape of the force and force-rate trajectories appears to have a distinct position dependency.

Net torque profiles have not been included in this section because they are calculated from absolute muscle forces, and absolute forces have not yet been estimated from the data. Net torque profiles are shown in Chapter 5.

4. Discussion

The data appear to be reliable, although they have not yet been verified in a second monkey. The eye and force profiles recorded from a particular initial position to a particular final position are, in most cases, quite repeatable. Peak velocity and duration as functions of saccade magnitude follow the expected main sequence. Even the temporal/nasal asymmetry exhibited in the position and velocity trajectories is commonly observed (Robinson, 1964; Fig. 2.3). Moreover, in spite of this asymmetry, general trends observed in nasal saccades are also observed in temporal saccades. (For examples see "Results".) Also, when the muscles and transducers were excised after the animal was euthanized, a thin layer of connective tissue had grown over the transducer, which probably helped keep the transducer properly aligned, and no scar tissue had built up around it (Miller & Robins, 1992). Overall, it appears that implanting the transducers did not significantly affect the system.

The symmetry in the agonist and antagonist force trajectories contradicts data recorded during human saccades in which the antagonist muscle showed an initial increase in force before it dropped (Collins et al., 1975). The increase was attributed to the force-velocity relationship of muscle, in which muscle force increases above

isometric force when the muscle is lengthening with a constant level of innervation. However, the data presented here suggests that the reported increase may be an artifact and the drop in innervation dominates in determining antagonist muscle force during the onset of the saccade. The force transducer used in the former experiment was in series with the tendons of the eye muscle (whereas ours were in parallel), which may have made the former transducer more susceptible to an artifact with the rapid onset of movement.

The symmetry between the agonist and antagonist force profiles is also surprising because of the reported differences in the force velocity relationship for lengthening muscle verses shortening muscle. First, the shape of the force-velocity relationship is different for shortening and lengthening muscle. In addition, forces recorded during isoinnervation experiments in which the muscle is stretched at constant velocity exhibit transient yielding (Joyce & Rack, 1969), while no similar effect is observed in shortening muscle. However, even though the eye is moving up to 1000 deg/sec, the antagonist muscle does not show any unusual transient behavior.

As expected, the monkey fixation data is consistent with human fixation data. When the data was scaled such that the minimum of the range of forces is 0% and the maximum is 100% and, then steady-state muscle force at primary position averaged about 32% of the total range of forces recorded in the monkey for saccadic eye movements within ± 20 degrees of primary position (Figs. 2.4,2.5); similarly, when the range considered was just fixation force, the steady-state muscle force at primary position was about 30% of the range of fixation forces recorded. Human data showed

the steady-state muscle force at primary position was about 20% of the range of *isometric* forces over the same range of positions, but the fixation force at primary position was about 30% of the range of fixation forces (extrapolated from Robinson et al., 1969). Although isometric forces were not recorded in this monkey for a direct comparison with human data, the monkey data is consistent with the human data. The finding that the range of forces is smaller during saccadic eye movements than during isometric recordings is expected because we know that the velocity-dependent, dissipative forces in muscles and orbit are high. Therefore, when the innervation is high during the high-velocity saccade, we wouldn't expect the muscle forces to approach maximum isometric forces, which do not have to overcome the large viscous forces. Moreover, the fixation forces themselves fall within the same range after one accounts for the difference in cross-sectional area of the monkey and human horizontal rectus muscles by scaling.

A characteristic of the data which was quite surprising was the large peak force (more properly, torque) acting on the orbit during saccades to extreme eccentric positions (± 20 degrees), i.e., a position dependent non-linearity. The peak force is considerably larger for these saccades than saccades of similar magnitude ending in less eccentric positions. (For example, compare the agonist force during 10-degree temporal saccades (Fig. 2.7) when initiated from 10 nasal (dash) versus 10 degrees temporal (dot).) This suggests the orbital mechanics are significant because the forces we are measuring are the external muscle forces acting on the globe not the internal muscle forces, which include the dissipative forces. (If one considers a Hill muscle model such

as that described in Chapter 1 or Chapter 3, a large internal force, or active state force, is generated to overcome large, internal, velocity-dependent forces within the muscle; however, the output of the model produces a much lower force. The data we record is equivalent to the output of the model, so the forces measured are what are driving the orbit.) As mentioned in "Results", peak agonist force (and torque) is reached after peak velocity is reached and prior to the end of the saccade. This peak is followed by a rapid decrease in agonist force (and torque) prior to the end of the saccade. After the eye reaches its final position, the muscle forces continue to change such that net torque continues to decrease. In this manner, the eye is fixed even though the orbital mechanics have not reached steady-state.

Moreover, the non-linearity is not symmetric with respect to primary position. The relationship amongst agonist force profiles for nasal saccades of one size from varying initial positions is different than the relationship amongst analogous profiles for temporal saccades. Considering only 10-degree saccades, with the MR as the agonist (Fig. 2.8), when the initial position is -10 degrees (i.e., the MR is stretched), peak force is only slightly larger than the initial fixation force; when the initial position is 0 degrees, peak force is larger; and when the initial position is 10 degrees, peak force is even larger. In contrast, with the LR as the agonist (Fig. 2.7) no such gradual progression is apparent. When the initial position is 10 (i.e., the LR is stretched) or 0 degrees, peak force is only slightly larger than the initial fixation force; when the initial position is -10 degrees, however, peak force is much higher. This could be due to differences between the medial and lateral recti (due to muscle properties or

innervation), to asymmetric orbital mechanics, or to the MR force transducer interfering with muscle shortening. If the muscles had the same properties and the orbit had symmetric mechanical properties, the increase in force during the saccade should occur at the analogous eccentricity (e.g., ± 10 degrees). However, if the orbital properties were asymmetric with respect to primary position and non-linear, then the MR agonist force, for example, would have to overcome an increasing orbital passive force earlier (at primary position, for example) than the LR would (-10 degrees). The orbital mechanics will be studied in Chapter 5. Note, however, that antagonist force profiles are also different for analogous temporal and nasal saccades (e.g. Figs. 2.4,2.5), which suggests that differences in muscle properties probably contribute this asymmetry.

Actually, there are several additional factors further complicating the picture, including our assumption about innervation. The firing pattern of a single neuron may not accurately represent muscle innervation by a population of neurons. For example, neuron recruitment and, therefore, muscle innervation vary as a function of eye position. As eye position moves from the muscle's off-direction (stretched) to the on-direction (contracted), the number of neurons firing during steady-state increases. At the same time the percentage increase from the steady-state firing rate to the burst firing rate is decreasing (Goldstein & Robinson, 1992). In addition, as the muscle contracts, the active force developed at a given level of innervation is decreasing due to the length-tension relation (see Fig. 2.1), i.e., for a slowly shortening muscle to remain at a constant force, the innervation must increase to compensate for the decrease in the muscle's ability to generate force. For the contracted muscle to hold the eye further in

the on-direction, recruitment and/or firing rate must increase the muscle activation enough to compensate for the length-tension relationship and the force of the displaced orbit.

The increase in recruitment and tonic firing rate that occurs as the eye moves further into the muscle's "on" direction (i.e., as the muscle shortens in contraction) appears well suited to compensate for the commensurate decrease in maximum force as the muscle shortens. However, an apparent contradiction arises with respect to the ability of the agonist muscle to generate more force during saccades initiated from shorter muscle lengths while the burst firing rate is increasing less relative to the tonic firing rate. If muscle force were directly proportional to firing rate, the difference between agonist peak force and initial force should be the smallest for saccades initiated from the shortest muscle lengths. One possibility is that muscle fiber recruitment compensates for this. The order (and significance) of fiber recruitment in extraocular muscle is not known (see Chapter 1 for more details); however, in other skeletal muscle, the larger, fast twitch fibers that are able to generate the most force are recruited last. Since the fast twitch fibers tend to develop more force, it appears possible that the relatively small increase in burst rate during saccades initiated when the agonist is already contracted may recruit additional fast twitch fibers that contribute a relatively large amount of force.

The data shows many interesting features that can best be further examined by turning to models of the system.

Do the Currently Accepted Models of the Horizontal Saccadic System Predict the Extraocular Muscle Forces Recorded During Saccades?

1. Introduction

Designing a model forces one to explicitly formulate ideas about how a system works. Models help us clarify our understanding of the relationship between different components and the role of different properties of the system. An additional advantage of models is that they can be used to predict the outcomes of untried experiments, which can be useful in designing future experiments.

The orbit and extraocular musculature involved in horizontal eye movements have been modelled by several researchers (Robinson, 1981). This eye movement subsystem was commonly studied from the perspective of classical control theory beginning in 1954 with Westheimer (Westheimer, 1954) and continuing into the early 1980's. Because all the relevant circuitry lies within the cranium, the neurophysiology can be studied directly. In addition, its structure is geometrically simple, with two muscles pulling the globe in opposite directions within a single plane. As a result, several models were developed with the same basic structure: two Hill-type models attached to a second order linear model of the orbit.

The research driving the development of these models was the measurement of

macroscopic muscle properties primarily in human strabismus patients (e.g., see Robinson, 1981, Collins, 1975), cats (Robinson, 1964, Collins, 1971), and monkeys (Fuchs & Luschei, 1971) and measurements of eye kinematics. In these studies the parameters of the mechanical models were measured including the passive muscle length-tension relation, the active muscle length-tension relation and the series elasticity in the Hill-type muscle model. (See Chapter 1 for more details.) In addition the inertia of the globe has was estimated and the elasticity and damping constants of the human orbit were estimated with the medial and lateral recti were detached.

This type of model could generate realistic saccade position, velocity and acceleration trajectories. Even so, with the available measurements, the model was still under-determined. With the advancement of technology and the resulting availability of bio-compatible materials, we can now chronically implant force transducers on each of the horizontal recti and subsequently measure the individual muscle forces during normal saccadic eye movements in the alert, behaving monkey. In light of the new data provided by these force transducers, we need to reexamine the existing models to see if they predict realistic muscle force records.

In this chapter, the predictions of a particular version of the Hill-type model of horizontal saccadic eye movements will be compared with eye position and muscle force profiles recorded during horizontal saccades. The model simulated was modified from one developed by Lehman and Stark (Lehman & Stark, 1979). Their model is several generations from the original conception (Cook & Stark, 1968, Clark & Stark, 1974, Hsu et al., 1976) and was chosen because it had been well analyzed and subjected to an

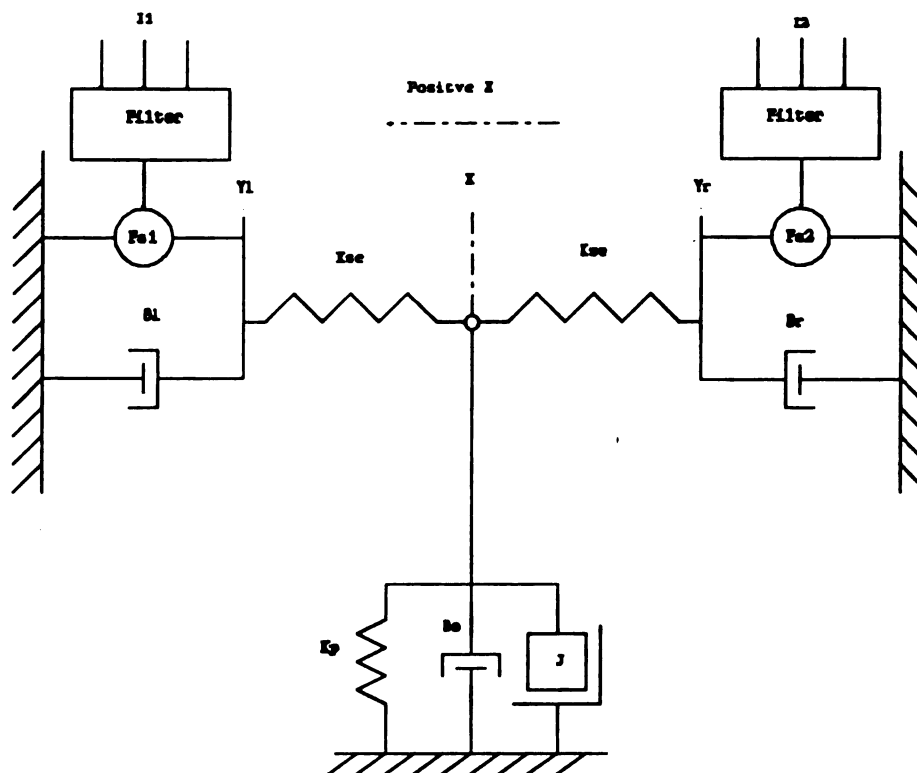
extensive sensitivity analysis. First, the model will be described in its original form, followed by a discussion of its merits and limitations. Next, the modifications that were made to convert it from a model of human saccades to monkey saccades will be presented. Then, after a brief description of the methods, a comparison of the model and the physiological system will be made. Finally, the implications of those results with respect to potential improvements to the model will be discussed.

2. Model of Human Horizontal Saccades based on Hill-type Muscle Models

2.1 Description

The model used in this study is shown in Fig. 3.1 (Lehman & Stark, 1979). It was generated from a model designed to accurately produce realistic position, velocity, and acceleration trajectories of human saccades initiated from primary position over a range of saccade sizes.

The orbital mechanics of the original model were estimated from human data. The globe was approximated by a rigid sphere of radius of 11 mm and density 1 g/ml, yielding a moment of inertia of $J = 4.3 \times 10^{-5} \text{ g-force sec}^2/\text{deg}$. The parameters representing the passive viscoelasticity of the orbit, $B_o = .015 \text{ gf sec/deg}$ and $K_p = .86 \text{ gf/deg}$, are the lumped effects of the optic nerve, orbital fat, the other extraocular muscles, other surrounding tissue, and the passive elasticity of the medial and lateral recti on the orbital mechanics.



Mechanical Model of Horizontal Saccadic Eye Movements. The mechanical circuit model simulated in this study is shown. The orbital mechanics and passive muscle elasticity are modelled as a second-order system consisting of an inertia (J), dashpot (B_0), and spring (K_p). Each muscle is modelled as a parallel combination of a force generator (F_{e1} , F_{e2}), which is a filtered version of the envelope of the assumed innervation (I_1 , I_2), and a non-linear dashpot (B_1 , B_2), which represents the force-velocity relationship of skeletal muscle; this combination is attached in series to a spring (K_{ee}). The eye position (x) is in degrees, and the hypothetical node of each muscle (y_l , y_r) is also in degrees. (This figure was modified from Lehman & Stark, 1979.)

Figure 3.1

The muscle properties were estimated from human extraocular muscles and from skeletal muscles in other animals. In addition, the medial and lateral recti were assumed to have identical properties. Muscle series elasticity was estimated from quick release experiments on human extraocular muscle, $K_{se} = 1.8 \text{ g/deg.}$. The force-velocity relationship was estimated from experimental work on skeletal muscle in other animals. It had been shown that tetanized muscle shows a hyperbolic force-velocity relationship during shortening, and the parameters describing the asymptotes of the hyperbola are related to the muscle's maximum rate of shortening (V_{max}) and maximum isometric force (F_0) (Hill, 1938), where $V_{max} = 3600 \text{ deg/s}$ was chosen. (See Chapter 1 for more detail on the force-velocity relation.) Moreover, the whole force-velocity relationship was assumed to scale with innervation.

Finally, the input to the muscle is assumed to be similar in shape to the envelope of the firing pattern of a single ocular motoneuron, i.e., pulse-step pattern (Robinson, 1970). The pulse duration was assumed to be half the duration of the saccade (pulse width); the pulse height is scaled non-linearly with saccade magnitude; and the step level is scaled with saccade magnitude. Finally, the innervation envelope is filtered and converted into an equivalent active state force.

The differential equations describing the model are as follows:

$$\begin{aligned}\frac{dx}{dt} &= v \\ \frac{dv}{dt} &= \frac{1}{J}(-K_p x - B_o v + K_{se}(y_L - x) - K_{se}(x - y_R)) \\ \frac{dy_L}{dt} &= \frac{1}{B_L}(F_{A1} - K_{se}(y_L - x)) \\ \frac{dy_R}{dt} &= \frac{1}{B_R}(-F_{A2} - K_{se}(y_R - x)) \\ \frac{dF_{A1}}{dt} &= \frac{1}{T_a}(I_1 - F_{A1}) \\ \frac{dF_{A2}}{dt} &= \frac{1}{T_a}(I_2 - F_{A2})\end{aligned}$$

where

$$\begin{aligned}B_L &= \frac{(F_{A1} + .25F_{A1})}{(b_H + \frac{dy_L}{dt})}, \quad \frac{dy_L}{dt} \geq 0 \\ &\quad \frac{3F_{A1}}{d_{len}}, \quad \frac{dy_L}{dt} < 0 \\ B_R &= \frac{3F_{A2}}{d_{len}}, \quad \frac{dy_R}{dt} \geq 0 \\ &\quad \frac{(F_{A2} + .25F_{A2})}{b_H + \frac{dy_R}{dt}}, \quad \frac{dy_R}{dt} < 0\end{aligned}$$

x ,	eye position [deg]
v ,	eye velocity [deg/s]
y_L, y_R ,	position of hypothetical nodes [deg]
F_{A1}, F_{A2}	"active state" i.e. hypothetical isometric force [gf]
I_1, I_2	Innervation to each muscle; pulse-step [equivalent gf]
B_L, B_R ,	muscle viscosity [gf sec/deg]

K_{se} ,	series elasticity 1.8 [gf/deg]
$J=2MR^2/5$	moment of inertia 4.3 e-5 [gf sec ² /deg];
M, mass; R, radius	
B_o ,	orbital viscosity .015 [gf sec/deg]
K_p ,	total passive elasticity .86 [gf/deg]
$T_s; T_d$	time constant of filter 13 [msec]
$b_H=V_{max}/4$,	constant defined by Hill; 900 [deg/s]
d_{len} ,	parameter scaling lengthening force-velocity relation; 900 [deg/s]

for 10 deg saccade: agonist pulse height = 60 gf; step height = (16 .8*size) gf, size =10
deg

antagonist pause height = 2 gf; step height = (16-.06*size) gf

pulse duration = 20 msec

2.2 A Discussion of the Merits and Limitations of the Model Based on the Data from which It Was Derived

The globe can be considered as a rigid sphere rotating about a fixed center in the head even though this is not truly accurate. The main effect of the rigid sphere assumption is on the estimation of the moment of inertia, which has been shown to be negligible anyway (Robinson, 1964). Also, the amount the center of rotation is translated is minimal. Although the data suggests the orbital mechanics are best represented by two series Voigt elements (parallel combinations of a spring and a dashpot) (Collins, 1971),

a sensitivity analysis of a similar version of the model showed that the orbital tissue was adequately modelled by a single Voigt element (Bahill, 1981); however, this was only considering the kinematics of the response, not the muscle forces; the validity of this conclusion will be further explored in Chapter 5. The linear approximation is probably good within ± 20 degrees of primary position (Robinson et al., 1969) as long as the vertical extraocular muscles do not affect this characteristic very much.

Several simplifications were made in deriving the muscle model that should be made explicit. First, the series elasticity was assumed to be represented by a linear spring even though the data suggests otherwise (Collins, 1975: shows stiffness varies with force resulting from both stretch and innervation); with activation and force varying significantly during a saccade it is possible that this non-linearity has a significant effect. Second, several aspects of the force-velocity relationship should be mentioned: 1) The estimate of the maximum velocity of shortening ($V_{\max}$) is difficult to make. If extrapolated from rat inferior rectus (25-30 lengths/s; Close & Luff, 1974), the estimate of $V_{\max}$ would be as high as 6000 deg/sec (Robinson, 1981). 2) The estimate that the force-velocity relation of shortening muscle scales with innervation is supported by data (Collins, 1971). 3) The lengthening relationship is known to be wrong because transient properties such as yielding, exhibited in real muscle (Joyce & Rack, 1969), are ignored in the model; however, the effect of the approximation on the resulting dynamics has not been explored. (4) Finally, the question of an appropriate representation of muscle activation is an open question. There are a lot of unknowns in estimating the activation because it reflects the population input and muscle fiber recruitment. (For more

explanation see Chapters 1 and 2.)

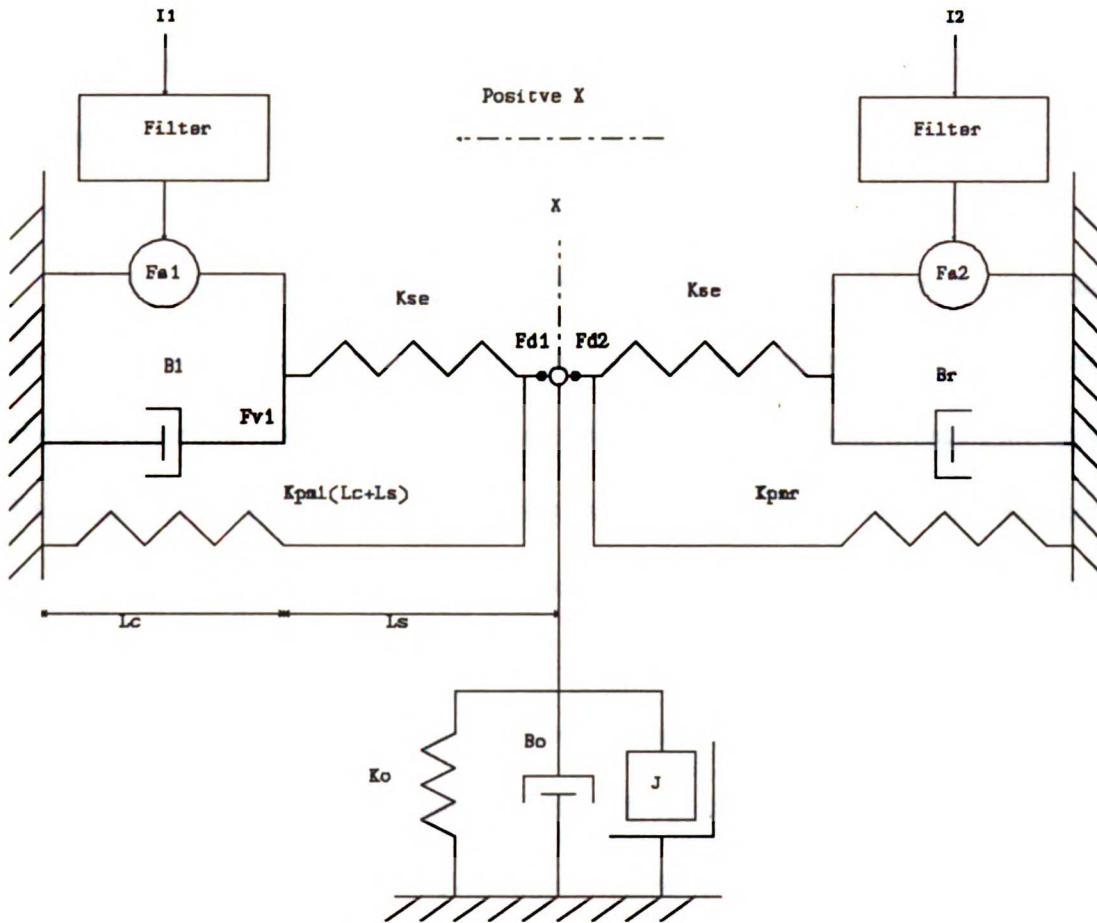
Although the model does not accurately reflect all the known biomechanics, it is a general representation of the properties thought to be most significant. Moreover, it does generate realistic position and velocity trajectories for human saccades, so it is a good starting point for this study.

However, to compare the forces recorded to those predicted by the model, we must divide the passive elasticity into its components, which consists of the passive muscle elasticities and the orbital elasticity (see Fig. 3.2) in parallel. The orbital elasticity has been measured in humans with the medial and lateral recti detached and was found to be .5 gf/deg (Robinson et al., 1969), which leaves .36 gf/deg for the net passive muscle elasticity. Although the individual passive muscle elasticities are non-linear, the nonlinearities tend to cancel each other such that the parallel combination is linear. However, to compare the individual force profiles predicted by the model with the data, the individual elasticities must be considered. The following equation was estimated to fit the passive length-tension curve shown in Fig. 1.8, it and was used to calculate the passive muscle force for the LR, while a symmetric equation was used to calculate the passive force for the MR:

$$F_p = a \cdot (x + 25)^2, x > -25^\circ$$

0, otherwise

F_p ,	passive muscle force [gf]
$a=.004$,	constant [gf/deg ²]
x ,	eye position (positive is nasal) [deg]



Modified Mechanical Circuit Model of Horizontal Saccadic Eye Movements for Comparison with Measured Monkey Force Data. This figure is modified from Fig. 3.1 to explicitly separate the passive elastic contribution of each muscle and the orbit i.e., K_p in Fig. 3.1 has been divided into three components consisting of the orbital elasticity (K_o), and passive muscle elasticities (K_{pm1} , K_{pm2}). In addition, the length of the contractile component (L_c) and the length of the series elastic element (L_s) are labelled. Finally, the nodes that represent the points at which force was experimentally measured are shown in the figure (F_{d1} , F_{d2}).

Figure 3.2

3. Model Modifications to Generate a Model of Monkey Horizontal Saccadic Eye Movements

To directly compare the force profiles predicted by this model to those recorded in the monkey we must convert the model based on human data to reflect the mechanics of the monkey musculature and orbit. In the monkey the extraocular muscles are shorter (20 mm Miller & Robins, 1987, human 40 mm Goldstein et al., 1989) and smaller in cross-sectional area (16.9 mm human Goldstein et al., 1989; 9 mm monkey Miller & Robins, 1987). Also, the globe is smaller (9.3 mm radius Miller & Robins, 1987, human 11 mm Collins, 1971) and the orbit may have different viscoelastic properties, but they probably have the same time constants (Collins, 1971: cat and human orbital mechanics have similar time constants). Finally, the monkey saccades are faster than the same size human saccades.

To compensate for these differences, the following parameter modifications were made. First, the passive muscle force was estimated from monkey data similar to that measured in humans (Fuchs, 1967). For the LR:

$$F_p^M = a^M * (x+25)^2, x, > -25^\circ$$
$$0, \text{ otherwise}$$

F_p^M , monkey passive muscle force [gf]

$a^M = .001975$, constant [gf/deg²]

x , eye position (positive is nasal) [deg]

This estimate is consistent with scaling the human force by cross-sectional area. Next, since muscle stiffness should increase with area (analogous to parallel springs) and decrease with length (analogous to series springs), the series elasticity was scaled from the human to the monkey; at the same time, it was scaled relative to the size of the globe:

$$K_{se}^M = K_{se}^H * \frac{A^M}{L^M} * \frac{L^H}{A^H} * \frac{R^H}{R^M}$$

$K_{se}^M = 2.3$	monkey series elasticity [gf/deg]
$K_{se}^H = 1.8$	human series elasticity [gf/deg]
$A^M = 9$	monkey cross-sectional area [mm ²]
$A^H = 16.9$	human cross-sectional area [mm ²]
$R^M = 9$	monkey globe radius [mm]
$R^H = 11$	human globe radius [mm]
$L^M = 20$	monkey muscle length [mm]
$L^H = 40$	human muscle length [mm]

V_{max} was scaled by muscle length and globe radius:

$$V_{max}^M = V_{max}^H * \frac{L^M * R^H}{L^H * R^M}$$

$V_{\max}^M = 2200$ monkey maximum velocity of shortening [deg/s]

$V_{\max}^H = 3600$ human maximum velocity of shortening [deg/s]

The moment of inertia was calculated for the radius of the globe (9.3 mm Miller & Robins, 1992):

$J^M = 2.88e-5$ monkey moment of inertia

The amount of tissue contributing to the orbital mechanics is expected to be less in the monkey than in the human. It was assumed that the tissue contributing to the elasticity was proportional to the surface area of the globe, so passive elasticity was scaled by the ratio of the surface areas of the globes and viscosity was scaled such that the time constant remained unchanged:

$K_o^M = .35$ monkey orbital passive elasticity [gf/deg]

$B_o^M = .01$ monkey orbital viscosity [gf sec/deg]

$K_p^M = .59$ monkey total passive elasticity [gf/deg]

(K_o^M and B_o^M will be discussed in Chapter 5 where the data will be used to derive them in a more complicated form. However, the parameters derived from a linear fit of all the data.)

Finally, because monkey saccades are faster, the input and filtering had to be changed:

pulse duration = $.5 * \text{saccades duration} = 12.5 \text{ msec (10-deg); } 20 \text{ msec (20-deg)}$

fixation forces and equivalent input were scaled by cross-sectional area (.5)

agonist step = $(8 + .55 * \text{size}) \text{ gf}$

antagonist pause = 1 gf; antagonist step = $(8 + .04 * \text{size}) \text{ gf}$

The agonist pulse and filter time constants were determined by simulation.

The motivation for studying eye movements in monkeys is that their eye movements are very similar to humans (Fuchs, 1967), but the animal preparation allows more invasive studies and better control of the experiments. Consequently, it may be hypothesized that the muscles work in a similar manner with respect to one another, and, therefore, should produce similarly shaped trajectories. There are some known differences between the geometrical structure of the monkey's and human's eye movement systems (Miller & Robins, 1987), but these are not considered in a model this simple.

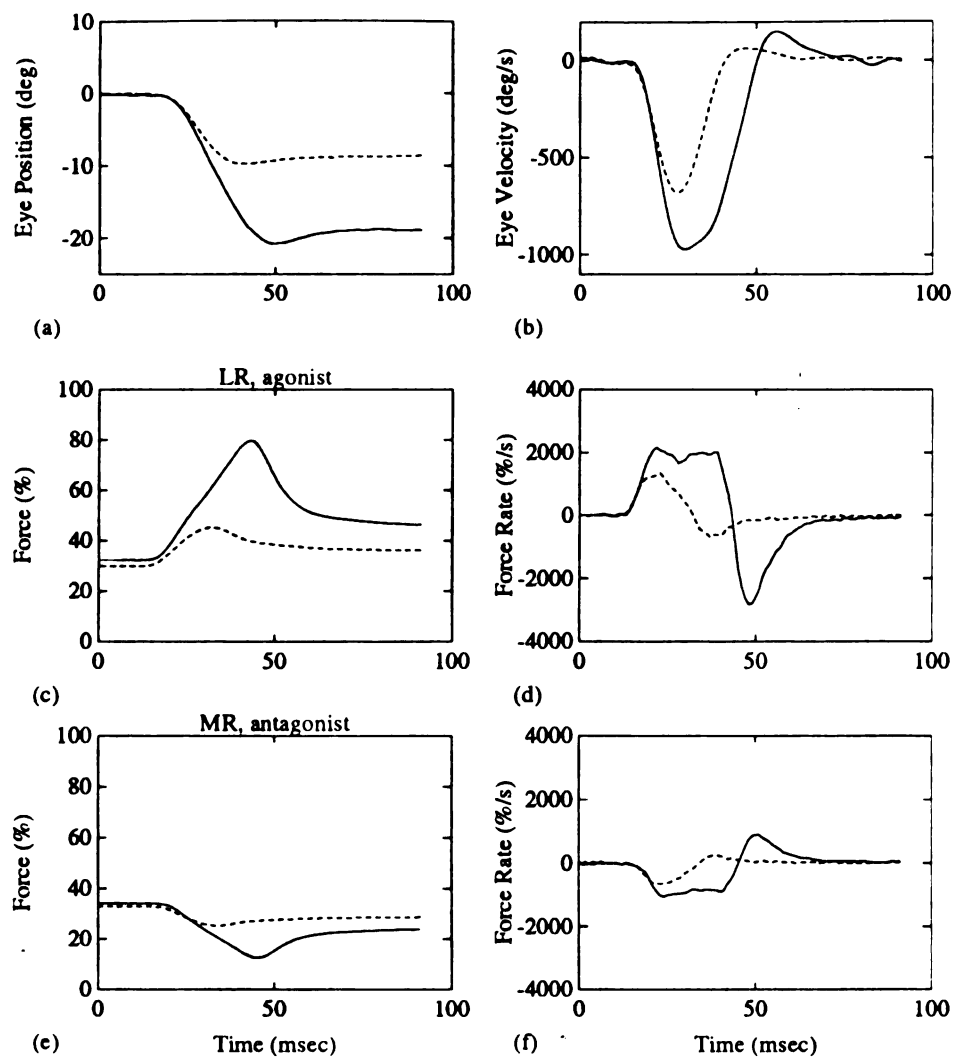
4. Methods

The methods for obtaining the physiological data were described in Chapter 2.

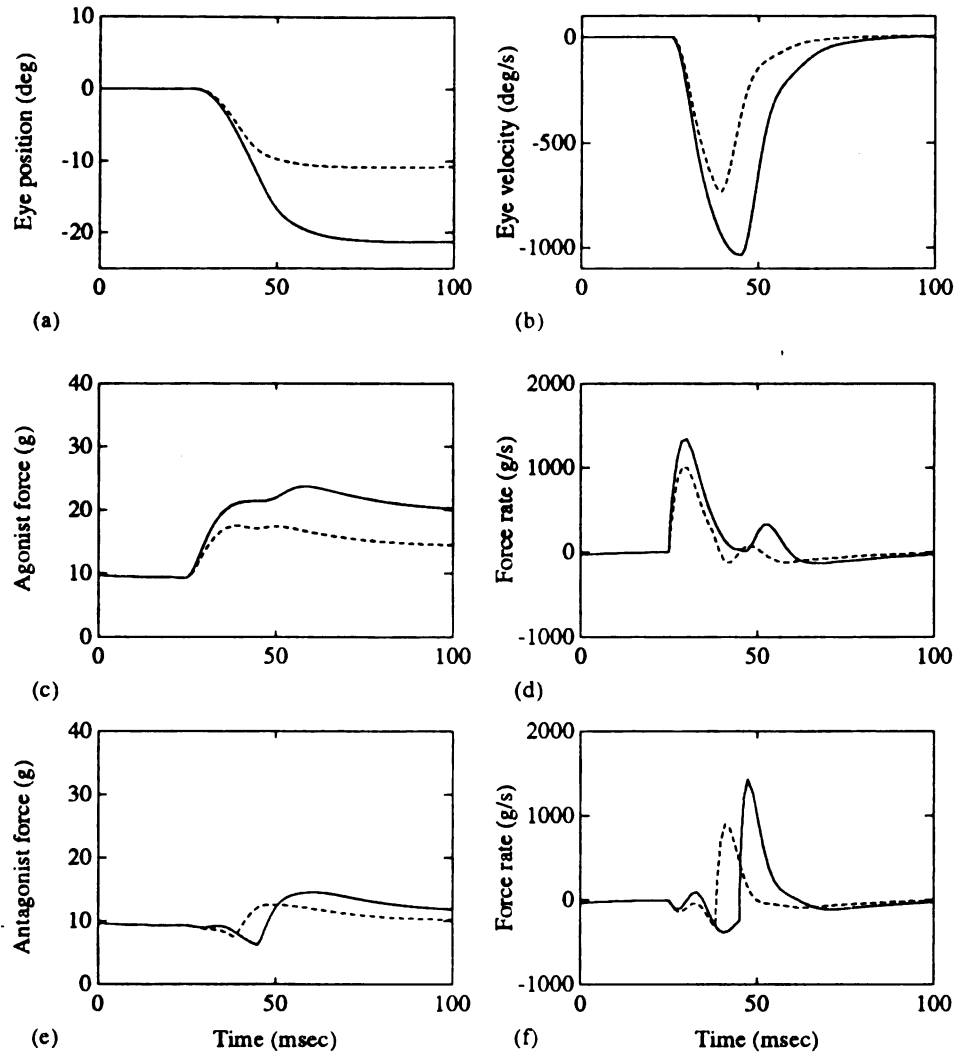
The previously described model of human saccadic eye movements was simulated with Simnon, a non-linear dynamic systems simulation package (Åström, 1982). Most of the parameters used for the monkey saccade model were given in section 2.3, with the following exceptions: filter time constants = 7 msec (trial and error); for 10 degree saccades, pulse height = 65 (trial and error), pulse duration = 12.5 msec (half saccade duration); for 20 degree saccades, pulse height = 120 (trial and error), pulse/pause duration = 20 msec (half saccade duration); the parameters were adjusted so the model generated saccades of the appropriated magnitude with a peak velocity within the range observed in the recorded data (see Chapter 2).

5. Comparison of Simulated and Measured Force Profiles

Fig. 3.3 shows experimentally measured eye position and velocity profiles, agonist force and force rate profiles, and antagonist force and force rate profiles recorded during a 10- (dashed) and a 20-degree (solid) saccades. The actual forces exerted by the muscles have not yet been estimated because the shapes of the trajectories are adequate for the comparisons being made in this chapter. (This estimate will be discussed in Chapter 4.) Fig. 3.4 shows the trajectories generated by simulations of the model of monkey saccadic eye movements, and Fig. 3.5 shows a comparison of the data and model force profiles. The most obvious feature found in the experimental records is the qualitative symmetry in the shape of the agonist and antagonist force trajectories in the actual muscle. In contrast, the simulated force profiles show a definite asymmetry between agonist and antagonist trajectories. In conclusion, in spite of generating reasonable position and velocity profiles, the model does not generate realistic force profiles.

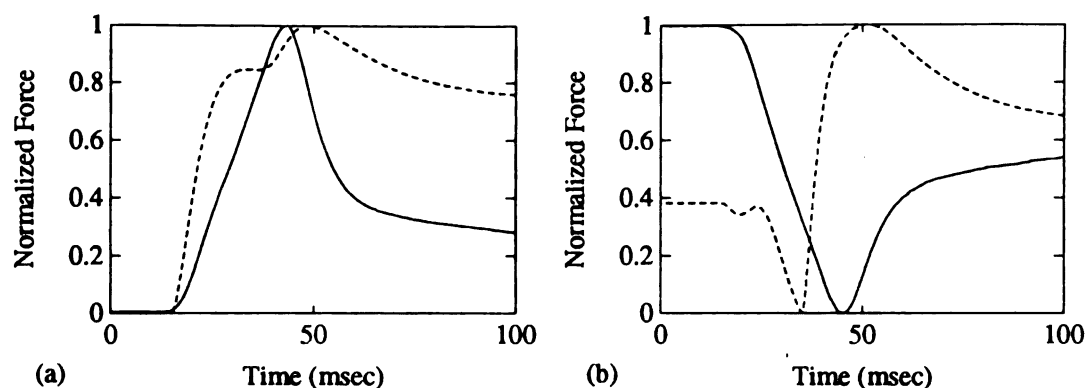


Trajectories Recorded from a Monkey During Horizontal Saccadic Eye Movements. Eye position (a) and velocity (b), agonist force (c) and force rate (d), and antagonist force (e) and force rate (f) recorded during a 10- (dash) and 20-degree (solid) saccade initiated from primary position.



Trajectories Generated by the Model of Monkey Saccadic Eye Movements. Eye position (a) and velocity (b), agonist force (c) and force rate (d), and antagonist force (e) and force rate (f) generated by the monkey saccade model for 10- (dash) and 20-degree (solid) horizontal saccades.

Figure 3.4



Comparison of Normalized Force Profiles from Data and Model.

Normalized agonist (a) and antagonist (b) force profiles from data (solid) and model simulations (dash) for a 20-degree temporal saccades initiated from primary position.

Figure 3.5

6. Conclusions

In its present form, the model does not accurately reflect the dynamics of the extraocular muscles during horizontal saccadic eye movements. This could be due to errors in the model of the globe, the model of the muscles, and/or the model of innervation. With the experimental data, the model of the globe can be independently examined by calculating the net torque operating on the globe and deriving the mechanical properties of the orbit; this will be the subject of Chapter 5. The muscle model will be examined in Chapter 4.

Modelling the Mechanics of Extraocular Muscle: Hill-type and Distribution Moment Muscle Models

1. Introduction

For a muscle model to be useful in studies of movement on a macroscopic scale, the model (1) should not require too much computation time and (2) must accurately represent the characteristics of whole muscle during movement. Hill-type models are commonly used because they easily satisfy the first requirement and, to some extent, satisfy the second. However, the model does not exhibit known transient properties of lengthening muscle such as yielding. For this reason, it may not be a useful representation for high velocity movements, which, presumably, exhibit transient characteristics to the greatest extent. This provides the motivation for more closely examining the ability of the muscle model to exhibit the dynamics of extraocular muscle during saccadic eye movements.

Another muscle model, the distribution moment (DM) model (Zahalak, 1990), was simultaneously studied for comparison purposes because it does exhibit some of the transient properties of lengthening muscle, while remaining computationally feasible. The DM model is based on the molecular mechanism of contraction rather than a functional representation of macroscopic muscle properties.

The derivation of the Hill-type model for monkey extraocular muscle was

described in Chapter 3 (modified from Lehman & Stark, 1979), while the derivation of the DM model for extraocular muscle will be described later in this chapter.

The approach taken to compare the models was to calculate the input necessary to generate the recorded force trajectories, given the muscle length and velocity derived from the recorded eye position. It is important to recognize that the inputs to the two models cannot be directly compared because the input to the Hill model is active state and the input to the DM model is activation of cross-bridge sites. However, they can be compared with respect to the types of single-unit firing patterns from which they could be derived. In this chapter, the methods used to estimate absolute force from the force measurements and to simulate the models will be described first. Next, the derivation of the DM model for monkey extraocular muscle will be described, followed by some simulation results. Then, the Hill model for monkey extraocular muscle will be reintroduced and simulation results will be presented.

2. Methods

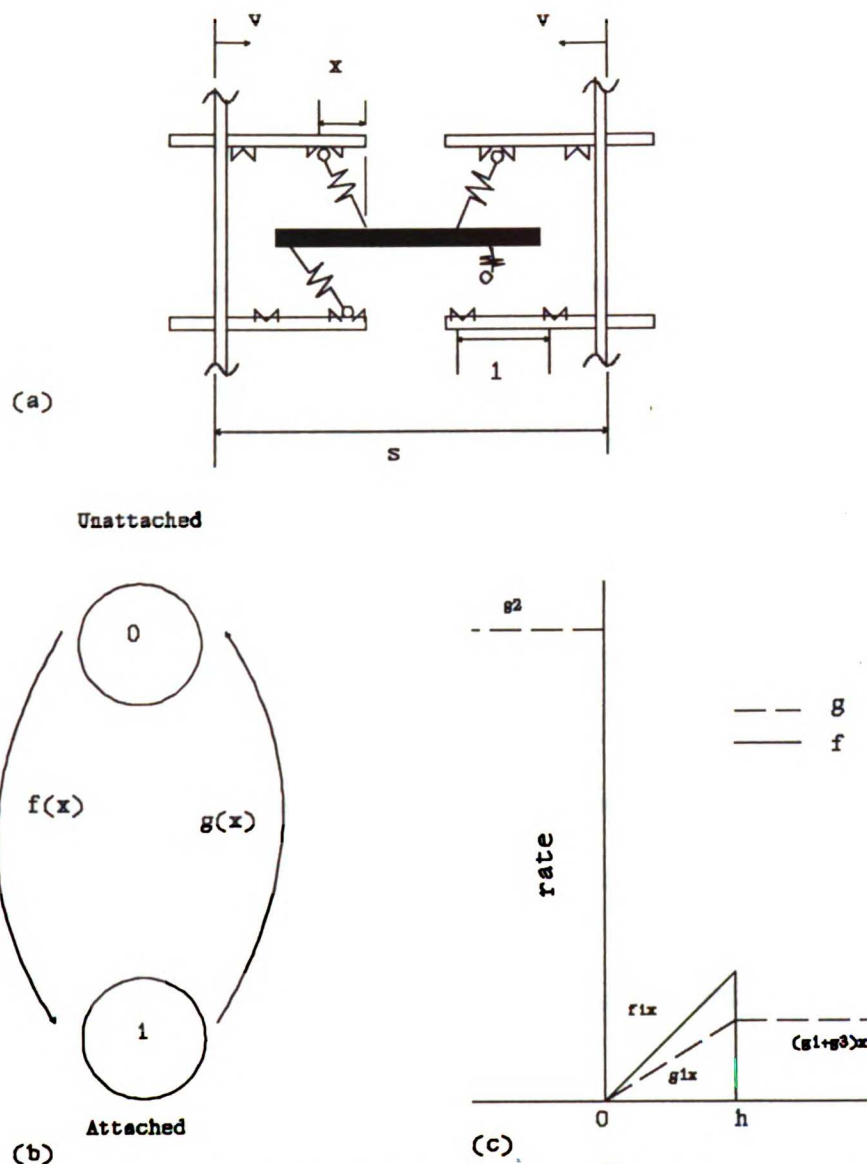
The methods for collecting the physiological data were described in Chapter 2.

Before the data could be used with the simulations, actual muscle force had to be estimated from the recorded data. Because the amplifiers were modified during the course of the experiments, we could not directly compare the original calibrations to the recorded data to determine absolute forces. Instead, we estimated force in the following manner: first, we assumed that the forces at primary position and the range of forces

generated during each session were the same in the LR and MR. In humans, some data suggests the MR may exert higher forces than the LR, which suggests this assumption may be inaccurate (Collins et al., 1981); however, other data supports the assumption (Collins et al., 1975, Collins, 1975). As of this time, the issue has not been explored in monkeys, so we will make the above assumption. Second, we assumed the force developed in monkey extraocular muscle could be estimated by scaling the force developed in human extraocular muscle by the ratio of cross-sectional areas of the two muscles. To this end, we noted that the monkey fixation force at primary position corresponded to 32.5% of the total range of forces recorded in the monkey, i.e., the minimum force measurement was considered 0% and the maximum 100%. Then we noted that the human fixation force at primary position in the LR is, on average, about 13.7 gf (Robinson et al., 1969). Moreover, the ratio of monkey to human cross-sectional area is about 0.57 (.0965 cm² monkey, Miller & Robins, 1987; .169 cm² human, Goldstein et al., 1989). Therefore, we assumed 32.5% corresponded to 7.8 gf (7800 dynes) and scaled the force data accordingly. This derivation was based on three observations. First, the force developed by muscles with the same fiber composition scales by cross-sectional area (for a given level of innervation). Second, the maximum active isometric force for monkey and human LR scale approximately the same as cross-sectional area (Fuchs & Luschei, 1971, 55 gf monkey; Collins, 1975, 100 gf human). Finally, we noted that the position dependent fixation forces recorded in our monkey scaled relative to each other just as those fixation forces recorded in the human

extraocular muscle scaled relative to each other (see Chapter 2). These observations suggest our force estimates are probably realistic.

The Hill-type model of monkey extraocular muscle described in Chapter 3 and the DM muscle model described in the subsequent section were studied. For simplicity, the passive elasticity was assumed to be zero in both models even though it makes a small contribution at the extremes of the eye movements explored (± 20 degrees). The inverse models were simulated using Borland C/C++ (). Recorded force and position records were used as input and the optimal muscle activation profiles were calculated using a modified version of "brent.c" optimization algorithm from Numerical Recipes in C (Press et al., 1988). The optimization was checked by running forward simulations with the calculated activation and the recorded position as input and verifying that the model forces matched the recorded forces. The parameters used in the simulations were the same as those described in the text except where specified. (For example, some variations of the lengthening force-velocity relation were used with the Hill model, which will be described in a subsequent section.) Also, the optimal active state in the Hill model was calculated instead of the unfiltered input described in Chapter 3.



Schematic of the Cross-bridge Model of Muscle Contraction. (a) shows a schematic of cross-bridges in a sarcomere. A myosin filament is represented by the thick line and actin filaments are represented by the thin lines. Cross-bridge sites are represented by balls attached to the myosin filament by springs. Actin sites are represented by two triangles. The figure shows both attached and unattached cross-bridges. "x" reflects the length of an attached spring; "v" is the velocity; "l" is the distance between actin sites; and "s" is the sarcomere length. (b) shows the two-state model of cross-bridge formation, and (c) shows the rates of attachment and detachment as a function of "x".

Figure 4.1

3. Derivation of DM Model for Monkey Extraocular Muscle

3.1 Model Description

As discussed in Chapter 1, Zahalak's DM muscle model is an approximation to Huxley's 1957 cross-bridge model of sarcomere contraction. Figure 4.1 shows a schematic of the model. A single cross-bridge is represented by a spring and the force developed is proportional to the length (x) of the spring. If one knows the distribution of cross-bridge bond lengths ($n(x,t)$) in the sarcomere and the number of cross-bridge sites, one can calculate the force developed in the sarcomere. Huxley assumed a simple two state model of cross-bridge formation (attached state, detached state). When partial activation and myosin/actin filament overlap is also considered, the following partial differential equation describes the rate of change of the bond distribution:

$$\frac{\partial n(x,t)}{\partial t} - v(t) \frac{\partial n(x,t)}{\partial x} = f(x)(\alpha(t)c(s(t)) - n(x,t)) - g(x)n(x,t)$$

$n(x,t)$,	bond distribution
$v(t)$,	velocity of shortening
$f(x)$,	rate of bond attachment
$g(x)$,	rate of bond detachment
$\alpha(t)$,	fraction of cross-bridge sites activated
$c(s(t))$,	fraction of sites in region of actin/myosin filament overlap
$s(t)$,	sarcomere length

(Note that both the activation (α) and the cross-bridge overlap (c) scale the fraction of cross-bridge sites that are available.) Through mathematical manipulation, this partial differential equation can be rewritten as an infinite series of ordinary differential equations of the moments of the bond distribution. Zahalak assumed the bond distribution could be described by a Gaussian, which is completely described by its first three moments. Consequently, the infinite series of differential equations was reduced to three differential equations (see Chapter 1). If we normalize these equations by h (the maximum length at which a cross-bridge can be formed) we arrive at the following equations:

$$\xi = \frac{x}{h}, \quad Q_\lambda = \frac{M_\lambda}{h^{\lambda+1}}, \quad \beta_\lambda = \frac{b_\lambda}{h^{\lambda+1}}, \quad u = \frac{v}{h},$$

$$p = \frac{\mu}{h} = \frac{Q_1}{Q_0}, \quad q = \frac{\sigma}{h} = \sqrt{\frac{Q_2}{Q_0} - \left(\frac{Q_1}{Q_0}\right)^2}$$

$$\phi_\lambda = \frac{F_\lambda}{h^{\lambda+1}} = \int_{-\infty}^{\infty} \xi^\lambda [f(\xi) + g(\xi)] n(\xi, t) d\xi$$

$$\text{with } n(\xi, t) = \frac{Q_0}{\sqrt{2\pi}q} e^{-\frac{(\xi-p)^2}{2q^2}}$$

$$\frac{dQ_\lambda}{dt} = \alpha(t)c(s(t))\beta_\lambda - \phi_\lambda(Q_0, Q_1, Q_2) - \lambda u Q_{\lambda-1}, \quad \lambda = 0, 1, 2.$$

h , maximum distance over which a cross-bridge can form [cm]

M_0, M_1, M_2 , first three moments of the distribution $n(x, t)$

μ , mean of Gaussian $n(x, t)$

σ , standard deviation of Gaussian $n(x, t)$

$s(t)$, sarcomere length at time t

where

$$\begin{aligned} \text{force} &= \frac{ms_{pp}k}{2l} \int_{-l}^l xn(x,t)dx \\ &= \frac{ms_{pp}kh^2A_{pp}}{2l} Q_1 \\ \epsilon &= \frac{ms_{pp}kh^2A_{pp}}{2l} \end{aligned}$$

m ,	# cross-bridge sites/[cm ³]
s_{pp} ,	sarcomere length in reference state (primary position) [cm]
k ,	cross-bridge spring constant [dyne/cm]
l ,	distance between actin binding sites [cm]
A_{pp} ,	cross-sectional area in reference state [cm ²]
ϵ ,	coefficient of Q_1 that generates force

and f and g defined as follows:

$$\begin{aligned} f(\xi) &= \begin{cases} 0, & \xi < 0, \\ f_1 \xi, & 0 < \xi < 1, \\ 0, & 1 < \xi, \end{cases} \\ g(\xi) &= \begin{cases} g_2, & \xi < 0, \\ g_1 \xi, & 0 < \xi < 1, \\ g_1 \xi + g_3(\xi - 1), & 1 < \xi \end{cases} \end{aligned}$$

f ,	rate of attachment [s ⁻¹]
g ,	rate of detachment [s ⁻¹]

Also note that maximum isometric force at a particular length is give by the following equation found by solving the partial differential equation for steady-state, zero velocity condition:

$$\max force(x) = \frac{ms_{pp}kh^2A_{pp}}{2l}c(x)\frac{f_1}{f_1+g_1}$$

There are also several factors involved in converting eye velocity to the normalized sarcomere velocity:

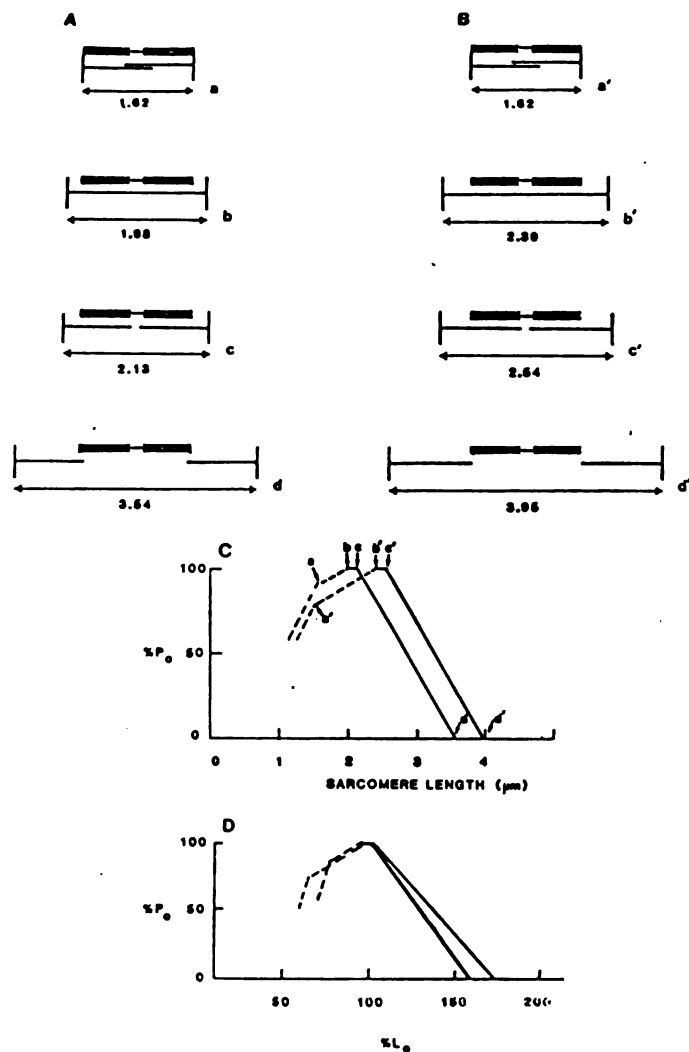
$$v = \frac{dE}{dt} \frac{\gamma}{2n_s} SGN$$

$$u = \frac{v}{h}$$

$$\text{where: } \gamma = \frac{2\pi R}{360}$$

$$SGN = \begin{matrix} 1, & \text{for medial rectus} \\ -1, & \text{for lateral rectus} \end{matrix}$$

v ,	velocity of half-sarcomere [cm/s/half-sarcomere]
n_s ,	# of sarcomeres in 1 myofibril running the length of the muscle
u ,	normalized velocity [actin sites/s/half-sarcomere]
R ,	radius of globe [cm]
γ ,	conversion from degrees to cm [cm/deg]
SGN ,	convert sign of velocity to positive for shortening muscle
dE/dt ,	eye velocity



Comparison of the Sarcomere Length-Tension Curves in Amphibian and Mammalian Skeletal Muscle. Schematic for the relative overlap of actin and myosin filaments at different sarcomere lengths at which the slope of the tension-length curve would be expected to change in (A) frog muscle and (B) rat muscle. The small letters in (A) and (B) correspond to the letters in (C) and (D). (C) and (D) Comparison of the predicted length-tension relation of frog and rat muscle as a function of length and as a percentage of L_0 , respectively. (From Woledge et al., 1985.)

3.2DM Parameter Derivation for Extraocular Muscle

The parameters were derived mostly from extraocular muscle data, and, wherever possible, from monkey extraocular muscle data; however, several estimates were made from studies on other skeletal muscle. Some parameters were measured directly, some calculated from measured parameters, some estimated to be consistent with measured muscle properties, and, finally, some were estimated by trial and error in simulation. All parameters estimated by simulation were estimated for one saccade trajectory and then tested with other trajectories.

The cross-bridge overlap function was estimated from the length-tension curves of human LR (see Fig. 1.8;) and the sarcomere length-tension curve of mammalian muscle (Fig. 4.2). Figure 4.2 shows the length-tension relationship of a single sarcomere and the corresponding extent of myosin/actin filament overlap in amphibian (A, frog) and mammalian muscle (B, rat). If all sarcomeres are assumed to be identical, then the plateau phase of the whole-muscle length-tension curve should correspond to the plateau region in the sarcomere length-tension curve. Comparing the sarcomere length-tension curve of mammalian muscle with the active length-tension curves for human extraocular muscle (Fig. 1.8 dash lines; Robinson et al., 1969) suggests that about 25 degrees extension beyond primary position corresponds to a sarcomere lengths about 2.39 μm , i.e., the corresponding points where the curves flatten. In addition, if the active

length-tension curves are extrapolated to intersect with the muscle length axis, it appears that they would cross at about -80 degrees (rough estimate). This would suggest that -80 degrees corresponds to about .7 μm (extrapolated from curve in Fig. 4.2c). Moreover, a curve describing the relative amount of actin/myosin overlap, i.e., the length-tension curve, can be defined in terms of sarcomere length, muscle length, or degree equivalent of muscle length (since we are only considering horizontal saccades in the plane containing primary position). For simplicity, this curve will be approximated by a linear curve from zero (no overlap) at -80 degrees (.7 μm) to one (100% overlap) at 25 degrees (2.39 μm); since we are only considering saccades from -20 to 20 degrees, we are not concerned with the rest of the curve. The resulting function for the LR follows:

```

if (eye < -80) then    ce(eye) = 0.0
else if (eye < 25) then ce(eye) = 0.0095(eye + 80)
else                  ce(eye) = 1.0

```

eye, eye position relative to primary position [deg]

c_e(eye), cross-bridge overlap function [1/1]

or (for both the LR and MR):

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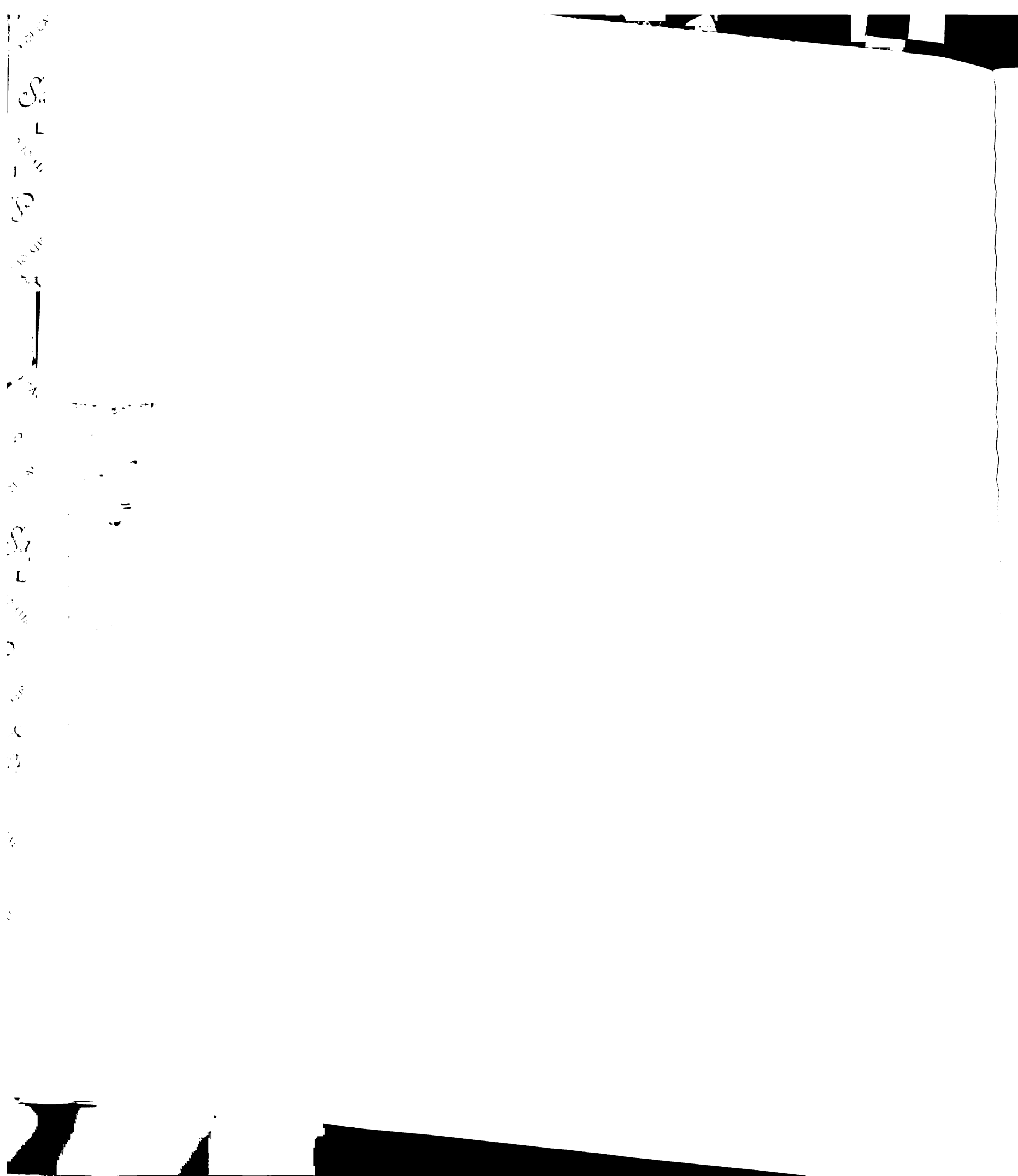
if (slen < .7  $\mu\text{m}$ ) then    cs(slen) = 0.0
else if (slen < 2.39  $\mu\text{m}$ ) then cs(slen) = 5917(slen - .7)
else                      cs(slen) = 1.0

```

s_{len}, sarcomere length [μm]

c_s(s_{len}), cross-bridge overlap function [1/1]

The partially innervated active length-tension curves of whole muscle are calculated by



scaling the whole length-tension curve by the level of innervation.

The following parameters were measured or calculated directly from measured parameters (when available plus/minus one standard deviation is included):

$L_{pp} = 1.985 \text{ cm}$ muscle length at primary position (pp); (monkey:

$1.97 \pm .04 \text{ cm LR}$, $2.00 \pm .21 \text{ cm MR}$, which we assumed to be close to primary position values; Miller & Robins, 1987)

$A_{pp} = .0965 \text{ cm}^2$ muscle cross-sectional area at pp (monkey: $.0104$

$\pm .0005 \text{ LR}$, $.0089 \pm .0018 \text{ MR}$, which we assumed to be close to primary position values; Miller & Robins, 1987)

$s_{pp} = 1.98e-4 \text{ cm}$ sarcomere length at pp (estimated from cross-bridge

overlap function that is described above. First, the correspondence of the cross-bridge overlap function with the data is verified for primary position:

$$c_s(pp) = .76 \approx (\text{max iso. force at pp})/(\text{max iso. force}) = 78\text{gm}/100\text{gm} = .78$$

Then the value s_{len} is calculated such that $c_s(s_{len}) = .78$

$R = .93 \pm .05 \text{ cm}$ radius of globe (monkey; Miller & Robins, 1987)

$m = 5.7e16 \text{ molec/cm}^3$ cross-bridge sites per unit volume (frog sartorius: assumed to be the same as the number of myosin molecules per unit volume; Huxley, 1957)

$F_0 = 55 \text{ g (53900 dyne)}$ max. active isometric force (monkey LR, Fuchs &

[Faint, illegible markings and bleed-through from the reverse side of the page are visible.]

Luschei, 1971)

$F_{opp} = 45 \text{ g (44100 dyne)}$ max. active isometric force (monkey LR, Fuchs & Luschei, 1971)

$P_0 = 670 \text{ g/cm}^2$ maximum force/area of extraocular muscle (range 664-678 cat, Robinson, 1964. Moreover, it is within the right range to be consistent with the cross-sectional area and maximum active isometric force, i.e., $P_0 * A_{pp} * c_e(pp) = 49 \approx 45$)

$SV_{max} = 25 \text{ lengths/sec}$ maximum velocity of shortening (estimated from rat inferior rectus, assuming sarcomere length of $2.39 \mu\text{m}$; Close & Luff, 1974 (compare to estimate from rat extensor digitorum longus, assuming sarcomere length of $2.5 \mu\text{m}$ used in derivation of hill model, which leads to an estimate of 20 lengths/sec Close & Luff, 1974))

$n_s = L_{pp}/s_{pp} = 10025$ number of sarcomeres in series

$\gamma = .0162 \text{ cm/deg}$ conversion factor: degrees to cm

$V_{max} = SV_{max} L_{pp}/\gamma = 3070 \text{ deg/s}$ maximum velocity of shortening

$h = 1.85 \text{ e-6 cm}$ maximum distance over which a cross-bridge can form. Model assumption: $h \ll l$ (Huxley, 1957). (This value of h is the average of two estimates in the literature, $h = 1.0\text{e-6}$ (Huxley, 1957) and $h = 2.7\text{e-6}$ (Woledge et al., 1985).)

$u = SGN * dE/dt * \gamma / (2 * n_s * h)$ normalized velocity

$= SGN * dE/dt * .437 \text{ actin sites/s/half-sarc}$

$e = 7\text{e-13 erg/molecule}$ energy per cross-bridge cycle



$w/e = .8$ efficiency of cross-bridge cycle: the ratio of work to energy. (As Huxley mentioned, this value must be less than 1 and he chose a value of .75 (Huxley, 1957). The value chosen here is slightly higher because it led to a higher estimate of g_1 (see discussion of g_1), while remaining close to Huxley's estimate.)

$a_H/P_0 = .5$ dimensionless ratio described by Hill (see Chapter 1), where a_H partially characterizes the force-velocity relationship of shortening muscle. (In Huxley's derivation of the model he used $a_H/P_0 = .25$, which is the value for frog muscle (Huxley, 1957). This ratio varies for different muscles from less than .1 to .5, and the value correlates with V_{max} (Woledge et al., 1985). Since V_{max} is very high for extraocular muscle, the upper limit was chosen for this value.)

$b_H/V_{max} = .33$ dimensionless ratio described by Hill (see Chapter 1), where b_H partially characterizes the force-velocity relationship of shortening muscle. (In Huxley's derivation of the model he used $b_H/V_{max} = .25$, which is the value for frog muscle (Huxley, 1957). This ratio varies for different muscle from less than .1 to .5 with many muscles clustering about one-third (Woledge et al., 1985). The ratio was arbitrarily chosen to be one-third.)

$g_1 = 425$ 1/s agonist; 220 1/s antagonist rate of cross-bridge detachment (see Fig. 4.1c). (First, the derivation of the agonist rate will be described. g_1 was chosen to satisfy Hill's result that the maintenance heat, E_0 (see Chapter 1) equals $a_H b_H$. E_0 is derived from the cross-bridge

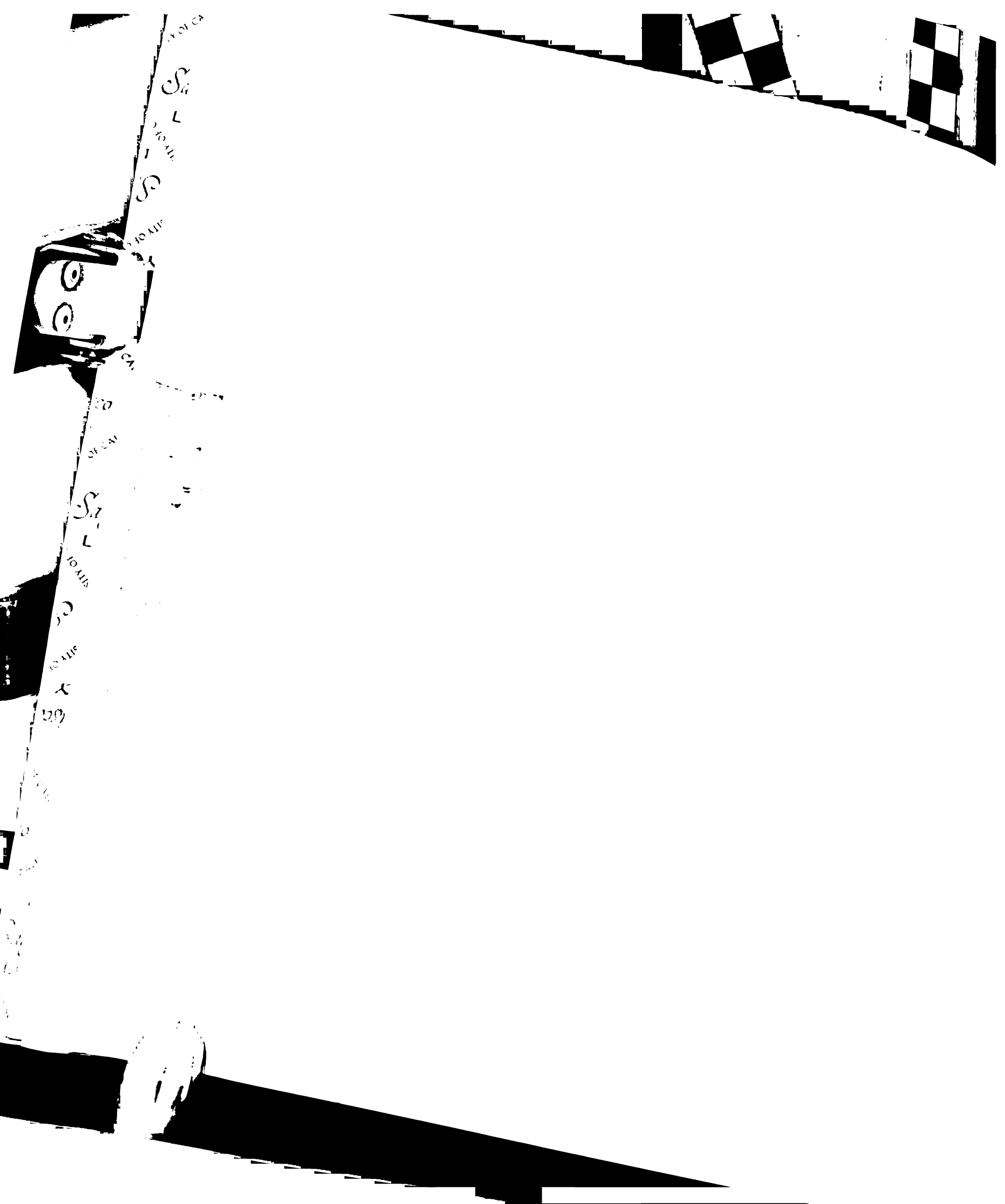
$$E_0 = \frac{mehg_1}{2l} \frac{f_1}{f_1 + g_1} \approx a_H b_H = \frac{P_0 V_{\max}}{6}$$

$$\text{Recall: } P_0 = \frac{mskh^2}{4l} \frac{f_1}{f_1 + g_1} = \frac{msw}{2l} \frac{f_1}{f_1 + g_1}$$

model. Substituting for P_0 in the equation for E_0 and solving for g_1 yields:

$$g_1 = \frac{V_{\max} w}{6h e}$$

w/e was chosen to be .8 instead of .75 because it led to a slightly higher estimate of g_1 , and simulations suggested that a higher g_1 was desirable for the agonist muscle. Different parameters were needed for agonist and antagonist muscle. A relatively large g_1 is needed to allow the agonist force rate to decrease rapidly after peak force is reached. If g_1 is too low, muscle activation has to decrease more rapidly and to a larger extent to compensate for the slow rate of detachment; as a result, agonist muscle activation dips well below the final steady-state activation level (pulse-



negative pulse- step), which contradicts the observed pulse-slide-step firing patterns of ocular motoneurons. (See Chapter 1 for details on innervation during saccades and motor unit behavior). In contrast, in the antagonist muscle, if g_1 is too high, then muscle activation must decrease slowly throughout most of the saccade instead of "turning off" in the pause-slide-step pattern of ocular motoneurons. The use of different detachment rates for agonist and antagonist muscles is consistent with our basic understanding of extraocular muscle. The large fast fibers are thought to dominate force generation in the agonist muscle (even though all fibers contribute). In contrast, at the low levels of innervation in the antagonist muscle, the slow fibers are believed to contribute a much larger proportion of the force; moreover, slow fibers have a slower rate of decay, which, presumably, corresponds to a lower rate of cross-bridge detachment and would, therefore, be the limiting factor in the rate at which the antagonist muscle force decreases during a saccade. Note that a better representation would be to model both components of the muscle (slow and fast) and assume a recruitment scheme, so there would be a smooth transition between muscle properties dominated by slow fibers and those dominated by fast fibers. However, modelling the agonist and antagonist muscles separately with representative parameters serves the basic purpose in a much more simple manner. Also note that a lower g_1 would result from a lower a_H/P_0 .)



$l = 3.75 \text{ e-6 cm}$ distance between cross-bridge sites (An estimate of 3.5e-6 (2906) was originally chosen. However this led to an estimate of f_1 that was less than two times g_1 (see discussion of f_1). As a compromise between overestimating l and underestimating f_1 relative to g_1 , the above value for l was chosen.)

$f_1 = 950 \text{ 1/s}$ rate of cross-bridge attachment (see Fig. 4.1c). (f_1 was estimated by solving E_0 for f_1 :

$$E_0 = \frac{mehg_1}{2l} \frac{f_1}{f_1 + g_1} = \frac{P_0 V_{\max}}{6}$$

$$\frac{f_1}{f_1 + g_1} = 174415l, \quad g_1 = 425$$

As a result, as the estimate of l increases, so does the estimate of f_1 . f_1 is usually chosen to be considerably larger than g_1 so the force-velocity relationship shows a non-linearity at 0 velocity Huxley, 1957. As mentioned above, the values chosen were a compromise between overestimating l and underestimating f_1 .

Note that changing a_H , b_H , w/e , or h affects the derivation of g_1 and f_1 , and changing l affects the derivation of f_1 .

$g_2 = 2200 \text{ 1/s}$ rate of detachment (see Fig 4.1c). (g_2 was adjusted so the model force approached zero as the velocity of shortening approached $V_{\max}$. Consider the cross-bridge model in steady state. If the



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muscle is shortening, springs (cross-bridges) attach at some length "x" and produce a force "kx". Since the muscle is shortening, as long as the cross-bridge does not detach, it will become shorter and produce less force. At some point it crosses the point of producing zero force and begins to be stretched in the opposite direction such that it produces negative force. If g_2 is infinitely high, then the instant the spring crosses into the region in which it generates negative force, the cross-bridge will detach. In this case V_{max} is infinite. If g_2 is finite, then the faster the velocity of shortening, the higher the probability that a cross-bridges will be in this region and that it will be stretched more before it is broken. The velocity at which the force of the cross-bridges in this region equals the force of the cross-bridges in the positive force region is V_{max} . Since increasing g_2 increases the probability of a cross-bridge detaching, the higher g_2 the large V_{max} . Huxley made the arbitrary assumption that $(f_1+g_1)h/s = b_H$ because it simplified the steady-state solution of the partial differential equation; as a result, he concluded that $g_2/(f_1+g_1) = 3.919$. This was not followed in the present derivation.)

$g_3 = -220$, rate of detachment (see Fig. 4.1c); g_3 was chosen such that g would be a constant in the region beyond which cross-bridges were not likely to form and piecewise continuous with the rate of detachment in the region in which cross-bridges are likely to attach (0 to 1). g_3 affects the force- lengthening velocity relationship.



Since $P_0 = ms_0kh^2f_1/(4l(f_1 + g_1))$ (solve the partial differential equation for steady-state, zero velocity), where s_0 is the sarcomere length at which the maximum developed force is achieved, "k" must be:

$k = P_0 4l(f_1 + g_1)/(ms_0h^2f_1) = 0.3$ dyne/cm spring constant of cross-bridge; the spring constant is derived from measurements made at maximum isometric force, and, therefore, is based on g_1 of the agonist muscle. We have assumed that the spring constant is the same in both fiber types (slow and fast). (In addition, this estimate is within the range estimated from experimental measurements: frog semitendinosus, $k = .25$ dyne/cm, Huxley & Simmons, 1971; frog sartorius, $k = .1$ dyne/cm Flitney & Hirst, 1978; and from theoretical derivation $k = .1-.8$ dyne/cm with $h = 2.7e-6$ cm, Ma, 1988 based on derivation by Hill et al., 1975)

Integrating the equations for β_0 - β_2 (see model description) yields:

$$\beta_0 = f_1/2 = 262.5$$

$$\beta_1 = f_1/3 = 175$$

$$\beta_2 = f_1/4 = 131.25$$

(Note: since the general affects of varying individual parameters are fairly well known from other work (Ma, 1988), a sensitivity analysis will not be presented here. Instead, a sensitivity analysis on the whole model of the horizontal saccadic system, including the DM muscle models, will be presented in the Chapter 5.)



3.3DM algorithm

The basic algorithm for calculating the muscle activation necessary for the model to generate the measured force given the measured eye position and velocity is described for the LR. An analogous algorithm is used for the MR.

1. Initialize parameters

2. For each i ,

read $F_{d_{i+1}}, X_{i+1}$;

$F_{d_i}, X_i, dX_i/dt$;

calculate $F_p(X_{i+1})$:

$$F_p(X_{i+1}) = a(X_{i+1} + 25)^2, \quad X > -25$$

0 otherwise

optimize α_i such that

$$\epsilon(Q_{1_i} + \frac{dQ_{1_i}}{dt} \Delta t) = F_{d_{i+1}} - F_p(X_{i+1})$$

is i.e., find α_i such that the error between model force and measured force is minimized:

$$\min [\epsilon(Q_{1_i} + \frac{dQ_{1_i}}{dt} \delta t) - (F_{d_{i+1}} - F_p(X_{i+1}))]^2$$



where,

$$\frac{dQ_{0_i}}{dt} = \alpha_f c_e(X_i) \beta_0 - \Phi_0(Q_{0_i}, Q_{1_i}, Q_{2_i})$$

$$\frac{dQ_{1_i}}{dt} = \alpha_f c_e(X_i) \beta_1 - \Phi_1(Q_{0_i}, Q_{1_i}, Q_{2_i}) - u(X_i) Q_{0_i}$$

$$\frac{dQ_{2_i}}{dt} = \alpha_f c_e(X_i) \beta_2 - \Phi_2(Q_{0_i}, Q_{1_i}, Q_{2_i}) - 2u(X_i) Q_{1_i}$$

$$\text{and} \quad Q_{\lambda_{i+1}} = Q_{\lambda_i} + \frac{dQ_{\lambda_i}}{dt} \Delta t$$

3. next i

Note: all parameters were as defined in the description of the model derivation. In

addition

X_i , eye position

F_d , measured force

$F_p(X)$, passive muscle force as a function of muscle length (or equivalent deg.)

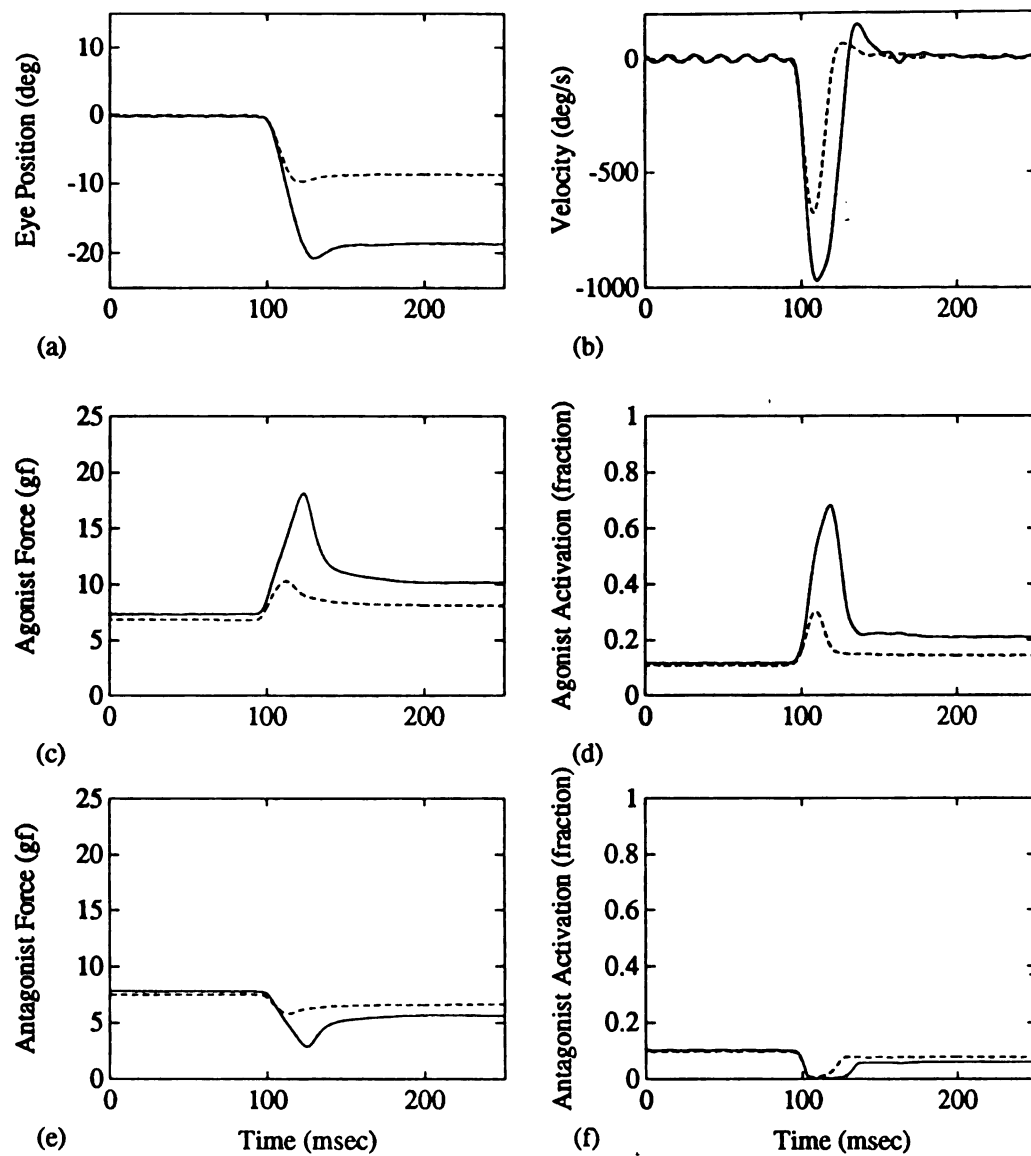
Also note that the algorithm for the calculation of muscle force given muscle activation, eye position, and velocity is a straight forward application of the differential equations without any optimization needed.



3.4 DM Model Simulations

Figure 3 shows the DM model predictions of agonist and antagonist muscle activation for 10- and 20-degree saccades from primary position (d,f) as well as the forces (c,e) and eye kinematics (a,b) produced during those saccades. The muscle activations are consistent with known neural activations during saccades; their durations are between half and full saccade duration. Agonist activation is much greater for 20-degree saccades than 10-degree saccades. At the same time, motoneuron burst frequency is higher and longer in duration during 20-degree saccades than during 10-degree saccades. As a result, one would expect muscle activation to increase for a longer time and to a greater extent during the larger saccades. Antagonist activation is consistent with the motoneurons being "turned off" (pause) or reduced to a very low firing rate. Antagonist activation decreases at about the same rate; activation for 10-degree saccades appears to begin to return to its tonic level just before the minimum activation is reached, whereas activation for 20-degree saccades plateaus at its minimum. As a side note, the difference in activation for the agonist and antagonist muscles at primary position is a result of using separate parameters to model the two muscles instead of modelling the slow and fast fibers in both muscles, which would result in an activation dependent, smooth transition from the dominant properties of the agonist muscle to the dominant properties of the antagonist muscle.

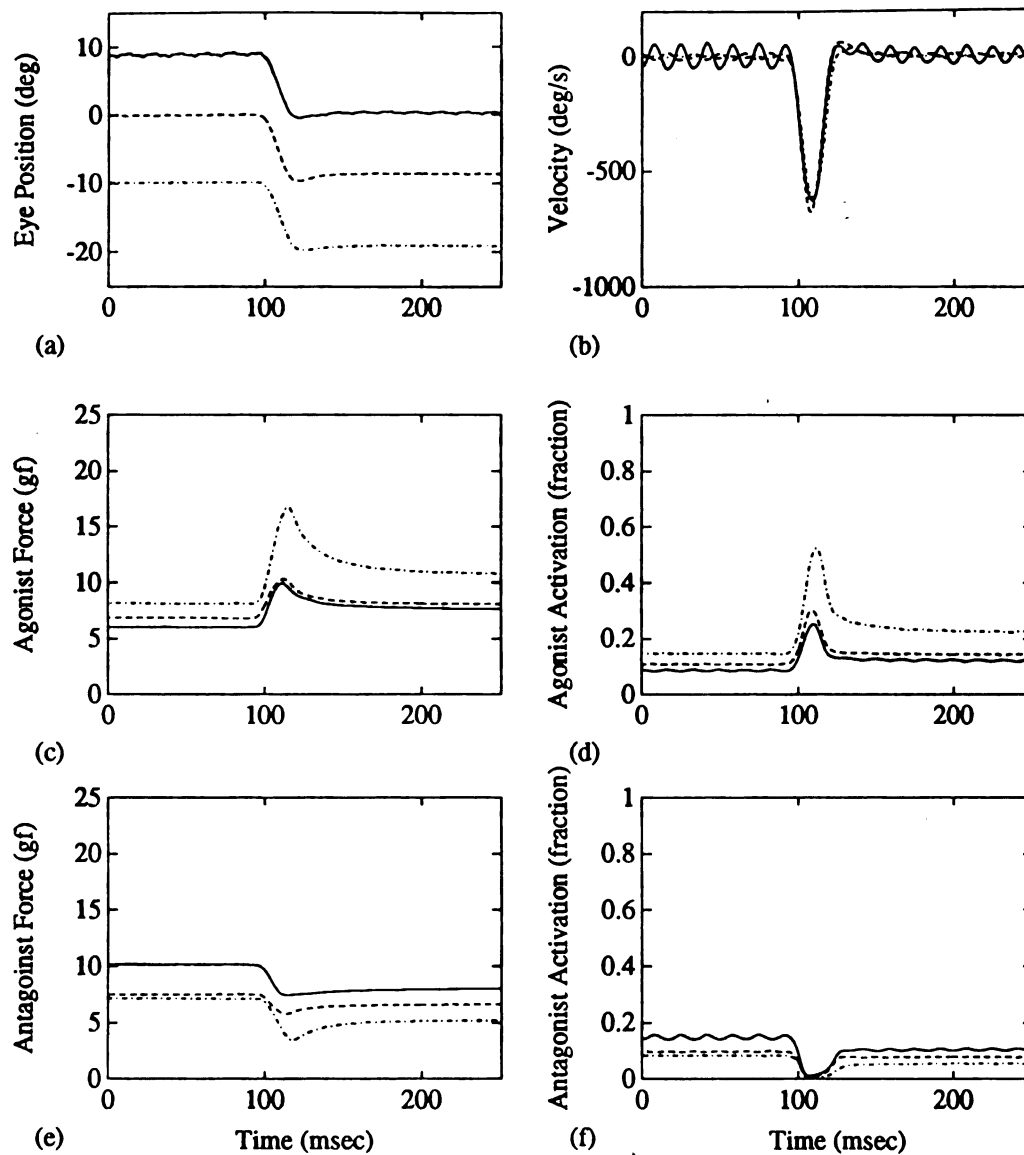




Activations of DM Model for 10- and 20-Degree Saccades Initiated from Primary Position. Eye position (a) and velocity (b), agonist and antagonist forces (c,e) and agonist and antagonist activations (d,f) during 10- (dash) and 20-degree (solid) saccades initiated from primary position are shown. The activations were calculated so the DM model generated the measured force profiles given the measured kinematics.

Figure 4.3





Activations of the DM Model for 10-Degree Saccades Initiated from Different Initial Positions. Eye position (a) and velocity (b), agonist and antagonist force (c,e), and agonist and antagonist activation (d,f) profiles during 10-degree saccades initiated from 10 degrees nasal (solid), primary position (dash), and 10 degrees temporal (dot-dash) are shown. Activations were calculated so the DM model generated the measured forces given the measured kinematics.

Figure 4.4



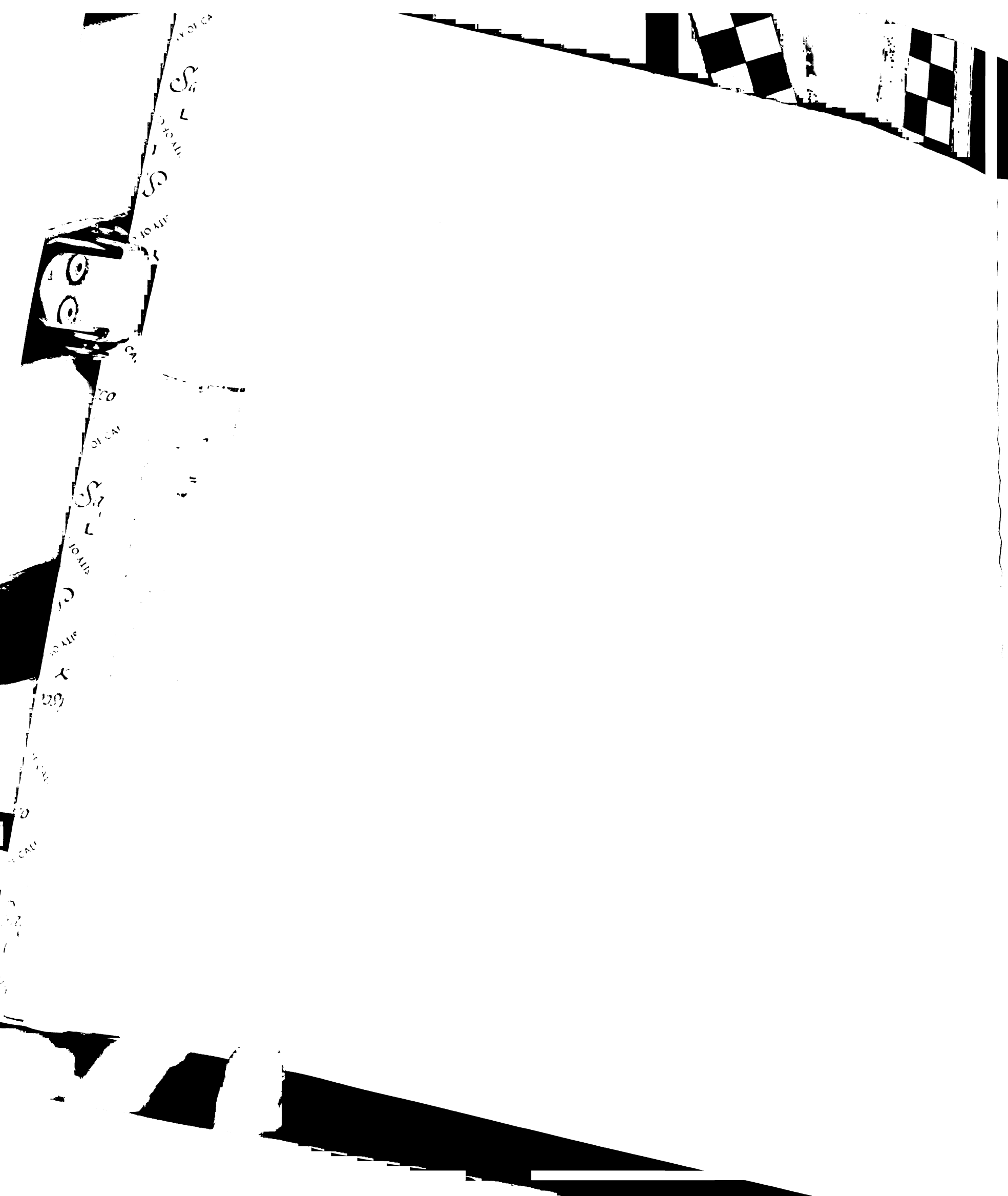
Figure 4 shows the model predictions for activation during 10-degree saccades from different initial positions (d,f) as well as the forces (c,e) and eye kinematics (a,b) produced during those saccades. Of course, agonist activation profiles vary in a manner analogous to the variations in the force profiles. Agonist activation during the saccade initiated when the muscle was longest (solid) is basically a shifted version of the activation during the saccade initiated from primary position (dash). However, activation during the saccade initiated when the muscle was shortest (dot-dash) is considerable larger, not only during the saccade (pulse) but also during fixation (step). Although this result is not necessarily an obvious result of motoneuron and motor unit recruitment, it is not inconsistent with known neural firing patterns. The fixation activation is certainly consistent with motoneuron recruitment. Over the range of eye positions studied, motoneurons are recruited approximately linearly with eye position (in the "on" direction). Moreover, motoneurons with higher thresholds tend to have larger discharge rate - position slopes, so the large increase in tonic activity at 20 degrees in the "on" position over 10 degrees in the "on" direction reflects the more rapid increase in firing rates of the most recently recruited motoneurons. The increase in the pulse activation is more ambiguous. The peak burst rate for a 10-degree saccade is expected to be highest during the saccade initiated from the shortest muscle length; however, the difference between peak firing rate and tonic firing rate is smallest during that saccade. If the fibers generating the most force are recruited last, then an increase in peak firing rate could generate a relatively large proportion of force. This would be reflected in the model as an increase in muscle activation, since we have modelled force generation as

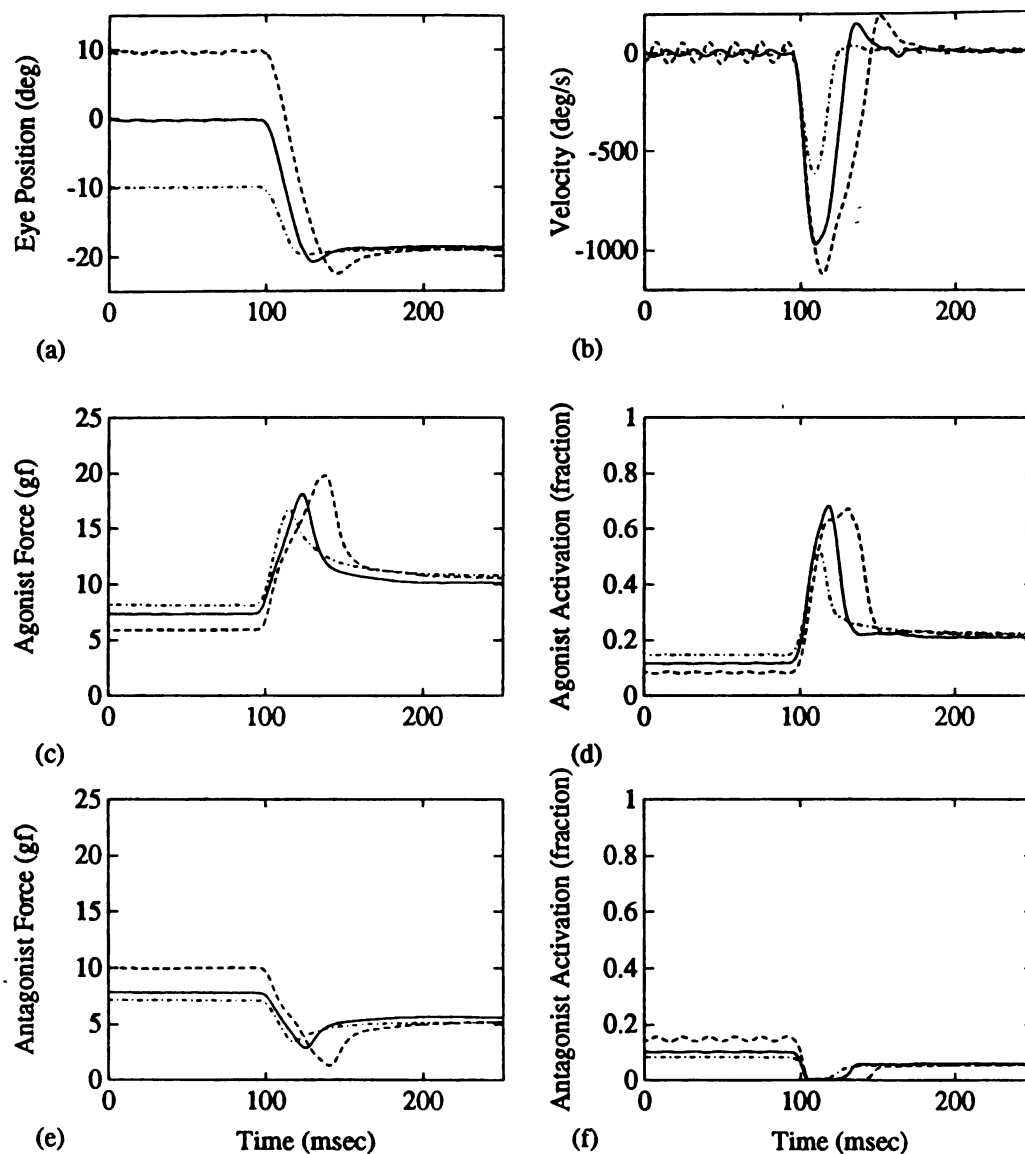


an "average" fiber. From this, we conclude that agonist activation is, at the very least, not inconsistent with neural activation. Antagonist activation is consistent with the "pause" during the saccade and the position dependent tonic activity.

For a more complete picture of the predicted activations during saccades, Fig. 4.5 and Fig. 4.6 are shown. Fig. 4.5 shows how activation varies for different size saccades all ending in the same position and Fig. 4.6 shows how activation varies for different size saccades initiated from the same position. The activations are consistent with the pulse-slide-step (pause-slide-step) neural activations.

Figure 4.7 shows the forces predicted for 10- and 20-degree "isometric saccades" at primary position, using the activations shown in Fig. 4.3, as well as the forces during regular saccades. "Isometric saccades" are generated by holding one eye fixed (isometric), while the other eye makes a saccade. As a result, the isometric eye receives the innervation to make a saccade, but the eye is held fixed so the force profiles are different than during normal saccades. Figure 4.8 shows the forces predicted for 10-degree "isometric saccades" at different initial positions, using the activations shown in Fig. 4.4, as well as the forces during regular saccades. And Fig. 4.9 show the forces predicted for "isometric saccades" of varying sizes at 10 degrees nasal, using the activations shown in Fig 4.6, as well as the forces during regular saccades.

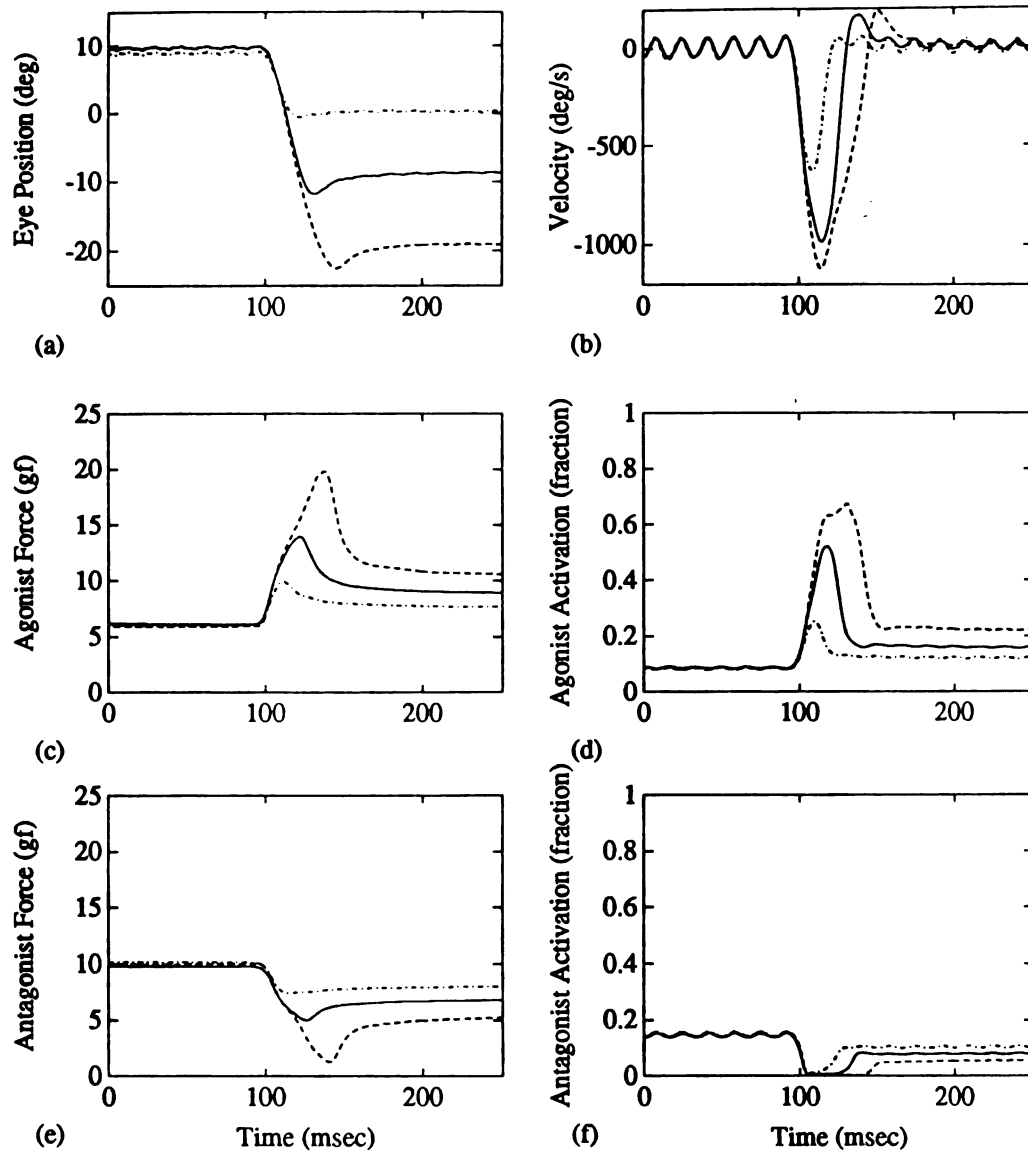




Activations of DM Model for Saccades of Different Magnitudes, Finishing 20 Degrees Temporal. Eye position (a) and velocity (b), agonist and antagonist force (c,e), and agonist and antagonist activation profiles (d,f) for saccades ending in the same position are shown. A 30-degree saccade initiated from 10 degrees nasal (dash), a 20-degree saccade initiated from primary position (solid), and a 10-degree saccade initiated from 10 degrees temporal (dot-dash) are included. Activations were calculated so the DM model generated the measured forces given the measured kinematics.

Figure 4.5

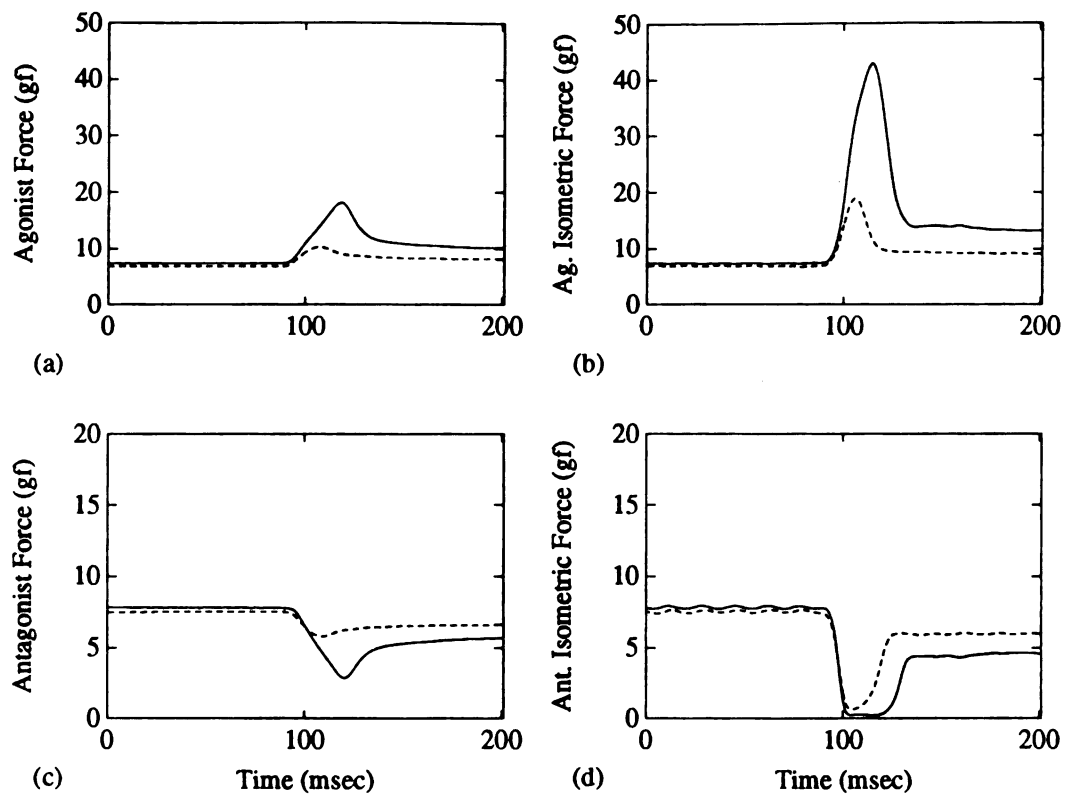




Activations of DM Model for Saccades of Different Magnitudes, Initiated from 10 Degrees Nasal. Eye position (a) and velocity (b), agonist and antagonist force (c,e), and agonist and antagonist activation profiles (d,f) for saccades initiated from the same position are shown. A 30- (dash), a 20- (solid), and a 10-degree (dot-dash) saccade initiated from 10 degrees nasal are shown. The activations were calculated so the DM model generated the measured force profiles given the measured kinematics.

Figure 4.6

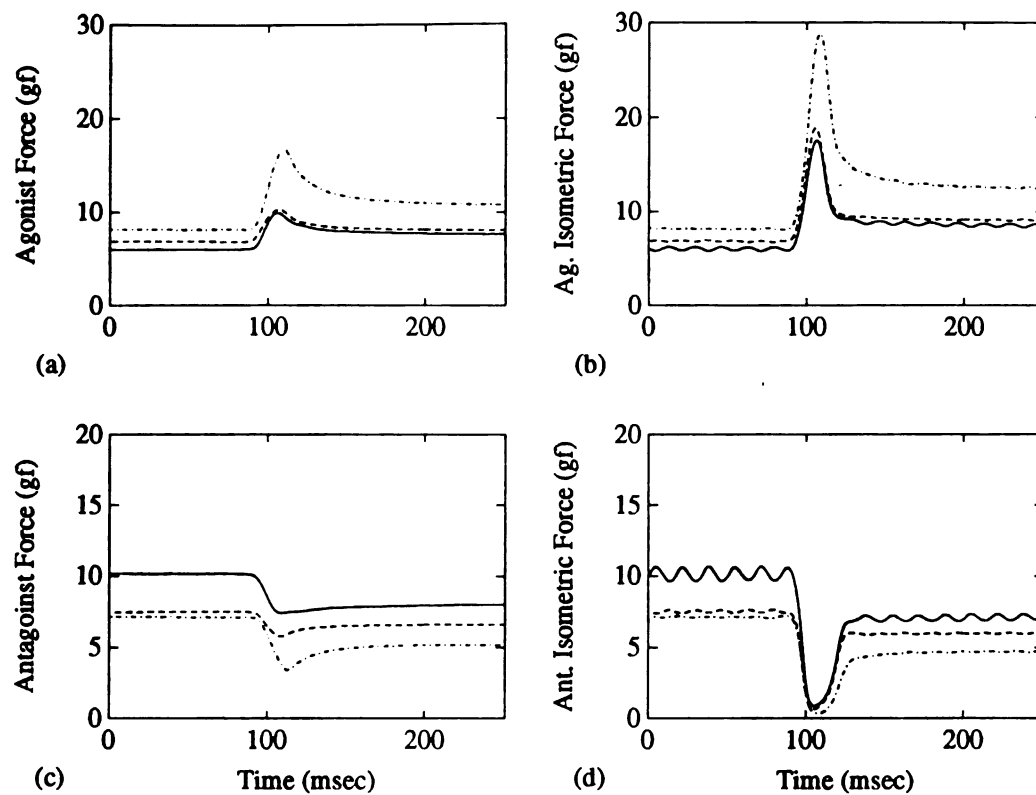




DM Model Simulations of 10- and 20-Degree "Isometric Saccades" at Primary Position. Agonist and antagonist isometric forces (b,d) generated by the Hill Model are shown when the predicted activations for the normal saccades were used as input under isometric conditions. Also shown are the agonist and antagonist forces measured during normal saccades (a,c). Responses to the activations for 10- (dash) and 20-degree (solid) saccades are shown.

Figure 4.7

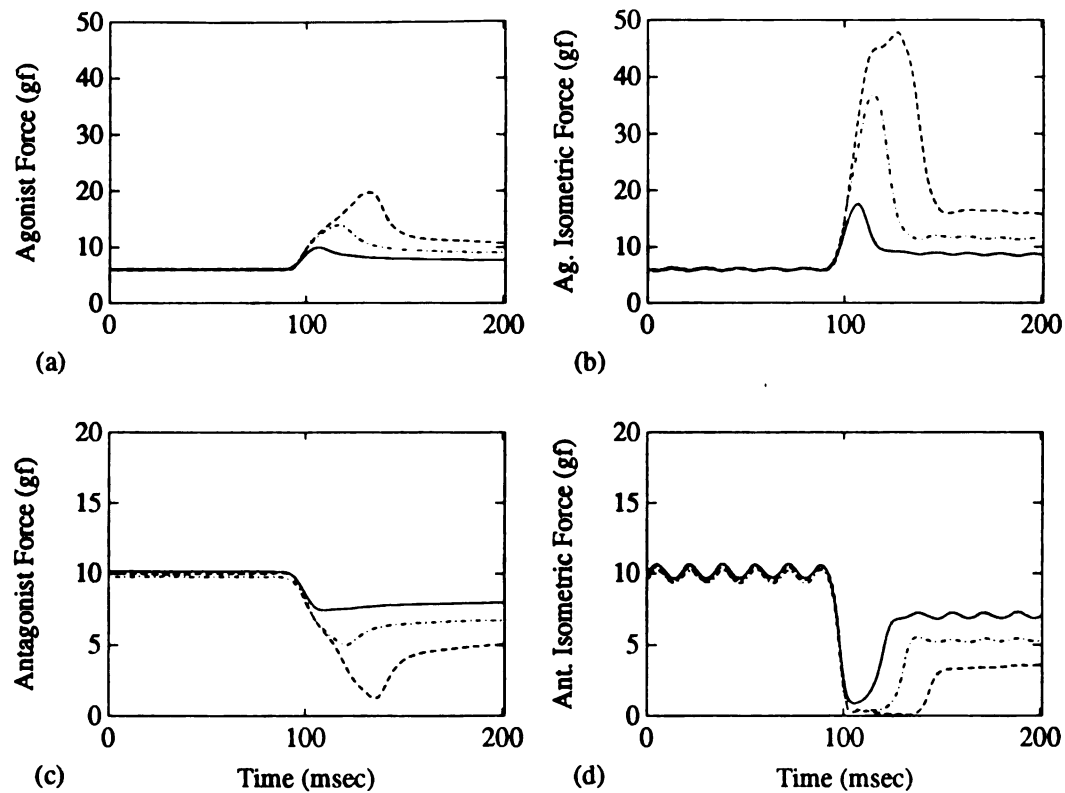




DM Model Simulations of 10-Degree "Isometric Saccades" at Different Eye Positions. Agonist and antagonist isometric forces (b,d) generated by the DM model are shown when the predicted activations for the normal saccades were used as input under isometric conditions. Agonist and antagonist forces measured during each saccade under normal conditions (a,c) are also shown. Ten-degree isometric saccades are shown at 10 degrees nasal (solid), primary position (dash), and 10 degrees temporal (dot-dash).

Figure 4.8

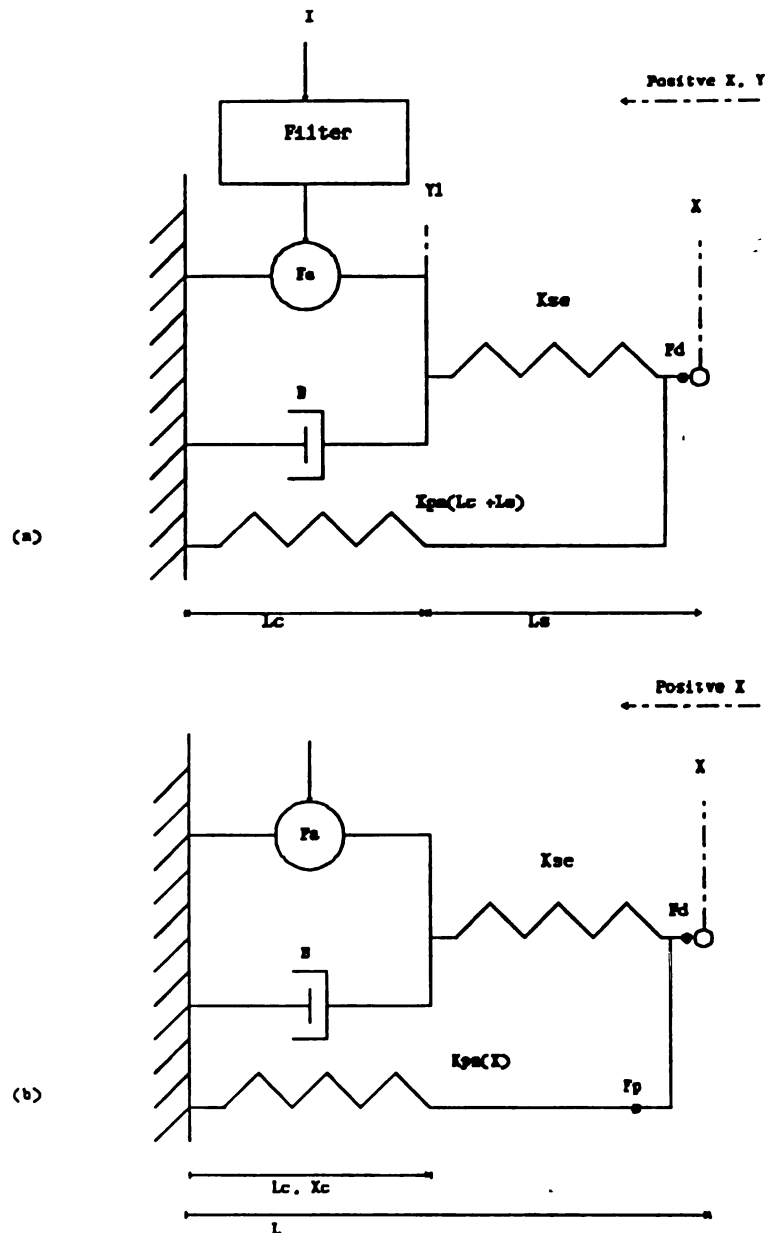




DM Model Simulations of 10-, 20-, and 30-Degree "Isometric Saccades" at 10 Degrees Nasal. Agonist and antagonist isometric forces (b,d) generated by the DM model are shown when the predicted activations for normal saccades were used as inputs under isometric conditions. Agonist and antagonist forces measured during normal saccades are also shown (a,c). Responses to the activations for 10- (solid), 20- (dot-dash), and 30-degree (dash) saccades are shown.

Figure 4.9





Hill Muscle Model. (a) Hill Model as described in Chapter 3. A filtered version of the input, I , is the active state, F_a , a force generator. The force generator is in parallel with a non-linear dashpot, B , and the combination is in series with a spring, K_{se} . The unit is in parallel with another spring, K_{pm} . X and Y_1 are lengths in equivalent degrees. L_c is the length of the contractile component and F_d is the extrinsic muscle force, which corresponds to the forces we measured in the monkey. (b) Hill Model referred to in this section. The changes are: 1) muscle activation refers to active state (F_a), not the assumed neural correlate (I in (a)); 2) The length of the contractile component (L_c) will be measured in equivalent degrees (X_c) and has the opposite sign to Y_1 of part (a); (3) Force contribution of the passive muscle is explicitly marked, F_p .

Figure 4.10

4. Single Hill Muscle Model and Algorithm

In this chapter, a single Hill muscle model such as that shown in Fig. 4.10 was used. Part (a) shows the model as described in Chapter 3, while part (b) shows the model that will be referred to in this chapter. The main differences are that 1) instead of using y to describe the hypothetical node, x_c will be used where x_c is the degree equivalent of the length associated with the contractile component (L_c) instead of length in cm; consequently x_c becomes larger when the contractile component lengthens. As before, " x " represents eye position and can be thought of as the degree equivalent of muscle length (L). In addition, the node at which passive muscle force is measured is explicitly labelled, F_p .

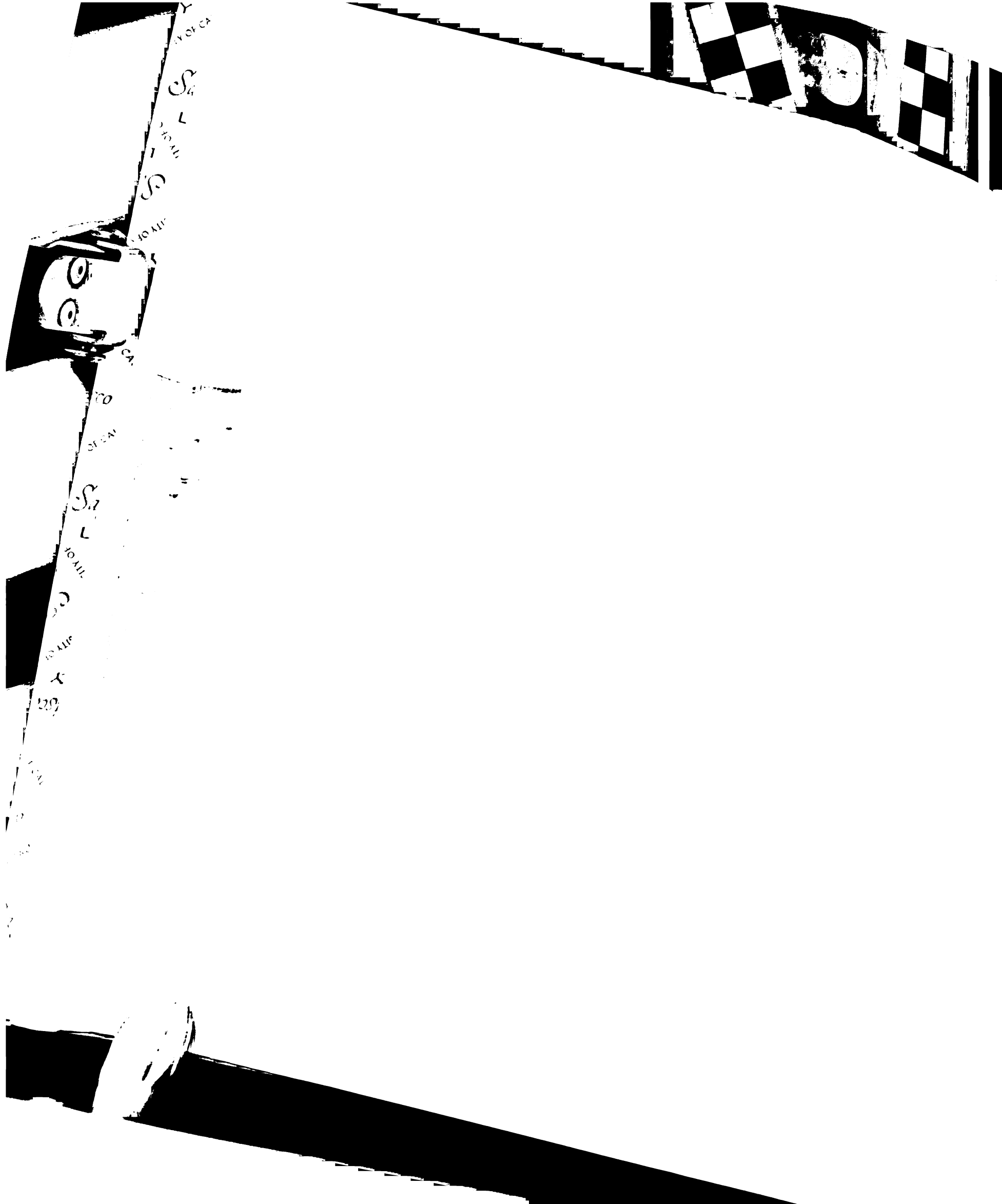
4.1 Algorithm for Lateral Rectus

The equations of motion for the model are:

$$F_d = K_{se}(X - X_c) + F_p$$
$$K_{se}(X - X_c) = B \frac{dX_c}{dt} + F_d$$

Where,

- F_d , input: force recorded in the monkey, [gf]
- X , input: eye position recorded in the monkey, [deg]
- X_c , degree equivalent of length of contractile component, [deg]
- K_{se} , series elasticity , [gf/deg]



- B, non-linear dashpot, [gf/deg/s]
 F_p, passive muscle force, [gf]
 F_a, output: active state, [gf]

The basic algorithm for calculating the active state for the LR is as follows:

(Note that the algorithms are similar for the MR except the relationship between the signs of the eye velocity and muscle velocity is reversed.)

1. Initialize:

$$\begin{aligned} & \text{read } F_{d0}, X_0 \\ & F_{p0} = .001975(X+25)(X+25) \\ & X_{c0} \text{ s.t. } F_{d0} - F_{p0} = K_{se}(X_0 - X_{c0}) \end{aligned}$$

2. For each i:

$$\begin{aligned} X_{ci} &= X_i - \frac{(F_{di} - F_{pi})}{K_{se}} \\ \frac{dX_{ci}}{dt} &= \frac{(X_{ci} - X_{ci-1})}{\Delta t} \end{aligned}$$

where Δt = sampling period (1 ms)



if $dX_{c_i}/dt > 0$:

$$\begin{aligned}
 F_{a_i} &= (F_{d_i} - F_{p_i}) - B_i \frac{dX_{c_i}}{dt} \\
 &= (F_{d_i} - F_{p_i}) - \frac{3F_{a_i}}{d_{len}} \frac{dX_{c_i}}{dt} \\
 \rightarrow \\
 F_{a_i} &= \frac{(F_{d_i} - F_{p_i})}{1 + \frac{3 \frac{dX_{c_i}}{dt}}{d_{len}}}
 \end{aligned}$$

otherwise:

$$\begin{aligned}
 F_{a_i} &= (F_{d_i} - F_{p_i}) - B_i \frac{dX_{c_i}}{dt} \\
 &= (F_{d_i} - F_{p_i}) - \frac{F_{a_i} + a_{H_i}}{b_H - \frac{dX_{c_i}}{dt}} \frac{dX_{c_i}}{dt} \\
 \text{where, } a_{H_i} &= .5F_{a_i} \\
 \rightarrow
 \end{aligned}$$

$$F_{a_i} = (F_{d_i} - F_{p_i}) \frac{(b_H - \frac{dX_{c_i}}{dt})}{b_H + \frac{dX_{c_i}}{2dt}}$$

where,

b_H , constant characterizing the force-shortening velocity relationship

d_{len} , constant characterizing the force-lengthening velocity relationship

3. next i:

$i=i+1$

if more data, return to step 2; otherwise stop



Note: $a_H/P_0 = .5$ and $b_H/V_{max} = .33$ were used to be consistent with the DM model derivation. In Chapter 3, $a_H/P_0 = .25$ and $b_H/V_{max} = .25$ were used. Finally, d_{len} was varied until the model activations were consistent with expected activations.

4.2 Variations Simulated

Variations in the estimate of the force-velocity relationship were explored to a small degree. For example, the hyperbola representing the force-velocity relation of shortening muscle was varied by changing the asymptotes $b_H = V_{max}/3$ over the range of maximum shortening velocities that are likely to apply to extraocular muscle.

$$\begin{aligned} V_{max} &= 20-25 \text{ lengths/s} \\ &= 40-50 \text{ cm/s (monkey)} \\ &= 2450-3075 \text{ deg/s (monkey)} \end{aligned}$$

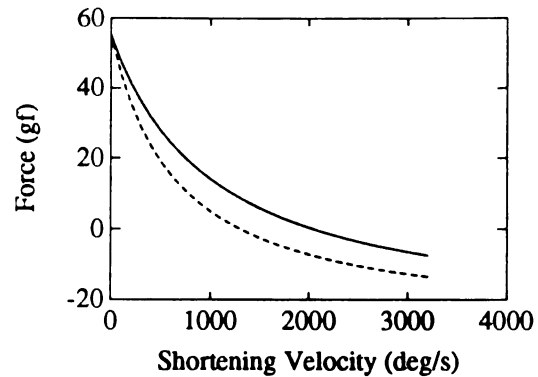
so,

$$b_H = 800-1025$$

The effect of b_H on the force-velocity relationship of shortening muscle is shown in Fig. 4.11. Finally, $b_H = 1025$ was used in the subsequent simulations. Not only is it based on the assumption that $V_{max} = 25$ lengths/s but also the active state (F_a , i.e., roughly the force that would be developed if the muscle were held isometrically) remained within a physiological range for the movements simulated. In other words, the smaller the value of b_H , the larger the active state of the agonist muscle, and, to be consistent with physiological data, active state should be less than or equal to 55 grams (i.e., less than



or equal to maximum isometric force recorded in monkey extraocular muscle; Fuchs & Luschei, 1971) .



Effect of b_H on the Force-Velocity Relationship of Shortening Muscle.

The figure shows the force-velocity relationship at maximum innervation for the assumed physiological range of parameters, $b_H = 1025$ (solid) and $b_H = 800$ (dash).

Figure 4.11



In addition, an alternate representation of the lengthening force-velocity relationship was explored. First, the representation described above was used, which is a linear approximation of a hyperbola that was previously used (e.g., Hsu et al., 1976):

$$\begin{aligned} F_c &= F_a + F_v \\ &= F_a + \frac{3F_a}{d_{len}} \frac{dX_c}{dt} \end{aligned}$$

where,

F_c , force of the contractile component

F_a , active state

F_v , force represented by the dashpot

X_c , degree equivalent of the length of the contractile component

d_{len} , scaling factor

The resulting force-velocity relationship of lengthening muscle is shown in Fig. 4.12.

Second, an alternate representation was tested in which a hyperbola was explicitly defined to represent F_v :

$$\begin{aligned} F_c &= F_a + F_v \\ &= F_a + \frac{c}{\left(\frac{dX_c}{dt} - v_0\right)} \end{aligned}$$

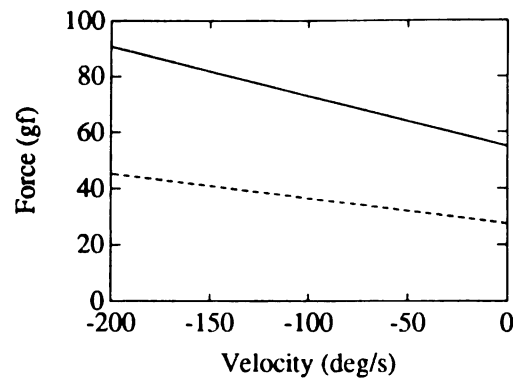
therefore,

$$(F_c - F_a) \left(\frac{dX_c}{dt} - v_0 \right) = c$$

c, v_0 parameters of hyperbola

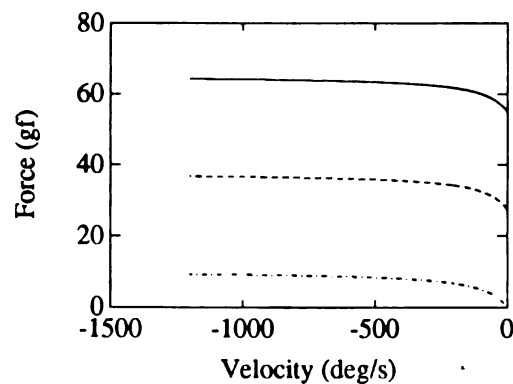
The resulting force-velocity relationship of lengthening muscle is shown in Fig 4.13.





Original Representation of the Force-Velocity Relationship of Lengthening Muscle in the Hill Model. The force-velocity relationship of lengthening muscle is shown for two levels of innervation, max (solid), half (dash); at zero innervation, no force is generated at any velocity (not shown).

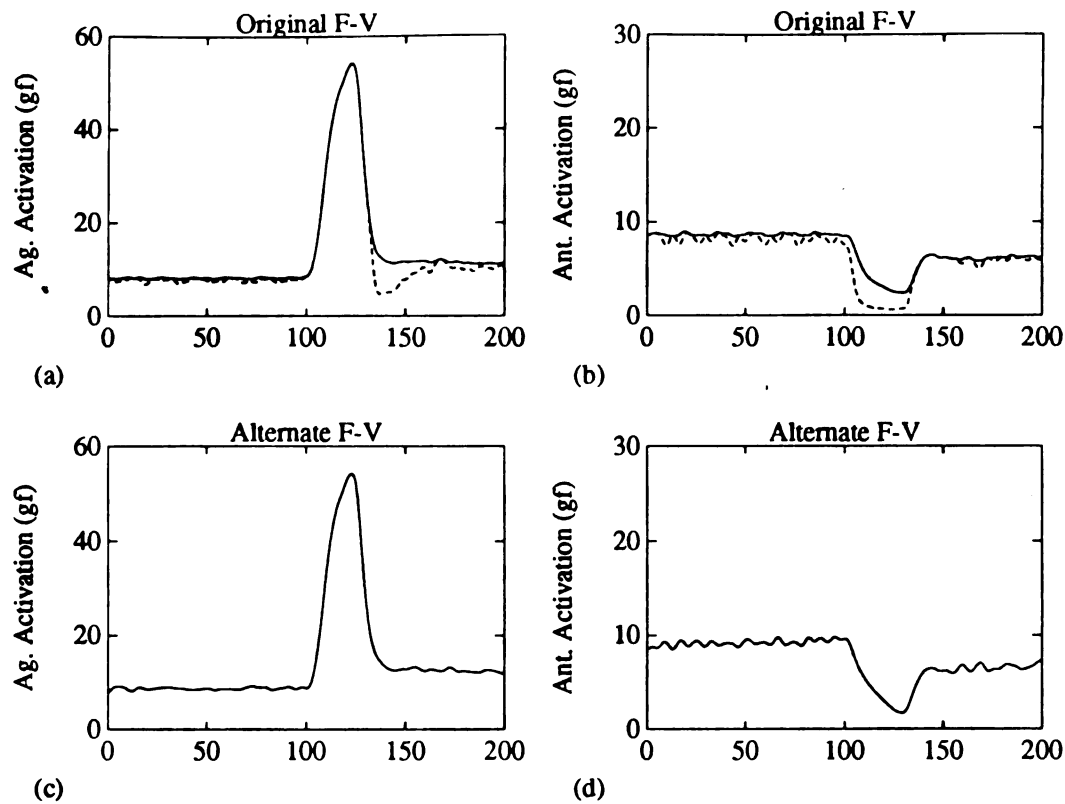
Figure 4.12



Alternate Representation of the Force-Velocity Relationship of Lengthening Muscle in the Hill Model. The force-velocity relationship for lengthening muscle is shown for three levels of innervation: max (solid), half (dash), min (dot-dash).

Figure 4.13





Effect of the Function Used to Describe the Force-Velocity Relationship in Lengthening Muscle. The figure shows the Hill model predictions of activation for a 20-degree saccade from primary position for different force-velocity relationships. The left panels (a,c) show agonist activations and the right panels (b,d) show antagonist activations. The upper panels (a,b) show activations using the original force-velocity relation (i.e., an innervation dependent, linear approximation, where the slope is scaled by the inverse of the parameter d_{len}). The effect of varying parameter d_{len} is also shown, $d_{len} = 4150$ (solid), $d_{len} = 450$ (dash). The bottom panels (c,d) show the activations for the explicitly defined hyperbola (for one set of parameters). (For a description of the force-velocity relationships, see the text.)

Figure 4.14



4.3 Hill Muscle Model Simulations

Figure 4.14 shows the effects of different representations of the force-lengthening velocity relationship on the predicted agonist and antagonist activation during a 20-degree saccade initiated from primary position. Fig. 4.14a, b shows the original force-velocity relationship (see Fig. 4.13), with d_{len} varying from 450 (dash) to 4150 (solid) for both the agonist and antagonist muscles. Because this monkey tends to overshoot the target, the agonist muscle has a brief period of lengthening at the end of the saccade. As a result, the lengthening force-velocity relationship does affect the agonist muscle. (Note that the following results applied to the nasal saccades as well even though the overshoot is small.) In the agonist muscle, d_{len} must be large (solid; Fig. 4.14a) or else a pulse- negative pulse-step (dash; Fig. 4.14a) activation pattern is required; a large dip in agonist activation does not seem to be consistent with the pulse-slide-step pattern of single motoneurons. In contrast, in the antagonist muscle, d_{len} must be small (dash; Fig. 4.14b) or else a slowly decreasing activation is predicted (solid; Fig. 4.14b), which is inconsistent with the pause-slide-step pattern of motoneurons. The larger d_{len} , the smaller the force at a given lengthening velocity and level of innervation. Increasing d_{len} has a similar affect on the lengthening force-velocity relationship as increasing g_1 in the DM model. If the velocity-dependent force is relatively large at low levels of innervation (relative to isometric force), which corresponds to low d_{len} and low g_1 , and relatively small at high levels of innervation (i.e., not too much above isometric force), then the Hill model predicts activations consistent with those expected base on

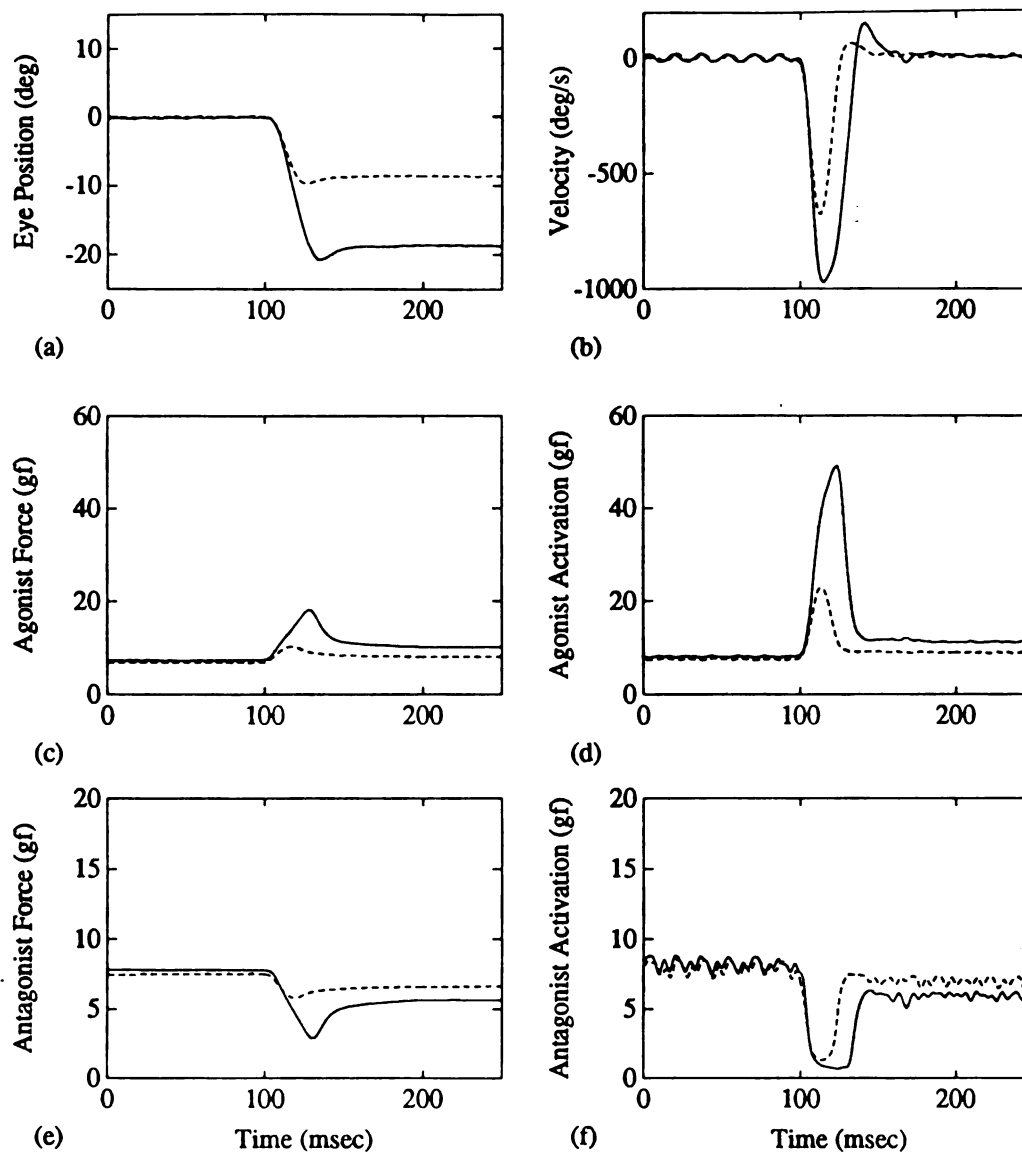


ocular motoneuron behavior. At first, varying d_{len} appeared to be a mathematical manipulation without any connection to actual properties of the muscle. However, simulations of the DM model suggest a connection between the manipulation and possible muscle properties. This also suggests a strong need to explore the force-velocity properties of different fiber types within extraocular muscle as well as the force-velocity relationship of extraocular muscle for varying degrees of innervation. The results presented here suggest, at the very least, that the force-lengthening velocity relationship is important in the simulation results.

The figure also suggests that the exact form of the force-velocity relationship is not too important. Figure 4.14 c & d show the predicted activations for the same saccade using an explicitly defined hyperbola to represent the force-velocity relationship (see Fig. 4.12). The particular parameters shown predict activations very similar to that of the original representation of the force-velocity relationship with $d_{len} = 4150$. By varying the parameters used to describe the curve, results similar to those obtained with $d_{len} = 450$ can be generated. As a result, the original model will be used, with different values of d_{len} for the agonist and antagonist muscles.

Figure 4.15 shows the predicted activation for 10- and 20-degree saccades initiated from primary position (d,f) as well as force profiles (c,e) and eye kinematics (a,b). Agonist and antagonist activations are similar to those predicted by the DM model (see Fig. 4.16 or compare with Fig.4.3).

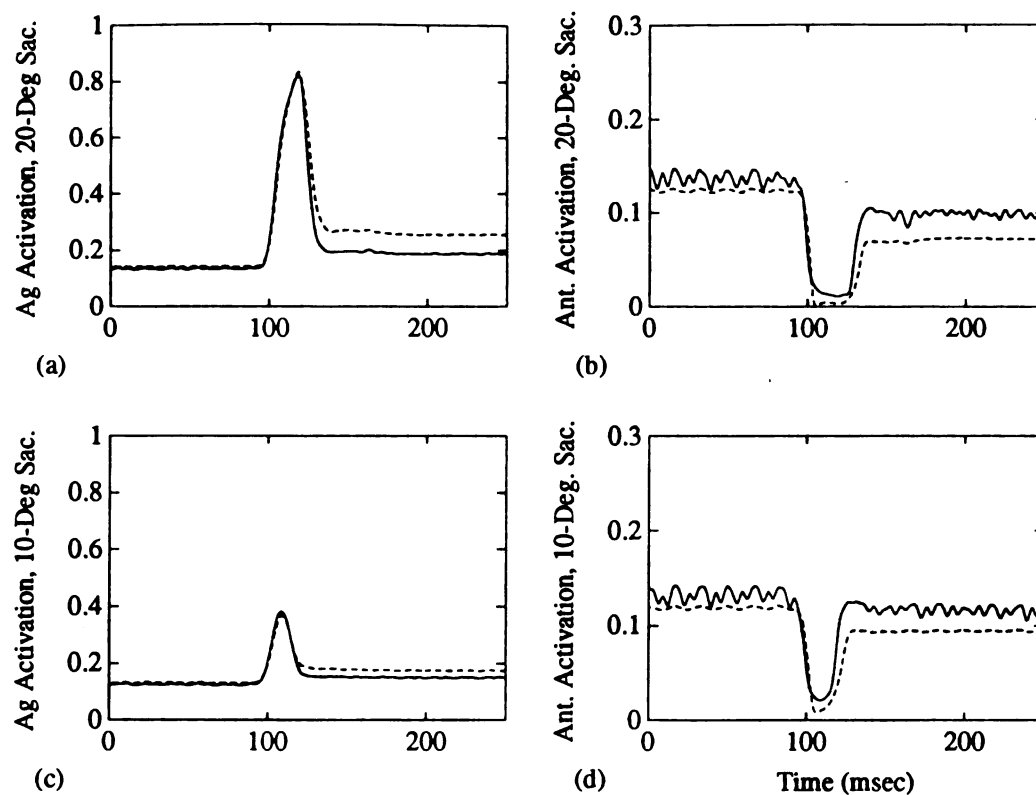




Activations of Hill Model for 10- and 20-Degree Saccades Initiated from Primary Position. Eye position (a) and velocity (b), agonist and antagonist force (c,e), and agonist and antagonist activation profiles (d,f) during 10- (dash) and 20-degree (solid) saccades initiated from primary position are shown. The activations were calculated so the Hill model generated the measured force profiles given the measured kinematics.

Figure 4.15





Comparison of Normalized Activations from DM and Hill Muscle Models. DM (dash) and Hill model (solid) activations for agonist (a,c) and antagonist (b,d) muscles during 20- (a,b) and 10-degree (c,d) saccades.
Figure 4.16

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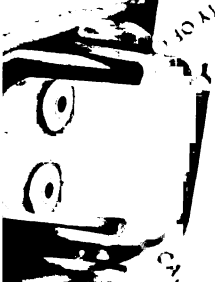
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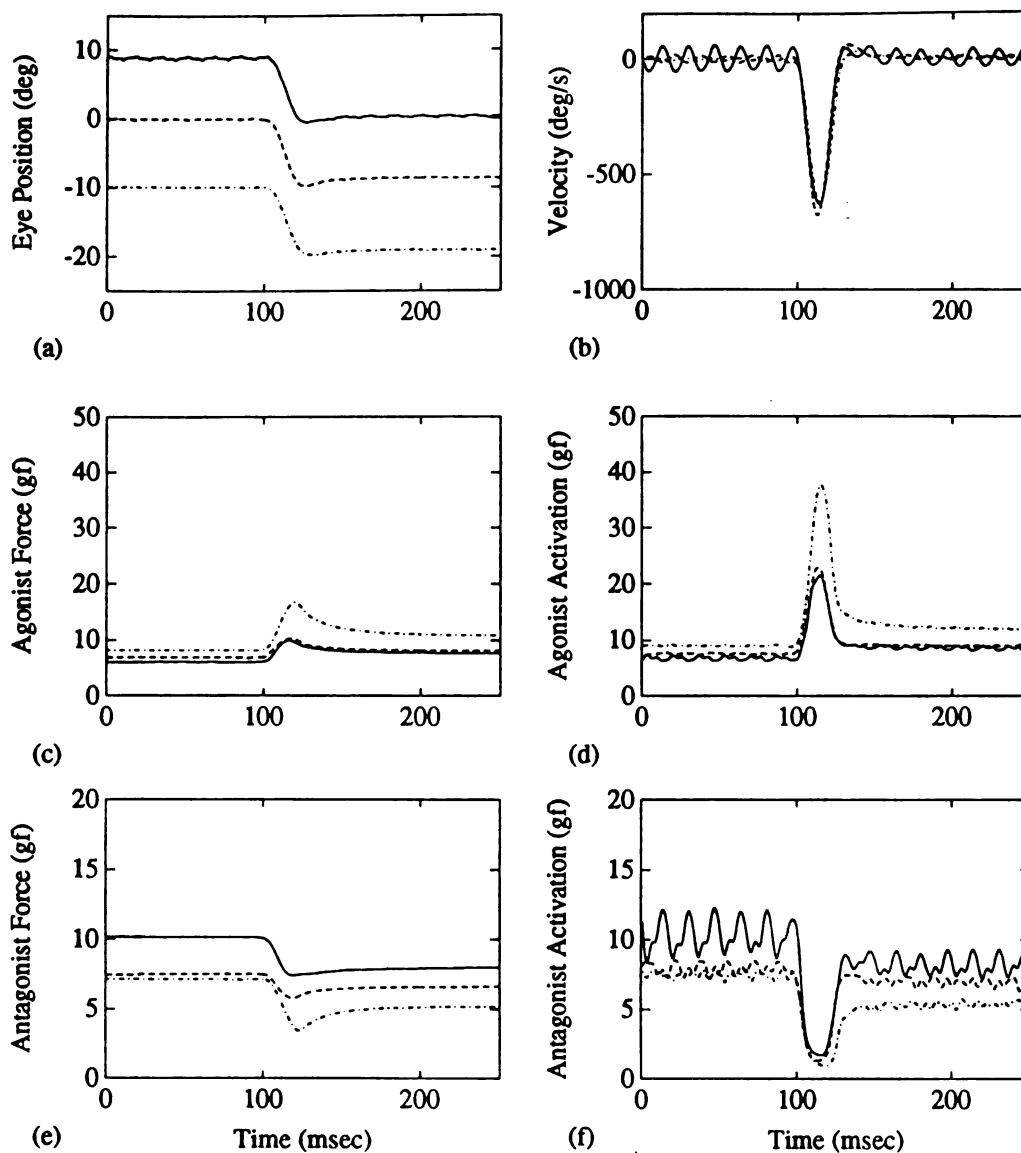
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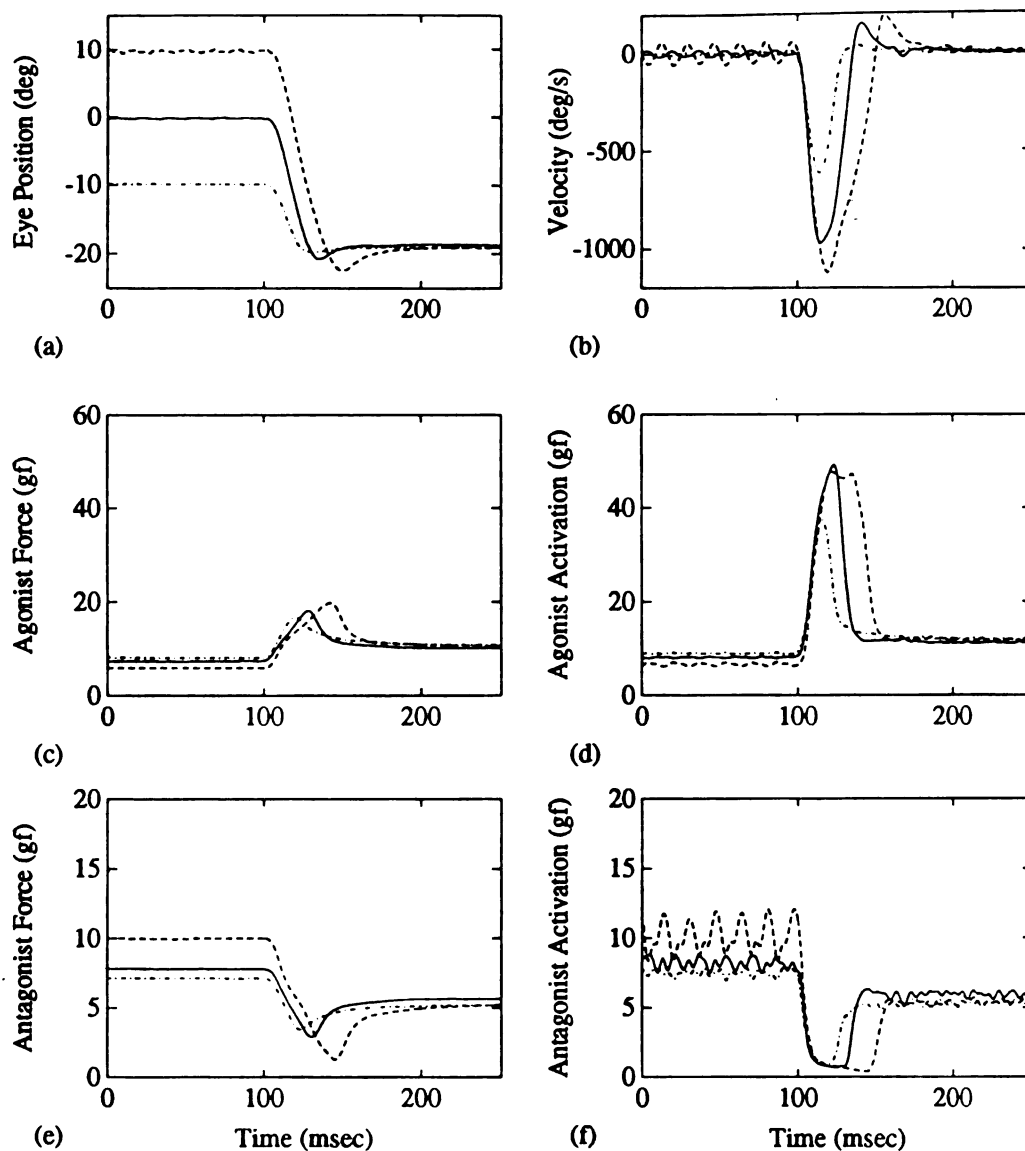
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Activations of Hill Model for 10-Degree Saccades Initiated from Different Initial Positions. Eye position (a) and velocity (b), agonist and antagonist force (c,e), and agonist and antagonist activation profiles (d,e) during 10-degree saccades initiated from 10 degrees nasal (solid), primary position (dash), and 10 degree temporal (dot-dash) are shown. The recorded kinematic and force profiles were used as input and the activations were calculated so the Hill model generated the force profiles given the kinematic profile.

Figure 4.17

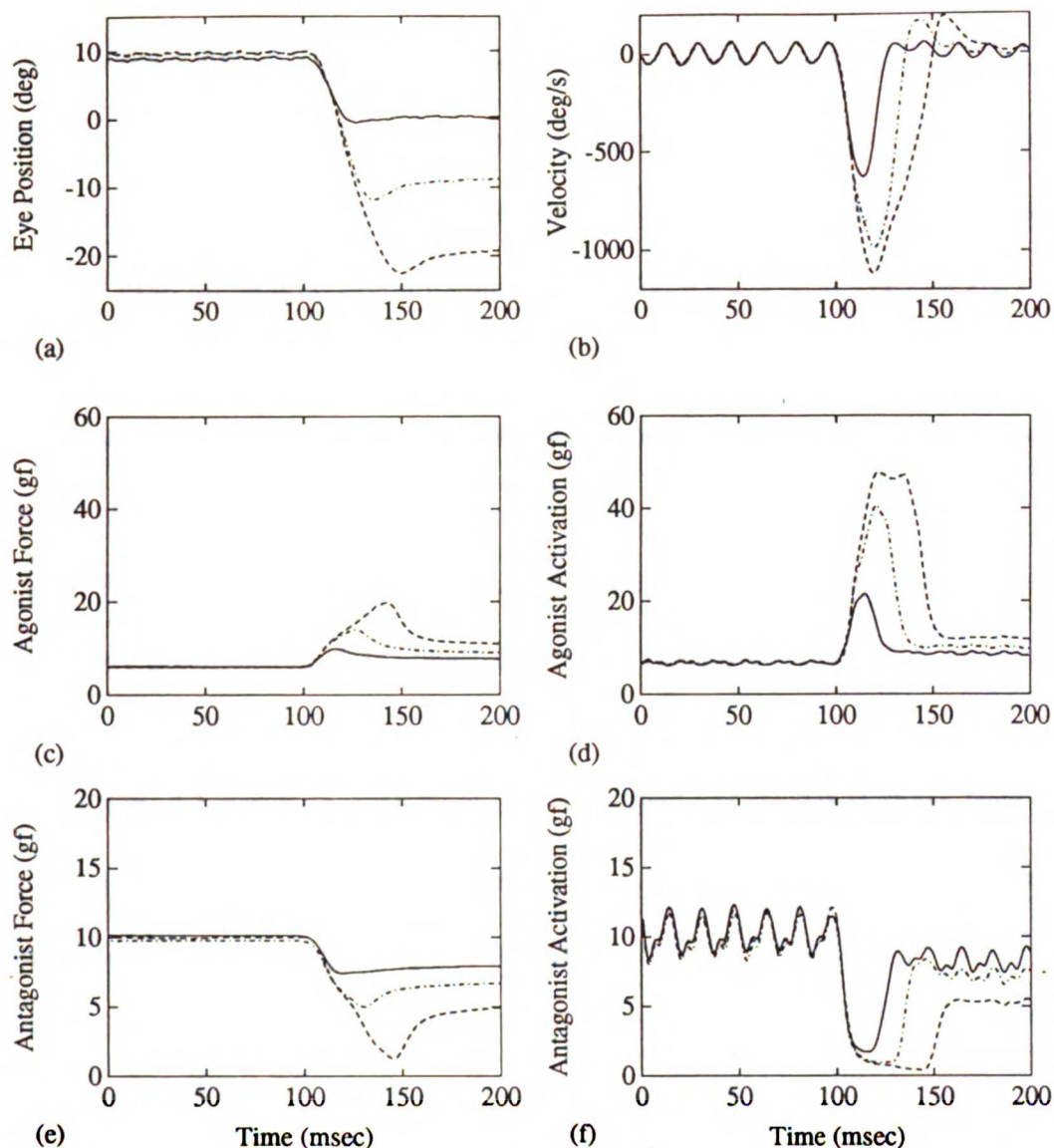
This image shows a blank, aged, cream-colored page, likely an endpaper or flyleaf of a book. The paper has a slightly textured appearance with some minor discoloration and faint smudges, characteristic of old paper. The left edge of the page is bound, showing the stitching and the inner cover material. There is no text or other markings on the page.



Activations of Hill Model for Saccades of Different Magnitudes, Finishing 20 Degrees Temporal. Eye position (a) and velocity (b), agonist and antagonist force (c,e), and agonist and antagonist activation profiles (d,f) for saccades ending in the same position are shown. A 30-degree saccade initiated from 10 degrees nasal (dash), a 20-degree saccade initiated from primary position (solid), and a 10-degree saccade initiated from 10 degrees temporal (dot-dash) are shown. Activations were calculated so the Hill model generated the measured forces given the measured kinematics.

Figure 4.18

This image shows a blank, aged, cream-colored page, likely an endpaper or flyleaf of a book. The paper has a slightly textured appearance with some minor discoloration and faint, illegible markings, possibly from a previous page or a stamp. A dark binding edge is visible on the left side.



Activations of Hill Model for Saccades of Different Magnitudes, Initiated from 10 Degrees Nasal. Eye position (a) and velocity (b), agonist and antagonist force (c,e), and agonist and antagonist activation profiles (d,f) for saccades initiated from the same position are shown. A 30- (dash), a 20- (dot-dash), and a 10-degree (solid) saccade are shown. The activations were calculated so the Hill model generated the measured force profiles given the measured kinematics.

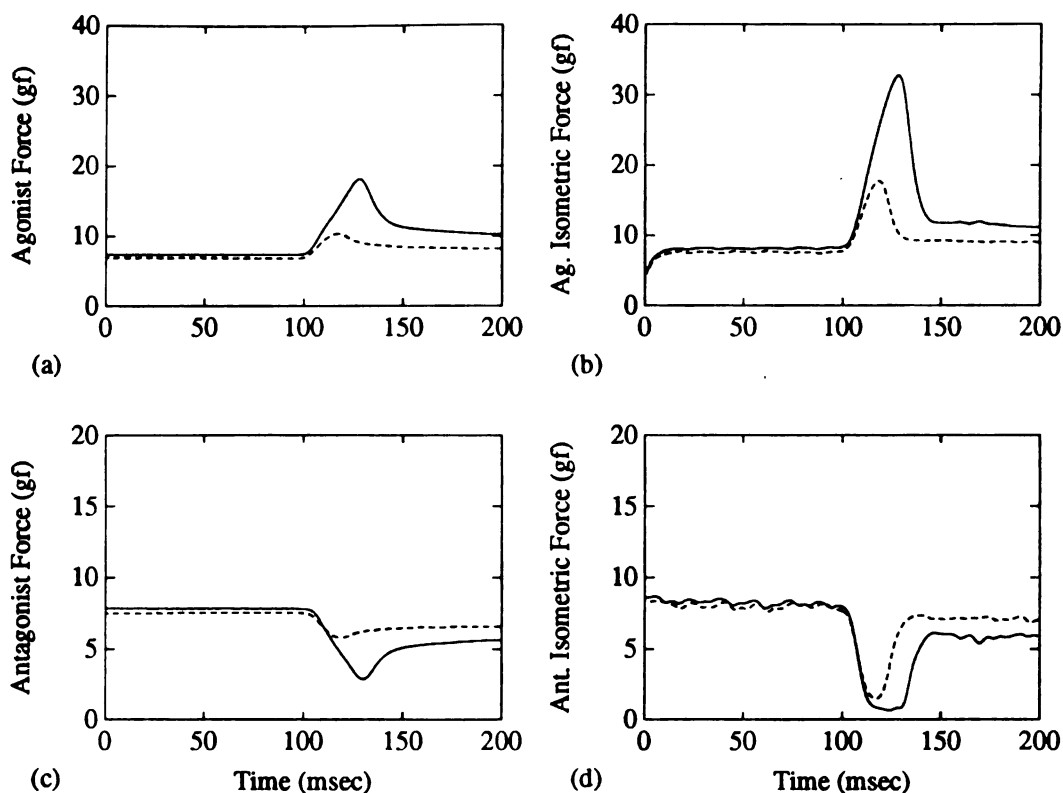
Figure 4.19



Similarly, Fig. 4.17 shows the predicted activations for 10-degree saccades initiated from different initial positions (compare with Fig. 4.4); Fig. 4.18 shows the predicted activations for different size saccades ending in the same position (compare with Fig. 4.5); and Fig. 4.19 shows the predicted activations for different size saccades initiated from the same position (compare with Fig. 4.6). The activations are similar to those predicted by the DM model; however, the activation for the saccade initiated from 10 degrees temporal has a more accentuated "slide" phase in the DM model than in the Hill model.

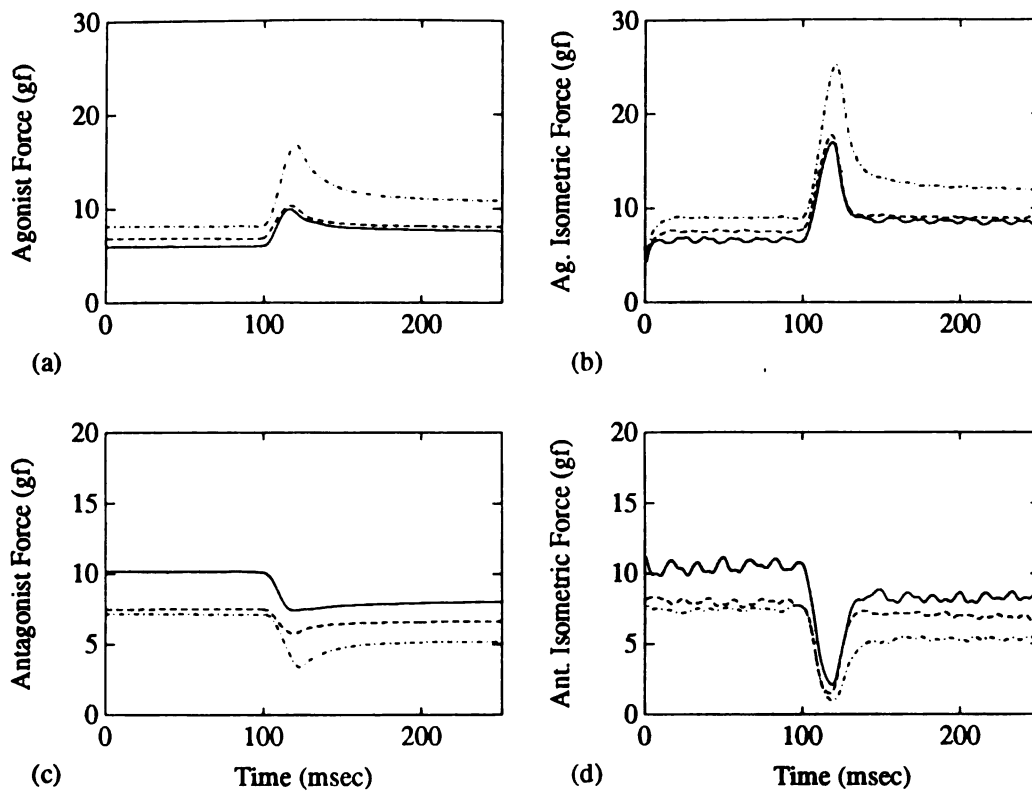
For further comparison, Fig. 4.20 shows 10- and 20-degree "isometric saccades" at primary position, Fig. 4.21 shows 10-degree "isometric saccades" at different initial positions, and Fig. 4.22 shows different size "isometric saccades" at 10 degrees nasal. The Hill model simulations of "isometric saccades" are similar to those from the DM model. (Compare with DM model in Figs. 4.7-4.9, respectively.) Some differences do exist, but it is not clear how significant they are.

This image shows a blank, aged, cream-colored page, likely an endpaper or flyleaf of a book. The paper has a slightly textured appearance with some minor discoloration and faint, illegible markings, possibly from a previous page or a watermark. The left edge of the page is bound, showing the stitching and the inner cover material. The overall tone is warm and vintage.



Hill Model Simulations of 10- and 20-Degree "Isometric Saccades" at Primary Position. Agonist and antagonist isometric forces (b,d) generated by the Hill model when the predicted activations for the normal saccades were used as input under isometric conditions. Agonist and antagonist (a,c) forces measured during normal saccades are also shown. Responses to the activations for 10- (dash) and 20-degree (solid) saccades are shown.
Figure 4.20

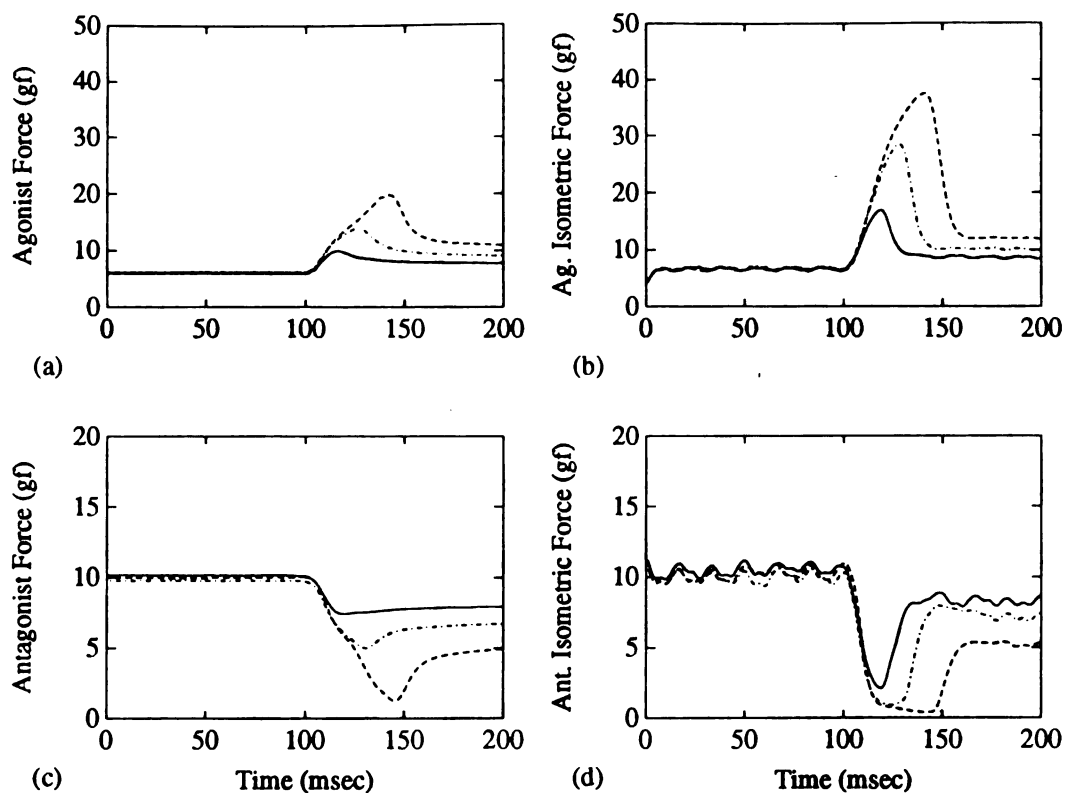




Hill Model Simulations of 10-Degree "Isometric Saccades" Initiated from Different Initial Positions. Agonist and antagonist isometric forces (b,d) generated by the Hill model are shown when the predicted activations for normal saccades were used as input under isometric conditions. Agonist and antagonist forces (a,c) measured during each saccade under normal conditions are also shown. Ten-degree isometric saccades are shown at 10 degrees nasal (solid), primary position (dash) , and 10 degrees temporal (dot-dash).

Figure 4.21





Hill Model Simulations of 10-, 20-, and 30-Degree "Isometric Saccades" at 10 Degrees Nasal. Agonist and antagonist isometric forces (b,d) generated by the Hill model are shown when the predicted activations for the normal saccades were used as input under isometric conditions. Agonist and antagonist forces measured during normal saccades (a,c) are also shown. Responses to the activations for 10- (solid), 20- (dot-dash), and 30-degree (dash) saccades at 10 degrees nasal are shown.

Figure 4.22

5. Comments on the DM and Hill Muscle Models

5.1 Sarcomere Stability

One of the assumptions of the DM model is that all the sarcomeres are the same. How valid is this assumption? Consider a single myofibril, i.e., a chain of sarcomeres connected in series, and assume all sarcomeres are initially identical. Moreover, assume the sarcomeres are $2.5\ \mu\text{m}$ (L_0), at the corner of the plateau region and the negative slope region of the sarcomere length-tension curve (see Fig. 4.2). Now, if one sarcomere in the chain is a little weaker than the others, it will begin to stretch because the forces pulling on it will be slightly larger. The force-lengthening velocity relationship will increase the force of that sarcomere, thereby balancing the forces. However, the resulting lengthening of the sarcomere moves the sarcomere down the length-tension curve, so it generates even less force. As a result, the sarcomere will stretch faster because the velocity dependent force must increase to compensate for the decrease in the length-dependent force. Obviously, this is unstable and the sarcomere will stretch until the passive elasticity dominates. Note, however, that extraocular muscle has a different operating point than L_0 . Instead, the operating point is on the positive slope side of the sarcomere length-tension curve ($1.98\ \mu\text{m}$, see Fig. 4.2). Therefore, if one sarcomere in the chain is a little bit weaker than the others, it begins to stretch, it moves up the length-tension curve, and, therefore, generates more force. The positive slope side of the length-tension curve is stable. Because the normal

operating range of extraocular muscle is in this stable region and because fibers have more inhomogeneity than whole muscle, the assumption that we can model the dynamics of extraocular muscle by a single sarcomere may be reasonable.

5.2 Force-Velocity

The DM and Hill models have similar force-velocity relationships for shortening muscle but not for lengthening muscle. Even the steady-state force-velocity relationship for lengthening muscle is not the same for these two models. However, the exact form of the assumed force-lengthening velocity relationship did not appear to significantly affect the simulations in the Hill model (Fig. 4.14). Therefore, the steady-state force-velocity relationship for the Hill model could probably be modified to match that of the DM model without any significant effects. Even then, however, the Hill model would not produce the same transient lengthening mechanics.

From simulations of the DM model, it is apparent that, with the rate parameters assumed (f and g), the transient properties of lengthening muscle are rapid. (Simulations show that yielding, resulting from sudden changes in lengthening velocity, lasts about 5-7 msec and is small in magnitude-- not shown.) The high rate of attachment may account for the rapid recovery.) The importance of transient properties does not appear to be as great as anticipated. The measured muscle forces do not show unusual transient properties; instead the antagonist muscle always shows a smooth change, qualitatively symmetrical to the agonist force trajectory (see Chapter 2). The question

arises: why aren't transients observed?

The answer may be that the transition to high speeds during saccades is smooth enough that yielding doesn't occur. The DM model exhibits yielding when the steady-state velocity is suddenly changed but not when saccadic velocity profiles are assumed. Since the DM model is based on a single sarcomere and the model does not exhibit transients during saccades, the lack of transients does not have to be explained by properties of sarcomeres in series or parallel combinations of fibers, which are not included in the DM model..

On the other hand, as discussed in the last section, the force- lengthening velocity relationship does appear to play a significant role in the dynamics of eye movements. And, simulations of the DM model gave insights into that. Moreover, they gave insights into the meaning of the manipulations of the Hill model that best generated the force trajectories of extraocular muscle.

5.3 Series Elasticity

As stated earlier, the series elastic element is included in the Hill model to represent the result of quick release experiments. When the force applied to an activated, isometric muscle is suddenly reduced, the muscle length exhibits a sudden reduction in length followed by a more gradual reduction until a new steady-state length is reached. Since a spring has the property that a change in force results in a corresponding change in length, a spring is used to represent the functional component

of muscle that shows a sudden reduction in length whenever there is a sudden reduction in force. This characteristic is often attributed to the tendon, which is made of elastic, collagenous tissue. However, a quick estimate of the stiffness of tendon suggests that this is an unlikely explanation:

$$\text{Young's Modulus, } E_{\text{ten}} = 10^9 \text{ N/m}^2 \quad (\text{Wainwright et al., 1976})$$

$$= 10^{10} \text{ dyne/cm}^2$$

$$= 10^7 \text{ gf/cm}^2$$

$$\text{Tendon stiffness, } K_{\text{ten}} = E_{\text{ten}} A_{\text{ten}} / L_{\text{ten}}$$

A_{ten} , cross-sectional area of tendon

L_{ten} , length of tendon

$$L_{\text{ten}} = .6 \text{ cm LR; } .05 \text{ cm MR (Miller \& Robins, 1987)}$$

$L_{\text{ten}} = .6 \text{ cm}$ will be used because the longer the tendon, the less stiff the tendon (all else being equal).

Since the tendon has a fairly wide insertion, it probably has a relatively large cross-sectional area. As a rough estimate we will assume:

$$A_{\text{ten}} = A_{\text{mus}} / 4 = .024 \text{ cm}^2$$

$$K_{\text{ten}} = 3.92\text{e}8 \text{ dyne/cm}$$

$$= 4.0\text{e}5 \text{ gf/cm}$$

$$= 6480 \text{ gf/deg}$$

$$\text{Series elasticity, } K_{\text{se}} = 2.3 \text{ gf/deg (estimated from human data, see Chapter 3)}$$

$$= 143 \text{ gf/cm}$$

$$= 1.4e5 \text{ dyne/cm}$$

So,

$$K_{ten} \gg K_{se}$$

Since tendon stiffness is three orders of magnitude greater than the series spring stiffness for these muscles, the elasticity must be in the muscle itself.

The most likely location for the series elasticity is in the cross-bridges, although elastic, connective tissue throughout the muscle may also contribute. Cross-bridge sites are the only ones that can directly explain experimental results that show the magnitude of the series elasticity varies with innervation (cat; Collins, 1971). Fortunately, the DM model can be used to explore this possibility since muscle stiffness is proportional to the zeroth moment of the bond distribution and is derived as follows:

$$\begin{aligned} K_{\frac{1}{2}\text{-sarc}}(t) &= \frac{msk}{2l} \int_{-\infty}^{\infty} n(x,t) dx \\ &= \frac{msk}{2l} M_0(t) \\ &= \frac{mskh}{2l} Q_0(t) \end{aligned}$$

Because springs added in parallel increase the stiffness and springs added in series decrease the stiffness and because all cross-bridges are assumed to have the same linear stiffness, the total muscle stiffness is the half-sarcomere stiffness times the number of half-sarcomeres in parallel divided by the number of half-sarcomeres in series, or:

$$K_{mus} \propto \frac{A}{L}$$

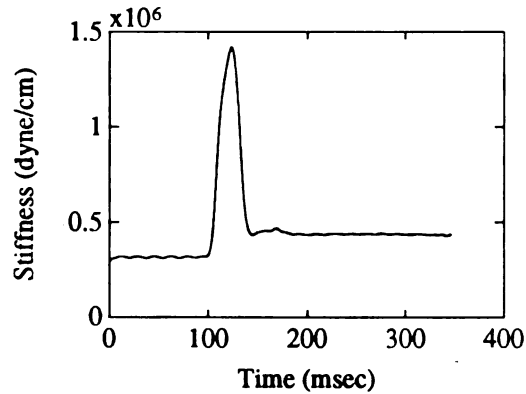
$$K_{mus}(t) = \frac{A_{pp} m_s k h}{4 l n_s} Q_0(t)$$

$$= \frac{A_0}{2 n_s} k_1 \frac{1}{2}^{-sarc}$$

where the parameters are defined as earlier and

$K_{mus}(t)$, instantaneous muscle stiffness

Fig. 4.23 shows the instantaneous muscle stiffness during a 20-degree saccade from primary position. Note that the stiffness is the same order of magnitude as that expected from experimental measurements. Therefore, the DM simulations support the idea that the series elasticity of extraocular muscle is primarily in the cross-bridges.



DM Simulation of Muscle Series Elasticity during a 20-Degree Saccade from Primary Position.
Figure 4.23



5.4 Modelling Extraocular Muscle

The initial work on this project suggested that the DM model gave a much more realistic representation of extraocular muscle than the Hill model did. However, isolating the Hill muscle model from the saccade model (orbit and muscle pair model) and exploring parameter variations in it alone, led to straight forward modifications that resulted in the Hill model also reflecting the measured properties of extraocular muscle.

It is, however, important to recognize that deriving a Hill model that generates responses similar to those recorded in extraocular muscle is not necessarily very useful in and of itself. As already mentioned, simply mathematically fitting a model does not yield any insight into the system.

In this study, the DM model was a necessary step to making a connection between the mathematical parameter adjustment in fitting the Hill model to the data and a potential biological correlate of that adjustment. The DM model gave insights that suggest the roles of the different fiber types in extraocular muscle are important to consider. Moreover, if one assumes that the agonist muscle has a much higher proportion of large fibers active than antagonist muscle and that the properties of agonist and antagonist muscle are dominated by the assumed dominant fiber type, then the force-velocity relationship will be different in the agonist and antagonist muscles. This idea corresponds with the parameter modification that allowed the Hill model to generate the data. Without this insight, there would be no physiological justification for the parameter modification in which case it would be difficult to justify the model as



representative of the system.

One can generate many different models with the same input/output characteristics. Therefore, the purpose of the model must be considered. For example, in this study extraocular muscle is modelled to further our understanding of the oculomotor system. Therefore, the structure of the system is important. Another model with the same input/output characteristics would not be useful. The DM model is directly based on the mechanism of contraction and is, therefore, useful for making new associations between the data and the physiology. For example, it is certainly a more useful model if one is studying how a disease affects the system. However, the DM model is more complicated and computationally slower than the Hill model. The Hill model represents the macroscopic manifestations of the molecular interactions. With appropriate modifications in the Hill model (as dictated by insights gained from the DM model), the former model appears to adequately reflect the functional macroscopic components of extraocular muscle. As a result, the Hill model may be useful for additional simulation studies on a gross scale. For example, the Hill model could be used to explore the interactions of the six extraocular muscles during eye movements.

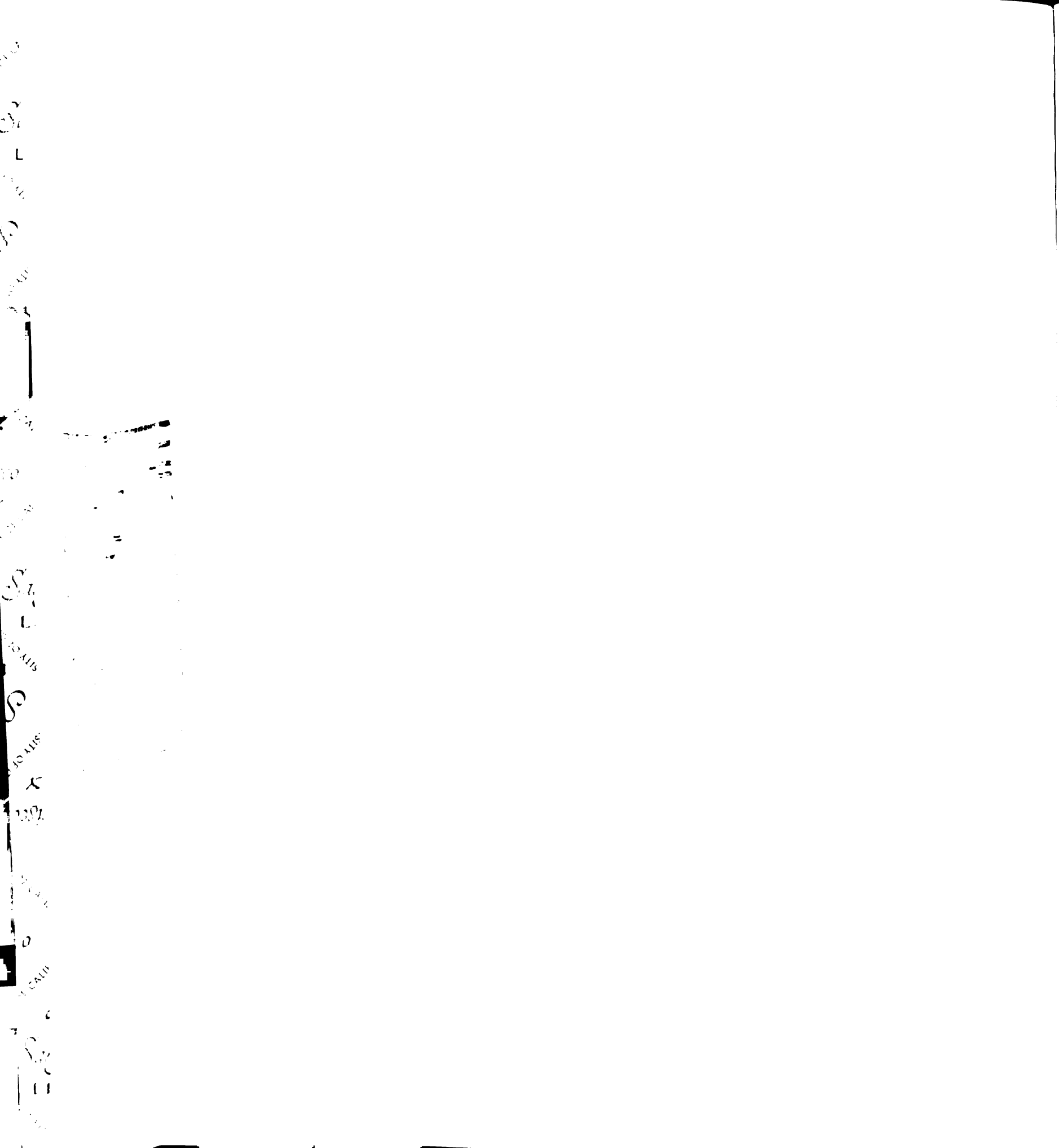


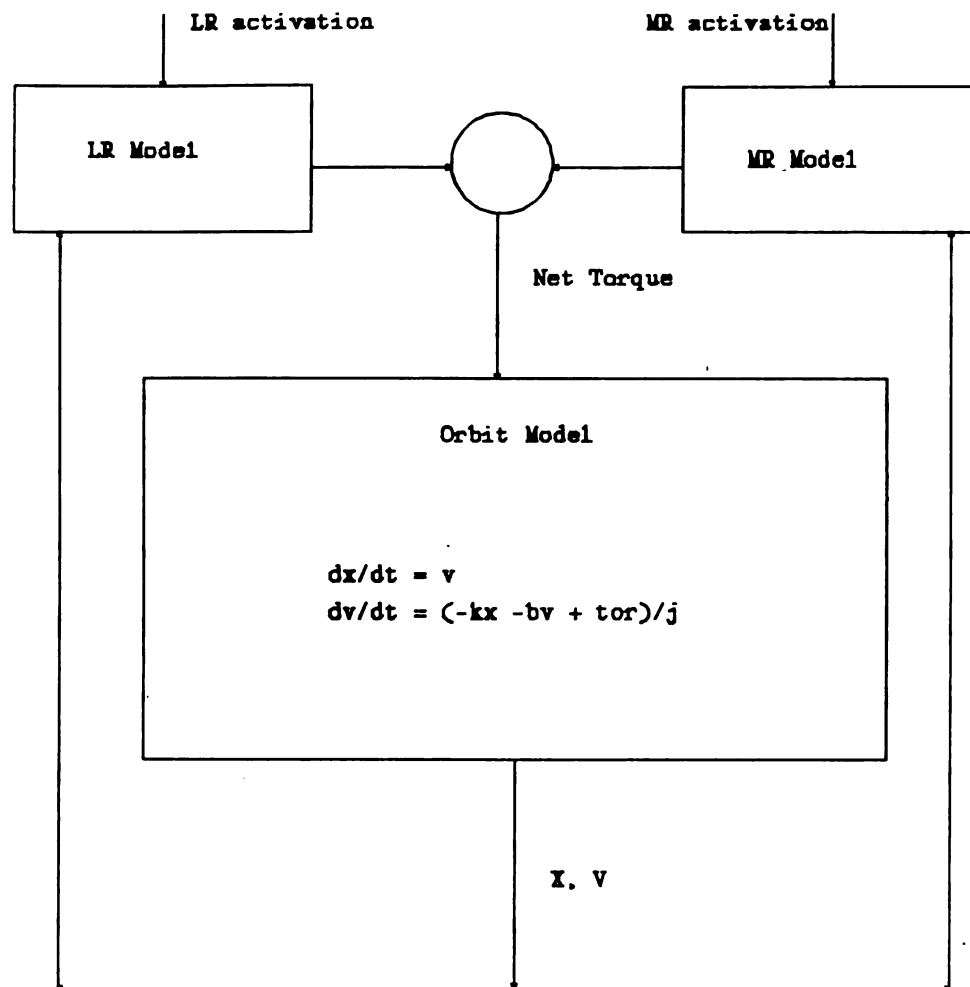
Orbital Mechanics

A model of the horizontal saccadic system includes the agonist muscle, antagonist muscle, and orbital models. In Chapter 4, two models were developed (Hill and DM) for each extraocular muscle in this subsystem of the oculomotor system. In this chapter, the orbital model will be studied. A model of the orbital mechanics will be derived from the force and kinematic data recorded in the monkey during saccades (see Chapter 2). Then, an experiment in which the step response of the globe was measured will be discussed.

1. The Whole Picture

Fig 5.1 shows the interaction of the muscle models and the orbital model. Basically, the output of the muscle models is combined to calculate net torque, which is the input to the orbital model; the outputs of the orbit model (eye position and velocity) are received as input by the muscle models along with activation, and the cycle continues. Therefore, if the orbital model exactly represents the monkey's orbit (at this level of resolution), the trajectories generated by simulations of the model of the saccadic system would replicate the recorded data.





x = eye position
 v = eye velocity
 k = stiffness
 b = damping
 j = inertia

**Interaction of Components in the Horizontal Saccadic System Model.
Figure 5.1**



2. Determining a Model of the Orbit from Force and Kinematic Data

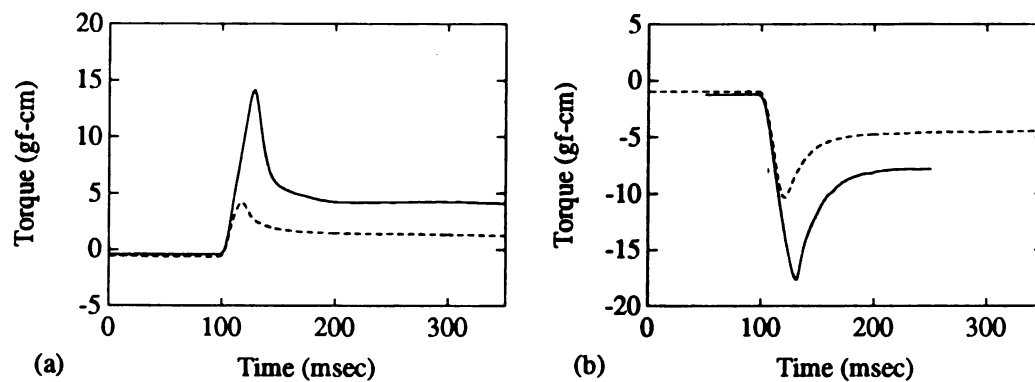
The orbital mechanics affect the dynamics of horizontal saccadic eye movements, and, therefore, must be adequately represented in the model of eye movements. By Newton's second law, we know the sum of the torques exerted by the two muscles and the orbit equals zero, so the mechanics of the orbit will interact with the forces and affect the trajectory of the eye.

In the model of the horizontal saccadic system described in Chapter 3, the globe was represented by an inertia-spring-dashpot combination and the equation of motion was a linear, second-order differential equation with constant coefficients. This assumes either that there are no non-linearities or asymmetries in the orbital mechanics or that the variations from the linearity assumption are negligible. Moreover, even though the orbital mechanics have been shown to be better represented by a series of at least two viscoelastic units (spring-dashpot combinations) (Robinson, 1964), a sensitivity analysis on a saccade model, similar to the one simulated in Chapter 3, suggested the mass-spring-dashpot representation was sufficient to reproduce the saccade kinematics (Bahill, 1981). In this section, the data from the alert, behaving monkey will be used to determine a model of the orbital mechanics, and the significance of any apparent non-linearities will be explored.

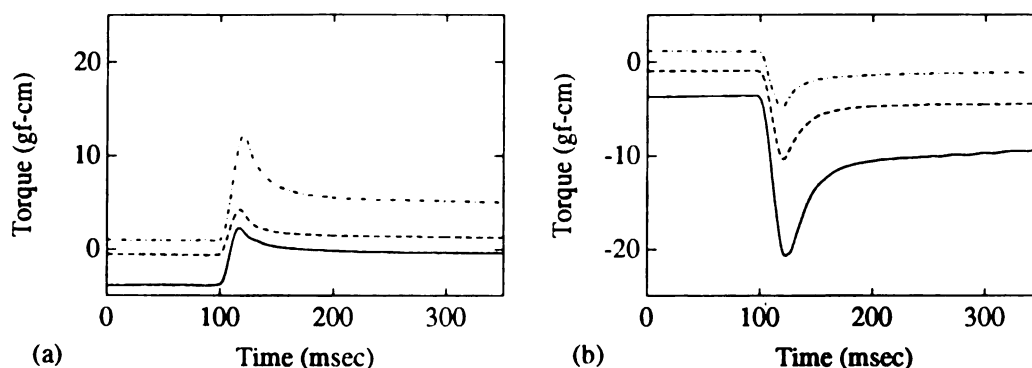
2.1 Net Torques during Monkey Saccades

The following two figures show the net torque calculated from the forces recorded in the monkey during temporal and nasal saccades. (See Chapter 2 for the methods on data collection and Chapter 4 for the methods on estimation of absolute force from the data.) Figure 5.2 shows the net torques during 10- and 20-degree saccades and Fig 5.3 shows net torques during 10-degree saccades initiated from different positions (10, 0, -10 degrees). A position-dependent non-linearity and a temporal/nasal asymmetry are especially apparent in Fig. 5.3. First, recall that the velocity profiles during 10-degree temporal saccades were the same, independent of initial position (see Chapter 2). As a result, if a linear differential equation with constant coefficients describes the system, the net torque profiles for all the 10-degree temporal saccades should be the same shape; the only difference should be a shift in the baseline net torque (i.e., the curves should be centered about the net torque for fixation). However, this is clearly not the case, the torque profiles vary significantly in peak change in torque. In addition a directional asymmetry is observed. During temporal saccades, the net torque applied from primary position is less than that applied in the other positions. In contrast, during nasal saccades the net torque increases as the agonist muscle moves more in the "on" direction. (Note that the observation of an asymmetry does not depend on the estimate of muscle force and the assumption that the muscles exerted the same forces at primary position; not shown.) The torque profiles are not expected to be the same during

temporal and nasal saccades, because the kinematics are not the same. However, the position-dependent variations should be the same.



Net Torque Profiles Recorded from a Monkey during a 10- and 20-Degree Saccade from Primary Position. Net torques during 10-(dash) and 20-degree (solid) temporal (a) and nasal (b) saccades are shown.
Figure 5.2



Net Torque Profiles Recorded from a Monkey During 10-Degree Temporal and Nasal Saccades Initiated from Different Positions. Net torques during 10-degree saccades are shown. In (a), temporal saccades are initiated from 10 degrees nasal (solid), primary position (dash), and 10 degrees temporal (dot-dash). In (b), nasal saccades are initiated from 10 degrees temporal (solid), primary position (dash), and 10 degrees nasal (dot-dash).

Figure 5.3

Evidence from cats suggest the elasticity and viscosity are position dependent (Collins, 1971); stiffness and viscosity increases monotonically (although in different manners) with rotation from primary position. There is evidence from human strabismus patients that the orbital elasticity is non-linear in the extremes of the range of eye movements (Collins, 1971); however, within the range of movements studied here, the elasticity is expected to be linear (Collins, 1971, Robinson et al., 1969), even in cats (Collins, 1971).

2.2 "Best Fit" Orbit Model

The model of the orbit was assumed to be of the basic form described in Chapter 3: a combination of an inertia, spring, and dashpot; however, only J was assumed to be constant. Therefore, the equation of motion for the orbital model was assumed to be:

$$J\frac{d^2\theta}{dt^2} + B(\theta, \frac{d\theta}{dt}) + K(\theta) = T$$

where,

J,	inertia
B($\theta, d\theta/dt$),	viscosity
K(θ),	elasticity
T,	net torque

J was assumed known ($J = 2.88 \times 10^{-6}$) only B($\theta, d\theta/dt$) and K(θ) had to be identified.

Identifying these parameters was approached using two methods. Method 1 used two steps. First, K(θ) was estimated from the steady-state, isometric data by assuming K(θ) was a first or second order polynomial (K(θ) equals $p_0 + p_1\theta$ or $p_0 + p_1\theta + p_2\theta^2$) and minimizing the error between K(θ) and net torque, i.e.,

$$\min \sum (K(\theta_i) - T_{ss_i})^2$$

where T_{ss} is the net torque under steady-state, isometric conditions. Then B($\theta, d\theta/dt$) was found in a similar manner by assuming it is a first or second order polynomial

$(B(\theta, d\theta/dt) = p_3 d\theta/dt + p_4 \theta d\theta/dt + p_5 (d\theta/dt)^2)$ minimizing:

$$\sum (B(\theta_i, \frac{d\theta_i}{dt}) - [T_i - J \frac{d^2\theta_i}{dt} - K(\theta_i)])^2$$

where T, J, and K are known.

Method 2 used a single step in which $B(\theta, d\theta/dt)$ and $K(\theta)$ were identified simultaneously using all the data (i.e., not just steady-state isometric data for K). In this case, $B(\theta, d\theta/dt) + K(\theta)$ was assumed to be a first or second order polynomial with terms involving $d\theta/dt$ describing B and the remaining terms describing K (i.e., the system was defined as $p_0 + p_1\theta + p_3 d\theta/dt$ or $p_0 + p_1\theta + p_2\theta^2 + p_3 d\theta/dt + p_4 \theta d\theta/dt + p_5 \theta^2$, where p_0-p_2 are associated with K and p_3-p_5 are associated with B). In this case the following equation was minimized:

$$\sum ([B(\theta_i, \frac{d\theta_i}{dt}) + K(\theta_i)] - [T_i - J \frac{d^2\theta_i}{dt}])^2$$

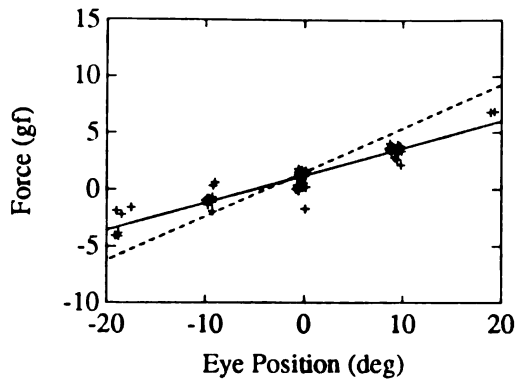
where T and J are known.

The main difference between method 1 and method 2 is that method 1 derives K from steady-state isometric data only and method 2 derives it from all the data.

The two methods generated different estimates of K. The first order polynomial fits were:

$$K(\theta) = .24\theta + 1.23, \quad \text{method1}$$

$$K(\theta) = .385\theta + 1.73, \quad \text{method2}$$



K(θ) of Orbital Model. The steady-state isometric fixation data recorded in the monkey (+) is plotted. Two estimates of the orbital elasticity, $K(\theta)$ are shown. The estimate of elasticity derived by method 1 (described in text) is shown by the solid line and the estimate derived by method 2 (see text) is shown by the dotted line.

Figure 5.4

Figure 5.4 shows the steady-state isometric data (+) used to calculate K in method 1 along with the estimates of K by method 1 (solid) and method 2 (dash). For the second order polynomial fit of K , p_2 was negligible in both cases.

In both cases, the first and second order polynomial fits for B are:

$$B(\theta, \frac{d\theta}{dt}) = .0092 \frac{d\theta}{dt}, \quad 1st \text{ order}$$

$$B(\theta, \frac{d\theta}{dt}) = .0098 \frac{d\theta}{dt} + (2.8e-6) \frac{d^2\theta}{dt^2} - (1.7e-4) \theta \frac{d\theta}{dt}, \quad 2nd \text{ order}$$

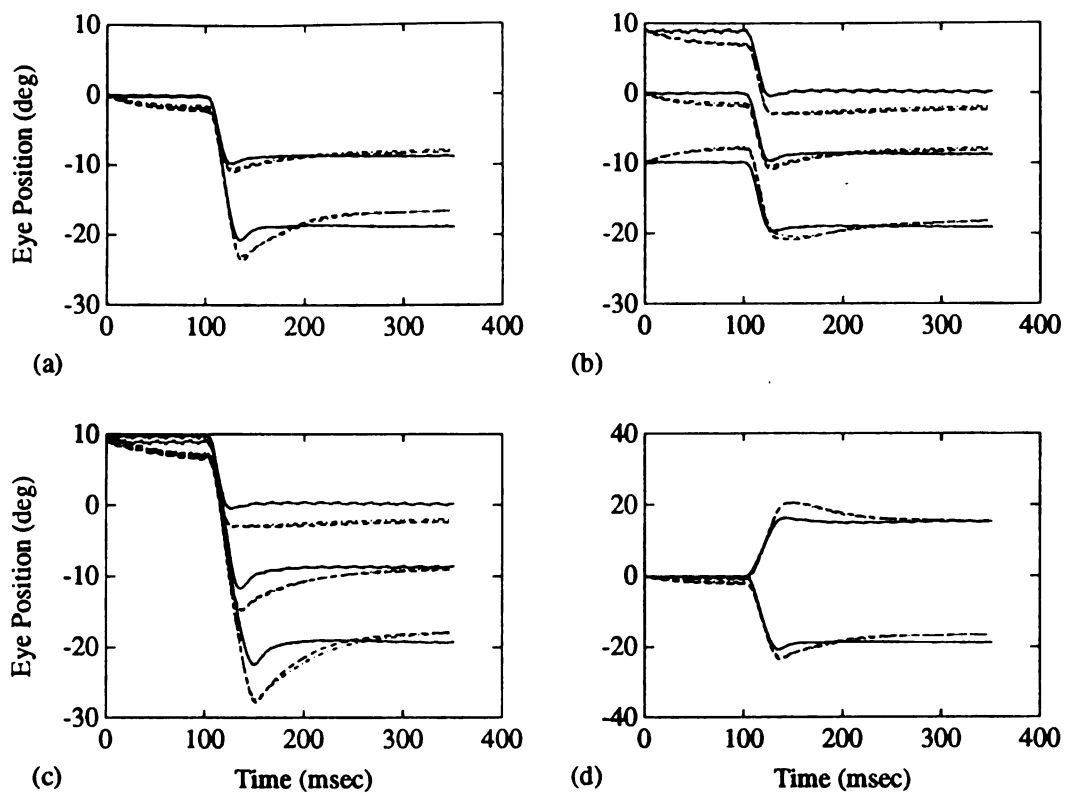
As mentioned, if the orbital model reflects the dynamics of the orbit, then

simulations of saccades with the muscle models derived in Chapter 4 and the orbital model derived above will produce saccade trajectories that replicated those measured in the monkey.

Figure 5.5 shows simulations of the DM muscle models and the orbital model estimated with method 1. The solid lines represent monkey eye position trajectories, the dashed lines represent the linear orbital model results (first order polynomial) and the dash-dot lines represent the non-linear orbital model results (second order polynomial). Figure 5.5 a shows 10- and 20-degree temporal saccades initiated from primary position, b shows 10-degree temporal saccades initiated from different initial positions, c shows different size temporal saccades initiated from the same position, and d shows 20-degree temporal and nasal saccades initiated from primary position.

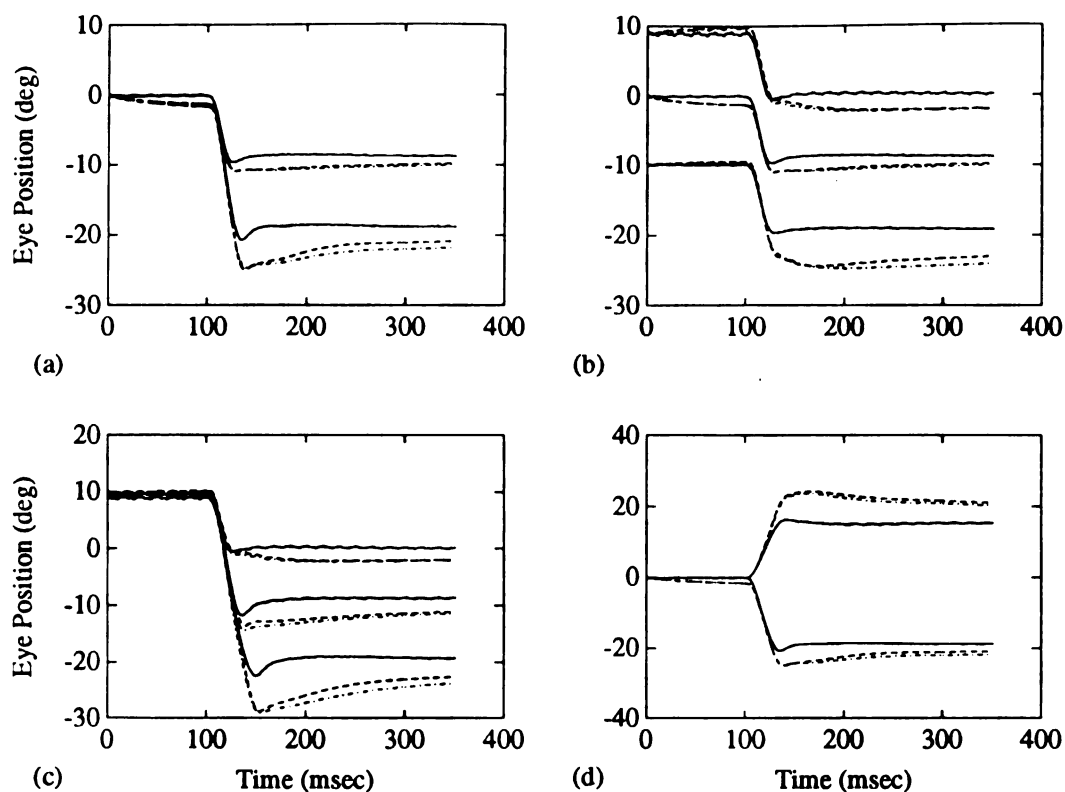
Figure 5.6 shows analogous trajectories generated with the orbital models estimated with method 2.

Notice that the non-linear models do not improve the eye position profiles. Therefore, the second order terms can be neglected. Also, the model estimated by method 1 reproduces the initial position fairly well but not the final position whereas the model estimated by method 2 has similar error to method 1 in initial position but less in the final position. Overall, the model estimated by method 2 appears to be slightly better at generating the saccadic trajectories recorded in the monkey.



Simulated Eye Position Profiles Using the Orbital Model Derived by Method 1. Saccade trajectories from the linear orbital model (dash), the non-linear orbital model (dot-dash), and the monkey (solid) are shown for 10 and 20-degree temporal saccades (a); 10-degree temporal saccades initiated from different positions (b); different size saccades initiated from the same position (c); and 20-degree temporal and nasal saccades initiated from primary position (d).

Figure 5.5



Simulated Eye Position Profiles Using the Orbital Model Derived by Method 2. Saccade trajectories from the linear orbital model (dash), the non-linear orbital model (dot-dash), and the monkey (solid) are shown for 10 and 20-degree temporal saccades (a); 10-degree temporal saccades initiated from different positions (b); different size saccades initiated from the same position (c); and 20-degree temporal and nasal saccades initiated from primary position (d).

Figure 5.6

Moreover, the parameters derived from method 2 are similar to those derived in Chapter 3:

$$K(\theta) = .35\theta \quad (\text{Chapter 3}); \quad K(\theta) = .385\theta + 1.73$$

$$B\left(\frac{d\theta}{dt}\right) = .01 \frac{d\theta}{dt} \quad (\text{Chapter 3}); \quad B\left(\frac{d\theta}{dt}\right) = .0092 \frac{d\theta}{dt}$$

The original estimates are fairly representative.

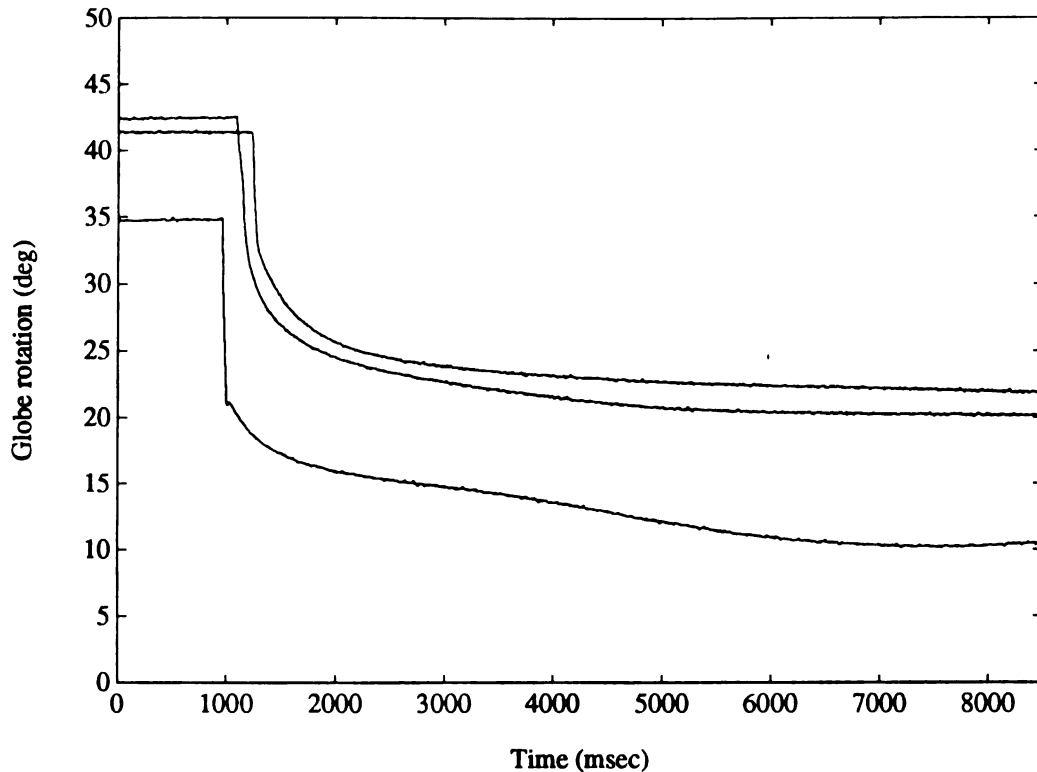
For individual trials, the orbital mechanics can be better fit by a model with two viscoelastic elements (spring-dashpot) than with one. However, a physical explanation in terms of the properties of the tissues making up the orbit is not apparent and, therefore, will not be further explored here.

One problem in deriving the orbital model with the existing data is that the data in the space over which we are interested in defining our parameters ($\theta = \pm 20$ deg, $d\theta/dt = \pm 1000$ deg/s) is not very dense. We only have data at high velocities over a very narrow range of positions. To better fit the parameters over the range of interest we need saccade data over a much larger field so that we can get high velocity data at ± 20 degrees eccentricity.

3. Preliminary Data of Orbit Step Responses

At the completion of the neurophysiological experiments an experiment was carried out on one monkey to measure the step response of the orbital mechanics. The monkey was deeply anesthetized by using intravenous sodium pentobarbital (50 mg/kg).

The conjunctiva in the eye with the implanted search coil was opened and the insertions of the medial and lateral rectus muscles were located and completely severed while care was taken not to disturb the implanted search coil that was already on the eye for the purposes of the chronic neurophysiological experiments. The vertical rectus and oblique eye muscles were left intact. The animal was then placed inside the eye movement measurement system where the previously obtained calibration procedures, made when the monkey was alert, allowed us to measure the position of the globe with the horizontal muscles now detached. A suction contact lens was placed on this eye (see Keller & Robinson, 1971, for details on this contact lens system). Through a system of threads and pulleys attached to this contact lens, the eye was slowly rotated to an eccentric position in the orbit and then was suddenly released to return toward the rest position under the passive influence of the orbital tissues. The motion of the eye during this rapid release response was measured by the search coil magnet recording system already described. The recorded motion signal was digitized at 1 khz and was stored on disk for subsequent analysis. Nasally directed rotations were alternated with temporally directed movements, since the eye failed to return to the original rest position after each rotation. Following this series of measurements (which took about 15 min to complete), the animal was removed from the eye measurement system and taken immediately to the histology laboratory for euthanasia without regaining a state of alertness.



Step Response of Orbit (with Medial and Lateral Recti Detached) in Anesthetized Monkey
Figure 5.7

The intent was to verify the order of the spring and dashpot constant estimates. Figure 5.7 shows the trajectories for those three trials. Note that the final position was very different for different initial displacement. This was unexpected because we had expected a constant equilibrium point. Although no strong conclusions can be drawn from this brief experiment, the results strongly suggest that the contribution of the

vertical extraocular muscle to the orbital mechanics in our model is significant. The orbit step response measured in a human under topical anesthesia only, with the medial and lateral recti detached, returned to primary position (Collins, 1971). Therefore, innervation of the vertical extraocular muscle appears to be important. The step responses of the orbit in the anesthetized animal is highly dependent on initial position, and, therefore, the step responses from several more initial positions has to be measured before $B(\theta, d\theta/dt)$ and $K(\theta)$ can be characterized.

4. Conclusions

In this chapter, a model of the orbital mechanics was derived from the physiological data described in Chapter 2. The model does not accurately reproduce the mechanical properties of the orbit, so these properties should be further explored. The step response of the orbit in an anesthetized animal showed very different properties than those exhibited in the alert, behaving animal. Most notably, in the anesthetized animal the globe did not return to the same position after each trial. This suggests the innervation of the vertical and oblique muscles are critical in producing the elastic properties of the orbital mechanics in the horizontal saccadic system.

General Discussion and Conclusions about the Mechanical Properties of the Oculomotor Control System

1. Implications of the Physiological Results

The physiological results (Chapter 2) were somewhat surprising in light of the established non-linear properties of muscle. Agonist and antagonist force profiles are qualitatively symmetric and smooth. However, the macroscopic muscle properties are innervation, length, speed, and direction (of movement) dependent and non-linear. At the same time, the neural inputs to the agonist and antagonist muscle are reciprocal in nature i.e., any increase in firing rate to the agonist muscle is accompanied by a decrease in firing rate to the antagonist muscle. Because the neural inputs are reciprocal while the muscle properties are highly non-linear, and asymmetrical (shortening versus lengthening), the qualitative symmetry at the output (force) is very surprising. The DM model simulations suggest that the variety of fiber types in extraocular muscle may play an important role in the resulting symmetry in shape of the muscle profiles (see Chapter 4).

One expected result of the individual muscle force measurements is the verification that all saccades within ± 20 degrees of primary position are driven by contraction of the agonist muscle. This is not surprising, but it is mechanically possible

to move the eye inward (toward primary position) by relaxing the contracted muscle. Since the dynamics of relaxation differ from those of contraction, this would have resulted in different kinematics during inward and outward saccades, which was not observed. As a matter of fact, the constancy of the saccade kinematics for a particular saccade magnitude and size, independent of initial position, is surprising given the non-linear length-dependent properties of muscle. As has been discussed in the literature (Robinson, 1971), the static, length-dependent non-linearities of the LR and MR tend to cancel each other; however, the constancy of kinematics during saccades is more complicated. For example, the agonist muscle that drives the movement is centered about different operating points and the ocular motoneuron properties are also position dependent. It brings to question why the system bothers to generate this kinematic constancy. It does not seem essential since the system does not generate the same kinematics for comparable nasal and temporal saccades. The answer may simply be that the exact kinematics are not critical, but, within the range of movements studied, the kinematics are constant.

2. Single Muscle Models

2.1 Implications of DM Model Simulations

The DM model yielded insights into a possible physiological correlate of the parameter manipulations of the Hill model. In this way the DM model provides a

helpful link between a functional, lumped parameter model and the actual mechanism of contraction. The same insights suggest that the force-velocity relationship for lengthening muscle should be studied in both the slow and fast fibers of extraocular muscle. Moreover, this model is especially useful for studying things like muscle activation because the biological link is explicit.

2.2 Implications of Hill Model Simulations

Because the force profiles were less complicated than expected, the Hill model appears to be effective in representing the dominant properties of extraocular muscle. It is important to note, however, that even though the Hill model could be fixed to fit the data without the DM simulations, the results would not have had any meaning in terms of physiological correlates of the parameter modifications. With the results of this study, however, the Hill model can be effectively used in future simulations of the oculomotor system.

2.3 Validity of the Assumption That All Sarcomeres Are Identical

As discussed in Chapter 4, the validity of the assumption that all sarcomeres are identical is uncertain. In many skeletal fibers, the ends contract while the middle stretches. Although the operating point on the length-tension curve of extraocular muscle offers some stability for eye movements within a normal range, the issue has not

been explored in an extensive manner. The lack of yielding in the force profiles of lengthening muscle suggests that any existing instabilities do not dominate the behavior. One way to begin addressing this question is suggested here. We could look at deviations in the expected kinematics and dynamics of saccadic eye movements outside the normal range of movements i.e., eye movements operating in the plateau region and negative slope region of the length-tension curve. Unexpected behavior may result from instabilities not occurring in the range of movements already studied. Also, it has been shown that sarcomere instabilities can account for a wide range of results from single fiber studies (e.g., Morgan, 1990). However, the effects of inhomogeneity on macroscopic muscle properties is not known.

3. Theoretical Experiments

As mentioned, models can be helpful in extending our basic understanding of the oculomotor system (and muscle systems in general). The models allow us to run theoretical experiments. We can vary model parameters and simulate the effects on the resulting eye movements. This can lead to insights at several levels. First, it helps us understand the system itself and the role of different components. In this case, both the DM and Hill models are useful because they give insights into different aspects of the system. Second, these theoretical experiments may be able to aid in localizing the source of eye movement disorders, or, at least, a better understanding of them (the DM model, especially); and, thereby, lead to insights for potential treatments. Third,

theoretical experiments of treatments to eye movement disorders could prove useful (Again, the DM model more so than the Hill model). For example, the effect of implanting synthetic materials as muscle substitutes could be simulated. With an improved model (i.e. separate representation of different fiber types in the DM model), the results of the application of a drug that preferentially affects one fiber type could even be simulated. (For example, curarization blocks all the twitch fibers leaving only the slow component active.) Fourth, theoretical experiments may prove to be very insightful into understanding adaption, especially post-surgical, of the oculomotor system.

4. Improvements in Experimental Procedures

4.1 Procedural Modifications

A few aspects of the experiment limit the amount of information we can derive from the data; however, these can be remedied in the future. First, the extent to which the force transducers affected the eye position, velocity, and muscle force profiles during saccades is not known. As discussed in Chapter 2, circumstantial evidence suggests any damage was limited, but this is not a strong conclusion. The issue can be resolved in the future by recording eye position and velocity profiles before as well as after the implantation of the force transducers. By establishing baseline eye kinematics, we can

establish whether or not the implanted force transducers caused any change in the kinematics.

Second, absolute forces could not be determined from the present measurements. The reason for this was that the force transducer amplifiers underwent several modifications during the course of the experiment, after the gauges were already implanted. We couldn't adequately track the effects of these changes, and, therefore, couldn't establish the correspondence between the original calibrations, the experimental measurements, and the final, post-experimental calibrations. This problem can be remedied by using the same amplifier throughout the experiment, by more carefully determining the effect of each change as the change is made, or by removing the force transducers before failure and recalibrating.

4.2 Reasons for Procedural Modifications

Obviously, knowing the extent to which the force transducers affected the saccade trajectories is important in determining the mechanical properties of the system. At this point, we may be attributing abnormalities caused by the transducers to the normal eye movement system.

Knowing the absolute forces is important for a couple of reasons. First, the net torque acting on the globe can only be established when the absolute forces are known. Therefore, the mechanical properties of the orbit can not be determined with certainty until the absolute forces are known. Second, as mentioned in Chapter 4, there is some

evidence that the MR may exert higher forces than the LR. Obviously, knowing the absolute forces would clarify this situation in the monkey.

5. Related Experiments

5.1 MR Twitch and Length-Tension Profiles During Electrical Stimulation

Even if the MR were found to exert more force than the LR, it would not be apparent, with the existing data, whether the larger forces resulted from different muscle properties or from different levels of muscle activation. Measuring the total, active, and passive length-tension curves of the MR for several levels of electrical stimulation as well as the twitch response would be very useful. First, the maximum tetanic force profile, the rate of rise in tension, the passive force profile, and the twitch response could be compared to similar measurements in the LR (Fuchs & Luschei, 1971). This would help establish the degree of similarity between the MR and LR, which would allow us to begin to establish mechanical or neural sources of observed asymmetries. This information would allow us to model each muscle individually. Then, simulations may lead to interesting insights into the similarities and differences in MR and LR activations. For example, we could explore how symmetrical the activations are for analogous saccades i.e., is the LR activation for a 10-degree temporal saccade from primary position the same as the MR activation for a 10-degree nasal saccade from primary position, even though the resulting trajectories are asymmetric (temporal/nasal



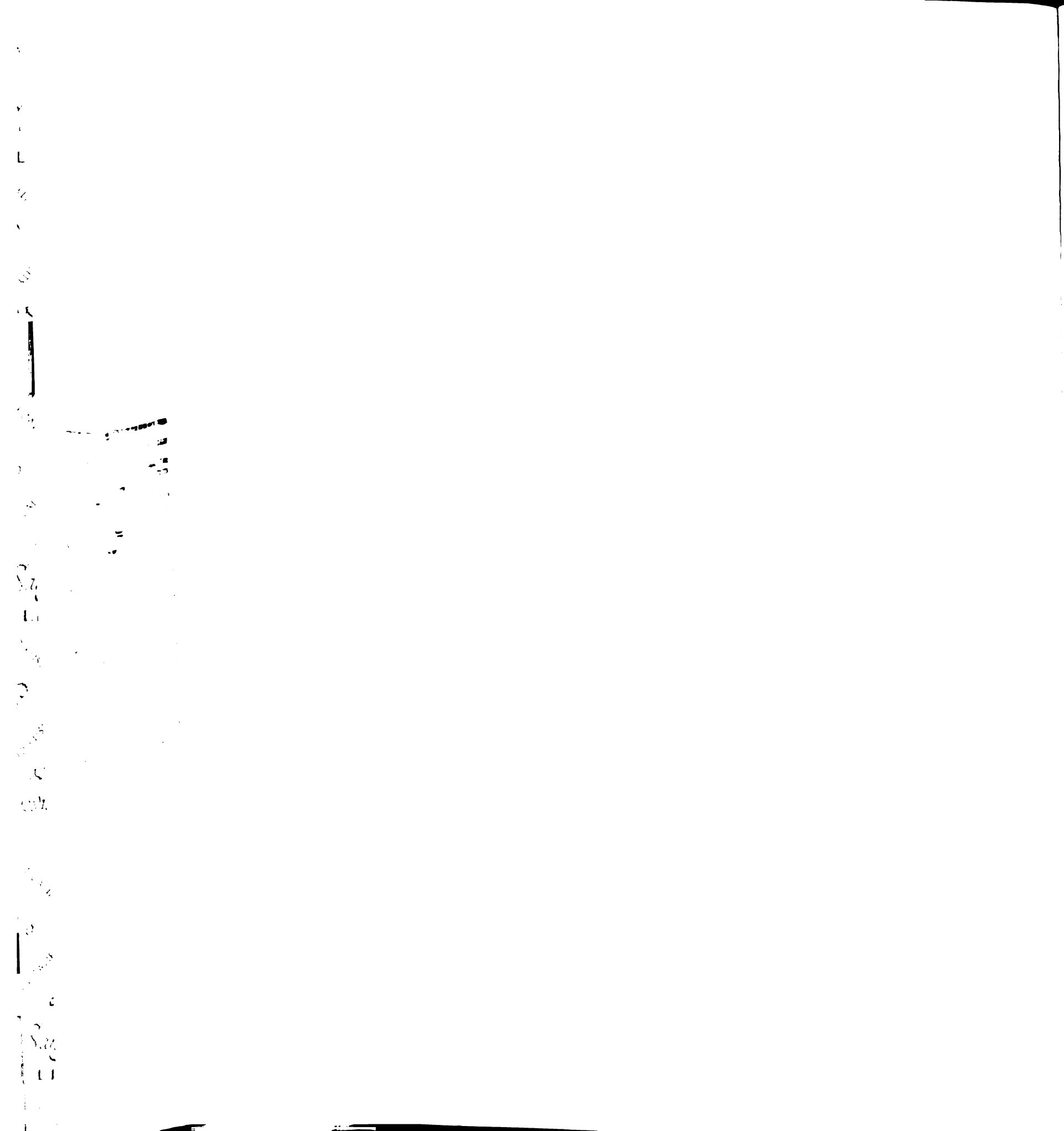
asymmetry). This would give insight into how general the central nervous system command signals have to be. (The partially innervated curves provide useful information in conjunction with the next suggested experiment.)

5.2 MR and LR Length-Tension Profiles in an Active, Alert Monkey

Using the implanted force transducers to record the length-tension relationship of the LR and MR in the alert, behaving monkey (i.e., use Hering's law to vary the level of innervation by having the monkey fixate different positions with eye not being manipulated) would provide a foundation for comparison with the human data recorded during strabismus surgery. It would help to further establish the degree to which the direct comparison of the monkey and human eye movement systems is valid and to fine tuning the model. Moreover, when combined with the results of the above mentioned experiment (length-tension curve under artificial stimulation), we could establish the relationship between levels of artificial stimulation and normal levels of muscle activation.

5.3 MR and LR Force Profiles During "Isometric Saccades"

Another useful experiment would be to measure LR and MR forces during "isometric saccades" (the unmanipulated eye makes a saccade, while the measured eye is held isometric). The most information would be gained from recorded forces during



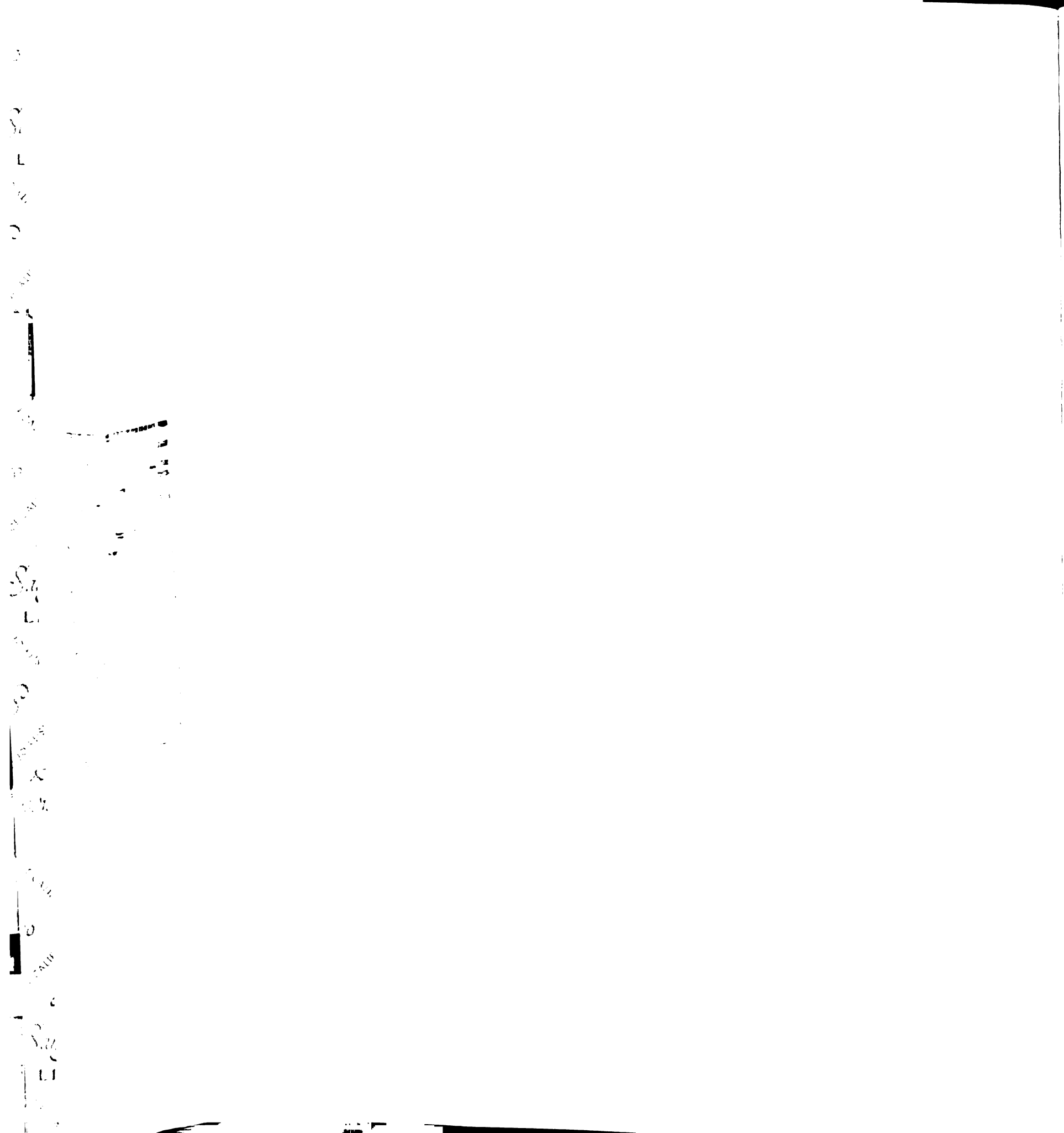
saccades of 10-, 20-, and 30-degrees from the same initial position as well as the same size saccade from several different initial positions. This would provide information that can be used to test the model by comparing the predicted responses to the measured responses.

5.4 Implant Force Transducer on Vertical Extraocular Muscles

Another interesting experiment would be to implant a transducer on the superior oblique and other vertical extraocular muscle. Since some data suggests the orbital elasticity is not symmetrical with respect to primary position (Chapter 5 and Collins et al., 1981) and that the orbital mechanics are significant during saccades (Chapter 2), it is possible that the vertical extraocular muscles play a more significant role than ordinarily assumed in determining the apparent properties of the orbital mechanics during horizontal saccades. Force measurements in the vertical extraocular muscles would help answer this question.

5.5 Measure Orbital Mechanics (LR and MR detached) While Varying Innervation

Another experiment that would address the same question is to measure the orbital mechanics (with the LR and MR detached) while the unmanipulated eye fixates at different horizontal eye positions. For each fixation position of the unmanipulated eye, measure the force necessary to hold the eye at several eye positions and measure



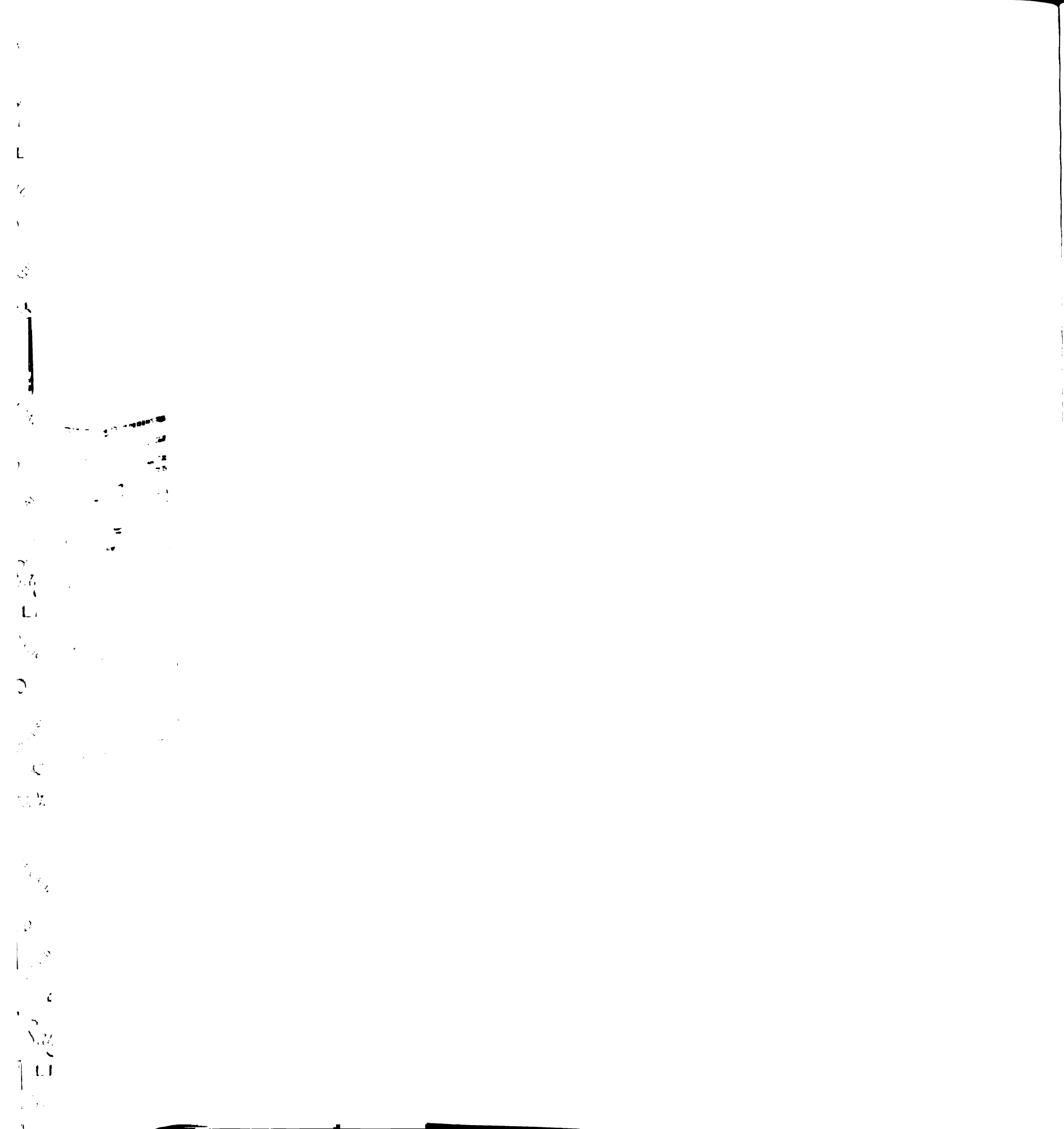
the step response of the eye by holding it at a deviated position and suddenly releasing it. From this data, the elasticity and damping can be calculated. Moreover, any statistically significant variations in the mechanical properties resulting from changes in the fixation position of the unmanipulated eye, must be a result of position dependent innervational changes in the vertical and oblique extraocular muscles.

Of course, a baseline measurement of the orbital mechanics would also be helpful. It could be approximated by measuring the mechanical properties in an anesthetized monkey (as shown in Chapter 5). As above, under this condition, the force necessary to hold the eye at different positions as well as the step responses from each can be measured. The responses from several initial positions is necessary to explore non-linearities.

6. Other Issues in Oculomotor Control

6.1 Is the Asymmetrical Saccadic Response of the Eyes During Simultaneous Vergence Movements Mechanically or Neurally Based?

Another puzzling question has to do with a phenomenon observed during the simultaneous combination of slow vergence and fast conjugate (saccadic) horizontal eye movements. The phenomenon is an apparent enhancement of the saccade in the eye in which the saccade and vergence movements are in the same direction (i.e. the saccade is larger than expected) and an apparent hindrance of the saccade in the eye in which



the saccade and vergence movements are in opposite directions (i.e. the saccade is smaller than expected). Before discussing the use of the model in regards to this question, a little more background will be given to clarify the issue. First, it is important to recognize that during convergence, the MR of both eyes are contracting and both eyes are moving nasally; during divergence, the opposite occurs. In addition, vergence movements are generally quite slow (peak velocities around 20 deg/s). Second, recall Hering's law, which states that the yoked muscles in conjugate eye movements receive the same inputs. Now, if Hering's law is applicable for all saccades, even when they occur simultaneously with a vergence movement, then we would expect that the input for a combined saccadic and vergence movement is the summed input for each movement individually i.e., the same size saccade is programmed for each eye. If this is true, the resulting increase in saccade magnitude in one eye and decrease in the other eye would have to result from some mechanical property of the muscles. Moreover, muscles have very non-linear properties, so there is no reason to expect superposition of the outputs (i.e., the sum of the saccadic response and the vergence response shouldn't be expected to equal the response of the two movements occurring simultaneously, just because the inputs summed).

The experimental method could be used to test the feasibility of a mechanical explanation. The best approach would be to record forces and kinematics during vergence movements, vergence movements with saccades, and saccades alone. Then, use the models to predict the activations in each case and see if the activations for vergence and saccades alone sum to generate the combined response.



As a side note, data suggests that the superior oblique relaxes during convergence (Mays et al., 1991). Therefore, if (as speculated) the vertical and oblique extraocular muscles contribute to the orbital mechanics, the variation in orbital mechanics during a combined convergence and saccadic eye movements may also contribute to the apparent modification of the saccade.

6.2 How Generic are the Saccadic Control Signals?

A central control system that only needs to generate a stereotypical command for each movement magnitude is much more simple than one that has to specialize each such command for each muscle and for each initial and final position. For this reason, one might expect the LR and MR activations to be very symmetrical. At the same time, however, the system is known to be highly flexible and adaptable. It is beneficial for the control signals to each muscle to be modified separately to account for individual variations in muscle properties and/or injuries to individual muscles. For this reason, one may not expect to see a lot of symmetry in the LR and MR activations. Of course, there will always be a trade off between simplicity (or cost in man made systems) and performance of a control system. For the saccadic system, performance must be good enough to move the eye "rapidly enough" to the new fixation position and with "enough accuracy" to focus the region of interest on the fovea. (Although these are not well quantified definitions, they suffice for this discussion. However, one should keep in mind that "accurate enough" may vary with saccade size. For example, small saccades

usually move the eye much closer to the visual target than do large saccades. The error in large saccades may even be intentional; an intentionally generated visual error signal could be used by the saccadic system to adaptively calibrate itself.) For example, the exact path (time and space) of the saccade is not critical, only the final position is really important; therefore, if the LR and MR are "similar enough" the same control signal could be used for saccade generation in either direction; the deviations in path or timing may not be significant. However, if the muscles are not "similar enough" the control system needs to be able to send the correct control signal to each muscle. A control structure which would allow simplicity in generating the original command while also allowing fine tuning for each muscle would be desirable. Such a controller might include central controller that generates the basic saccade command signal and local controllers that fine tune the basic command so that it is appropriate for each particular muscle. With accurate mechanical models of the oculomotor system, we can start to explore underlying control strategies such as these.

7. Conclusions

7.1 Kinematic and Force Profiles (Chapter 2)

We believe that the data is fairly representative of that for a normal monkey and that the implantation of the force transducers did not cause extensive damage. Admittedly, verification is needed. For example, the saccades show the expected (main



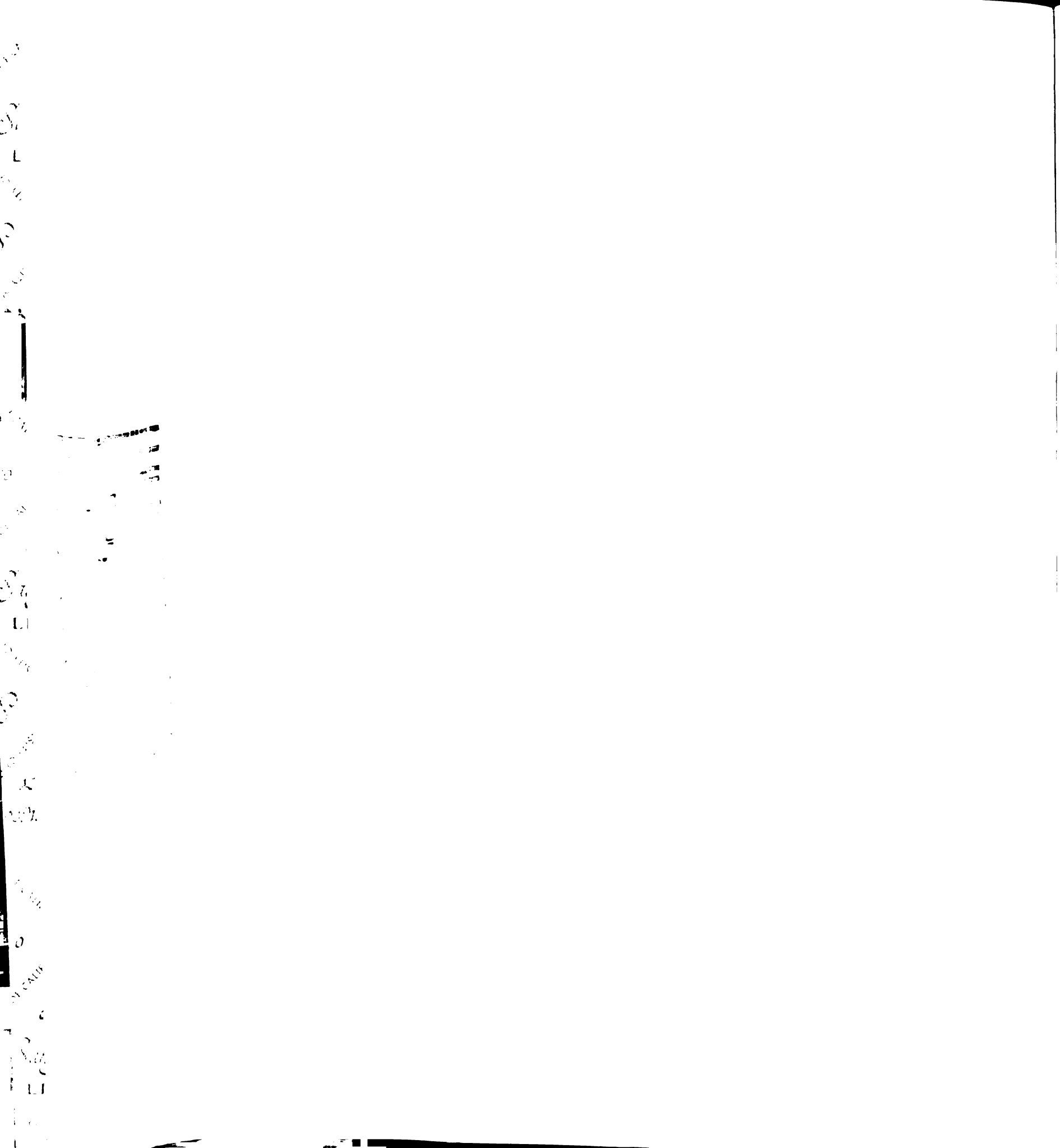
sequence) relationships between peak velocity and saccade magnitude and between saccade duration and magnitude. In addition, the kinematics were very reproducible. Moreover, there was no evidence of scar tissue build-up surrounding the implanted transducers.

Kinematic profiles exhibit a temporal/nasal asymmetry, and it is not clear if this asymmetry has a neural or a mechanical basis. In contrast to the directional asymmetry, there is no initial position dependent asymmetry in the velocity profiles during saccades of a given size/direction.

Force profiles were reproducible, which is consistent with the stereotypical nature of the kinematics and the ocular motoneuron firing patterns during saccades. Also, peak force and time to peak force have a similar relationship to saccade magnitude as the main sequence relationships already mentioned.

More surprising was the qualitatively symmetrical agonist and antagonist force profiles. This was surprising not only because it contradicted model predictions (Chapter 3) but also because the inputs are qualitatively symmetrical (reciprocal innervation) while the muscle properties are asymmetric (e.g., force-velocity relationship). Moreover, the lengthening (antagonist) muscle exhibits a smooth force profile, even with peak velocities around 1000 deg/s; this was surprising in light of the reported transient force responses of muscle during isovelocity pulls (cat soleus; Joyce & Rack, 1969, see Chapter 1, Fig.12).

Force profiles during saccades of different magnitudes initiated from the same initial position follow the same initial trajectory and deviate only when the peak force



is approached. In contrast, force profiles for the same size/direction saccade initiated from different initial positions do not exhibit similar profiles when the saccade is initiated in a muscle shortened beyond some threshold (which contrasts with the constancy of the velocity profiles during the same saccades). Moreover, the agreement of these force profiles with the activations expected from the known ocular motoneuron firing patterns is controversial.

7.2 Predictions of Original Saccadic System Model (Chapter 3)

Simulations of a standard model of the horizontal saccadic eye movement system that was designed to produce normal position, velocity, and acceleration profiles, do not predict forces such as those recorded in the monkey during saccades. The inaccuracies in the model have three sources: the muscle model, the orbital mechanics model, and the assumed input.

7.3 DM and Hill Muscle Models (Chapter 4)

Simulations of single DM and Hill models suggest that the added complexity of the DM model is not necessary to generate the properties of extraocular muscle, even at high saccadic velocities. Two points contributed to this result. First, the lack of transient behavior in the antagonist muscle apparently eliminates the need for the model to exhibit this characteristic. Second, simulations of the DM yielded insights into a



potential physiological correlate of parameter manipulations in the Hill model, thereby justifying the manipulations until further experiments are done.

The DM simulations also suggest that the different fiber types in extraocular muscle may play a significant role in the resulting macroscopic properties during movements. Moreover, the effects of the fiber types may be central to understanding the symmetry in the agonist and antagonist force profiles. This suggest that it would be useful to develop a model that explicitly models, at least, slow and fast fibers.

7.4 Orbital Mechanics (Chapter 5)

The contribution of the vertical and oblique extraocular muscles to the orbital mechanics in the subsystem studied are not usually addressed. However, the difference between the orbital mechanics in the alert, behaving monkey and the anesthetized monkey suggests that the contribution of the extraocular muscles is significant.

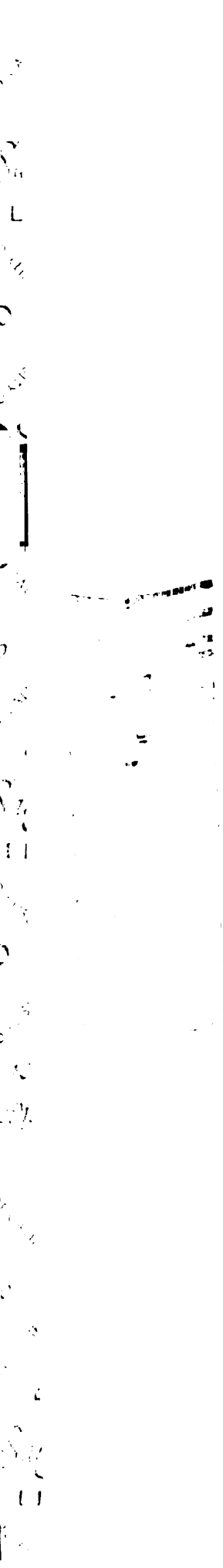


Effect of Electrical Microstimulation in Dorsal Lateral Pontine Nucleus on Monkey Pursuit Eye Movements

Another approach to studying the oculomotor control system is to try to understand the central control processes themselves. To this end, researchers focus on regions of the brain thought to be involved in control of a particular movement. They record the firing patterns of the neurons in the region and correlate the patterns with aspects of the eye movement (e.g., eye position, eye velocity, target position, etc.). These studies, along with anatomical studies suggesting the patterns of connections amongst the regions in the control pathway, are combined to yield a picture of the control process. The basic role of a particular region can be further studied using experimental perturbation techniques; a region is lesioned or electrically stimulated and the effects of the perturbation on the movement are examined.

For several reasons, monkeys are often used in these studies. First, they are believed to best represent the human system (Fuchs, 1967). Second, they can be easily trained to make the desired eye movements. An third, the recordings can be made in an alert, behaving animal.

In this chapter, an example of this type of study is presented. The effects of electrical microstimulation in the dorsal lateral pontine nucleus (DLPN) on smooth pursuit eye movements are examined. A brief report of the data is presented in May et



al., 1985. In this chapter, the work is extended: data is further analyzed, compared to similar stimulation studies, and examined with respect to existing models of pursuit.

1. Introduction

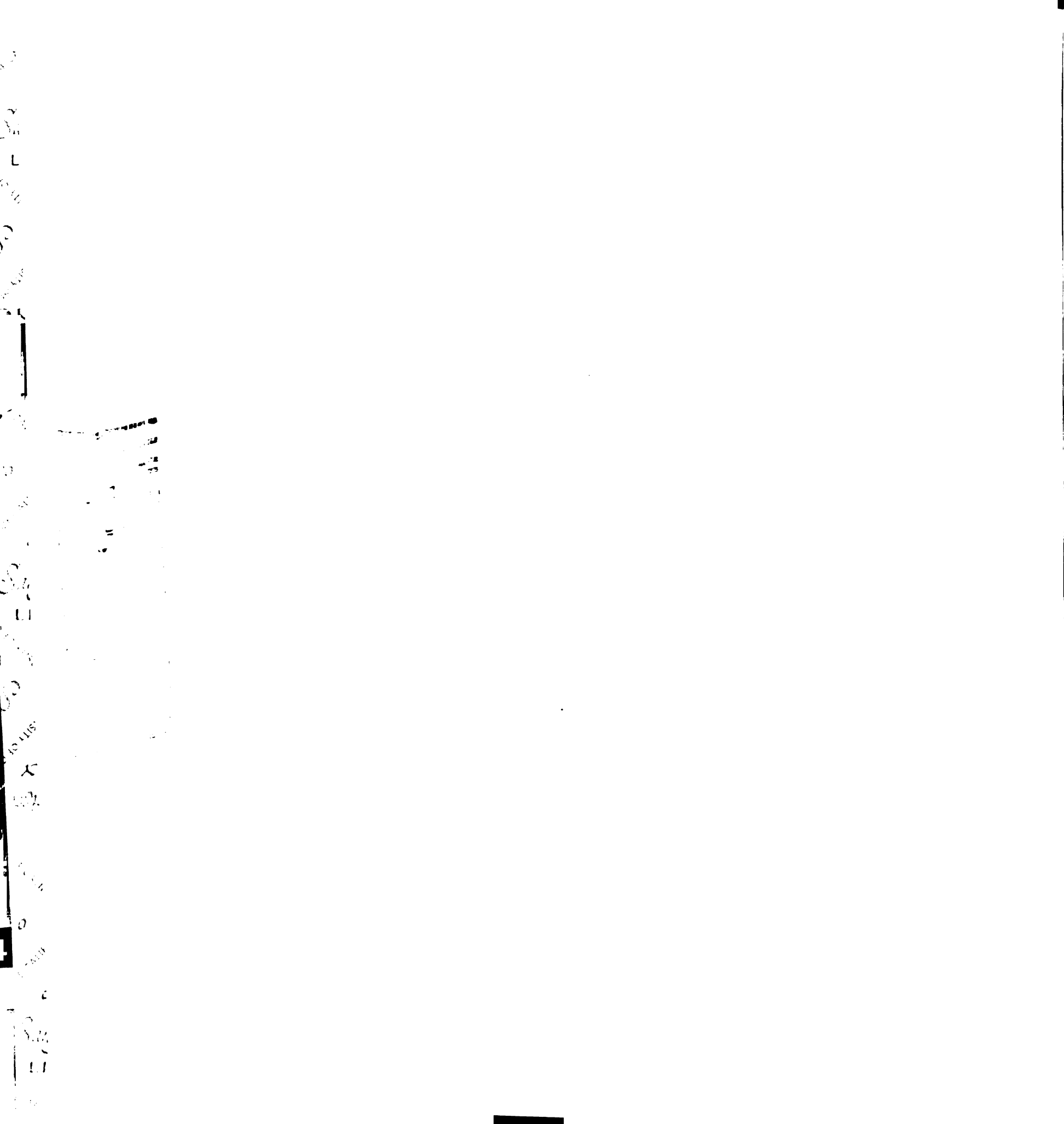
To further clarify the role of the dorsal lateral pontine nucleus (DLPN) in controlling smooth pursuit eye movements, we performed an experimental perturbation analysis on monkeys using electrical microstimulation. Stimulation was applied in DLPN during both horizontal smooth pursuit trials and fixation. It modified both open and closed loop pursuit responses but did not perturb fixation responses. The perturbation produced by stimulation was in the same direction regardless of the direction of the ongoing steady state pursuit response. Stimulation applied during pursuit initiation increased eye acceleration and decreased the time to peak velocity. Stimulation applied during the maintenance phase (when eye velocity approximately equalled target velocity) produced different effects under closed and open loop tracking conditions. For closed loop conditions, stimulation initially forced the eye velocity away from target velocity; however, after 150-200 ms, eye velocity returned toward target velocity. In contrast, under open loop conditions, the stimulation continuously pushed the eye velocity away from the initial target velocity. Although the effects of DLPN stimulation more closely resemble those produced by stimulation in cortical areas MT/MST than those produced by stimulation in the frontal eye fields, significant differences with the former area also exist.



To better interpret the experimental results, we modelled the effects of stimulation using two widely used but structurally different smooth pursuit models. One model used several retinal motion signals to control pursuit, while the other used an efference copy feedback. In both types of models, stimulation was implemented by adding a disturbance signal to or modifying the gain of a pathway. Neither model could generate the complete range of experimental results we obtained. This is probably not surprising considering both models simplify the pursuit structure into distinct functional pathways whereas the stimulated area, DLPN, is known to carry a variety of visual and eye-movement related signals.

2. Background

Smooth pursuit eye movements, or tracking movements, function to maintain the image of a moving object on the fovea. A typical monkey pursuit response to a step-ramp stimulus, which consists of an initially stationary target that jumps to a new position and then moves at a constant velocity, is most easily described in three phases. The first is the latency phase, which averages about 100 ms. The second is the pursuit initiation phase, which involves a rapid increase in eye velocity that often overshoots the desired target velocity. The last is the pursuit maintenance phase, which maintains the eye velocity near the target velocity and often exhibits oscillations at 3-5 Hz. This normal pursuit response is also called the closed-loop tracking response because the anatomical structures that produce this behavior form a natural closed-loop negative



feedback control system. The input, or controlled error, to this system is retinal slip, the difference between target and eye velocity. The negative feedback loop can be opened experimentally by using computer generated feedback signals. For example, to open the loop during the maintenance phase, the image of the target is stabilized on the retina, forcing retinal slip to zero deg/s, thereby eliminating visual motion feedback. Under such an experimental paradigm, a typical pursuit response parallels the closed-loop response until the loop is opened at which point the eye velocity simply remains constant. Previous studies suggest there is an attention-related neural switch that determines whether or not a pursuit movement will be made in response to a pursuit stimulus (Robinson et al., 1986, May et al., 1985, Goldreich et al., 1992). It is apparent that the control of pursuit movements involves both high and low level neural processing (Kowler, 1990).

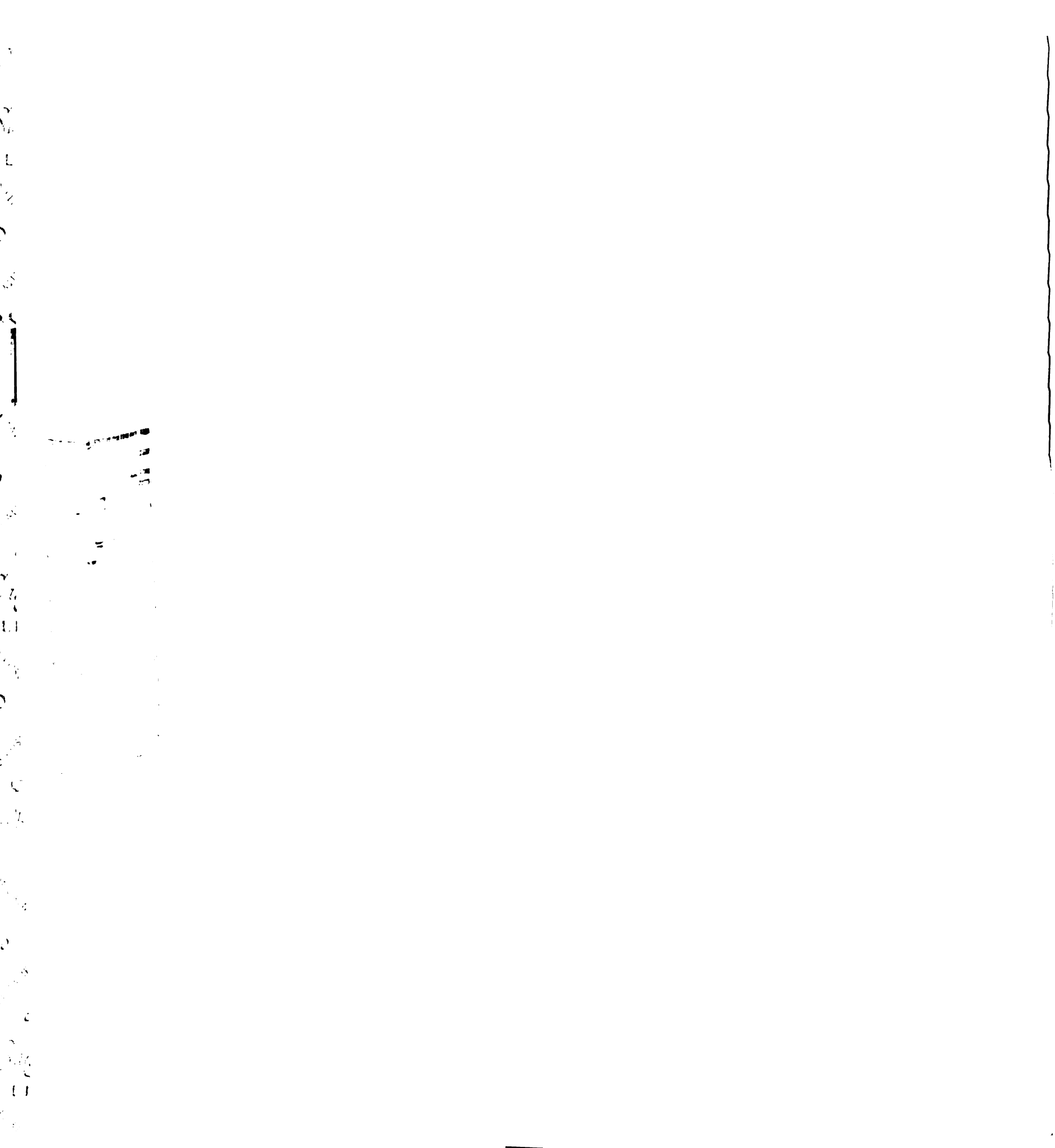
2.1 Background on the neural organization of the pursuit system

Over the past few years there has been considerable progress made in defining the neural structures and pathways involved in generating pursuit eye movements (see, Keller & Heinen, 1991, for a review). These pathways originate in the visual motion processing substrates in cortex, beginning in layer IVb of striate cortex and from there proceed both directly and indirectly to cortical area MT. Area MT in turn projects to area MST. At this point there appears to be a sensory-motor interface, since cells in MT respond principally to visual motion aspects of the stimulus, whereas MST units



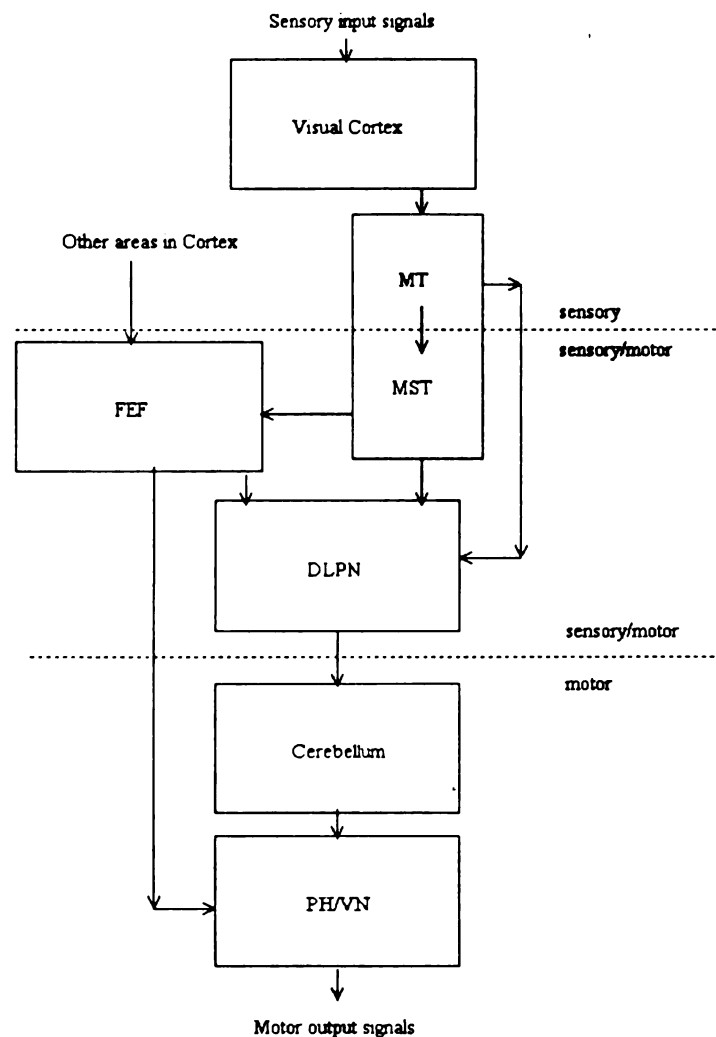
respond to both the visual dimensions of the moving stimulus and the extraretinal correlates of pursuit eye movements. Extensive descending projections emanate from both of these areas to reach several regions of the pontine nuclei in the brain stem. Among these multiple descending pathways those to the dorsolateral pontine nucleus (DLPN) are the most prominent. A second pursuit pathway originates from the region of the frontal eye fields (FEF), a cortical area which receives projections from MST directly and indirectly via other extra-striate areas in the posterior parietal cortex. The FEF also projects to the DLPN, an arrangement that points to the role of this pontine region as a major junction point in the organization of pursuit. It is also important to note that the DLPN receives inputs from both visual motion (MT) and pursuit related structures (MST and FEF), a fact which suggests that this nucleus may play an important role in the further integration of sensory-motor transformations. Parallel pathways from FEF also go directly to the nucleus prepositus hypoglossi (PH), a brainstem structure (along with the vestibular nucleus) believed to be part of the final motor pathways for all types of eye movements.

The visual pontine nuclei, including the DLPN, project to the cerebellum. Finally this latter structure projects to the vestibular nuclei and prepositus hypoglossi. As mentioned above the VN/PH complex forms the immediate premotor structure for all types of eye movements. It has been shown that all input signals to this complex are related to eye velocity commands, whereas the ocular motor neurons forward a signal related predominately to eye position. Thus it has been suggested that one primary role of the this complex is to provide a neural integration of these velocity command signals



to eye position signals, a suggestion that has been confirmed by lesions placed in the VN/PH (Cannon & Robinson, 1987 chemical lesions in the medial VN).

Figure 7.1 shows a block diagram of some of the neural circuitry involved in the control of smooth pursuit. The diagram is divided by dotted lines into three regions which separate visual areas (sensory), mixed areas (sensory/motor), and motor areas.



Simplified Block Diagram of Neural Circuitry Involved with Control of Smooth Pursuit Eye Movements.
Figure 7.1



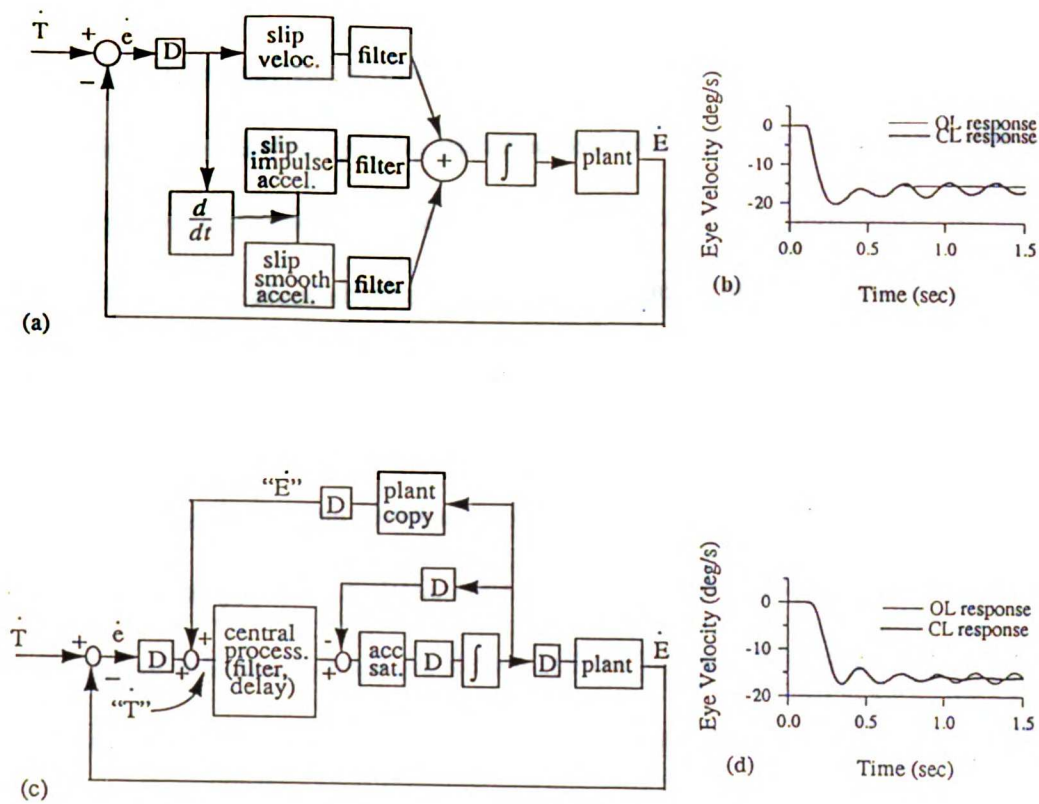


Image Motion Model and Corollary Discharge Model. Model structures which generate realistic horizontal pursuit trajectories. $\dot{T}$ = target velocity; $\dot{E}$ = eye velocity; $\dot{e}$ = retinal slip ($\dot{T} - \dot{E}$); D = delay element; $\int$ = neural integrator; " $\dot{T}$ " = internal neural estimation of target velocity (c only); " $\dot{E}$ " = corollary discharge coding eye velocity (c only). (a) The structure of the image motion model as modified from (Krauzlis and Lisberger 1989). (b) Open-loop (thin line) and closed-loop (thick line) response of the image motion model. (c) The structure of the corollary discharge model as modified from (Robinson et al. 1986). (d) Open-loop (thin line) and closed-loop (thick line) response of the corollary discharge model.

Figure 7.2



2.2 Description of Pursuit Models

In the present study, in order to gain a better understanding of the function of DLPN in the control of pursuit movements, we electrically stimulated this structure during pursuit movements. The stimulation perturbed the normal functioning of the system, generating clues about the basic signal processing carried out by DLPN. To aid in interpretation of the stimulation studies, we examined similar perturbations made in dynamic system models of the pursuit system. The models used in these simulations were representative of the two basic classes of pursuit models present in the literature both of which generate realistic, one-dimensional pursuit trajectories. The control structures of the models used are shown in Figs 7.2a and 7.2c, the image motion model (Krauzlis & Lisberger, 1989) and the corollary discharge model (Robinson et al., 1986), respectively.

The structure of the image motion model (Fig. 7.2a) uses visual motion processing with three functionally different parallel visual pathways and minimizes the role of motor processing. The impulse acceleration pathway contributes to the rising phase of the pursuit response, while the smooth acceleration pathway contributes to the deceleration of the eye velocity as it approaches the target velocity, resulting in a reduction of the overshoot. The smooth acceleration pathway also contributes the high frequency oscillation properties (Krauzlis & Lisberger, 1989). In contrast, the structure of the corollary discharge model (Fig. 7.2c) consists of an efference copy, or internal model, of the eye velocity (" $\dot{E}$ ") which is added to the retinal slip signal ($\dot{e} = \dot{T} - \dot{E}$)



thereby canceling the effect of negative feedback and creating an internal representation of the target velocity (" $\dot{T}$ " = $\dot{T} - \dot{E} + \ddot{E}$ "). This effectively opens the loop, eliminating the stability problems associated with delays in a feedback loop. An internal negative feedback loop, representing a portion of the motor processing, generates the high frequency oscillation (Robinson et al., 1986). In spite of fundamentally different control structures, it can be shown that, with an appropriate choice of parameters, that the two versions, when linearized about a particular operating point, are equivalent (Deno et al., 1989), so there is some common ground between the models.

The open and closed-loop responses of the image motion model are shown in Fig. 7.2b. The parameters were adjusted so the closed-loop response closely resembles a normal physiological response. If retinal slip ($\dot{e}$) is non-zero when the loop is opened, it is instantaneously set to zero. In this case, there is an initial impulse in the acceleration pathway followed by zero signal in all of the visual processing pathways. The impulse pathway may thereby shift the output slightly. The output then remains constant because no additional signals enter the integrator. The response shown in Fig. 7.2b is similar to the actual physiological open-loop pursuit response.

The open and closed-loop responses of the corollary discharge model are shown in Fig 7.2d. Again, the parameters were adjusted so the closed-loop response closely resembles a normal physiological response. Upon opening the loop, the eye velocity trajectory in this class of models may oscillate about the target trajectory due to the internal feedback loop. If the oscillations are negligible at the time the loop is opened, the eye velocity simply remains constant, similar to the actual physiological response.



The ability of the open-loop response to remain close to the target velocity is actually very sensitive to the gain in the efference loop. If the gain is slightly high (or low), the eye speed escalates (or decreases to zero deg/s) (not shown).

An essential feature in each model is the neural integrator, which represents the property that the pursuit system interprets desired velocity signals as acceleration commands which allows the system to maintain a steady output eye velocity when the retinal slip is forced to zero by opening the visual feedback loop (Lisberger et al., 1981, Morris & Lisberger, 1987). Since the visual feedback loop is dictated by the anatomy, the models also share this feature.

The models are not strongly tied to the physiology. The neural circuitry relates to the models on a functional basis only, i.e., sensory, sensory/motor, or motor (see Fig. 7.1). For example, visual cortex and MT are sensory regions and correlate to the sensory visual processing portions of the models (velocity, slip and impulse acceleration pathways in the first model; a delay element in the second model). As another example, the integrator in the models corresponds to part of the motor pathways in the brain.

In this paper, after describing experimental and simulation methods, we present the eye movement responses recorded in monkeys during electrical microstimulation in DLPN. First, we show the results recorded during fixation and compare them with results obtained in similar stimulation studies in foveal MT and lateral MST (MTf/MSTl) (Komatsu & Wurtz, 1989) and in FEF (MacAvoy et al., 1991). Next, we discuss results recorded during pursuit within the framework provided by simulations of the previously mentioned pursuit models (Fig. 7.2). Finally, we compare and discuss



the similarities and differences in the pursuit responses recorded during MTf/MSTl (Komatsu & Wurtz, 1989) and DLPN stimulation. Brief reports of the experimental data (May et al., 1985) and the computer simulations (Pfann & Keller, 1991) were presented earlier.

3. Methods

3.1 Physiological Methods

Three juvenile monkeys (*Macaca fascicularis*) were prepared for these studies by the chronic implantation of three devices. The care and use of all animals used followed the procedures of the Animal Research Committee at the California Pacific Medical Center. Each animal was implanted with a coil of Teflon-coated stainless steel wire mounted under the conjunctiva of one eye (Judge et al., 1980) to record eye movements using the search coil method (Robinson, 1963). A stainless steel chamber (17 mm diameter) was stereotaxically positioned over the DLPN to allow single-cell recording and electrical microstimulation in this brainstem region. Finally, two transverse stainless steel rods were implanted to allow immobilization of the head with respect to the magnetic fields during subsequent experimental sessions. The chamber and the rods were fixed in place with dental acrylic cement. All surgeries were performed under sodium pentobarbital anesthesia and sterile conditions. Sutured incisions were treated with antibiotic ointments, and penicillin was administered during the post-surgical

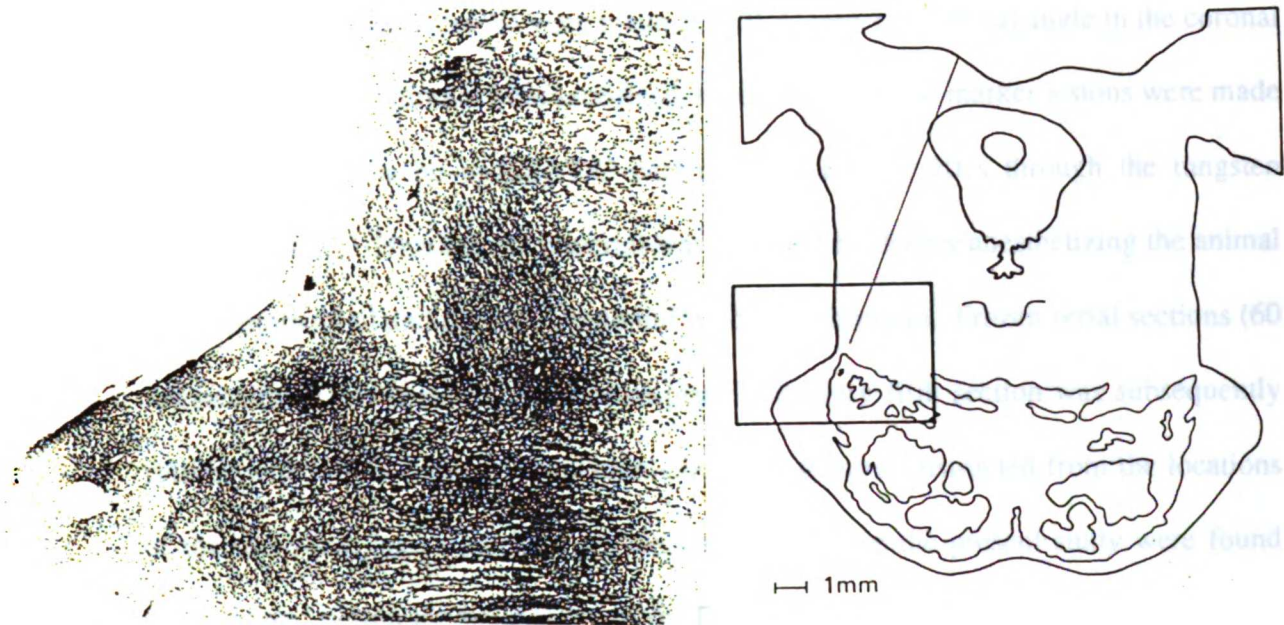


recovery period. Analgesics (torbutrol, 0.05mg/kg, i.m.) were given after recovery from the anesthesia to relieve any post-surgical pain. Following recovery from these surgical procedures (about two weeks), the monkeys were taken to the recording room on a daily basis for sessions lasting several hours to obtain the electrical stimulation results described here.

We recorded single cells in the DLPN as previously described (Suzuki et al., 1990). After recording the activity of single units related to pursuit eye movements in this region, we delivered electrical stimulation through the same microelectrode that we had used for recording. High-frequency pulse trains (bipolar pulses of width 0.25 msec , frequency 300 pulses/s) were used while current strength and pulse train length were varied as described below. In addition to stimulation during fixation, control (no stimulation) and stimulation trials were run during pursuit toward the left, toward the right, upward and downward on a quasi-random schedule. However, at each stimulation site, only the pursuit direction generating the largest result was studied extensively. Unless stated otherwise, the results refer to this "best" direction. (Only the effects generated by stimulation during horizontal pursuit are reported in this paper.)

Stimulation during pursuit initiation was triggered by the onset of the pursuit movement, and the pulse train duration was 100 ms. Stimulation during pursuit maintenance began 300 ms after the pursuit movement started, a time at which eye velocity was approximately equal to target velocity. Pulse train durations during maintenance phase varied from 100 to 600 ms. Whenever the open-loop condition was run, the loop was also opened 400 ms after the target began to move and remained open





Typical Stimulation Site in Dorsal Lateral Pontine Nucleus (DLPN). The figure shows the small lesion placed at a stimulation site in DLPN in one animal. The figure on the right is a schematic view of a brain stem section cut in the coronal plane. One sample electrode track is shown and the box marks the region shown in the accompanying micrograph. The small dark spot on the micrograph shows the lesion created after obtaining stimulation results at this location.

Figure 7.3

10

for the duration of the trial. Computer generated feedback signals reflecting the current eye position were added to the desired target position to generate a stimulus whose image was stabilized on the moving retina.

3.2 Location of Recording Sites and Histology

Microelectrode tracks were made at a 20-degree, off vertical angle in the coronal plane. Before the animals were sacrificed, several electrolytic marker lesions were made at stimulation sites by passing DC current at 20 μ A for 20 s through the tungsten microelectrodes. Histological material was obtained by deeply anesthetizing the animal with pentobarbital and perfusing with buffered 10% formalin. Frozen serial sections (60 microns thick) were cut in the coronal plane and every fifth section was subsequently stained with cresyl violet. Stimulation sites were then reconstructed from the locations of the recovered lesion marks. All the sites reported in the present study were found to be located within the boundaries of the DLPN as defined by (Nyby & Jansen, 1951). A typical stimulation site is shown in Fig. 7.3.

3.3 Data analysis

During stimulation sessions eye position signals were differentiated by analog hardware to produce voltages proportional to eye velocity (high-frequency cutoff at 150 Hz). Eye position and eye velocity signals and a signal giving the time envelope of the



stimulus pulse train were digitized at 500 Hz. Data was stored on computer disk during stimulation sessions and then was analyzed off-line using either a PDP 11/73 or a PC/AT compatible computer. Velocity records were desaccaded individually. Each trace in "Results" is an average of 3-5 trials recorded under the same conditions (i.e. the same stimulation site, stimulation duration, open/closed-loop condition, and the same stimulus velocity).

3.4 Simulation

The specific image motion model simulated was developed in (Krauzlis & Lisberger, 1989), and the specific corollary discharge model simulated was developed in (Robinson et al., 1986). The models were implemented with SIMNON (Ästrom, 1982), a non-linear dynamic systems simulation package. The parameters in each model were adjusted to produce closed-loop responses that closely resembled an actual pursuit response. The open-loop condition during the maintenance phase was implemented by setting the retinal slip (velocity error) to zero deg/s. Two different representations were used to model the effect of electrical microstimulation. (See "Discussion" for an explanation.) Pathway perturbation was implemented by either substituting the stimulation signal for a pathway signal or by adding a weighted stimulation signal to an otherwise intact pathway. In either case the perturbation was held constant for the duration of the stimulation. Gain modulation was implemented by changing the gain in a pathway for the duration of the stimulation. As in the physiological studies,



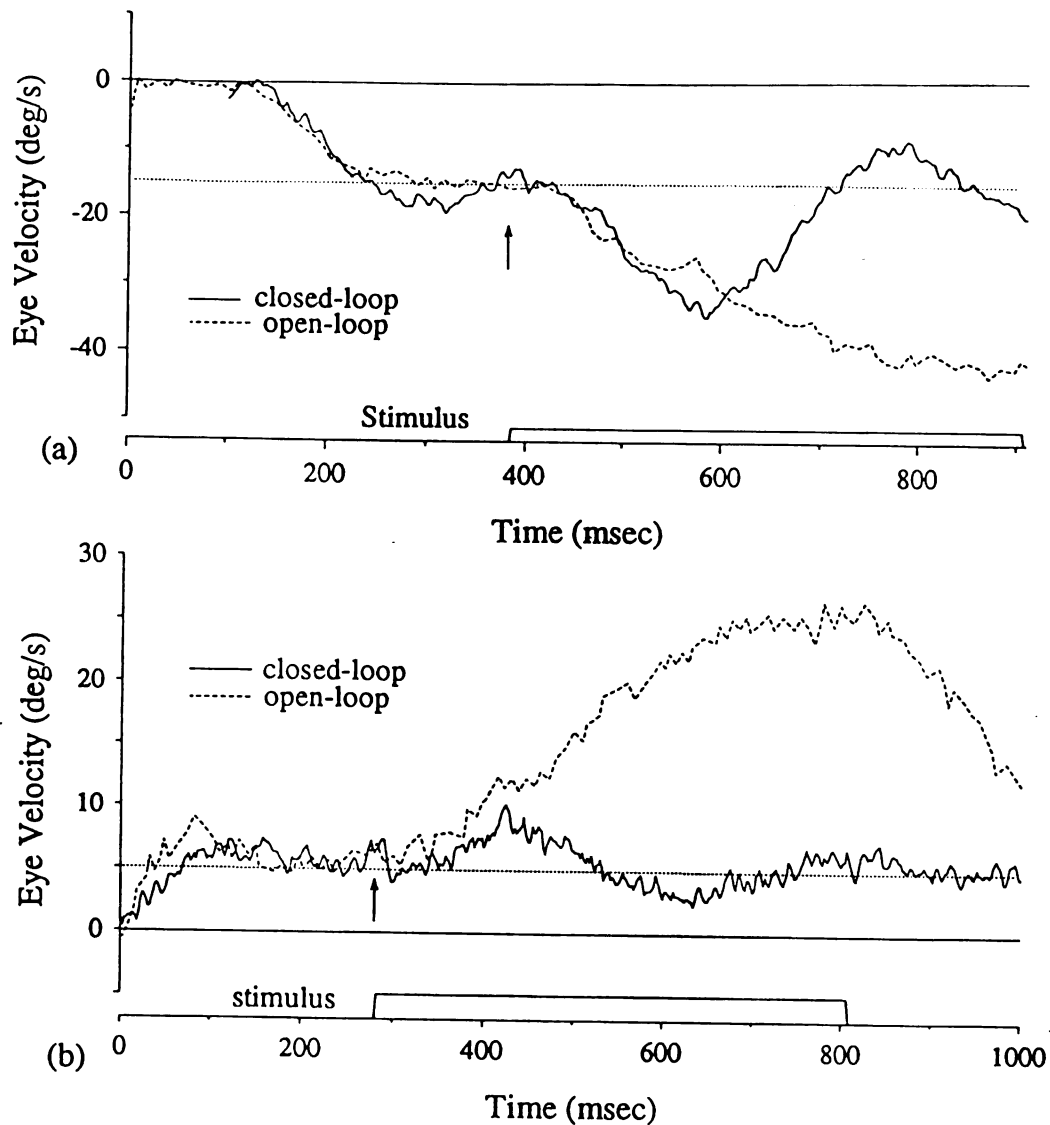
whenever stimulation occurred during the open-loop condition, the stimulation occurred at the same time the velocity error was set to zero deg/s. The effect of both representations of stimulation were examined over the full range of potential stimulation sites in both models.

4. Results

We delivered electrical microstimulation at 19 different sites in the DLPN of the three animals. In general, when this stimulation was made while the animal was fixing a stationary visual target or when its eyes were stationary in the dark, no eye movements were induced. In contrast, stimulation in DLPN during smooth pursuit eye movements had a significant effect on the ongoing movement at all 19 sites that were tested. The average latency for the perturbation of the ongoing pursuit was 22 ms (+/- 9SD). The average threshold current for producing an effect on pursuit was 36 μ A (+/- 14SD).

The effect of DLPN stimulation on horizontal pursuit responses was distinctly different under the open and closed-loop conditions. Typical responses during DLPN stimulation delivered during the maintenance phase are shown in Fig. 7.4, open-loop (dashed lines) and closed-loop (solid lines) responses. For example, Fig. 7.4a shows the effect of this stimulation during leftward pursuit at 15 deg/s. At the onset of stimulation, in both the open and closed-loop conditions, the eye was driven away from the initial target velocity. However, after 150-200ms, the closed-loop response deviated sharply from the open-loop response. Fig. 7.4b shows the effect of DLPN stimulation

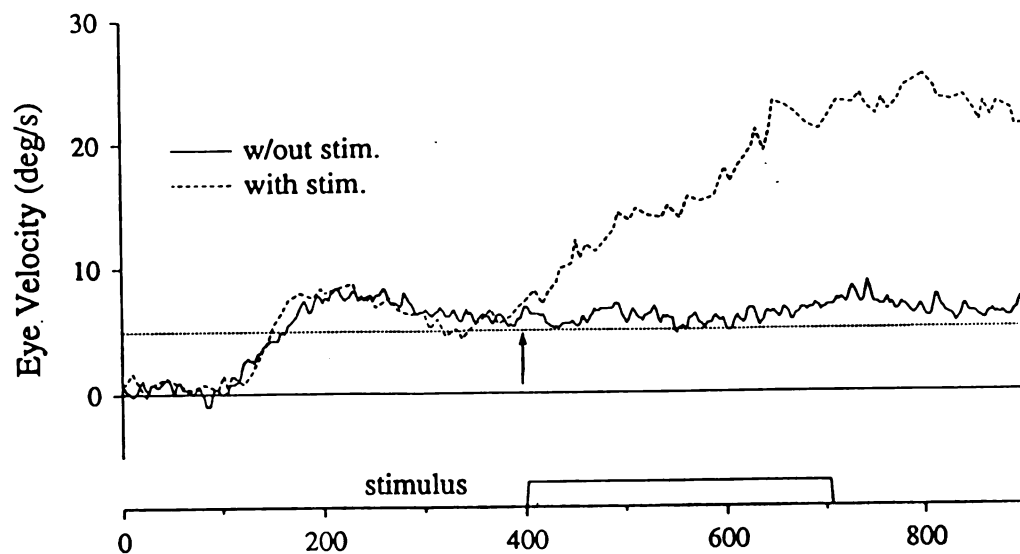




Open and Closed-loop Responses Perturbed by DLPN Stimulation During the Maintenance Phase of Horizontal Pursuit. Open-loop (dash) and closed-loop (solid) responses when perturbed by stimulation are shown. The dotted lines show the initial stimulus velocity (actual stimulus velocity under the closed-loop condition). The arrows mark the point at which the loop is opened under the open-loop condition. (a) monkey 15 undergoing leftward pursuit at 15 deg/s, stimulation at site 1. (b) monkey 15 undergoing rightward pursuit at 5 deg/s, stimulation at site 6.

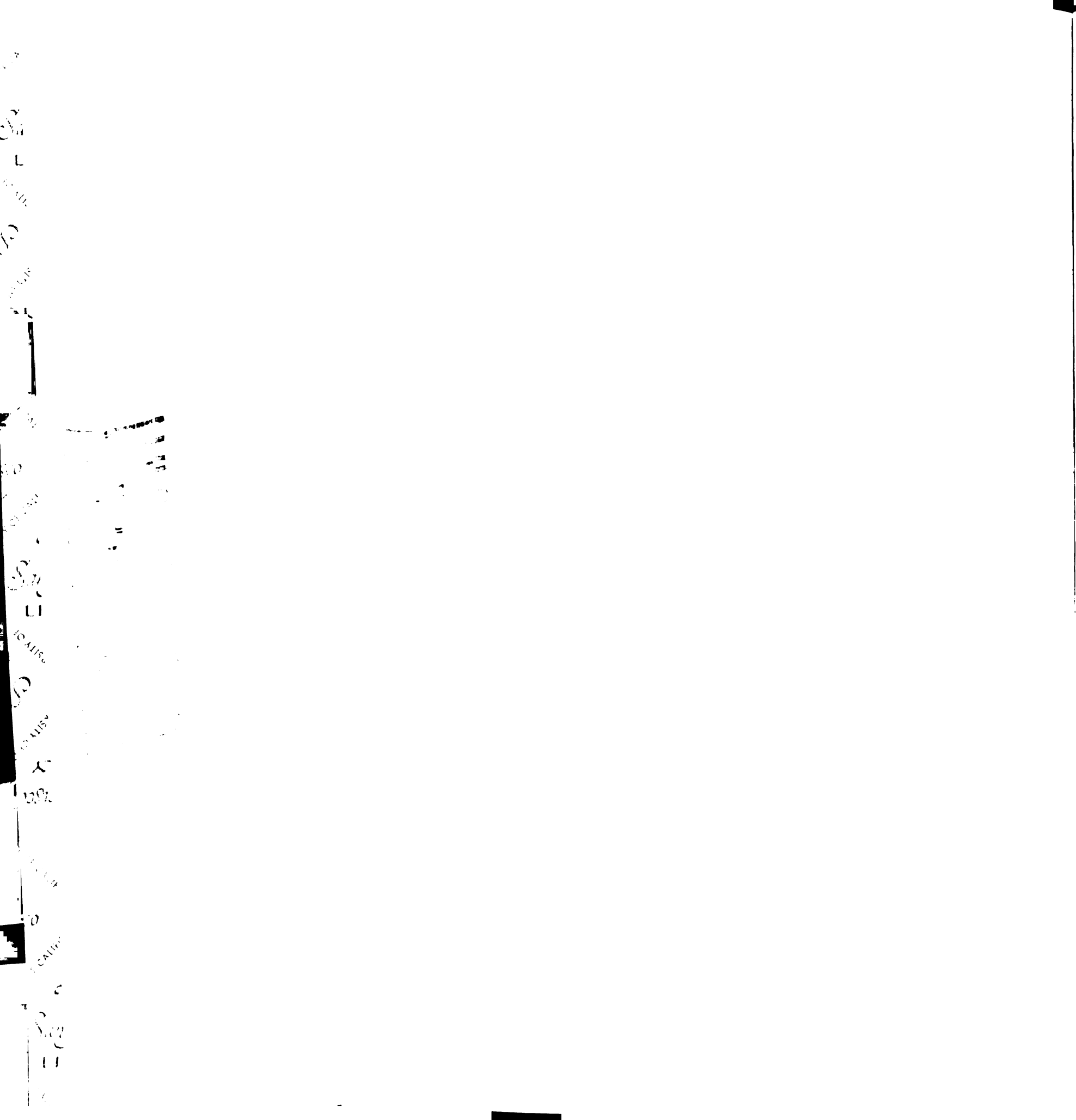
Figure 7.4





Open-loop Responses with and without DLPN Stimulation During the Maintenance Phase of Horizontal Pursuit. Open-loop pursuit responses with stimulation (dash) and without stimulation (solid) are shown during rightward pursuit (monkey 15, stimulation site 6. The dotted line represents the initial stimulus velocity. (Note that the open-loop condition requires the stimulus velocity to follow the eye velocity once the loop is opened.) The arrow marks the point at which the loop was opened.

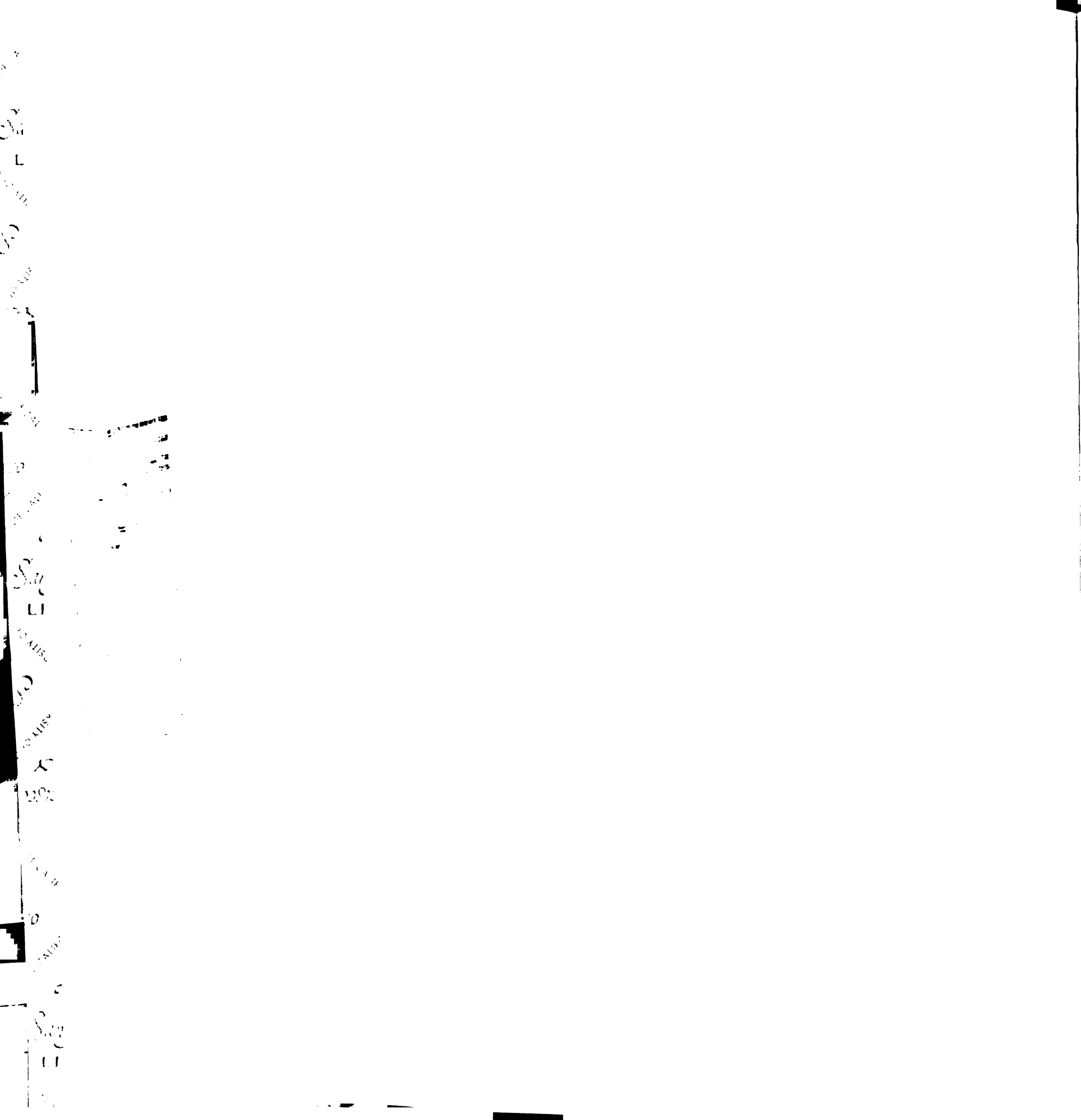
Figure 7.5



during rightward pursuit at 5 deg/s. Because of the slower target velocity, eye velocity has reached a constant steady-state speed (no oscillations) prior to the onset of stimulation. This emphasizes the effects due to the stimulation.

In the open-loop condition, stimulation drove the eye velocity from its steady maintenance value (Fig. 7.5), which was very close to the initial target velocity (dotted line). Initially, the trajectory resulting from this perturbation was a rather steady eye acceleration (recall that in the open-loop mode, stimulus velocity was made equal to the eye velocity so that stimulus velocity actually follows the eye velocity once the loop is opened -- only initial target velocity is shown by the dotted line). For shorter stimulus durations (Fig. 7.5), the altered eye velocity reached at the end of the stimulation remained constant upon the cessation of stimulation. This was consistent with the unstimulated open-loop response in which the eye velocity remained constant after the loop was opened (Fig. 7.5). For longer stimulus durations, however, there was usually a point at which the eye speed stopped increasing and returned toward zero deg/s (Fig. 7.4b). We attribute this to adaptive effects to the unnatural phenomenon of electrical microstimulation possibly related to turning off pursuit and will not address this issue further in this paper.

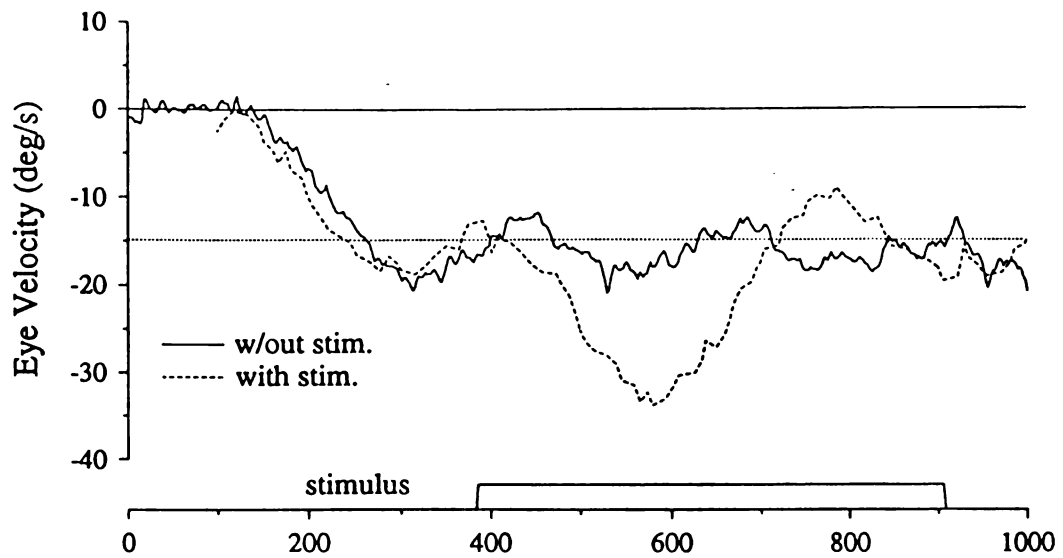
A typical closed-loop horizontal pursuit response perturbed by DLPN stimulation during the maintenance phase is shown in Fig. 7.6. Stimulation during normal, closed-loop horizontal pursuit initially drove the eye velocity away from the target velocity. After a period of 150 to 200 ms, there was a compensatory response that brought the eye velocity back toward the target velocity and that increased the magnitude and



decreased the frequency of the oscillations about the target velocity. The duration of the stimulation was not long enough to clearly determine the steady-state effect. It was clear, however, that the response to the offset of stimulation was not a mirror image of the response to its onset. (Also see response to stimulus offset in Fig. 7.4b.) At first, this surprised us. We originally examined horizontal pursuit responses perturbed by a 200 ms long pulse trains in which the records showed a strong response in one direction to stimulation and a strong response in the opposite direction to the cessation of stimulation. However, after examining responses to longer periods of stimulation (as shown in Figs. 7.4 and 7.5), we found that cessation of stimulation after 200 ms just happened to coincide with the first peak in the evoked oscillation after stimulation began, i.e. the response turned back toward the target velocity whether or not stimulation continued.

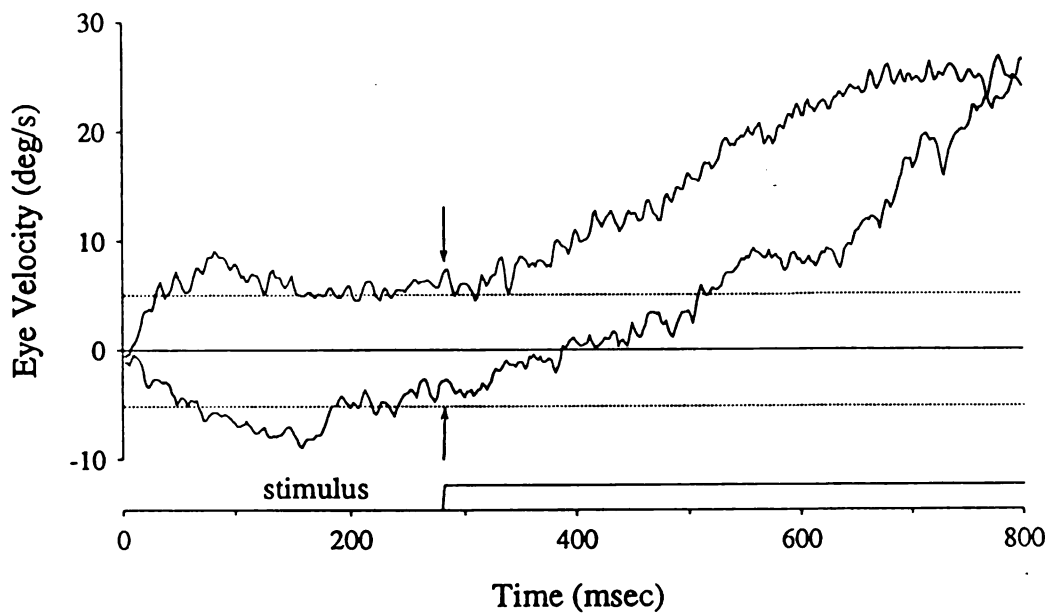
Figure 7.7 demonstrates the directional effect of stimulation on horizontal pursuit movements. This figure shows the results of stimulation at a site in the left DLPN. The open-loop response to stimulation is shown during pursuit toward the left (ipsilateral) and toward the right (contralateral). Note that in one case (pursuit toward the right, positive in the figure) the stimulation produced a positive acceleration of the ongoing eye speed and in the other (pursuit toward the left) a deceleration; the stimulation produced a maintained rightward (contralateral) eye acceleration in both cases. At 15 sites where this directional effect was carefully measured (using open-loop condition during horizontal pursuit), 7 sites produced contralateral and 8 sites produced ipsilateral acceleration, independent of the original direction of the pursuit movement.





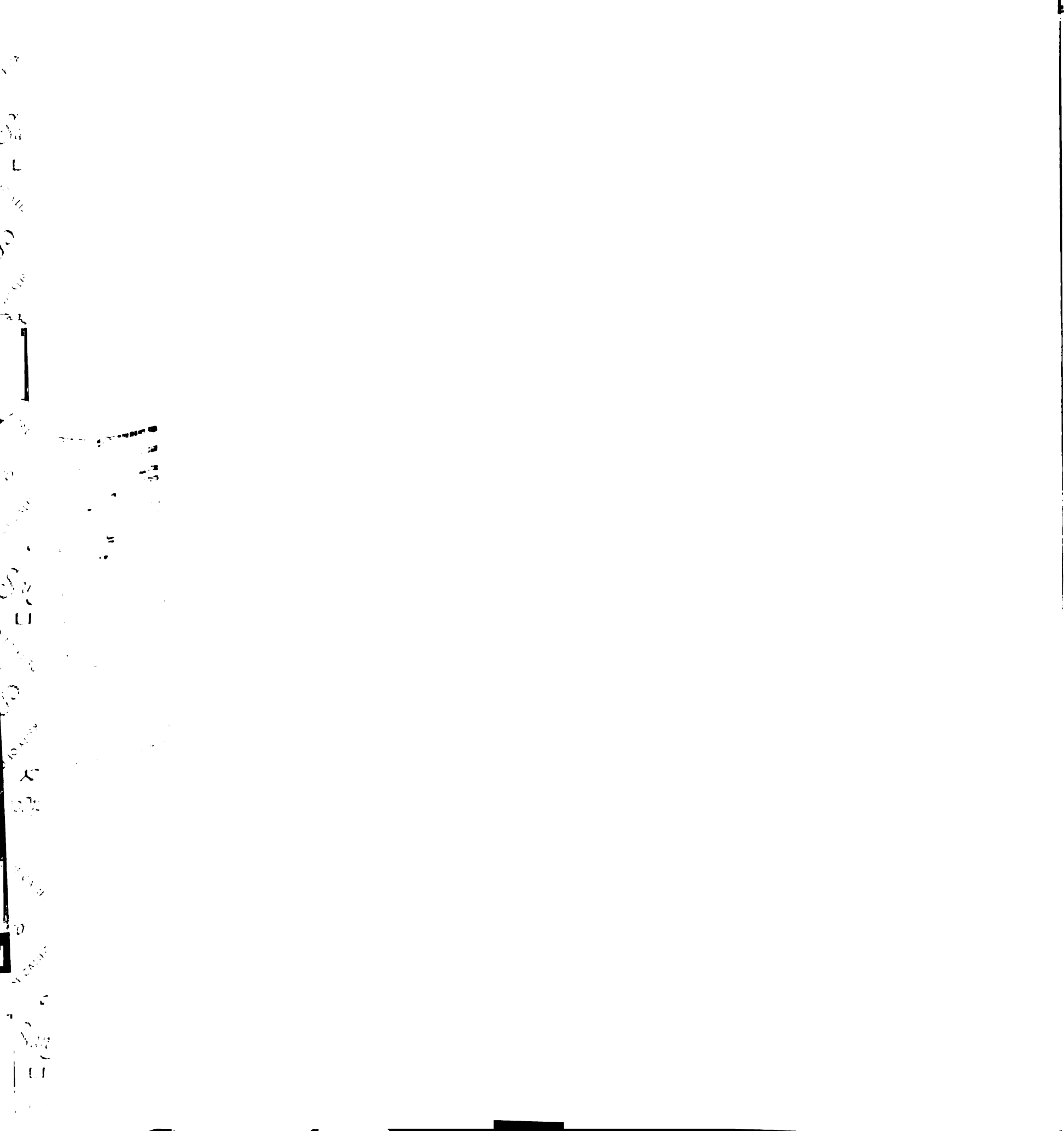
Closed-loop Response with and without DLPN Stimulation During the Maintenance Phase of Horizontal Pursuit. Closed-loop responses with stimulation (dash) and without stimulation (solid) are shown during leftward pursuit (monkey 15, stimulation site 1).
Figure 7.6

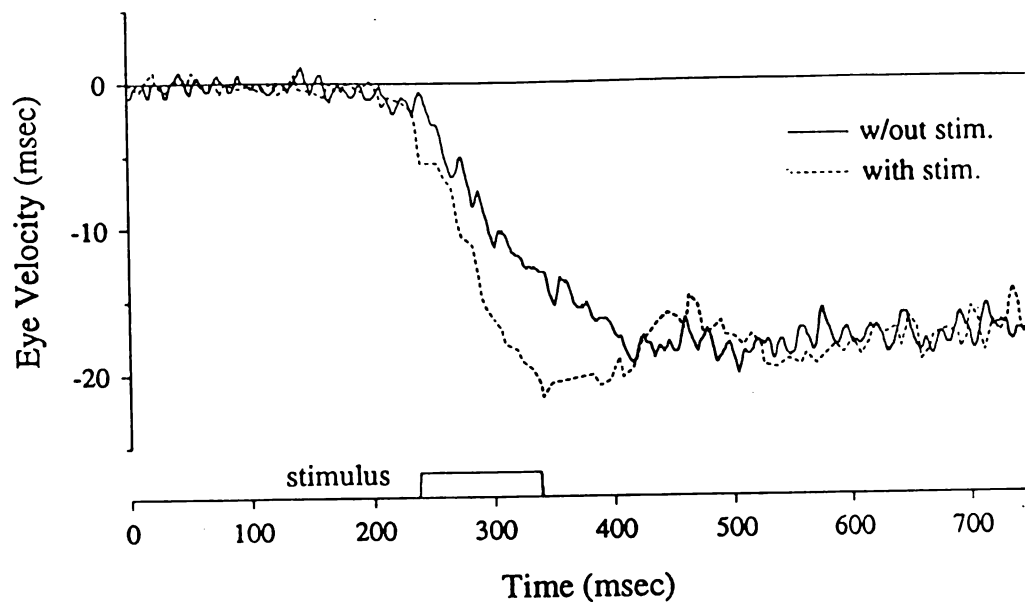




Directional Effect of DLPN Stimulation During the Maintenance Phase of Horizontal Pursuit. Open-loop responses perturbed by DLPN stimulation during leftward (negative) and rightward (positive) pursuit with an initial target speed of 5 deg/s (monkey 15, stimulation site 6). The dotted lines represent the initial target velocities and the arrows mark the points at which the loop was opened.

Figure 7.7





Closed-loop Pursuit Responses with and without DLPN Stimulation During the Pursuit Initiation Phase. The pursuit responses with 100 ms of stimulation during pursuit initiation (dashed) and without stimulation (solid) are shown (monkey 17, stimulation site 18).
Figure 7.8



The effect of a 100 ms pulse train of stimulation during pursuit initiation on the closed-loop pursuit response is shown in Fig. 7.8. The stimulation increased eye acceleration and decreased the time to peak velocity. In contrast to stimulation during the maintenance phase, stimulation during pursuit initiation appeared to have little or no effect on pursuit in the direction opposite the "best" direction (not shown).

5. Discussion

5.1 Fixation

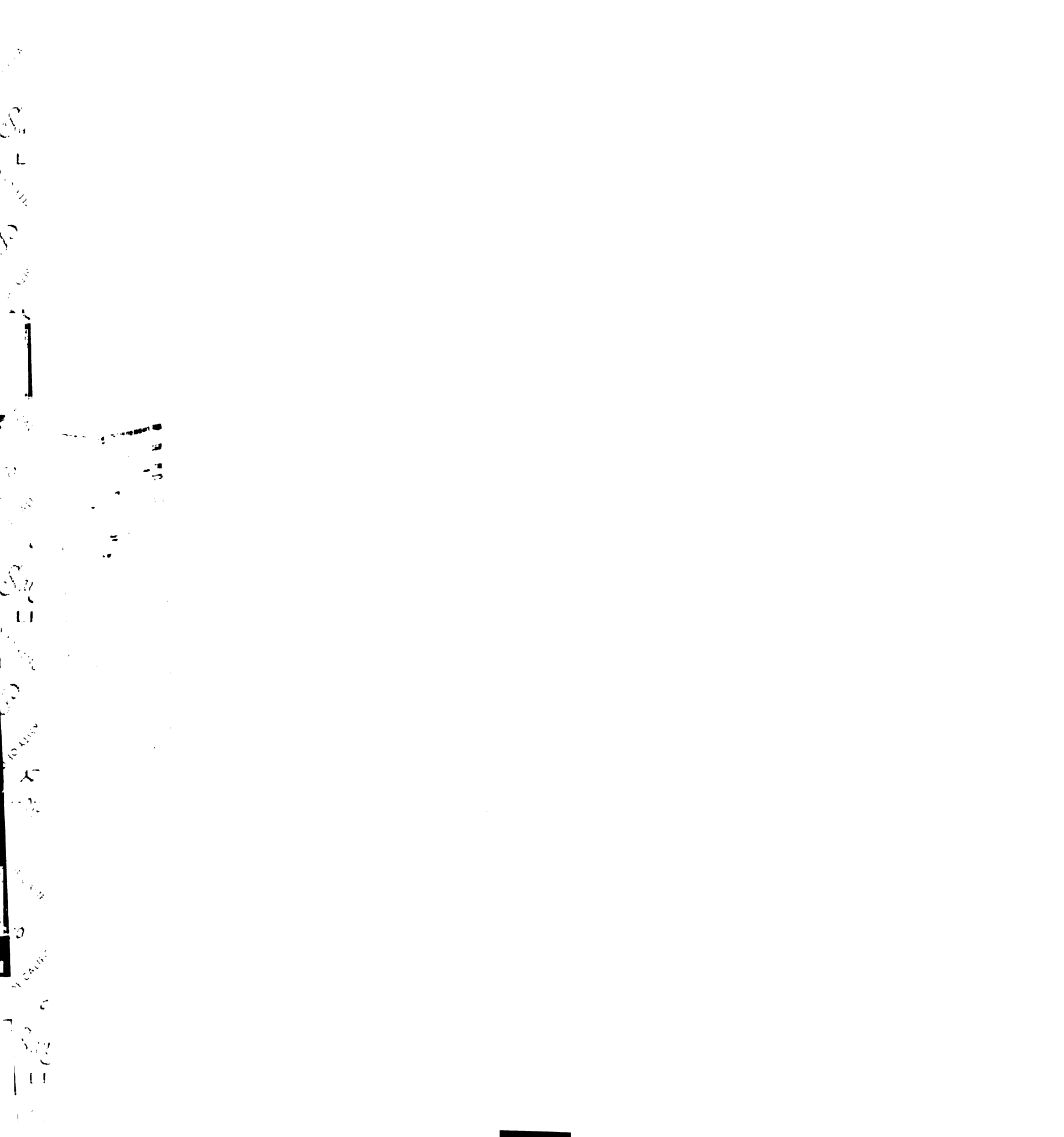
Our results, using electrical microstimulation in DLPN, show that stimulation during fixation does not generate pursuit eye movements while stimulation during an ongoing pursuit movement modifies the ongoing movement. This supports the idea that fixation is fundamentally different from pursuit rather than pursuit at zero deg/s (Robinson et al., 1986). In similar fashion, stimulation in MTf/MSTl during fixation was reported to elicit only very small smooth eye movements or none at all (Komatsu & Wurtz, 1989). It appears as if the pursuit system must be turned on before stimulation in either DLPN or MTf/MSTl can elicit a significant effect on smooth eye movements. In contrast, stimulation in FEF during fixation was reported to generate smooth pursuit movements (MacAvoy et al., 1991). This suggests that MT, MST, and DLPN influence pursuit generation prior to an attention-related switch that turns on/off the pursuit response; whereas FEF influences the system after this switch. This notion is



conceivable within the framework of known anatomical projections (see Fig. 7.2). MTf/MSTl projects heavily to DLPN. Since DLPN appears to be prior to the switch, it is consistent that MTf/MSTl also appears to be prior to the switch. On the other hand, FEF is thought to be a partially parallel motor pathway that projects to both DLPN (Stanton et al., 1988) and the region of the nucleus prepositus hypoglossi (Leichnetz, 1985). Since the prepositus hypoglossi is part of the final staging area for the coordination of all types of eye movements, it is these projections that might serve as the parallel path around the hypothesized pursuit switch. Another explanation may be that FEF is more directly involved in the operation of the switch. FEF is associated with predictive aspects of pursuit movements (MacAvoy et al., 1991); therefore, a strong signal from FEF may trigger the switch or suggest that pursuit has already been turned on and, thereby, bypass the switch.

5.2 DLPN Stimulation During Pursuit Movements

In contrast to the lack of effect during fixation, stimulation in DLPN during pursuit movements clearly affects the ongoing movement. To help understand these effects, we turn to modelling and simulation. Two models of the primate pursuit system, which have been useful in explaining many of the features of this motor response, are the image motion model (Fig. 7.2a) and the corollary discharge model (Fig. 7.2c). It has been shown that only the image motion model reflects the experimentally determined relationships between the frequency of the oscillations found



during typical primate pursuit and the visual feedback loop delay as well as the agreement between the frequency of these spontaneous oscillation and f_{180} (the frequency of target vibration at which eye velocity lagged target velocity by 180 deg) (Goldreich et al., 1992). However, we thought the corollary discharge model may have other characteristics that could prove to be important for explaining our stimulation results, and, therefore, used both models in our study. We conducted simulations of the effects of electrical microstimulation on each of these models to see which could best reproduce the types of physiological responses we observed during DLPN stimulation. In these types of engineering block diagram models, a single line represents a distributed functional pathway and the signal carried on that line represents the information coded by a population of active neurons.

Unfortunately, it is not clear exactly how electrical stimulation affects the neural signals within the region of the brain to which it is delivered. Since the maximum firing rate of cells in DLPN is 100-300 sps, microstimulation at 300 sps should saturate whatever cells are being stimulated. It is often assumed that stimulation drives the neural elements within a particular region at or near their maximum firing rates, leaving regions farther away unaffected. If the neural elements stimulated constitute a homogeneous and complete functional pathway, then the effect of such maximal stimulation would be to substitute for the original signal carried by in that pathway. If, instead, the stimulation perturbed only a portion of the elements in a functional pathway, the stimulus might be expected to bias the population coded information toward the functional properties associated with the stimulated neurons. In the simulations, these

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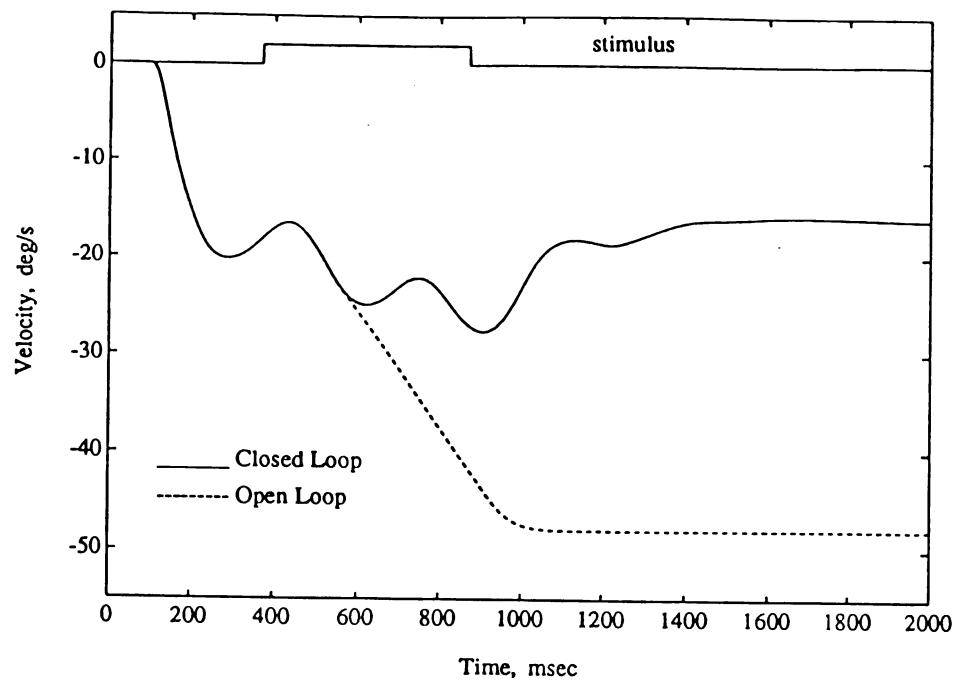
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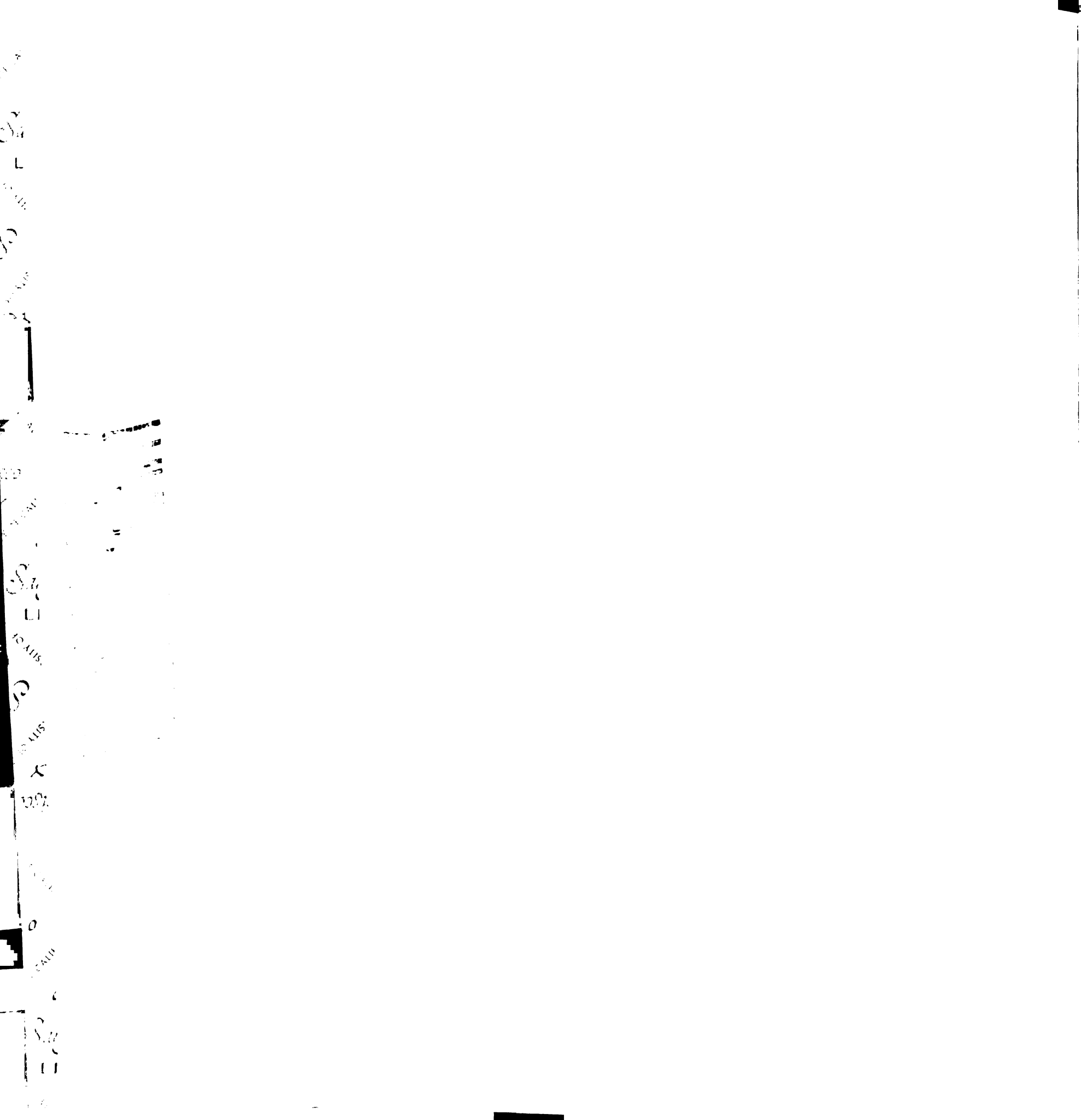
effects are easily modelled by substituting for a neural pathway signal with a constant stimulation signal or by perturbing a pathway signal by adding in a weighted stimulation signal. In this latter situation, the rest of the pathway is free to assume whatever values are dictated by the rest of the model connections.

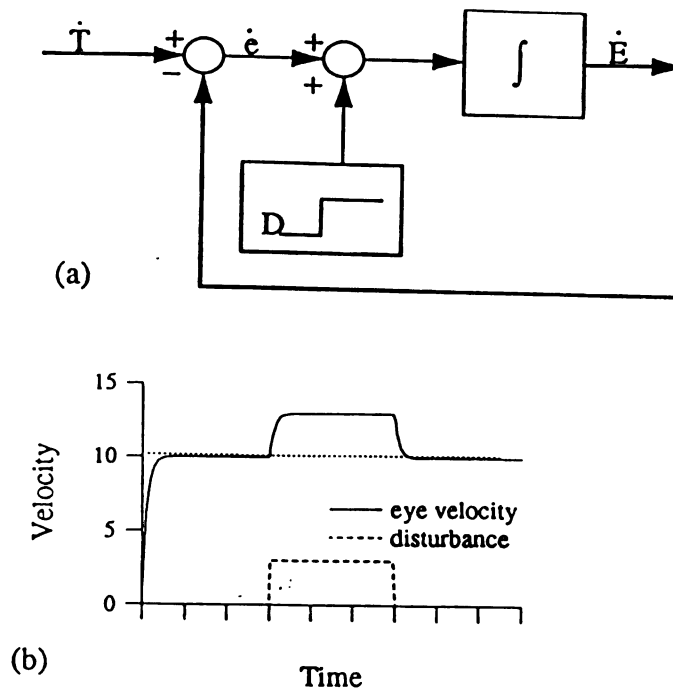
Under the open-loop condition, in both the image motion model and the corollary discharge model, stimulation anywhere prior to the integrator drives the eye velocity away from the initial target velocity, similar to the physiological response (e.g. Fig. 7.5). This result may be understood by examining the models' structures. Any constant stimulation signal is continuously integrated, yet there is no visual feedback signal to compensate for the perturbed eye motion. For example, Fig. 7.9 shows the image-motion model stimulated (pathway modulation) in the slip velocity pathway (i.e. prior to the integrator). As mentioned, under the open-loop condition, stimulation drives the eye velocity away from the initial target velocity. Upon cessation of stimulation, the open-loop response remains constant. However, notice that closing the loop does not completely compensate for the constant stimulation disturbance; instead, there is an offset from the desired target velocity, which is not consistent with the physiological closed-loop response during DLPN stimulation. (Compare with unstimulated model trajectories in Fig. 7.2b.) (Similar open and closed-loop responses are found in the corollary discharge model with pathway perturbation prior to the integrator.) In short, with pathway modulation, neither class of pursuit model can produce the observed closed-loop responses obtained with DLPN stimulation.





Example of the Effect of Stimulation (Pathway Perturbation) Prior to the Integrator in the Image Motion Model. Open-loop (dash) and closed-loop (solid) model pursuit responses with stimulation (pathway perturbation) in the slip velocity pathway.
Figure 7.9





Simplified Model. The model is meant to represent a simplified version of either pursuit model and the stimulus (D) applied prior to the integrator. (a) a block diagram of a simple feedback control structure is shown. (b) the response of the model in (a) to a constant target velocity with and without an added disturbance signal is shown.

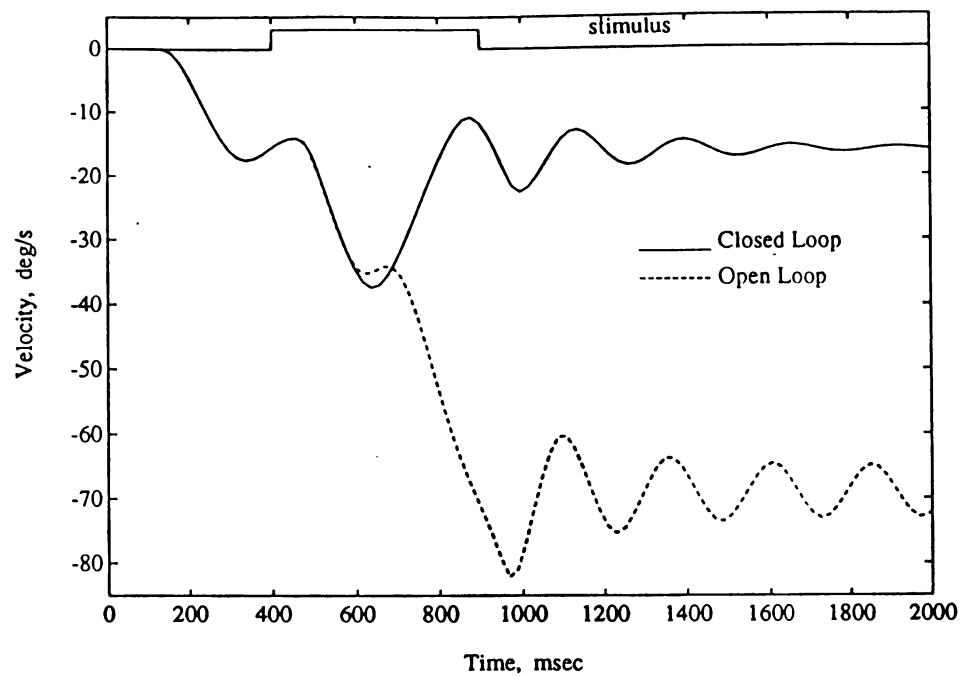
Figure 7.10



Consider the simplified system in Fig. 7.10a. If there is no disturbance ($D \equiv 0$), the error signal is integrated until eye velocity equals target velocity ($\dot{E} = \dot{T}$) at which point the signal to the integrator (retinal slip) is zero and the output remains constant. If there is a constant disturbance ($D \neq 0$), then the signal to the integrator (retinal slip plus disturbance) is only zero (i.e. the output only remains constant) when retinal slip ($\dot{T} - \dot{E}$) cancels the disturbance (D), so eye velocity ($\dot{E}$) does not equal target velocity ($\dot{T}$) (Fig. 7.10b). In addition, there is an explicit off-response, corresponding to the cessation of stimulation, that results in the eye velocity returning to match the target velocity (Fig. 7.10b).

Because the models failed to generate some characteristics of the closed-loop response during DLPN stimulation (such as the increase in magnitude of oscillations, the lack of an off-response, and the oscillations about the target velocity -- not offset from the target velocity), we reevaluated our interpretation of stimulation. It is conceivable that the stimulated neurons represent a conglomerate of conflicting signals, such that stimulating them all has no net biasing effect. (For example, stimulating a group of cells, which individually respond best to different directions of image motion ranging over 360 deg, may not signal any net direction of image motion because signals representing opposing directions negate each other.) The overall effect may be to simply modulate the efficacy of the pathway. In simulation, this effect is readily implemented by modulating the gain of the pathway.





Example of the Effect of Stimulation (Gain Modulation) in the Corollary Discharge Model. Open-loop (dash) and closed-loop (solid) model pursuit responses with stimulation (gain modulation) yielding a differential effect at two adjacent locations (the junction of the efference pathway and the retinal slip pathway).

Figure 7.11



Figure 7.11 shows the open and closed-loop pursuit responses of the corollary discharge model during stimulation implemented by gain modulation in both the efference and retinal slip pathways (different gain levels). (Compare with the unstimulated model trajectories in Fig. 7.2d.) An increase in gain in the efference pathway drives the eye velocity away from the initial target velocity under the open-loop condition, typical of the physiological response. (Although an increase in gain seems like an unlikely effect of stimulation, the idea is in the realm of possibility. The stimulation could increase the resting potential in cells responding to all directions, which would prime the system for subsequent signals. Then, when the normal control signals were processed, their effect would be enhanced.) The gain mismatch between the retinal slip and the efference pathways generates the decrease in frequency of oscillations caused by the oscillations associated with the delay in the outer feedback loop dominating the system (i.e. the efference pathway no longer cancels the modulated eye velocity signal, so the outer loop is no longer effectively open). The increase in magnitude of the oscillations is a consequence of the increase in gain of the retinal slip signal. A gain change in the smooth acceleration pathway of the image motion model can generate an increase in the magnitude of existing oscillations; however, no gain change in the image motion model can generate the type of open-loop response to stimulation observed in the experiments.

Characteristics of the physiological pursuit response to stimulation during pursuit initiation (Fig. 7.8) can be generated from each model with an appropriate choice of stimulation sites and stimulation representations. However, no site or combination of



sites were found in either model that generated the range of responses recorded from the monkey under the conditions discussed.

It is not necessarily surprising that the models could not generate the combination of pursuit responses observed under the different conditions of stimulation. Firing patterns of neurons in DLPN correlate with a variety of signals related to the pursuit movement including sensory and motor-related signals and combinations thereof (Thier et al., 1988, Suzuki et al., 1990, Leichnetz, 1985). It is reasonable to assume that stimulation affects several functional pathways in a complicated manner resulting in a complex effect on the eye movements. This suggests that models which divide signals into functional pathways, while useful conceptually, may not aid extensively in interpretation of stimulation results.

Similarly, since the models do not reflect the topography of the visual system, they cannot be expected to explain the directional effects observed. The models would have to be extended to at least include separate leftward and rightward pathways.

5.3 Comparison of Pursuit Responses During DLPN and MTf/MSTl Stimulation

The comparison to stimulation in MTf/MSTl is based on the results of our study and Komatsu & Wurtz, 1989.

In contrast to the very different responses evoked by DLPN stimulation in the maintenance phase of open and closed-loop horizontal pursuit, the responses recorded during electrical stimulation in cortical areas MTf and MSTl are often similar to each



other (Komatsu & Wurtz, 1989). During MTf/MSTl stimulation the open and closed-loop responses show an initial increase in the difference between eye velocity and initial target velocity that quickly levels off and remains constant for the duration of the stimulation. (Sometimes, the closed-loop perturbation is more transient.) The insensitivity to visual motion error during cortical stimulation in these areas led the authors to suggest that MTf/MSTl stimulation may substitute for visual motion signals usually carried by pathways through these structures. An analogous conclusion about DLPN stimulation can not be drawn because there is a definite effect due to visual feedback, since the open and closed-loop responses are different. It suggests that normal neural signals related to visual motion are not critically affected by stimulation in DLPN, while normal visual motion signals are blocked or taken over by MTf/MSTl stimulation.

Analysis of the models has shown that the models are inconsistent with the results obtained by stimulation in MTf/MSTl; both classes of models show that pathway modulation in the visual pathways under open-loop condition elicits an acceleration signal that continues to increase the eye velocity until stimulation is ended (the effect observed during DLPN stimulation). Only stimulation after the integrator (motor pathway) can generate a shift in eye velocity under the open-loop condition; however, this is too late in the pathway to explain effects from stimulation in MTf/MSTl. It is somewhat surprising that MTf/MSTl stimulation in the open-loop condition, results in a constant velocity offset from the initial target velocity. It is as if the MTf/MSTl signals are never integrated even though the signals in DLPN, a structure at a higher

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level in the pursuit system hierarchy, are integrated. Possibly, the MTf/MSTl signals are effectively differentiated prior to reaching DLPN. This would negate the later effect of integration and thereby account for a constant open-loop velocity error. The physiological system could implement differentiation with neural adaptation to the unnatural affect of electrical microstimulation.

Since a functional closed-loop visual feedback pathway would readily compensate for the constant open-loop velocity offset observed under the open-loop condition, it appears that stimulation in MTf/MSTl takes over the normal pathway signals. Although neither model in its present form accounts for the responses generated by MTf/MSTl stimulation, they are still useful in understanding the implications of stimulation substituting for a pathway signal. Substitution in a serial pathway prevents all prior signals from affecting the output. Substitution by a maximal stimulation signal at a particular site along a serial pathway in the image motion model has the same modifying affect on the output independent of the initial pursuit trajectory. The analogous statement in the corollary discharge model is only true if the site is after the efference signal feeds into the forward loop. Otherwise the efference signal contributes a trajectory dependent signal to the pathway. A speed dependent effect of MTf/MSTl stimulation was reported, leading the authors of that study to conclude that MTf/MSTl stimulation affects the pursuit system prior to the extraretinal inputs. Obviously, with substitution in a parallel pathway, signals earlier in the pathway can contribute to the output along the unaffected pathways. Consequently, taking over the usual signals in a pathway has different effects depending on the structure of the system.

Another interesting difference between the effects of stimulation during the maintenance phase in DLPN and MTf/MSTl, is the difference in the directional effect. MTf/MSTl stimulation during horizontal pursuit always increases the eye speed in the ipsilateral direction, independent of the initial horizontal direction of pursuit. In contrast, DLPN stimulation during horizontal pursuit always increases the speed in the same direction independent of the initial horizontal direction of pursuit, but the increase may be in the ipsilateral or contralateral direction. MTf/MSTl stimulation during vertical pursuit always decreases the speed of pursuit.

The effects of electrical microstimulation in DLPN during pursuit eye movements cannot be easily explained by the control structures we have used to understand the system. It appears that a structure that accounts for the variety of information carried by individual neurons may be necessary to understand the complicated affects of stimulation. In addition, the differences in the effects found during stimulation in MTf/MSTl and DLPN may suggest that our simplified hierarchial structure is not adequate.



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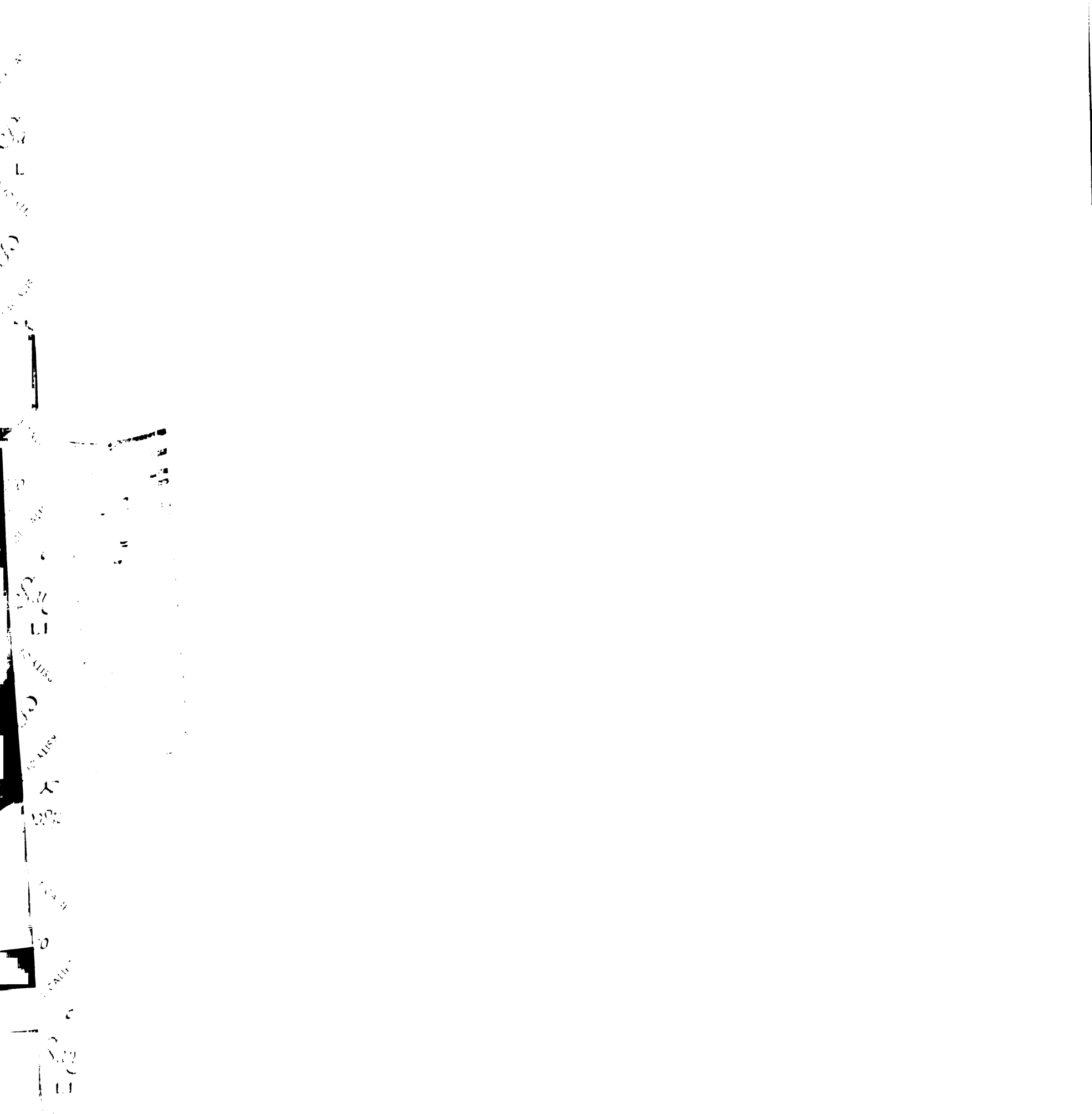
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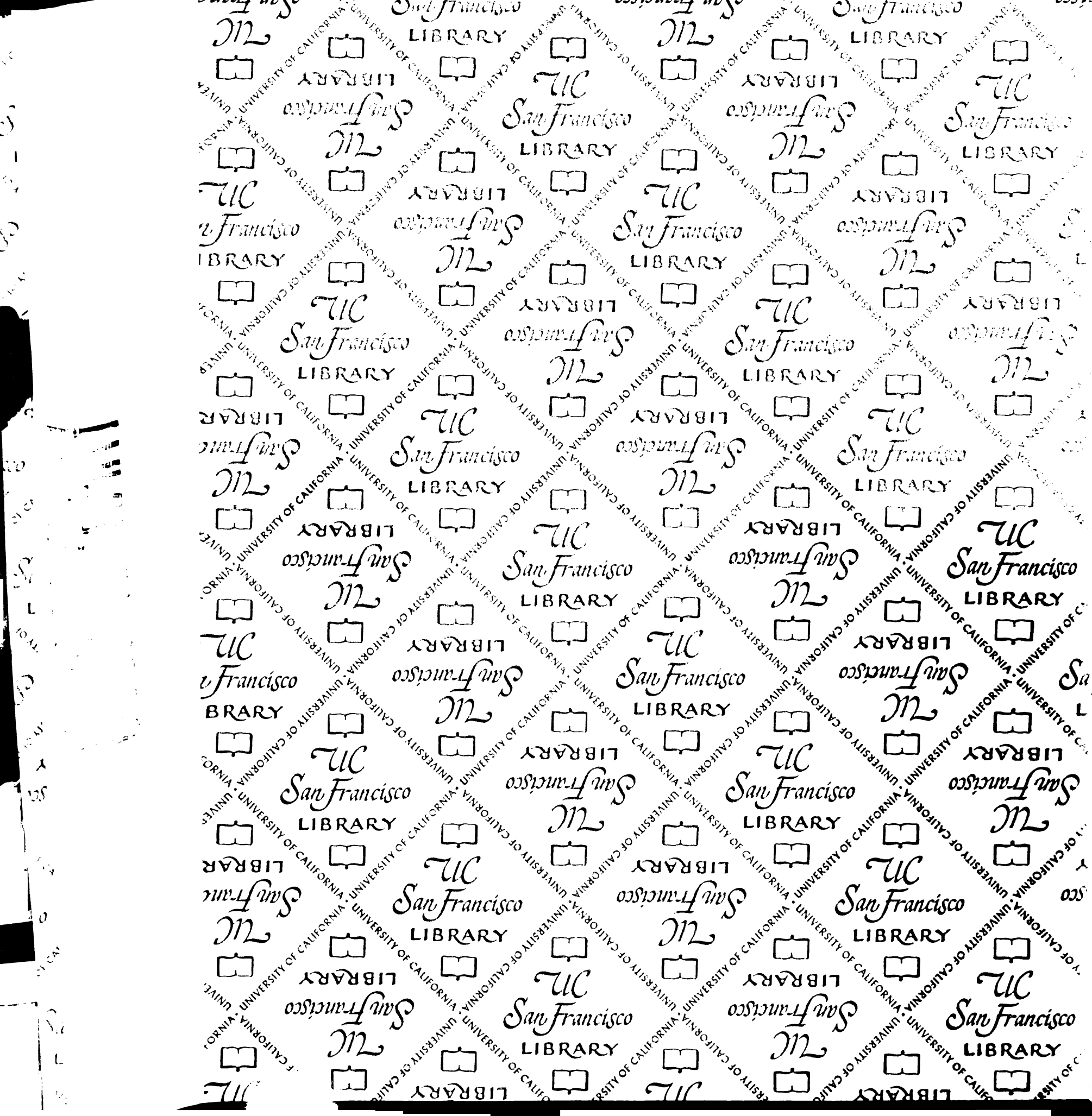
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For reference

Not to be taken
from the room.

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