A UNIFYING HYPOTHESIS FOR THE MULTIPLE WAVEFORMS OF INFANTILE NYSTAGMUS AND THEIR IDIOSYNCRATIC VARIATION WITH GAZE ANGLE AND THERAPY

by

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SCHOOL OF GRADUATE STUDIES

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(date) March 19th, 2008

*We also certify that written approval has been obtained for any proprietary material contained therein.

Dedication

To my parents

献给我的父母

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All these years I have been picturing myself writing the “acknowledge” page of my dissertation, for I owe so much gratitude to so many people in my life. They made the long process of pursuing a Ph.D. much more enjoyable and pleasant than it could have been otherwise.

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A Unifying Hypothesis for the Multiple Waveforms of Infantile Nystagmus and their Idiosyncratic Variation with Gaze Angle and Therapy

Abstract

by

Zhong Wang

Infantile Nystagmus Syndrome (INS) is an ocular motor instability characterized by involuntary oscillations of the eyes. The purpose of this thesis is to better understand the underlying mechanisms of INS in terms of static characteristics, dynamic properties, and changes after extraocular muscle (EOM) surgeries, and to incorporate these findings into a behavioral Ocular Motor System (OMS) model. Accurate recordings of eye-movement responses to visual stimuli under certain experimental paradigms were analyzed and used as templates for model simulations. The effectiveness of the four-muscle tenotomy surgical procedure was evaluated and the post-surgical effects were categorized in order to set up the clinical criteria governing the use of this procedure. Also, combinations of tenotomy with other commonly practiced strabismus/nystagmus surgeries was explored. The eXpanded Nystagmus Acuity Function (NAFX), which is a mathematical function that linearly relates foveation quality of nystagmus waveforms to the maximum possible visual acuity, was used as the direct measurement of post-surgical waveform changes. The differential effect of tenotomy on the fast and slow eye movements of INS was carefully examined to elucidate a working mechanism for

tenotomy. The effects of target timing in INS on target acquisition (of both step and pursuit stimuli) was also investigated as an initial exploration of the INS dynamic characteristics. Incorporating the above INS properties to our OMS model, as well as simulating the mechanisms that determine the idiosyncratic gaze angle where the NAFX peak/nystagmus "null" (the field of gaze angles in which the NAFX is maximal) appears, had greatly expand the behavioral OMS by allowing simulations of more diverse variations of pathological conditions, and therefore greatly assist in our understanding of the OMS.

Chapter 1

An Introduction to Eye Movements and Infantile Nystagmus Syndrome

1.0 Introduction

We move our eyes more than one hundred thousand times a day, without ever thinking about task. The neural system that controls eye movements—the ocular motor system (OMS)—has evolved to provide clear and stable vision for us under a great variety of visual stimuli. The major sub-functions of the OMS share a common purpose: they always attempt to align the fovea with the intended target. The OMS has been a popular subject of study to explore functions of the brain, since its outputs, in the form of eye movements, can be accurately recorded. Over the past several decades, researchers have accumulated invaluable information on eye-movement control mechanisms through data analysis, patient observation, neural transmitters, brain circuits and control-systems models.

1.1 Structure of the eye and the extraocular muscles

To understand the functions of the OMS, it is primarily important to be familiar with anatomy of the eyes. A schematic plot of the structure of the eyeballs is shown in Figure 1-1 (a). When light enters the pupil, the lens accommodates, based on the distance of the target, so that the image is focused and projected onto the back of the eye where the retina lies. The retina has seven layers of nerve cells, one of which contains light

sensors, i.e., rods and cones, which convert the light signal into a neural electrical signal. That signal is sent through the optic nerve to the brain stem and cerebral cortex. The fovea lies in the center part of the retina. This tiny area is responsible for our sharpest vision. A healthy fovea is key for seeing details and colors of the viewing target because it has a much higher concentration of cones. In humans, the fovea occupies only ±0.5° of the eye, about 1/10,000th the area of our full visual field. The density of the cones drops steeply with increasing distance from the fovea, corresponding to acuity dropping by a factor of two or three (Carpenter, 1988). All eye movements are made in an attempt to focus the target image precisely on the fovea. That image also has to be stabilized, since any relative motion between the fovea and the target image will immediately degrade acuity.

Each eyeball has 3 pairs of extraocular muscles (EOM) to make precise movements upon target change. Figures 1-2 (b) and (c) demonstrate the location of the EOMs. The medial and lateral recti are in charge of horizontal eye movements; they work in a push-pull scheme, i.e., when the agonist muscle contracts, the antagonist muscle relaxes, and therefore the eye is rotated to a new position. The main function of the superior and inferior recti is elevation and depression, although they also contribute to torsional eye movements. The superior and inferior oblique muscles are mainly responsible for torsional eye movements. EOM neural innervations are discussed in 1.3.

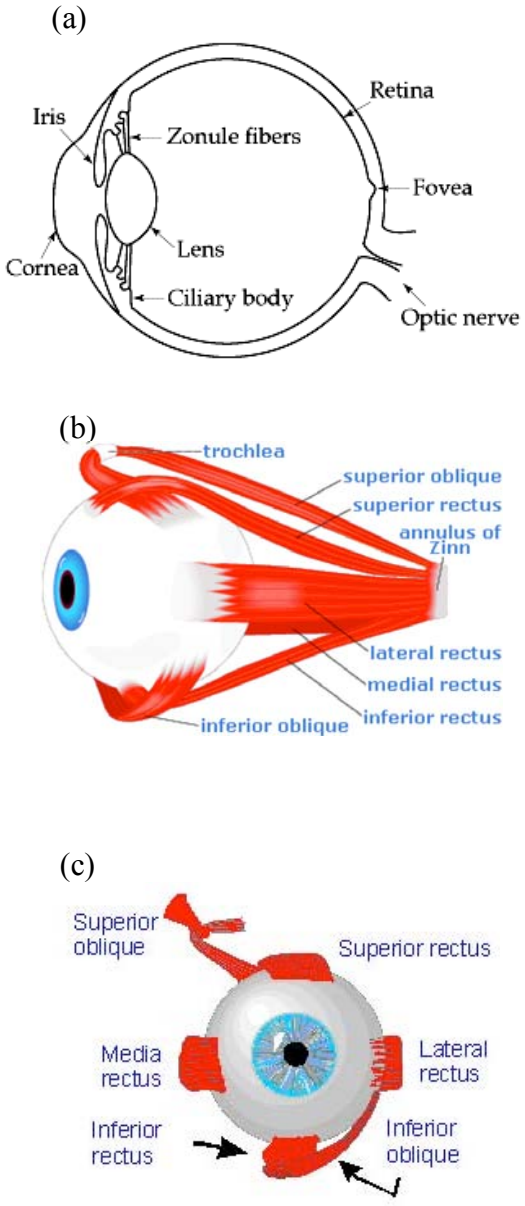


Figure 1-1. (a) Structure of the eyeball. (b) Location of the extraocular muscles in a side view. (c) Location of the extraocular muscles in a front view.

(Adapted from http://thalamus.wustl.edu/course/eyeret.html

http://www.yorku.ca/eye/muscle.htm

http://www.health.howstuffworks.com/eye1.htm)

1.2 Functional classes of eye movements

Functional classes of the ocular motor system include version eye movements and vergence eye movements. They both shift or maintain the gaze (defined as sum of head position and eye position, assuming the body is stationary) on the target. When the target changes its location, eye movements should occur in a timely fashion to acquire the new target position and velocity and hold the gaze on the new target. Functional classes of the version and vergence eye movements are categorized in Table 1-1.

Version eye movements		
Gaze-shifting	Saccades:	Bring target image onto the fovea
Gaze-holding	Fixation:	Hold target image on the fovea
	Smooth Pursuit:	Hold moving target image on the fovea*
	VOR:	Hold visual scene steady on the retina during brief head or body rotation
	OKR:	Hold visual scene steady on the retina during sustained head or body rotation
Vergence eye movements		
Gaze-shifting	Unequal Saccades: Bring target image onto the fovea	
Gaze-holding	Vergence Pursuit: Hold moving target image on the fovea	

Table 1-1. Functional classes of the version eye movements. (VOR=Vestibulo-Ocular Reflex; OKR=OptoKinetic Response)

* Smooth pursuit may be regarded as either gaze-shifting or gaze-holding. It matches the eye velocity with the target velocity and *holds* the eye on target, therefore it can be considered as gaze-holding. Also, gaze in smooth pursuit does *shift* in space, and therefore it can also be regarded as gaze-shifting. Smooth pursuit may have evolved for gaze-holding of the fovea on eccentrically placed targets when we walk through the visual environment.

Saccadic eye movements (also called fast eye movements) are sensitive to a target image displacement, with a latency of ~200 ms to ~250 ms. A corrective saccade that follows an initial voluntary saccade has a shorter latency of ~125 ms because it is pre-programmed. Also, express saccades can be generated with ~100 ms latency (Fischer & Ramsperger, 1984, 1986). Saccades are what we use to redirect our attention from place to place. The saccadic velocity ranges from 30°/s to 800°/s, and the duration ranges from 30 ms to 120 ms. The relationship between the saccadic peak velocity and amplitude follows what's historically called "main sequence", i.e., a exponentially increasing curve with saturation. The relationship between the saccadic duration and amplitude follows a more linear relationship (Leigh & Zee, 2006). The saccadic eye movements are conjugate and ballistic. There is no active braking to stop the saccade; the overdamped plant (the globe and the musculature) passively stops it.

Pursuit eye movements smoothly track slowly moving objects in the visual field and are sensitive to target velocity. The pursuit latency is ~125 ms; the pursuit velocity is usually less than 50°/s. Pursuit eye movements are conjugate and smooth. Usually, saccadic and pursuit eye movements are coordinated to track moving targets efficiently. For most people, pursuit requires a moving target to operate properly, whereas you can make saccades to imaginary targets, even in the dark.

When there is a head or body movement, the eyes should be moved an equal and opposite amount in the other direction. This is called the vestibulo-ocular reflex, or VOR, driven by the balance organs of the inner ear. It has a very short latency of ~16 ms, and its velocity can be as high as 400°/s. The VOR eye movements are conjugate and smooth. The OptoKinetic Response, or OKR is triggered by the retinal image motion itself

(Carpenter, 1988); it occurs when the body and head are in sustained motion. The VOR and OKR eye movements act in concert to maintain gaze during body motion.

In all version eye movements, the eyes are yoked to move conjugately. In vergence eye movements, however, the two eyes move disconjugately to view targets at a far or near distance.

Neural integrators are the group of neurons that perform integration; they exist in a number of places in the OMS. The final neural integrators transform eye-velocity signals to eye-position commands for the motor neurons of the EOMs. The Rosen model of a neural integrator (Rosen, 1972) consists of a network of neurons with extremely strong self-excitation; the individual neurons had an "off" and an "on" state of firing. The major disadvantage of Rosen's model was that real ocular motor neurons do not exhibit binary "on/off" behavior (Cannon, Robinson, & Shamma, 1983). Subsequent models (Cannon & Robinson, 1985; Kamath & Keller, 1976; Seung, Lee, Reis, & Tank, 2000) substituted these binary neurons with continuous firing rate versus injected current relationships. Arnold et al also reported a novel neural network model with a local, Hebbian-like synaptic learning rule to simulate neural integrator behaviors (Arnold & Robinson, 1997).

1.2.1 Saccades

Electrophysiological studies of EOM activity in humans and animals have demonstrated that during a saccade, a high-frequency burst of phasic activity can be recorded from the agonist muscles; this burst generates the forces necessary to overcome orbital viscosity so that the eye will quickly move to the new position. Following a

saccade, the agonist eye muscle and its ocular motor neurons assume a new level of tonic innervation, which holds the eye in its new position (Boghen, Troost, Daroff, Dell'Osso, & Birkett, 1974; Carpenter, 1988; Dell'Osso, 1989; Heywood & Churcher, 1979).

The starting of the saccades needs higher neural innervation to overcome the viscosity of the plant, as shown in Figure 1-2 (a). The top scheme shows how a simple step input to the plant yields slow target acquisition. The bottom scheme demonstrates how a pulse-step speeds up the arrival at the new target. This scheme corresponds with neurophysiological recordings and is widely used in saccadic models. Panel (b) of Figure 1-2 shows a model realization utilizing the pulse from the "pulse generator" and integrating that pulse to form the required step. The pulse and the step need to be matched for the eyes to arrive on the target properly.

1.2.2 Smooth Pursuit

The stimulus to the pursuit system is the velocity of motion, or slip, of the visual image as it moves away from the fovea. The retinal error velocity ("slip") is defined as the difference between target velocity and eye velocity. This error is the signal used by the pursuit system to generate an eye-velocity command. The pursuit system is a negative feedback system, thereby reducing this error to zero (Collewijn & Tamminga, 1984; Gellman & Carl, 1985).

Like the saccadic system, in pursuit, a simple ramp input to the plant would not achieve target acquisition in a timely fashion. Instead, a step-ramp input is required to generate the proper eye velocity for the new target. Panel (c) of Figure 1-2 demonstrates this point.

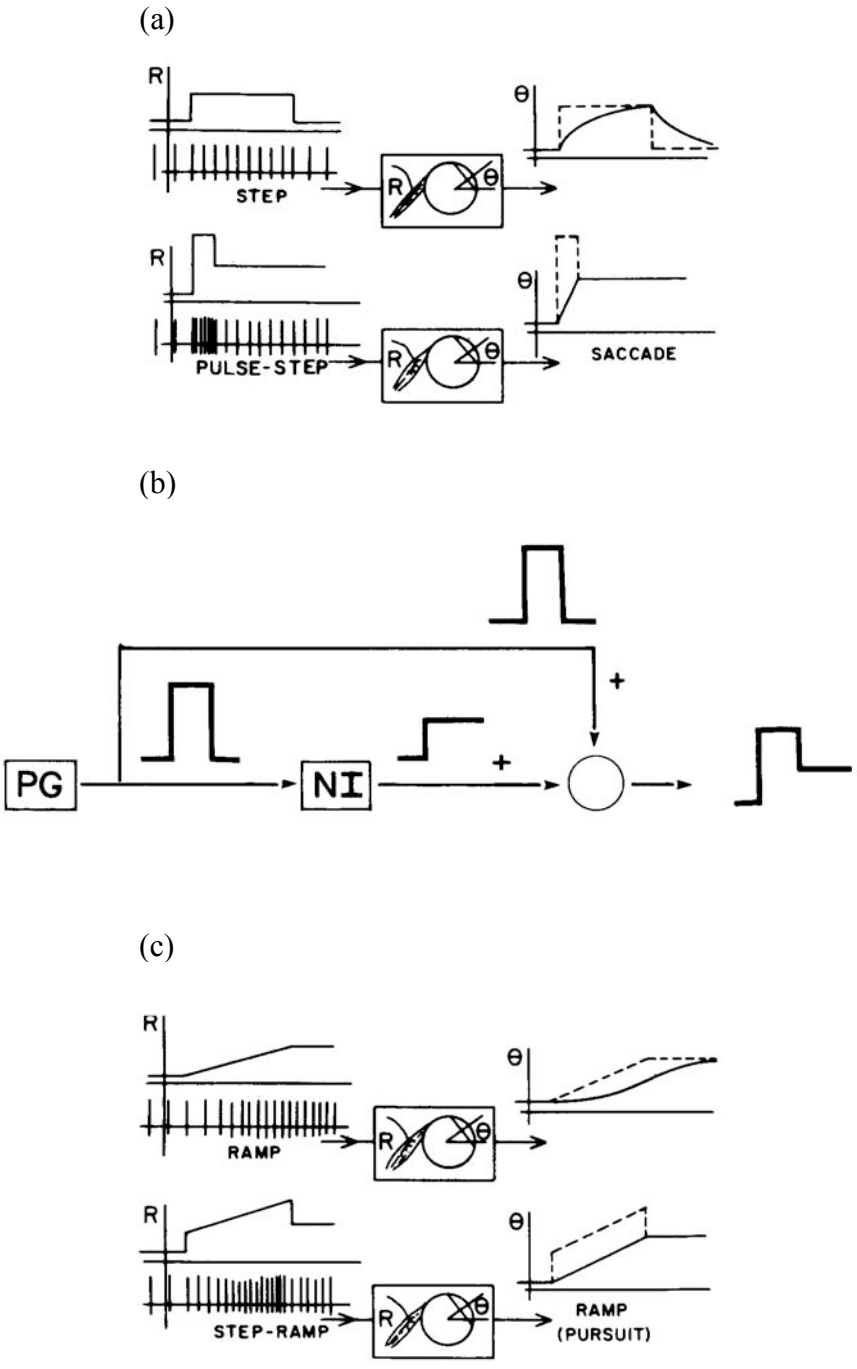


Figure 1-2. (a). Two possible schemes for saccade generation. (b) Generation of a pulse-step using the neural integrator output. (c). Two possible schemes for pursuit generation. (Adapted from Robinson, DA: Oculomotor control signals. In *Basic Mechanisms of Ocular Motility and their Clinical Applications.* New York, Pergamon Press, 1975.)

1.3 Neural innervations of the Extraocular muscles

The extraocular muscles are innervated by cranial nerves III (oculomotor nerve), IV (trochlear nerve), and VI (abducens nerve). Cranial nerve VI originates from the pons in the midbrain, and sends axons into the orbits to innervate the contralateral lateral rectus muscles. Therefore, cranial nerve VI is responsible for abducting each eye. The left and right trochlear nuclei are in the midbrain. Their axons, which make up cranial nerve IV, innervate the left and right superior oblique muscles. Therefore, cranial nerve IV is primarily responsible for turning each eye downward when it is already looking inward toward the nose. Cranial nerve III innervates all of the remaining extraocular muscles, and is also responsible for parasympathetic constrictions of the pupils. The superior branch of cranial nerve III innervates the superior rectus and the levator palpebrae superioris. The lower branch innervates the medial rectus, inferior rectus, and inferior oblique (Leigh & Zee, 2006).

Proprioception plays an important role in the development of visual analyses in the visual cortex, and the maintenance of normal visual motor behavior. In skeletal muscles the predominant proprioceptor is the muscle spindle, but this is not the case for EOMs, in which spindles are absent in the majority of species. In Man, the eye muscles contain large numbers of spindles, more per unit weight than other human finely controlled muscles. They also show various structural peculiarities, including lack of expansion of the equatorial zone and “abnormalities” of the intrafusal fibers (Blumer, et al., 1999; Hertle, Chan, Galita, Maybodi, & Crawford, 2002; Porter, 1986). Among all other receptors, palisade endings are present in all species and are sensitive to deformation by contraction of its parent muscle fiber, therefore might serve

proprioceptive functions (Donaldson, 2000; Porter, Baker, Ragusa, & Brueckner, 1995; Porter & Donaldson, 1991). Immunolabeling studies have also shown that palisade endings are sensory and non-nociceptive (Jaggi, Laeng, Müntener, & Killer, 2005). Wang et al recently reported a proprioceptive representation of eye position in monkey primary somatosensory cortex (X. Wang, Zhang, Cohen, & Goldberg, 2007). The exact functions of proprioception and its physiological loops are still being discovered. The hypothesis, based on implications from the tenotomy procedure, that the proprioceptors monitor the static EOM tension is proposed in later Chapters of this thesis.

1.4 Eye-movement recording techniques

Accurate eye-movement recordings are a prerequisite for studying ocular motor functions. The recording technique that has the longest history is the electro-oculogram (EOG). EOG recording makes use of the fact that the electric potential on the back of the eye, i.e., the retina, has a more negative value than that from the front of the eye. The polarity of this potential exists because of the higher metabolic rate in the retina. Therefore, when an eye movement occurs, the resulting dipole moves also. Placing a pair of electrodes at the outside of the left and right eye ("bitemporal electrodes") has been used to record the voltage difference induced by eye movements. As shown in Figure 1-3, when both eyes are straight ahead, the electrodes are at the same potential and no voltage is generated. The rotation of both eyes to the right results in a higher positive value at the right electrode and a lower value at the left, and a positive output will be produced.

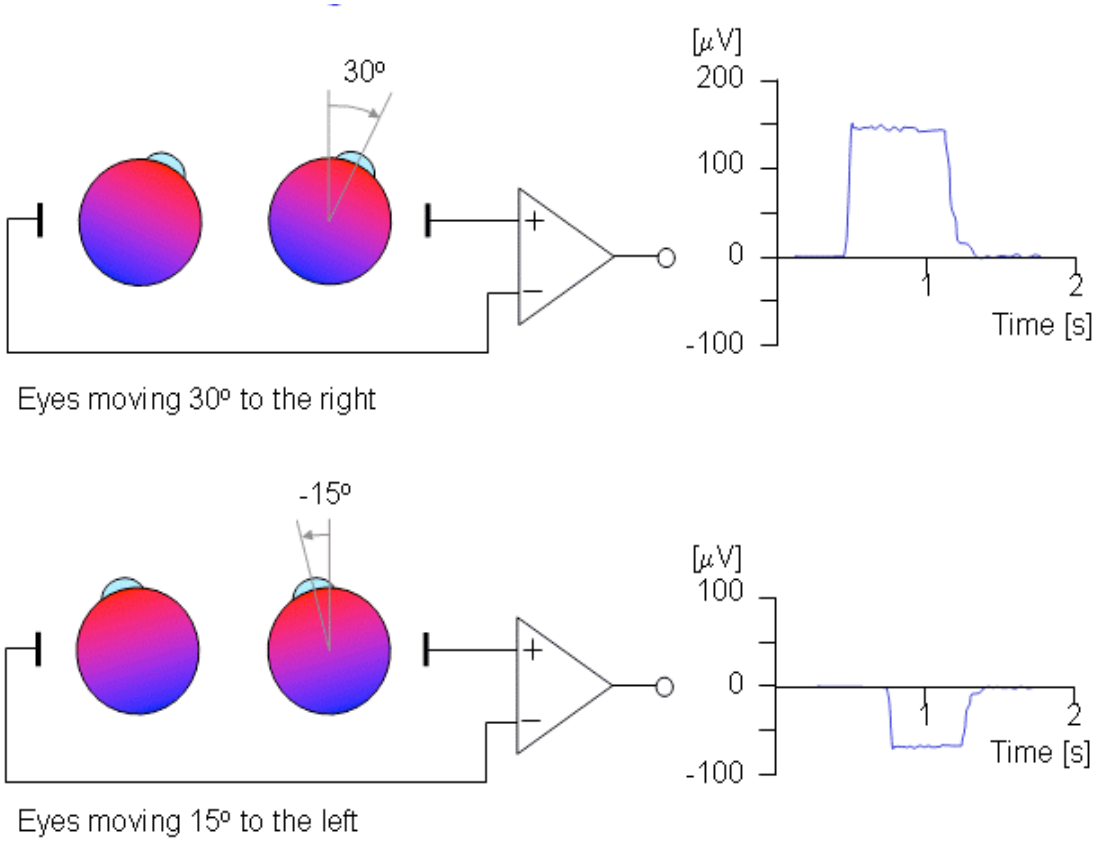


Figure 1-3. "Bitemporal" EOG recording setup and output. Shown for illustrative purposes only; this is a method with limited usage in recording accurate eye movements. (Adapted from http://butler.cc.tut.fi/~malmivuo/bem/bembook/28/28.htm)

Although EOG is easy to setup and convenient for coarse eye-movement recordings and monitoring, unfortunately the basic premise upon which the bitemporal electrode placement was based is incorrect—the eyes do *not* always move with precise conjugacy, even in normals and certainly not in ocular motor dysfunction. Thus, the EOG method has quite limited usage for ocular motor research. Another attractive feature of EOG is that by placing electrodes on the upper and lower side of the eyes, vertical eye movements can be detected along with horizontal eye movements. However, because of the eyelid artifact (the eyelids behave like resistors to the vertically moving dipole), this too is an unacceptable method for ocular motor research. Moreover, EOG recording is prone to noise and it also picks up muscle contraction activity (e.g., orbit muscle movements and facial expressions). For all these reasons, EOG is not suitable for accurate eye-movement data analysis.

The infrared reflection (IR) system illuminates the eyes with a low-level infrared light and measures (with photo diodes) the reflection at the border between the iris and the sclera, as shown in Figure 1-4 (a). The signals from each sensor are then compared to calculate the eye movement. IR is a non-invasive technique and requires minimal setup. It has been widely used for human eye-movement recordings (Figure 1-4 (b)). With proper changes, it can also be used on canines (Figure 1-4(c)). For best recording quality, the IR system should be head-fixed, reducing the head-movement artifact. The head position of the subject should be fixed or monitored to make sure the gaze angles are accurately measured. Usually, only one plane of eye movements is recorded using IR. The main shortcomings of the IR system include: system nonlinearity, susceptibility to extraneous light and inability to wear visual corrections except for contact lenses.

Remote IR systems have also been developed recently to allow minimal restrictions on the subjects. Infrared light and the reception cameras are placed a distance away from the subject, as shown in Figure 1-4 (d). That setup requires the head position to be fixed throughout the recording, so that the eye movement detected does not contain head movement artifact. The remote IR system is a great candidate for recording eye movements on infants or children of small age.

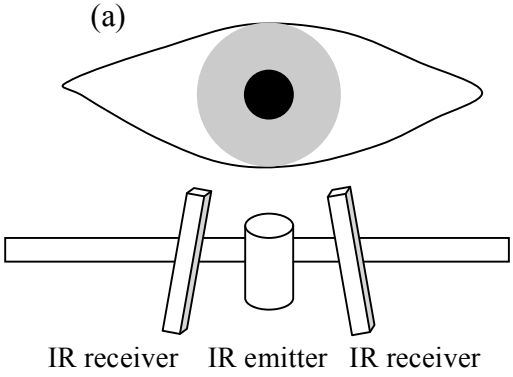
Over the last few years, the digital video system (DV) has been used extensively for eye- movement recording applications. DV is also a non-invasive technique; it is usually head-fixed to remove head movement artifact. Figure 1-5 (a) shows the DV system setup for a human subject, with two 250 or 500 Hz digital cameras pointing at both eyes, centering each eye in its field. The image acquired is then processed to determine the pupil center movement. Figure 1-5 (b) shows the control panel when the recording is in process. With proper modifications this system can also record canine eye movements (Figure 1-5 (c)).

The magnetic search coil (SC) system is often considered as the gold standard of eye-movement recording techniques because of its accuracy and ability to record horizontal, vertical, and torsional eye movements and head position. A coil of copper wire embedded in a silicone annulus that's inserted into the eye (Figure 1-5 (d)), and the subject is placed in a time-varying magnetic field. The movements of the eyes induce electric current in the coil and are reconstructed to eye-position signals. This system allows calibration before the coil is inserted into the eye, therefore greatly reduces the testing time. It is, however, an invasive recording technique, which requires great care

placing the coil in the anesthetized eye. It has some limitations on recordings of infants and young children.

No matter which recording technique we use, the output of the system needs to be properly calibrated to yield accurate eye-position signals. Usually, the subject is required to look at targets at known locations to allow equipment gain adjustments or subsequent digital calibration. In patients with eye-movement disorders, especially strabismus, each eye should be calibrated separately to allow detection of any tropia or phoria.

(a)



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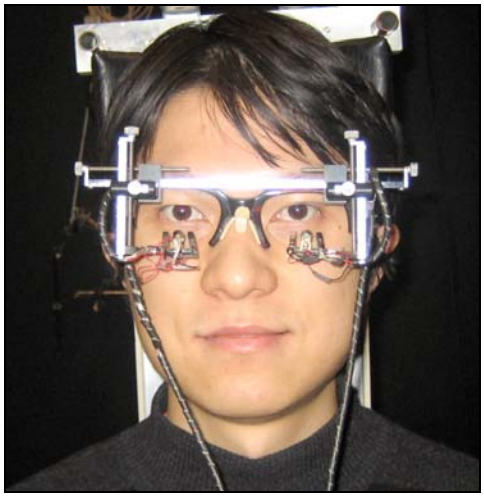

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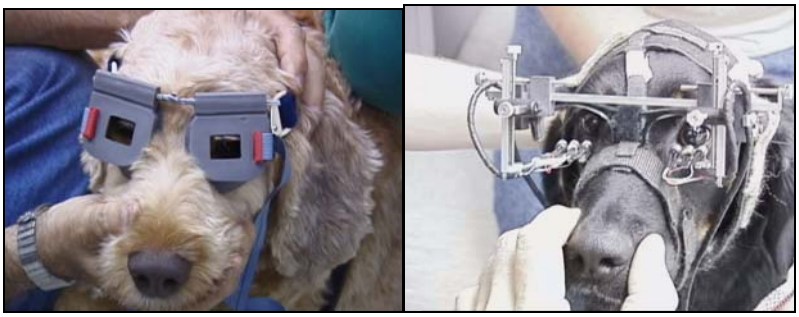

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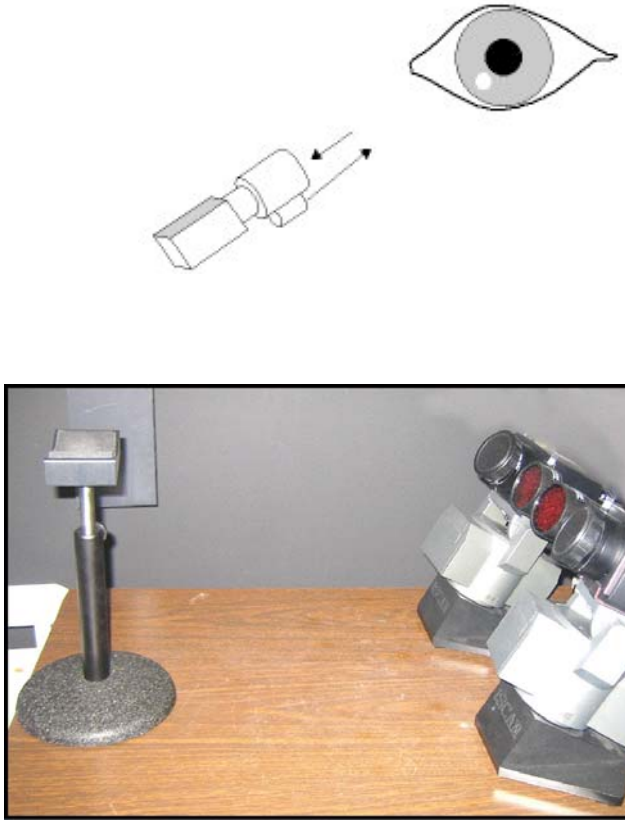
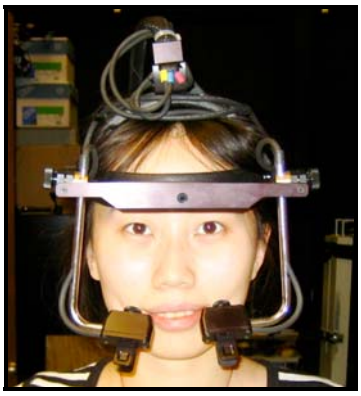


Figure 1-4. (a) Working mechanism of the infrared reflection (IR) recording system. (b) Human IR recording setup. (c) Canine IR recording setup. (d) Remote IR system setup. (Images (a) and (d) are adapted from http: //www.sph.sc.edu/comd/rorden/eyemon.html)

(a)



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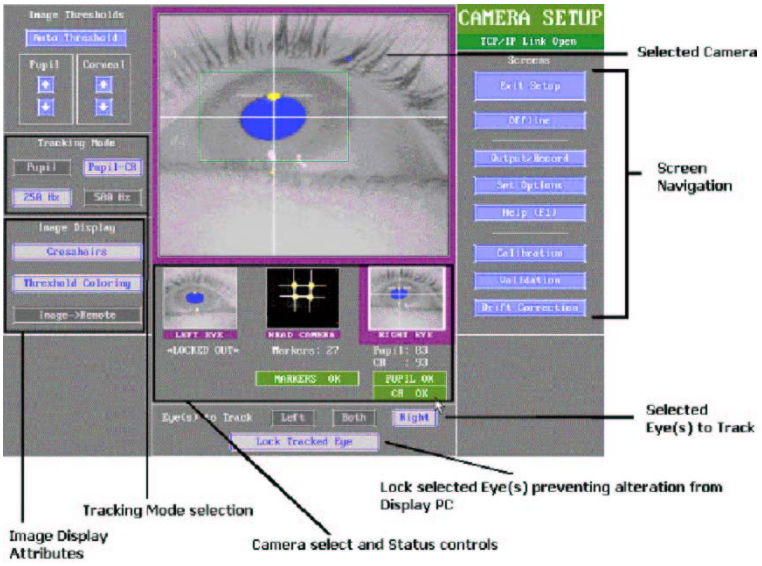
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CR : 93
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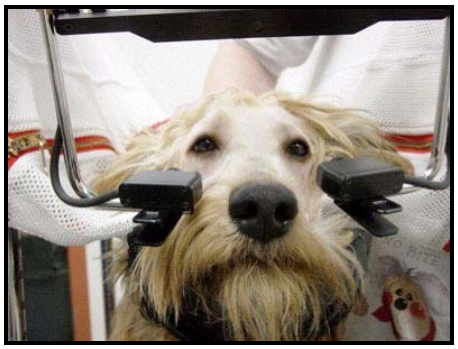
(c)



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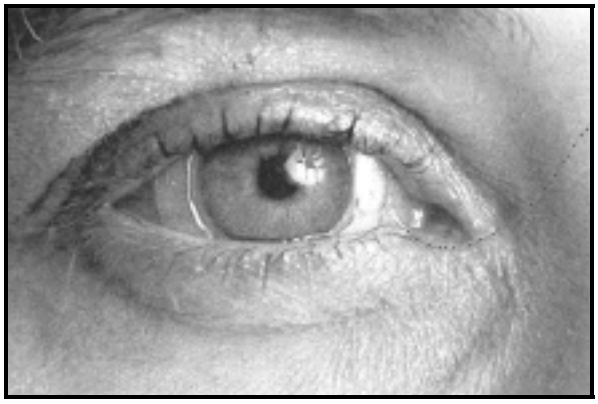


Figure 1-5. (a) Digital video (DV) recording system set up on a human subject. (b) Control panel of the DV system while recording is in process. (c) DV setup on a canine subject. (d) Search coil inserted into a subject's right eye.

1.5 Nystagmus

Nystagmus, the rhythmic to-and-fro oscillation of the eyes, has been regarded as enigmatic since ancient times. The word "nystagmus" comes from the Greek word, νυσταγμός (drowsiness); it is derived from νυστάζειν, meaning, "to nod in one's sleep." Nystagmus is characterized by involuntary movements of the eyes and could be one of several infantile types or acquired later in life.

A series of neurological disorders can cause acquired nystagmus (AN), the most common ones are Multiple Sclerosis (MS) and stroke. These disorders affect the fixation mechanism, the VOR, or the neural integrator. AN patients usually suffer from oscillopsia.

Nystagmus can also be elicited in normal subjects. Optokinetic nystagmus (OKN) is an ocular motor reflex that contributes to the stabilization of retinal images; it has a drifting slow phase and a fast phase that reset the eye position. It allows the eye to follow objects in motion when the head remains stationary (e.g., observing individual telephone poles on the side of the road as one travels in a train). The reflex develops at about 6 months of age. Some normal subjects have slight gaze-evoked nystagmus, especially in darkness. Nystagmus could also occur temporarily with the intake of certain drugs (alcohol and other central nervous system depressants and stimulants).

Infantile Nystagmus Syndrome (INS) is also known as congenital nystagmus. It is usually noticed right after birth and persists throughout life (CEMAS_Working_Group, 2001; Dell'Osso & Daroff, 1975; Gresty, Bronstein, Page, & Rudge, 1991). It is agreed that INS affects about one in several thousand people. INS is predominantly horizontal, with some torsional and, rarely, vertical motion (Dell'Osso & Daroff, 1999a). A recent

study has also identified sub-clinical see-saw nystagmus in some INS patients (Dell'Osso, Jacobs, & Serra, 2007). The eye movements may be pendular or jerk. In jerk waveforms, each cycle consists of a slow phase that takes the eye away from the target, and a fast phase (foveating saccade) that attempts to bring it back. The frequency of INS oscillations is typically 3 Hz to 5 Hz. The peak-to-peak nystagmus amplitude can range from <1° to 40°. The direction of the slow and fast phases of INS does not change with the viewing eye (however, if they have a "latent component" the direction will change). The slow phase of INS has either an accelerating velocity or, less frequently, is linear. INS frequently accompanies additional afferent defects of the visual sensory system such as albinism, achromatopsia, congenital cataracts, optic nerve and/or foveal hypoplasia. When these defects are present, visual acuity could be substantially impaired. When INS occurs in isolation (or of unknown origin), it may still reduce visual acuity to a variable extent, depending on the foveation characteristics of the nystagmus waveform. The genetic transmission of INS may be X-linked, from unaffected mother to affected son. There are also autosomal dominant forms (Dell'Osso, Flynn, & Daroff, 1974; Forssman & Ringnér, 1971; Hayasaka, 1986; Kerrison, Koenekoop, Arnould, D., & Maumenee, 1998; Tarpey, et al., 2006).

Fusion Maldevelopment Nystagmus Syndrome (FMNS) was formerly known as latent/manifest latent nystagmus. It is also usually noticed right after birth. Pure latent nystagmus occurs only when one eye is covered; it beats in the direction of the open eye and disappears when both eyes are open. Pure latent nystagmus is rare. Manifest latent nystagmus occurs when both eyes are open; it beats in the direction of the viewing eye. The slow phase of FMNS is linear or may have a decelerating velocity. FMNS is a

different type of nystagmus than INS, although they can co-exist in some patients (Dell'Osso, Schmidt, & Daroff, 1979).

INS is often confused with Spasmus Nutans Syndrome (SNS), which also begins early in life. SNS usually diminishes in several months to years. The amplitude of nystagmus in each eye can be quite unequal and the nystagmus may be "out of phase". The phase relationship is variable and sometimes the eyes are in phase. In INS and FMNS, the eye movements are always "in phase" (Dell'Osso & Daroff, 1999b; Weissman, Dell'Osso, Abel, & Leigh, 1987). The nystagmus seen in SNS mimics that seen in brain tumors and therefore, an MRI is necessary to rule out that possibility.

Acquired forms of nystagmus may be a result of an accident or a range of illnesses, especially those affecting the motor system. The waveforms of acquired nystagmus might be pendular or linear.

Despite the oscillation, individuals with INS experience no oscillopsia (illusory perception of environmental movement) under most circumstances. It is generally believed that an efference copy of the eye position is fed back to the decision-making circuits of the brain, subtracting extraneous movements of the retina. In congenital forms of nystagmus, the constant eye oscillations are present throughout ocular motor system development and efference copy can be effectively used to compensate for the oscillations (Abadi, Whittle, & Worfolk, 1999; Bedell & Currie, 1993; Dell'Osso & Leigh, 1992; Goldstein, Gottlob, & Fendick, 1992; Leigh, Dell'Osso, Yaniglos, & Thurston, 1988). Additionally, it was reported that efference-copy signals reduce perceived motion smear INS, preferentially for target motion opposite to the slow phase (Bedell, 2000; Bedell & Bollenbacher, 1996). Under certain testing conditions,

oscillopsia can be elicited in INS patients (Abel, Williams, & Levi, 1991; Tkalcevic & Abel, 2003). In the case of acquired forms of nystagmus, the efference copy cannot be subtracted from the nystagmus oscillations, and therefore, oscillopsia is almost always present.

INS has been reported to be autosomal dominant, autosomal recessive, or X-linked, the latter being the most frequent. By linkage analysis, the major X-linked locus was localised to chromosome Xq26-q27 (Kerrison, Giorda, Lenart, Drack, & Maumenee, 2001; Kerrison, et al., 1998; Kerrison, Vagefi, Barmada, & Maumenee, 1999); also, a novel gene named *FRMD7* was discovered at Xq26.2 in which 22 different mutations were identified (Tarpey, et al., 2006).

1.5.1 Characteristics of infantile nystagmus syndrome

There are three main classes of INS waveforms: pendular (with variations dependent on the nature of corrective saccades inserted into the waveform); jerk with accelerating slow phases; and jerk with linear slow phases. An additional class consists of one of the INS waveforms (usually jerk) plus a low-amplitude, higher frequency (around 10 Hz) pendular oscillation superimposed on it, the dual jerk waveform. Figure 1-6 shows the variety of INS waveforms. Most individuals with INS exhibit several types of waveforms. All the waveforms shown in Figure 1-6 are pathognomonic of INS, except for the pure pendular, asymmetric pendular, and the linear-slow-phase jerk waveforms. The accelerating slow phases of the jerk INS waveforms serve as an important and powerful tool to distinguish INS with other forms of nystagmus. For example, vestibular

nystagmus, caused by a tonic imbalance in the vestibular nuclei, has a linear slow phase (Leigh & Zee, 2006); FMNS waveforms have linear or decelerating slow phases.

The major component of INS is usually horizontal. Abadi et al noted that horizontal oscillations were found in 78% of their INS sample (n = 224) and 14% (n=32) also displayed a recordable torsional component (Abadi & Bjerre, 2002). Dell'Osso et al have also identified sub-clinical see-saw nystagmus embedded in some INS patients (Dell'Osso, et al., 2007).

The INS spatial contrast sensitivity function is distinctly different than that of normals, in that it has no, or much reduced, low spatial frequency roll-off, a shifted peak of contrast sensitivities (towards low spatial frequencies), and a significantly reduced high spatial frequency cut off (Abadi & Bjerre, 2002; Abadi & Sandikcioglu, 1975; Bedell, 2006). This means that the medium-to-high spatial frequencies are attenuated in INS. It was also found that contour interaction on letter acuity ("crowding" effect) in INS is greater than that of normals (Chung & Bedell, 1995; Pascal & Abadi, 1995). A number of studies have indicated that motion perception thresholds are raised in CN (Abadi, et al., 1999; Bedell, 1992; Dieterich & Brandt, 1987; Kommerell, Horn, & Bach, 1986; Shallo-Hoffmann, Bronstein, Acheson, Morland, & Gresty, 1998).

It is hypothesized that INS is a pursuit-system instability, whether the waveforms are of a pendular or jerk type. High-frequency components seen in dual jerk waveforms are from nucleus of the optic tract. The OMS in normal subjects has initial damped ringing when pursuing a ramp target (Robinson, Gordon, & Gordon, 1986). In INS, a high-gain instability of the pursuit system may alter the damped ringing, resulting in a sustained oscillation. Although the ringing of the oscillation in normals exists both

horizontally and vertically, the horizontal plane seems to be more vulnerable to the high-gain instability, since INS is mostly horizontal. Chapter 9 summarizes the subsystems hypothesized to be the origins of INS oscillation with the evidence for and against each. It also demonstrates how multiple waveforms can be simulated under a unifying pursuit-system instability in our model, consistent with INS recordings, especially when inattention occurs. A possible argument against the pursuit-system hypothesis of INS, is that the torsional component did not appear to conform to the torsional variations predicted from Listing's law (Averbuch-Heller, Dell'Osso, Leigh, Jacobs, & Stahl, 2002; Bedell, Tong, S., & M., 2007 (in press)). whereas smooth pursuit does. However, that finding does not necessarily imply that INS does not obey Listing's Law. Moreover, even if the torsional component of INS did not conform to Listing's Law predictions, it does not mean the horizontal *oscillation* cannot come from the pursuit system, i.e., the adherence of the torsional component of INS to Listing's Law is not a necessary condition for the horizontal oscillations' pursuit-system origin. Perhaps a more careful examination of the foveation periods during INS smooth pursuit would elucidate whether INS truly obeys Listing's Law predictions.

A foveation period is defined as the time period in each nystagmus cycle when the eye position is in a position-threshold window around the desired target position, and the slip velocity is also within a velocity-threshold (Dell'Osso, 1973); The foveation period follows the foveating saccade in each nystagmus cycle, except for pseudo cycloid waveforms. It is only during the foveation periods that INS patients can see details of the target. The position and velocity window thresholds are highly idiosyncratic; a small window means the eye arrives at the target with a slow enough velocity for steady

foveation, and therefore indicated good visual function. The parts of the INS waveform other than the foveation period are not taken into account perceptually by the OMS because the image is out of the fovea and moving with a high slip velocity; it is beyond the capability of the OMS to stabilize that image.

The nystagmus eye movements as first seen in infants can have large amplitudes and no distinct foveation periods. As the ocular motor system develops, foveating saccades are generated to allow target foveating, and the amplitude of the nystagmus reduces. INS worsens with excitement, nervousness, tiredness, anger and illness. Inattention also changes the INS waveforms. During complete inattention, the nystagmus oscillation ceases and the eye starts to drift away; as soon as attention is resumed, the nystagmus comes back. It is thought that "fixation attempt" starts and maintains the INS oscillations. Recent studies have shown that INS is not exacerbated by visual demand per se, but rather the stress associated with the importance of the visual task (Tkalcevic & Abel, 2005; Wiggins, Woodhouse, Margrain, Harris, & Erichsen, 2007).

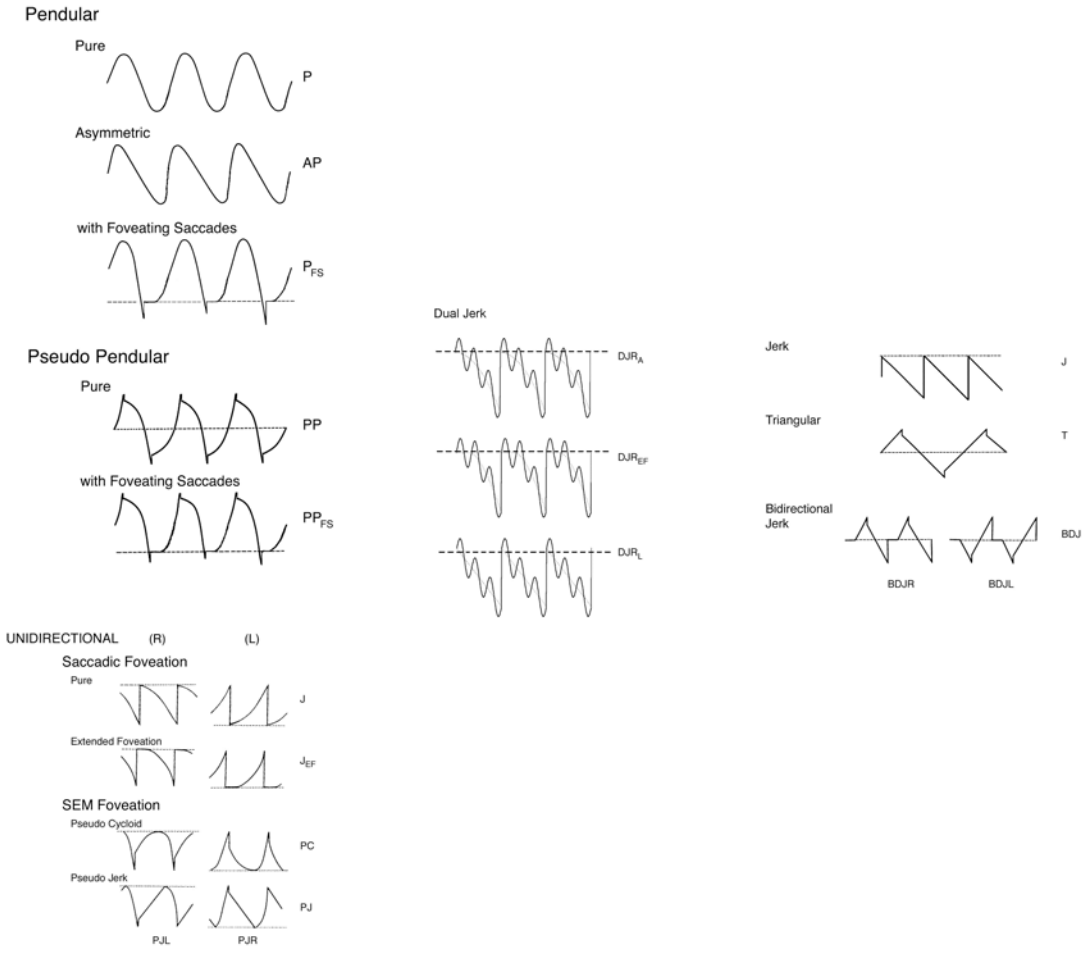
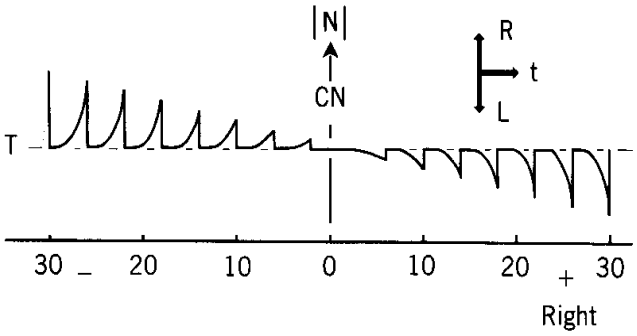


Figure 1-6. Typical waveforms of infantile nystagmus syndrome categorized by their origins. The left column of waveforms are hypothesized to originate from the pursuit system; the middle column from the pursuit system (top two) or vestibular system (bottom) and the nucleus of optic tract; the right column from the vestibular system.

A gaze-angle null in INS refers to the range of gaze angles where the nystagmus intensity is lowest, usually corresponding to the highest visual function. As will be discussed below, it is actually the "peak" in the eXpanded Nystagmus Acuity Function (NAFX) that determines the region of highest acuity. Figure 1-7 (a) demonstrates a gaze-angle null at 0° (primary position). The farther the patient looks to the left or the right of the null position, the more nystagmus amplitude increases. The direction of jerk nystagmus also varies with the gaze angle, the slow phase always accelerating towards the null. Normally, INS patients prefer to use their null position to maximize visual acuity; in this case, a null at primary position would be most desirable. However, INS nulls can be at any number of degrees to either side of primary position. Those who have a null at far lateral gaze usually adopt head turns early in life, which might lead to neck muscle problems.

The broadness of the null also has marked visual function consequence. Figure 1-7 shows a comparison between a broad null (b) and a sharp null (c). These photos depict what an INS patient with a central null might see when looking at the group of people without turning his head. The farther away from the center, the worse he sees. With a sharp null, the image quality drops steeply once out of the null zone, and visual acuity degrades accordingly.

(a)


N
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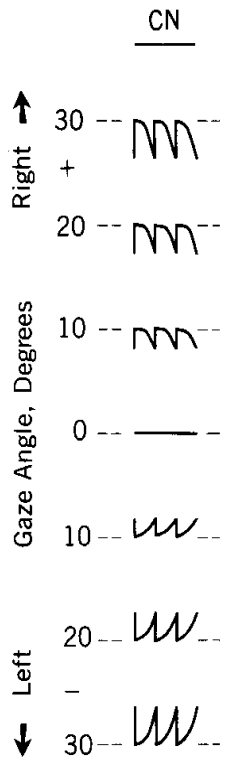
R
t
L
T
30 – 20 10 0 10 20 + 30
Right


CN
Right
Left
Gaze Angle, Degrees
30
+
20
10
0
10
20
–
30

(b)

(c)

Figure 1-7. (a) Nystagmus null at primary position and waveform changes at lateral gazes. (b) and (c) are photos depictions of what an INS patient with a central null might see when looking at the group of people without turning his head. In (b), the patient has a broad null; in (c), the patient has a sharp null.

The nystagmus amplitudes of FMNS patients and Vestibular Nystagmus (VN) patients follow Alexander's law, i.e., the nystagmus is more intense when the patient looks in the quick-phase direction. Therefore, these patients do not have a "null" per se; their nystagmus amplitude is governed by the fixating eye (in FMNS) or the direction of the tonic imbalance (in VN). Doslak et al proposed that Alexander's law was caused by a copy of intended eye position added to the integrator input, which resulted in a linear slow phase (Doslak, Dell'Osso, & Daroff, 1982). Robinson at al suggested that Alexander's law is due to the sum of vestibular nystagmus and gaze-evoked nystagmus (Robinson, Zee, Hain, Holmes, & Rosenberg, 1984). However, the latter hypothesis would predict exponential slow phases, not linear ones as observed in patients. We chose to simulate Alexander's law arising from a vestibular tonic imbalance input; this hypothesis has been embedded in a model that simulated FMNS behaviors (Dell'Osso & Jacobs, 2001).

INS patients with a convergence null have less nystagmus when they look at near targets. Convergence damping also has an additional broadening effect, i.e., the nystagmus is reduced over a large range of gaze angles. Therefore, INS patients who have both a gaze-angle null and a convergence null are usually best treated by using the latter. The effectiveness of the convergence null relies on both eyes working together (i.e., no strabismus).

INS is a motor instability, which, as mentioned above, may or may not co-exist with additional sensory deficits. The visual acuity impairment caused by the nystagmus is separate from that caused by the retina, the optic nerve, or any other sensory defects. Therefore, in measuring and treating nystagmus, it is important to focus on the waveform

characteristics rather than the clinical visual acuity measurement. In INS, the nystagmus is greatly affected by emotions; in a high-stress environment, e.g., vision testing at the Bureau of Motor Vehicles office, the visual acuity might be greatly reduced by increased magnitude of the nystagmus oscillation. To study nystagmus characteristics, an objective measure of the waveform characteristics and the foveation quality is needed.

"Good" INS waveforms have long foveation periods. The amplitude of the nystagmus is relatively a less important factor than the foveation periods in terms of visual acuity, e.g., on line 1 in Figure 1-8, assuming no afferent visual defects, the waveform on the left produces better vision because it has much longer foveation periods (shown with arrows) than the one on the right. The foveation periods also need to be lined up well to produce good vision. In line 2 and 3 of Figure 1-8, if the left and the right waveforms have the same amount of steady time per cycle, the left ones have better vision because the foveation periods are much more aligned (less jagged) than the right ones. It is also entirely possible for a large nystagmus to have the same or even better foveation periods than a small nystagmus. On line 4 of the Figure 1-8, both waveforms are equal in terms of foveation, although different in their peak-to-peak magnitude. Therefore, the nystagmus amplitude does not necessarily correlate with the patient's visual acuity, although it is sometimes a cosmetic concern. Only through eye-movement recordings can we accurately measure the foveation periods in INS.

The Nystagmus Acuity Function (NAF) (Dell'Osso & Jacobs, 2002) was developed to objectively quantify the foveation quality based on waveform characteristics. It is a mathematical function containing crucial waveform parameters such as foveation-period duration, standard deviations of foveation-period positions and

velocities, and number of cycles in a fixation interval. The NAF provides an objective and repeatable measure of nystagmus foveation quality; it uses eye-movement data of foveation periods to accurately predict the best-corrected visual acuity possible for subjects without afferent visual system defects, independently of the eye-movement recording system, the nystagmus type and waveforms (Dell'Osso & Jacobs, 2002). More specifically, it is calculated by the following equations:

$$NAF = (1 - \sigma_{pv})[1 - \epsilon^{-t_f/\tau}]$$

where the pooled estimator

$$\sigma_{pv} = \sqrt{(SD_p^2 + SD_v'^2)/2}, SD_v' = 0.125(SD_v)$$

SDp and SDv are the standard deviations of the foveation-period position and velocity. t_f is the foveation-period duration, and the time constant, τ was derived for use in the NAF using data from acuity studies of normals.

The usage of NAF was expanded to a wider group of INS patients in the NAFX. In the absence of afferent deficits, the NAFX was shown to be highly correlated with measured acuity. Coupled with a pre-operative acuity measurement, The NAFX can also be used to estimate the post-operative *measured* visual acuity (Tomsak, et al., 2005; Z. I. Wang & Dell'Osso, 2007a; Z. I. Wang, Dell'Osso, Tomsak, & Jacobs, 2007). The measurement of NAFX at each gaze angle provides an assessment of how broad the high-visual-function field is. The longest foveation domain (LFD) (Serra, Dell'Osso, Jacobs, & Burnstine, 2006; Z. Wang, Dell'Osso, Jacobs, Burnstine, & Tomsak, 2006) is defined as the range of the gaze angles in which the subject's NAFX stays above 90% of the NAFX vs. gaze-angle curve peak value. LFD is used as a measurement of the broadness of the

NAFX vs. gaze-angle curve. Comparison of pre- and post- surgical primary-position NAFX and LFD provides a good estimate of the static visual function improvement for INS patient post-surgically.

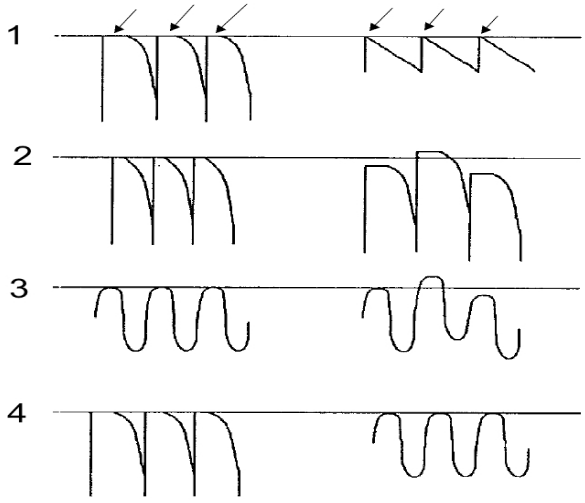


Figure 1-8. The contribution of amplitude and foveation period to visual acuity in infantile nystagmus waveforms. (Adapted from Dell'Osso LF, Jacobs JB: An expanded nystagmus acuity function: intra- and intersubject prediction of best-corrected visual acuity. *Doc Ophthalmol* 2002:104:249-276.)

Another crucial factor of INS visual function is how fast the patients acquire moving targets. Pre- and post-surgically target acquisition latencies are *dynamic* visual function assessments. Applications of NAFX, LFD, and target acquisition latency are demonstrated in later chapters.

1.5.2 Treatments of infantile nystagmus syndrome

Most nystagmus therapies are applied in an effort to directly reduce the eye's oscillation, and hopefully improving visual acuity, without changing the brainstem-generated central signal. Examples of this in INS are extraocular muscle surgeries that either take advantage of idiosyncratic null regions (gaze or vergence) of the INS or damp the INS over a wide range of gaze angles. Base-left or -right and base-out prisms are also used to correct gaze-angle nulls and convergence nulls, respectively. Contact lenses damp the nystagmus in some patients. Visual stabilization might help AN patients to reduce their oscillopsia, but do not seem to be effective for INS (Stahl, Kofman, & C., 2007 (in press)).

Pharmacological treatments have been used for acquired nystagmus; however, they have limited effects in infantile nystagmus. Studies have shown that weakening the EOMs by botulinum toxin injections only elicited transient effects, with significant side effects (Leigh, et al., 1992; Repka, Savino, & Reinecke, 1994; Tomsak, Remler, Averbuch-Heller, Chandran, & Leigh, 1995). A recent study showed that memantine (up to 40 mg) and gabapentin (up to 2400 mg) can improve significantly visual acuity in INS with no serious adverse events and no major side effects (McLean, Proudlock, Thomas,

Degg, & Gottlob, 2007). Memantine was also shown to be effective in a dual-therapy treatment for horizontal acquired pendular nystagmus (Tomsak, et al., 2005).

A new approach, gene therapy applied at the retinal level, aims to alleviate an afferent condition that triggers nystagmus. The goal of this afferent therapy is to improve visual acuity directly and to indirectly damp or eliminate the nystagmus by allowing recalibration of ocular motor subsystems. The suppression of nystagmus in older canines after retinal gene therapy suggests that the ocular motor system may be capable of recalibration throughout life and not subject to a "critical period" similar to the afferent visual system (Acland, et al., 2001; Bennicelli, et al., 2008; Jacobs, Dell'Osso, Hertle, Acland, & Bennett, 2006).

Surgical treatments for nystagmus have a long history, beginning in the 1950s. For INS patients who have a gaze-angle null, the Kestenbaum procedure (Anderson, 1953; Kestenbaum, 1953, 1954) is usually performed to move the eye muscles so that the null will be located at primary position post-surgically, eliminating the need for head turns. The Kestenbaum procedure detaches the medial and lateral rectus muscles (or the superior and inferior rectus muscles, depending on the plane of the nystagmus) from the globe, recessing and resecting them so that the eyes, when at rest, will be in a position equal and opposite to the null. The same amount of innervation will be produced to place the eyes straight ahead as the patients used previously to put them into the null position.

Dell'Osso and Flynn showed in 1979 that the Kestenbaum procedure had an accompanying therapeutic effect (Dell'Osso & Flynn, 1979). The null region after this null-moving procedure was broader than pre-surgically. The muscle recessions and resections were only responsible for the null movement and it was hypothesized that the

four-muscle tenotomies embedded in the Kestenbaum procedure produced the secondary beneficial broadening effects. It was therefore hypothesized that the four-muscle tenotomies alone would induce the same broadening effects. Post-surgical data analysis on a canine and then on patients who underwent the four-muscle tenotomy procedure demonstrated its effectiveness (Dell'Osso, Hertle, Williams, & Jacobs, 1999; Hertle, et al., 2002; Hertle, et al., 2003; Hertle, Dell'Osso, FitzGibbon, Yang, & Mellow, 2004; Z. Wang, et al., 2006; Z. I. Wang, et al., 2007). Some of these studies are in later Chapters of this thesis.

The beneficial effects of tenotomy explained the historically high success rate of the Kestenbaum procedure despite different formulae used by different surgeons. The broadening effect of tenotomy made their exacting calculations and specific formulae unimportant. As long as the null is moved to near primary position, the broadening effect will decrease the nystagmus intensity for straight-ahead viewing and therefore, diminish the need for an abnormal head position. Therefore, it was recommended that the amount of total muscle movement (determined by the null position) be split in equal amounts on the lateral and medial rectus muscles (Dell'Osso & Flynn, 1979). This ensures that the muscles are at a more homeostatic state post-surgically (i.e., the changes in innervational levels to both the agonist and antagonist muscles required to bring the eyes back to primary position are equal).

The characteristics of INS usually remain unchanged for years; therefore the effects of a properly preformed Kestenbaum procedure will last, and the post-surgical null will be stable. About 30% of INS patients also have varying degrees of strabismus (misalignment of the eyes) (Dell'Osso, 1994), which usually is corrected during the

nystagmus surgeries. Since the strabismic eye is not under the tight control of the OMS (being essentially open loop), the strabismus might return several years after the strabismus portion of the surgery.

Binocular INS patients who have a convergence null can benefit from the bimedial recession surgery. This surgery moves the medial recti muscles from their original insertions to more posterior locations on the globes. The eyes are thereby artificially diverged, requiring the patient to converge at primary position. That induced convergence damps the nystagmus. This procedure works only on patients with sufficient stereoscopic capabilities, i.e., binocular patients without strabismus. In the presence of both a gaze-angle null and a convergence null, the latter usually has the greatest damping effect on the nystagmus and therefore should be exploited surgically.

It must be noted that accurate eye movement recordings and analysis are critical for optimally tailored therapeutic planning for individual INS patients. Since INS is highly idiosyncratic, attempts to generalize INS treatment to a fixed formula are therapeutically problematic.

1.6 Models of infantile nystagmus syndrome

Understanding a complex biological system requires both top-down and bottom-up thinking. In the early1960's, Drs. Larry Stark, Laurence Young, and David Robinson pioneered the use of control systems models to study the ocular motor system (OMS) (Robinson, 1964, 1965; Young & Stark, 1963). The top-down control systems modeling and anatomical approaches, such as single neuron recordings, have successfully identified

several ocular motor sub-functions with their physiological locations, leading to significant clinical applications.

An important feature needs to be taken into account when constructing an INS model. Based on eye-movement recordings of INS patients, it was hypothesized that their OMS are not dramatically different from normals; their ability to make saccades and pursue are still preserved despite the constant oscillation. Therefore, INS models should also produce normal ocular motor responses to visual stimuli, in addition to nystagmus waveform simulations. Also, being a physiologically based model, it should not be in contradiction with known functions and structures of the OMS.

The fast-eye-movement portion of the model must be able to produce saccades of a realistic amplitude range at correct latencies. The accuracy of the saccades should duplicate that observed in human subjects: slightly hypermetric below 5° and hypometric above 17°. These "inaccurate" saccades must be followed by short-latency corrective saccades. The pulse-step signal (described in Figure 1-2) that drives the eye quickly in response to a step target requires a brief pulse summed with its integration; physiologically, the pulse for horizontal saccades originates from the paramedian pontine reticular formation area and the integration happens in an interconnected cell group in the nucleus prepositus hypoglossi and the medial vestibular nucleus in the brainstem (Leigh & Zee, 2006). The summed output from the ocular motor neurons is passed through the plant, which is usually modeled with a two-pole transfer function in simple applications.

The slow-eye-movement portion of the model must also duplicate human responses to velocity inputs, in terms of accuracy and latency. As described earlier in Figure 1-2, a step-ramp input to the plant is desirable for making accurate pursuit

responses. Both the fast and slow eye movements must still perform accurately in the presence of the internal nystagmus oscillations, using only the foveation-period position and velocity signals as the perceived stabilized input.

An early hypothesis (Dell'Osso, 1968) was that the OMS could *not* function properly using only retinal error position and velocity signals as its inputs. Thus, models that depend solely on retinal inputs cannot duplicate the behavioral responses of subjects with INS, and are also limited in their ability to simulate normal ocular motor behavior (e.g., pursuit of the imaginary hub of a moving wheel, making saccades in the dark to imagined targets, etc.). Either efference copy of motor output commands or the use of proprioceptive eye-position signals was necessary to reconstruct target information when internal oscillations were present. Figure 1-9 demonstrates how a simple "internal monitor" was used to reconstruct target position in this initial model of INS behavior. Although a mechanism for generating INS was not hypothesized, a method to simulate the modulation of INS with eye position was; as Figure 1-9 shows, it used a proprioceptive measure of the latter. At that time, the use of proprioceptive eye-position information was a reasonable hypothesis since it was known that proprioceptive signals were present in the V cranial nerve as well as in the III, IV, and VI cranial nerves. (Dell'Osso, 1968)

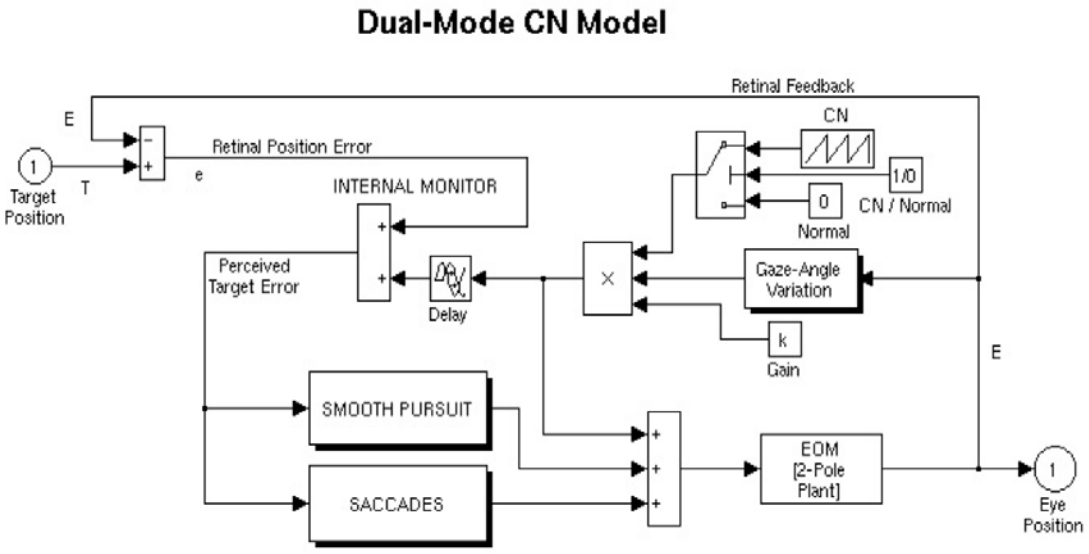


Figure 1-9. Block diagram of the first INS model using an "Internal Monitor" to reconstruct target position. (Adapted from Dell'Osso, L.F.: Nystagmus basics. Normal models that simulate dysfunction. *Models of the Visual System*, 2002: 711-739)

The normal smooth pursuit subsystem is underdamped; velocity step responses of normal smooth pursuit show a damped velocity oscillation. Some ocular motor subsystems appear to be on the brink of instability and require careful calibration; a visual defect associated with INS may act as a trigger for oscillations in such subsystems. INS has been described as a disorder "waiting to happen" in all humans; its common occurrence with or without visual deficits supports this conclusion. The hypothesized mechanism is recently embodied in a behavioral model of the OMS, supported by accurate model simulations of individuals with INS during fixation, saccades to known targets (steps, pulses, and pulse-steps), and smooth pursuit (ramps and step-ramps). A smooth pursuit system (modified from a model of normal pursuit eye movements) with a high-gain oscillation is used in this model as the source of pendular INS waveforms (Robinson, et al., 1986). That model also continued to use an "internal monitor" to coordinate the saccadic and pursuit sub-functions in the presence of constant sinusoidal oscillation. The top panel of Figure 1-10 is a block diagram of the aforementioned model; the bottom panel shows the pursuit system utilized in that model, generating a sinewave oscillation in INS and a damped oscillation in normals.

When constructing function-based models, it is important to bear in mind that there are numerous ways to simulate waveforms; however, a simple waveform-generator model might mimic one aspect of the OMS behavior but be incapable of duplicating other equally important ones. Far more superior than waveform-generator models are robust, behavioral models, which are not only compatible with known OMS behaviors, but also can predict new behaviors (Jacobs & Dell'Osso, 2004; Z. I. Wang & Dell'Osso, 2007b). The following is a list of the emergent behaviors that the original OMS model exhibited:

1. The size of voluntary saccades was modulated by the INS slow phases;

2. The oscillation automatically shifts to allow foveation at either peak;

3. Occasional “missing”, or suppression of braking or foveating saccades results in enlarged nystagmus amplitude;

4. Small corrective saccades could occasionally cause spontaneous bias reversals;

5. The eyes could “ride on” the INS slow phases to accomplish target acquisition; corrective saccades could be suppressed in this case;

6. There are minor (<0.075°) variations in foveating saccades motor commands, resulting in magnitude variability;

7. Catch-up saccades were diminished due to the INS slow phases during initial stage of ramp and step-ramp pursuit;

8. The catch-up saccades during high-speed pursuit distorted the classic INS waveforms.

These properties were not designed into the model but emerged afterwards, strongly supporting the embedded hypotheses and mechanisms. In our recent studies using this model and its updated versions, we continued to discover emergent properties to add to this list; they are discussed in model-related Chapters.

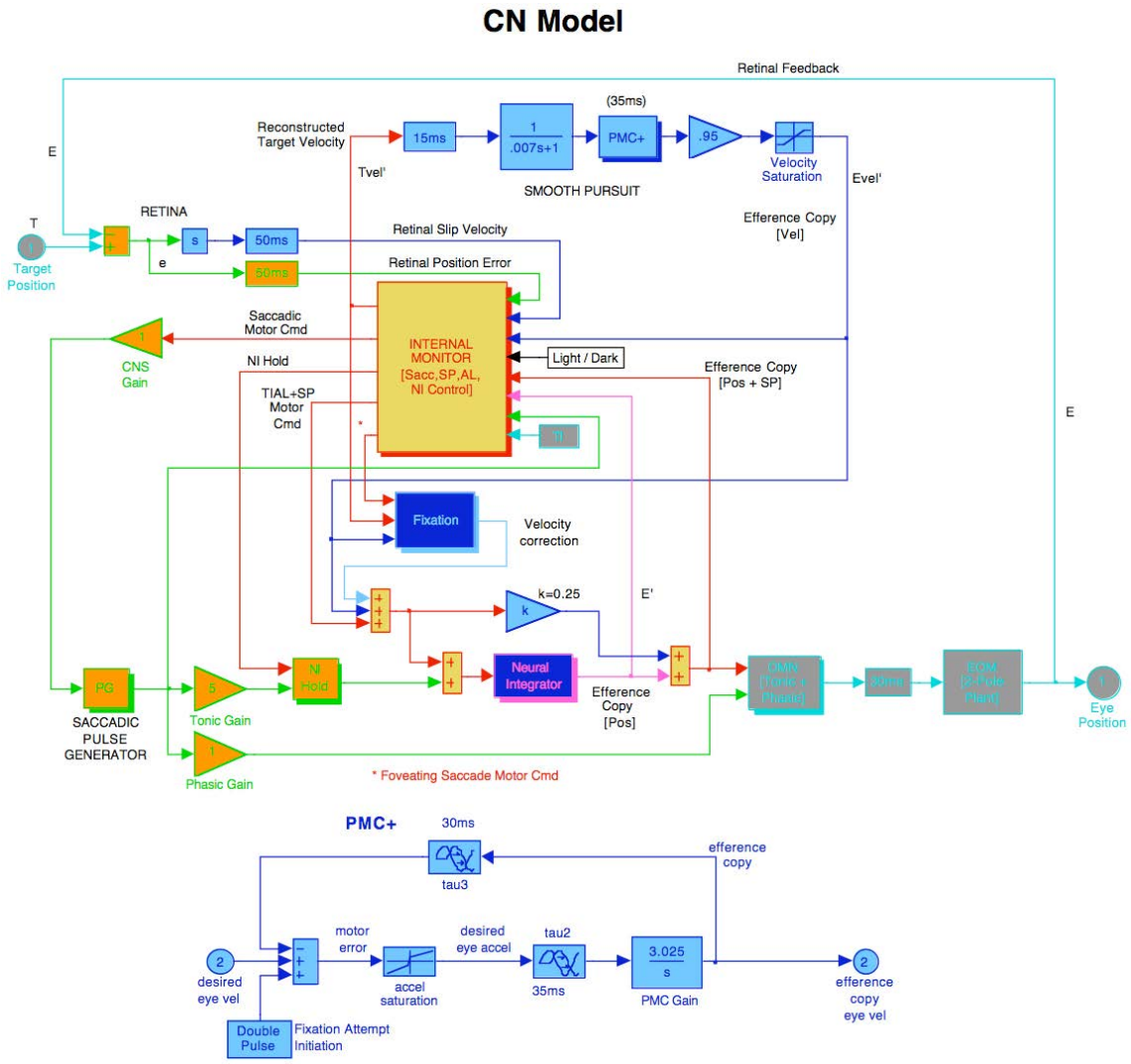


Figure 1-10. Block diagram of the original ocular motor system model. (Adapted from Jacobs JB, Dell'Osso LF: Congenital nystagmus: hypothesis for its genesis and complex waveforms within a behavioral ocular motor system model. *JOV* 2004:4:604-625.)

The following chapters of this thesis are focused on how the understanding of INS characteristics and treatment effects improved both the INS model and the general understanding of OMS functions, especially proprioception. Chapters 2, 3 and 4 evaluate and summarize the effectiveness of the tenotomy procedure on INS and acquired nystagmus patients in terms of static characteristics. Chapter 5 postulates a working hypothesis for tenotomy based on saccadic-characteristic examination. Chapters 6 and 7 are focused on dynamic properties of INS and their post-tenotomy changes. Chapter 8 demonstrates how Alexander's law variation of nystagmus can be responsible for the INS null position and the off-null waveform transitions. Chapter 9 demonstrates how jerk waveforms and gaze-angle variation were built into the model based on a unifying hypothesis of pursuit-system instability. Chapter 10 concludes by discussing implications of the above findings. Details of the new and improved model can be found in the Appendix.

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Chapter 2

Effects of Tenotomy on Patients with Infantile Nystagmus Syndrome: Foveation Improvement Over a Broadened Visual Field

2.0 Abstract

In this study we aimed to investigate the effects of four-muscle tenotomy on visual function and gaze angle in patients with infantile nystagmus syndrome (INS). Eye movements of 9 patients with infantile nystagmus were recorded using infrared reflection or high-speed digital video techniques. Experimental protocols were designed to record the patients' eye-movement waveforms, pre- and post-tenotomy, at different gaze angles. We used the eXpanded Nystagmus Acuity Function (NAFX) to measure tenotomy-induced changes in the nystagmus at primary position and various gaze angles. The longest foveation domains (LFD) were measured from fitted curves. Peak-to-peak nystagmus amplitudes and foveation-period durations were also measured. Five patients showed large NAFX improvement (39.9-162.4%) at primary position, 3 showed moderate improvement (13.9-32.6%), and 1 showed no change (due to his high pre-tenotomy NAFX). Primary-position measured acuities improved in 6 patients. All seven patients with narrow, high-NAFX, gaze-angle regions showed broadening of these regions of higher visual function up to 200%. All patients had reductions in nystagmus amplitudes ranging from 14.6-37%. The durations of the foveation periods increased in all 9 patients (11.2% to 200%). The percentage improvements in both the NAFX and LFD decreased with higher pre-tenotomy values. In summary, in addition to elevating

primary-position NAFX, tenotomy also broadened the high-NAFX regions. This broadening effect is more prominent in patients who had sharp pre-tenotomy NAFX peaks. Four-muscle tenotomy produces higher primary-position NAFX increases in infantile nystagmus patients whose pre-tenotomy values are relatively low, with the improvement decreasing at higher pre-tenotomy values. The tenotomy procedure improves visual function beyond primary-position acuity. This extends the utility of surgical therapy to several different classes of patients with INS for whom other procedures are contraindicated. The pre-tenotomy NAFX can now be used to predict both primary-position acuity improvements and broadening of a patient's high-NAFX range of gaze angles.

2.1 Introduction

Surgical therapies for infantile nystagmus syndrome (INS) have been performed for decades, the Kestenbaum procedure (bilateral recessions and resections of the horizontal rectus muscles) being one of the most successful. The main goal of any nystagmus treatment should be to increase the foveation quality, e.g., lengthening foveation time, reducing nystagmus intensity, and increasing foveation-period accuracy. This goal may be achieved by the four-muscle Kestenbaum procedure, which was originally designed to shift nystagmus patients' null regions, thereby straightening head (face) turns (Anderson, 1953; Kestenbaum, 1953, 1954). The tenotomy procedure emerged from analysis of accurate, objective eye-movement recordings in a study of the Kestenbaum procedure that showed secondary beneficial effects in addition to the null shifting (Dell'Osso, 1973; Dell'Osso & Flynn, 1979; Flynn & Dell'Osso, 1980, 1981).

Later studies (Dell'Osso, 1998; Dell'Osso, Hertle, Williams, & Jacobs, 1999; Dell'Osso, Williams, Jacobs, & Erchul, 1998; R.W. Hertle, et al., 2003; R. W. Hertle, Dell'Osso, FitzGibbon, Yang, & Mellow, 2004) provided evidence that tenotomy was effective on human and canine subjects, and quickly caught the attention of ophthalmologists, patients, and researchers. With this new technique performed over the past few years, a database of pre- and post-surgical data is being compiled. Previous studies focused solely on the primary-position visual acuity evaluation, which is only one aspect of the expected post-tenotomy changes and may be inadequate to measure the total clinical response. The broadening effect, suggested by the Kestenbaum procedure data analysis, was not studied. In this study, we used the eXpanded Nystagmus Acuity Function (NAFX), measured at different gaze angles to determine if tenotomy did increase potential acuity across a wider range of gaze angles. Moreover, we categorized types of possible post-tenotomy changes, and set up criteria for this procedure (when patients should/should *not* have it, how much benefit the patient might expect to receive, etc.). Specifically, our data suggest the need for acuity measures at different gaze angles to better assess the clinical effects of therapy.

2.2 Methods

Patient Selection

We restricted our study to the effects of tenotomy on INS (CEMAS_Working_Group, 2001) *alone*, e.g., patients that had fusion maldevelopment nystagmus or asymmetric (a)periodic alternating nystagmus were not included. The

patients studied were considered candidates for the tenotomy procedure if they could not benefit from other known surgical or non-surgical therapies; they typically came from the following sub groups:

(1) Patients with unchanged nystagmus throughout the whole gaze-angle domain (Patients 3, 4, 7, and 8)

(2) Patients whose damping at near could not be exploited due to lack of stereoscopic fusion (Patients 7 and 8)

(3) Patients with a "null" at primary position (Patients 1, 5, 6, and 9)

(4) Patients with a slight and intermittent "null" which could not be exploited (Patient 2).

To guarantee uncontaminated data, the patients accepted in this study were only treated for their nystagmus, i.e., no strabismus surgeries were performed. Patients were informed that the surgery would not straighten their eyes. We now routinely recommend combined strabismus and nystagmus surgery when indicated.

Recording

Infrared reflection was used for 8 patients and high-speed digital video for 1. The infrared reflection system (Applied Scientific Laboratories, Waltham, MA) was linear to 20° in the horizontal plane and monotonic to 25-30° with a sensitivity of 0.25°. The total system bandwidth (position and velocity) was 0-100 Hz. The data were digitized at 500 Hz with 16-bit resolution. The digital video system (EyeLink II, SR Research, Mississauga, ON, Canada) had a linear range of ±30° horizontally and ±20°vertically. System sampling frequency was 500 Hz, gaze position accuracy error was 0.5°-1° on

average, and pupil-size resolution was 0.1% (0.02 mm change in diameter reliably detectable). The data were digitized at 500 Hz with 16-bit resolution. The infrared reflection or Eyelink signal from each eye was calibrated with the other eye behind cover to obtain accurate position information; the foveation periods were used for calibration. This accurate position data of each eye allows determination of both the smallest amount of strabismus throughout the trial and the fixating eye. Eye positions and velocities (obtained by analog differentiation of the position channels) were displayed on a strip chart recording system (Beckman Type R612 Dynograph). Monocular primary-position adjustments for all methods allowed accurate position information and documentation of small tropias and phorias hidden by the nystagmus.

Protocol

This study was approved by the local IRB and written consent was obtained from each subject before the testing. All test procedures were carefully explained to the subject before the experiment began, and were reinforced with verbal commands during the trials. Subjects were seated in a chair with headrest and a chin stabilizer, far enough from an arc of red light-emitting diodes to prevent convergence effects (>5 feet). At this distance the light-emitting diode subtended less than 0.1° of visual angle. The room light could be adjusted from dim down to blackout to minimize extraneous visual stimuli. An experiment consisted of from one to ten trials, each lasting under a minute with time allowed between trials for the subject to rest. Trials were kept this short to guard against boredom because infantile nystagmus intensity is known to decrease with inattention.

Analysis

All the analysis was unmasked and done in MATLAB environment (The MathWorks, Natick, MA) using OMLAB software (OMtools, available from http://www.omlab.org). Only eye position was sampled directly; velocity was derived from the position data by a 4^{th}-order central-point differentiator. Position data were pre-filtered with a low-pass filter with the cutoff frequency of 20 Hz to eliminate noise without changing the nystagmus signals to be studied. The differentiating and filtering were applied equally to the pre- and post-tenotomy data sets to ensure consistency. Horizontal eye movements were analyzed in all 9 patients; vertical eye movements were studied in only one (Patient 4) who had a large vertical component. Analysis was always done on the fixating eye, as determined from the calibrated eye-movement data. We specifically did not assume that the subject's dominant or preferred eye was always the fixating eye; in most individuals, it is not. The post-tenotomy records examined in this study were obtained from 3 to 12 months after the procedure since it has been reported that visual functions were stable within this time period.

The NAFX was used to measure tenotomy-induced changes in the infantile nystagmus at primary position and various gaze angles. It is an objective measure of waveform quality and a predictor of potential visual acuity for nystagmus patients, assuming that no afferent deficits are present. Because it is a quantitative measure of the direct, eye-movement effects of nystagmus therapies, it is preferred over visual acuity, which is indirect, idiosyncratic, and dependent on many other afferent and cortical factors. When combined with pre-therapy measured acuity, the NAFX can also predict the improvement in that medically desirable outcome. It could be applied to any

nystagmus waveform whose foveation variability (position and velocity) lies within the maximum foveation window of ±6° and ±10 °/s. Five primary-position NAFXs for each patient in this study were calculated and averaged; a particularly high or low NAFX was regarded as an outlier and not used. At each gaze angle, two or three NAFX calculations were made and averaged, depending on the data availability. The segments chosen for NAFX analysis avoided blinks and inattention periods. When choosing the segments, we maintained consistency in the pre- and post-tenotomy data sets, i.e., the best segments for foveation were chosen, so that the NAFX average would reflect the best potential visual acuity for the patient; this methodology duplicates that used in masked clinical trials (R.W. Hertle, et al., 2003; R. W. Hertle, et al., 2004). Outputs of the NAFX function consist of the NAFX value, foveation time per foveation period, foveation time per second, position and velocity standard deviation in the chosen segment, and position and velocity foveation-window size. The first two outputs will be listed and discussed in Results. Details about the NAFX may be found elsewhere (Dell'Osso & Jacobs, 2002).

Primary-position visual acuities were obtained by the referring physician and recorded in the patients' clinical notes. Potential visual acuities were provided by the NAFX program as a comparison. Stereopsis was measured with the Stereo FLY and RANDOT Stereo Tests (Stereo Optical Co., Inc., Chicago, IL).

Pre- and post-tenotomy peak-to-peak amplitude in primary position was measured by taking the average of 16 amplitude measurements from different nystagmus cycles. The samples were chosen with the same criteria as described previously for the NAFX analysis.

After obtaining the NAFX values at each gaze angle, second-order polynomial curves were fitted to pre- and post-tenotomy results in Excel. The NAFX percentage improvement (defined by the primary-position NAFX improvement divided by the pre-tenotomy primary-position NAFX) was plotted against the pre-tenotomy primary-position NAFX and fitted with a second-order polynomial. The longest foveation domain (LFD) is defined as the range of the gaze angles in which the patient's NAFX stays above 90% of the NAFX peak value (the NAFX peak equivalent to the IN null). The LFD percentage improvement (defined as the primary-position LFD improvement divided by the pre-tenotomy LFD) was plotted against the pre-tenotomy LFD and fitted with a logarithmic curve. If the NAFX vs. gaze-angle curve was flat, the LFD was defined as the whole gaze-angle domain where data were available.

2.3 Results

Patients

The average age of the patients at the time of the surgery was 20.3 (range: 6 to 49; median: 16). Four of the 9 patients were female. Six patients were white, 2 were African-American and 1 was Arabic. None of the patients had previous eye-muscle surgery; Patient 6 had a previous Lasik surgery (12 months before). Table 1 shows the age, gender, infantile nystagmus waveforms and associated pre-tenotomy clinical conditions of each patient. Pupils, fundus, gross visual field and slip-lamp exam were all normal unless stated otherwise in the table.

Direct Outcome Measure—NAFX at Primary Position

NAFX values calculated during pre- and post-tenotomy fixation periods are shown in Table 2 Column 3, in which patients are ordered by NAFX improvement. Eight of the 9 patients had increases in primary-position NAFX values; the remaining one showed no change. Figure 2-1 is a comparison of pre- and post-tenotomy primary-position fixation data taken from Patient 7, demonstrating greatly improved foveation quality post-tenotomy. Data analysis showed that the foveation periods were extended from 45.6 ms to 183 ms (301.3% increase). Additionally, the position window was smaller; the velocity window was unchanged, it was already at the lowest value (4 °/s). The net improvement in the NAFX was from 0.565 to 0.748, an increase of 32.4%. Given that the x-axes have the same scale, it is also evident that post-surgical nystagmus waveforms have lower frequency, consistent with some cosmetic improvement in this case.

Patient #	Gender /Age	Nystagmus Waveforms	Pre-tenotomy Clinical Notes			
			Primary-Position Strabismus	Stereopsis	Preference	Other
1	F/15	P, AP, Pfs, Jef, PPfs, DJ	OD ET 3°	>3000”	OS	-
2	F/21	J, Jef, DJ	OS XT 6°	1400”	OD	Slight null at near; weak, intermittent null at left-gaze and up-gaze
3	M/16	J, Jef, PC, DJ	OD XT 10°	400”	OS	-
4 *	F/24	P, AP, Pfs, J, Jef, PC, PJ, DJ	OS ET 3°	>3000”	OD	Circular, elliptical, oblique nystagmus; impaired color vision; hypoplasia of both optic nerves; bitemporal hemianopic defect in visual field; Demorsier’s syndrome
5	M/49	J, Jef, PC	OS XT 3°	800”-1600”	OD	Frequent direction reversals (Primary position, JL>>JR); JR ≥10° to the right; convergence null
6	M/28	P, Pfs, PC	OS ET 4°	800”	OD	Prior Lasik surgery
7	F/9	J, Jef	None	200”	None	Frequent direction reversals at all gaze angles
8	M/6	P, Pfs, J, PC, PJ, DJ	None	50”	OS	Difficulties in gaze holding pre-surgically
9	M/15	J, Jef	OS XT 15°	800”-1600”	OD	Near (but not convergence) null; frequent direction reversals at all gaze angles

Table 2-1. Patient demographics. F=Female; M=Male; P=Pendular; AP=Asymmetric Pendular; Pfs=Pendular with Foveating Saccades; PPfs=Pseudo Pendular with Foveating Saccades; DJ=Dual Jerk; J=Jerk; Jef=Jerk with Extended Foveation; PC=Pseudo Cycloid; PJ=Pseudo Jerk; OD=Right Eye; OS=Left Eye; XT=Exotropia; ET=Esotropia.

* Patient 4 was on gabapentin 300mg/2 times per day on pre-surgical examination.

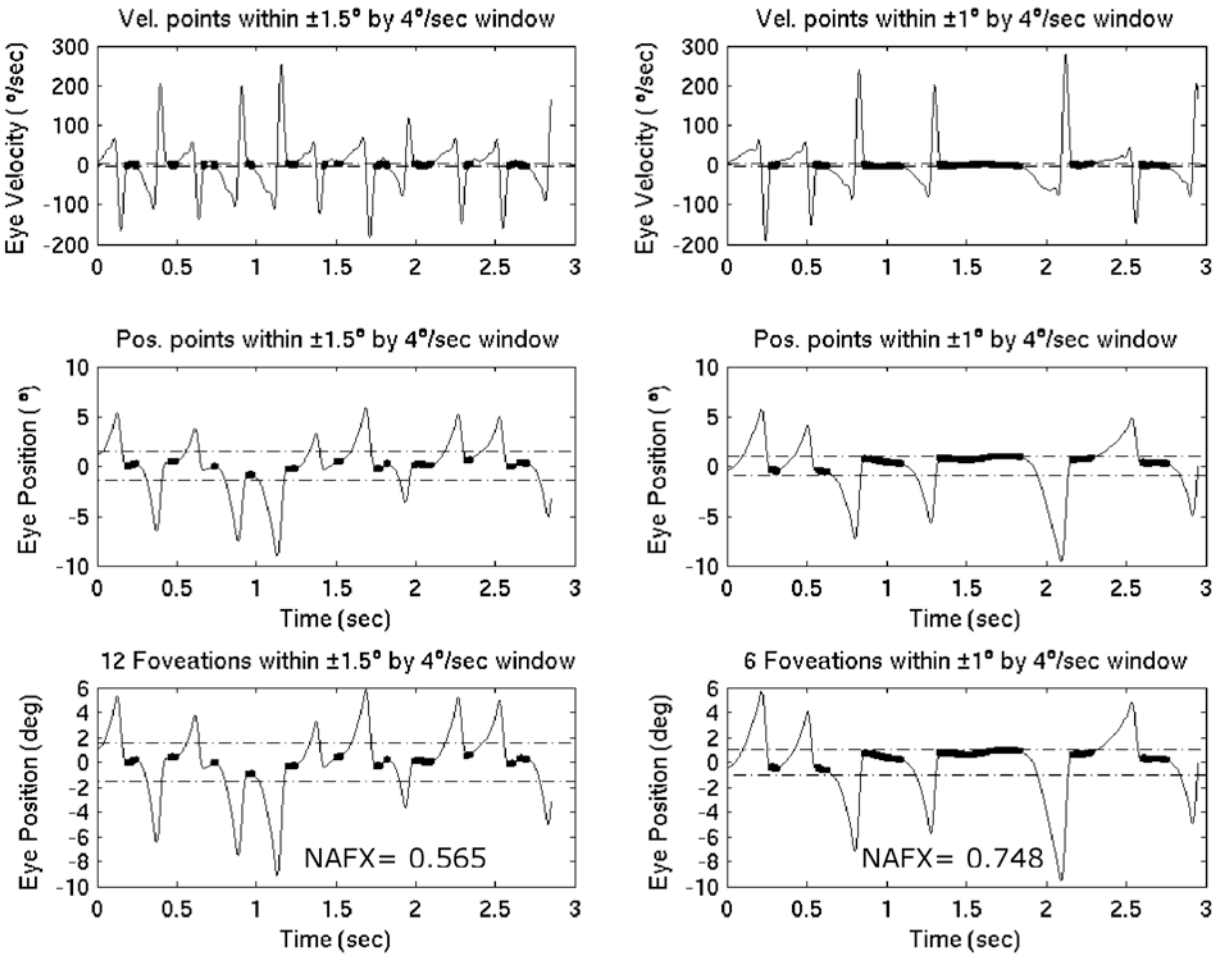

Figure 2-1. Comparison of pre- and post-tenotomy nystagmus waveform from Patient 7. NAFX outputs are presented. Left column, pre-tenotomy data; right column, post-tenotomy data. Velocity traces (upper row), position traces (middle row), position traces with the NAFX-algorithm-determined foveation periods (lower row) are shown. In each subplot, time periods that satisfy velocity and position criteria for fixation are marked with bold lines. For better visual inspection, pre- and post-tenotomy traces are shown with equal scales. Tenotomy produced the long, flat extended foveation, as seen in post-tenotomy data, which contributed to the NAFX increase.

Patient #	Gender /Age	Primary-Position NAFX Change (%increase) [Potential Acuities]	Primary-Position Visual Acuity Change	
			Visual Acuity	Test Condition
1	F/15	0.125 to 0.328 (**162.4%**) [20/115- to 20/45+]	20/200 to 20/100+1	OU with correction: 1.25+1.50×134; 1.5+1.00×70
2	F/21	0.067 to 0.171 (**155.2%**) [20/215- to 20/85-]	20/70 to 20/60	OU with correction: -3.00+3.25×96; -2.75+3.25×89
3	M/16	0.239 to 0.414 (**73.2%**) [20/60- to 20/35-]	20/80- to 20/60+	OU with correction: -8.00+1.75×60; -7.25+1.75×138
4	F/24	0.191 to 0.272 (**42.4%**) [20/75- to 20/55+]	20/200 OD, 20/400 OS remained unchanged	OU without correction
5	M/49	0.371 to 0.519 (**39.9%**) [20/45+ to 20/30-]	20/40+ remained unchanged	OU without correction
6	M/28	0.417 to 0.553 (**32.6%**) [20/35+ to 20/25-]	20/60+ to 20/60+2	OU with correction: 1.00-0.75×178; 1.50-1.25×34
7	F/9	0.474 to 0.580 (**22.2%**) [20/30- to 20/25-]	20/60-2 to 20/60	OU with correction: -6.00+0.25×78; -6.25+75×141
8	M/6	0.302 to 0.344 (**13.9%**) [20/50+ to 20/40-]	20/60-2 to 20/60+	OU with correction: -4.00+0.25×30; -4.00+1.50×144
9	M/15	0.739 to 0.750 (**1.5%**) [20/20+ to 20/20+]	20/30- OD, 20/70 OS remained unchanged	OU without correction

Table 2-2. NAFX and Visual Acuity results. F=Female; M=Male; OD=Right Eye; OS=Left Eye; OU=Both Eyes; NAFX= eXpanded Nystagmus Acuity Function.

Gaze-angle Variation

Patients with nystagmus often have "acuity-tunnel vision"; the gaze-angle domain of high visual acuity is often narrow, causing reduced lateral-gaze vision. The NAFX vs. gaze-angle curves showed 7 of the 9 patients had a narrow peak region. One, Patient 2, with a broad peak had highly scattered NAFX values, and most of them were lower than 0.1 (<20/200). In her case, the broad peak may reflect a poor curve fit and inferior visual function. The other, Patient 6, who had a flat gaze-angle curve, had a previous Lasik operation (see Discussion).

Patient 1 (Figure 2-2) is typical in that her lateral-gaze vision was much worse than that for the peak region (in this case between 0 and 5° to the right). Pre-tenotomy NAFX in primary position was 0.125, and dropped to 0.075 at –15° and 0.039 at 15° (40% and 68.8% decreases). Tenotomy both elevated the primary-position NAFX to 0.328 (an increase of 162.4%) and broadened the region of good visual function. Post-tenotomy NAFX stayed at ~0.3 throughout the gaze angles from –15° to 15°; these values were ~140% higher than the pre-tenotomy primary-position NAFX.

Figure 2-3 shows the NAFX vs. gaze-angle curve for the patient whose primary-position NAFX value stayed the same (Patient 9). Despite the absence of an elevation effect, the post-tenotomy curve is much flatter, indicating a broader region in which NAFX is high. At the extremes of the ±15° range, the post-tenotomy NAFX values were approximately 27% higher than the pre-tenotomy values.

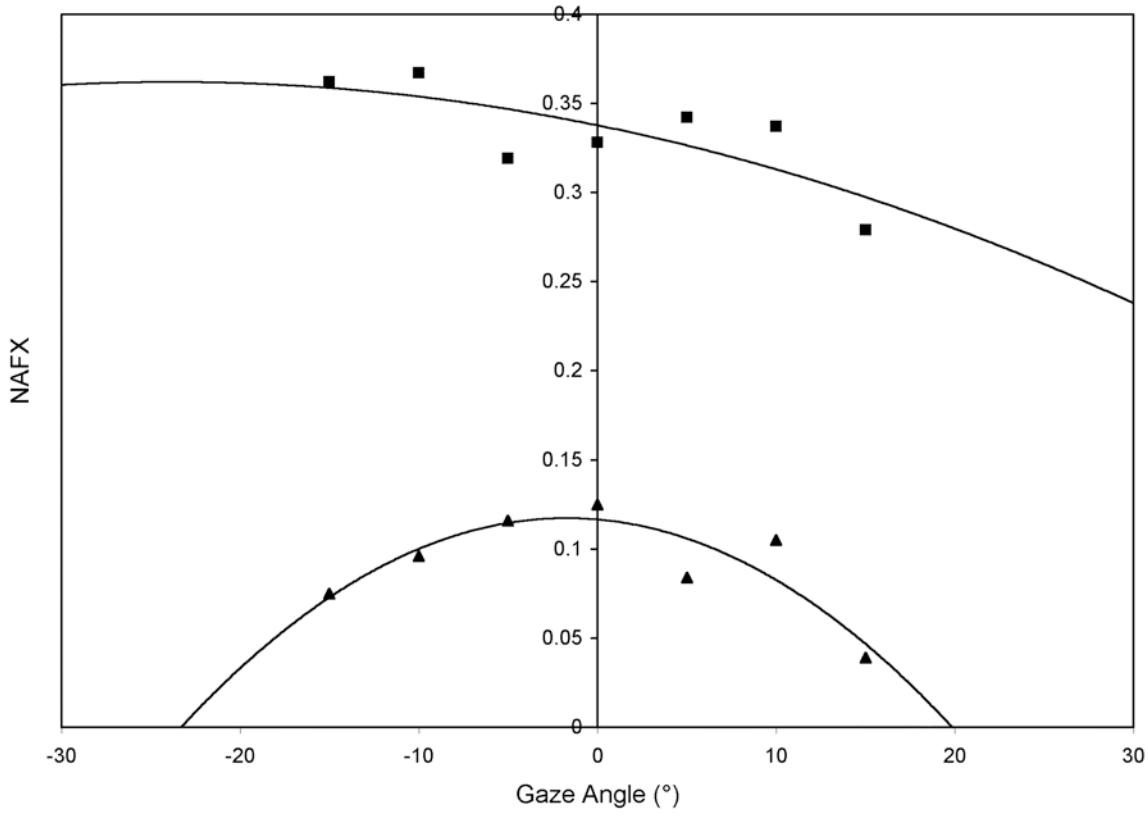

Figure 2-2. NAFX vs. gaze-angle curve of Patient 1 with a sharp peak region pre-tenotomy and a much-broadened peak post-tenotomy. In this and Figures 3 and 4, NAFX values at various gaze angles were plotted across the gaze-angle domain with triangles denoting pre-tenotomy data and squares denoting post-tenotomy data. Second-order polynomial curves were fitted for both pre- and post-tenotomy data sets.

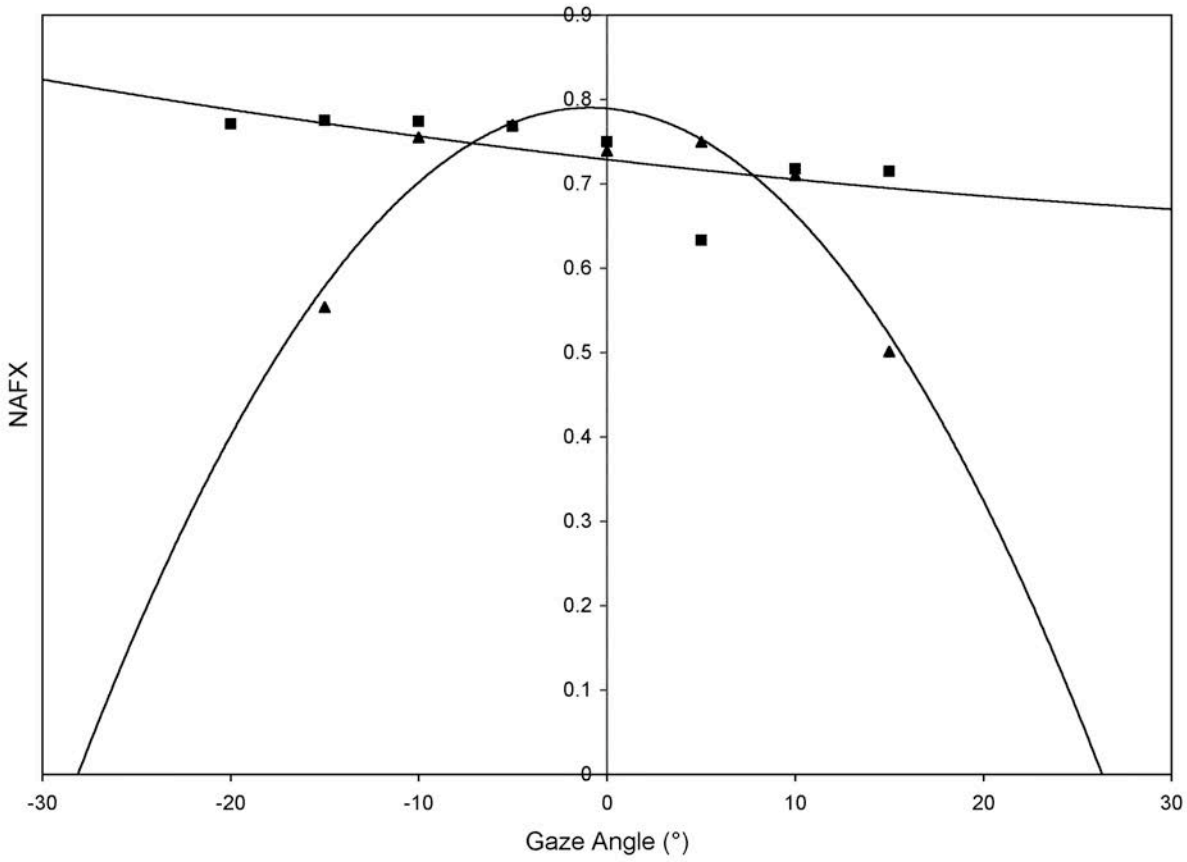

Figure 2-3. NAFX vs. gaze-angle curve of Patient 9 whose high pre-tenotomy NAFX precluded any further improvement at primary position; this patient exhibited great improvement at lateral angles.

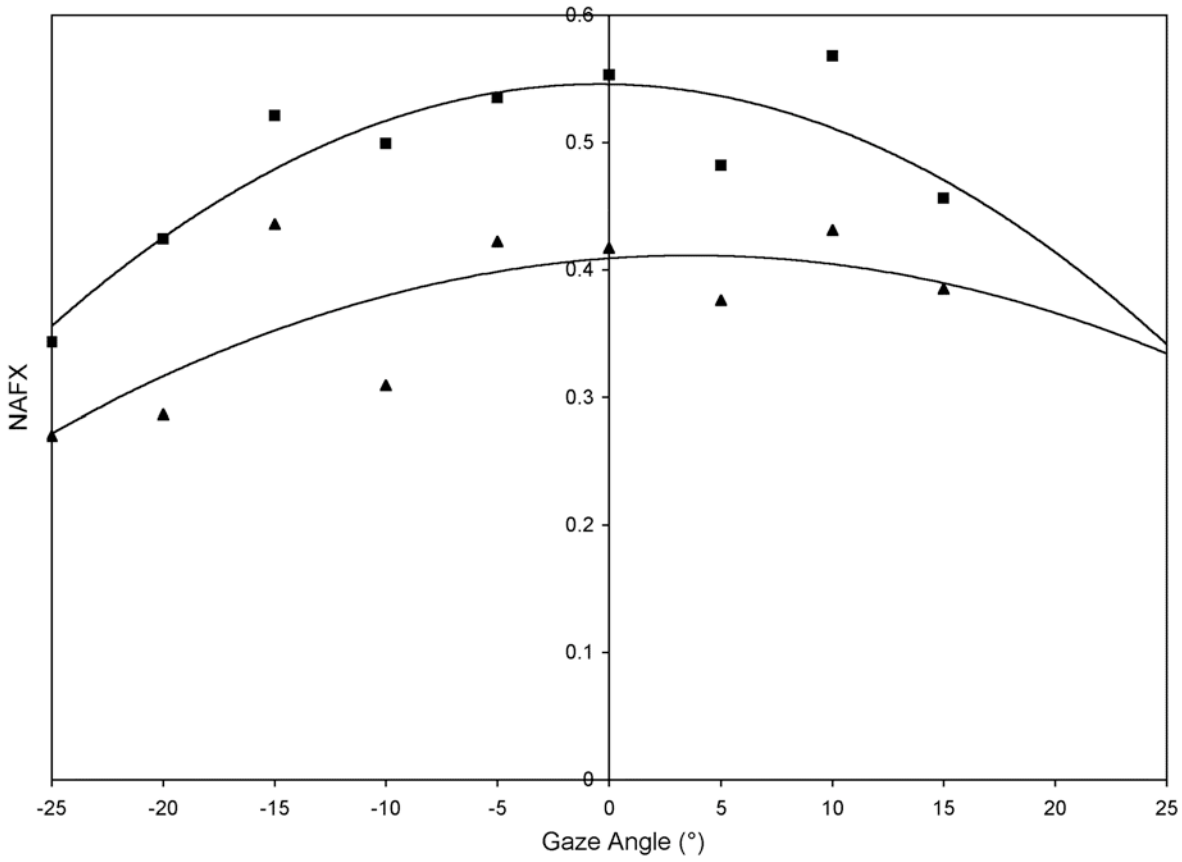

Figure 2-4. NAFX vs. gaze-angle curve of Patient 6 who had broad pre-tenotomy peak; tenotomy elevated the entire curve without additional broadening.

Patient 6, in Figure 2-4, already had a broad, pre-tenotomy region of good visual function. The tenotomy procedure elevated the NAFX at each gaze angle without further broadening. The NAFX at primary-position was increased by 32.6%, at -25° by 27%, and at 15° by 18%. Overall, pre- and post-tenotomy NAFX gaze-angle curves have similar broad regions of good visual acuity.

Direct Outcome Measure—Peak-to-Peak Amplitudes and Foveation-Period Durations

Table 3 shows the amplitude and foveation-period duration changes induced by the tenotomy. All 9 patients exhibited peak-to-peak nystagmus amplitude decreases, ranging from 14.6% to 37%; they also had foveation-period increases ranging from 11.2% to 200%.

Indirect Outcome Measure—Visual Acuity

Column 4 of Table 2 shows the patients' visual acuity changes under the specified testing conditions. Three patients showed more than one line improvement; three showed a few letters' improvement; Patients 4, 5, and 9 showed no changes in measured visual acuity at primary position. We assume that improvements in visual acuity were due to the surgical procedure and not due to age, learning, or change in refractive status.

Behavioral Changes

Beyond the visual acuity improvement aspect of the procedure, we also observed behavioral changes resulting from tenotomy. Patients 2 and 8 showed improved ability to

hold fixation at specific gaze angles. Patients 4 and 5 had strabismus pre-tenotomy, but post-tenotomy were able to fuse better so that they alternated fixating eyes.

Patient #	Gender /Age	Pre- and Post-Tenotomy Amplitudes in °p-p (% decrease)	Pre- and Post-Tenotomy Foveation-Period Durations in ms (% increase)
1	F/15	9.8 to 7.9 **(19.8%)**	13 to 39 **(200%)**
2	F/21	11.6 to 8.5 **(26.7%)**	6 to 17 **(183.3%)**
3	M/16	5.9 to 4.1 **(30%)**	26 to 47 **(80.8%)**
4*	F/24	LE: 7.9 to 5 **(37%)** RE: 7.2 to 5.2 **(28%)**	17 to 26 **(52.9%)**
5*	M/49	LE: 4 to 3.5 **(14.6%)** RE: 3.7 to 2.7 **(27%)**	20 to 57 **(185%)**
6	M/28	4.2 to 3 **(30%)**	35 to 65 **(85.7%)**
7	F/9	11 to 7.6 **(31%)**	41 to 80 **(95.1%)**
8	M/6	6.1 to 5.1 **(16.4%)**	18 to 26 **(44.4%)**
9	M/15	1.35 to 0.93 **(34%)**	119 to 135 **(11.2%)**

Table 2-3. Tenotomy-induced amplitude and foveation changes. F=Female; M=Male; RE=Right Eye; LE=Left Eye.

* Patients 4 and 5 had alternating fixation; both eyes were examined for the amplitude decrease in these two cases.

2.4 Discussion

The effective treatment of infantile nystagmus can best be achieved by distinguishing INS from other types of nystagmus that appear in infancy, accurately recording patients' eye movements with proper calibration, and quantifying idiosyncratic foveation characteristics that may be exploited to improve visual function. This paradigm

is also important for evaluating the effectiveness of new or existing therapeutic procedures. In this study we analyzed the changes in primary-position NAFX, foveation time, amplitude, and visual acuity that may be compared to existing studies in the literature. Data were analyzed for individual patients then grouped to reveal inter-subject characteristics.

Primary-position visual acuity is the most routine clinical examination performed. However, in real-world situations the eyes do not remain in primary position. Good lateral-gaze vision could greatly reduce the stress that patients experience when viewing targets without moving their head. Therefore, lateral-gaze vision should be assessed when evaluating surgical effectiveness. The NAFX vs. gaze-angle curves serve this purpose and document the positive effects of tenotomy. The NAFX documentation of better foveation over a broader range of gaze angles was the foundation for recent studies of post-surgical visual acuity improvement at lateral gaze angles (Yang, Hertle, Hill, & Stevens, 2005). We recommend that surgeons measure visual acuity in lateral gaze before and after nystagmus surgeries to better characterize the effectiveness of surgical interventions for nystagmus.

The pre- and post-tenotomy curves showed three types of improvement: (1) patients with a narrow NAFX peak region had both an elevation in primary-position NAFX and broadening effects in lateral gaze (Patients 1, 3, 4, 5, 7, and 8, e.g., Patient 1 in Figure 2-2); (2) patients with a broad peak had an approximately homogeneous elevation of NAFX throughout the whole gaze-angle domain (Patients 2 and 6, e.g., Patient 6 in Figure 2-4); (3) patients who had high pre-tenotomy primary-position NAFX

did not have improvement in primary position but did in lateral-gaze vision (Patient 9 in Figure 2-3). These changes will be discussed and quantified in the following sections.

The infantile nystagmus foveation periods (where the eyes remain at or close to desired fixation with little or no movement) greatly affect visual acuity. The tenotomy-induced foveation improvement is prominent in Figure 2-1. Although the amplitude of nystagmus was not greatly reduced, the patient was able to foveate the target longer. As was demonstrated elsewhere, nystagmus amplitude alone is not a good indicator of visual function (Dell'Osso, 2002a, 2002b; Dell'Osso & Jacobs, 2002). The improvement in foveation quality was idiosyncratic, as shown by Table 3. Patient 9 is noteworthy: tenotomy did not produce a large increase of primary-position NAFX and this patient had a high pre-surgical NAFX. Patients with high percentage increases (e.g., 1, 2, and 3) also had low pre-tenotomy NAFX values. This implies that a high pre-tenotomy NAFX leaves little room for primary-position improvement. To quantify this, we plotted the 9 patients' NAFX increases vs. pre-tenotomy NAFX values in Figure 2-5. Equivalent data from the studies by Hertle et al. (R.W. Hertle, et al., 2003; R. W. Hertle, et al., 2004) and one acquired pendular nystagmus patient were also included (Tomsak, et al., 2005).

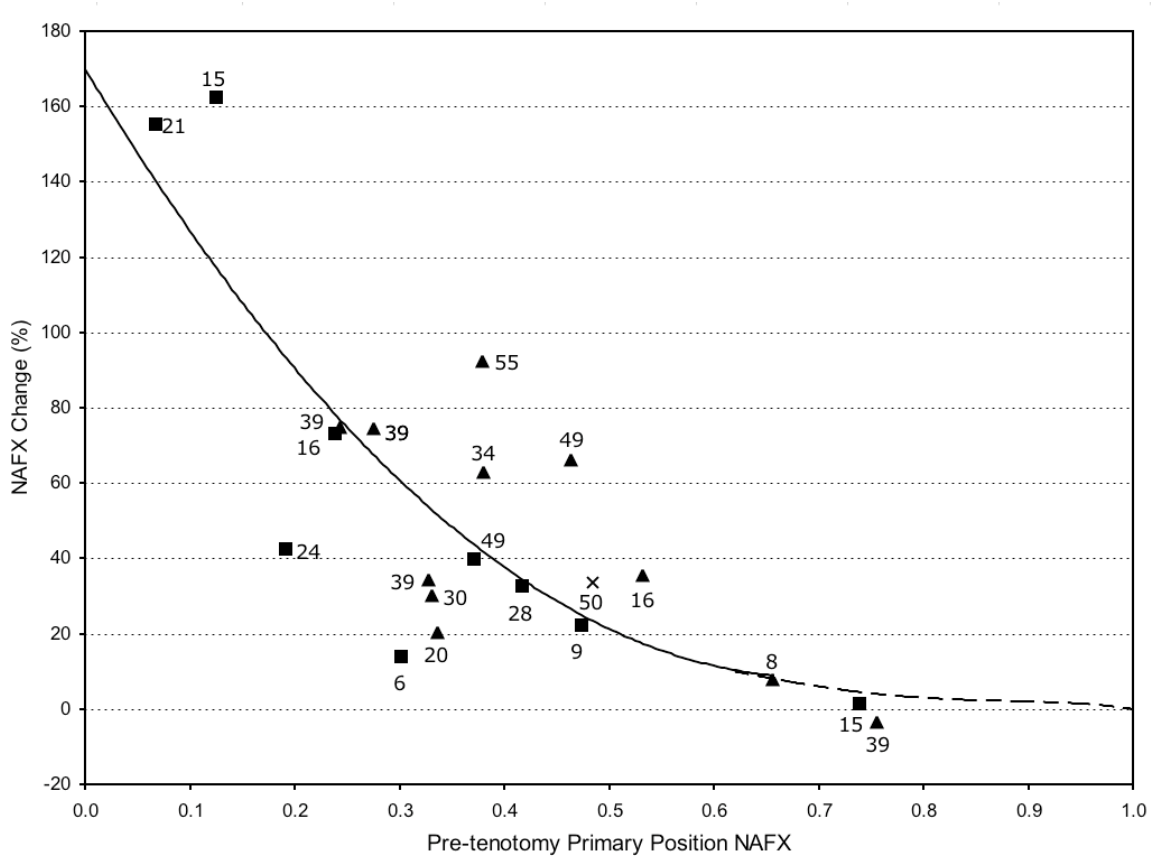

Figure 2-5. NAFX percentage change curve derived from the NAFX percentage change data plotted vs. pre-tenotomy NAFX values. Data from this study are denoted with squares; data from studies by Hertle et al. are denoted with triangles; data from one acquired pendular nystagmus patient is denoted with a cross. Data are fitted with a second-order polynomial curve (solid line). Dashed curve is a hypothetical curve if more data from higher pre-tenotomy NAFX values could be obtained and evaluated. Patient age is indicated by the number near each data point.

The NAFX percentage change curve is monotonically decreasing, approaching 0 as the pre-tenotomy NAFX approaches 1 (highest possible value). For patients ≥6 years old, the curve does not suggest age-dependent effects of tenotomy; it predicts that if we expect to have at least a 20% increase in primary-position NAFX, the pre-tenotomy NAFX should be lower than 0.5. The NAFX provides additional data that may help in surgical decision-making: for the past 10 years, it has been an essential tool in our Laboratory for enhancing the therapeutic and predictive relevance of pre-surgical planning.

Improvement in lateral-gaze vision is indicated by changes in the breadth of the NAFX vs. gaze-angle curve for each patient. Seven of 9 patients showed flattened post-tenotomy NAFX vs. gaze-angle curves, supporting the original hypothesis based on the observation of null broadening after Kestenbaum procedures. We hypothesized that patients with sharp peak region should have a broader region of good acuity while patients with pre-existing broad peaks should experience a minimal broadening effect. To test this hypothesis, the longest foveation domains (LFD) were measured for each patient; Figure 2-6 shows the percentage LFD increase vs. pre-tenotomy LFD data from 8 subjects (the LFD of Patient 2 could not be obtained due to the shape of the NAFX vs. gaze-angle curve). The LFD percentage change curve is monotonically decreasing, approaching 0 as the pre-tenotomy LFD goes to 33°. This supports the hypothesis stated above. Thus, the LFD percentage change curve is an additional criterion to predict post-surgical broadening the high-acuity visual field. For patients ≥6 years old, the LFD curve also does not suggest age-dependent effects.

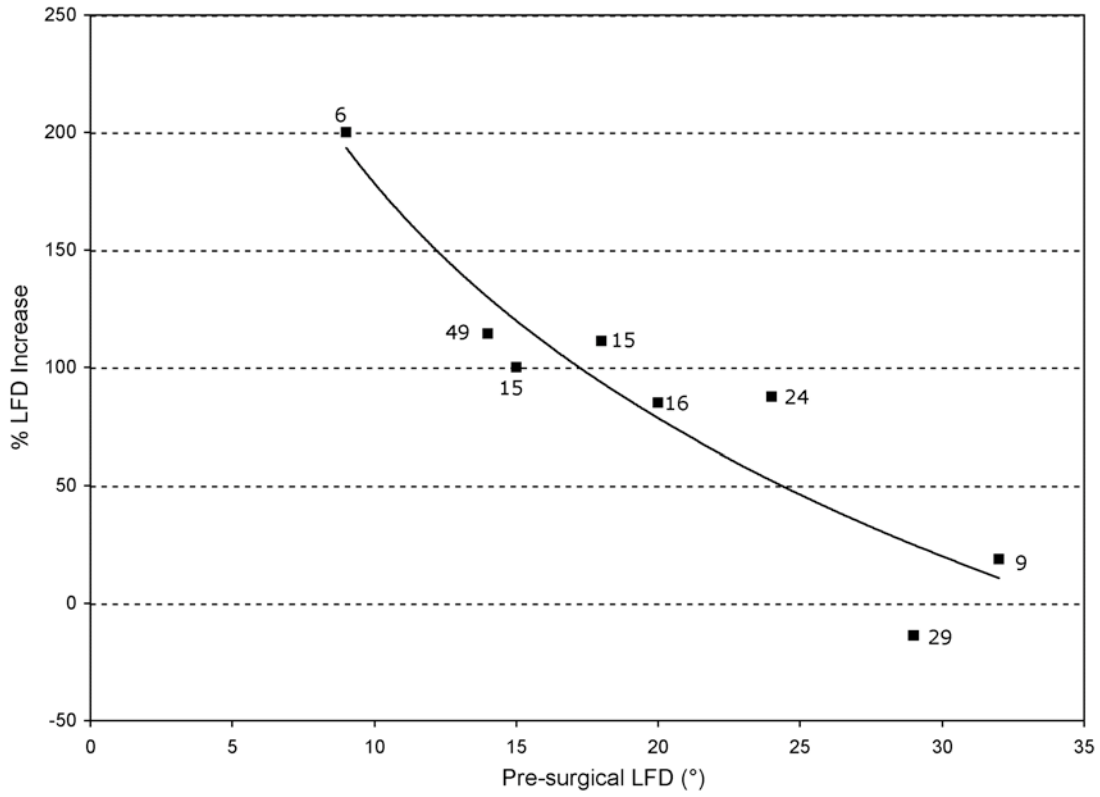

Figure 2-6. LFD percentage change curve derived from the LFD percentage change data plotted vs. pre-tenotomy LFD values. A logarithmic curve (solid line) is fitted to the data points. Patient age is indicated by the number near each data point.

Having large horizontal and vertical eye-movement components, Patient 4 underwent the horizontal four-muscle tenotomy as a first-stage operation. Horizontal eye movement showed a 42.4% increase in NAFX at primary position. Vertical eye movement data were also analyzed, showing no changes in NAFX or amplitude. This suggests that a second-stage vertical tenotomy could be done to further benefit the patient. Based on our experience with a 2-stage tenotomy procedure of all 12 extraocular muscles of both eyes of a canine (Dell'Osso, et al., 1999) and that of others in patients (especially children), anterior segment had no ischemic problems if a second, vertical stage were done at a later date (i.e., after circulation in the region operated was re-established). Since there might be some increased risk, the risk/benefit ratio would have to be assessed on an individualized basis. The horizontal four-muscle tenotomy affected only horizontal eye movements whereas, in a case of acquired pendular nystagmus in an MS patient, it also damped the vertical component (Tomsak, et al., 2005).

Examining the NAFX vs. gaze-angle curve of Patient 3, we found a slight peak at 10° to the right. This property remained the same after tenotomy. At the time of the initial examination, this peak was missed because the changes in waveforms in right gaze were virtually indistinguishable by visual inspection. The tenotomy procedure increased the primary-position NAFX by a 73.2% with an 85% broadening of the LFD. This suggests that the absence of head turn does *not* exclude a four-muscle Kestenbaum procedure and the patient might have benefited further from shifting the NAFX/visual acuity peak to the primary position.

In Patient 2 the NAFX predicted a lower value of potential visual acuity than actually measured. The NAFX predicts the potential best-corrected visual acuity;

measured acuity should be less than or equal to that value. This may be explained by the patient's slight, intermittent left-gaze and up-gaze null. The clinical acuity measurement was made with a free head, probably using the patient's preferred rightward and downward head position, whereas we fixed the patient's head in primary position during our recordings. The best NAFX occurred at –15° pre-tenotomy (0.119) and –20° post-tenotomy (0.226). If we use the NAFX at these gaze angles to make the comparison with the clinically measured visual acuity, the difference is reduced; the NAFX-predicted visual acuity improved from 20/123 to 20/65+. The remaining difference could be explained by the up-gaze null, which was not recorded by the infrared reflection system, which was used only for horizontal movements.

Patients 4 and 5 showed no improvement in Snellen acuities despite increases in NAFX values; this was anticipated because of the complex relationship between nystagmus, other sensory deficits, and Snellen visual acuity. Since the improvement of measured acuity is dependent on a number of unpredictable factors, it is necessary to use ocular motility recordings as an objective measurement. The difference between the predicted visual acuity changes from NAFX values and the clinically measured changes could be explained as follows. The NAFX is calculated with the assumption of an intact visual system, which is not always the case with infantile nystagmus patients (e.g., Patient 4). As a result, although the foveation quality might be markedly improved, it is the presence of additional afferent deficits that limits the visual acuity improvement. Additional factors could be: patient age, associated strabismus, amblyopia, uncorrected refractive errors, and associated central nervous system disease. Also, since IN is affected by psychological factors, it could have been exacerbated from its baseline level at the

time of examinations. Clinical examination differs from daily life experience in that patients may feel stressed by the former; this stress is not only idiosyncratic but also may differ from one exam to the next. Thus, slight improvements in primary-position visual acuity due to tenotomy (e.g., Patient 5) might not necessarily be reflected in measured visual acuity.

Tenotomy is a muscle-sparing procedure that presumably does not provoke a confounding central response. In addition to infantile nystagmus, tenotomy has been reported to be effective in other types of nystagmus, e.g., asymmetric (a)periodic alternating nystagmus, acquired pendular nystagmus, and see-saw nystagmus (Dell'Osso, et al., 1998; Tomsak, et al., 2005). Tenotomy has also been reported to reduce oscillopsia (Tomsak, et al., 2005). Because each of these types of nystagmus has a different mechanism and putative anatomical site, it is unlikely that tenotomy affects central signals. In Figure 2-5, data points were included from infantile nystagmus, asymmetric (a)periodic alternating nystagmus, and acquired pendular nystagmus patients and were all fit with the same curve. The coincidence of the data points from this diverse group of patients suggests that tenotomy improves all three types of nystagmus in the same way.

In conclusion, the overall therapeutic effect of four-muscle tenotomy is a broadened area of heightened visual function; patients with more impaired visual function (i.e., low pre-tenotomy NAFX, sharp NAFX-curve peak) have a larger chance of improvement. The tenotomy procedure extends the possibility of surgical therapy to several different classes of patients with INS for whom other procedures are contraindicated, e.g., patients who had no NAFX peak, a peak at primary position, or a time-varying peak (Dell'Osso, 1998; Dell'Osso & Flynn, 1979). It could also benefit

patients with acquired nystagmus and oscillopsia. The NAFX and LFD percentage change curves are two additional examples of the use of the NAFX to both predict and measure the effectiveness of nystagmus therapies, for inter-subject comparison, and planning of therapeutic intervention in infantile nystagmus. Accurate eye-movement recording data makes it possible to predict different therapeutic changes using the corresponding percentage-change curves developed in this paper. Only patients with *both* a high primary-position NAFX (>0.6) and a large LFD (>25°) would not be expected to receive either benefit from tenotomy; all others remain candidates.

The predictive value of both the NAFX and LFD for infantile nystagmus patients ≤6 years old should be studied to determine if there may be even greater therapeutic effects during the early stages of ocular motor and visual system development. Future studies should also include tenotomy-induced gaze-angle variation and broadening studies of other types of nystagmus, such as acquired nystagmus. Tenotomy combined with other nystagmus treatments, including drug therapy, strabismus procedures, or refractive (prism) modifications, requires more study. The possibilities of chemical/mechanical/thermal tenotomy still need to be assessed. Also, the proprioceptive feedback loop, by which the tenotomy is hypothesized to work, needs to be studied and incorporated into a more realistic model of the ocular motor plant (Jacobs, 2001; Jacobs & Dell'Osso, 2004; Wang, Dell'Osso, Zhang, Leigh, & Jacobs, 2006).

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Chapter 3

Combining Recessions with Tenotomy Improved Visual Function and Decreased Oscillopsia in Acquired Downbeat Nystagmus and Horizontal Infantile Nystagmus

3.0 Abstract

We aim to investigate the effects of combined tenotomy and recession procedures on both acquired downbeat nystagmus and horizontal infantile nystagmus syndrome (INS). Patient 1 had downbeat nystagmus with a chin-down (upgaze) position, oscillopsia, strabismus, and diplopia. Asymmetric superior rectus recessions and inferior rectus tenotomies reduced right hypertropia and rotated both eyes downward. Patient 2 had horizontal INS, a 20° left-eye exotropia, and alternating (***ab***ducting-eye) fixation. Lateral rectus recessions and medial rectus tenotomies were performed. Horizontal and vertical eye movements were recorded pre- and post-surgically using high-speed digital video. The eXpanded Nystagmus Acuity Function (NAFX) and nystagmus amplitudes and frequencies were measured. Post-surgical results are reported. Patient 1: The NAFX peak moved from 10° upgaze to primary position where NAFX values improved 17% and visual acuity increased 25%. Vertical NAFX increased across the -10° to +5° vertical range. Primary-position right hypertropia decreased ~50%, foveation time per cycle increased 102%, vertical amplitude, oscillopsia, and diplopia were reduced, and frequency was unchanged. Patient 2: Two lateral, narrow high-NAFX regions (due to alternating fixation) became one broad region with a 43% increase in primary position

(acuity increased ~92.3%). Diplopia amplitude decreased; convergence and gaze holding were improved. Primary-position right exotropia was reduced, foveation time per cycle increased 257%, horizontal-component amplitude decreased 45.7%, and frequency remained unchanged. In summary, combining tenotomy with nystagmus (vertical Anderson) or strabismus recession procedures increased NAFX and visual acuities and reduced diplopia and oscillopsia, in downbeat nystagmus and INS.

3.1 Introduction

Previous investigations have demonstrated the efficacy of recessions (Anderson) (Anderson, 1953), resections (Goto), or both (Kestenbaum, 1953; Dell'Osso & Flynn, 1979) to treat infantile nystagmus syndrome (INS). More recently, four-muscle tenotomy was shown to both improve nystagmus waveforms and broaden the range of gaze angles with improved waveforms (Dell'Osso, 1998, 2002; Hertle, et al., 2003; Hertle, Dell'Osso, FitzGibbon, Yang, & Mellow, 2004). It was also reported to be effective in reducing acquired pendular nystagmus (APN) and oscillopsia in a patient with multiple sclerosis (MS) (Tomsak, et al., 2005).

Surgical treatment of nystagmus should be tailored to the eye-movement and clinical characteristics of each individual patient. In this study, we investigated surgical treatments with recessions combined with tenotomy. We chose two patients with both different types of nystagmus and clinical characteristics. In one patient, tenotomy was combined with bilateral inferior rectus recessions (a vertical Anderson nystagmus procedure) to improve acquired downbeat nystagmus, plus a small unilateral inferior rectus recession (a strabismus procedure) to improve a vertical tropia. In the other, it was

combined with bilateral lateral rectus recessions (a strabismus procedure) to improve horizontal infantile nystagmus. The nystagmus caused oscillopsia in the downbeat nystagmus patient and reduced visual acuity in both. The post-surgical changes of different aspects of the nystagmus, tenotomy's broadening effect in particular, were evaluated using the eXpanded Nystagmus Acuity Function (NAFX) (Dell'Osso & Jacobs, 2002).

3.2 Methods

Recording

The digital video system (EyeLink II, SR Research, Mississauga, ON, Canada) had a linear range of ±30° horizontally and ±20°vertically. System sampling frequency was 500 Hz, and gaze position accuracy error was 0.5°-1° on average. The data were digitized at 500 Hz with 16-bit resolution. The Eyelink signal from each eye was calibrated with the other eye behind cover to obtain accurate position information; the foveation periods were used for calibration (Dell'Osso, 2005). Monocular primary-position adjustments for all methods allowed accurate position information and documentation of small tropias and phorias hidden by the nystagmus.

Protocol

This study was approved by the local IRB and written consent was obtained from each subject before the testing. All test procedures were carefully explained to the subject before the experiment began, and were reinforced with verbal commands during the trials. Subjects were seated in a chair with headrest and a chin stabilizer, far enough from

the stimulus screen to prevent convergence effects (>5 feet). At this distance the LED subtended less than 0.1° of visual angle. The room light could be adjusted from dim to blackout to minimize extraneous visual stimuli. An experiment consisted of from eight to ten trials, each lasting under a minute with time allowed between trials for the subject to rest. Trials were kept this short to guard against boredom because infantile nystagmus intensity is known to decrease with inattention.

Analysis

All the analysis was unmasked and done in MATLAB environment (The MathWorks, Natick, MA) using OMLAB software (OMtools, available from http://www.omlab.org). Only eye position was sampled directly; velocity was derived from the position data by a 4^{th}-order central-point differentiator. Position data were pre-filtered with a low-pass filter with the cutoff frequency of 20 Hz to eliminate noise without changing the nystagmus signals to be studied. The differentiating and filtering were applied equally to the pre- and post-surgical data sets to ensure consistency. Analysis was always performed on the fixating eye. The post-surgical records for Patient 1 were obtained 6 weeks after the procedure, and for Patient 2, 8 weeks. It has been reported that visual functions were stable within this time period (Hertle, et al., 2003).

The NAFX was used to measure tenotomy-induced changes in the infantile nystagmus in primary position and various gaze angles. It is an objective measure of waveform quality and a predictor of potential visual acuity for nystagmus patients assuming that no afferent deficits are present. It can be applied to any nystagmus waveform whose foveation variability (position and velocity) lies within the maximum

foveation window of ±6° and ±10°/s. Five or more primary-position NAFXs for each patient in this study were calculated and averaged; the segments chosen avoided blinks and inattention periods. At each gaze angle, two or three NAFX calculations were made and averaged, depending on the data availability. When choosing the segments, we maintained consistency in the pre- and post-surgical data sets, i.e., the best segments for foveation were chosen, so that the NAFX average would reflect the best potential visual acuity for the patient; this methodology duplicates that used in masked clinical trials (Hertle, et al., 2003; Hertle, et al., 2004). Two outputs will be listed and discussed in RESULTS. Details about the NAFX may be found elsewhere (Dell'Osso & Jacobs, 2002).

Primary-position visual acuities were obtained by the referring physician (Snellen chart at distance and near card using Jaeger scale). Potential visual acuities were provided by the NAFX program as a comparison. Stereopsis was measured with the Titmus and Randot Stereo Tests. Pre- and post-surgical peak-to-peak amplitude in primary position was measured by taking the average of 16 amplitude measurements from different nystagmus cycles. The samples were chosen with the same criteria as described previously for the NAFX analysis. Second-order polynomial curves were fitted to pre- and post-surgical NAFX values at each gaze angle.

3.3 Results

Patient 1

This patient was a 44 year-old man who had intractable oscillopsia for 14 years that was resistant to drug therapy. He preferred left-eye fixation; he had stereopsis of 50”

of arc, rightward internuclear ophthalmoplegia, and predominantly vertical nystagmus (downbeat nystagmus). The patient also had right-eye hypertropia of 7° and esotropia of 3-5°. He exhibited a marked chin-down position. Eye-muscle surgery was done 12 years prior for diplopia from a traumatic 4th Nerve palsy, but no surgical notes could be obtained. At the time of our surgery no evidence of conjunctival scarring was evident and the operated muscles were in their normal anatomic positions, indicating that surgery on these muscles had not been done previously. Superior rectus muscles were recessed asymmetrically (left, 5 mm and right, 6 mm) to simultaneously rotate both eyes 10° downward (5 mm both eyes) and reduce the right hypertropia (1 mm right eye); both inferior rectus muscles were tenotomized to complete the 4-muscle tenotomy. Thus, a *vertical* (Anderson + strabismus + tenotomy) procedure was performed.

Following the combined procedure, the patient's primary-position NAFX values were improved by 17%, foveation time per cycle increased 102% from 88 ms to 178 ms and visual acuity increased 25% from 20/25 to 20/20+1. Vertical-component amplitude was reduced by 46%, and frequency was unchanged at ~3 Hz. Vertical NAFX values increased across the -10° to +5° vertical range, suggesting improved visual function. As is shown in Figure 3-1, in primary position, the post-surgical foveation periods were longer and better aligned. The NAFX values for these intervals increased 29.6% from 0.652 to 0.845. Similar changes at 10° down gaze are shown in Figure 3-2, with the NAFX values increased 87.5% from 0.391 to 0.733.

The broadening effect may be observed in the patient's NAFX vs. gaze-angle curves, as shown in Figure 3-3. His NAFX peak was moved from 10° up to primary position (eliminating the chin-down position) and the curve was effectively broadened,

increasing the patient's high-acuity region. The right hypertropia was reduced to 3-4° and stereopsis was maintained. The reduction of the amplitude post-surgically is also evident. The patient reported decreased frequency of diplopia and improvement in oscillopsia.

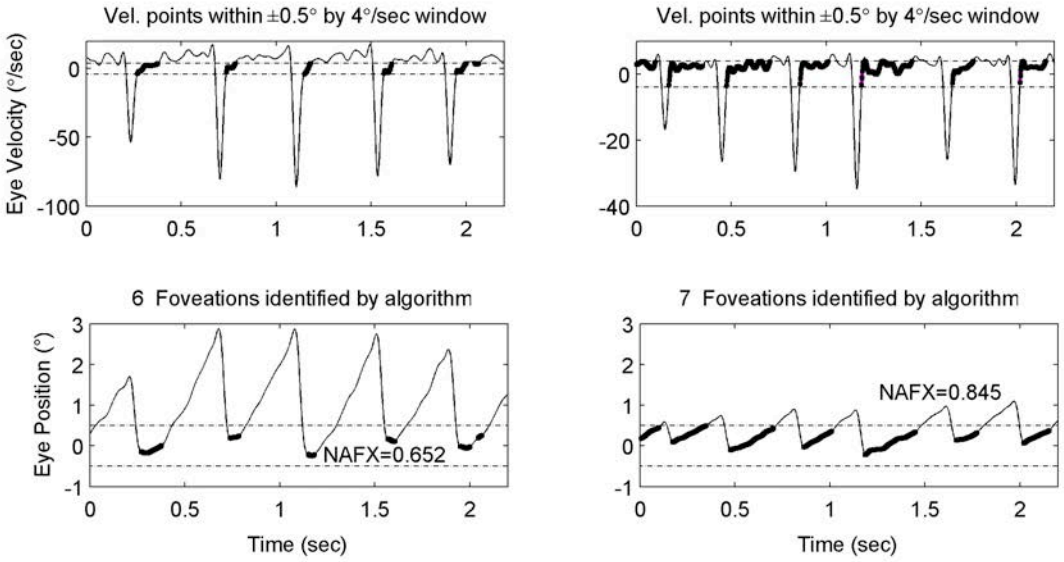

Figure 3-1. NAFX-program outputs comparing pre- and post-surgical waveforms from Patient 1 during left-eye fixation with both eyes open, in primary position (due to a small, prior head movement between recording trials, the post-surgical data were at -2.5°). In this and Figures 3-2, 3-4, and 3-5, left columns are pre- and right columns are post-surgical data. Velocity traces (upper row) and position traces scaled for ease of interpretation (lower row) are shown. In each subplot, the NAFX-algorithm-determined foveation periods satisfying the foveation-window criteria are shown thickened. NAFX values for each corresponding segment are noted on the plots.

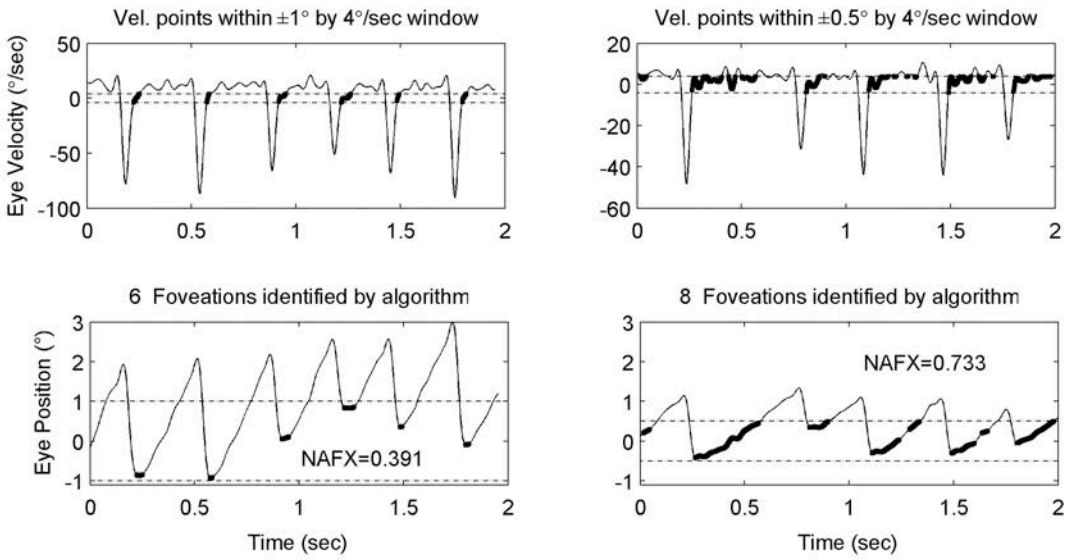

Figure 3-2. NAFX-program outputs comparing pre- and post-surgical waveforms from Patient 1 during left-eye fixation with both eyes open, at 10° down gaze. Due to a small, prior head depression, the post-surgical data were at 9° down.

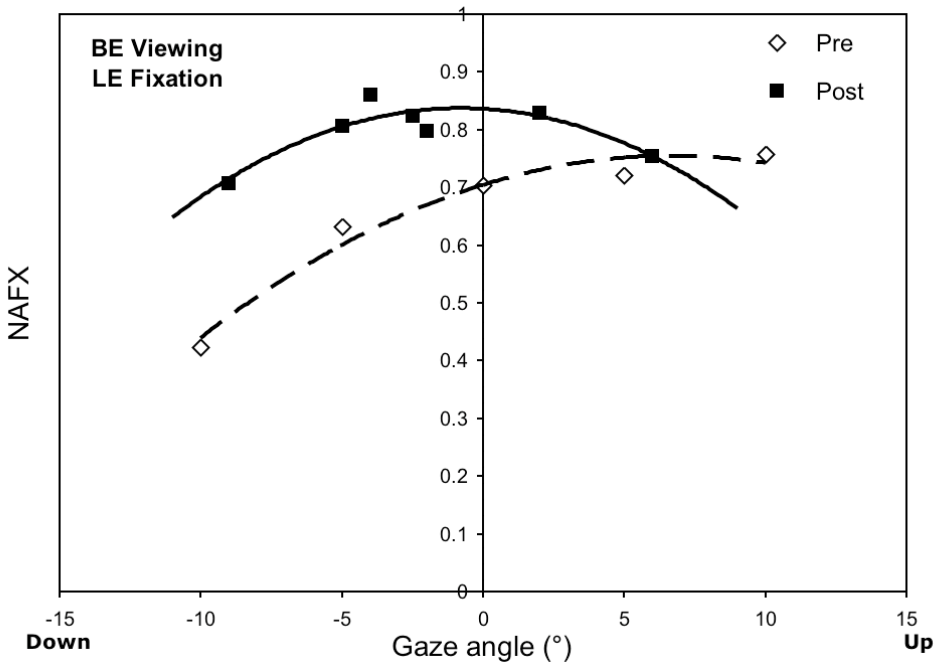

Figure 3-3. NAFX vs. gaze-angle curves for Patient 1, who had a null at 10° down gaze pre-surgically. BE, both eyes; LE, left eye. For this and Figure 3-6 and 3-7, unfilled symbols denote pre- and filled denote post-surgical data, the pre-surgical NAFX curve is dashed, and the post-surgical NAFX curve is solid.

Patient 2

The second patient was a 49 year-old man who had predominantly horizontal INS and diplopia. The patient preferred left-eye viewing in left gaze and right-eye viewing in right gaze. Stereopsis was >3000° of arc. There was a left-eye exotropia of 20°. A *horizontal* (recession + tenotomy) procedure was performed, with both lateral rectus muscles recessed 8 mm and both medial rectus muscles tenotomized.

The procedure transformed two lateral, narrow NAFX vs. gaze-angle curves (due to fixating-eye changes) into one broad curve with a 43% increase in primary position where acuity increased 92.3% from 20/150 to 20/80. There was a slight decrement in left gaze. In primary position, foveation time per cycle increased 257.4% from 35.5 ms to 126.9 ms, horizontal-component amplitude was reduced by 45.7%, and frequency remained unchanged at ~4 Hz. Fixation data of left-eye viewing in primary position is shown in Figure 3-4; there was a 550% NAFX increase post-surgically (from 0.107 to 0.696). In Figure 3-5, which is right-eye viewing, a 118% NAFX increase occurred (from 0.279 to 0.609). Also, This exotropic patient had an interesting fixation preference—left-eye fixation in the left field of gaze and right-eye fixation in the right field (in primary position, either eye was used); fixation in abduction is opposite to the fixation pattern (adduction) normally shown in esotropia. The data contained no evidence of any adduction lags. Pre- and post-surgically (Figure 3-6), the two lateral, narrow NAFX peaks were transformed into one broad peak, with the NAFX in primary position greatly increased. Thus, although the left eye was still preferred for all targets to the left of center and the right eye for all targets to the right of center, the potential acuity across the central 30° was improved, especially the acuity in primary position for either eye.

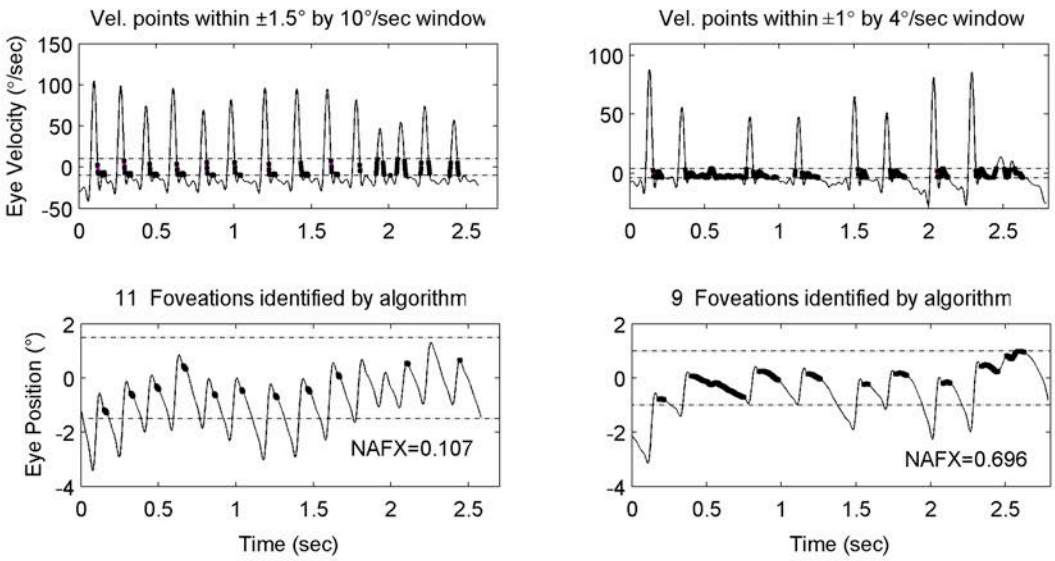

Figure 3-4. NAFX-program outputs comparing pre- and post-surgical waveforms from Patient 2 during forced left-eye fixation (right eye occluded) in primary position.

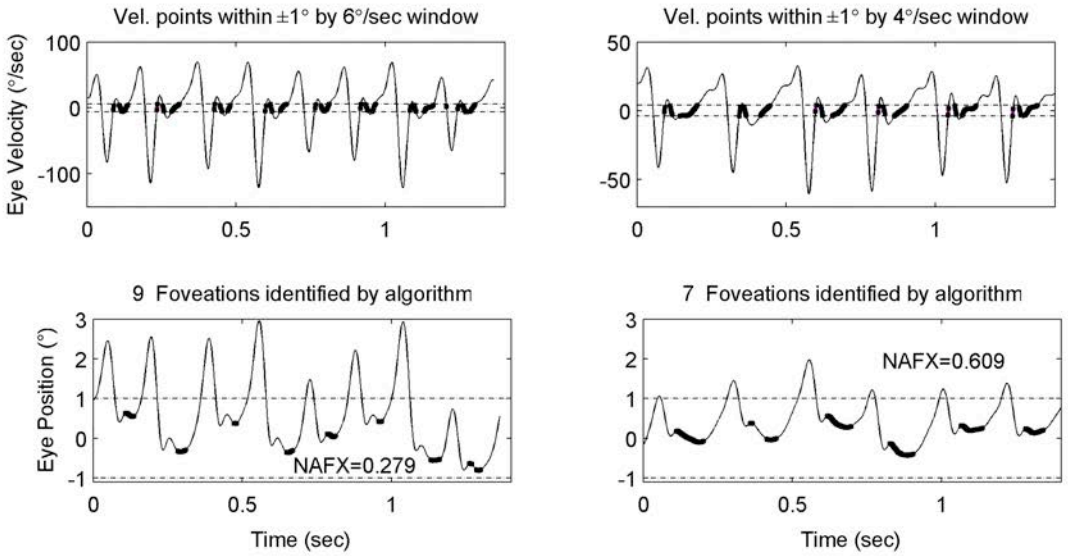

Figure 3-5. NAFX-program outputs comparing pre- and post-surgical waveforms from Patient 2 during both-eye viewing and right-eye fixation in primary position.

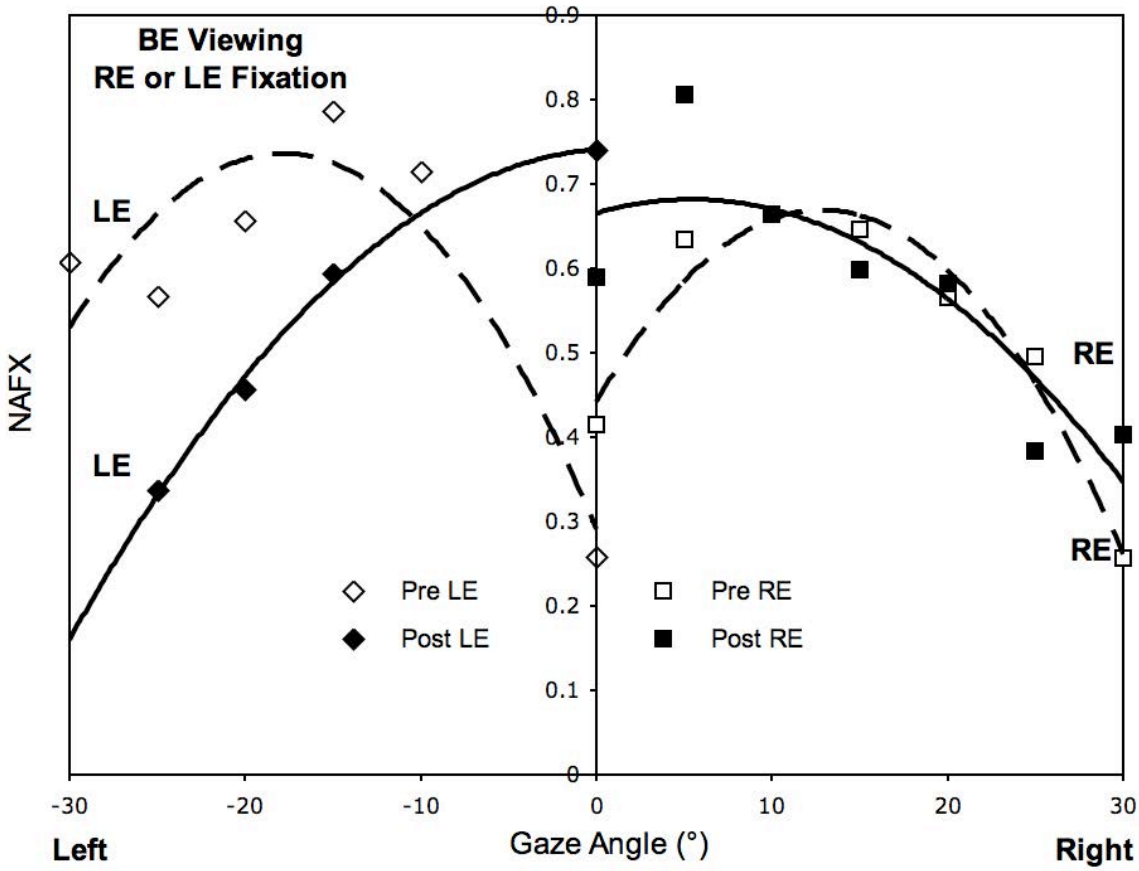

Figure 3-6. NAFX vs. gaze-angle curves for Patient 2, binocular viewing and monocular fixation. BE, both eyes; RE, right eye; LE, left eye. Square symbols are RE-fixation data and diamond symbols are LE-fixation data.

The patient's diplopia amplitude was decreased, his ability to converge was regained, and to hold gaze was improved. The right exotropia was reduced to ~10°. Stereovision was not restored after the surgery.

3.4 Discussion

The purpose of this study is to investigate the effects of combined tenotomy on two different kinds of nystagmus. Listed in Table 1 is a comparison of the two patients' clinical profiles. They have different nystagmus types, planes, sensory deficits and pre-surgical visual acuities; however, they both benefited from the combined procedures, in primary position and lateral gaze, as shown in Table 2.

Because it is impossible to recess or resect a muscle without an obligate tenotomy, one could not separate out the effects of the muscle-moving and muscle-detaching components of either. Sequentially recessing or resecting two muscles and then tenotomizing the other two can only differentiate the combined recession or resection plus tenotomies from the additional two tenotomies. However, prior studies, using four-muscle tenotomies alone, demonstrated that the waveform improvements and null broadening effects of Kestenbaum procedures were due solely to the obligate tenotomies; i.e., the recessions and resections only shifted the null position (Dell'Osso & Flynn, 1979). Thus, in these two patients, we also attribute the improvements in waveforms and the broadening of the null regions to the four-muscle tenotomy component of each procedure.

In Figure 3-7, the age-adjusted NAFX (40-60 year-old group) vs. visual acuity line (established in previous studies from normal population data (Tomsak, et al., 2005))

is plotted along with data points from both patients. Previous studies demonstrated the linear relationship between the NAFX values and the potential visual acuity of individuals with nystagmus, in the presence of a constant, or minimally changing, deficit in the afferent visual system (Dell'Osso & Jacobs, 2002). Patient 1 had no afferent deficits and the data points for potential and measured acuities were close to each other; they overlapped for the post-surgical data. For patient 2, the vertical difference between the potential and the measured values reflects the decrement in acuity due to the afferent visual system deficits. This difference was relatively fixed during the course of our study; therefore the decrement was preserved post-surgically. By drawing a second (dashed) line with the same slope as the age-adjusted line through the pre-surgical measured-acuity data point, we found that the post-surgical data fell along this line of estimated, *measured* visual acuity. Note that the intersection of the dashed line with the NAFX value of 1.0 (i.e., no nystagmus) is ~20/25, indicating that even if the nystagmus was abolished, the visual acuity would still be reduced ~32% (1.176 to 0.8) by the afferent visual system deficit. In both patients (one with an afferent visual deficit and one without, one acquired and one infantile), the pre-operative NAFX and measured acuity values *predicted* both the best potential visual acuities (as they were designed to do) and the *estimated* post-operative measured acuities. Our prior publications on the NAFX have also demonstrated many patients' NAFX and acuity values fall on or near the appropriate age-determined line.

It was previously reported that, in addition to elevating primary-position NAFX, tenotomy also broadens the high-NAFX regions in infantile nystagmus patients, therefore resulting in improvements in visual function beyond primary-position acuity (Wang, et

al., 2006). The broadening effect was also observed in the two patients in our study. The types of nystagmus that tenotomy has now been demonstrated to be effective include INS (plus asymmetric (a)periodic alternating nystagmus), acquired pendular nystagmus, downbeat nystagmus, and see-saw nystagmus (Dell'Osso, Hertle, Williams, & Jacobs, 1999; Hertle, et al., 2003; Hertle, et al., 2004; Tomsak, et al., 2005). Because each of these types of nystagmus has a different mechanism and putative anatomical site, it is unlikely that tenotomy affects central signals. We previously hypothesized that tenotomy works by changing the proprioceptively controlled resting tension in the extraocular muscles, thereby reducing the small-signal (i.e., nystagmus slow-phase) gain of the ocular motor plant (Dell'Osso, et al., 1999). We subsequently demonstrated that large signals, i.e., saccades, were not affected by tenotomy (Wang, et al., 2006). Recent studies on palisade endings and their proprioceptive role in the extraocular muscles have supported the proposed mechanism for tenotomy's effects and suggested anatomical sites for ocular motor proprioceptors (Eberhorn, Horn, Fischer, & Büttner-Ennever, 2005; Jaggi, Laeng, Müntener, & Killer, 2005; Niechwiej-Szwedo, et al., 2006).

The combined procedures reduced acquired nystagmus and oscillopsia and improved visual acuity in both downbeat nystagmus (Patient 1) and INS (Patient 2). Because binocularity was not restored, the improvement in nystagmus at far cannot be attributed to convergence damping. Since the muscle insertions are several mm anterior to the equator of the eyes, small-to-moderate recessions do not diminish muscle action until the eye is moved into the field of action of that muscle. Thus, the damping of small signals in primary position (e.g., nystagmus) was not due to mechanical changes secondary to recession. The post-surgical improvements demonstrated the necessity of

tailoring each procedure based on the evaluation of the idiosyncratic eye-movement characteristics. We believe that combined muscle-movement (for nystagmus null shifting or strabismus correction) and tenotomy (for nystagmus damping and waveform quality improvement) procedures produce more effective and individualized nystagmus treatments.

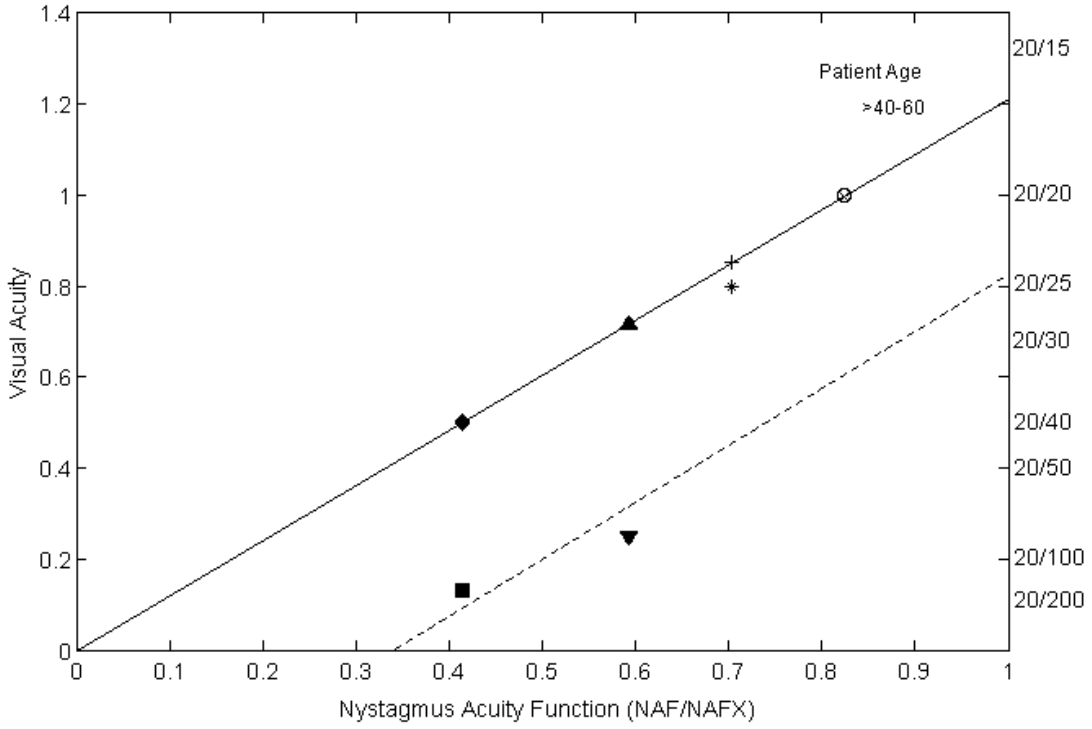

Figure 3-7. NAFX vs. visual-acuity, age-adjusted line with pre- and post-surgical data points for both potential and measured acuities for both patients. Patient 1, open symbols: plus sign, pre-surgical and cross, post-surgical potential acuities; star, pre-surgical and circle, post-surgical measured acuities. Patient 2, solid symbols: diamond, pre-surgical and up-triangle post-surgical potential acuities; square, pre-surgical and down-triangle post-surgical measured acuities.

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Chapter 4

A Review of the Tenotomy Nystagmus Surgery: Origin, Mechanism, and General Efficacy

4.0 Abstract

Tenotomy nystagmus surgery neither "weakens" nor "strengthens" the extraocular muscles; it is *not* strabismus surgery. Tenotomy effectively decreases the gain of the ocular motor plant to small, non-saccadic signals and was hypothesized to be efficacious for other types of nystagmus in addition to infantile nystagmus; it has subsequently been shown to damp various types of *acquired* nystagmus (pendular and jerk, horizontal and vertical) and reduce their associated oscillopsia. The eXpanded Nystagmus Acuity Function now allows visual acuity improvements to be estimated prior to surgery—something never before possible. More research into proprioceptive tension control should provide non-surgical methods to achieve the therapeutic improvements of tenotomy.

4.1 The Origin of the Tenotomy Procedure

The history of the development of the four-muscle tenotomy nystagmus surgery is interesting because of its departure from that of its predecessors. Classically, ophthalmic surgeons developed methods to damp nystagmus based on the clinical characteristics of their patients and the approaches used in strabismus procedures (i.e., "weakening" or "strengthening" extraocular muscles). These procedures usually involved muscle recessions (Anderson, 1953), resections (Goto, 1954), or their combination (Kestenbaum,

1953, 1954) to either move both eyes conjugately opposite to a nystagmus null or to artificially create an exotropia in a binocular patient who had a convergence null (Cüppers, 1971). Because the surgical procedures were similar to those used in the correction of strabismus, they were referred to as strabismus surgery even though their purpose was not to correct a misalignment and, in the case of artificial divergence, was designed to produce one.

Tenotomy has very different roots; it was hypothesized based on pre- and post-Kestenbaum surgery eye-movement data analyzed by a non-surgeon (a biomedical engineer) (Dell'Osso & Flynn, 1979) and it does not involve moving the insertions of any muscle (i.e., it is *not* a strabismus procedure) (Dell'Osso, 1998). The tenotomy procedure was the first nystagmus surgery proven effective on an animal model of infantile nystagmus syndrome (INS, fka congenital nystagmus, CN) (Dell'Osso, 1998). The concept of tenotomy was anathema to some classically trained ophthalmic surgeons, many of whom were vociferous in their skepticism, claiming it "could not work," or "did nothing." Never the less, in an NIH-sponsored, masked-data, clinical trial (the first such trial of a nystagmus surgery), tenotomy successfully improved INS waveforms and increased visual function (Hertle, et al., 2003; Hertle, Dell'Osso, FitzGibbon, Yang, & Mellow, 2004). In addition to tenotomy's efficacy in treating INS patients who either had no nulls or a primary-position null, (both populations are not candidates for the "muscle-moving" procedures) (Z. Wang, Dell'Osso, Jacobs, Burnstine, & Tomsak, 2006 (in press)) it has subsequently been shown to damp acquired nystagmus (both pendular and jerk, horizontal and vertical) (Tomsak, et al., 2005; Z. I. Wang, Dell'Osso, Tomsak, & Jacobs, 2007).

4.2 The Mechanism of the Tenotomy Procedure

Initial observations of secondary effects of the Kestenbaum procedure suggested that they were due to the tenotomy and reattachment of the muscles whereas, the shifting of the null was due to their repositioning (Dell'Osso & Flynn, 1979; Dell'Osso, Hertle, Williams, & Jacobs, 1999). If that was so, then it was reasoned that the detachment and reattachment of the muscles left them less responsive to the unchanged nystagmus signal from the brain stem. That is, the gain to these relatively small signals (compared to the maximal signals driving saccades) was reduced. Examination of post-tenotomy saccades verified that saccades were unaffected and the gain changes were limited to small signals (Z. Wang, Dell'Osso, Zhang, Leigh, & Jacobs, 2006). Prior to the demonstrated damping of tenotomy, it had been thought that the extraocular muscle tendons contained no neural substrate that could affect muscle tension; tenotomy's success suggested otherwise. Subsequent investigations into the anatomy of the enthesial tendons revealed such neural substrate (Eberhorn, Horn, Fischer, & Büttner-Ennever, 2005; Hertle, Chan, Galita, Maybodi, & Crawford, 2002). Thus, the anatomy exists for the hypothesized proprioceptive changes produced by tenotomy (Dell'Osso, et al., 1999; Hertle, et al., 2003; Hertle, et al., 2004). Although proprioceptive tension control does not effect individual eye movements in real time (i.e., there is no stretch reflex) (Keller & Robinson, 1971), the long-term calibration and control of muscle tension is important for accurate ocular motor control and tenotomy appears to take advantage of altering this control by reducing resting muscle tension and the plant gain determined by that tension.

4.3 The Applicability of the Tenotomy Procedure

Infantile Nystagmus Syndrome

In 1998, the hypothesis of four-muscle tenotomy, i.e., detaching the muscles at the insertional end of the extraocular muscle tendons and reattaching them in the same place with absorbable sutures, was officially proposed based on the post-operative results of the Kestenbaum procedure (Dell'Osso, 1998). Depending on the plane of the dominant nystagmus component, the four-muscle tenotomy may be done on the medial and lateral rectus muscles (two per eye, four in total) for damping the horizontal component, or superior and inferior rectus muscles (two per eye, four in total) for damping the vertical.

The INS patients who underwent the Kestenbaum procedure had pre-operative null regions from 3° - 9°; they were extended to 23° - 25° (Dell'Osso & Flynn, 1979). Primary-position visual acuities improved from 20/60 – 20/100 pre-operatively to 20/25 – 20/40 post-operatively. The net results of the procedure were: 1) moving the null regions to primary position and 2) damping the nystagmus at both the null and over a broader range of gaze angles. Although the exact mechanisms involved in these secondary effects were not clear at that time, the tenotomy procedure was hypothesized to benefit INS patients who have either a null point at or near primary position, no null, or a non-stationary null (asymmetric (a)periodic alternating nystagmus, APAN) (Dell'Osso, 1998; Hertle, et al., 2004). This unexpected, generalized damping effect over a broad range of gaze angles suggested that the amount of surgical eye rotation might not need to be precise; it offered a margin of error in which the Kestenbaum procedure could achieve positive post-operative effects. This also helped to explain the high success rate of Kestenbaum procedure despite the different formulas used by individual surgeons to

calculate the amounts of recessions and resections they employed to shift the null position.

In 1991, an animal model appeared in an achiasmatic Belgian sheepdog family (Hogan, Garraghty, & Williams, 1996; Hogan & Williams, 1995; Williams, Garraghty, & Goldowitz, 1991; Williams, Hogan, & Garraghty, 1994), who had horizontal INS plus see-saw nystagmus (SSN). A two-stage tenotomy procedure was performed on one dog. In Stage 1, all of the horizontal rectus muscles were tenotomized and reattached at their original site. The post-surgical reduction was visibly obvious immediately after the operation. The ocular motility data documented a peak-to-peak amplitude reduction of 67% in the horizontal pendular component of the waveform and 65% in the jerk component. Post-surgical waveforms also had an increased *centralisation* (i.e., within the area centralis) time per cycle, which resulted in long intervals of stable fixation. Such fixation periods were not seen in the pre-surgical data taken over the previous 6 years. These effects persisted for at least 1 year after the surgery. A control procedure was performed on 1 healthy member of the family, with no changes in ocular motility (Dell'Osso, et al., 1999). Stage 2 of this operation (on the SSN component) will be reviewed in the next section.

The success of the animal model was followed by a clinical trial approved by National Eye Institute (Hertle, et al., 2003; Hertle, et al., 2004). Ten adult patients with varied associated sensory deficits as well as INS (including APAN) received the tenotomy surgery. Search-coil eye movement recordings were made before and 1, 6, 24, and 52 weeks after the operation. Masked-data analysis on the fixating eyes showed persistent, significant post-surgical increases in the eXpanded Nystagmus Acuity

Function (NAFX) in 9 of the 10 patients (the NAFX is an objective measurement of nystagmus waveform foveation quality, which includes velocity and position thresholds for stable vision) (Bedell, White, & Abplanalp, 1989; Dell'Osso, 1973; Dell'Osso & Jacobs, 2002; Dell'Osso, Van der Steen, Steinman, & Collewijn, 1992; Sheth, Dell'Osso, Leigh, Van Doren, & Peckham, 1995). Average foveation time increased in all 9 patients' fixating eyes. Five of the 10 patients had more than a 5-letter increase, corresponding to at least a line's increase in Snellen acuity. The NEI-VFQ-25 showed an improvement in vision-specific mental health in 9 patients. These post-surgical effects stabilized within 6 weeks and were shown to persist for at least 52 (see Figure 4-1 for 4 patients' NAFX increases over the 52 weeks' follow-up period). There were no adverse events. The one patient who had no increase in the NAFX had a good pre-surgical acuity, which indicated an upper bound beyond which no waveform improvement should be expected. This was supported by later studies (Z. Wang, Dell'Osso, Jacobs, Burnstine, & Tomsak, 2006).

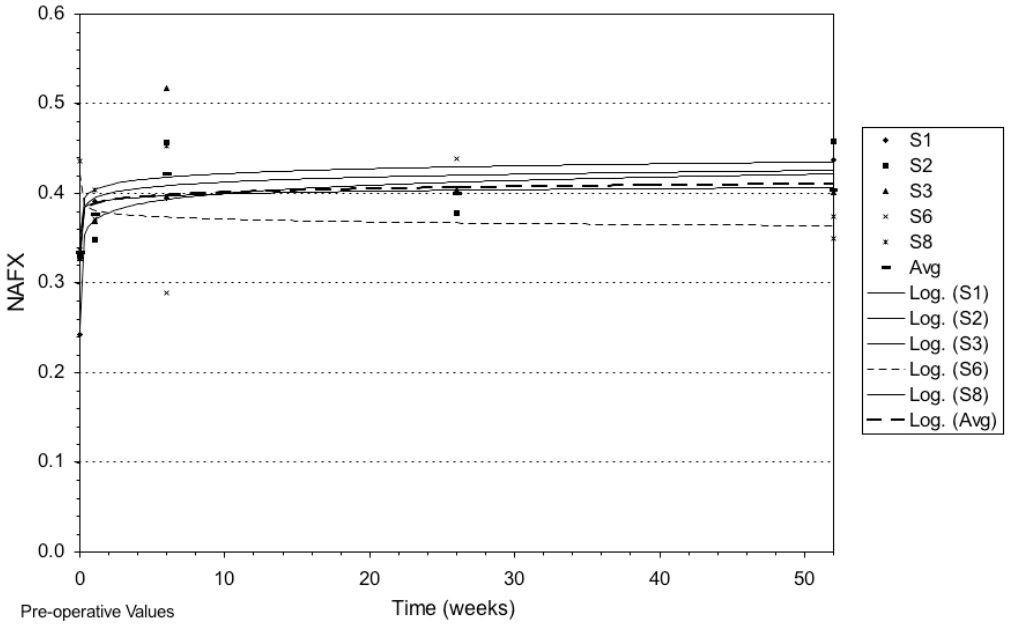

Figure 4-1. Plots of NAFX data for 5 INS patients over the course of the NIH clinical trial. Avg = average of patients in each graph, Log = logarithmic curve fits of the NAFX vs. Post-Op Time data, NAFX = eXpanded Nystagmus Acuity Function.

In the second part of the NEI clinical trial, the same procedure and analysis protocol as in the first part were performed on 5 children with INS (including APAN) and sensory deficits (Hertle, et al., 2004). At a year after tenotomy and under binocular viewing conditions, two of the three patients whose NAFX could be measured had persistent and significant improvement, with an increase in average foveation time per cycle. Measured visual acuity improved in 4 children; the remaining one had retinal dystrophy. There were no adverse effects.

The animal model and the two-part NEI trial demonstrated the effectiveness of four-muscle tenotomy. However, the clinical standards for this procedure were not yet determined. In 2006, the effects of four-muscle tenotomy on foveation quality in both primary position and at lateral gaze angles were reported (Z. Wang, Dell'Osso, Jacobs, et al., 2006). Eye movements of 9 patients with INS were recorded using infrared reflection or high-speed digital video techniques. The NAFX was measured in primary position and at various gaze angles and the longest foveation domains (LFD) were measured from fitted NAFX curves. Five patients in this study showed large improvements (39.9-162.4%) in primary position; 3 showed moderate NAFX improvements (13.9-32.6%); 1 showed no NAFX change (due to his high pre-tenotomy NAFX). The seven patients who had narrow, high-NAFX, gaze-angle regions pre-tenotomy showed broadening of these regions post-tenotomy. All patients had reductions in nystagmus amplitudes ranging from 14.6-37%. Foveation-period duration increases for all 9 patients ranged from 11.2-200%. The patient in Figure 4-2 had an NAFX increase of 39.9% (from 0.371 to 0.519) in primary position, and a much-broadened area of improved visual function post-surgically.

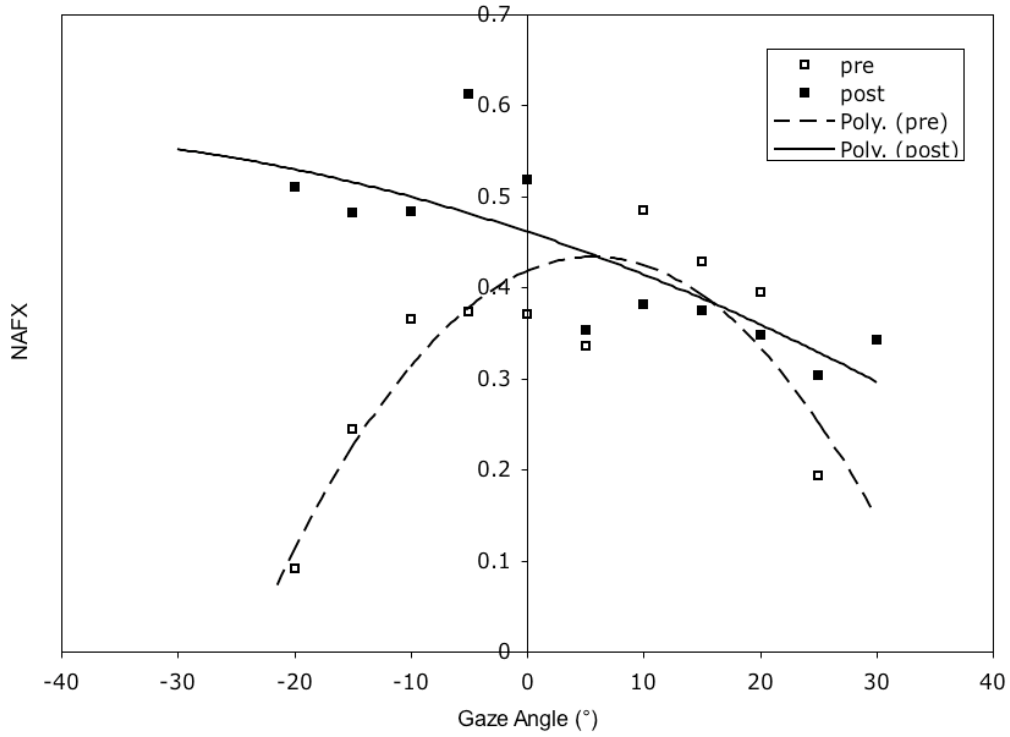

Figure 4-2. NAFX improvement of one INS patient both in primary position and at lateral gaze angles. A much-broadened post-surgical curve demonstrates elevated visual function over a larger visual domain.

This study showed the percentage increases in both the NAFX and LFD decreased as their pre-tenotomy values increased respectively. Thus, the worse the pre-surgical NAFX is, the higher percentage improvement the patient could expect to receive, both in terms of visual acuity elevation and high-acuity region broadening. Only patients with *both* a high primary-position NAFX (>0.6) and a large LFD (>25°) would not be expected to receive either NAFX or LFD improvement from tenotomy; all others remain candidates. The NAFX analysis, for the first time, enabled the *prediction* of post-tenotomy improvements. Figure 4-3 shows the NAFX and LFD percentage increase curves, demonstrating that, above the age of 6, there were no age effects in either the NAFX or the LFD curves.

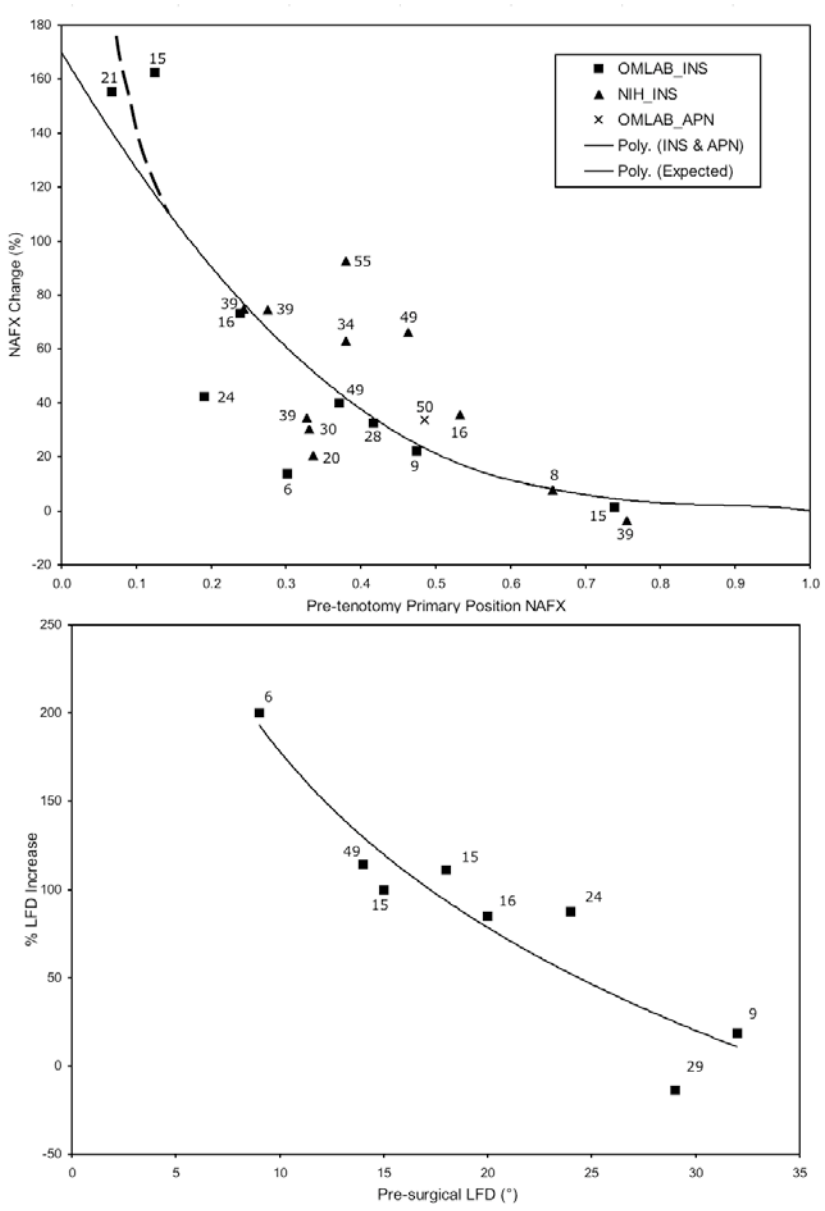

Figure 4-3. NAFX percentage change vs. pre-tenotomy NAFX curve (top) and LFD percentage change vs. pre-tenotomy LFD curve (bottom), including data from several trials (Hertle, et al., 2003; Hertle, et al., 2004; Tomsak, et al., 2005; Z. Wang, et al., 2006). The solid line is an exponential curve fit of the data; the dashed line is tailored at one end to demonstrate the expected curve when more data become available. All data points are accompanied by the age of the patient.

See-Saw Nystagmus

The Stage 1 surgery performed on the sheepdog from the achiasmatic family only damped the horizontal component of the congenital nystagmus; the SSN component was unchanged. Stage 2 was performed 4 months after Stage 1; all four vertical rectus and all four oblique muscles were tenotomized and reattached at their original insertions. Reduction in the vertical and torsional nystagmus components was documented by post-surgical videotape, and eye-movement recordings showed the absence of the vertical component over a 25-second fixation interval. The SSN was barely perceptible in primary position on visual inspection. These effects remained for at least 8 months when postmortem anatomic studies confirmed that the dog was an achiasmatic mutant (Dell'Osso, et al., 1999). This 2-stage tenotomy procedure of *all* extraocular muscles provided a possible therapy for those rare individuals with INS and SSN that accompany human achiasma (Dell'Osso, 1996; Dell'Osso, Williams, Jacobs, & Erchul, 1998). Subsequently, this two-stage, all-muscle procedure has been successfully applied to two human achiasma patients to damp both their INS and SSN (R.W. Hertle, personal communication).

Horizontal and Vertical Acquired Pendular Nystagmus

A horizontal tenotomy was performed on a 50 year-old man with MS, in combination with a horizontal strabismus procedure (bilateral, lateral rectus muscle recessions) to treat an existing exotropia (Tomsak, et al., 2005). The patient had intractable oscillopsia that had been slowly progressing over the prior 8-9 years due to his multiplanar acquired pendular nystagmus (APN). A two-stage surgical approach was

planned similar to that employed in treating the achiasmatic Belgian sheepdog (Dell'Osso, et al., 1999). Based on these experiences and those of others in patients (especially children), no anterior segment ischemia problems will occur if a second, vertical stage was done after circulation in the operated region has been re-established, although risks might be involved.

Stage 1 was a four-muscle tenotomy of the horizontal rectus muscles combined with recessions of both lateral rectus muscles (to correct his exotropia). Following the combined procedure, APN decreased by ~50% and NAFX values in primary position increased by 34%. Measured Snellen visual acuity increased 100% from 0.125 to 0.25. Voluntary saccades and abducting saccadic pulses of INO were unaffected. The exotropia was reduced to less than 2°. In addition to damping the horizontal component of the APN, tenotomy also damped the vertical and torsional components to a lesser degree. The patient reported reduced oscillopsia after the Stage 1 operation.

Stage 1 was to be followed, in 4-6 months, by a Stage 2 procedure (vertical rectus-muscle tenotomies to damp the vertical component) if vertical oscillopsia was still interfering with the patient's visual function. However, memantine became available and was prescribed (Mobius, Stoffler, & Graham, 2005; Starck, Albrecht, Pollmann, Straube, & Dieterich, 1997). The dosage increased over six weeks to a daily dose of 40 mg (twice the dose used for Alzheimer's disease) without complication. After 6 weeks, the APN was damped an additional 69% and NAFX increased by an additional 9%. Visual acuity further increased to 0.4 (60%). Other drugs' effects on damping nystagmus have also been investigated (Averbuch-Heller, et al., 1997; Bandini, Costello, Mazella, Mancardi, & Solaro, 2001).

In this case of multiplanar APN, the cumulative effects of tenotomy + memantine were: APN reduced by 82%; NAFX increased by 46%; acuity increased by 220%; and oscillopsia reduced by 75%. This dual-mode therapy, with the tenotomy damping the slow-phase eye movements peripherally and memantine reducing the central nystagmus signal, optimized the improvement of visual acuity and reduction of oscillopsia in this APN patient. No substantial post-operative changes in saccadic dynamics, smooth-pursuit, optokinetic, or vestibular eye movements were observed.

Horizontal, Uniocular Acquired Pendular Nystagmus

A two-muscle tenotomy was performed on a 39 year-old female with MS, who experienced reduced vision and intractable oscillopsia in her right eye (Dell'Osso, et al., 2006). Her vision was 20/100 in the affected right eye and 20/20 in the normal left eye. A clinically evident horizontal pendular nystagmus was documented by videotape; the nystagmus was also only in her right eye. Six weeks after surgery, her right-eye nystagmus was substantially reduced (confirmed by video tape) and her visual acuity was 20/70 OD. She had no complications from the tenotomy. She also reported a marked reduction in the oscillopsia.

Acquired Downbeat Nystagmus

A *vertical* (Anderson + strabismus + tenotomy) procedure was performed on a 44 year-old man who had predominantly vertical nystagmus (downbeat nystagmus) and intractable oscillopsia for 14 years (the oscillopsia was resistant to drug therapy) (Z. I. Wang, et al., 2007). The patient had a marked chin-down position and had right-eye

hypertropia of 7° and esotropia of 3-5°. Superior rectus muscles were recessed asymmetrically to simultaneously rotate both eyes downward and reduce the right hypertropia; both inferior rectus muscles were tenotomized to complete the 4-muscle tenotomy.

This combined procedure elevated the patient's primary-position NAFX values by 17% and visual acuity increased 25% from 20/25 to 20/20+1. The reduction of vertical-component amplitude was ~46%, which agreed with his post-surgical observations that the oscillopsia was reduced by half. Vertical NAFX values increased across the -10° to +5° vertical visual range, suggesting improved visual function in this region. His NAFX peak, which used to be at 10° up, was moved to primary position (eliminating the chin-down position). His INS foveation improvement and amplitude reduction are demonstrated in Figure 4-4. The time of the cycle spent in the dashed box (the foveation window) contributes to clear and stable vision; the much increased time in the foveation window post-surgically indicates elevated visual function. The right hypertropia was reduced to 3-4°. Figure 4-5 shows the reduction of strabismus on monocular viewing; also note that the amplitude of downbeat nystagmus was greatly reduced. Combined strabismus and nystagmus surgeries provided individualized treatment for the patient's visual function. As a simple, low-risk, one-time surgical therapy with no long-term side effects or costs, tenotomy should be considered for treatment plans of acquired nystagmus.

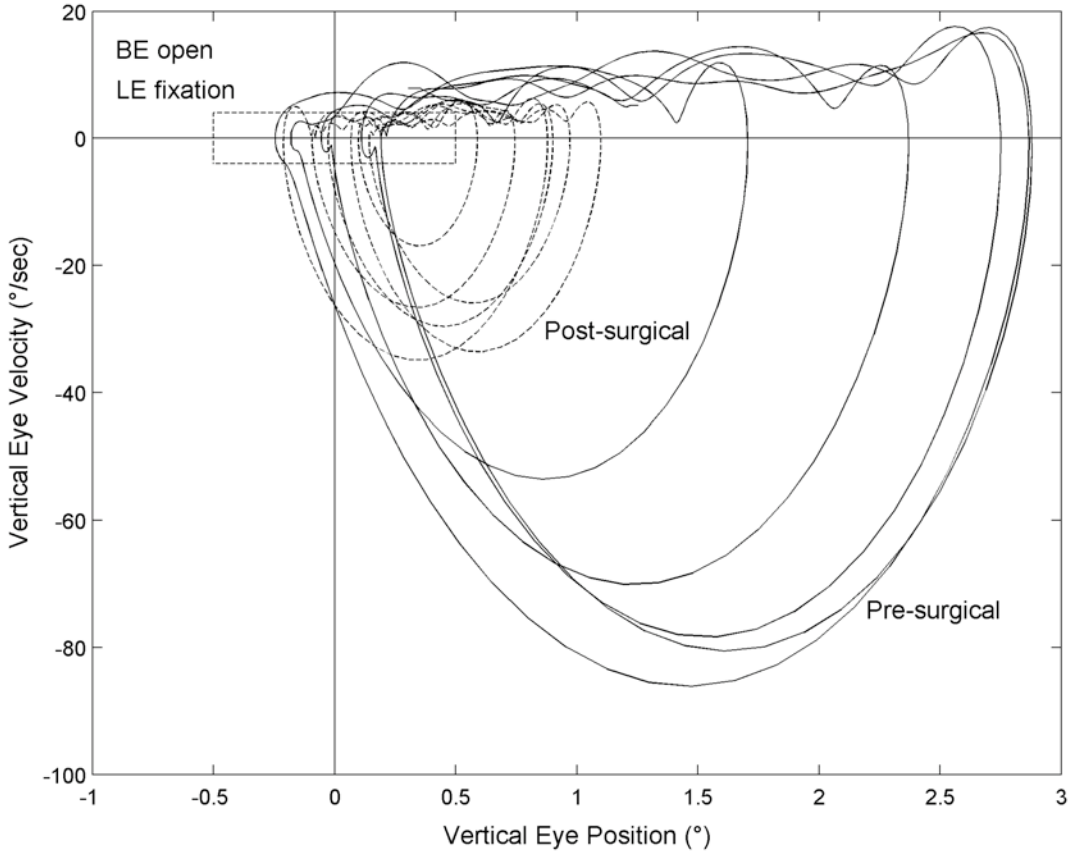

Figure 4-4. Phase-plane of the downbeat nystagmus patient's primary-position fixation data. BE = both eyes; LE = left eye. The dashed box indicates the foveation window (velocity and position thresholds for clear and stable vision).

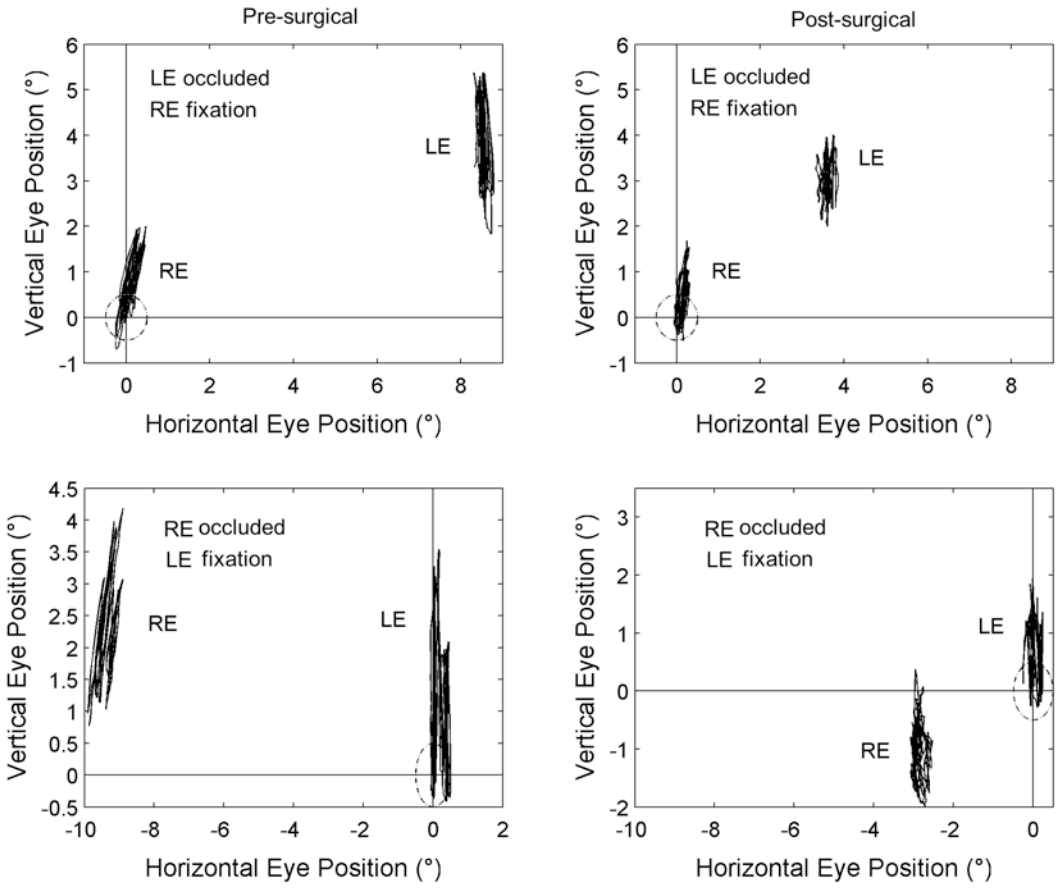

Figure 4-5. Pre-surgical (left) and post-surgical (right) reductions of hypertropia and nystagmus amplitude in the downbeat nystagmus patient, monocular viewing in primary position. LE = left eye; RE = right eye. The dashed circle indicates the fovea (± 0.5° around the target position).

4.4 Discussion

The tenotomy procedure represents a new direction in nystagmus surgery. It is the antithesis of strabismus procedures that rely on movement of one or more muscles to achieve their desired repositioning of the eyes; tenotomy is an integral part of recessions or resections. It is the purest form of nystagmus surgery, relying only on reducing the plant gain to unchanged nystagmus signals without any muscle repositioning. As such, tenotomy is applicable to a population of individuals with INS who exhibit no gaze- or vergence-position improvements in waveform or those whose null is in primary position; prior to tenotomy, these patients would not have received any surgical therapy. In addition, because of its different mode of action, tenotomy works synergistically with muscle-moving procedures and should be combined with them to maximize nystagmus damping, waveform improvement, and potential acuity improvement (i.e., tenotomize the remaining muscles in the plane of action of the nystagmus along with the recessions and resections).

In conjunction with the NAFX method of waveform analysis, the visual acuity improvements of tenotomy can now be predicted *a priori*. That is, based on the pre-tenotomy NAFX value and the measured visual acuity, we can now estimate the percentage improvement in NAFX, and therefore, measured acuity, as a result of tenotomy. Figure 4-6 demonstrates the procedure used to estimate the post-tenotomy measured visual acuity from the pre-tenotomy NAFX and measured visual acuity values. The ability to inform patients how much their nystagmus may improve is unique in the history of nystagmus surgery and could not be done without the advent of the NAFX measure of waveform quality (Dell'Osso & Jacobs, 2002). The NAFX at different gaze

angles has provided a way to measure another visual-function benefit of tenotomy, the broadening of the range of gaze angles with higher quality waveforms and therefore, better acuity. The LFD measure graphically demonstrates improvements not evident from measures of primary-position visual acuity (Z. Wang, Dell'Osso, Jacobs, et al., 2006). As described above for the peak NAFX values, the LFD improvement can also be estimated *a priori* providing another benefit that can be discussed with the patient.

The demonstration that tenotomy affects only small signals to the ocular motor plant requires a reevaluation of commonly used linear models of the plant; they simply cannot simulate the effects of tenotomy. Despite the non-linear muscle force relationships, the plant may be approximated by a linear function for small signals because of the push-pull nature of the antagonist pairs of muscles. However, during saccades, the agonist muscle is fully on while the antagonist is turned off; thus, there is no push-pull action and no linearization of the agonist's non-linear action. More accurate plant models that contain this dual-mode operation are needed (Z. Wang, Dell'Osso, Zhang, et al., 2006).

Now that the tenotomy procedure has demonstrated the power of using proprioceptive muscle tension control to damp nystagmus, other methods should be explored to alter the firing rate of the proprioceptive sensors in the extraocular muscle tendons. The approaches to altering the functions of the distal tendons might include: mechanical, merely suturing or otherwise mechanically changing them without actual tenotomy; cryogenic, heat or cold application; or pharmaceutical, microinjection. Thus, mechanical, cryogenic or pharmaceutical tenotomy might preclude the need for surgical tenotomy. Clearly more research into the proprioceptive tension control system is needed

to both better understand its function and use that knowledge therapeutically.

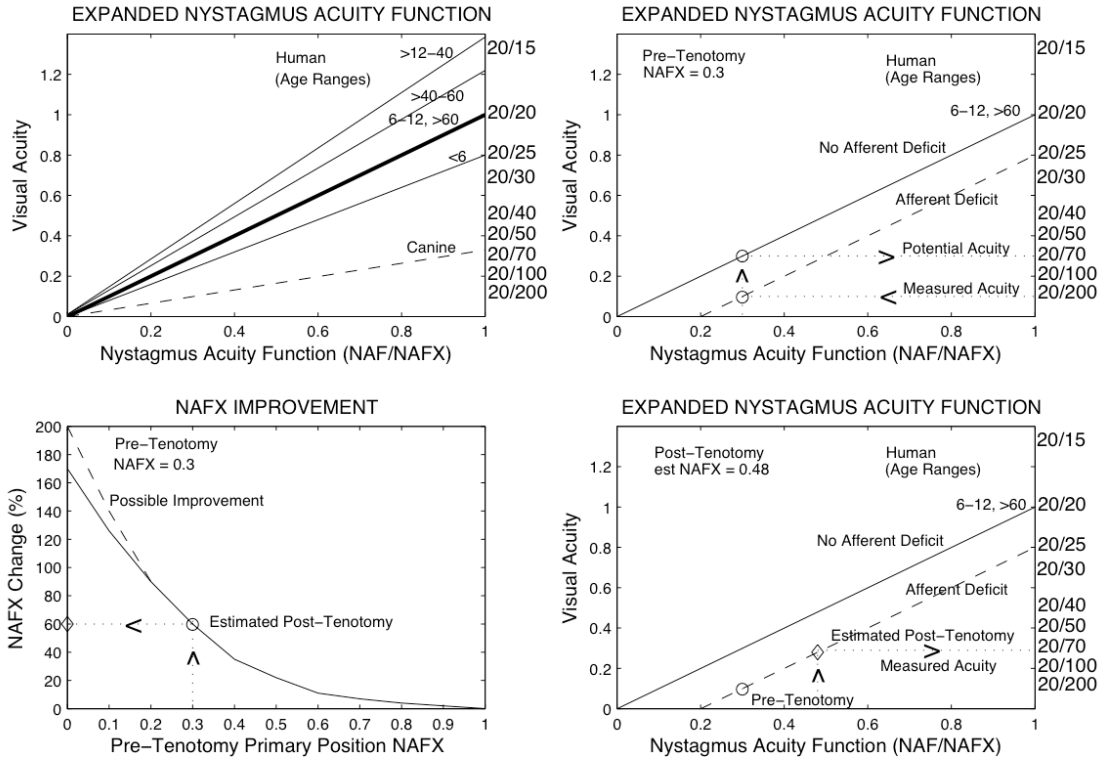

Figure 4-6. Procedure for using pre-tenotomy NAFX and visual acuity measurements to estimate post-tenotomy visual acuity. First (top left), choose the proper age-matched NAFX vs. acuity line. Second (top right), plot the pre-tenotomy NAFX and potential and measured visual acuity points on the graph and draft a dashed line with the same slope as the solid line through the NAFX and measured acuity point. Third (bottom left), plot the estimated post-tenotomy point on the NAFX improvement curve and read off the percentage increase expected in the NAFX. Fourth (bottom right), calculate the expected post-tenotomy NAFX (e.g., 0.3 + 60%(0.3) = 0.48) and plot it on the dashed line. The estimated post-tenotomy measured visual acuity can then be read from the acuity axis of the graph.

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Chapter 5

Tenotomy Does Not Affect Saccadic Velocities: Support for the "Small-Signal" Gain Hypothesis

5.0 Abstract

We investigated the effects of four-muscle tenotomy on saccadic characteristics in infantile nystagmus syndrome (INS) and acquired pendular nystagmus (APN). Eye movements of ten subjects with INS and one with APN were recorded using infrared reflection, magnetic search coil, or high-speed digital video. The eXpanded Nystagmus Acuity Function (NAFX) quantified tenotomy-induced foveation changes in the INS. Saccadic characteristics and peak-to-peak nystagmus amplitudes were measured. Novel statistical tests were performed on the saccadic data. Six out of the 10 INS subjects showed no changes in saccadic duration, peak velocity, acceleration, or trajectory. In the other 4, the differences were less than in peak-to-peak amplitudes (from 14.6% to 39.5%) and NAFX (from 22.2% to 162.4%). The APN subject also showed no changes despite a 50% decrease in peak-to-peak amplitude and a 34% increase in NAFX. The "small-signal" changes (peak-to-peak nystagmus amplitude and NAFX) were found to far exceed any "large-signal" changes (saccadic). Tenotomy successfully reduced INS and APN, enabling higher visual acuity without adversely affecting saccadic characteristics. These findings support the peripheral, small-signal gain reduction (via proprioceptive tension control) hypothesis. Current linear plant models, limited to normal steady-state muscle tension levels, cannot explain the effects of the tenotomy.

5.1 Introduction

Infantile nystagmus syndrome (INS),(CEMAS_Working_Group, 2001) previously known as congenital nystagmus, is an ocular motor disorder characterized by involuntary oscillations of the eyes secondary to, as the term implies, specific disorders in several ocular motor subsystems. INS frequently accompanies additional afferent defects of the visual sensory system such as albinism, achromatopsia, congenital cataracts, optic nerve and/or foveal hypoplasia. When it occurs without other sensory deficits, INS may still reduce visual acuity to a variable extent, depending on the foveation characteristics of the nystagmus waveform.(Dell'Osso & Jacobs, 2002)

Currently INS cannot be cured, but its effects can be treated. To reduce the intensity of nystagmus, these treatments act by either reducing the nystagmus signal centrally (drugs), or affecting the oscillation peripherally (surgery or prisms). A successful treatment may increase the visual acuity at the primary/null position and also broaden the range of gaze angles at which good foveation takes place.

The Kestenbaum resection and recession procedure has been performed for decades with a high success rate (Dell'Osso & Flynn, 1979; Zubcov, Stärk, Weber, Wizov, & Reinecke, 1993). Eye-movement studies revealed that Kestenbaum procedure not only shifts the nystagmus null but also produces several beneficial and long-lasting secondary effects, most notably a broadened null region and an overall reduction in nystagmus intensity at all gaze angles.(Dell'Osso & Flynn, 1979) These effects suggested that much of the improvement could be achieved by simply tenotomizing the four horizontal rectus muscles and reattaching them at their original insertions (Dell'Osso, 1998; Dell'Osso, Hertle, Williams, & Jacobs, 1999), extending the treatment to those

individuals with nulls at or near primary position, who had not previously been considered surgical candidates.

Four-muscle tenotomy is hypothesized to improve INS waveforms by interfering with a proprioceptive feedback loop that controls muscle tension, effectively reducing the small-signal gain of the ocular motor plant, i.e., how the globe responds to low-intensity neural signals. Eye-movement studies have demonstrated the effectiveness of four-muscle tenotomy in reducing the small-signal gain of the ocular motor plant, thus improving INS and APN subjects' visual acuities.(R.W. Hertle, et al., 2003; R. W. Hertle, Dell'Osso, FitzGibbon, Yang, & Mellow, 2004) However, the effects of this surgery on voluntary and breaking saccades, which are the plant's response to large signals, have never been evaluated. According to the small-signal gain hypothesis, *only* the small-signal gain is reduced, which means saccades should not be affected. To test this hypothesis, this study examined the effects of tenotomy on the peak velocity, duration, acceleration and trajectory of saccades. For each of the 11 subjects, data analysis was based on observations of approximately 50 saccades whose amplitude ranged from close to zero to the largest exhibited by the subject (some subjects only made small saccades, e.g. 5° in amplitude, and arrived at the target via their nystagmus slow phases, while others made 50° saccades).

5.2 Methods

Subjects and Protocol

We studied 10 subjects with INS and 1 with MS and APN. Written consent was obtained from subjects before the testing. All test procedures were carefully explained to

the subject before the experiment began, and were reinforced with verbal commands during the trials. Subjects were seated in a chair with headrest or a chin stabilizer, far enough from an arc of red LEDs to prevent convergence effects (>5 feet). At this distance the LED subtended less than 0.1° of visual angle. The room light could be adjusted from dim down to blackout to minimize extraneous visual stimuli. An experiment consisted of from one to ten trials, each lasting under a minute with time allowed between trials for the subject to rest. Trials were kept this short to guard against boredom because INS intensity is known to decrease with inattention.

Surgical Procedure

The conjunctiva and Tenon's capsule is incised near the insertion of the tendon (enthesis) and the tendon grabbed on a hook; the anterior Tenon's is gently freed from the tendon insertion. A suture is placed 1.0 mm posterior to the tendon insertion, the tendon is disinserted, and the needles are placed immediately through the original insertion site and the tendon pulled back up to the original insertion. The Tenons and conjunctiva are closed with an interrupted suture in one layer ("Parks fornix" approach to extraocular muscle surgery). The only tissues disrupted include the: a) conjunctiva near the muscle insertion; b) anterior Tenon's capsule near the muscle insertion; and c) EOM enthesis. The only "damage" done to another tissue when doing tenotomy is incising the conjunctiva and repositioning is at its former location at the end of surgery; this has no mechanical effects on orbital anatomy. We did not intentionally isolate, cut, or otherwise modify the muscle pulleys (“check ligaments”).

Recording

Infrared reflection was used for 8 INS subjects, high-speed digital video for 2 INS subjects, and magnetic search coil for the APN subject. The infrared reflection system (Applied Scientific Laboratories, Waltham, MA) was linear to 20° in the horizontal plane and monotonic to 25-30° with a sensitivity of 0.25°. The total system bandwidth (position and velocity) was 0-100 Hz. The data were digitized at 500 Hz with 16-bit resolution. The digital video system (EyeLink II, SensoMotoric Instruments, Boston, MA) had a linear range of ±30° horizontally and ±20°vertically. System sampling frequency was 500 Hz, gaze position accuracy error was 0.5°-1° on average, and pupil size resolution was 0.1% (0.02 mm change in diameter reliably detectable). Data from this system were digitized at 500 Hz with 16-bit resolution. The IR or EyeLink signal for each eye was calibrated with the other eye behind cover to obtain accurate position information; the foveation periods were used for calibration. Eye positions and velocities (obtained by analog differentiation of the position channels) were displayed on a strip chart recording system (Beckman Type R612 Dynograph). The search-coil system (C-N-C Engineering, Seattle, WA) had a linear range greater than 20°, a sensitivity of 0.1°, and crosstalk less than 2.5%. Each coil was pre-calibrated using a protractor device. The total system bandwidth was 0-100 Hz; the data were digitized at 500 Hz with 16-bit resolution. Monocular primary-position adjustments for all methods allowed accurate position information and documentation of small tropias and phorias hidden by the nystagmus.

Analysis

All the analysis except for the statistics was done in MATLAB environment (The MathWorks, Natick, MA) using custom-written software (OMtools, available from http://www.omlab.org). Only eye position was sampled directly; velocity was derived from the position data by a 4^{th}-order central-point differentiator; acceleration was derived from the velocity data by the same differentiator. Position data were pre-filtered with a low-pass filter with the cutoff frequency of 50 Hz to reduce the noise while minimally affecting the data. The differentiating and filtering were applied equally to the pre- and post-data sets to ensure consistency. A mixture of voluntary and breaking saccades were picked throughout the records to provide a statistical pool at each saccadic amplitude. Only horizontal eye movements were analyzed in this study. The analysis was always performed on the fixating eye. The post-surgical records examined in this study were obtained at least 3 months after the procedure; it was reported that visual functions stabilized before this time and remained stable thereafter.(R.W. Hertle, et al., 2003)

Because of the continuous eye movements of nystagmus subjects, saccadic characteristic definitions must take into account the baseline velocity and eye position at the time the saccade is made. In this study, saccade duration was defined as the time between the beginning and end of the saccade as determined by the velocity record; saccade peak velocity was measured from the *initial velocity* of the saccade (the underlying slow-phase velocity) instead of from zero. Saccade amplitude was defined as the distance the eye traveled between the velocity-derived and position-derived saccade onset/offset times added to the position-derived amplitude. Figure 5-1 shows the results

of the interactive program used to pick the onset/offset points that determine saccadic characteristics.

The saccadic amplitude should not only include the peak-to-peak difference, but also take into account the fact that at the beginning of the saccade the eye was moving with great velocity in the other direction due to the INS slow phase. Either a_i or f (as shown in Figure 5-1) could serve as a decent approximation of the factor described above; we chose a_i in this study, making A+ a_i the corrected saccade amplitude. These modifications were proven to be appropriate and necessary for saccade analysis of nystagmus subjects. Further details can be found elsewhere.(Jacobs, Dell'Osso, & Leigh, 2003) This analysis was performed for all INS subjects; in the case of the APN subject, a fixed velocity threshold of 20°/s was applied since the underlining pendular component was rather constant in velocity and low in amplitude. Again, for each subject, pre- and post-analysis methodologies were applied consistently.

The points at which the velocity reverses determine the beginning and end of a saccade. This method is different from the "fixed-threshold" method, where the first point that exceeds a pre-defined threshold baseline velocity (e.g., 5°/s) is regarded as the onset point. This is because the slow-phase velocity is always changing in INS waveforms, making it impossible to use one fixed threshold.(Jacobs, et al., 2003) Peak velocity should be measured from the baseline velocity, since measuring the velocity from zero would ignore a large segment of the saccade and lead to a lower value for the peak velocity. This effect was first recognized by Winters et al. (Winters, Nam, & Stark, 1984).

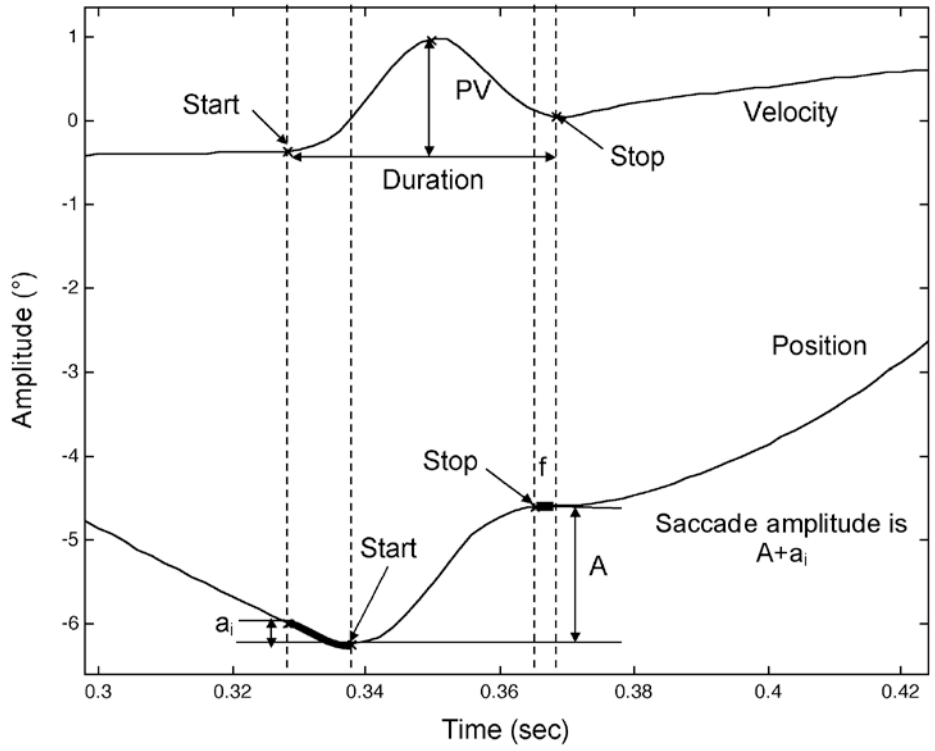


Figure 5-1. Definitions used to determine saccadic characteristics. Bottom trace shows position, top shows velocity. Actual values for the velocity are 50 times larger than shown on the Figure. The outer two dashed lines show the start and stop points of the saccade as determined by the velocity data. 'PV' denotes the measurement for peak velocity. 'A' is the classical definition of saccade amplitude. The heavy segment 'a_i' on the position trace is the distance the eye traveled between the velocity- and position-derived onsets; 'f' denotes the distance traveled between the position- and velocity-derived offsets; 'a_i' is used here for the modification of the saccade amplitude. Thus, the saccade amplitude used in this study is A+ a_i.

The eXpanded Nystagmus Acuity Function (NAFX) and the peak-to-peak nystagmus amplitude were used to measure tenotomy-induced changes in the nystagmus.(Dell'Osso & Jacobs, 2002) The NAFX is a mathematical function that linearly relates nystagmus waveform to the maximum possible visual acuity, assuming no afferent visual deficits. Details about the NAFX may be found elsewhere.(Dell'Osso & Jacobs, 2002)

Pre- and post-surgical peak-to-peak amplitude at the primary position were measured by taking the average of 16 samples of peak-to-peak amplitude from different nystagmus cycles. The samples were chosen randomly throughout the records. Inattention periods and blinks were avoided.

Statistical analysis was performed using SigmaPlot (Systat Software Inc, Richmond, CA) and R (Open-source Environment for Statistical Computing and Visualization). Saccadic peak velocities and durations were plotted vs. saccadic amplitudes pre- and post-surgically. To evaluate the changes in a statistical manner, a variety of tests in SigmaPlot were applied to the pre- and post-tenotomy data sets. To determine whether the changes are significantly different requires a statistical examination of either the data points or the fitted curves both pre- and post-surgically. For examination of the data points, the data sets need to be paired. That was not possible in our case: since saccades picked throughout the records were not necessarily at the same amplitude pre- and post-tenotomy. We tried to fit exponential curves in SigmaPlot, but encountered convergence problems because of the variability in the data, especially the duration data. These issues made it difficult to find an appropriate testing methodology.

To overcome these difficulties, we turned to a new statistical test procedure recently developed and implemented in the Department of Statistics at Case Western Reserve University. Ctest can determine if two curves measured with errors are statistically equal (Zhang, 2005). It does not require the two data sets to be paired up but does require both data sets to be in the same domain (e.g., the range of saccade amplitudes), and can be performed assuming either equal or unequal variance. The ctest procedure runs as follows: it first tries to fit a smooth curve for each data set using a local smoothing method, e.g., locfit;(Loader, 1999) it then calculates the tail probability (P value) based on calculated test statistic. If this P value is less than the pre-specified level, the null hypothesis would be rejected, i.e., the hypothesis that there is no significant difference between the two data sets is not true. To fit a smooth curve using locfit, the algorithm calculates the predicted value at each point in the domain by using only a fraction of neighboring data points with a kernel function, e.g., tri-cube function. Curves across the whole domain can thus be fitted. Also calculated were the variations from the smooth curve of each data set, so that the standard deviation at each fitted point can be obtained. At each point, we can calculate the t-statistic. The overall statistic to test if the two fitted smooth curves are equal is defined to be the maximum test statistic over the whole domain:

$$T = \sup_{x \in X} \frac{\left| \hat{f}_1(x) - \hat{f}_2(x) \right|}{std(\hat{f}_1(x) - \hat{f}_2(x))}$$

where $\hat{f}_1(x)$ and $\hat{f}_2(x)$ are the fitted smooth curves (functions) for the two data sets, respectively. Let t_0 be the realized value of T calculated from data, the tail probability or the P value for null hypothesis is:

$$H_0 : P = \Pr(T > t_0)$$

Assuming a significance level $\alpha = 5\%$, if this P value > α, there is no evidence to reject H_0, meaning there are significant changes before and after the procedure. The average distance between these two fitted curves measured the percentage change of saccadic peak velocity.

This statistical method resembles the piecewise-linear approach used by engineers to approximate nonlinear relationships. Here, small intervals are approximated by curve segments that join each other and the statistical analysis is performed on each short segment.

5.3 Results

Peak velocity and duration change

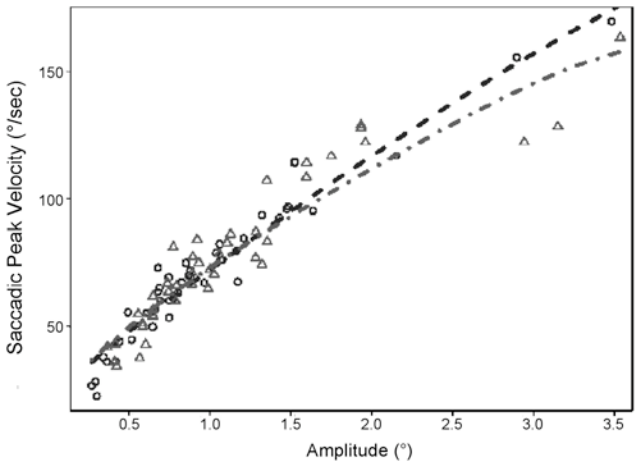
Table 1 shows the P values when using both peak velocity and duration as the measurements for the 10 INS subjects. Subjects were listed in order of the therapeutic improvement measured by NAFX. Because values obtained under both equal and unequal variance assumptions were close, these assumptions do not play an important role in the statistical testing. Six of 10 subjects showed no significant changes (P value > 0.05) in peak velocity; while 8 of 10 showed no significant changes in duration.

INS Subjects (age)	Pre- and Post-Tenotomy P Values			
	Peak Velocity		Duration	
	Equal Variance	Unequal Variance	Equal Variance	Unequal Variance
9 (15)	7.51×10^{-4}	4.89×10^{-4}	0.257	0.259
8 (9)	0.0333	0.0320	0.0967	0.0935
3 (16)	0.279	0.282	0.442	0.419
5 (49)	0.0807	0.0926	0.279	0.295
10 (35)	0.101	0.102	0.281	0.305
2 (21)	7.22×10^{-7}	9.09×10^{-7}	6.66×10^{-8}	6.79×10^{-8}
1 (15)	0.324	0.330	0.110	0.108
7 (28)	0.539	0.539	0.168	0.169
6 (6)	2.87×10^{-5}	2.39×10^{-5}	8.74×10^{-6}	9.78×10^{-6}
4 (24)	0.520	0.523	0.345	0.409

Table 5-1. P Values for INS Subjects using peak velocity and duration as measurements, under equal and unequal variance assumption.

Figure 5-2 shows the scatter plot of peak velocity data for two different INS subjects with the fitted smooth curves superimposed on the plot, one having no significant change and the other having the most significant change (18.7%) as a comparison. The locally fitted curves shown on the plot were obtained using ctest. For the 4 subjects where saccadic velocity did change, the post-surgical fitted curves were always below the pre-surgical curves, indicating slightly decreased peak velocities.

(a)



(b)

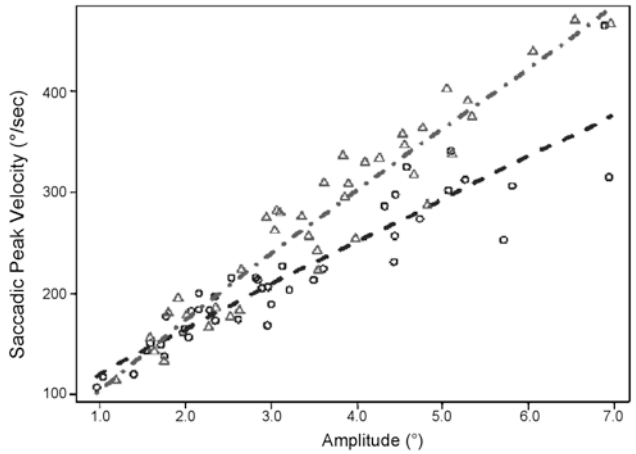


Figure 5-2. Peak saccadic velocity vs. amplitude plots of INS subjects with the smallest (a) and largest (b) peak velocity changes, respectively. In this and Figure 5-3, triangles denote pre- and circles denote post-surgical data. Respective curve fits are shown with dash-dot and dashed lines.

The results of the APN subject are shown in Figure 5-3. Again, peak velocity values were plotted against saccade amplitude. Rightward and leftward saccades are shown separately in (a) and (b). Only normal abduction was examined, and it showed no differences pre- and post-surgically.

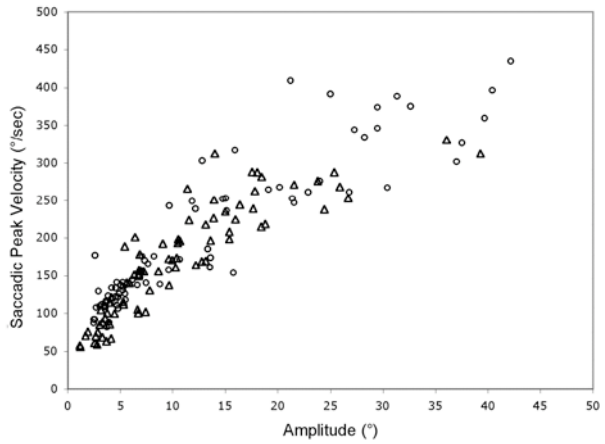
Acceleration and trajectory change

We examined the possibility of more subtle changes in saccades in the 6 INS subjects whose peak velocity remained unchanged. Acceleration and dwell time (defined by the acceleration time / total time of the saccade) were compared. These are the two main factors that determine saccade trajectory. In 5 of the 6 INS subjects, pre- and post-tenotomy values for peak-to-peak acceleration overlapped. All 6 subjects showed no change in dwell time. Overall, there was no difference in terms of acceleration and saccadic trajectory in those INS subjects who showed no difference in peak velocity or duration.

Comparison of NAFX and peak-to-peak amplitude with saccadic characteristics changes

Table 2 summarizes the NAFX increases, the peak-to-peak nystagmus amplitude reductions and the saccadic peak velocity decreases for the INS subjects. Subjects were arranged by the therapeutic improvement measured by NAFX. The tenotomy procedure produced NAFX increases (ranging from 22% to 162%) in 8 of the 10 INS subjects. The remaining two had little change because of high pre-surgical NAFX values. In all subjects, peak velocities were reduced; the percent decrease ranged from 14.6% to 39.5%. As mentioned in previous sections, in 6 of the 10 subjects, saccadic characteristics showed no change; in the other four, there were small changes.

(a)



(b)

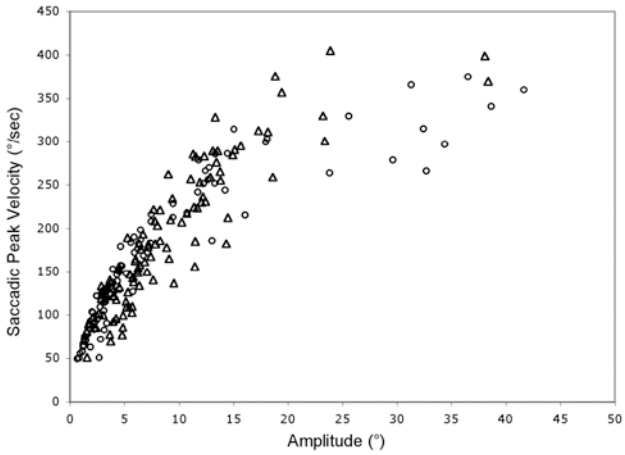


Figure 5-3. Peak saccadic velocity vs. amplitude plots for the APN subject with MS and INO; saccades to the right (a) and left (b) are examined separately. Only normal abduction data (leftward saccades of the left eye and rightward saccades of the right eye) were plotted and examined.

INS Subjects (age)	NAFX* -> Increase	Peak-to-peak Nystagmus Amplitude Decrease	Saccadic Peak Velocity Decrease
1 (15)	0.125 -> 162.4%	19.8%	0%
2 (21)	0.067 -> 155.2%	26.7%	15%
3 (16)	0.239 -> 73%	30%	0%
4 (24)	0.191 -> 42.4%	RE: 28% / LE: 37%*	0%
5 (49)	0.371 -> 39.9%	RE: 27% / LE: 14.6%*	0%
6 (6)	0.2 -> 37.5%	25.4%	18.7%
7 (28)	0.417 -> 32.6%	30%	0%
8 (9)	0.474 -> 22.2%	31%	8.9%
9 (15)	0.739 -> 1.5%	34%	14.3%
10 (35)	0.521 -> 0%	39.5%	0%

Table 5-2. INS waveform changes: NAFX, peak-to-peak nystagmus amplitude, and saccadic peak velocity.

** Subjects whose fixating eye alternated; both eyes were examined for the amplitude decrease in these two cases.*

Examining the 6 subjects whose saccadic characteristics were not changed, five (subjects 1, 3, 4, 5, 7) showed changes in NAFX and peak-to-peak nystagmus amplitude. One subject (subject 10) did not show any change in the saccadic characteristics or NAFX values, but she did have some changes in the peak-to-peak nystagmus amplitude (39.5%).

Examining the 4 subjects whose saccadic characteristics did change, in three (subjects 2, 6, 8), the level of the change was much less than that of both the NAFX and the peak-to-peak nystagmus amplitude. Subject 9 exhibited some idiosyncratic changes; the saccadic peak velocity decreased by 14.3% while the NAFX increased by only 1.4%. The peak-to-peak nystagmus amplitude, however, did decrease by 33.6%, which was greater than the saccade change.

In the APN subject, a 34% increase in the NAFX from 0.485 to 0.648 and a 50% decrease in peak-to-peak amplitude were reported as a result of the tenotomy (Dell'Osso, et al., 2005a, 2005b).

5.4 Discussion

The goals of this study were to examine the characteristics of saccades before and after the tenotomy surgery and to speculate on the possible changes in the ocular motor system that resulted from the tenotomy procedure. We wished to test the small-signal gain hypothesis: tenotomy improves nystagmus waveforms by lowering *only* the small-signal gain of the ocular motor plant. We also intend to incorporate this hypothesis into a new plant model that would help to explain the findings of this study.

Extraocular proprioception probably does not play a role in active (short-term) ocular motor control for there is no stretch reflex in monkeys (Keller & Robinson, 1971). Also, even in the absence of afferent feedback, monkeys were found to make accurate saccades (Guthrie, Porter, & Sparks, 1983). However, neither of these findings preclude either a long-term or short-term stabilization of muscle tension (a "tonic" stretch reflex) in humans that could be altered by the tenotomy surgery (i.e., the neural substrate is

present in the musculotendon and enthesial ends of the muscle tendons and afferent information has been shown to affect ocular motor function, including smooth pursuit) (Mon-Williams & Tresilian, 1998; Eberhorn, Horn, Fischer, & Büttner-Ennever, 2005). To our knowledge, no one has studied the possible role of newly discovered relevant enthesial cells (R. W. Hertle, Chan, Galita, Maybodi, & Crawford, 2002).

Examination of the velocity and duration changes as shown in Table 1, reveals that most of the subjects exhibited no significant changes pre- and post-surgically. We found duration to be a less sensitive measurement, having larger P values and fewer significant changes. This could be explained by the variability of the duration data. Because nystagmus subjects' eye-movement velocities are non-zero before and after each saccade, it is difficult to accurately determine their starting and ending points. This results in a degree of uncertainty in the duration data, as has been reported previously (Jacobs, et al., 2003). The fact that the majority of the INS subjects tested had no saccadic characteristic changes and that the APN subject also showed no changes, support the small-signal gain hypothesis and demonstrate that this peripheral therapy is equally effective for both infantile and acquired nystagmus. The idiosyncratic saccadic changes in some of the INS subjects will be discussed in later paragraphs.

Table 2 demonstrates that changes of peak-to-peak nystagmus amplitude and NAFX were not proportional to changes in saccadic characteristics. As predicted, amplitude change was unrelated to the NAFX-measured therapeutic improvements, is mainly cosmetic, and does not always result from tenotomy (Dell'Osso & Jacobs, 2002; R.W. Hertle, et al., 2003); also, age was unrelated to these changes. In this study, peak-to-peak nystagmus amplitudes were reduced 19.8-35%, implying a reduced plant gain to

small signals post-tenotomy. Peak-to-peak nystagmus amplitude is one measurement of the reduction of slow-phase amplitude. NAFX, however, is an indication of how the ocular motor and visual systems perform in terms of foveation and potential visual acuity; it is an indirect result of the slow-phase changes. As we see from the 10 INS subjects, in most cases tenotomy increases the foveation quality and NAFX values. However, in the presence of high pre-surgical NAFX values, as in subjects 9 and 10, little change could be achieved because the basic curve relating foveation time to acuity is a saturating exponential, leaving little room for improvement at higher levels. Therefore, although in these two subjects tenotomy lowered the plant gain and reduced the peak-to-peak nystagmus amplitude, there could be only limited improvement in NAFX values. Saccadic characteristics were unchanged in most cases because the large-signal gain was unaltered, as predicted by the small-signal gain hypothesis.

The disproportion of the three measurements may be due to changes in the length tension curve of the extraocular muscles induced by the tenotomy. A recent study of muscle insertions of the lateral and medial rectus muscle, involving light microscopy, histochemistry and immunohistochemistry techniques, demonstrated that the tissue at the scleromuscular junction contained striated muscle with minimal connective (tendinous) tissue connecting to the sclera (Jaggi, Laeng, Müntener, & Killer, 2005). Another study of palisade endings using antibodies to a synaptosomal-associated protein (SNAP-25) showed that those endings were not motor and supported the hypothesis that palisade endings were non-nociceptive sensory receptors and could serve a proprioceptive function (Eberhorn, et al., 2005). These studies backed up the proposed mechanism for tenotomy's effects: 1) tenotomy disturbs the proprioceptive feedback loop in such a way

that the cells at the enthesial ends of the “tendons” sense increased tension due to inflammation followed by scarring after the procedure; 2) the proprioceptive feedback loop decreases the tension in the muscles by decreasing the ocular motor discharge rate; and 3) the nystagmus intensity is reduced and foveation quality increased. We propose that the steady-state length tension curve for each muscle is lowered due to the lowered discharge rate, and the net tension curve after the push-pull linearization moves closer to zero. During saccades, however, there is additional tension (to overcome the plant viscosity) (Carpenter, 1988; Collins, 1975; Robinson, 1964) resulting in the elevation of the steady-state length-tension curve. The lowered steady-state length-tension curve resulting from the tenotomy has a less prominent effect at this elevated tension level, leaving the dynamic properties of saccades unchanged. However, the existence of small changes in saccades in subjects 2, 6, 8, 9 suggest some idiosyncratic effects. In these cases, changes of the steady-state length-tension curve may have variable effects on the elevated tension level. More research about the plant and the role of proprioception is needed to fully explain the effects of tenotomy.

When the tenotomy procedure was initially hypothesized, scarring was mentioned as a possible factor in the resulting nystagmus damping (Dell'Osso, 1998). However, the clinical trial results showed damping within several days of the procedure, long before scarring occurs. If it has a role, scarring may add to the initial irritation of the efferent fibers at a later date.

The results in this study serve as supportive evidence for the “small-signal” gain hypothesis of the tenotomy procedure. The complexity of the plant when processing the slow phases and saccades suggests that current linear models are limited to normal

steady-state muscle tension levels and need to be revised. A tentative "top-down" model of two functioning blocks is proposed in Figure 5-4. This preliminary plant model contains two distinct pathways to handle the large and small innervational signals representing, respectively, the high-frequency burst signals and the low-frequency slow eye movement and tonic position signals. Although physiologically there is considerable overlap in peak velocity between very small saccades and high pursuit velocities, the innervational signals responsible for each do not overlap substantially. Saccadic pulse height (representing burst frequency) is very high, even for small saccades and is more a function of acceleration than velocity. High saccadic peak velocities are achieved rapidly due to the duration of the saccadic pulse, not its height, which saturates for saccades over 10°. Thus, even small saccades can have the same velocity-amplitude relationship as large ones. In contrast, smooth pursuit signals have much lower acceleration due to the low-pass nature of the pursuit system. This supports our use of two paths based on the differing characteristics of the *innervational signals*, not the resulting velocity. As mentioned above, the steady-state length-tension curve is lowered due to the tenotomy. In this model a gain-reduction coefficient (between 0 and 1) is used to represent that effect; the coefficient would be different for individual subjects. The saccades are not affected by this coefficient. This new model takes into account the different processing mechanisms for saccades and slow phases in the plant, and can simulate the effects of tenotomy found in this study.

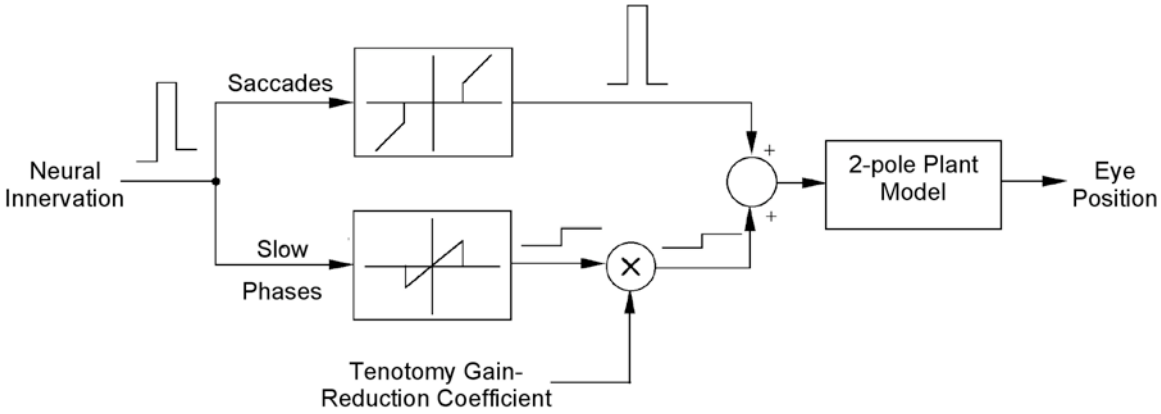


Figure 5-4. Preliminary revised model of the plant. Saccades and slow phases are processed by different nonlinear gain functions and summed as the total output. The slopes of both nonlinearities are nominally set to 1. The tenotomy gain-reduction coefficient is only present in the slow-phase pathway. The combined signal is then sent to the 2-pole plant transfer function.

We believe the data from tenotomized patients support the more peripheral, slow-acting, muscle-tension control hypothesis (i.e., action at the periphery) rather than an alternative efference-copy hypothesis (central action) because the nystagmus slow-phase signal has not been altered by muscle surgery (Dell'Osso, 1998, 2004). The nystagmus signal appears to emanate from the inherent instability in the pursuit system and is *not* related to proprioceptive feedback (Jacobs & Dell'Osso, 2004). Thus, the NI signal would neither be changed by the tenotomy nor account for our results. Additionally, the schema in Figure 5-4 can be used to model peripheral disease that differentially affects saccades (i.e., myasthenia or Lambert-Eaton syndrome) (Abel, Dell'Osso, Schmidt, & Daroff, 1980; Dell'Osso, Ayyar, Daroff, & Abel, 1983; Schmidt, Dell'Osso, Abel, & Daroff, 1980a, 1980b). More robust plant models will require proprioceptive muscle-tension control loops and non-linear gain functions. The above model proposed is only a preliminary one because of the many unknown proprioception-related parameters. New plant models should also be incorporated into a behavioral ocular motor system model(Jacobs & Dell'Osso, 2004) to better observe their effects on ocular motor responses.

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Chapter 6

Being "Slow to See" is a Dynamic Visual Function Consequence of Infantile Nystagmus Syndrome: Model Predictions and Patient Data Identify Stimulus Timing as its Cause

6.0 Abstract

The objective of this study was to investigate the dynamic properties of Infantile Nystagmus Syndrome (INS) that affect visual function; i.e., which factors influence latency of the initial reflexive saccade (Ls) and latency to target acquisition (Lt). We used our behavioral Ocular Motor System (OMS) model to simulate saccadic responses (in the presence of INS) to target jumps at different times within a single INS cycle and at random times during multiple cycles. We then studied the step responses of 4 INS subjects with different waveforms to test the model's predictions. We repeated the patient studies for ramp responses of 5 INS subjects. Infrared reflection was used for 1 INS subject, high-speed digital video for 8. We recorded and analyzed human responses to large and small target-step stimuli, and ramp stimuli with ±10°/s velocities. We evaluated the following factors for step-target acquisition: stimulus time within the cycle (Tc), normalized Tc (Tc%), initial orbital position (Po), saccade amplitude, initial retinal error (e_i), and final retinal error (e_f). We also measured the pursuit gain of the ramp-stimuli responses. The ocular motor simulations were performed using MATLAB Simulink and the analysis was performed in the MATLAB environment, using OMLAB software. Both the OMS model and OMtools software are available from http://www.omlab.org. Our

data analysis showed that for each subject, Ls was a fixed value that is typically higher than the normal saccadic latency. Although saccadic latency appears somewhat lengthened in INS, the amount is insufficient to cause the "slow-to-see" impression. For Lt, Tc% was the most influential factor for each waveform type. The main refixation strategies employed by INS subjects made use of slow and fast phases and catch-up saccades, or combinations of them. These strategies helped the subjects to foveate effectively after target movement, sometimes at the cost of increased target acquisition time. In both step- and ramp-testing conditions, foveating or braking saccades intrinsic to the nystagmus waveforms seemed to disrupt the OMS' ability to accurately calculate reflexive saccades' amplitude and refoveate. The pursuit gains of each INS subject showed marked idiosyncrasy. Our OMS model simulations demonstrated this emergent behavior and predicted the lengthy target acquisition times found in the patient data.

6.1 Introduction

Infantile Nystagmus Syndrome (INS, (CEMAS_Working_Group, 2001) previously known as congenital nystagmus, or CN), is characterized by involuntary oscillations of the eyes and degrades visual acuity to varying degrees (Dell'Osso, 1973; Dell'Osso & Daroff, 1975). Foveation quality in each nystagmus cycle and the ability to repeat accurate foveation from cycle to cycle determine the visual-acuity reduction (Abadi & Worfolk, 1989; Bedell & Loshin, 1991; Dell'Osso & Flynn, 1979; Dell'Osso, Flynn, & Daroff, 1974; Dell'Osso & Jacobs, 2002; Sheth, Dell'Osso, Leigh, Van Doren, & Peckham, 1995). INS frequently accompanies additional afferent defects of the visual

sensory system, which may cause the primary deficit in visual function (Dell'Osso & Daroff, 1997).

Primary-position visual acuity has been measured clinically for decades; however, it is questionable if this single, *static* measurement is sufficient to assess real-life visual function. A previous study in our laboratory showed the necessity of waveform quality measurements taken in lateral gaze for evaluating the tenotomy procedure's null broadening effect (Wang, Dell'Osso, Jacobs, Burnstine, & Tomsak, 2006). These measurements mimic the real-life situation of keeping the head still and looking around with just the eyes, a visual function highly desirable for driving and other daily routines. Assessing this clinically requires measuring visual acuity at different gaze angles (Yang, Hertle, Hill, & Stevens, 2005).

The waveform quality and visual acuity measurements mentioned above, both in primary position and in lateral gaze, are static measures of visual function. In those tests, subjects may be required to fixate on a small light-emitting-diode stimulus against a dark background or look at eye charts and identify letters. However, the real world contains a highly complex combination of object positions and velocities, requiring a mixture of saccadic and pursuit responses. How does the ocular motor system (OMS) perform in this environment, especially in the presence of INS? What factors determine the actual time needed to refoveate a target after it moves? Why do we hear complaints from INS patients that they are "slow to see?" Measurements of the *dynamic* characteristics of INS *foveation* are needed to answer these questions. A previous study on INS patients' recognition time of a fixed optotype target at their threshold visual acuity showed a decrease in recognition time after a four-muscle recession procedure. However, that

study just used “slow to see” as a patient-reported fact, it did not explore the reasons (Sprunger, Fahad, & Helveston, 1997).

For normal subjects, saccadic latency is 200-250 ms and pursuit latency is ~125 ms (Abel, Schmidt, Dell'Osso, & Daroff, 1978; Leigh & Zee, 2006). It is not known if INS subjects have normal saccadic latency. Normal individuals apply strategies like corrective saccades to quickly foveate step stimuli that have large amplitudes. Those with INS do that as well, and have other “tools” that can be utilized, e.g., the fast and slow phases of their waveforms. It would be informative to investigate INS foveating strategies and determine how they contribute to target acquisition.

This study focuses on the responses of INS subjects to step and ramp stimuli with a variety of amplitudes and aims to answer some of the questions asked above. Specifically, this initial study of the dynamic properties of INS foveation will examine possible influencing factors, such as waveform type, stimulus time within the cycle, saccade amplitude, and initial and final retinal error. We will use predictions from our OMS model (Jacobs & Dell'Osso, 2004) to guide and reinforce our data analysis. The OMS model for INS simulated the responses of individuals with several pendular waveforms (pendular with foveating saccades, Pfs, and pseudopendular with foveating saccades, PPfs) based on a hypothesized exacerbation of the normal pursuit-subsystem instability and its interaction with other OMS components. The OMS model consists of smooth pursuit (SP), fixation, and saccadic subsystems, and an “Internal Monitor” (IM) that receives afferent information from the retina plus position and velocity efference copy to determine the control signals that drive these motor subsystems. We will

demonstrate in this study another emergent behavior of this model and how it guided our data analysis to find out the relationship between stimulus timing and target acquisition.

6.1 Methods

Subjects

We studied the step responses of four INS subjects. They had different waveforms at primary position: jerk, pseudocycloid (PC), and pseudopendular with foveating saccades (PPfs) (Table 1). Note that Subject 1 had a pendular with foveating saccades (Pfs) waveform in right gaze and that Subject 3 also had Asymmetric, (a)Periodic Alternating Nystagmus (APAN), i.e., his nystagmus amplitude and null position changed with time.

Subject # for Step Responses	Waveform Type in Primary Position	Waveform Type in Lateral Gaze
S1	PPfs	Pfs in right gaze; PC in left gaze
S2	J	J and PPfs in the null region (-10° to -15°)
S3	**J***	**J***
S4	PC and occasionally, Pfs	PC and occasionally, Pfs

Table 6-1. Subjects' waveform types in primary position and lateral gaze for the step-response analysis. In Tables 1 and 2, * means the subject's jerk nystagmus had a time-varying component, i.e., he had Asymmetric, (a)Periodic Alternating Nystagmus (APAN).

We also studied the pursuit responses of 5 subjects , 4 of whom had Jerk type waveforms and 1 had pendular waveforms.

Subject # for Pursuit Responses	Waveform Type in Primary Position	Waveform Type in Lateral Gaze
P1	JL	JR in right gaze, JL in left gaze
P2	JL	JL
P3	JR and occasionally, Pfs	JR in right gaze, JL in left gaze
P4	J*	J*
P5	PPfs	Pfs in right gaze; PC in left gaze

Table 6-2. Subjects' waveform types in primary position and lateral gaze for the ramp-response analysis.

Recording

Infrared reflection (IR) was used for 1 subject, high-speed digital video for 8. The IR system (Applied Scientific Laboratories, Waltham, MA) was linear to 20° in the horizontal plane and monotonic to 25-30° with a sensitivity of 0.25°. The total system bandwidth (position and velocity) was 0-100 Hz. The digital video system (EyeLink II, SR Research, Mississauga, ON, Canada) had a linear range of ±30° horizontally and ±20°vertically. System sampling frequency was 500 Hz, and gaze-position-accuracy error was 0.5°-1° on average. The data from both systems were digitized at 500 Hz with 16-bit resolution. The IR or EyeLink signal from each eye was calibrated with the other eye behind cover to obtain accurate position information; the foveation periods were used for calibration. Eye positions and velocities (obtained by analog differentiation of the position channels) were displayed on a strip chart recording system (Beckman Type R612 Dynograph). Monocular primary-position adjustments for all methods allowed accurate

position information and documentation of small tropias and phorias hidden by the nystagmus.

Protocol

This study was approved by the local IRB and written consent was obtained from each subject before the testing. All test procedures were carefully explained to the subject before the experiment began, and were reinforced with verbal commands during the trials. Subjects were seated in a chair with headrest and a chin stabilizer, far enough from the stimulus screen to prevent convergence effects (>5 feet). At this distance the LED subtended less than 0.1° of visual angle. The room light could be adjusted from dim to blackout to minimize extraneous visual stimuli. An experiment consisted of from eight to ten trials (including large and small target steps), each lasting under a minute with time allowed between trials for the subject to rest. Trials were kept this short to guard against boredom because INS intensity is known to decrease with inattention. Step stimuli were presented to 4 subjects with a variety of amplitudes (5°, small steps; 15°, 20°, 25°, 30°, 35°, 40°, 45°, 50°, 55°, 60°, large steps), in left and right (all subjects had predominantly horizontal INS). The target was fixed at the new position for at least 5 seconds, allowing subjects enough time for steady fixation. We also studied five INS subjects who pursued a 10°/s ramp target to both left and right. We repeated these presentations to collect a pool of target jumps at different times of the nystagmus cycle, so that we could obtain enough data points for the curve fitting. Target fixation was monitored throughout the recording through the real-time display of the strip-chart recorder and verbally reinforced. The monocular calibration routine and post-recording data calibration allowed us to

determine the fixating eye from the deviated eye and made accurate analysis of the target acquisition possible. Details of accurate eye-movement recording and calibration can be found on http://www.omlab.org/OMLAB_page/Teaching/teaching.html.

Analysis

All the analysis was performed in MATLAB environment (The MathWorks, Natick, MA) using OMLAB software (OMtools, available from http://www.omlab.org). Only eye position was sampled directly; velocity was derived from the position data by a 4^{th}-order central-point differentiator. Position data were pre-filtered with a low-pass filter with the cutoff frequency of 50 Hz to reduce the noise while minimally affecting the saccadic data. Analysis was always done on the fixating eye. Segments with inattention or blinking were discarded.

We evaluated the following factors that might influence the saccadic latency (Ls) and the time to target acquisition (Lt) after the target step: stimulus time within the cycle (Tc), normalized Tc (Tc% = Tc / the length of that nystagmus cycle), initial orbital position (Po), saccade amplitude, initial retinal error (e_i), and final retinal error (e_f). We also recorded: waveform types; number of saccades to achieve target acquisition (including reflexive saccades and fast phases that are modified in amplitude—this number may or may not be equal to the number of cycles taken to reach the target); and direction of target jump vs. foveating saccade.

The measurement of Tc was always made from the beginning of the nystagmus cycle, i.e., the beginning of the foveation period. Figure 6-1 illustrates the four (most common) types of INS waveforms that we examined in this study; subjects may have

combinations of different waveforms as the gaze angle varies. Note that the beginning of each cycle immediately follows the termination of the foveating saccade, except in the case of PC waveforms (foveation occurs after a braking saccade followed by a slow movement of the eye onto the target). Jerk waveforms, which have a less "flat" foveation period than Jef waveforms, were measured with the same criteria as Jef, and therefore, are not shown.

Because of the continuous eye movements of individuals with nystagmus, saccadic characteristic definitions must take into account the baseline velocity and eye position at the time the saccade is made. Saccade amplitude was defined as the distance the eye traveled between the velocity-derived and position-derived saccade onset/offset times added to the position-derived amplitude. This modification was shown to be appropriate and necessary for the analysis of saccades made by nystagmus subjects (Jacobs, Dell'Osso, & Leigh, 2003; Wang, Dell'Osso, Zhang, Leigh, & Jacobs, 2006).

As illustrated in Figure 6-2, Ls, the latency to the initial reflexive saccade, is measured from the target-jump time to the beginning of the reflexive saccade (determined by the turning point of the velocity trace, arrow "a"). Lt, the latency to the target arrival time, is measured from the target-jump time to the beginning of the first foveation period on the target (also indicated by the turning point of the velocity trace, arrow "b"). Due to the variation of foveation quality, we defined "the first foveation period on the target" to be the first foveation period in the subject's foveation window that was followed by subsequent foveation periods within that window. In this particular section (Figure 6-2), the window was quite narrow (the ±0.5° of the fovea). Using the criteria described in the previous paragraph, Tc is shown as the time from the beginning of the current nystagmus

cycle to the target jump. Po (arrow "c"), initial orbital position, is the eye position when the target step occurred. e_i = Po – initial target position; e_f = Po – final target position. The data were fitted with either linear or higher order polynomial curves.

If the subject switched fixating eye after the saccade, the saccade amplitude was not measured, and only the other characteristics were examined. We categorized the data by the waveform type before the target jump, which may not be the same after the target acquisition; we noted such situations to help identify outliers.

In the ramp responses, the following parameters were studied: Lt (measured from the target-ramp initiation to the first on-target foveation period); target pursuit direction; and foveation-period pursuit gain (foveation velocity / target velocity, 1 being the ideal value).

Simulation

All ocular motor simulations were performed in MATLAB Simulink (Waltham, MA) environment. The OMS model is available from http://www.omlab.org.

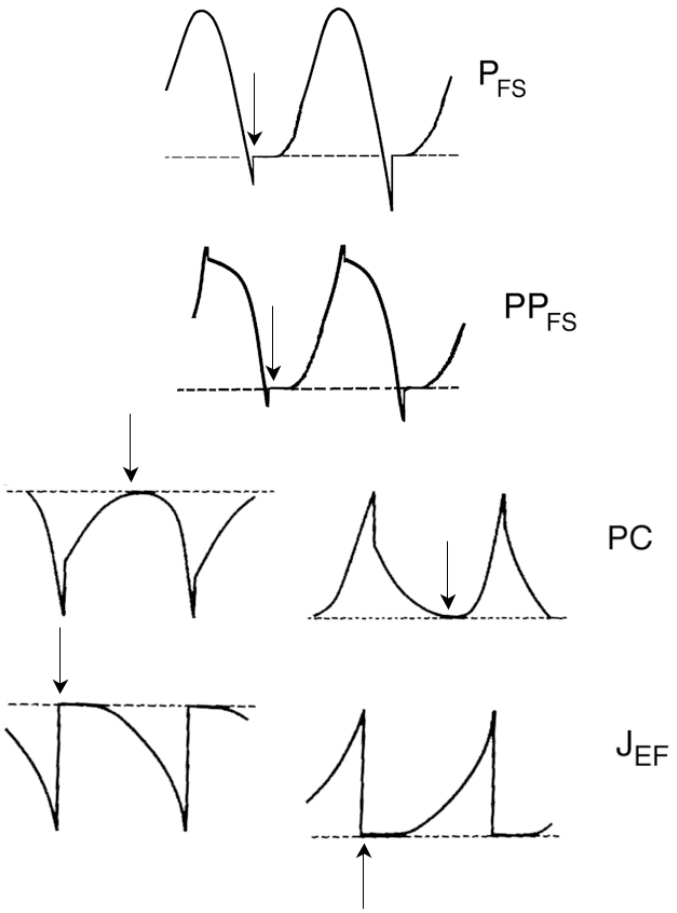

Figure 6-1. Illustrations of the nystagmus waveforms examined in this study. In this and the following figures, Pfs = pendular with foveating saccades; PPfs = pseudopendular with foveating saccades; PC = pseudocycloid; Jef = jerk with extended foveation. Arrows indicate the beginning of the cycle. PC and Jef waveforms are shown in both directions.

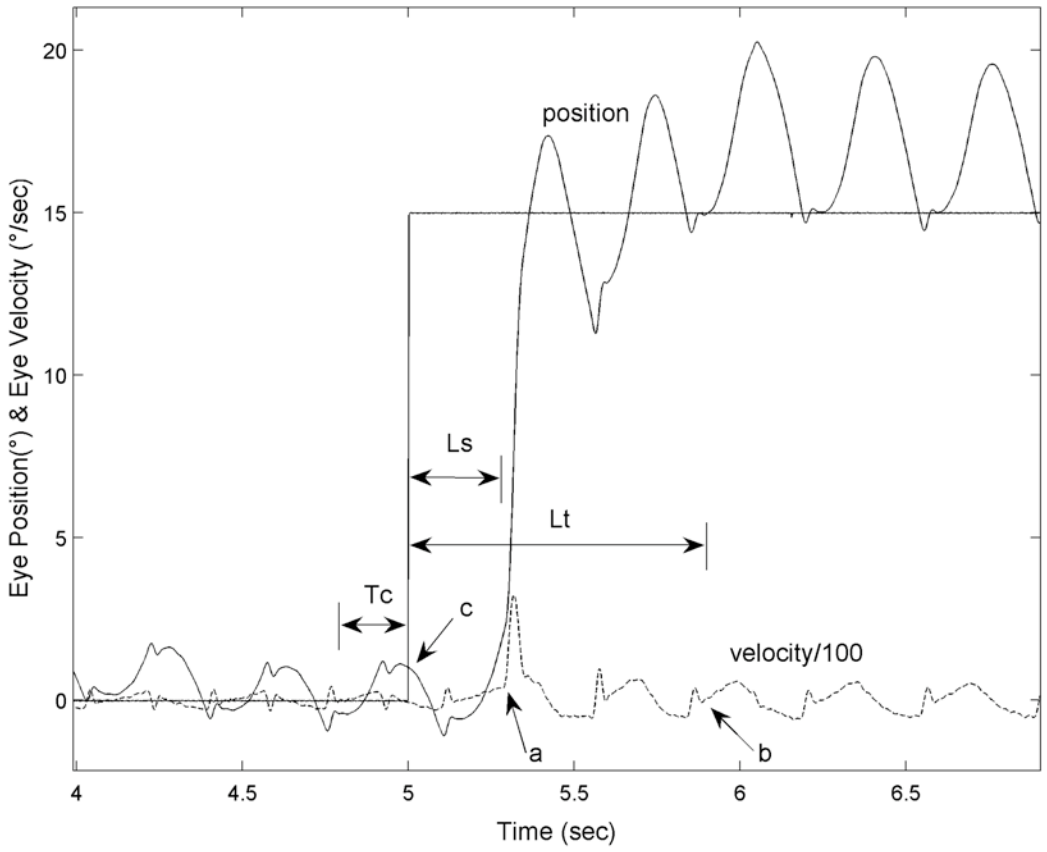

Figure 6-2. Position and velocity traces of a typical response to a 15° rightward target step from primary position (Subject 1). Measurements are indicated on the Figure. Arrow "c" points to the eye position when the target step occurred. In this and the following figures, Ls = latency to the initial reflexive saccade (measured from arrow "c" to arrow "a"). Lt = latency to the target arrival time (measured from arrow "c" to arrow "b"). Tc = time within the cycle.

6.3 Results

In the following sections we present the predictive model outputs, followed by the human response data under two different conditions, large target steps and small target steps. Additionally, we summarize typical foveation strategies employed by INS subjects. Ramp target acquisition will also be shown.

Model Simulations for Pfs and PPfs

We performed model simulations of saccadic responses using two different paradigms. Ls was set to 250 ms in our model; we measured Lt for different stimulus-onset times. Firstly, stimuli were presented at variable times within the same nystagmus cycle (single-cycle paradigm) and secondly, we presented the stimuli to several different nystagmus cycles, also at variable times within each cycle (multiple-cycle paradigm). The single-cycle paradigm was an over-simplified version of the multiple-cycle paradigm; it was used to clearly show the trend in the data. The multiple-cycle paradigm was more realistic and simulated what the INS subjects experienced. Figure 6-3 (a) shows the results of Pfs simulations in the single-cycle paradigm (fitted with two-point moving average) and 3 (b) shows results from the multiple-cycle paradigm (fitted with second-order polynomial). Figures 3 (c) and (d) show PPfs simulations in these same two paradigms. Figure 6-3 (e) and (f) are model outputs of eye positions when the stimuli jumped in different parts of the cycle. Note that for the rightward saccade in (f), the system "misses a cycle", which results in the elongation of target acquisition time (from 510 ms in (e) to 620 ms in (f)). The single-cycle and multiple-cycle curves had the same trend, although the latter had more variation. These model outputs predict that: 1) for

both Pfs and PPfs waveforms, the latency will be larger when target jumps at the beginning or end of the cycle (near the foveating saccade); 2) for the PPfs waveform, the latency will also be larger when target jumps near the middle of the cycle (near the braking saccade). These model predictions will be reinforced in the following sections.

Large Target Steps

Figure 6-4 shows a typical set of Lt data, from Subject 1 who had Pfs waveforms. Except for Tc%, data points were scattered, and little ($R^2 = 0.0479$) or no trend could be found. Attempts to fit linear or polynomial curves to the other data resulted in either a low R^2 value (<0.1), or a low slope (<0.001). Note that, as the model predicted (Figure 6-3 (a and b)), Lt tends to be longer towards the beginning and end of the cycle (Figure 6-4, Lt vs. Tc%), which is where the foveating saccade occurs.

Figure 6-5 shows the results for each waveform type. Note that for all waveforms, Lt tends to be larger if the target step occurs near the embedded foveating saccades. In the case of the PPfs waveform, the system is also prone to error near the braking saccade in the middle of the INS cycle, making Lt larger. Note the similarities between the multiple-cycle model output (Figure 6-3 (b and d)) and the human data (Figure 6-5 (a and b)). In the case of the PC waveform, the curve appears to differ because a braking saccade occurs in the middle of the cycle (defining the beginning of a nystagmus cycle as target foveation) and there is no foveating saccade per se. Transforming the reference starting time to the end of the braking saccade results in a curve that resembles the others, as shown in Figure 6-5. Subject 3 had a time-varying component in his INS (APAN). We noted the amplitude with each data point on his curve, which is an indication of the time

variation in his INS. No influence of the APAN time variation on Lt was found. For some subjects, Lt vs. Tc showed trends with higher R^2 values than Subject 1 in Figure 6-4.

Examination of the data (for all waveforms) revealed that none of the factors seem to influence Ls. Attempts to fit linear or polynomial curves to any of the data sets resulted in either a low R^2 value (<0.01), or a low slope (<0.001). There was no evidence of influence (even Tc%), nor did the APAN subject show any time variance. Since it was not influenced markedly by any of the factors we examined, we averaged Ls for each category, as shown in Figure 6-6. For each category, the averaged value for the initial reflexive saccade fell on the higher end of the normal Ls range of 200-250 ms (indicated by the dashed zone). Idiosyncratic variations among the subjects occurred. Note that waveforms Pfs and PPfs share similar averaged values and variation, since the data came from the same subject (Subject 1), but for different waveforms.

Small Target Steps

INS subjects used additional foveating strategies for smaller steps (5° steps in our recordings). There were often no reflexive saccades associated (no Ls data were available). Details of these foveating strategies are discussed below. Figure 6-7 is a typical set of Lt data illustrating responses under this circumstance. All subjects exhibited the same trend as for the large target-step data, i.e., Tc% was the most influential factor. However, occasionally other factors seemed to have an influence (e.g., Subject 1, Pfs, initial orbital position). The values of Lt were typically smaller than those in the large target-step case. Also, we did not find the direction of target jump vs. foveating saccade influenced Lt or Ls, in either large or small target jumps

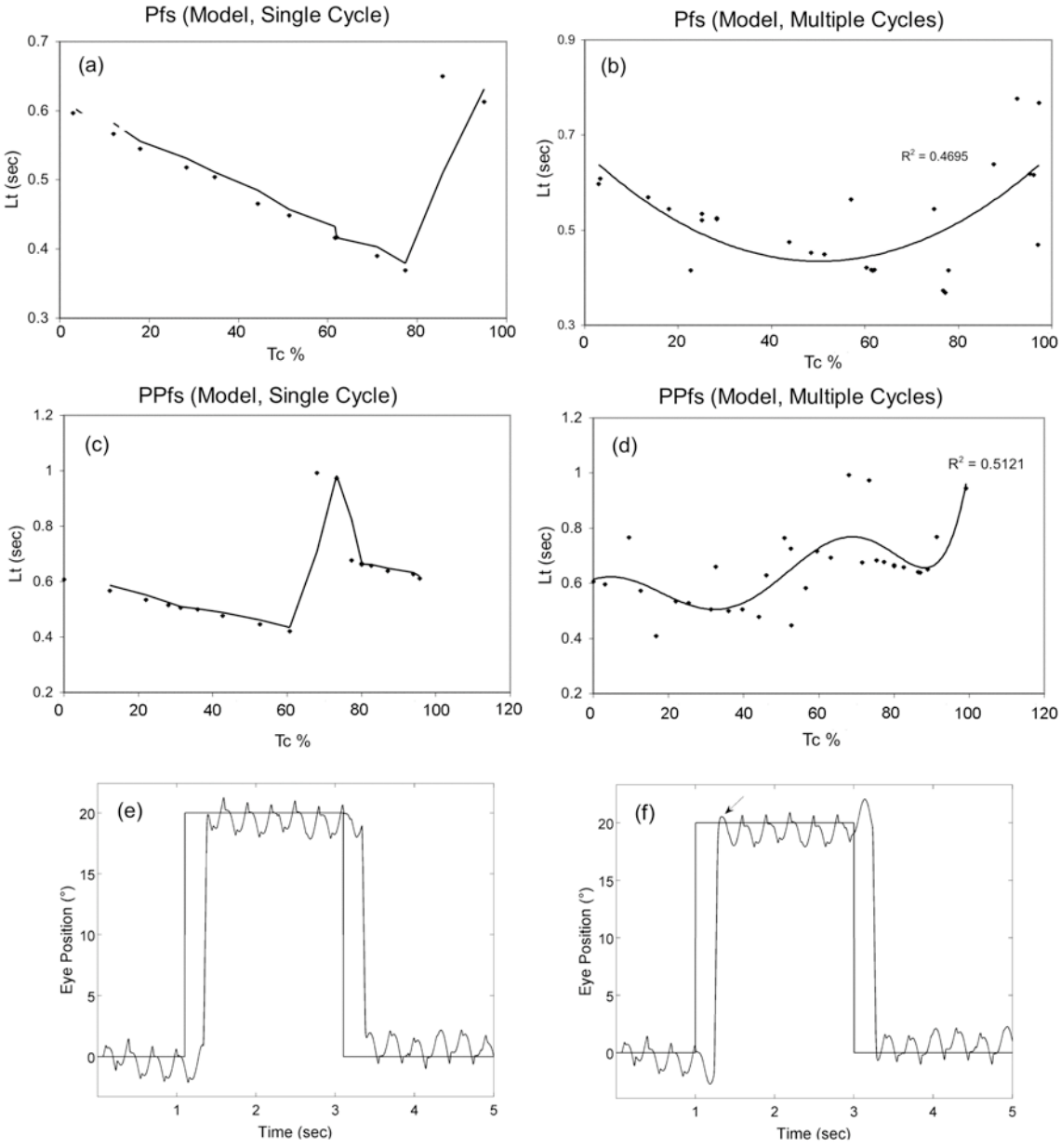

Figure 6-3. Model simulations in multiple-cycle and single-cycle paradigms, both Pfs and PPfs waveforms. (e) and (f) show model response difference with respect to the target timing.

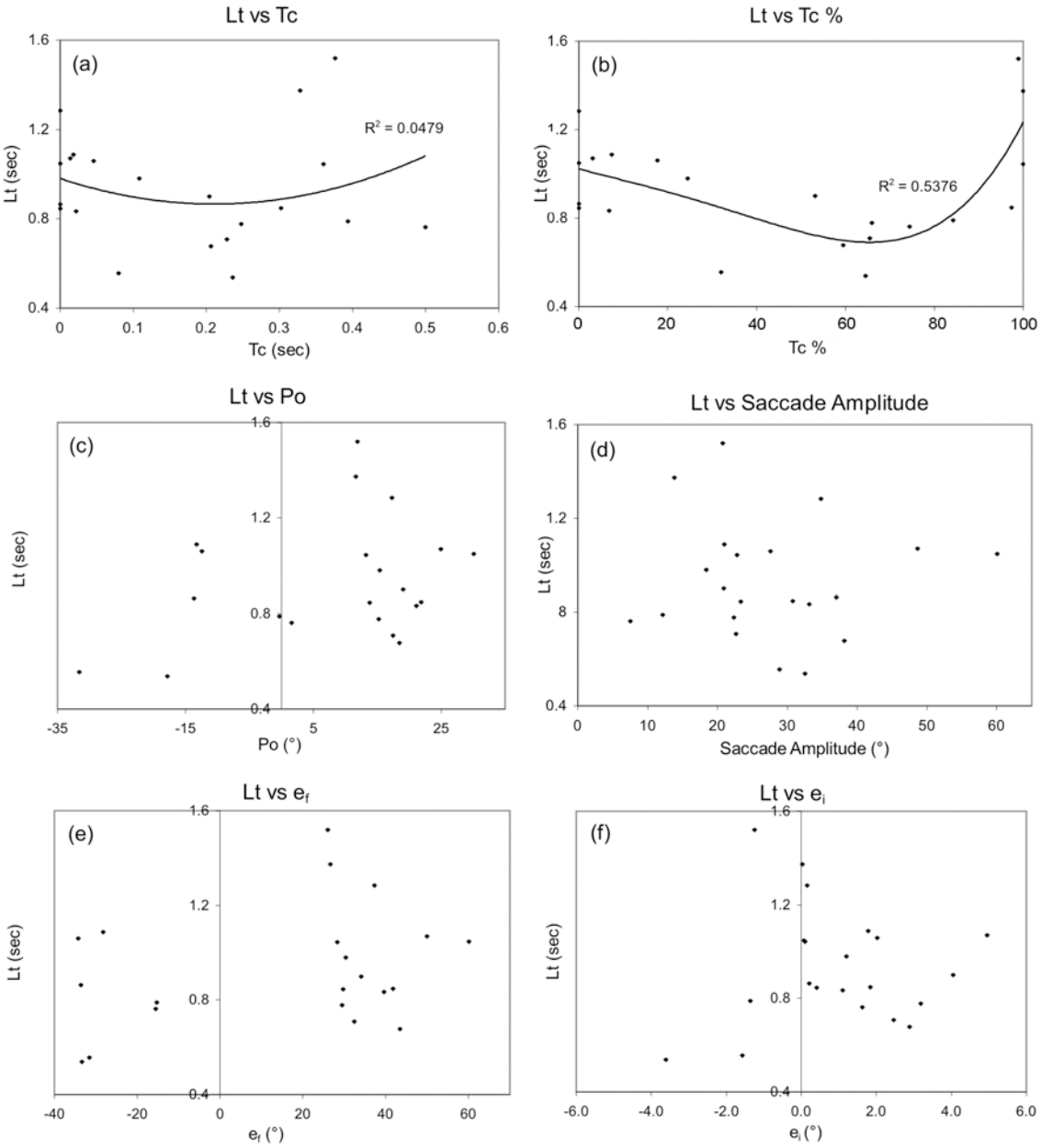

Figure 6-4. A typical set of Lt data (Subject 1, Pfs waveform), in response to large target steps. In this and the following figures, Po = initial orbital position; e_f = final retinal error; e_i = initial retinal error.

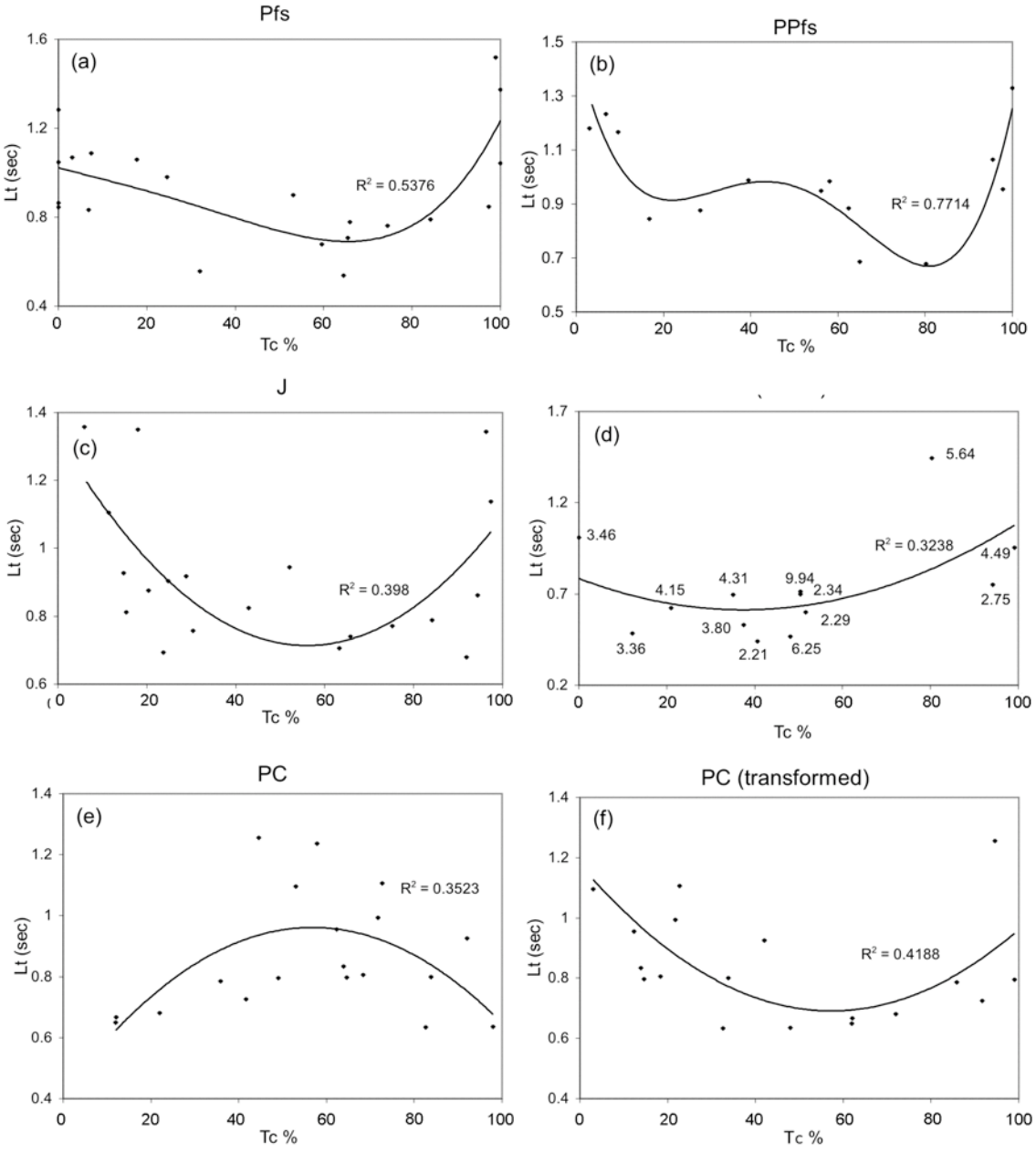

Figure 6-5. Lt vs. Tc% curve for each waveform type, in response to large target steps. In this and the following Figures, J = Jerk, APAN = Asymmetric (a)Periodic Alternating Nystagmus. The subject with a J waveform who also had APAN is labeled as J*, the peak-to-peak amplitude (in °) at each data point is noted.

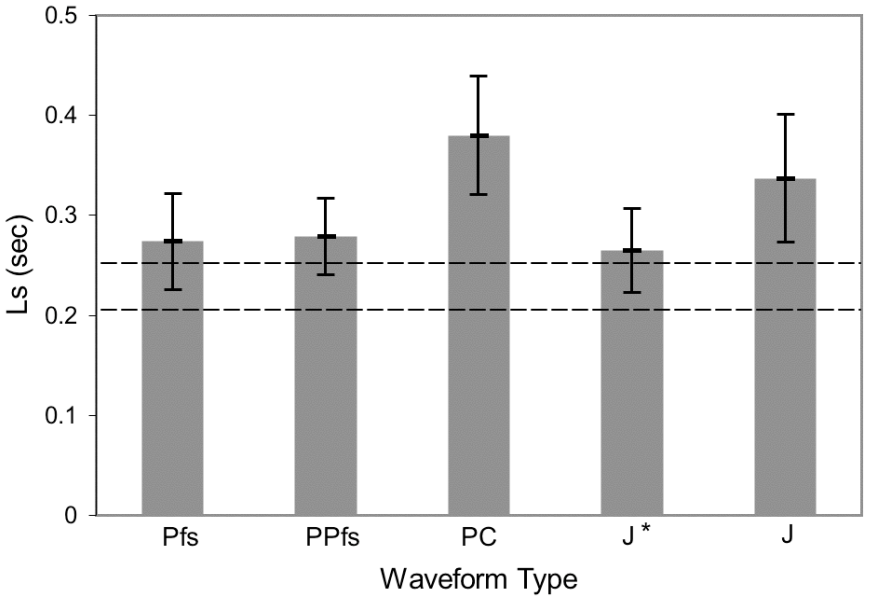

Figure 6-6. Average value of Ls for each waveform type, with their respective standard deviations. The subject with a J waveform who also had APAN is labeled as J*. Dashed lines indicate the normal range of saccadic latencies.

Foveating Strategies

1. Small Target Steps

INS subjects vary the fast and slow phases of their nystagmus waveform to achieve target foveation. Figure 6-8 (a and b) shows subjects' responses to a 5° leftward target jump. In (a), after a programmed fast phase, another fast phase with a greater amplitude acquired the target at ~300 ms (at arrow). The nystagmus waveform was affected, interfering with the ability to maintain target foveation. In (b) a different strategy was used. After a small saccade, the subject "rode" the slow phase to the target; the eye reversed direction with no associated saccades. The target was acquired ~1 s after the target jump (at arrow). Figure 6-8 (c) shows *anticipation* of a 5° rightward target jump. No reflexive saccades were made; instead, the OMS varied the slow-phase amplitude from cycle to cycle and the eye gradually migrated to the new target position (at arrow); there is no Lt per se.

2. Large Target Steps

Responses to large target steps showed greater variation. The response in Figure 6-2 was the most common. The response to a 15° rightward target jump occurred after a braking saccade. The foveating saccade was already programmed and was followed by a large reflexive saccade. The eye went past the target and turned around, followed by a foveating saccade that had a larger peak velocity than those after target acquisition, as shown in the velocity trace. Steady target foveation did not occur until ~900 ms after the target jump.

Figure 6-9 (a) shows a response to a 15° rightward target jump occurring shortly after a foveating saccade. The next fast phase was already programmed and executed; however, the amplitude of the reflexive saccade was hypometric, possibly due to interference from the internal mechanism that was programming the fast phase. The second reflexive saccade brought the fixating eye closer to the target, enabling the following foveation period to be within the foveation window. Steady target foveation occurred ~600 ms after the target jump (at arrow).

Response to a 55° rightward target jump is illustrated in Figure 6-9 (b). The waveform changed from PC to Pfs after the refixation. The first reflexive saccade fell short of the target and was followed by a second saccade (that went slightly past the target), ~280 ms from the beginning of the first saccade. Since the saccades brought the eyes close to the target, good foveation began in the following cycle, ~1.1 s after the target jump (at arrow).

Figure 6-9 (c) shows combined strategies (reflexive saccade plus slow-phase riding) that the subject used in response to a 30° leftward target jump. Because the next fast phase was already programmed, a reflexive saccade was not generated until ~400 ms after the target jump. The eyes then continued to ride the slow phase until a fast phase was made. Target acquisition did not occur until the next cycle, fully 1 s after the target jump (at arrow).

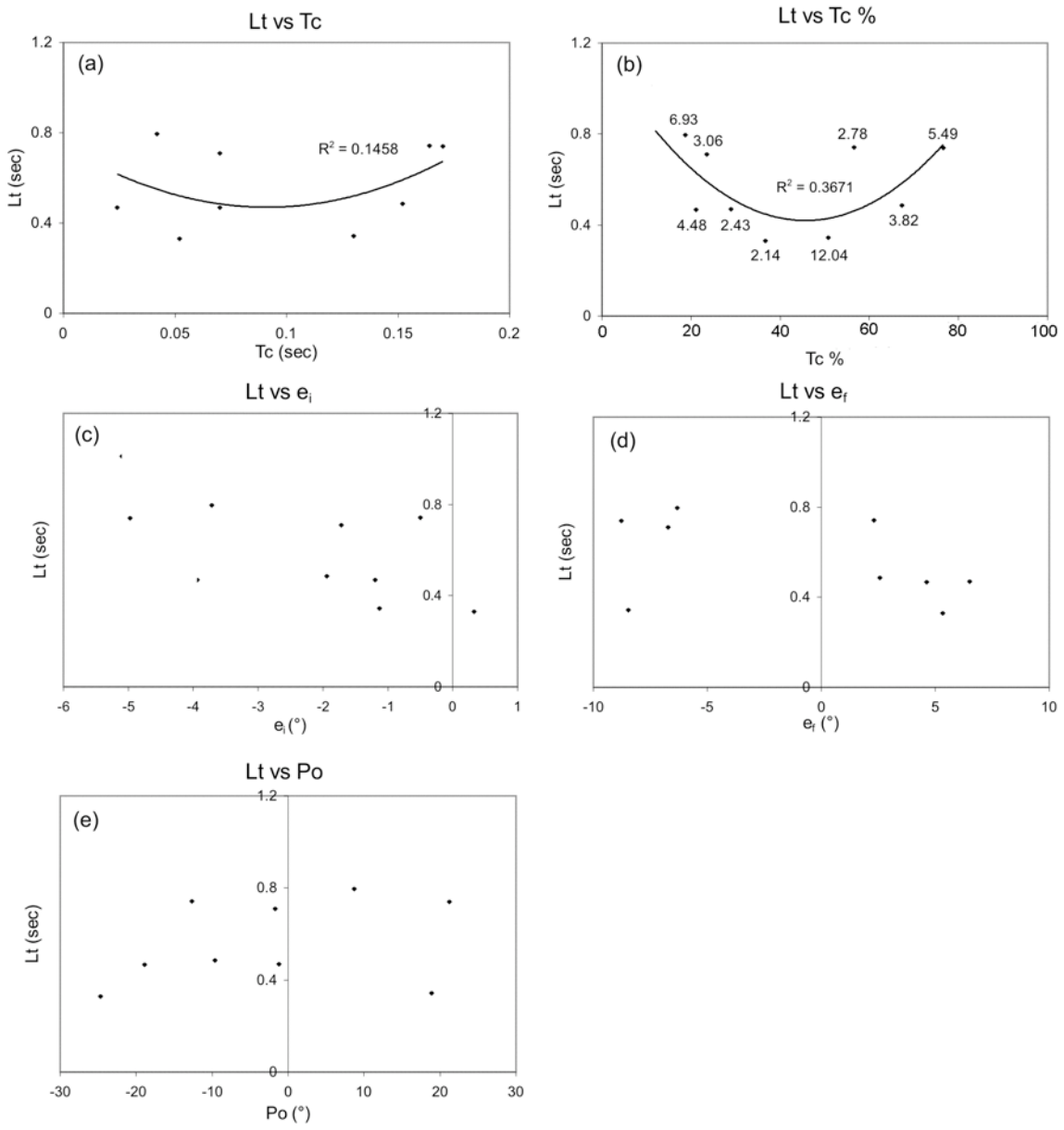

Figure 6-7. A typical set of Lt data, in response to small target steps (Subject 3). The subject had a J waveform (with APAN); the peak-to-peak amplitude (in °) at each data point is noted.

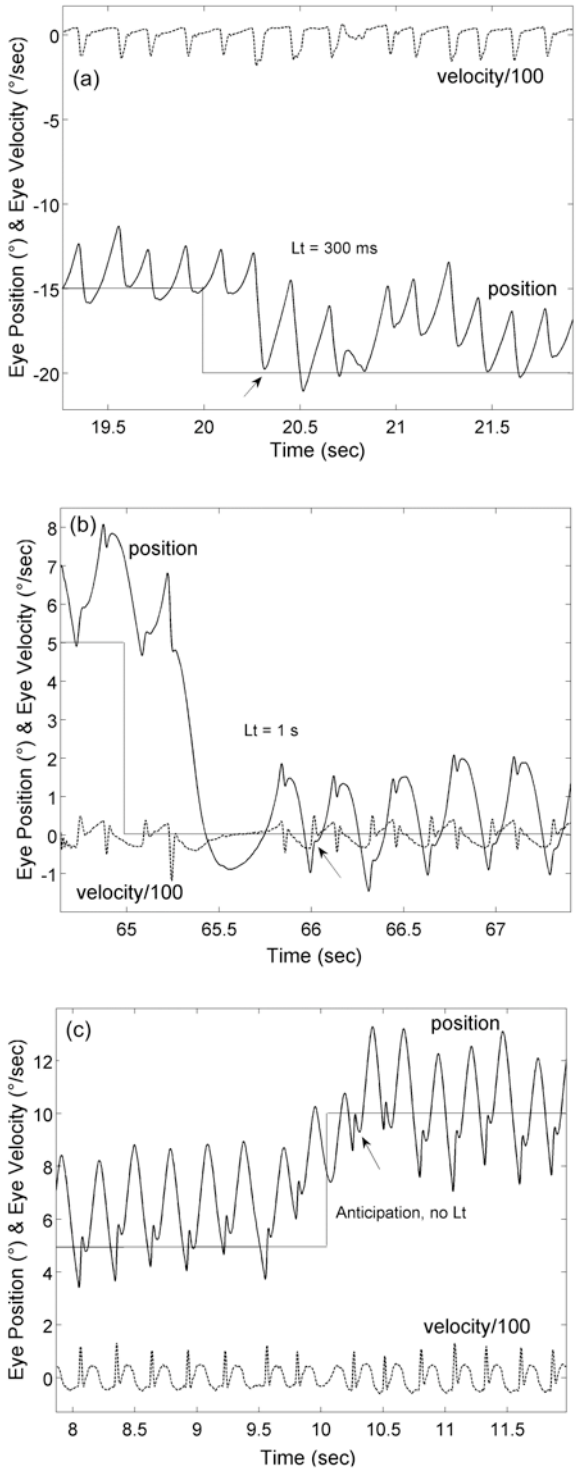

Figure 6-8. Foveating strategies employed by INS subjects in response to small target steps. Subject 2 (a), Subject 1 (b), and Subject 4 (c).

In Figure 6-9 (d), response to a 30° leftward target jump is demonstrated. At 30°, the subject's ability to hold gaze was impaired, and his fast-phase terminations kept drifting back from the target for a few cycles before one refoveated the target. To acquire the new target at 0°, the OMS relied solely on the centripetally accelerating slow phase; *no reflexive saccade was made*. The target was initially acquired ~400 ms after the target jump but it took a few cycles for the subject to reliably maintain and extend foveation (at arrow); Lt was ~900 ms.

Figure 6-9 (e) shows a pulse-step mismatch that occurred after the initial saccade, in response to a 45° rightward target jump. The pulse-step mismatch resulted in a leftward glissade of ~5°. Target acquisition occurred with the next fast phase, ~700 ms after the target jump (at arrow).

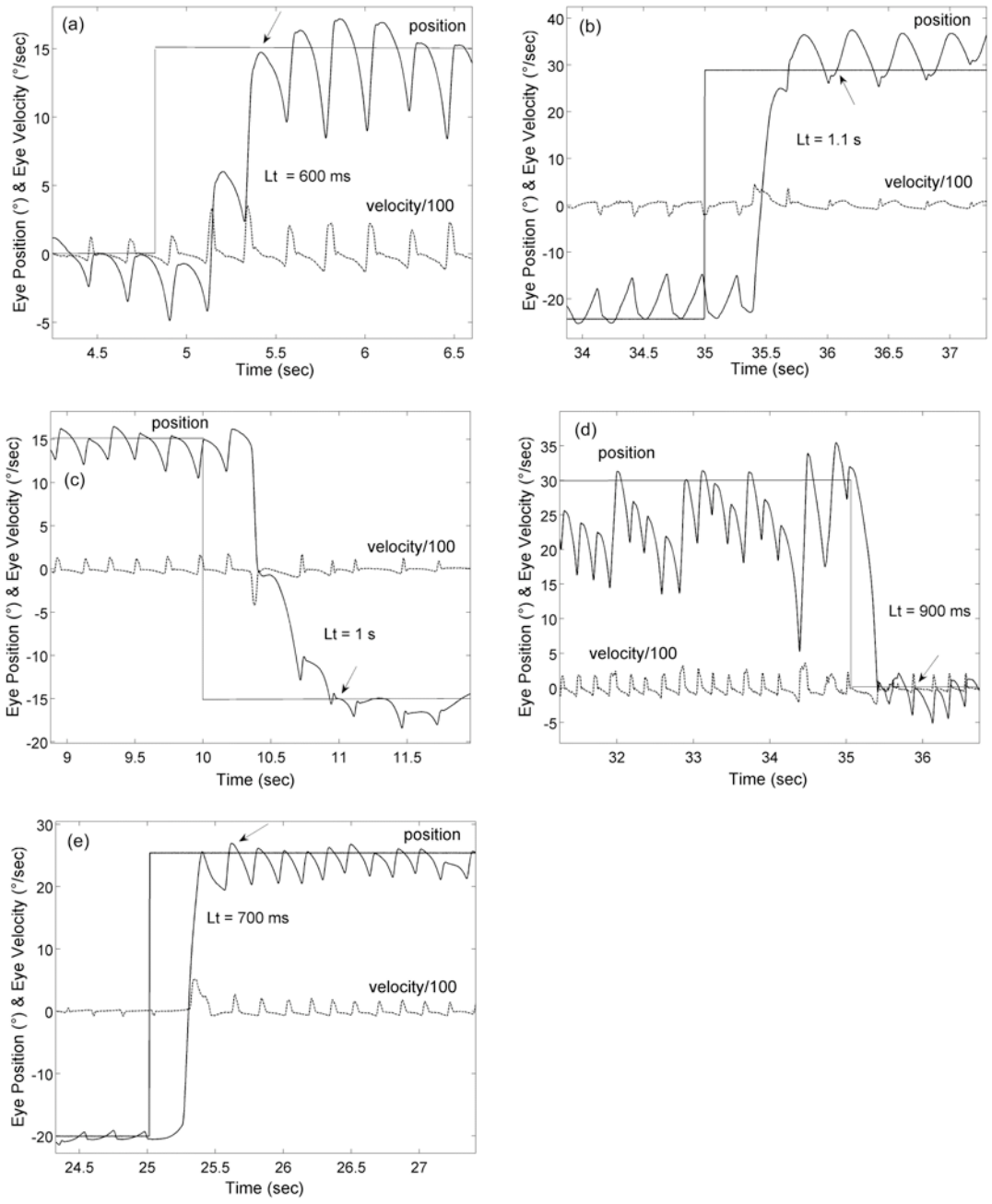

Figure 6-9. Foveating strategies employed by INS subjects in response to large target steps. Subject 3 (a and d), Subject 1 (b), Subject 2 (c), and Subject 2 (e).

Ramp Target

When evaluating ramp target acquisition, both a position criterion and a velocity criterion have to be satisfied. When the eyes acquire and pursue the new target, which is moving with a ±10°/s velocity, the foveation periods should be aligned with the current target position, and the foveation velocity must also match the target velocity. To differentiate the effects of both criteria, we measured the target acquisition time solely based on position, while also calculating the pursuit gain during the acquisition, which was a good indication of the velocity criteria.

We examined 5 INS subjects' responses to ramp targets and found a trend in the data (Figure 6-10) that's consistent with the step responses. P1 – P4 had Jerk type waveforms, and the target ramps initiated close to the intrinsic saccades (before, during, and after) were prone to a longer target acquisition time. P5 exhibited different foveating strategies when pursuing a leftward target (bottom left panel of Figure 6-10) than a rightward one (bottom right panel of Figure 6-10); therefore a target acquisition curves for both directions are shown. Meanwhile, P5 had a PPfs waveform, the braking saccade showed larger effect on target acquisition on the rightward pursuit data.

Demonstrated in Figure 6-11, is an example of the importance of pursuit gain. The two panels were from the same subject (P1), pursuing in different directions. She exhibited markedly better pursuit to the right, yielding a pursuit gain of almost 1. When pursing to the left, the first 7 cycles had almost 0 gain, which means even if she was "on target", she still could not see the target well due to high foveation velocity. Direction played an important role in determining this subject's capability in ramp-target acquisition.

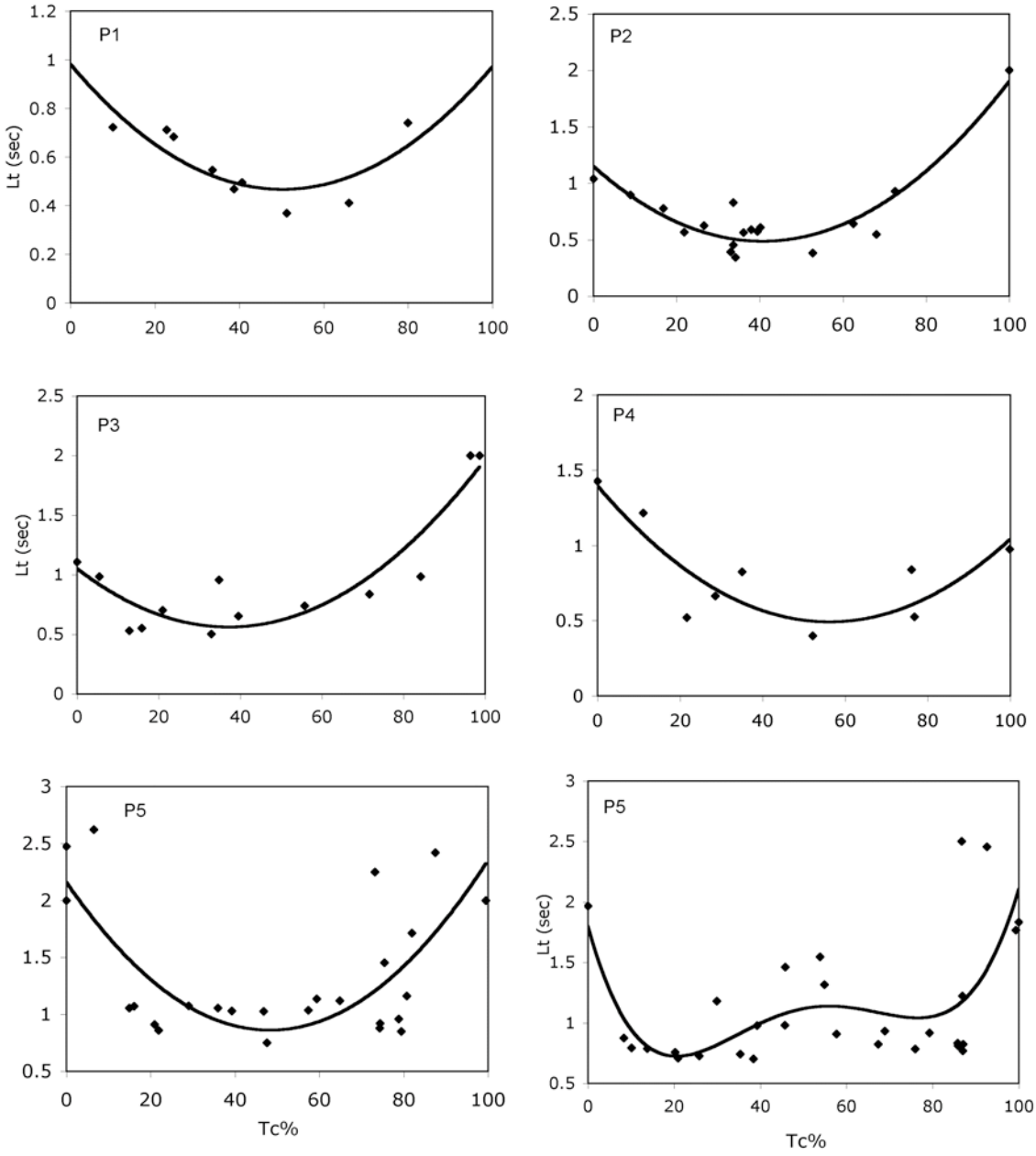

Figure 6-10. Lt vs. Tc% curve for all 5 subjects' responses to ramp stimuli.

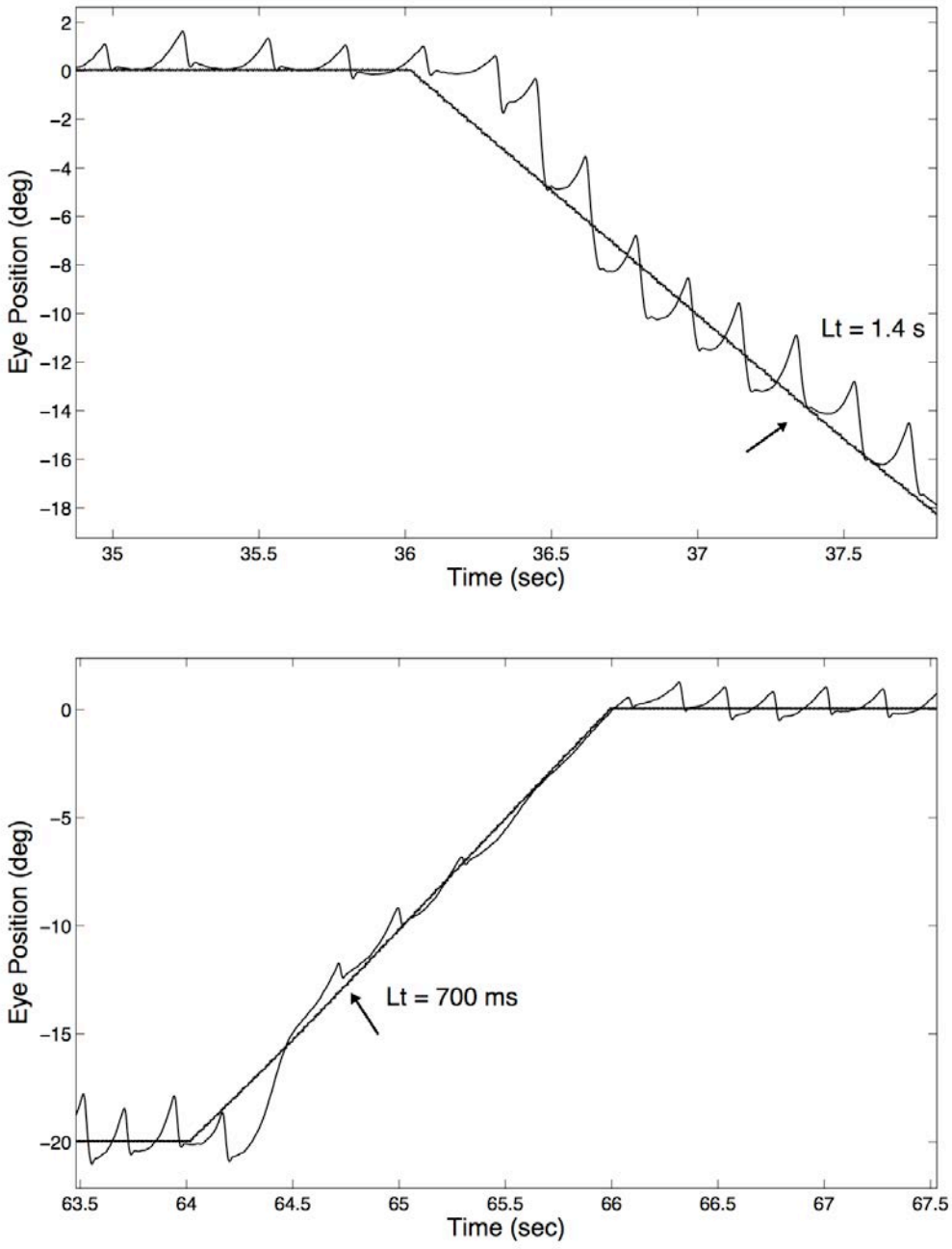

Figure 6-11. P1 exhibiting drastically different pursuit gains when pursing to different directions.

We found great idiosyncrasy in the pursuit gains of each subject when pursuing targets with different directions (with or against the nystagmus slow phase) as indicated in Figure 6-12. The error bars shown with the averaged values depict the variability in the gains. P1 preferred pursuing targets moving with the slow phase, although in either direction the gains were less than 1. P2 had an average pursuit gain of almost 1 when pursuing targets moving with the slow phase; in the other direction, the average gain was much lower. P3 had an almost 0 gain when pursuing targets moving with the slow phase and a higher than 1 gain when pursuing against. P4's gains changed not only with direction but also with the type of waveform during the pursuit (probably due to his APAN component); the waveforms are specified for each column of averaged gains in the Figure. P5 had a pendular type waveform, i.e., the slow phase could be in either direction, and therefore direction did not influence the pursuit gains.

6.2 Discussion

Our OMS model predicted, and subject data demonstrated, that target timing, vis-à-vis its occurrence within the INS cycle, is one variable that may explain the difficulties experienced by those with INS when attempting to fixate a suddenly displaced target or when searching a visual scene by making voluntary saccades. Small changes in target timing can result in large increases in target acquisition time for the same sized target displacements. Saccades disrupt the OMS' ability to accurately calculate saccade amplitude and refoveate; the degree of this disruption can be idiosyncratic.

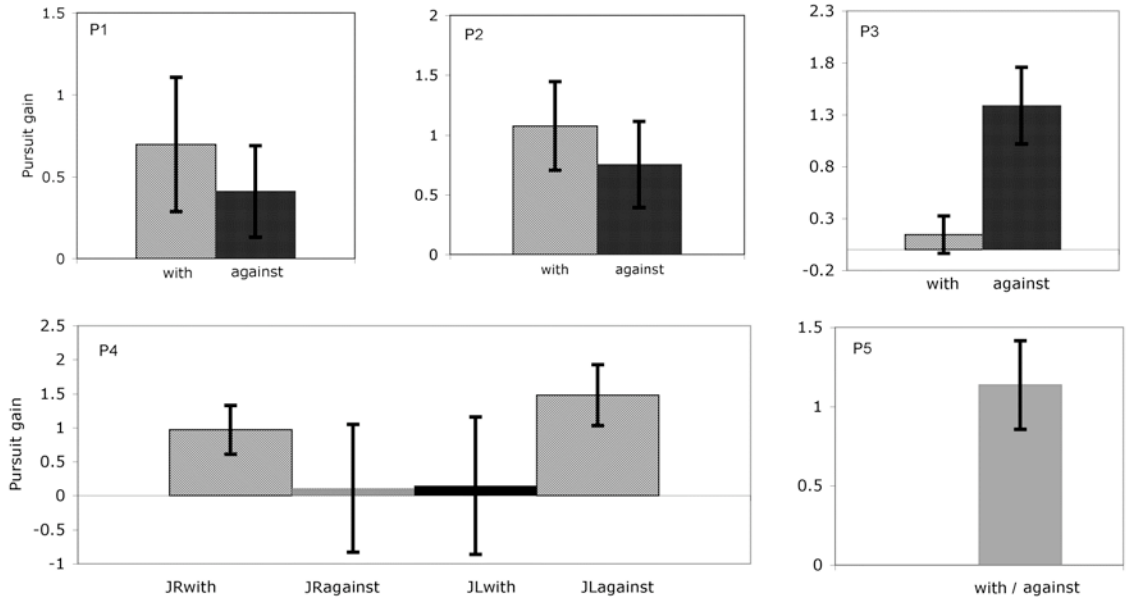

Figure 6-12. Idiosyncratic pursuit gains (averaged values and std) in each subject, when the slow phase was with or against the target velocity. In P4, the pursuit gains were also dependent on the waveform's jerk beating direction. JRwith= Jerk Right + target velocity with the slow phase; JRagainst= Jerk Right + target velocity against the slow phase; JLwith= Jerk Left + target velocity with the slow phase; JLagainst= Jerk Left + target velocity against the slow phase.

We used our OMS model to simulate the behavioral responses of INS individuals. As shown in RESULTS, the model outputs accurately predict/simulate human responses. This behavior was not built in; it emerged from the interactions among the required functional blocks in the total OMS model. The fact that this emergent property, along with many others published previously (Jacobs & Dell'Osso, 2004), is consistent with recorded human data, provided support for the basic ocular motor mechanisms and their interconnections embedded in the model. For the *first* time, we are using the model as a tool to make behavioral predictions and explore underlying ocular motor mechanisms. In this study, the model simulations were reinforced by the subsequent subject data, demonstrating its value in predicting behavior.

Further studies using this model, will allow exploration of which functioning block/blocks in the OMS contribute to the "missing" of a cycle, or the impaired ability to fixate. We will also use it to study the dynamic properties of INS subjects in response to other stimuli, e.g., ramp stimuli. Based on the finding of increased Ls in INS subjects, we can set the latency of the initial reflexive saccade to be an idiosyncratic value greater than 250 ms (reflecting an individual with INS), instead of the 250 ms value in the current model that was based on data from normals.

The curves in Figure 6-5 show a common characteristic: Lt is larger when the target jump occurs closer to a fast phase/saccade contained in the INS waveform. Any existing time-varying components of the waveforms (e.g., in APAN) do not disturb this trend. In most INS waveforms (except for PC), a foveating saccade occurs right before foveation begins. Therefore, the fast phase at the beginning (and end) of the cycle influences the acquisition of a new target. The lengthening of target acquisition time for

target steps occurring at these particular intervals in each waveform, suggests that new-target foveation capability is disrupted by the intrinsic saccades. For the PC waveform, whose saccade occurs in the middle of the cycle, this trend is also preserved. Although the data for each waveform came from different subjects (except for Pfs and PPfs which came from Subject 1), they all share the same dynamic characteristic. Tc% showed a greater influence on Lt than Tc in most subjects, probably due to variation in the absolute length of each nystagmus cycle.

Interestingly, in the PPfs waveform, we also observed an increase in Lt in the middle of the cycle, where the stereotyped, small, braking saccade occurred (Dell'Osso & Daroff, 1976). This demonstrated that it is not only *foveating* saccades that lengthen the target acquisition time, but also saccades in general. This disruption might come from the saccadic refractory period or the interaction between the saccadic and fixation subsystems, impairing the system's ability to accurately calculate the size of the next foveating saccade required to refixate the target. The OMS model accurately makes these calculations during fixation (both normal and with INS or other types of nystagmus) but they are impaired by the interaction between intrinsic and reflexive saccades. Note that, some INS subjects may have varying (both intra- and inter-subject) gaze-holding and fixating capabilities. Based on their baseline level, these capabilities are modulated by the timing of the target jump. This is in accord with anecdotal reports from an individual with INS that the time needed to catch up with a fast moving object (e.g., when aiming at a flushing bird) varies from one instance to another; sometimes acquisition takes more than a second while, at other times it is normal; needless to say, the former results in a miss while the latter, a hit.

Although the initial reflexive saccade is not necessarily the one that foveates the target, Ls is the foundation for prompt target acquisition. Our data in Figure 6-6 show that, on average, INS subjects also take a longer time to generate the first refixation saccade. The highest Ls in our study was 380 ms, from Subject 4 (PC waveform); that is 130 ms longer than the upper bound of normal saccadic latency (250 ms). This prolonged Ls adds to Lt, the time it takes to foveate the target after its movement. However, this amount is insufficient to cause the "slow-to-see" impression.

The suppression of vision during saccades is not a new topic. Back in the 1960s, the time course of saccadic suppression was measured (Carpenter, 1988; Leigh & Zee, 2006). Normal saccades and intrinsic saccades in INS waveforms shared a similar time-course curve. It was discovered that the threshold of seeing a brief flash of light was significantly elevated if it occurred 30 ms to 40 ms before, during, or 100 ms to 120 ms after the saccade. It is tempting to attribute the lengthening of Lt in our study to the initial suppression caused by the intrinsic saccades in the INS cycle. However, unlike the brief, dim flash used in those saccadic suppression experiments, we used a bright and steady laser beam target. The visibility of the target was well above the visual threshold for all the subjects; after the jump, the target remained visually salient at the new position. Therefore, we do not think the initial saccadic suppression caused by the intrinsic saccades played an important role to the elongated Lt, although its effects still need to be investigated.

The main refixation strategies employed by INS subjects are slow- or fast-phase changes and refixation saccades, or combinations of them. Note that, the pre-programmed fast phase seems to be modified in Figure 6-9 (a) in an attempt to foveate the target, with

the amplitude inaccurately calculated. In Figure 6-8 (a), however, the alteration of the fast-phase amplitude was good enough for acquiring the target, in this case a 5° target jump. These strategies are tools that individuals with INS can make use of (probably acquired as their OMS adapted to their INS oscillation) in order to achieve foveation in an effective fashion. It would be interesting to examine the presence and development of this adaptation in infants/children with INS, whose waveform foveation quality is also being refined.

We also found that for the same subject, Lt values for large target steps are generally larger than those for small target steps, mimicking normal subjects, who also take a longer amount of time to acquire large target steps. However, within each stimulus category (large/small steps), saccade size does *not* determine the value of Lt. This implies that the relationship between target amplitude and Lt could be a step function, although we think not. As shown in Figure 6-8 (a) and (b), when small target steps (5°) stimuli are presented, subjects often opt to not use reflexive saccades, but let their nystagmus slow phase take over, e.g., modifying their slow and fast phases to achieve foveation at the new target position. This strategy is totally different from the case in large target steps, in which subjects rely more on reflexive saccades. Therefore the influence of intrinsic saccades is more obvious in large target steps.

We examined the position and velocity criterion separately in the ramp-stimuli responses. The intrinsic saccades also influenced the target acquisition in these responses, consistent with the step-response findings. What we found interesting was the great idiosyncrasy of pursuit gains. Influential factors included the direction of the ramp and in one subject, the direction of his Jerk waveform. This idiosyncrasy adds more difficulty in

ramp stimuli acquisition for the INS subjects, because in real life, the intended target can be from any direction and occur at any time in their nystagmus cycle.

Foveating and braking saccades are adaptations of the OMS in the presence of the underlying pendular oscillation. The saccades not only bring the eye position back to the target allowing refoveation, but also, the foveation periods following foveating saccades enable individuals with INS to discern details in the target, i.e., foveation periods determine "how well they see". However, based on findings in this study, these intrinsic saccades seem to have an adverse effect on "how quickly they see". Throughout its development, the OMS may have made a trade-off between these two important aspects of visual function. In the case of INS, the former may have been chosen over the latter; alternatively, the observed data may be the best the OMS can do in the presence of an ongoing nystagmus containing intrinsic saccades. Target acquisition time emerges as an additional, dynamic factor determining visual function in individuals with INS. Along with visual acuity at lateral gaze angles (Wang, Dell'Osso, Jacobs, et al., 2006; Yang, et al., 2005), it should be part of both their initial clinical evaluation and the determination of therapeutic effectiveness.

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Chapter 7

Tenotomy Alleviates the "Slow to See" Phenomenon in Infantile Nystagmus Syndrome: Model Prediction and Patient Data

7.0 Abstract

Our purpose was to perform a systematic study of the post-tenotomy changes in target acquisition time by comparing predictions from the behavioral Ocular Motor System (OMS) model and data from Infantile Nystagmus Syndrome (INS) patients. We studied five INS patients who underwent only tenotomy for their INS treatment. We measured their pre- and post-tenotomy target acquisition changes using data from infrared reflection and high-speed digital video. Three key aspects were calculated and analyzed: the saccadic latency (Ls), the time to target acquisition after the target jump (Lt) and the normalized stimulus time within the cycle. Analyses were performed in MATLAB environment (The MathWorks, Natick, MA) using OMLAB software (OMtools, available from http://www.omlab.org). Model simulations were performed using MATLAB Simulink. The model simulation suggested an Lt reduction due to an overall foveation-quality improvement. Consistent with that prediction, improvement in Lt, ranging from ~200 ms to ~500 ms (average ~ 280 ms), was documented in all 5 patients post-tenotomy. The Lt improvement was not a result of a reduced Ls. In summary, INS patients acquired step-target stimuli faster post tenotomy; this target acquisition improvement may be due to the elevated foveation quality resulting in less inherent variation in the input to the OMS. A refined behavioral OMS model, with "fast"

and “slow” motor neuron pathways and a more physiological plant, successfully predicted this improved visual behavior and again demonstrated its utility in guiding ocular motor research.

7.1 Introduction

Infantile Nystagmus Syndrome (INS) patients (CEMAS_Working_Group, 2001), even without sensory deficits, are usually affected by more than one aspect of their wiggling eye movements: their best visual acuity may be reduced (Abadi & Worfolk, 1989; Bedell & Loshin, 1991; Dell'Osso & Flynn, 1979; Dell'Osso, Flynn, & Daroff, 1974; Dell'Osso & Jacobs, 2002; Sheth, Dell'Osso, Leigh, Van Doren, & Peckham, 1995), their high-acuity field may be narrow (Z. Wang, Dell'Osso, Jacobs, Burnstine, & Tomsak, 2006), and they may be “slow to see” (Z. I. Wang & Dell'Osso, 2007). INS treatments have been traditionally focused on alleviating head turns and tilts (Anderson, 1953; Kestenbaum, 1953, 1954) and, only more recently, improving the primary-position foveation (Dell'Osso & Jacobs, 2002; Hertle, et al., 2001). The tenotomy procedure (Z. Wang, Dell'Osso, Jacobs, et al., 2006) and Kestenbaum procedure (Dell'Osso & Flynn, 1979) (which had tenotomy embedded) have been shown to also broaden patients’ high-visual acuity field. However, the dynamic properties of the ocular motor system (OMS) after extraocular muscle surgery may also affect visual function; they have never been examined from a waveform-foveation point of view.

The purpose of this study was to perform a systematic study of the post-tenotomy changes in target acquisition time. Before we examined the patient data, we modified our behavioral OMS model based on recent anatomical findings (Ugolini, et al., 2006) and

used it to simulate and make predictions of tenotomy's effects. We then analyzed 5 patients' pre- and post-tenotomy target acquisition data, including one patient's improvement time course. In this study we not only confirm a post-tenotomy improvement, but also explore where this improvement might originate.

The behavioral OMS model we utilized for simulating post-tenotomy effects was an updated version of the original published in 2004 (Jacobs & Dell'Osso, 2004). We implemented the most recent discoveries in the motor neuron pathways (Ugolini, et al., 2006) and substituted a more physiologic, albeit simplified, plant model that is a precursor to one that includes proprioceptive feedback tension-control (X. Wang, Zhang, Cohen, & Goldberg, 2007) and enabled a tenotomy effect coefficient to simulate the small-signal (i.e., slow-phase) damping effects of tenotomy (Z. Wang, Dell'Osso, Zhang, Leigh, & Jacobs, 2006).

7.2 Methods

Subjects

We studied the pre- and post-tenotomy target-acquisition changes in five INS patients. Patients' ages, gender and INS waveforms are listed in Table 1. The foveation improvements of these patients were studied previously (Z. Wang, Dell'Osso, Jacobs, et al., 2006), where more detailed patient demographical information may be found (P1-5 were P9, P7, P5, P4, and P3 respectively in the prior study).

The five patients received only tenotomy surgery for their nystagmus treatment, i.e., no strabismus surgeries were performed. In 4 patients, the post-tenotomy records were performed from 3 to 12 months after the procedure. In one patient, we recorded 1

week, 6 weeks, 6 months, and 1 year post-surgically to observe the time course of the improvement.

Patient ID	Gender/Age	Nystagmus Waveforms
P1	M/15	J, Jef
P2	F/9	J, Jef
P3*	M/49	J, Jef, PC
P4	F/24	P, AP, Pfs, J, Jef, PC, PJ, DJ
P5	M/16	J, Jef, PC, DJ

Table 7-1. Patient demographics. F=Female; M=Male; P=Pendular; AP=Asymmetric Pendular; Pfs=Pendular with Foveating Saccades; PPfs=Pseudo Pendular with Foveating Saccades; DJ=Dual Jerk; J=Jerk; Jef=Jerk with Extended Foveation; PC=Pseudo Cycloid; PJ=Pseudo Jerk. *Patient was on gabapentin 300mg/2 times per day on pre-surgical examination.

Recording

Infrared reflection (IR) was used for 4 patients, high-speed digital video for 1. The IR system (Applied Scientific Laboratories, Waltham, MA) was linear to 20° in the horizontal plane and monotonic to 25-30° with a sensitivity of 0.25°. The total system bandwidth (position and velocity) was 0-100 Hz. The digital video system (EyeLink II, SR Research, Mississauga, ON, Canada) had a linear range of ±30° horizontally and ±20°vertically. System sampling frequency was 500 Hz, and gaze position accuracy error was 0.5°-1° on average. The data from both systems were digitized at 500 Hz with 16-bit resolution. The IR or EyeLink signal from each eye was calibrated with the other eye behind cover to obtain accurate position information; the foveation periods were used for calibration. Eye positions and velocities (obtained by analog differentiation of the

position channels) were displayed on a strip chart recording system (Beckman Type R612 Dynograph). Monocular primary-position adjustments for all methods allowed accurate position information and documentation of small tropias and phorias hidden by the nystagmus.

Protocol

This study was approved by the local IRB and written consent was obtained from each patient before the testing. All test procedures were carefully explained to the patient before the experiment began, and were reinforced with verbal commands during the trials. Patients were seated in a chair with a headrest and a chin stabilizer, far enough from the stimulus screen to prevent convergence effects (>5 feet). At this distance the reflected laser target subtended less than 0.1° of visual angle. The room light was adjusted from dim to blackout to minimize extraneous visual stimuli during the recording. An experiment consisted of from eight to ten trials, each lasting under a minute with time allowed between trials for the patient to rest.

Analysis

All the analysis was performed in MATLAB environment (The MathWorks, Natick, MA) using OMLAB software (OMtools, available from http://www.omlab.org). Only eye position was sampled directly; velocity was derived from the position data by a 4^{th}-order central-point differentiator. Position data were pre-filtered with a low-pass filter with the cutoff frequency of 50 Hz to reduce the noise while minimally affecting the

saccades. Analysis was always done on the fixating eye. Segments with inattention or blinking were not used for this analysis.

The eXpanded Nystagmus Acuity Function (NAFX) was used to measure tenotomy-induced changes in the nystagmus at primary position and various gaze angles. It is an objective and repeatable measure of INS waveform foveation quality that is directly proportional to potential visual acuity, assuming that no additional sensory deficits are present. Details of the NAFX's theory and application may be found elsewhere (Dell'Osso & Jacobs, 2002).

In a previous study (Z. I. Wang & Dell'Osso, 2007), we demonstrated the characteristics of target acquisition time in INS. Several dynamic measurements were established: the saccadic latency (Ls), the time to target acquisition after the target jump (Lt) and normalized stimulus time within the cycle (Tc%). Ls, the latency to the initial voluntary saccade, is measured from the target-jump time to the beginning of the first voluntary saccade. Lt, the latency to the target arrival time, is measured from the target-jump time to the beginning of the first foveation period on the target. Tc is the time from the beginning of the current nystagmus cycle to the target jump. Tc% is defined as Tc / the total nystagmus cycle length. Detailed illustration of these measurements can be obtained elsewhere (Z. I. Wang & Dell'Osso, 2007).

Model Simulation

All model simulations were performed using MATLAB Simulink (Waltham, MA). The original OMS model is available from http://www.omlab.org. The most current version (v1.4) will also be available at the same site.

7.2 Results

Model Modifications

Since the initial publication of our OMS model in 2004, we have been making changes and modifications in the model structure to make it more physiological and duplicate additional complicated human visual behavior, in both normal and INS conditions. After each modification, the whole model was back checked using different input stimuli. Just as the previously released model, the current model correctly responds to step, ramp, and step-ramp visual tasks with correct latencies and accuracies. Figure 7-1 shows a block diagram of the OMS model, with a "tenotomy" plant block. The key improvements in the current model are described below. Details of the model can be found in the Appendix.

A Re-distributed OMS Efferent Delay

The human OMS has ~200-250 ms delay to position error and ~100-150 ms delay to velocity error (Abel, Schmidt, Dell'Osso, & Daroff, 1978; Leigh & Zee, 2006). In our model, these delays were distributed in different sub-systems. The major delay limitation with the previous model was a lumped 30 ms efferent delay placed immediately before the plant, i.e., the latency from OMN firing to the induced eye movements. That lumped delay had no adverse effect for the overall performance to step or ramp stimuli, as shown in the previous study (Jacobs & Dell'Osso, 2004). However, the physiological value for the latency, as reported by Robinson et al. in an electrical stimulation study, is approximately 4-5 ms (Robinson, 1968). Also, the VOR response, which will be integrated to this model in the future, has a short latency of ~15 ms; the lumped efferent

delay of 30 ms would have made this short latency impossible to realize. Therefore, one major improvement of this current model is to re-distribute the 30 ms efferent delay throughout the functional blocks of the internal monitor, i.e., the "brains" of the model.

We divided the 30 ms delay into 5 ms, placed between the OMN and the plant, and the remaining 25 ms, re-distributed back into the upstream functional blocks. The re-distribution work was non-trivial, because of the multiple calculations using feedback signals for efference copy of eye position and velocity. Furthermore, the timings for making comparisons in the functional blocks of the internal monitor also had to be reset 25 ms earlier or later, depending on where in each block the 25 ms delay was placed.

A Built-in Gaze-angle Variation Mechanism

INS patients exhibit gaze-angle variations with a similar morphology as those seen in Vestibular Nystagmus (VN) and Fusion Maldevelopment Nystagmus Syndrome (FMNS). In a previous study, in which we successfully simulated the gaze-angle effects in FMNS (including foveating and defoveating fast-phase alternation), the waveforms were modulated by an Alexander's law factor (Dell'Osso & Jacobs, 2001). Alexander's law describes the increase in the amplitude of nystagmus as the eye is moved in the direction of the fast phase in VN and FMNS.

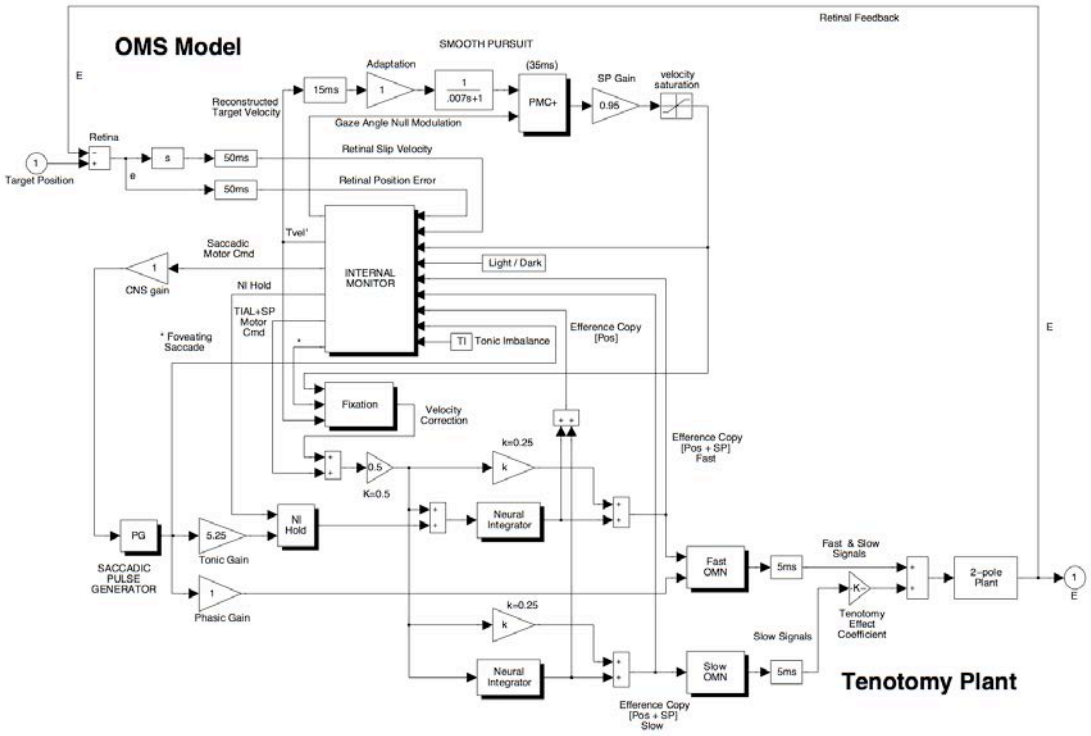

Figure 7-1. Ocular Motor System model showing distributed delays and separate pathways for Slow and Fast Ocular Motor Neurons (OMN). The Tenotomy Plant with a Tenotomy Effect Coefficient is shown in the lower right portion of the Figure.

Using the same methodology as described in a preliminary study (Z. I. Wang, Dell'Osso, & Jacobs, 2007 (in press)), the Alexander's law functional block in the Internal Monitor of the OMS model utilized a reconstructed eye-position signal that excluded the nystagmus signal, i.e., an indication of "where the eye should be." The output of the Alexander's law block was used to modulate the INS baseline sine-wave oscillation. The modulation was enabled by a variable gain in the PMC+ block. The null position and broadness can now be specified via the Alexander's law block and simulations of the INS variation with gaze angle of specific individuals easily made. Thus, INS gaze-angle variation was successfully simulated without creating additional functional blocks by using the same mechanism of Alexander's law regulation as in VN and FMNS. The resulting new version of the OMS model is more flexible and can accurately simulate the large range of null positions and broadness observed in INS patients. More details will be provided in Chapter 8.

A Separate Pathway for "Fast" and "Slow" OMNs and a "Tenotomy" Plant

It has long been thought that only one group of OMNs existed. These OMNs are the final motor pathway for saccadic, pursuit, and vestibular eye movements and, therefore, carried all signals. We have shown in a study of post-tenotomy saccades that saccadic eye movements were not affected while slow phase velocities were reduced after the tenotomy procedure (Z. Wang, Dell'Osso, Zhang, et al., 2006). The implication of that study was that the plant gain might be a nonlinear function of steady-state tension and that tension was turned down by a proprioceptive feedback loop post-tenotomy. Recently, the separation of slow and fast eye-movement signals were demonstrated in a

retrograde injection study from Buttner-Ennever's group (Ugolini, et al., 2006). The retrograde transneuronal transfer of rabies virus from the "en grappe" endplates (innervating "slow" muscle fibers) and "en plaque" endplates (innervating "fast" fibers) showed separate connections to "fast" and "slow" OMNs. Those "slow" OMNs are involved in only slow eye movements, (i.e., vergence and smooth pursuit), muscle length stabilization, and fixation, whereas the "fast" OMNs participate in all eye movements. Therefore, the "fast" muscle fibers may be involved in all eye movements and the "slow" fibers in an on-line proprioceptive tension control loop. If tenotomy only reduces the firing rate of the "slow" OMNs, lowering INS slow-phase velocity, it is reasonable that the saccades remained unchanged.

To incorporate the dual OMN paradigm in our model, we created functional blocks for both the fast and the slow OMNs, and connected saccadic pulse generator output to only the "fast" OMNs, while providing all other outputs to both OMNs. The ratio of these split signals is currently set to be 50% each, although this number could vary due to the percentage of non-twitch fibers and their contribution to the final muscle force generation (presently unknown, "a subject for the gods"—J. Büttner-Ennever, personal communication). Instead of just one OMN output to the plant, we now have a "fast" OMN output and a "slow" OMN output, both going to the plant.

With the dual-OMN model design, a "tenotomy" plant is more easily realized (see specified Tenotomy Plant region in Figure 7-1). Since the tenotomy exclusively reduces the slow-phase signals, we placed a reduction coefficient, the tenotomy effect coefficient (TEC) in the plant for small-signal inputs. This coefficient is idiosyncratic and could depend on the pre-surgical waveform quality and/or afferent deficits (Z. I. Wang,

Dell'Osso, Tomsak, & Jacobs, 2007). We do realize that a more complicated proprioceptive feedback control probably exists to reduce the nystagmus slow-phase components; more neuroanatomical and neurophysiological research is needed to accurately simulate the gains and time constants of that control system.

Model Predictions

Changing the TEC can simulate the foveation-improving effect of tenotomy. The TEC is defined as the coefficient of slow-phase velocity reduction, adjusted in the plant (see Tenotomy Plant region in Figure 7-1). In the upper panel of Figure 7-2, the pre-tenotomy (thick) trace was simulated with TEC = 0 (no effect); the post-tenotomy (thin) trace was simulated with TEC = 0.5 (50% effect). This simulation used a setting to mimic an INS patient with PPfs waveforms having a sharp null at -15°, giving increased velocities at 0° and 15°. The bottom panel is a zoomed-in section of the left panel showing the improvement in foveation and reduction of peak-to-peak amplitude. The post-tenotomy simulation shows "flatter" foveation periods. The reduction affects only the slow-phase signals in the plant, thus affecting foveation; foveating saccades and voluntary saccades are not affected and are still accurate. Such post-tenotomy improvements in foveation quality were found in patients and quantified by their higher NAFX values (note that the NAFX is only sensitive to foveation characteristics and is insensitive to changes in nystagmus amplitude).

We also tested the change in Lt vs. Tc% curves pre- and post-tenotomy, using a model simulation. In Figure 7-3, results of the OMS model output using Pfs parameters are displayed. The post-tenotomy curve was lower than the pre-tenotomy curve,

suggesting a possible overall improvement in Lt. The differences in the pre- and post-curves are smaller compared to real patient data, as will be discussed later.

Patient Data

The model simulations suggested that post-tenotomy foveation quality improvement might result in an overall improvement in target acquisition. To test that prediction, we examined the post-tenotomy effects of 5 INS patients. We studied in detail their foveation and target-acquisition improvement.

Figure 7-4 illustrates 4 patients' pre- and post-tenotomy data, foveation improvement (measured by the NAFX) on the left and target acquisition improvement on the right. All four had an elevated and/or broadened NAFX vs. gaze-angle curve, implying that these patients not only had a better peak-position acuity, but also a broader high-acuity field. In addition, all four had a lowered target acquisition time curve; the decrease in target acquisition time ranged from 200 ms to 500 ms (average ~280 ms). Note that all four curves are higher on either end, reflecting the influence of the intrinsic saccades (Z. I. Wang & Dell'Osso, 2007); this influence was preserved post-tenotomy. In Figure 7-5, P1's improvement time course is shown. We recorded the patient only one week after the tenotomy surgery to determine if improvement occurred at that early stage. Mimicking the rapid improvement in foveation (Hertle, et al., 2001), the target acquisition time was also reduced within one week. The later data recorded are in the same range as the data from the first week. There was no difference in the curve fitting of post-1-week data (dashed line), post-6-weeks to post-1-year data (dash-dotted line), or combined post-tenotomy data (thin solid line). The largest improvement in this patient occurred at either end of the curves, meaning that even when the target jumped during or

near an intrinsic saccade, the target acquisition time was still greatly reduced after tenotomy.

What about the post-tenotomy changes in saccadic latency (Ls)? Figure 7-6 shows the Ls changes from all five patients. The average value of Ls varies on an idiosyncratic basis, from ~200 ms to ~450 ms. However, there were no marked post-surgical changes in Ls.

7.4 Discussion

The purpose of this study was to evaluate if tenotomy alleviated the "slow to see" phenomena, i.e., the lengthening of target acquisition time after step target jumps. We found a consistent decrease in target acquisition time ranging from 200 ms to 500 ms in all patients. Our model simulations predicted this improvement as well as the improved foveation quality.

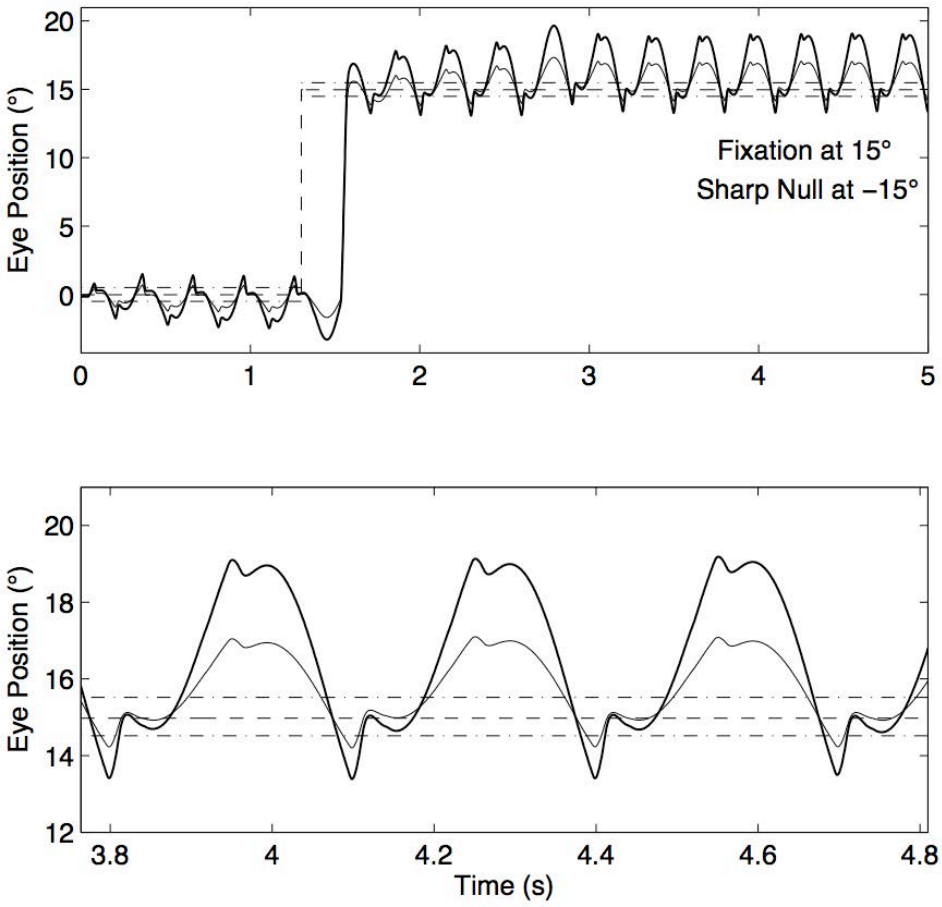

Figure 7-2. Model simulations of an INS patient with PPfs waveforms and a sharp null at -15°. Pre- and post-tenotomy responses to a 15° rightward target jump are shown. The thick line is the pre-tenotomy response and the thin line, the post-tenotomy response. The dashed line denotes the target and dash-dotted lines, the ±0.5° foveal window around the target trace. The bottom panel is a zoomed-in version of the upper panel trace at 15°, showing the improvements in the foveation periods.

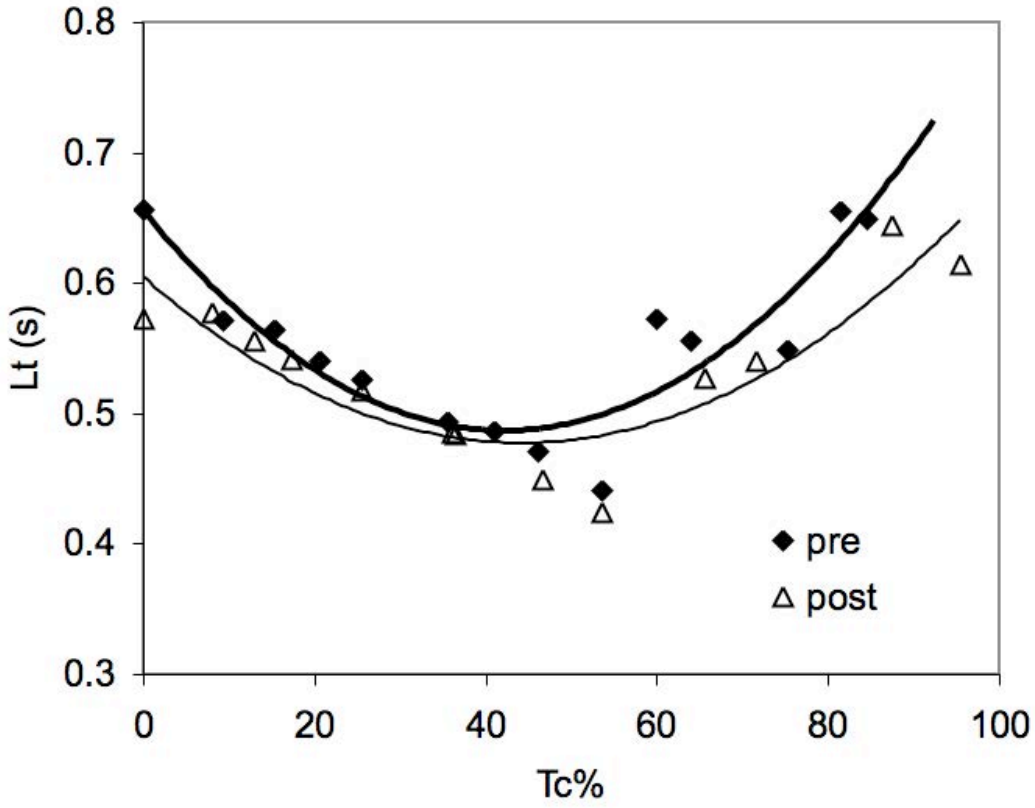

Figure 7-3. Model prediction of post-tenotomy target acquisition change (target jumping from 0 to 15°), showing a small improvement, even for this low-amplitude Pfs waveform. The thick curve is the pre-tenotomy response and the thin curve, the post-tenotomy response.

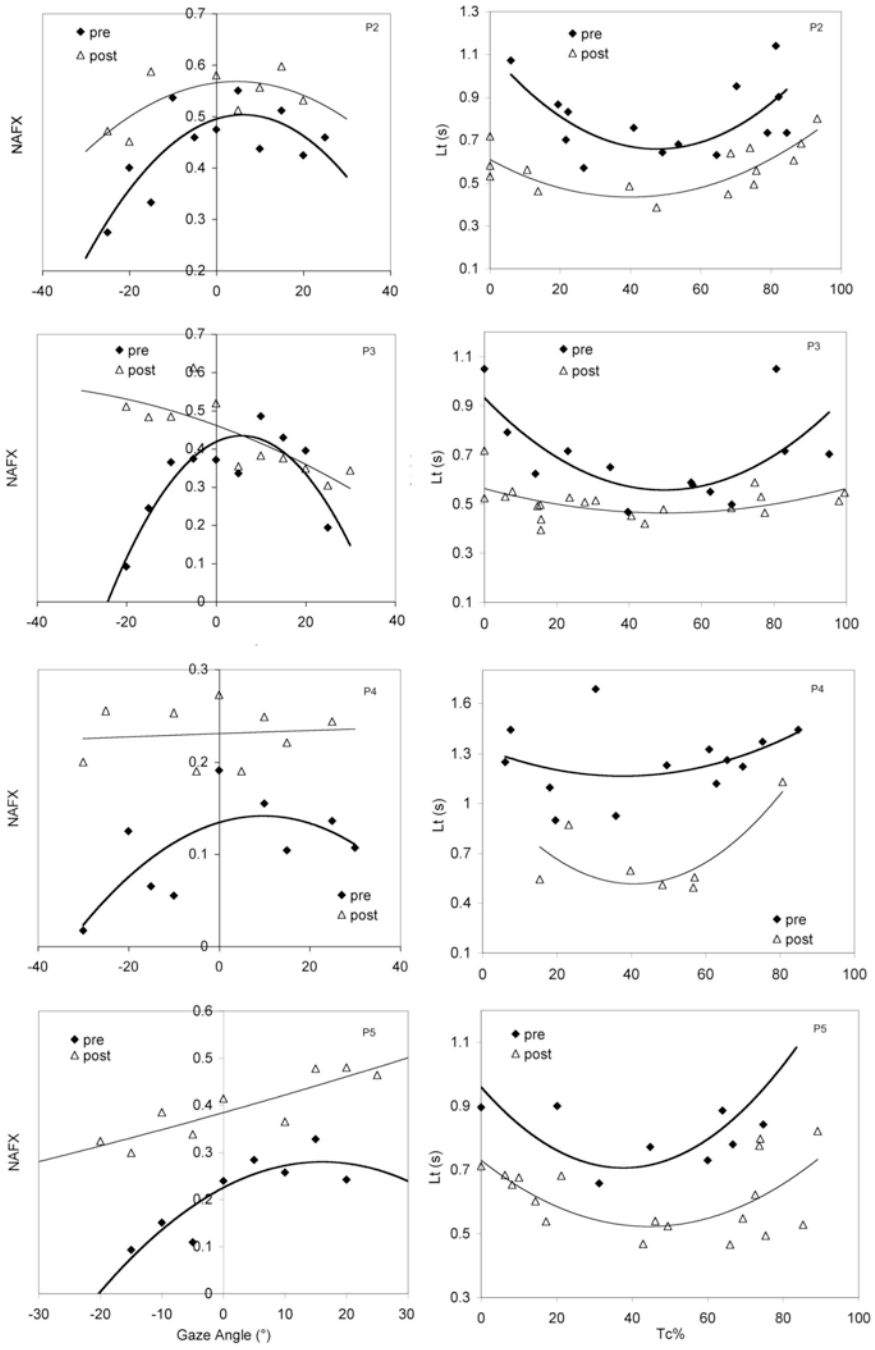

Figure 7-4. Foveation and corresponding target acquisition changes due to tenotomy in 4 patients. The left column contains NAFX vs. gaze-angle curves for each patient, the right column, target acquisition time curves. Filled diamonds are pre-tenotomy data, fitted by a second-order polynomial function (thick curve). Unfilled triangles are post-tenotomy data, also fitted by a second-order polynomial function (thin curve).

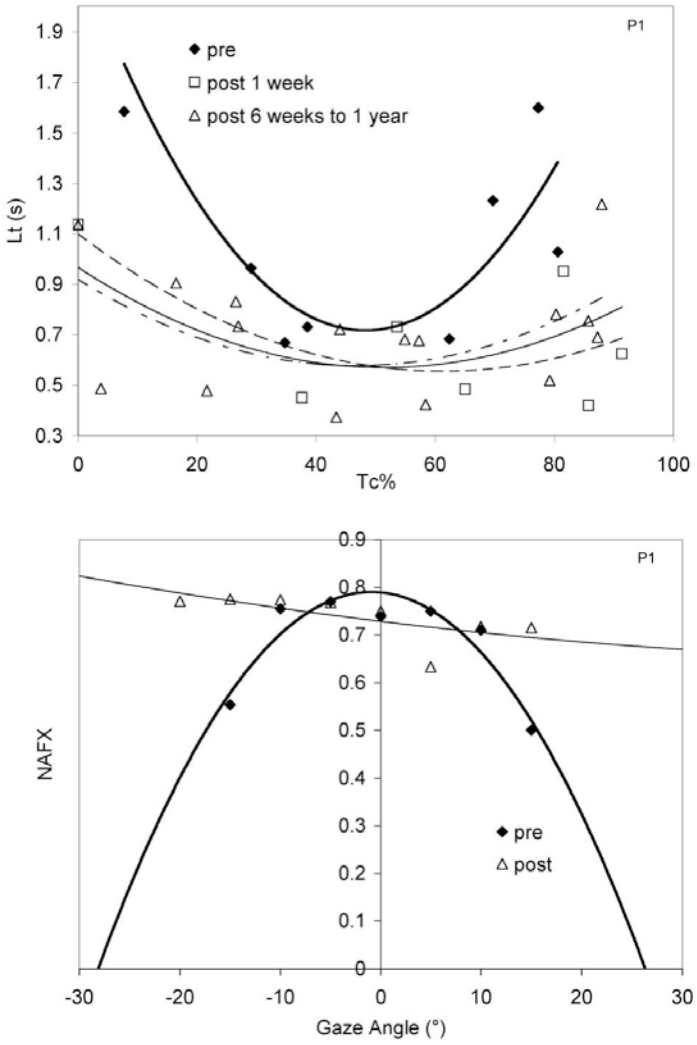

Figure 7-5. Time course of target acquisition changes in one patient. Filled diamonds are pre-tenotomy data; they are fitted by a second order polynomial function (thick curve). Unfilled squares are 1-week, post-tenotomy data, fitted by dashed curve, and triangles are 6-week-post- to one-year-post-tenotomy data, fitted by dash-dotted curve. The combined post-tenotomy data were fitted by the thin solid curve.

OMS Model Prediction and its Implications

The TEC of 50% yielded better target foveation, with the foveation periods having a much slower velocity. The general improvement in the foveation periods provided a more stable input signal to the OMS. Considering the model as a precise control system, with a visual stimulus as an input and an eye movement as an output, it is reasonable that, if the control system's input is improved, the output will also show improvement (i.e., better foveation quality). In INS, the visual input from the retina is the sum of the actual target position and the underlying nystagmus oscillation (i.e., the image on the retina is constantly moving). After the tenotomy reduction of slow-phase signals, the foveation quality was elevated (foveation time elongated and slow-phase velocity lowered) and therefore, the input to the INS ocular motor control system had less inherent variation. Hence, the calculations required by the brain after the target jump could be made faster and more accurately, resulting in a shorter target acquisition time. The mechanism of this improvement could probably be explained by Fitts' law, more discussion of which can be found in Chapter 10.

The above logic applies to both the model and INS patients, the difference being that the model is an idealized patient with less variation than most nystagmus seen in INS. Given the larger foveation instability in real patients, tenotomy had a much greater potential to improve the input to the OMS; therefore, additional improvement in target acquisition time resulted. In our future research, we will investigate adding random levels of both sensory and motor noise in our model to more realistically simulate INS patients with less accurate foveation capability.

Effectiveness of Tenotomy in Improving Target Acquisition

Does the human ocular motor system behave in the same way that our model predicts? The same improvement in target acquisition time was observed in all 5 patients post-tenotomy. This improvement did not come from a reduced Ls (shown in Figure 7-6); i.e., the slightly longer-than-normal saccadic latencies of INS patients (Z. I. Wang & Dell'Osso, 2007) are not reduced by extraocular eye-muscle surgery. These data reinforced the model prediction: elevating the INS waveform foveation quality did improve patients' target acquisition time post-tenotomy and also did not change saccadic latencies. We did not find any relationship between the change in Lt and pre-surgical NAFX, pre-surgical VA, or the change in either primary-position NAFX or VA. More data are needed to exclude the existence of any relationship among those factors. The amount of target-acquisition improvement could be idiosyncratic.

Figure 7-5 showed that the target-acquisition improvement occurred within one week post-tenotomy. Our results are in accordance with the time course of the NAFX increase reported by Hertle et al. (Hertle, et al., 2001). This is an indication of the brain's plasticity: a change in the slow-phase velocity occurs, the brain detects it and adjusts its calculation routines to account for this change. The behavioral OMS model, with its complex interconnections mimicking the functional principles of the brain, also exhibits this plasticity. It should be noted that this patient had a high pre-tenotomy NAFX peak value, indicating a high potential acuity, which was not likely to be improved by any therapy (Z. Wang, Dell'Osso, Jacobs, et al., 2006). We have previously shown that the model predicted a lengthened target acquisition time when target jumps occurred during or near intrinsic saccades (Z. I. Wang & Dell'Osso, 2007). The prediction of a post-

tenotomy decrease in target-acquisition time represents another emergent behavior of this model that guides our thinking in how the brain adjusts to post-surgical changes.

It has been reported that INS patients who underwent maximal recessions of their horizontal rectus muscles had decreased target recognition times of about 300 ms (Sprunger, Fahad, & Helveston, 1997). We have shown that tenotomy decreased target acquisition times by about the same amount. It has been suggested that the INS improvements of the maximal recession surgery is due to the obligate tenotomies that are part of each recession (Dell'Osso, Hertle, Williams, & Jacobs, 1999). We conclude that decreased target acquisition times were responsible for the decreased target recognition times in that study. This provides further evidence that maximal recessions are both unnecessary and problematic.

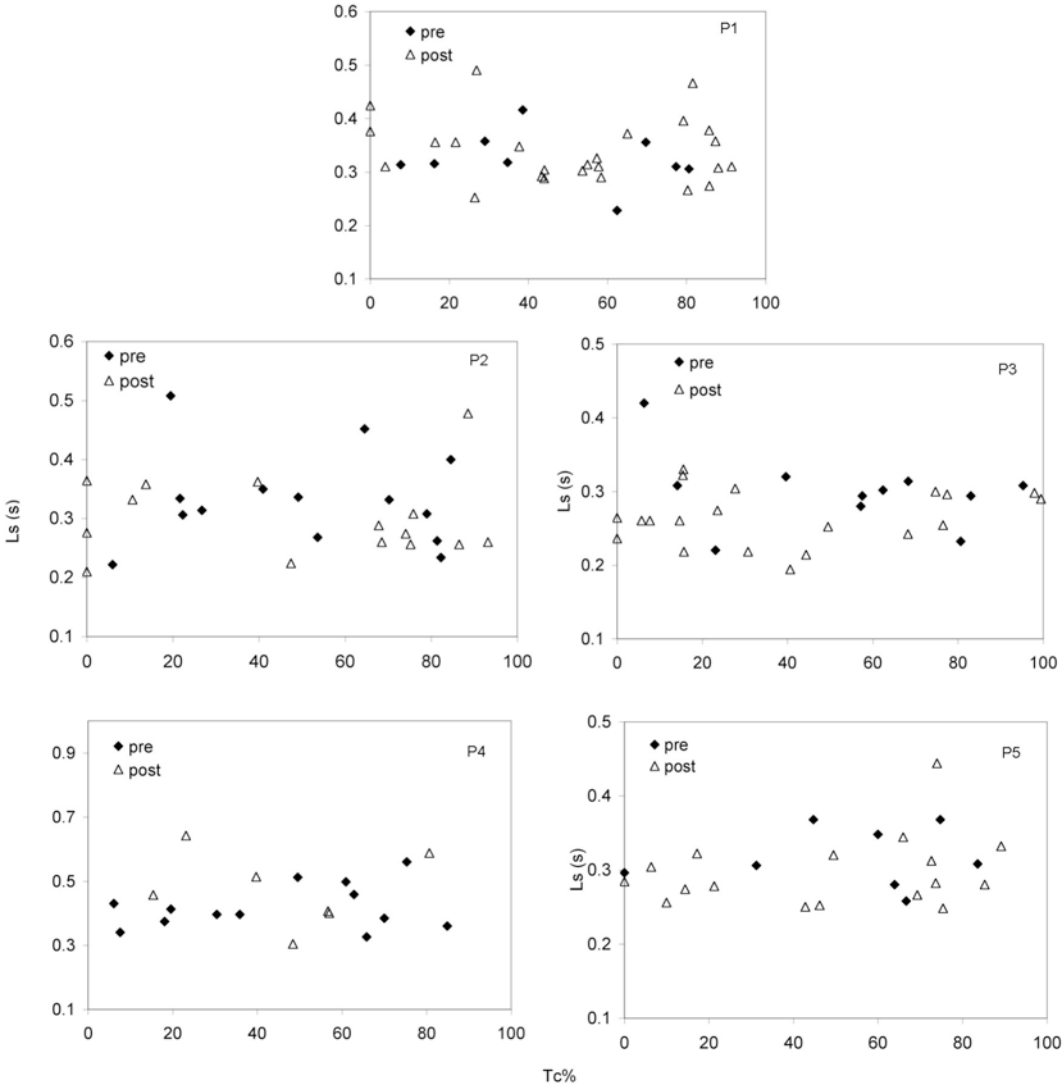

Figure 7-6. The relationship between saccadic latency and target timing, pre- and post-tenotomy in all 5 patients. Filled diamonds are pre-tenotomy data; unfilled triangles are post-tenotomy data.

This study is the first to evaluate the target-acquisition time-change after extraocular muscle surgery from a waveform analysis point of view and the first to use a behavioral OMS model to predict therapeutic outcomes in INS. It reveals a new and interesting aspect of post-surgical evaluation: target acquisition improvement. This is an aspect that can only be measured via analysis of eye-movement recordings; it could never be appreciated by just looking at the patients' eyes or making visual acuity measurements. However, target acquisition time is at least as important to total visual function as the improvement in visual acuity, both in daily and social life. Being able to visually acquire a new or suddenly moved target faster will greatly enhance the INS patients' responses while driving, engaged in sports, or in other speed-critical situations. It also enhances simple tasks, like finding and identifying familiar faces in a crowd.

We have now demonstrated that tenotomy has positive effects on primary-position foveation, broadening the high-quality foveation visual field, and improving target-acquisition responses to step stimuli. If INS patients receive improvement in all three aspects, they will have a broader visually functional field, better visual function at their preferred null position, plus faster responses to sudden movements of visual stimuli or to new stimuli. Summarizing the above, post-tenotomy patients will see "more (broader)," "better," and "faster."

What about stimuli other than step jumps? Our future work will focus on ramp stimuli and combinations of steps and ramps. The more complex the stimuli are, the closer they are to real-life scenarios. By observing how the patients respond to combinations of stimuli, we will have a better understanding of how the OMS functions

dynamically, how the subsystems interact, and the different ways treatments can improve INS.

7.5 References

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Chapter 8

Incorporating Gaze-angle Variations into the Original Behavioral Infantile Nystagmus Syndrome Model

8.0 Abstract

We aim to expand the behavioral Ocular Motor System (OMS) model for Infantile Nystagmus Syndrome (INS) by incorporating idiosyncratic variation of IN amplitude with gaze angles. Ocular motor recordings of humans, using infrared reflection, high-speed digital video, and magnetic search coil systems, were used as templates for the computer simulations. All simulations and analyses were performed using Simulink and in the MATLAB environment, respectively. Similar to a previous study of simulating Fusion Maldevelopment Nystagmus Syndrome, the Alexander's law relationships were used to produce desired INS null positions and sharpness. At various gaze angles, these Alexander's law relationships influenced the IN slow-phase amplitudes differently, thereby mimicking the same gaze-angle effects observed in INS patients. The simulations of a robust behavioral OMS model demonstrated that Alexander's law output effectively modulates the nystagmus variation at different gaze angles.

8.1 Introduction

The Ocular Motor System (OMS) model (Jacobs & Dell'Osso, 2004) for Infantile Nystagmus Syndrome (INS) simulated the responses of individuals with several pendular

waveforms (pendular with foveating saccades, Pfs, and pseudopendular with foveating saccades, PPfs) based on a loss of damping of the normal pursuit-subsystem instability and its interaction with other OMS components. Accurate model simulations during fixation, saccades to known targets (steps, pulses, and pulse-steps), and smooth pursuit (ramps and step-ramps), as well as many emergent properties and unexpected predictions of the model duplicated the recorded responses of humans with INS, providing strong support for the hypothetical mechanisms in the model.

There are, however, a number INS features that were not included in the original OMS model. To expand this behavioral model, we intend to first incorporate in an interim version of the model the gaze-angle variation commonly observed in INS patients.

Alexander's law (Robinson, Zee, Hain, Holmes, & Rosenberg, 1984) describes the increase in the amplitude of nystagmus as the eye is moved in the direction of the fast phase in Vestibular Nystagmus (VN) and Fusion Maldevelopment Nystagmus Syndrome (FMNS). The slope of the Alexander's law relationship is dependent on the tonic imbalance (in VN) or the viewing eye (in FMNS). Although INS slow-phase waveforms exhibit different accelerations than VN and FMNS waveforms, we hypothesize that the same Alexander's Law output could be utilized to simulate the amplitude changes affecting the eXpanded Nystagmus Acuity Function (NAFX) peak, i.e., the INS null.

8.2 Methods

The ocular motor recordings and observations used for the computer simulation came from approximately 1000 subjects with INS, who were recorded in our laboratory

over the past 37 years. Eye movements were measured using either an infrared reflection (IR, Eye-Trac 210, ASL, Waltham, MA), a magnetic scleral search coil (C-N-C Engineering, Seattle, WA), or a high-speed digital video (EyeLink II, SR Research, Mississauga, ON, Canada) system. Specifications of the recording systems can be found elsewhere (Wang, Dell'Osso, Zhang, Leigh, & Jacobs, 2006). All simulations were performed using MATLAB Simulink (Waltham, MA).

8.3 Results

In the original OMS model, the Alexander's law mechanism uses efference copy of eye position to modulate the tonic imbalance (TI) input (Dell'Osso & Jacobs, 2001; Jacobs, 2001; Jacobs & Dell'Osso, 2004). As shown in Figure 8-1, the eye-position signal is multiplied by the Alexander's law slope and filtered before summing with TI. The sign of TI dictates if this sum is kept greater than or less than 0. Then the sum is passed to a final switch that only produces an output when TI is present. Varying Alexander's Law slope will produce differing amounts of Alexander's Law effect. This effect leads to slow-phase velocity increases as gaze is directed in the abducting direction of the fixating eye, and that would cause the transition from foveating to defoveating fast phases in FMNS. Figure 8-2 demonstrates two cases with large and small Alexander's law effect, respectively (Dell'Osso & Jacobs, 2001). Note that in the top panel the large, decelerating slow phases and defoveating fast phases did not transition to smaller, linear slow phases and foveating fast phases until far adduction of the fixating right eye. Whereas in the bottom panel the transition occurred much closer to primary position.

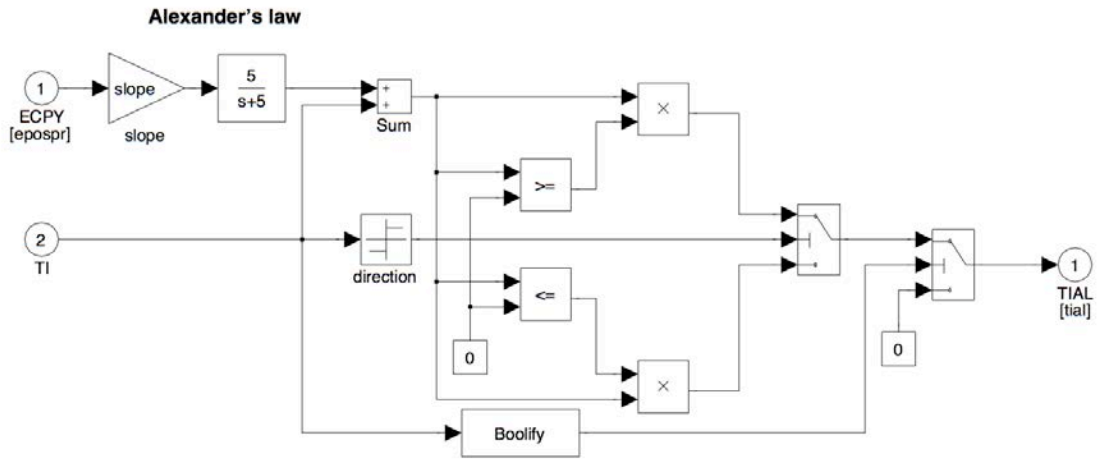

Figure 8-1. Alexander's law block in the original Ocular Motor System model.

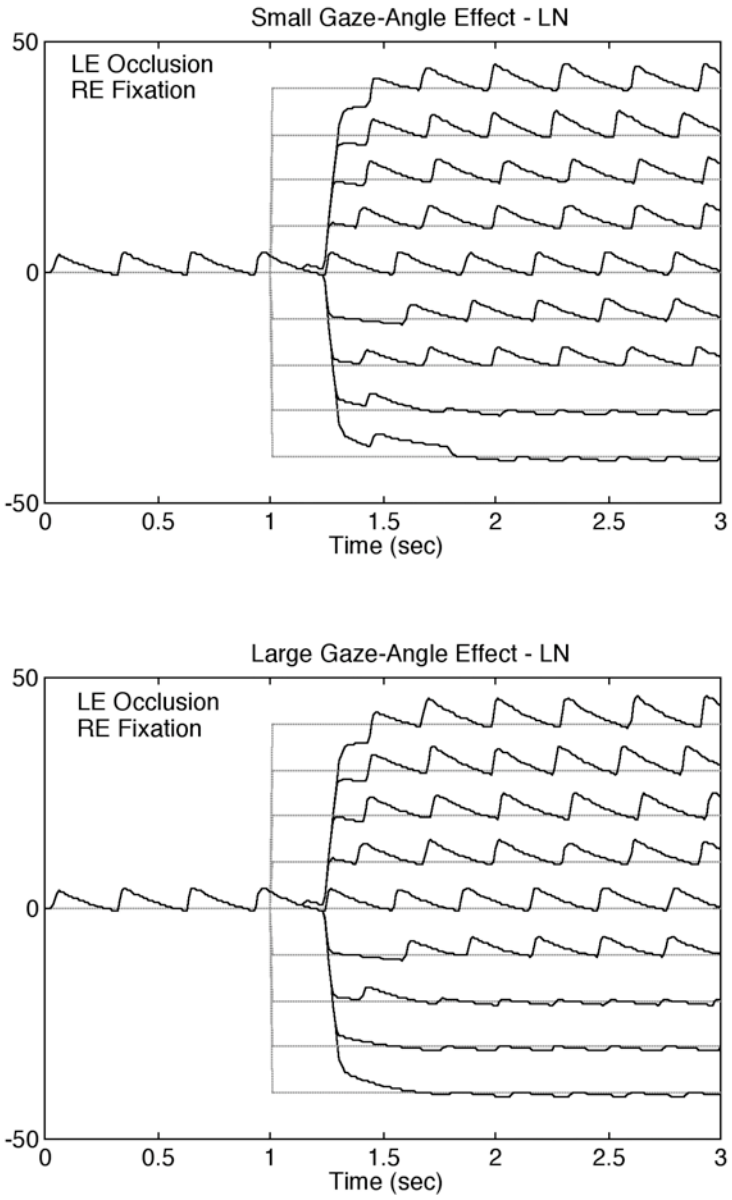

Figure 8-2. Simulations of Latent Nystagmus of fixation at various gaze angles with small Alexander's Law effect (top) and large effect (bottom). (Adapted from Dell'Osso LF, Jacobs JB: A normal ocular motor system model that simulates the dual-mode fast phases of latent/manifest latent nystagmus. *Biological Cybernetics* 2001:85:459-471.)

For FMNS patients, the two Alexander's law lines (one for each eye) operate independently of each other, with only one (depending on the fixating eye) determining the gaze-angle variation (Dell'Osso & Jacobs, 2001). In INS, we hypothesize that both Alexander's law relationships operate together—it is the same Alexander's-law imbalance produced by improper calibration of the vestibular system that may be the underlying reason for INS gaze-angle variation. The two linear functions act simultaneously, with their intersection establishing the null position and the slopes of the lines controlling the broadness of the null. The modulation is produced by a variable gain in the PMC+ block (Jacobs & Dell'Osso, 2004; Robinson, Gordon, & Gordon, 1986), controlling the amplitude of the sinewave oscillation.

Figure 8-3 is the modified Alexander's law block, using efference copy of the eye position as an input to calculate the modulation factor (the "Null Mod" output). Note that the efference copy of eye position used here is a nystagmus-free position signal, i.e., the desired eye position; this is a more stable signal for the oscillation amplitude modulation. No TI input is present now; it is only the relative position between the current eye position and the null that dictates the oscillation amplitude. Future versions of the model simulating INS with a latent component will require further modification of this block.

Figure 8-4 shows the modified PMC+ circuit, the origin of the nystagmus oscillation. The multiplier in the feed-forward loop is where the modulation from Alexander's law takes place.

Figures 8-5, 8-6 and 8-7 demonstrate model position output for different gaze-angle variation, corresponding to different null positions and width. Note that the voluntary saccades are still accurate, and foveating saccades are also fairly accurate once

target acquisition occurs. However, the farther away from the null position, the less "flat" the foveation periods. This is due to the fixation system's response to a higher velocity input (Dell'Osso, 2002). Now that the eye position guides the oscillation amplitude, the fixation's gaze-holding ability also varies according to different eye positions. This emergent property is consistent with recordings of INS patients.

A series of step stimuli are given to the model, as shown in Figures 8-8 and 8-9. The eye position output showed a much-reduced oscillation at the null zone, and enlarged oscillation out of the null zone; the extent of the enlargement depends on the null width. These model outputs correspond to recordings of patients with pendular types of waveforms under step visual stimuli.

8.4 Discussion

Since the gaze-angle variations in INS resemble those of FMNS, we used the same Alexander's law input to simulate the variation of IN waveforms across the whole visual field. The behavioral output of the OMS model at different gaze angles demonstrated the effectiveness of this hypothesis. Alexander's-law imbalance (possibly asymmetric) produced by improper calibration of the vestibular system may have caused the INS gaze-angle variation.

The Alexander's-law effects on INS amplitude can be used in future versions of the model to modulate other INS waveforms and control the idiosyncratic transitions between pendular and jerk waveforms. The effects of inattention on INS waveforms can also be incorporated into the model, through the same modulating gain in the PMC+ circuit.

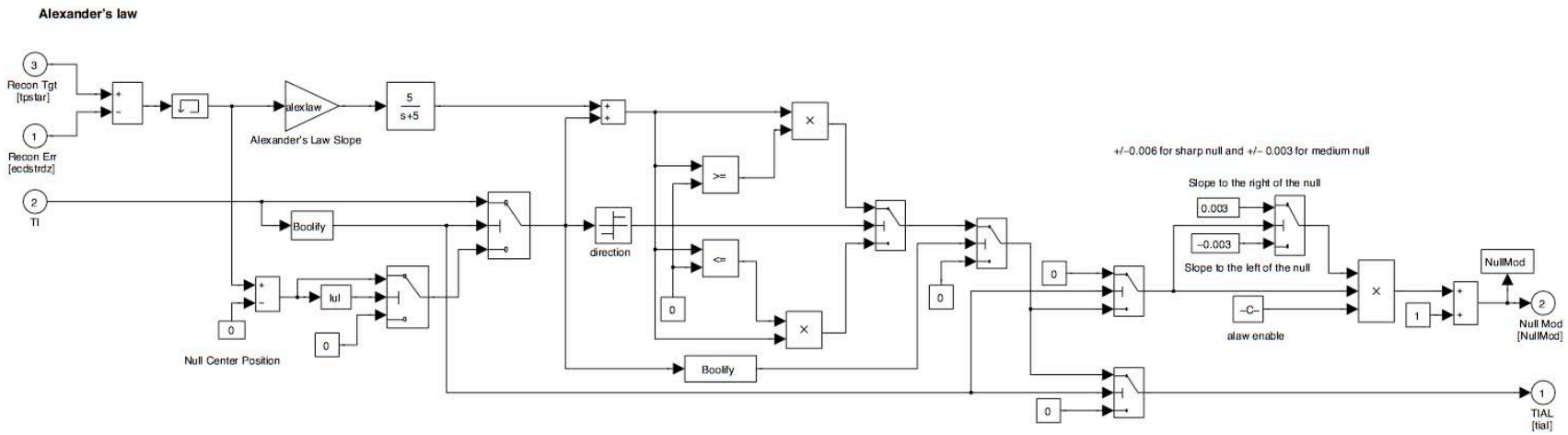

Figure 8-3. Alexander's law block in the modified Ocular Motor System model.

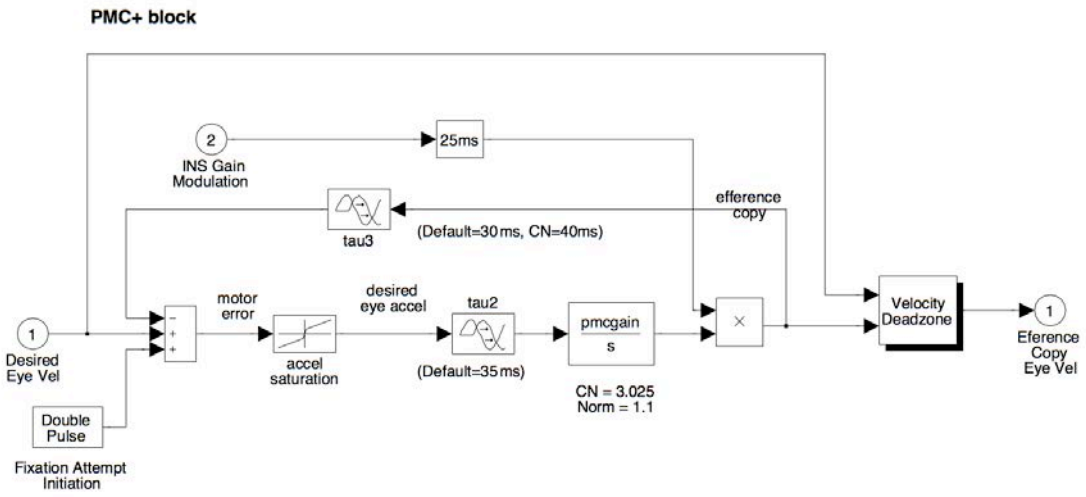

Figure 8-4. PMC+ circuit in the modified Ocular Motor System model. The "Velocity Deadzone" block is used to exclude artifacts in the simulations for normals, i.e., the initial underdamping of the pursuit system.

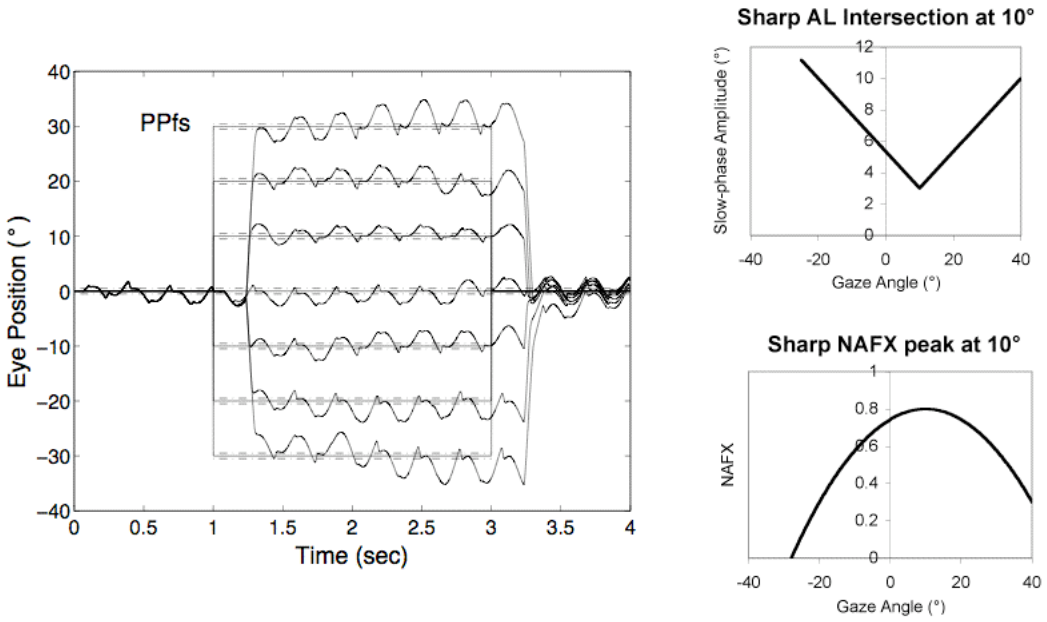

Figure 8-5. Model output of PPfs waveform with a sharp null at 10° and increased slow-phase amplitude to either side of the null. In this Figure, Figures 8-6 and Figure 8-7, right columns show the intersection and slopes of the two Alexander's Law lines, and the peak position and sharpness of the eXpanded Nystagmus Acuity Function (NAFX) vs. gaze-angle curve, corresponding to the position and sharpness of the null.

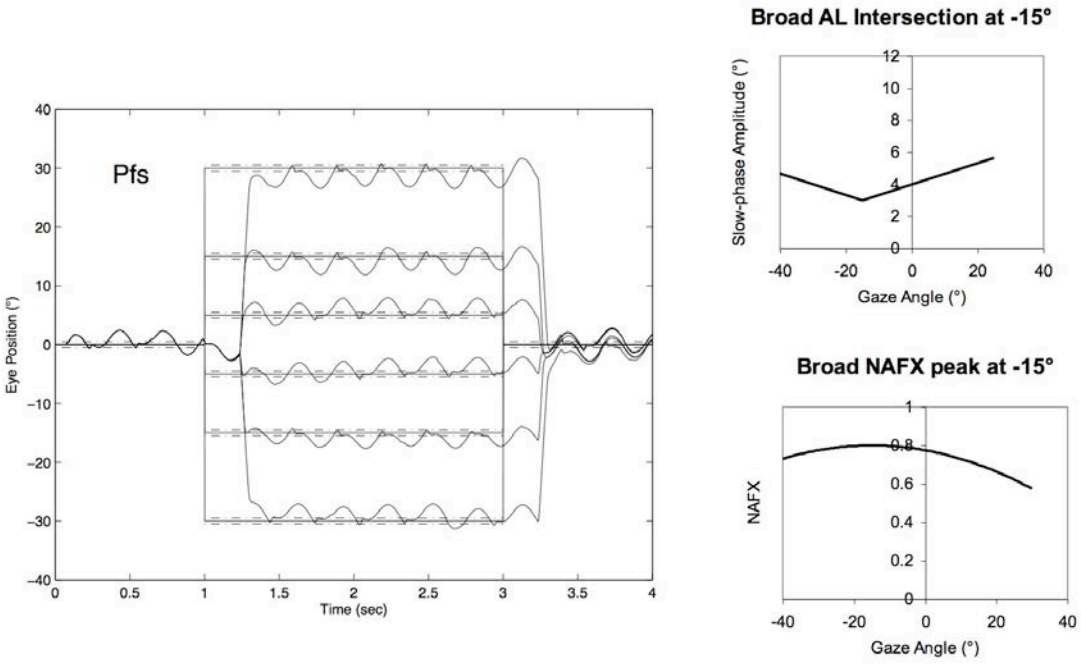

Figure 8-6. Model output of Pfs waveform with a broad null at -15° and increased slow-phase amplitude to either side of the null.

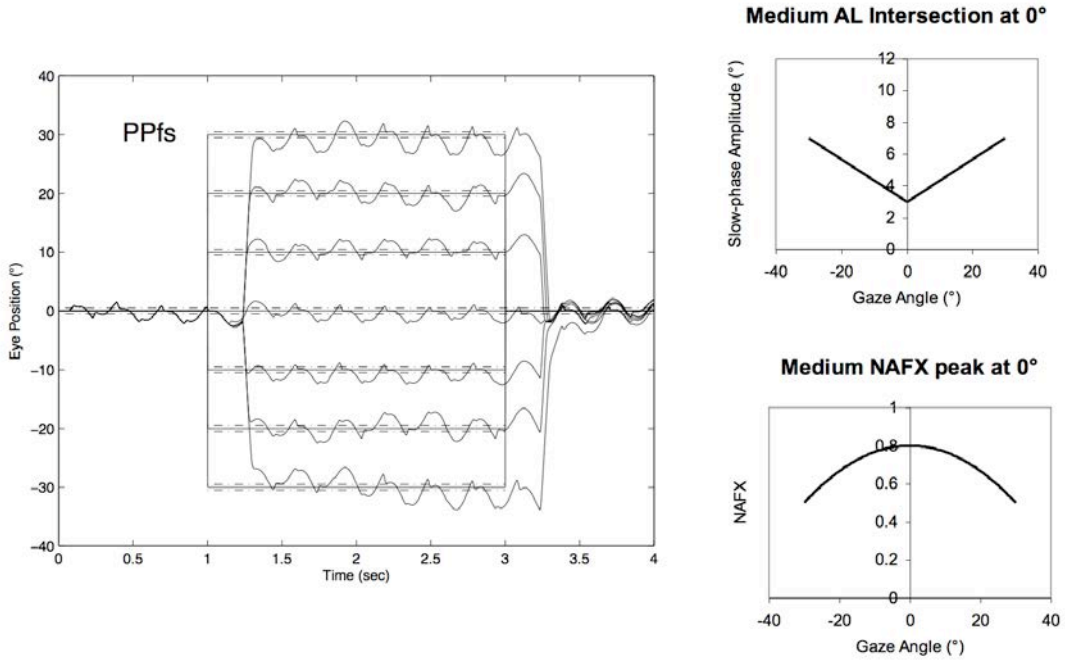

Figure 8-7. Model output of PPfs waveform with a medium null at 0° and increased slow-phase amplitude to either side of the null.

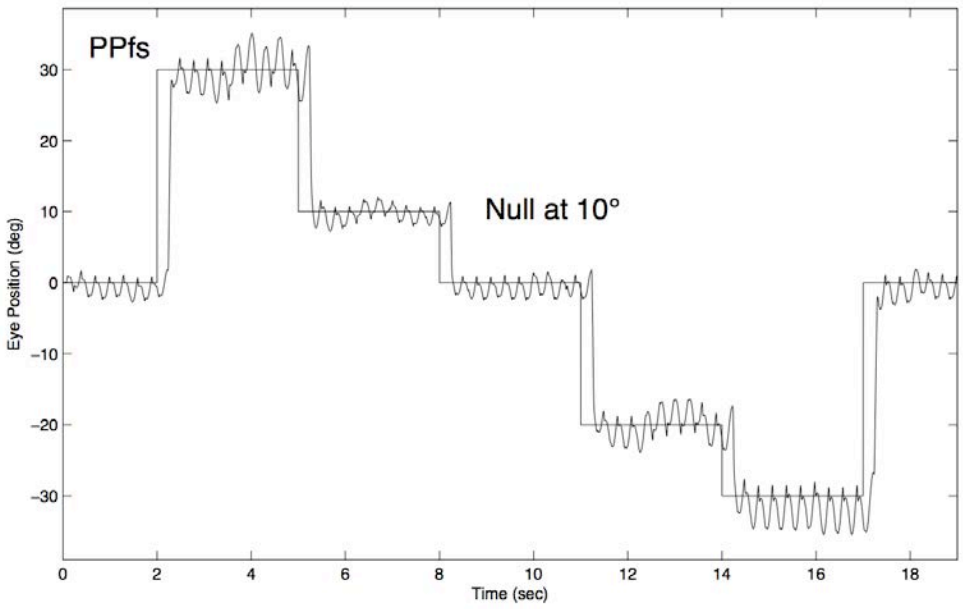

Figure 8-8. Model output of PPfs step responses with a null at 10°.

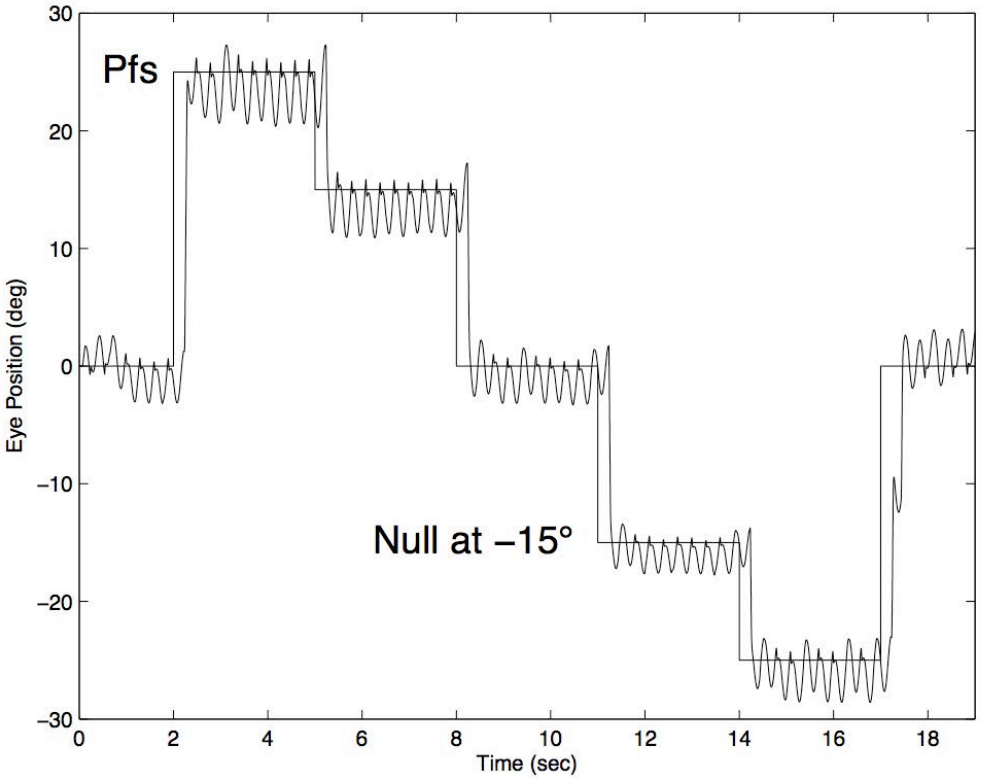

Figure 8-9. Model output of PPfs step responses with a null at -15°.

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Chapter 9

A Unifying Hypothesis for Pendular and Jerk Waveforms in Infantile Nystagmus Embodied in a Behavioral Ocular Motor System Model

9.0 Abstract

The original behavioral Ocular Motor System (OMS) model for Infantile Nystagmus Syndrome (INS) simulated the responses of individuals with several pendular waveforms (e.g., pendular with foveating saccades, Pfs, and pseudopendular with foveating saccades, PPfs) based on a hypothesized pursuit-subsystem instability and its interaction with other OMS components. We intend to expand this behavioral model by incorporating jerk waveforms within a unifying mechanism. The ocular motor recordings and observations used for the computer simulation came from approximately 1000 subjects with INS, who were recorded in our laboratory over the past 35 years. Eye movements were measured using an infrared reflection, a magnetic scleral search coil, or a high-speed digital video system. All model simulations were performed using MATLAB Simulink. The transition from PPfs waveforms to jerk waveforms required that braking saccades be replaced by foveating fast phases. That simple change produced an alternating direction jerk waveform. To simulate a unidirectional jerk waveform, the underlying pendular oscillation must be reset when each foveating fast phase is made. The use of a resettable neural integrator in the pursuit pre-motor circuitry (PMC+) enabled that resetting. The resulting waveform had foveating fast phases that approached

the target from the same direction. The “Breaking/Foveating Saccade Logic” functional block within the Internal Monitor of the OMS model was also modified. The robust simulations of accurate OMS behavior in the presence of pendular waveforms, jerk waveforms, and their transitions demonstrate that these waveforms can be generated by the *same* pursuit-system instability; this supports the hypothesis that most pendular and jerk INS waveforms are due to a loss of pursuit-system damping. Modeling OMS dysfunction (e.g., INS) continues to provide valuable insight into the functional structure of the OMS under both normal and pathological conditions.

9.1 Introduction

Infantile Nystagmus Syndrome (INS) (CEMAS_Working_Group, 2001) may exhibit either pendular or jerk waveforms, and the jerk slow phases are increasing velocity (or “runaway”) exponentials. These accelerating slow phases are always towards the neutral zone (Dell'Osso & Daroff, 1975; Dell'Osso, Flynn, & Daroff, 1974). The *primary* subsystem instability in INS is hypothesized to lie in the normally underdamped smooth pursuit system; vestibular dysfunction (imbalance) may also be present and would account for the linear waveforms seen in some patients. In the cases demonstrating an additional high-frequency sinusoidal oscillation (producing dual jerk waveforms), the nucleus of the optic tract may be involved (Dell'Osso & Daroff, 1981).

The original ocular motor system (OMS) model is a top-down, control systems model reproducing the ocular motor behavior of INS individuals (Jacobs & Dell'Osso, 2004). The OMS model evolved from models that were built on years of observation and analysis of normal and abnormal eye movement data; wherever applicable, adherence to known anatomical structure was maintained. Emphasis is put less on *where* each

functional block is located and more on and *how* they work together (i.e., the communication between them) under organizing principles resulting in known ocular motor system behaviors.

In the previous Chapter, we demonstrated the use of Alexander's law output to modulate the sinusoidal oscillation from the pursuit system for pendular waveforms of INS. In the current study, we intend to demonstrate that a unifying mechanism is capable of producing jerk waveforms. Alexander's law output will be used to determine the idiosyncratic transitions from one type of waveform to the other and their changes with gaze angle.

9.2 Methods

Recording

The ocular motor recordings and observations used for the computer simulations came from approximately 1000 subjects with INS, who were recorded in our laboratory over the past 35 years. Written consent was obtained from subjects before the testing. Subjects were seated in a chair with headrest or a chin stabilizer, far enough from an arc of red LEDs, or a reflected laser spot, to prevent convergence effects (>5 feet). At this distance the target subtended less than 0.1° of visual angle. The room light could be adjusted from dim to blackout to minimize extraneous visual stimuli. Experiments usually consisted of from eight to ten trials, each lasting a few minutes with time allowed between trials for the subject to rest. Trials were kept this short to guard against boredom because INS intensity is known to decrease with inattention.

Eye movements were measured using either an infrared reflection (IR, eye-trac 210, ASL, Waltham, MA), a magnetic scleral search coil (C-N-C Engineering, Seattle, WA), or a high-speed digital video (EyeLink II, SR Research, Mississauga, ON, Canada) system. The IR system was linear to ±20° in the horizontal plane and monotonic to 25-30° with a sensitivity of 0.25°. The search-coil system had a linear range greater than ±20°, a sensitivity of 0.1°, and crosstalk less than 2.5%. Each coil was pre-calibrated using a protractor device. The digital video system had a linear range of ±30° horizontally and ±20°vertically. System sampling frequency was 500 Hz; gaze position accuracy error was 0.5°-1° on average. The total system bandwidth for all systems (position and velocity) was 0-100 Hz. The data from all systems were digitized at 500 Hz with 16-bit resolution.

The position signal for each eye was adjusted with the other eye behind cover to obtain accurate position information; the foveation periods were used for zero-adjustment (all systems) and calibration (IR or video). Eye positions and velocities (obtained by analog differentiation of the position channels) were displayed on a strip-chart recording system. Monocular primary-position adjustments for all methods allowed accurate position information and documentation of small tropias and phorias hidden by the nystagmus.

Analysis and Simulation

All the analysis and graphics were done in MATLAB environment (The MathWorks, Natick, MA) using the OMtools software available on http://www.omlab.org ("Software and OMS Models" page). Only eye position was

sampled directly; velocity was derived from the position data by a 4th order central-point differentiator; acceleration was derived from the velocity data by the same differentiator. Position data were pre-filtered with a low-pass filter with the cutoff frequency of 50 Hz to eliminate the noise without changing the nystagmus signals to be studied. Only data from the fixating eyes were analyzed. All ocular motor simulations were performed using MATLAB Simulink (Waltham, MA).

9.3 Results

Historically, several hypotheses have been suggested for the origin of jerk types of INS waveforms. In this section, they will be discussed using human ocular motor data against or in support of them. We will also show the process used to evolve the original OMS model hypothesis to generate jerk waveforms and behaviors closely correlated with the data recordings.

The first hypothesis (Figure 9-1, top panel) is that the accelerating IN slow phases are caused by excessive positive feedback around the normally leaky (τ = 25 sec) neural integrator (NI). In control-systems analysis, this corresponds to a right-half plane pole (Dell'Osso & Daroff, 1981). However, INS patients with jerk waveforms, who simultaneously had gaze-holding problems, have been described (Dell'Osso, Weissman, Leigh, Abel, & Sheth, 1993). An example of such a combination is shown in Figure 9-1 bottom panel in which both eyes drifted back after a voluntary saccade, the left eye much more than the right eye. The eyes' drifting is a clear indication of *insufficient* gain in the NI feedback loop; the fact that it co-existed with the jerk waveforms contradicted with the hypothesis of *excessive* gain in that loop (for the same person, a gain can not be both insufficient and excessive).

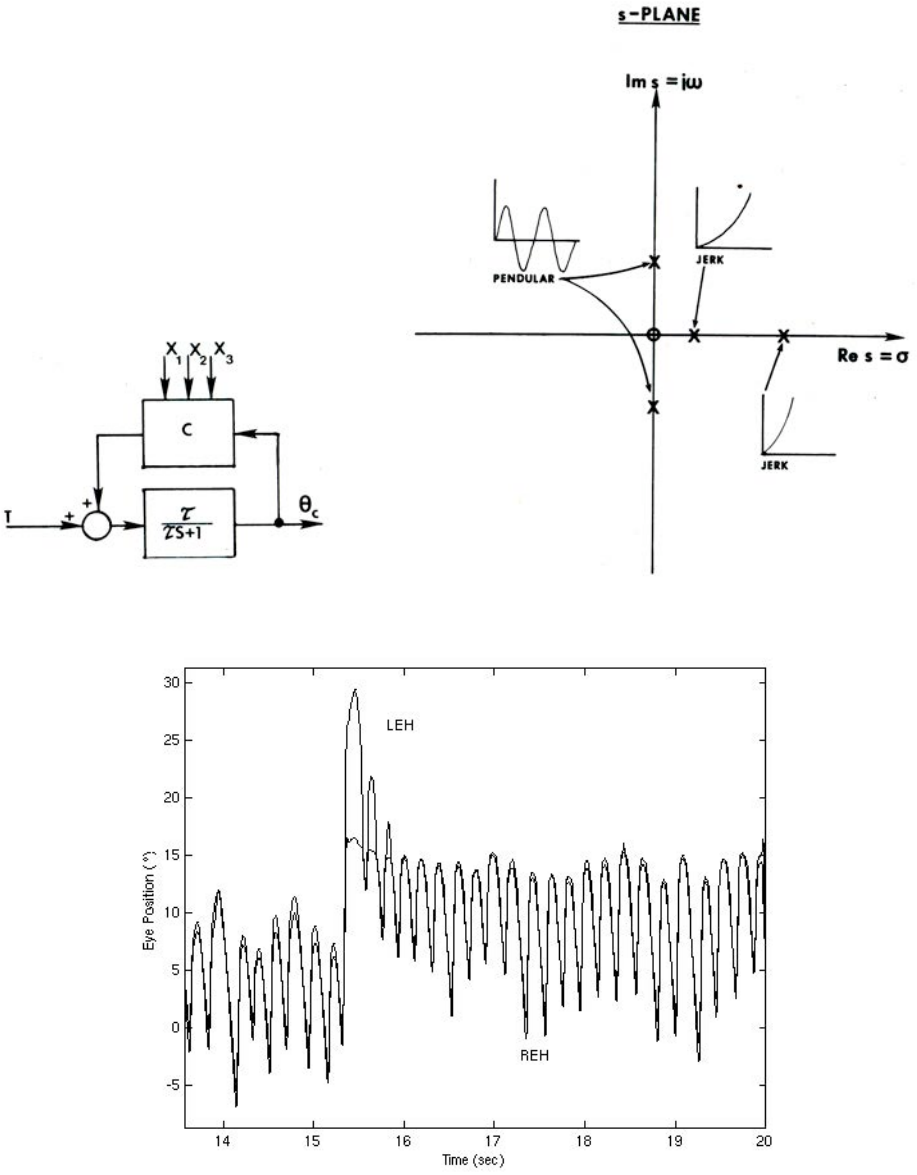


Figure 9-1. Excessive positive feedback around the normally leaky neural integrator (top left panel), a right-half plane pole generating jerk waveforms (top right panel) and human data exhibiting simultaneous jerk waveforms and gaze-holding dysfunction. LEH = Left Eye Horizontal; REH = Right Eye Horizontal. (Tops panels adapted from: Dell'Osso LF, Daroff RB: Clinical disorders of ocular movement, in Zuber BL (ed) *Models of Oculomotor Behavior and Control*. West Palm Beach: CRC Press Inc, 1981, pp 233-256.)

Another fact that disproves the excessive-gain hypothesis is that it would result in *centrifugal* acceleration but IN slow phases accelerate *centripetally* to the neutral zone. In Figure 9-1 bottom panel, the patient's neutral zone was in the left lateral gaze, the slow phases of the jerk right waveform are always centripetally towards it. Therefore, although it is possible to generate jerk waveforms with an excessive-gain around the NI, these waveforms only superficially resemble IN, i.e., they are not behavioral and the putative mechanism is a not realistic model of INS.

A second hypothesis for jerk waveforms originates from the saccadic system. However, several aspects of INS behavior strongly suggest that the saccadic system is normal in INS and unrelated to the genesis of the oscillation:

1. For static fixation, IN intrinsic saccades are *always* corrective in their direction, and two types accurately foveate the target (fs and foveating fast phases);

2. Spontaneous changes in slow-phase direction/acceleration occur in the *absence* of saccades;

3. After IN damping, new slow phases begin *without* a preceding saccade (Figure 9-2);

4. Gaze-angle variation of IN slow phases (amplitude or direction) is *independent* of the presence of saccades (Figure 9-3);

5. Voluntary saccades do *not* alter the amplitude or direction of IN slow phases and lead to accurate target foveation (Figure 9-3).

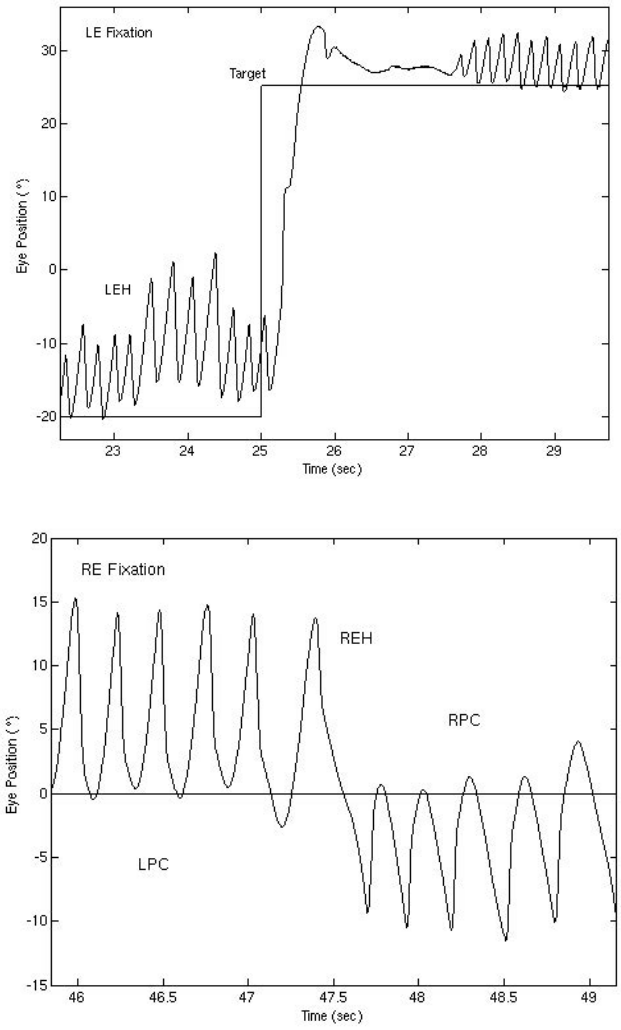


Figure 9-2. Human data showing spontaneous damping and starting of the oscillation (top panel) and spontaneous direction reversal of the jerk fast phase due to a time-varying component in the nystagmus (bottom panel). RE = Right Eye; LE = Left Eye; REH = Right Eye Horizontal; LPC = Left Pseudo Cycloid; RPC = Left Pseudo Cycloid.

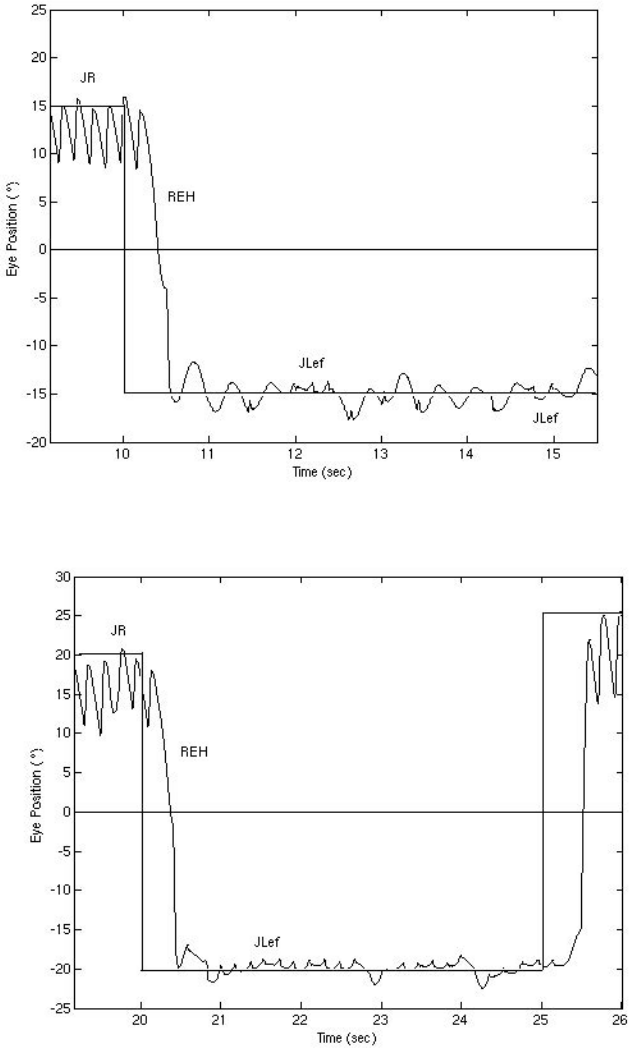


Figure 9-3. Human data showing a voluntary saccade that brings the eye from a jerk right zone to a neural zone with pendular and occasional jerk left waveforms (top panel). A larger voluntary saccade (in the same patient) that brings the eye from a more lateral jerk right zone, past the neural zone, to a jerk left zone (bottom panel). JR = Jerk Right; JLef = Jerk Left with Extended Foveation.

In Figure 9-2 top panel, the damping and starting of the INS oscillation are spontaneous; no saccades are required to enable these transitions. In the bottom panel, direction reversal of the jerk fast phase is also spontaneous, probably due to a time-varying component in the nystagmus; again, there were no saccades needed for the initiation of the reversal. Figure 9-3 shows two voluntary saccades from the same patient. One saccade (top panel) brings the eye from the jerk right zone to a neural zone with pendular and occasional jerk left waveforms; the other, larger saccade (bottom panel) brings the eye from a more lateral jerk right zone, past the neural zone, to a jerk left zone. Ocular motor data demonstrated that the gaze-angle variation of INS slow phases is independent of the presence or size of the preceding saccades.

The intrinsic saccades in the INS cycle are adaptations of the OMS for target foveation and the initiation and modulation of the INS oscillations are independent of both intrinsic and voluntary saccades. If anything, the saccadic system is performing extraordinarily well under the constantly present pendular oscillation; it cannot be the cause of that oscillation. Therefore, simple waveform models that are based on the saccadic hypothesis also produce waveforms that only superficially resemble those of INS and are neither realistic nor capable of simulating INS behavior.

Re-examination of INS inattention data suggested that the oscillation originated in the pursuit system. In this Chapter and the model, the foveating saccades made in the jerk waveforms, J and Jef, are termed “foveating fast phases” to differentiate them from the foveating saccades in Pfs and PPfs waveforms. The top panel of Figure 9-4 shows fixation in primary position with alternating direction jerk INS waveforms whose slow phases revert to pendular during inattention; the fast phases are suppressed during the

inattention and the underlying pendular component is revealed. Similarly, the bottom panel illustrates fixation at 15° right gaze with jerk right IN degenerating to pendular IN with inattention; the patient returned to jerk immediately upon verbal prompting, inhibiting the large pendular component. Figure 9-5 demonstrates some examples of enlarged show phases (including points of inflection) due to gradually occurring inattention. In this Figure, the foveating fast phase was delayed and the accelerating slow phase actually decelerated before the fast phase reset the fovea on target. As soon as attention to the target was reestablished (either spontaneously or after verbal prompting by the experimenter), a foveating fast phase was generated and jerk waveforms reoccurred. These effects can occur repeatedly, especially in young patients, as shown in the bottom panel of Figure 9-5.

Therefore, for static fixation, inattention: 1) suppresses corrective saccades; 2) results in a larger IN; and 3) uncovers the underlying pendular oscillation for most INS waveforms. Both the pendular and jerk waveforms are essentially pendular, as a result of poor calibration of the evolved damped instability in the smooth pursuit system. This unifying hypothesis is incorporated into our OMS model, as will be shown below.

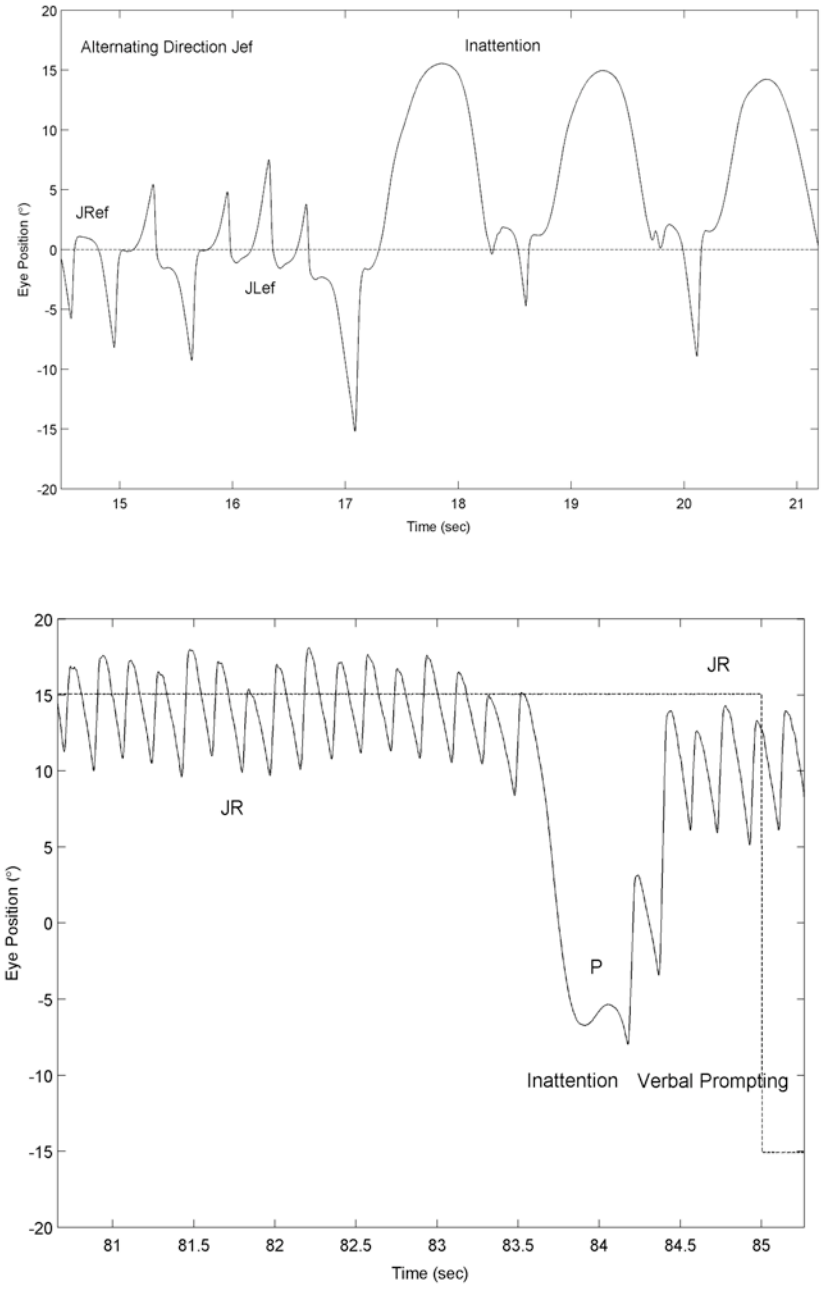


Figure 9-4. Human data showing fixation in primary position with alternating direction jerk IN waveforms whose slow phases become pendular when inattention suppresses the fast phases (top panel); Fixation at 15° right gaze with jerk right IN degenerating to pendular IN with inattention and returning to jerk after verbal prompting (bottom panel). JR = Jerk Right; JRef = Jerk Right with Extended Foveation; JLef = Jerk Left with Extended Foveation; Jef = Jerk with Extended Foveation; P = pendular.

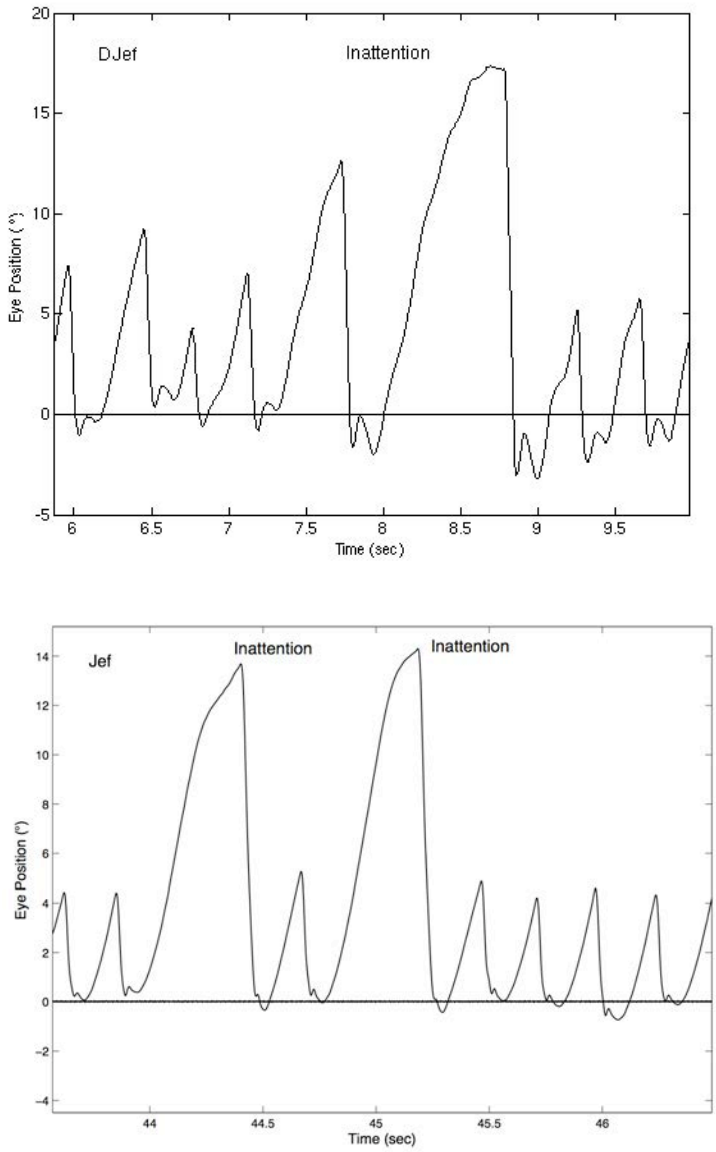


Figure 9-5. Human data showing fixation in primary position with duel jerk waveforms whose slow phases become enlarged as inattention gradually occurs (top panel); Fixation in primary position showing the waxing and waning of attention (bottom panel). DJef = Dual Jerk with Extended Foveation; Jef = Jerk with Extended Foveation.

We used the same "evolutionary" procedure to generate jerk waveforms as had been employed for pendular waveforms. To change the system's underlying pendular oscillation, the saccadic subsystem had to be modified to correctly perform under those conditions when foveating fast phases should be generated. Table 9-1 is a comparison among the intrinsic saccades made in both pendular and jerk waveforms; Figure 9-6 shows human recordings of these saccades. The transition from a PPfs waveform to a jerk waveform required that braking saccades be replaced by fast phases. We first altered the functional block ("Breaking/Foveating Saccade Logic") within the Internal Monitor. This block contains the logic that would normally trigger the braking saccades of IN or fast phases of induced nystagmus (e.g., vestibular or optokinetic). A simple modification to that functional block gave rise to alternating direction jerk nystagmus (i.e., unidirectional jerk cycles whose foveating fast phases were made in alternating directions from both sides of the target). Figure 9-7 shows an interval of fixation simulation at primary position, similar to INS individuals with alternating direction jerk nystagmus.

	PPfs		**Jerk**
	Braking Saccade	**Foveating Saccade**	**Foveating Fast Phase**
Position Criteria	The eye is running away from the target	The eye is approaching the target	The eye is running away from the target
Amplitude and Direction Calculation	Stereotyped (fixed amplitude)	Should accurately take into account the prediction of where the eye will be 60 ms later (default value based on current distribution of internal delays)	Should accurately take into account the prediction of where the eye will be 60 ms later (default value based on current distribution of internal delays)
Velocity Criteria	Velocity exceeds user-settable thresholds for idiosyncratic waveforms		
Acceleration Criteria	Acceleration is below user-settable thresholds for idiosyncratic waveforms		

Table 9-1. Comparison of braking and foveating saccades in PPfs and foveating fast phases in jerk waveforms.

To convert an alternating direction jerk waveform into a unidirectional jerk waveform, several modifications were necessary. First of all, the oscillation needed to be reset when each foveating fast phase was made. The use of a resettable neural integrator in PMC+ accomplished the resetting (Figure 9-8). This neural integrator has the same structure as the one in pulse generator (Abel, Dell'Osso, & Daroff, 1978; Abel, Dell'Osso, Schmidt, & Daroff, 1980; Kustov & Robinson, 1995), distinct from the common neural integrator that appears in the final motor pathway. We used the motor command for foveating fast phases as a resetting signal, i.e., when the BS/FS logic box indicated the need to generate a foveating fast phase, the pendular oscillation underlying pendular INS waveforms was reset. The foveating fast phase motor command was appropriately prolonged (35 ms) and delayed (5 ms). Due to the time delays in both the feedback and feedforward loops, the resetting required that those time delays also be reset (i.e., the stored energy needed to be dumped). The “Null Mod” block in the PMC+ is used to determine the starting direction of the oscillation, which in turn dictates the fast-phase direction.

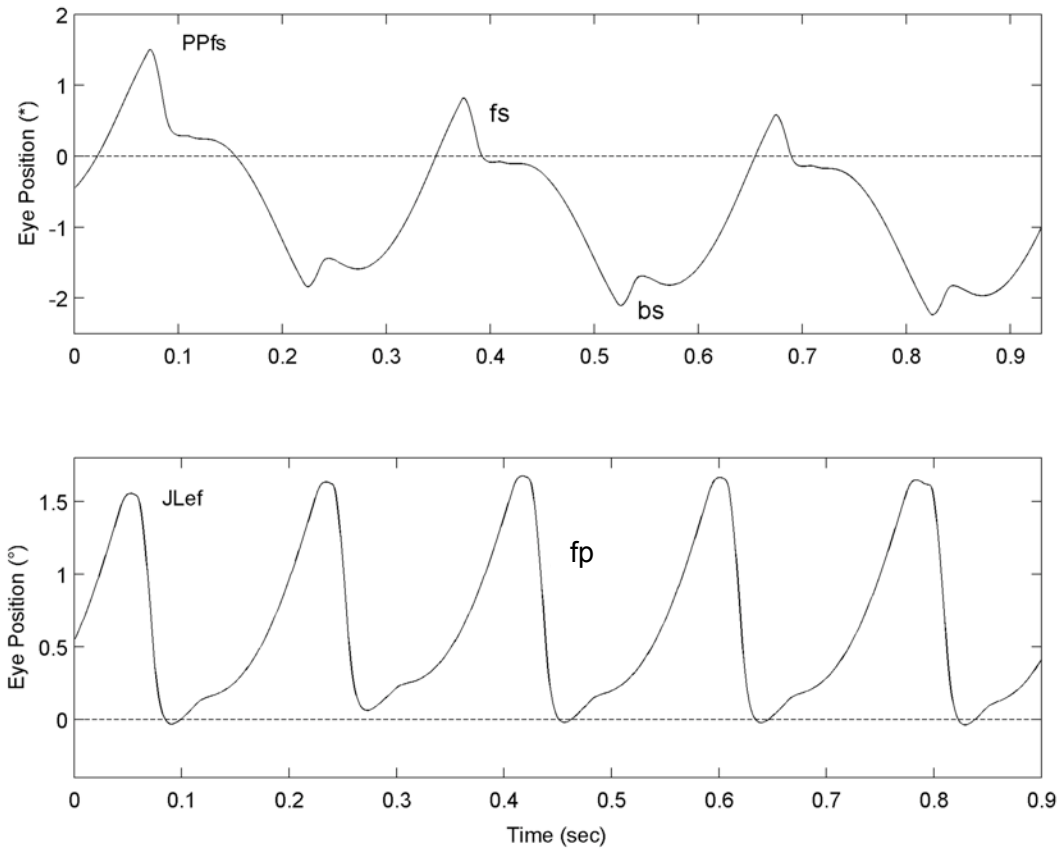


Figure 9-6. Human data showing comparison of foveating and braking saccades in PPfs and foveating fast phases in jerk waveforms. Fixation data at primary position are shown. PPfs = PseudoPendular with foveating saccades; JLef = Jerk Left with extended foveation, fs = foveating saccade, fp = fast phase, bs = braking saccade.

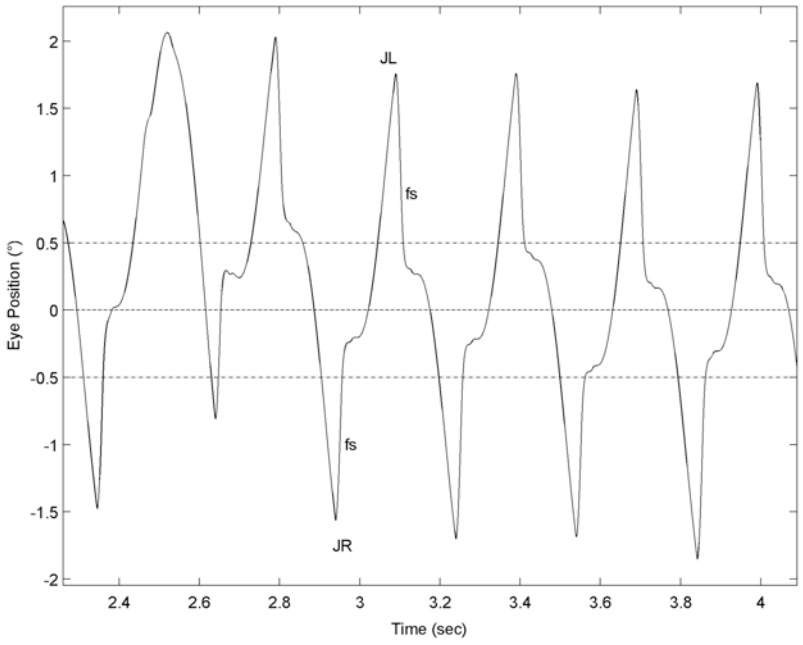


Figure 9-7. OMS model simulation of alternating direction jerk nystagmus. Fixation data at primary position are shown. In this and subsequent Figures, dashed lines indicate target position, dash-dotted lines around target-position indicate foveal extent (±0.5°), JR = jerk right, JL = jerk left, and fs = foveating saccade.

Secondly, the outputs of the Alexander's law circuit were rearranged. A "Null Side" output was used to determine which side of (and how far from) the neutral zone the current eye position is, based on efference-copy estimation. The neutral zone is defined as the gaze angles where pendular type waveforms exist; for some patients, it can be different than the null zone (the gaze angles where the amplitude/intensity is lowest). Most of the time, neutral zone is referred to when waveform transition is discussed; the null zone (more accurately, the NAFX peak) is referred to in regard to visual function. The "Null Side" Alexander's law output is critically important for enabling the transitions among waveforms, and allowing the simulated slow phases to accelerate centripetally toward the neutral zone. Figure 9-9 shows the Alexander's law circuitry used in this model, which is a slightly modified version of the original shown in Figure 8-3; for simplicity, part of the latter was relocated as the "Null Mod" block within the PMC+ block.

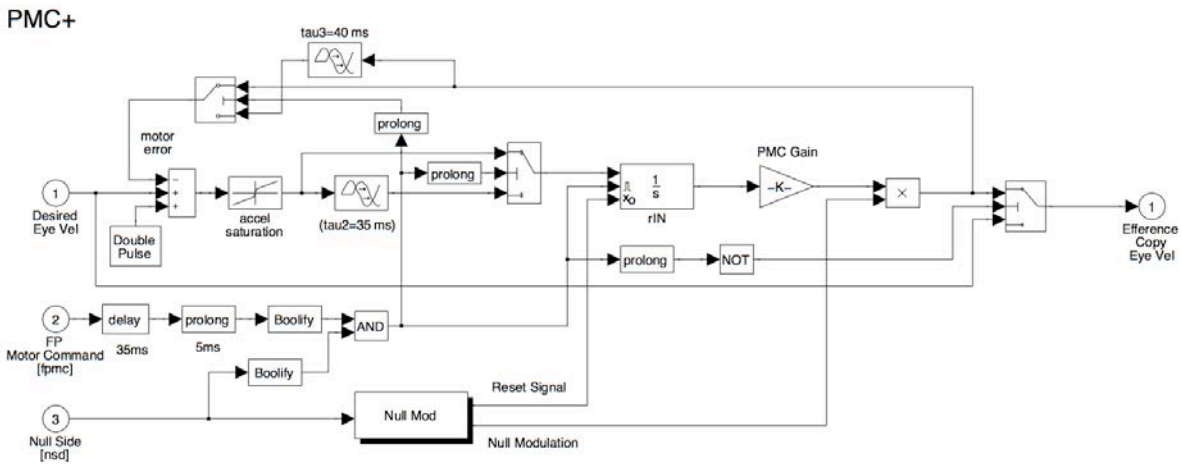


Figure 9-8. Modified premotor circuitry (PMC+) block in the OMS model. The PMC+ block generates a restarted oscillation for every jerk nystagmus cycle, using resetting signals (delayed, prolonged and boolified) from the foveating fast phase motor command (fpmc).

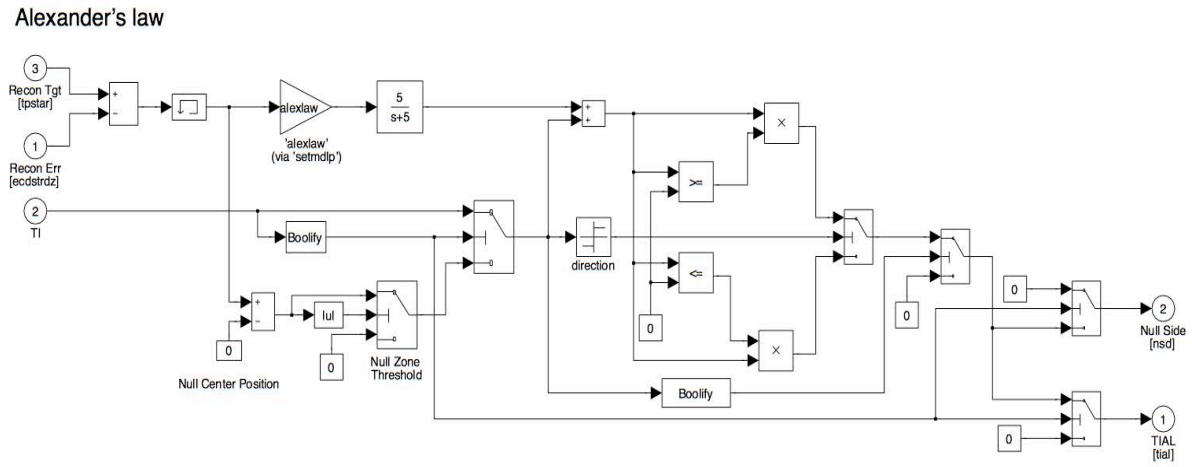


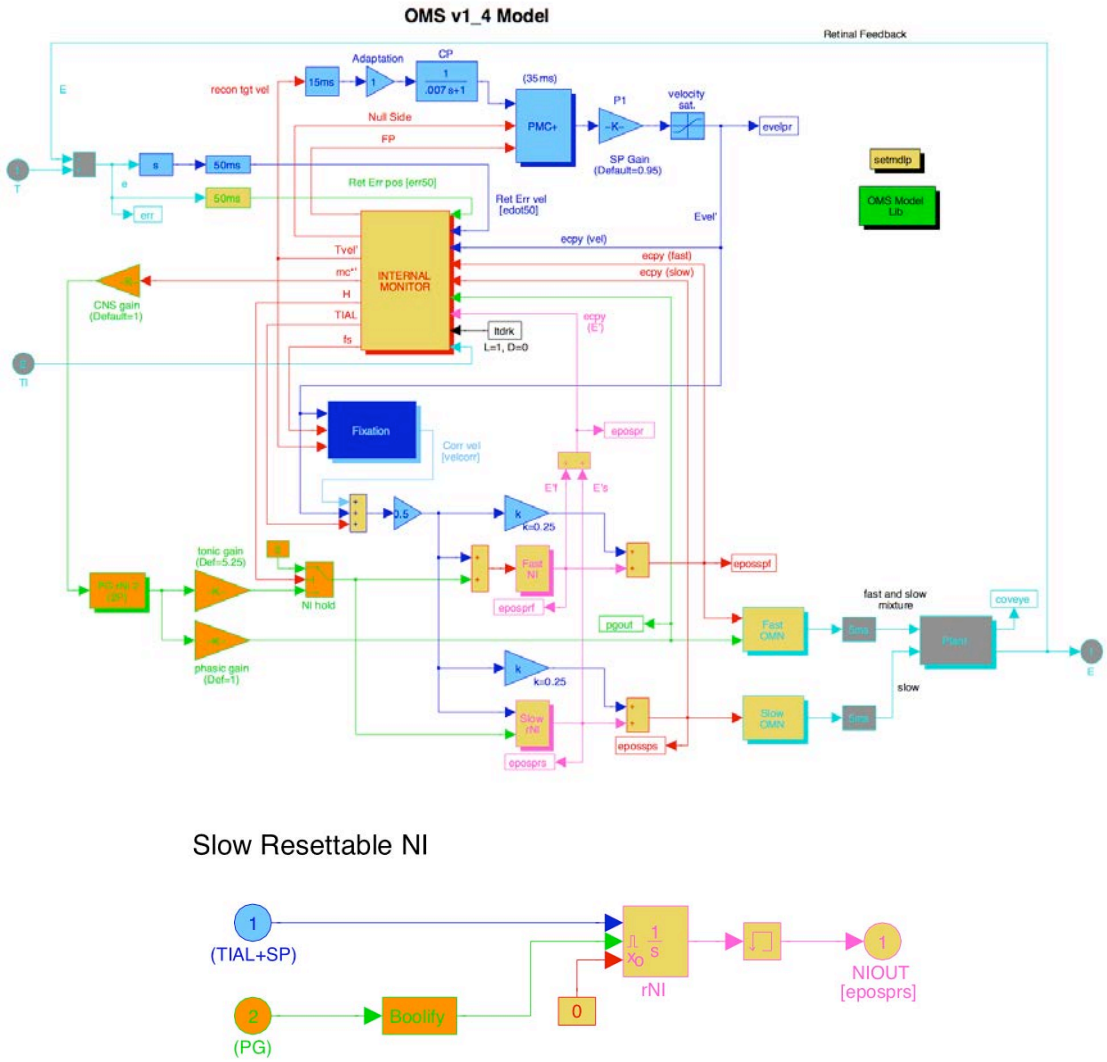
Figure 9-9. Modified Alexander's law block generating a "Null Side" signal.

Thirdly, the BS/FS logic was further modified to accurately generate foveating fast phases in jerk waveforms. Those fast phases are different from the foveating and braking saccades in the PPfs waveforms (Figure 9-6 and Table 9-1). Braking saccades are automatically generated to brake runaway eye velocities. For the PPfs waveform, the logic necessary to decide whether a saccade will be braking or foveating is the following: If the eye is running away from the target at the time of saccade programming (which precedes the actual time the saccade is generated), the velocity exceeds a user-settable threshold (default = 4°/s), and has passed its point of maximum velocity (i.e., is not still accelerating), a braking saccade will be generated. This is consistent with the definition of a braking saccade (Dell'Osso & Daroff, 1976; Jacobs, Dell'Osso, & Erchul, 1999). If, however, the eye is approaching the target at that time, and the velocity exceeds the threshold, and falls below the acceleration threshold, then the saccade will be foveating, with the magnitude and direction calculated by the predicting where the eye will be 60 ms later (default value based on the current distribution of internal delays in the model), when the saccade will occur. In jerk waveforms, foveating fast phases are made when the eye is running away from target, the same as braking saccades. Under this circumstance, the logic for fast-phase timing was the same as for braking saccades in the PPfs case. However, there are distinct differences between the amplitude of those two types of saccades. Braking saccades have small, stereotyped amplitudes independent of the eye's position vis-à-vis the target, while the foveating fast phases of jerk waveforms are larger and must accurately foveate the target by correcting the position error. The required magnitude is calculated by predicting where the eye would be 60 ms later (when the

saccade would occur), similar to the method for calculating the amplitudes of foveating saccades in PPfs.

The last modification required was on the neural integrator for the group of slow motor neurons. We incorporated the jerk waveform changes into the model presented in Chapter 7, which had separate groups of motor neurons for the slow and fast eye movements (Ugolini, et al., 2006). A potential problem occurs with that model if the pursuit system generates a velocity signal with a DC value (as would be the case for jerk waveforms). The integration output of the slow NI (the NI neurons associated with the slow motor neuron pathway) would constantly grow due to that DC value, whereas the output of the fast NI would be reset by its saccadic input. Left unchecked, the slow NI output could grow unbounded as the simulation ran, although the summed outputs of the fast and slow NIs would still reflect the true current eye position. This potential problem had to be solved because the NI represents a group of firing neurons and a potentially infinite output is not physiological. In the pendular waveforms we simulated using the original model (Jacobs & Dell'Osso, 2004), the DC value of the sine-wave velocity oscillation was always 0, therefore this problem did not arise when the single NI was expanded to fast and slow NIs.

We hypothesize that although the slow NI does not integrate the saccadic pulse signals, it might use signals derived from saccadic pulses to regulate its output. When the input has a DC value, the saccadic signals reset the slow NI output, similar to what saccadic pulses do automatically to the fast NI. The Model shown in Figure 9-10 has been updated with a resettable slow NI, the details of which are presented in the bottom panel.



Slow Resettable NI

Figure 9-10. Updated OMS model that simulates jerk waveforms (top panel); details of the slow resettable neural integrator (bottom panel).

The modifications described above allowed simulation of unidirectional jerk waveforms. Some fixation simulations are displayed in Figure 9-11. The three traces are all fixation at 0°; jerk right and jerk left waveforms are plotted at different locations for clarity. The PPfs simulation is shown for comparison. The dot-dashed lines are indication of the ±0.5° fovea. In all three waveforms, although there were slight differences between the sizes of each saccade, the final target-image position always remained within the ± 0.5° foveal area (which allows the best visual acuity). Like most pendular waveforms recorded in humans, the foveation period generated by the model extends up to 50 ms. The jerk waveforms simulated here have a much longer and flatter foveation period right on target (up to 300 ms), suggesting good visual function. An interesting side note is that if we reduce the calculation accuracy for the fast phases in jerk waveform generation (a scale factor in the model), pseudocycloid waveforms result, as shown in Figure 9-12.

The model also responded accurately to step changes in target position and smoothly transitioned to another type of waveform depending on eye position (Figure 9-13). In this Figure, the neutral zone of the "simulated subject" is set to be ±5° around the primary-position null; as long as the intended eye position is in this range, pendular waveforms will result. Right lateral gaze beyond that zone triggers jerk right waveforms, with the slow phases accelerating towards the neutral zone; left lateral gaze triggers jerk left waveforms. Also note that the size of the jerk nystagmus grows as the eye goes more laterally; this represents a "medium" null broadness setting so the gaze-angle amplitude variation is moderate. In all simulations, the voluntary and intrinsic saccades work in concert to acquire and foveate the target. For large target steps, it took a greater than

normal amount of time for the eye to arrive on target, also consistent with the findings in Chapter 6.

9.4 Discussion

When the behavioral OMS model was published in 2004 (Jacobs & Dell'Osso, 2004), it simulated the ocular motor responses of INS patients with Pfs and PPfs waveforms and demonstrated that our hypothesis for the generation of P, Pfs, and PPfs waveforms could be realized by a functionally normal OMS with accurate responses to a broad variety of visual stimuli. Although jerk INS is the simplest waveform to simulate using many methods, we did not hypothesize its mechanism at that time because of the need to allow easy transitions with pendular waveforms when gaze is shifted. In this study, we did not add a separate mechanism for jerk waveforms to the current version of the OMS model because, in agreement with observations and accurate eye movement recordings on inattention and waveform transition, the pendular and jerk waveforms are derived from the same underlying mechanism, i.e., an undamped smooth pursuit subsystem. For the first time, a model has been built that simulates both pendular and jerk INS behaviors, plus easy transitions from one to the other.

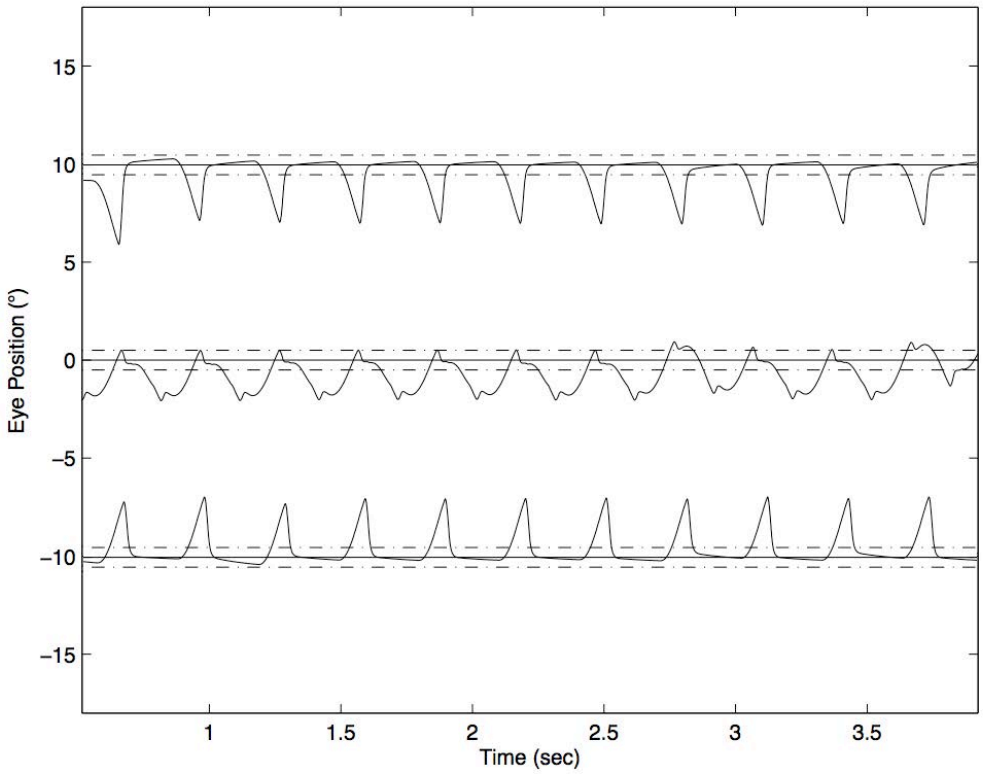


Figure 9-11. OMS model simulations of 0° fixation comparing jerk and pendular waveforms; jerk right and jerk left waveforms are plotted at different locations (10° and -10°, respectively) for clarity. The dot-dashed lines are an indication of the ±0.5° fovea.

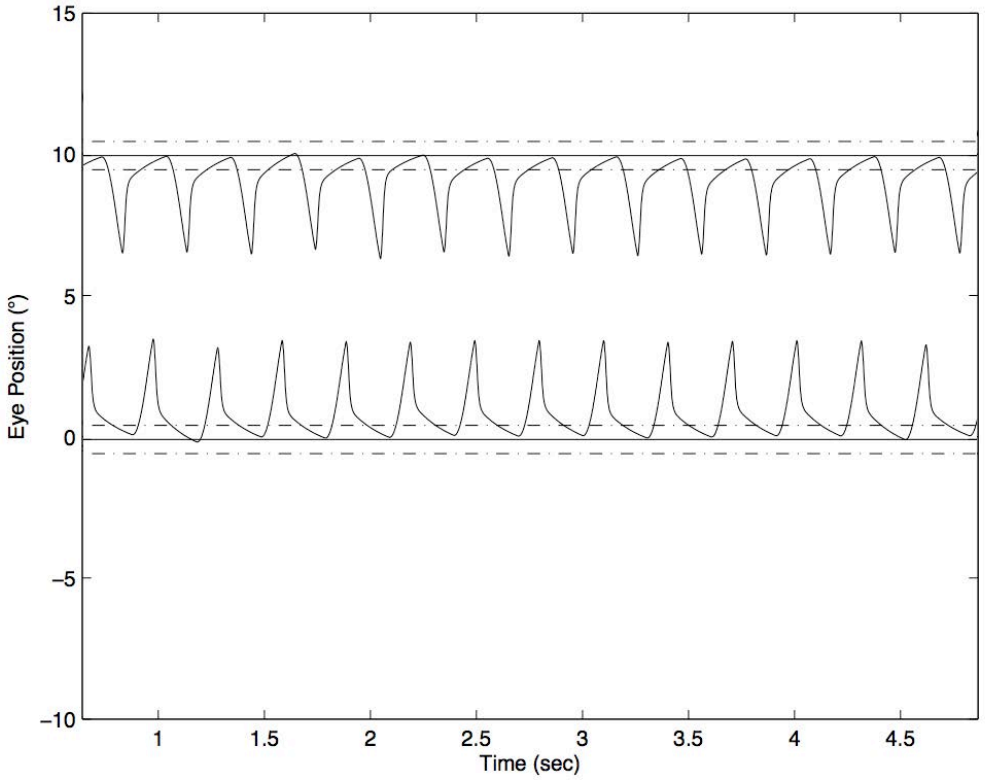


Figure 9-12. OMS model simulations of 0° fixation during pseudocycloid waveforms in either direction; right pseudocycloid waveforms are plotted at a different location (10°) for clarity. The dot-dashed lines are an indication of the ±0.5° fovea.

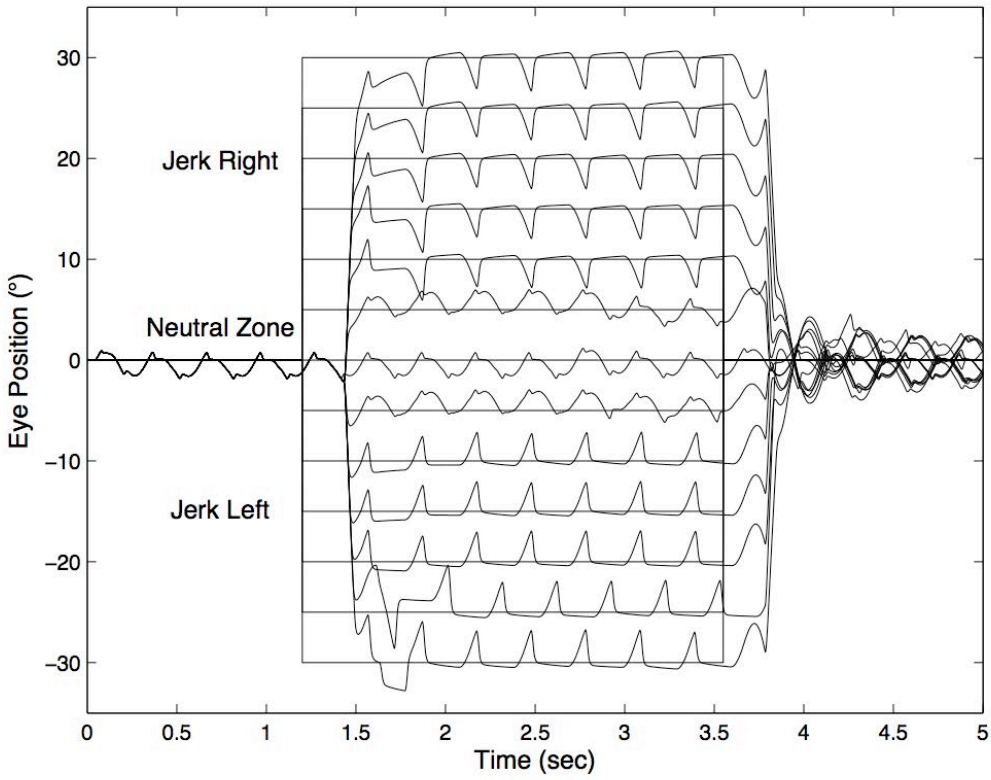


Figure 9-13. OMS Model simulation of a subject with a ±5°, primary-position neutral zone, and a medium null broadness; jerk right waveforms occur spontaneously in right lateral gaze, jerk left in left lateral gaze.

The conception of a resettable PMC+ is in accordance with the observations about inattention discussed above. The fast phases as shown in the recordings suppress the underlying pendular component; the delaying and inhibiting of the fast phases, spontaneously or due to attention, will eventually reveal that pendular oscillation. The resetting of an oscillation (i.e., dumping the energy) in a short amount of time is not a new concept in the ocular motor system. An eye-velocity storage mechanism has been postulated in the vestibulo-optokinetic system to account for the prolongation of vestibular nystagmus (VN) and the occurrence of optokinetic after-nystagmus (OKAN) (Kustov & Robinson, 1995). Presentation of a subject-stationary full-field surround during VN and OKAN rapidly reduces activity related to eye velocity of the storage mechanism. This decrease in activity occurs with a shorter time constant compared to that in control trials, it has been called "dumping" (Raphan, Matsuo, & Cohen, 1979). The PMC+ resetting is also reasonable in engineering terms. A damping circuit needs to be discharged with all its energy storing devices in order to be reset and restarted; this discharging takes time, which is consistent with the fact that our resetting signal from the fast phase motor command had to be prolonged. After the "dumping", it is also critical to restart the oscillation in a timely fashion; this is achieved by the Alexander's law output which governs the sign of the initial condition in the PMC+ resettable neural integrator. The long foveation times seen in patients with Jef waveforms probably emerged from the time needed to reset the pendular oscillation.

Incidentally, we also found that altering the fast-phase scale (e.g., an inaccurate estimation of required fast-phase size) would change the waveform from jerk to pseudocycloid. The emergence of this common INS waveform further supported the

hypothesis all the jerk waveforms, although having different morphology, originate from the *same* underlying pendular oscillation.

The hypothesis of a resettable slow NI is based on its behavioral input and output. Given a unidirectional signal with a DC value as an input, the slow NIs will constantly integrate if they are not periodically reset. In normals or INS subjects with pendular waveforms, this is not problematic because the slip-velocity input to the slow IN always straddles zero. In the case of FMNS simulations (Dell'Osso & Jacobs, 2001), this also caused no problem because the velocity input to the fast NI comes from a tonic imbalance, not from the pursuit system. Our hypothesis is that although the slow NI does not integrate the saccadic inputs, they are still used as reset signals for the velocity input signal from the pursuit system. Physiologically, the groups of slow NI neurons and fast NI neurons are located in adjacent regions (Ugolini, et al., 2006); it is possible that the slow NI neurons are connected through interneurons that enable its resetting.

Simulations with various target inputs confirmed the robustness of this unified model. Compared to most patient data, the model outputs had less cycle-to-cycle variation. This was because this model was constructed under the assumption that this oscillating OMS is otherwise healthy, i.e., no afferent deficits are present. This is usually not true in the case of a patient. Also, the abilities of gaze holding and generating accurate, consistent foveating fast phases differ greatly in patients, which explains the large idiosyncratic differences in beat-to-beat accuracy, even for patients with the same types of nystagmus waveforms.

The step-input responses shown in Figure 9-13 exhibited the model's ability to produce waveforms with accelerating slow phases *towards* the neural zone (which, in this

case, is at primary position). This is a property consistently found in INS eye-movement recordings; our model is the first model that successfully simulates this pathognomonic characteristic.

The values of saccadic latency in the simulations are in agreement with human data. Data analysis on patients with PPfs, jerk, and dual jerk waveforms showed that nystagmus subjects had a slightly higher latency than normal subjects for generating voluntary saccades (Wang & Dell'Osso, 2007). Average values for normal subjects are ~250 ms (Leigh & Zee, 2006). Depending on which time of the cycle that the stimulus change occurred, the time needed to arrive at the target varied. This model used the normal subjects' average value of ~250 ms as the saccade latency. It can easily be altered to match the value corresponding to the performance of an individual nystagmus subject.

This preliminary study strongly supports the hypothesis that both pendular and jerk waveforms can be generated by the same pursuit-system instability and that most pendular and jerk INS waveforms are due to a loss of pursuit-system damping. Future work will simulate idiosyncratic foveation quality with different durations of foveation time; the model will be tested on pursuit and more complex inputs; the transitional periods among all the waveforms will be made to occur more smoothly in the model. OMS dysfunction (e.g., INS), simulated by behavioral models, continues to provide valuable insight into the functional structure of the OMS under both normal and pathological conditions.

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Chapter 10

Conclusions

10.1 Summary

The goals of this dissertation were to better understand the underlying mechanisms of infantile nystagmus syndrome (INS) in terms of its static characteristics, dynamic properties, and changes after extraocular muscle (EOM) surgeries, and to incorporate these findings into a behavioral Ocular Motor System (OMS) model.

10.1.1 Effects of four-muscle tenotomy: "more", "better" and "faster"

In Chapter 2, the effects of four-muscle tenotomy on static fixation at various gaze angles were presented (Z. Wang, Dell'Osso, Jacobs, Burnstine, & Tomsak, 2006). The eXpanded Nystagmus Acuity Function (NAFX) and clinically measured visual acuities were used to quantify the tenotomy-induced changes at primary position and lateral gaze angles. It was shown that tenotomy produced higher primary-position NAFX increases in patients whose pre-tenotomy values were relatively low, and higher broadening effects in patients with a sharp null. This study confirmed the findings of primary-position foveation improvement in previous studies (Hertle, et al., 2003; Hertle, Dell'Osso, FitzGibbon, Yang, & Mellow, 2004), while quantifying the broadening effects using a longest-foveation-domain (LFD) measurement. The positive effects supported the hypothesis that tenotomy helped INS patients to see "more" (broadened range of high-foveation-quality field) and "better"(finer foveation quality at each gaze angle). This study, along with its predecessors (Dell'Osso, Hertle, Williams, & Jacobs, 1999; Hertle,

et al., 2003; Hertle, et al., 2004), extends the utility of surgical therapy to several different classes of patients with INS for whom other procedures are contraindicated.

Individual patients might have different amounts of improvement, dependant on their pre-surgical starting point. We found that most patients had either a sharp null or low NAFX values, or both; therefore, they can benefit from at least one aspect of improvement brought by tenotomy. It is also important to note that the proprioceptive nature of tenotomy's improvement effects require that the muscles operated on are "virgin" muscles. Prior EOM surgeries might exclude tenotomy from the surgical options.

Chapter 7 is a systematic study of the post-tenotomy changes in INS target acquisition time (Lt). Consistent with our model prediction, improvement in Lt, ranging from ~200 ms to ~500 ms (average ~ 280 ms), was documented in all 5 patients post-tenotomy. Therefore, tenotomy helped INS patients to see "faster", which is a highly desirable post-surgical effect in patients' daily life.

Every INS patient has some idiosyncrasies in waveforms, null positions, and foveation capabilities. Tailoring the nystagmus treatment in different patients is critically important, as shown in Chapter 3 (Z. I. Wang, Dell'Osso, Tomsak, & Jacobs, 2007). Any attempt to generalize INS therapies into a simple "best" equation is misleading and problematic. One should take the following steps to ensure an accurate diagnosis and treatment plan:

1. Through eye-movement recordings, determine type of nystagmus (INS or Fusion Maldevelopment Nystagmus Syndrome (FMNS), INS plus FMNS, or INS with a latent component);

2. Properly calibrate and analyze the eye-movement recordings to determine the fixating eye in each trail and the null position; compare the null with patients' report of their preferred head posture for consistency;
3. Once the null type and position is determined, the amount of surgical muscle movement on the fixating eye can be calculated;
4. If the non-fixating eye has strabismus, that amount has to be considered for alignment along with the nystagmus surgery on the fixating eye.

In Chapter 4 (Z. I. Wang & Dell'Osso, 2007a), we demonstrated the use of NAFX and LFD to predict both primary-position acuity improvements and broadening of a patient's high-NAFX range of gaze angles. With this extremely useful information, physicians and their patients can now know *a priori* how much improvement they might expect to receive, thereby guiding the decision about whether or not to have the surgery.

It would be ideal that all three aspects of INS be evaluated before and after treatments of nystagmus as a more realistic and complete evaluation: how well a patient sees at primary gaze, how broad the high-acuity field is and how fast the patient acquires moving targets; eye-movement data allow a measure of all three aspects.

10.1.2 Implications of Tenotomy's mechanism

Tenotomy, used in isolation or combination with existing nystagmus and strabismus surgeries, damps different types of nystagmus in their plane of action, as shown in Chapters 2, 3, and 4. A proprioceptive hypothesis for nystagmus damping has been postulated based on the tenotomy findings and may explain the damping from contact lenses, cutaneous stimulation and neck-muscle vibration. Recent neuroanatomical

and neurophysiological discoveries support the hypothesis that proprioception is the mechanism for INS damping and allow more realistic models of peripheral ocular motor pathways.

Studies and applications of INS therapies over the past two decades have led to a resurgence of interest in the role of proprioception in ocular motor control. The damping of INS with contact lenses implicated exteroceptive signals carried via the V cranial nerve (Dell'Osso, Traccis, Abel, & Erzurum, 1988). That is, afferent stimulation via the ophthalmic division of the trigeminal nerve was able to modulate the oscillation; the effect seemed to be immediate. Somehow, signals brought back to the trigeminal (semi lunar) ganglion were able to affect brainstem ocular motor signals. The discovery that other forms of afferent stimulation also damped INS (in ms) reinforced the hypothesis that proprioception played an important role in ocular motor control (Sheth, Dell'Osso, Leigh, Van Doren, & Peckham, 1995). Finally, the demonstration that the four-muscle tenotomy procedure improved INS waveforms (and eliminated seesaw nystagmus) in a canine, in less than 18 hours (Dell'Osso, et al., 1999) and in humans (noted immediately post-op by mothers) (Hertle, et al., 2003; Hertle, et al., 2004) provided strong evidence in support of the proprioceptive hypothesis. The success of the tenotomy procedure in many INS patients (Z. Wang, Dell'Osso, Jacobs, et al., 2006), in the acquired pendular nystagmus of MS (Tomsak, et al., 2005), and in downbeat nystagmus (Z. I. Wang, et al., 2007) further solidified the role of proprioception in nystagmus modulation in each plane, independent of the site or mechanism of the oscillation. Recent research has also identified proprioceptive signals in the cortex (X. Wang, Zhang, Cohen, & Goldberg, 2007). We note at this point that convergence also damps INS rapidly and broadens the

null region—the *same* effects as afferent stimulation and tenotomy (Serra, Dell'Osso, Jacobs, & Burnstine, 2006).

Chapter 5 demonstrated our findings that the tenotomy procedure affects only small signals (e.g., nystagmus slow phases) and not saccades, suggested that current models of the ocular motor plant are inadequate (Z. Wang, Dell'Osso, Zhang, Leigh, & Jacobs, 2006). Although the ocular motor neurons (OMN) studied by Keller and Robinson (presumably, the "fast" OMN) did not have a fast stretch reflex, they could still be part of a slower (e.g., a time constant of minutes, hours, or days) tension-control reflex, as is illustrated in Figure 10-1. The tension-control loop is independent of the main ocular motor control loop and serves to maintain the resting tension, and therefore (because muscle response is a function of its length) the small-signal gain of the extraocular muscles. Originally, our proprioceptive hypothesis for the mechanism behind the effects of tenotomy was built on the presumption that even in the absence of a short-time-constant stretch reflex, proprioceptive information is used by the OMS for long-term control and adjustment. Because afferent information from the V cranial nerve (e.g., from cutaneous stimulation of the eyelids or forehead) had an *immediate* damping effect on INS, this pathway provides a means of on-line modulation of eye movements. This had presented us with a dilemma; why is there a fast exteroceptive pathway but only a slow proprioceptive pathway? Also, how could cutting a tendon (especially at its distal end), which presumably had no neurological substrate, affect an afferent signal?

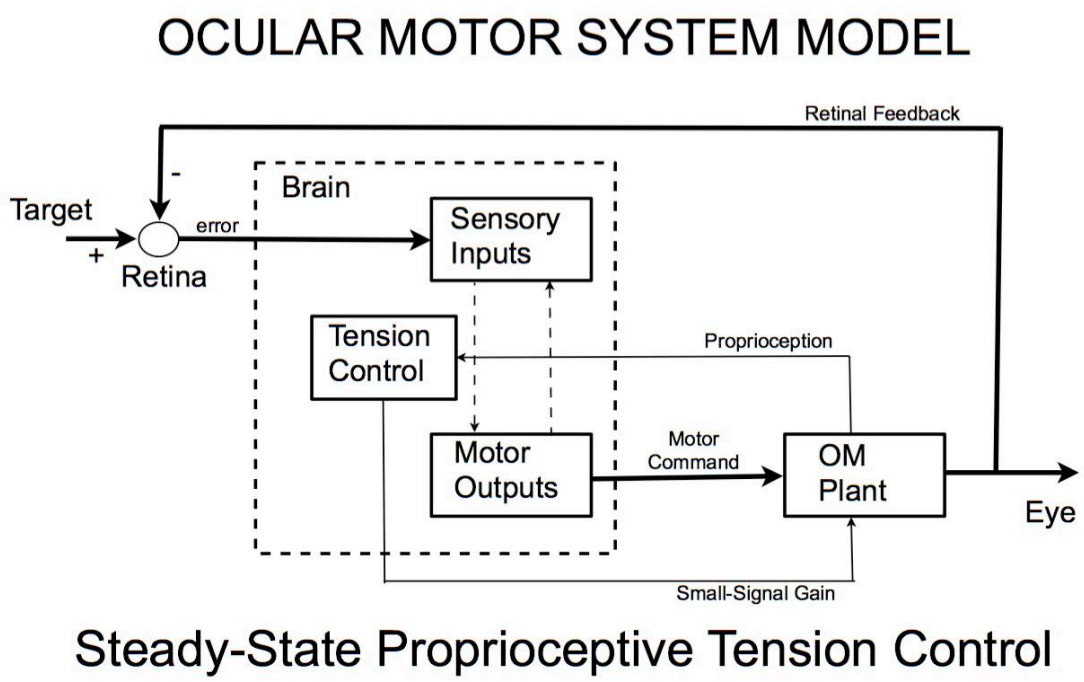

Figure 10-1. Block diagram of the OMS showing the addition of a putative proprioceptive tension-control loop. This latter loop was hypothesized to control resting muscle tension and with it, the small-signal gain of the ocular motor (OM) plant. The OMS operates on both retinal error and efference copy of motor commands.

The existence of two types of OMN, two major types of extraocular muscle fibers, palisade endings, and proprioceptive representation in the primary somatosensory cortex not only provided neuroanatomical and neurophysiological substrates for our conclusions but also allowed us to refine and extend our hypothesis (Büttner-Ennever, Horn, Graf, & Ugolini, 2002; Büttner-Ennever, Horn, Scherberger, & D'Ascanio, 2001; Eberhorn, et al., 2005; X. Wang, et al., 2007). In Figure 10-2, we show two possible tension-control loops, one for the fast OMN and another for the slow OMN. If the former exists, it would have to be a slow calibration/control for maintaining calibration to be consistent with earlier findings (Keller & Robinson, 1971). Although the slow-OMN loop may be similar, it more probably operates on a faster time scale, i.e., more like a skeletal stretch reflex. In Figure 10-3 (bottom), we show schematically, based on Büttner-Ennever's work, the efferent connections from the various ocular motor subsystems to both the fast and slow OMN.

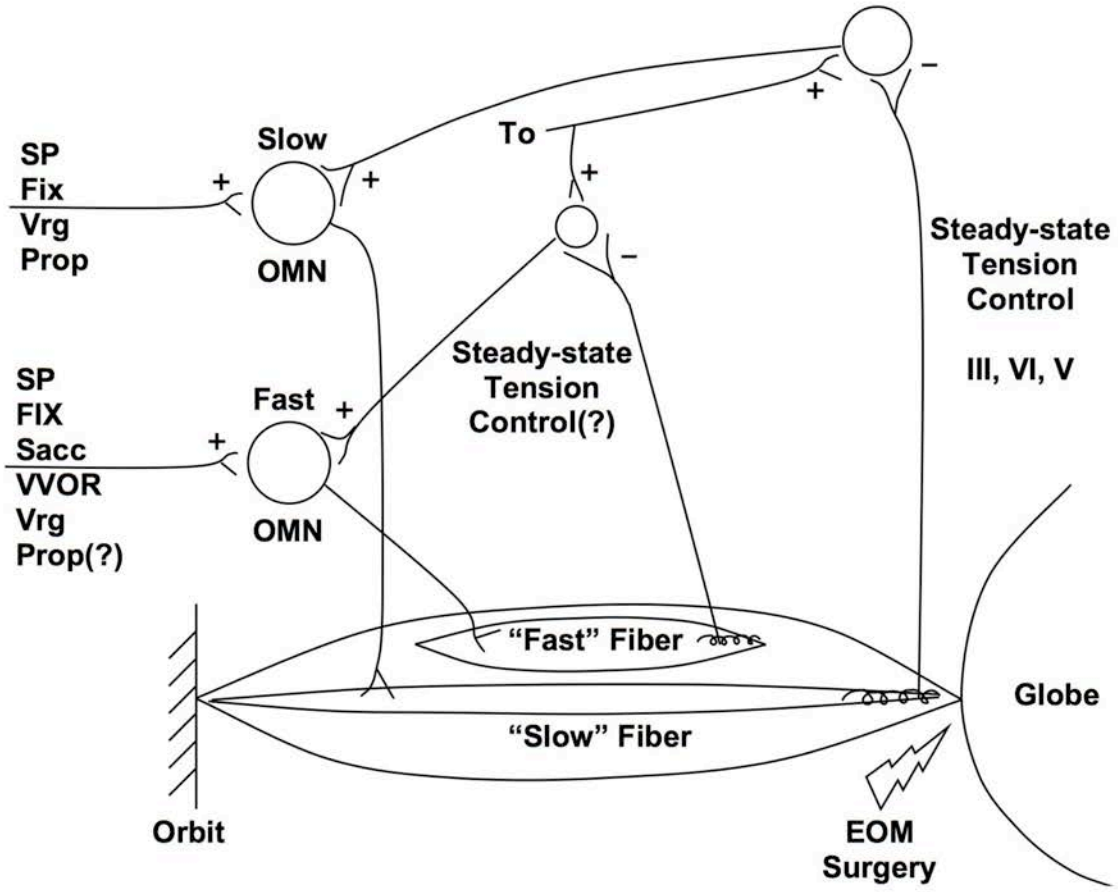

Figure 10-2. Putative proprioceptive, tension-control feedback loops for both the "fast" and "slow" OMN and fibers. The "fast" fibers may be involved in slow tension control and the "slow" fibers in a faster, on-line tension control loop. The site of extraocular muscle (EOM) surgery is identified.

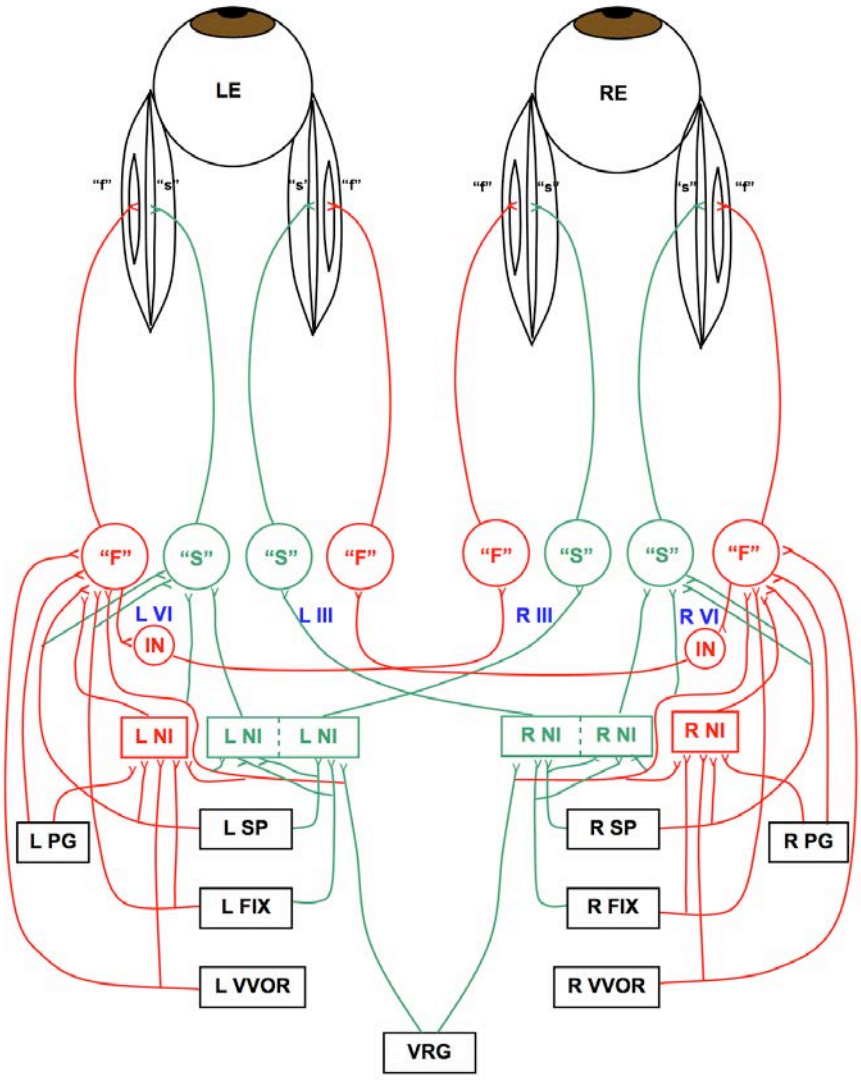

Figure 10-3. Putative wiring diagram for both the "fast" and "slow" OMN and the ocular motor subsystems. Different neural integrator populations on each side of the brain receive inputs from specific OM subsystems and send outputs to their respective OMN populations. The ocular motor subsystems are identified: SP = smooth pursuit; Fix = fixation; Vrg = vergence; Prop = proprioception; Sacc = saccadic; VVOR = visual vestibuloocular reflex. (R)E = (right) eye; (L)E = (left) eye; "f" or "F" = fast; "s" or "S" = slow; IN = interneuron; NI = neural integrator; PG = pulse generator. The fast pathways are in red and slow in green.

Based on our studies of the effects of tenotomy on INS, we hypothesize that the same on-line modulation of eye movements demonstrated for exteroception will be found for proprioception (i.e., there exists a short-time-constant stretch reflex mediated by the "slow" motor neurons). Figure 10-4 shows a block diagram of the efferent portion of the ocular motor system when two OMN populations are simulated with a simple means to adjust the small-signal gain of the ocular motor plant rather than via a tension-control loop. Although we could have used the latter, at this point too little is known about the time constants of such a loop or its exact function to justify its inclusion. In Chapter 7, we have shown how the two OMN populations and the simplified adjustable-gain plant have been implemented in our behavioral OMS model and produced behavioral outputs.

Although the power and utility of ocular motor proprioception has not been appreciated until recently, proprioceptively based therapies (beginning with the Kestenbaum procedure in 1953) have been used to damp INS and improve visual function for the past five decades. It has often been stated that, proprioception plays no significant role in ocular motor control. That statement is neither credible nor tenable. Top-down studies of ocular motor dysfunction and therapies have produced testable hypotheses that can elucidate the details of how proprioception does affect ocular motor control. Detailed neuroanatomic and neurophysiologic studies of the architecture and signal content of that role are needed to provide more complete understanding of ocular motor control in health and disease and provide the basis for more accurate models of the OMS.

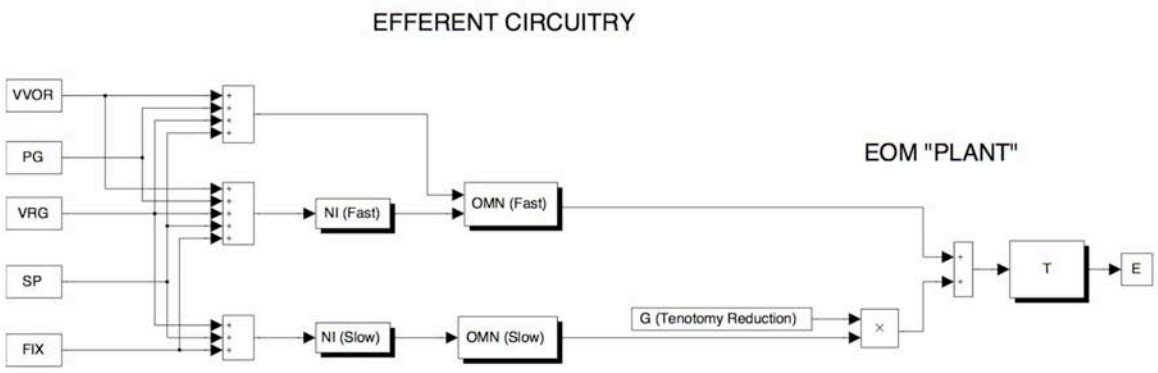

Figure 10-4. Efferent block diagram for a unilateral, bidirectional OMS model, including a plant model capable of simulating the effects of tenotomy surgery. Derived from the connections in Figure 10-3, this diagram demonstrates how an EOM plant could respond differently to slow signals after tenotomy.

10.1.3 Target acquisition time as a dynamic visual function measurement

In real life, the intended visual targets seldom stay stationary; a variety of target movement often occur, requiring the OMS to acquire the new target accurately in a timely fashion. In INS patients, the constant oscillations make target acquisition even more challenging; the patients often complain that they are "slow to see". Very few studies were carried out on the dynamic properties of INS target acquisition. Chapter 6 and 7 are the first studies that investigated this realistic aspect from a waveform foveation point of view (Z. I. Wang & Dell'Osso, 2007b). The important implications found in these two studies are that the intrinsic saccades in the INS cycle might negatively impact the target acquisition speed and accuracy, both of which can be improved by providing the OMS with a better visual input.

The fact that INS patients acquired step-target stimuli faster post tenotomy might be due to the elevated foveation quality resulting in less inherent variation in the input to the OMS. The improvement might be explained by Fitts' law, which encapsulates a tradeoff between speed and accuracy, existing for all motor behaviors. Fitts' law (P. M. Fitts, 1954; P. M. Fitts & Peterson, 1964) is a well-established equation; for movement along a single dimension, it is described as:

$$T = a + b \log_2 \left(\frac{D}{W} + 1 \right)$$

where T is the average time taken to complete the movement; a and b are constants determined experimentally by curve fitting; D is the distance from the starting point to the center of the target; W is the width of the target measured along the axis of motion. For INS patients target acquisition, D is the target location change; W is the foveation window and T is the target acquisition latency, as measured previously.

Basically, Fitts' law describes the phenomenon that for a given amount of noise in the motor-control system, the faster the movement is completed, the less accurate the movement is; on the other hand, the more accurate the movement is expected to be, the slower it is. Studies have shown that Fitts' law is consistent with the closed-loop step-response of a time-delayed, first-order system (Gawthrop, Lakie, & Loram, 2008).

The influence of noise on motor behavior is well-documented. An example of noise protuberance in a motor control system is stroke patients' limb movements on the affected side. McCrea et al (McCrea & Eng, 2005) showed that stroke resulted in greater neuromotor noise, which adversely influenced both motor execution and planning. In our specific example of INS target acquisition, the sensory and motor noise originates from the nystagmus eye movement. The level of the noise directly correlates with the nystagmus amplitude. Therefore, to arrive at a moved target, the ocular motor system either reduces the accuracy or speed of all the eye movements that enables the target acquisition.

In fact, movement accuracy can be controlled by opposite changes in signal-dependent sensory and motor commands (Guigon, Baraduc, & Desmurget, 2008). This might help explain the post-tenotomy INS target acquisition improvement. The motor noise level in INS surgical therapies is hypothesized to remain unchanged since the central nystagmus signal is not altered. The sensory noise level, however, is significantly dropped in INS patients with a great improvement in target foveation quality, i.e., the foveation time is longer, the waveforms are more aligned and smaller, and the image input on the retina has better quality. This dropped level of sensory noise indicates that post-surgically, either the accuracy or the speed will improve; no matter which one does

improve, a faster (lower) latency of target acquisition will result. Our model prediction and patient observation strongly supports this conclusion.

In drug therapy of INS and other forms of nystagmus, the central eye oscillation signal is reduced, therefore the motor noise level is reduced, and that in turn drops the sensory input noise level, resulting in faster target acquisition. Although the net result of the surgical and drug therapies are equivalent, the mechanisms differ, and therefore applying both forms of therapies on applicable nystagmus patients will achieve multiplicative visual function improvement.

10.1.4 A Unifying hypothesis for the genesis of infantile nystagmus

In 1968, the first OMS model containing an ocular motor dysfunction (INS) demonstrated how normal behaviors could be achieved despite the presence of an internal oscillation (Dell'Osso, 1968). Although it made no attempt to address the genesis of INS, it did provide gaze-angle variation of the waveform, something not duplicated until now. In 2004, the original behavioral OMS model simulated the responses of individuals with several pendular waveforms based on a hypothesized pursuit-subsystem instability (Jacobs & Dell'Osso, 2004). Although no gaze-angle modulation of the nystagmus was included, it did postulate the mechanism for the genesis of INS and exhibited many emergent behaviors not designed into it. Pendular and jerk waveforms are the two most commonly seen in INS; they also transition easily and seamlessly from one to the other. Moreover, INS patients with attention lapses showed delayed jerk fast phases and eventually large *underlying* pendular oscillations in their eye-movement recordings. These observations and recordings support our hypothesis that both pendular and jerk

waveforms originate from the same smooth pursuit system instability, and the jerk waveforms are based on a large-amplitude pendular oscillation, reset by each fast phase.

Chapters 8 and 9 are demonstrations of embedding this hypothesis into our OMS model. The addition of an Alexander's Law output greatly assisted modulating the nystagmus amplitude. The Alexander's Law output is essentially a signal that describes the relative position between the current eye and the null center. The amount of amplitude modulation was designed to be proportional to that output; this is the first time in over 40 years that an INS model has included gaze-angle variation. The same Alexander's Law output was also conveniently utilized in determining when to transition to jerk waveforms and which beating direction the jerk waveform has; no prior model has ever simulated the seamless transition of waveforms with gaze angle.

The resulting robust simulations of accurate OMS behavior in the presence of pendular waveforms, jerk waveforms, and their transitions strongly support our unifying hypothesis that most pendular and jerk INS waveforms are due to a loss of pursuit-system damping. These improvements in the OMS model add another step in the implementation of a complete and idiosyncratic OMS model.

As in previous studies, we relied on an "evolving" methodology to incorporate new functional blocks into the model. Each step is back-checked to ensure the already-established model behaviors are still accurate. The new functional blocks must be in action when triggered and remain silent when required for other conditions. We also paid great attention to the existing emergent behaviors in the model; the new functional blocks must not inhibit them. As pointed out in Chapters 8 and 9, the improved model not only preserved the previous model's emergent behaviors but also generated new ones,

continuing to support the embedded hypotheses. With the top-down control system scheme, we can conveniently plug in improved functional blocks of the subsystems when they are perfected by physiological, anatomical or imaging studies.

Our OMS model is a behavioral model that simulates OMS responses under both normal and pathological (e.g., INS) conditions: it is a research tool that sheds light on OMS mechanisms, predicting OMS behavior and suggesting future research; it is a teaching tool for INS waveforms, characteristics and target foveation strategies; and it is a subsystem test bed for new/changed subsystem models/mechanisms. Modeling OMS dysfunction continues to provide valuable insight into the functional structure of the OMS under both normal and pathological conditions.

10.2 Future work

This dissertation forms the foundation for a series of important future studies:

1. More data are needed to enhance the prediction accuracy of tenotomy's "more" and "better" effect. Our preliminary curve in Chapter 3 was based on three clinical studies of approximately 20 patients. More pre- and post-tenotomy data will benefit the accuracy of this prediction curve.

2. INS treatments for infants and young children have always been challenging because of patient-cooperation problems. However, the earlier the nystagmus treatments are applied, the more benefit the patient will receive, especially during nervous-system development. Therefore, studying the application of INS treatments in infants and young children would be a project with great significance.

3. If the proprioceptive hypothesis about tenotomy is true, the extraocular muscles do not necessarily have to be cut for the tenotomy effect to occur. The possibilities of chemical/mechanical/thermal tenotomy need to be assessed.

4. An INS model more easily capable of individualization needs to be built from our current version, e.g., the current control parameters, which are set from a front panel or internally, should be replaced by setting basic INS characteristics (null position, null width, etc.) corresponding to any individual. Noise can be added to the decision-making blocks of the model to increase *variability* in waveforms from cycle to cycle, as commonly observed in some patients. More ocular motor dysfunctions could also be built into the model, several of which could coexist, as may be seen in patients. The attention-level and the light/dark conditions should also be added to modulate the behaviors under those conditions.

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Appendix A

Summary of the Improved Functional Blocks in OMS Model V1_4

A.1 General

The behavioral Ocular Motor System (OMS) model contains Saccadic, Smooth Pursuit (SP), and Fixation subsystems controlled by an Internal Monitor (IM). It is capable of simulating normal ocular motor responses to commonly applied target stimuli (pulses, steps, ramps, and step-ramps) as well as behaviors to these same stimuli by subjects with various ocular motor system disorders. Among the latter are infantile nystagmus syndrome (INS, aka CN), fusion maldevelopment nystagmus syndrome (FMNS, aka LMLN), gaze-evoked nystagmus (GEN), myasthenia gravis (MG), and various types of saccadic intrusions and oscillations (Dell'Osso, 2002; Jacobs & Dell'Osso, 2004; Rucker, Dell'Osso, Jacobs, & Serra, 2006).

Realization of the actual functional block to accomplish each required motor or decision signal is only one of a very large set of solutions. Blocks deemed to be "non-physiological" by future research can (and will) be replaced by more physiological designs without changing the overall behavior of the model. As an example of that, we have already updated the ocular motor neuron pathways in this new release of the model (version 1_4) to conform to recent physiological findings (Eberhorn, Horn, Fischer, & Büttner-Ennever, 2005); details will be discussed below. The strength of the model lies in its organization and interconnecting feedback pathways; these reflect current knowledge

of the ocular motor system's organization and our interpretations of the mathematical and decision-making functions required to simulate the wide range of ocular motor behaviors recorded from both normals and those with the specific disorders.

The following section will be a detailed description of the updated blocks of OMS model 1_4 from the original release (v1.0).

A.2 Major Model Changes

A Re-distributed OMS Efferent Delay

We divided the final 30 ms delay immediately before the plant into 5 ms, placed before the plant, and the remaining 25 ms re-distributed back into the upstream functional blocks. The multiple internal calculations using feedback signals for efference copy of eye position and velocity required careful positioning of these delays; moreover, the timings for making comparisons in the functional blocks of the Internal Monitor also had to be reset by ±25 ms, depending on where in each block the 25 ms delay was placed. The functional blocks in the Internal Monitor that had a delay change include: Model Plant+, Saccade Enable, Target Change Detection, BS/FS Logic, Sampled Target & Error Reconstruction, Target & Slip Velocity Reconstruction.

A Built-in Gaze-angle Variation Mechanism

To simulate the gaze-angle variations in INS, we used the same Alexander's law functional block in the Internal Monitor of the OMS model (just as in the FMNS simulations (Dell'Osso & Jacobs, 2001)). That block utilized a reconstructed eye-position signal that excluded the nystagmus signal, i.e., an indication of "where the eye should

be." The output of the Alexander's law block was used to modulate the INS baseline sine-wave oscillation. The modulation was enabled by a variable gain in the PMC+ block. Figures 8-3 and 8-4 are from the updated version for model 1_4.

A Separate Pathway for "Fast" and "Slow" OMNs and a "Tenotomy" Plant

To incorporate the dual OMN paradigm in our model, we created functional blocks for both the fast and the slow OMNs, and connected saccadic pulse generator output to only the "fast" OMNs, while providing all other outputs to both OMNs. The ratio of these split signals is currently set to be 50%. Instead of just one OMN output to the plant, we now have a "fast" OMN output and a "slow" OMN output, both going to the plant.

We placed a reduction coefficient in the plant for small-signal inputs. This coefficient is idiosyncratic and could depend on the pre-surgical waveform quality and/or afferent deficits. We do realize, and indeed have hypothesized, that a more complicated proprioceptive feedback control probably exists to reduce the nystagmus slow-phase components. Figure 7-1 shows the OMN wiring and the plant of version 1_4.

A.3 Other Changes

The following is a summary of all the other minor changes to improve and update model v1.0.

Model Usage

The original model (v1.0) was developed in Simulink 2.2 (part of the MATLAB 5.2 release). We have updated the model in Simulink 7.0 (part of Matlab 7.5) and found

no significant differences in the model output. During the upgrading, we grounded all the unconnected ports (as required) and changed some incompatible parts (e.g., the integrator in the resettable neural integrator in PG) to their compatible equivalents.

There are a number of externally settable OMS-model parameters that allow simulation of different waveforms of INS and FMNS as well as normal behaviors. These are incorporated into profiles accessed using "setmdlp", a program with a graphical interface that allows the user to easily inspect and modify these parameters. The parameter folder “modelparams/v1_4” contains all the parameters for the new release; this should be the folder that "setmdlp" loads from.

Pulse Generator

The model uses a 2-pole plant and the pulse generator (PG) height and width functions are tuned for that plant. Since both the PG’s resettable neural integrator (NI) and the plant (with a tenotomy coefficient) are now different than in v1.0, the pulse-height table and the pulse-width block are tuned slightly differently. The default saccadic tonic gain is now set to 5.25. Figure A-1 shows the updated pulse-width table. Appendix B is the modified pulse-height table.

The “fast” OMN block only passes the NI signals in the absence of any PG signals. Because the “slow” OMNs do not receive PG signals, they function as relays of the NI signals.

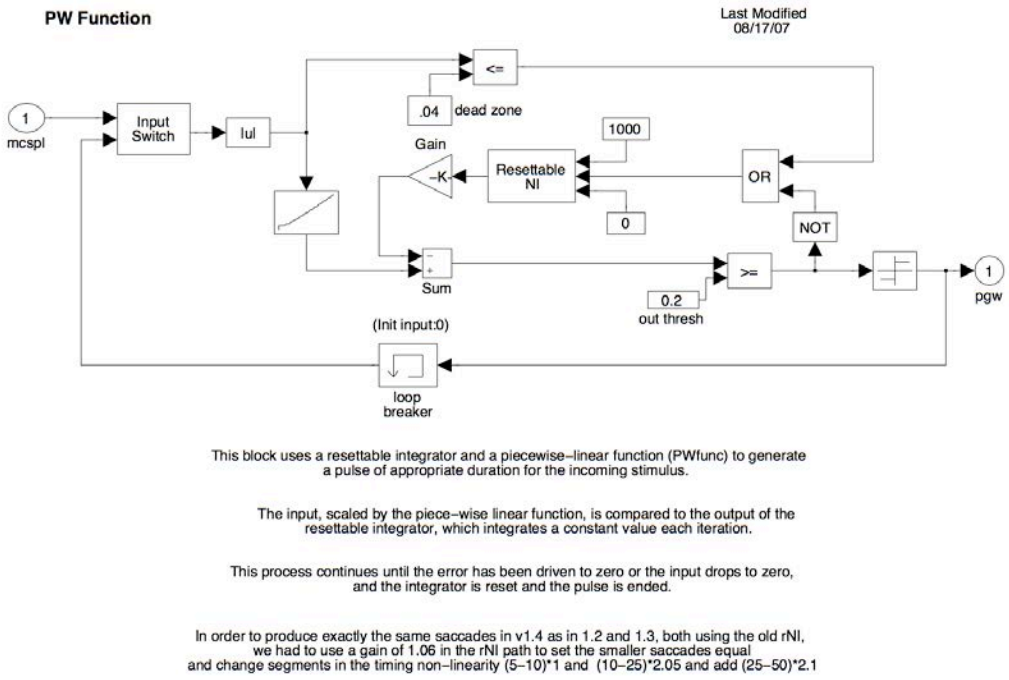

Figure A-1. The updated Pulse-Width block.

Fixation

The fixation system relies on a counter-velocity signal to cancel out the slow-phase runaway velocity after each foveating saccade, thus forming the foveation period. In the model, that counter signal is the "velcorr" output of the fixation system. One problem with v1.0 is that if the model remains steady fixation for a few cycles, the unidirectional counter signal pulses are always in one direction, pushing the position efference copy output to deviate from its desirable value. Once the deviation exceeds 0.3°, a corrective saccade is improperly generated. We used a bidirectional pulse for the counter signal output in v1_4 so that the overall integration of the signal each cycle is 0, i.e., the fixation system output no longer shifts the efference-copy signal. The second part of the pulse is delayed by 70 ms so that it does not interfere with the foveation period.

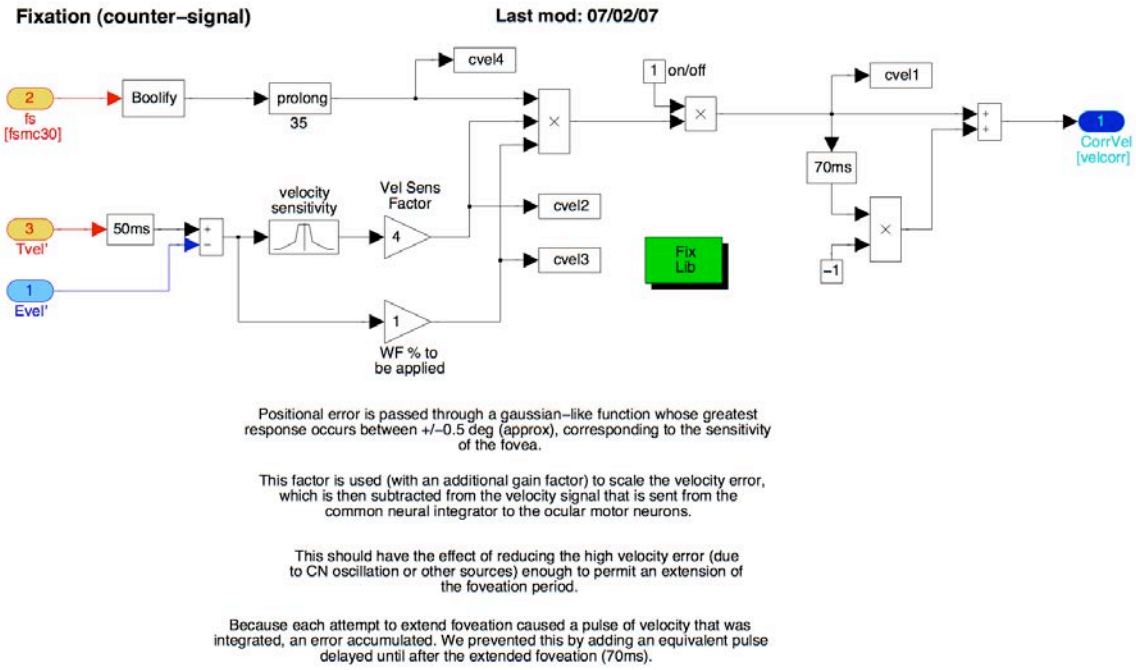

Figure A-2. The updated Fixation system.

Internal Monitor

This is the heart of the model, as it is responsible for separating true target position and motion from retinal image position and motion. It does this using efference copy of eye position and velocity commands and a target-change, decision-making circuit. The IM consists of several major functional blocks: Target Change Detection, Sampled Target & Error Reconstruction (utilizing a Model OMN and Plant), Target & Slip Velocity Reconstruction (utilizing Model Velocity circuitry and Plant), Saccade and Drift Blanking, Braking/Foveating Saccadic Logic, NI control, Alexander's Law variation, and Saccade Enabling.

This overall structure of the model (i.e., the functional blocks) remains the same as v1.0. However, several functional blocks were combined for simplicity and non-redundant use of the same input signals. Thus, “Sampled Target Reconstruction” and “Sampled Error Reconstruction” were combined into “Sampled Target & Error Reconstruction” and “Slip Velocity Reconstruction” and “Target Velocity Reconstruction” were combined into “Target & Slip Velocity Reconstruction.” Also, as mentioned before, since the delay immediately before the plant was reduced from 30 ms to 5 ms and the remaining 25 ms was redistributed in the internal monitor, the amount of delay in each of the sub functional blocks might differ from the first release. Figure A-3 shows the appearance of the Internal Monitor in Model v1_4.

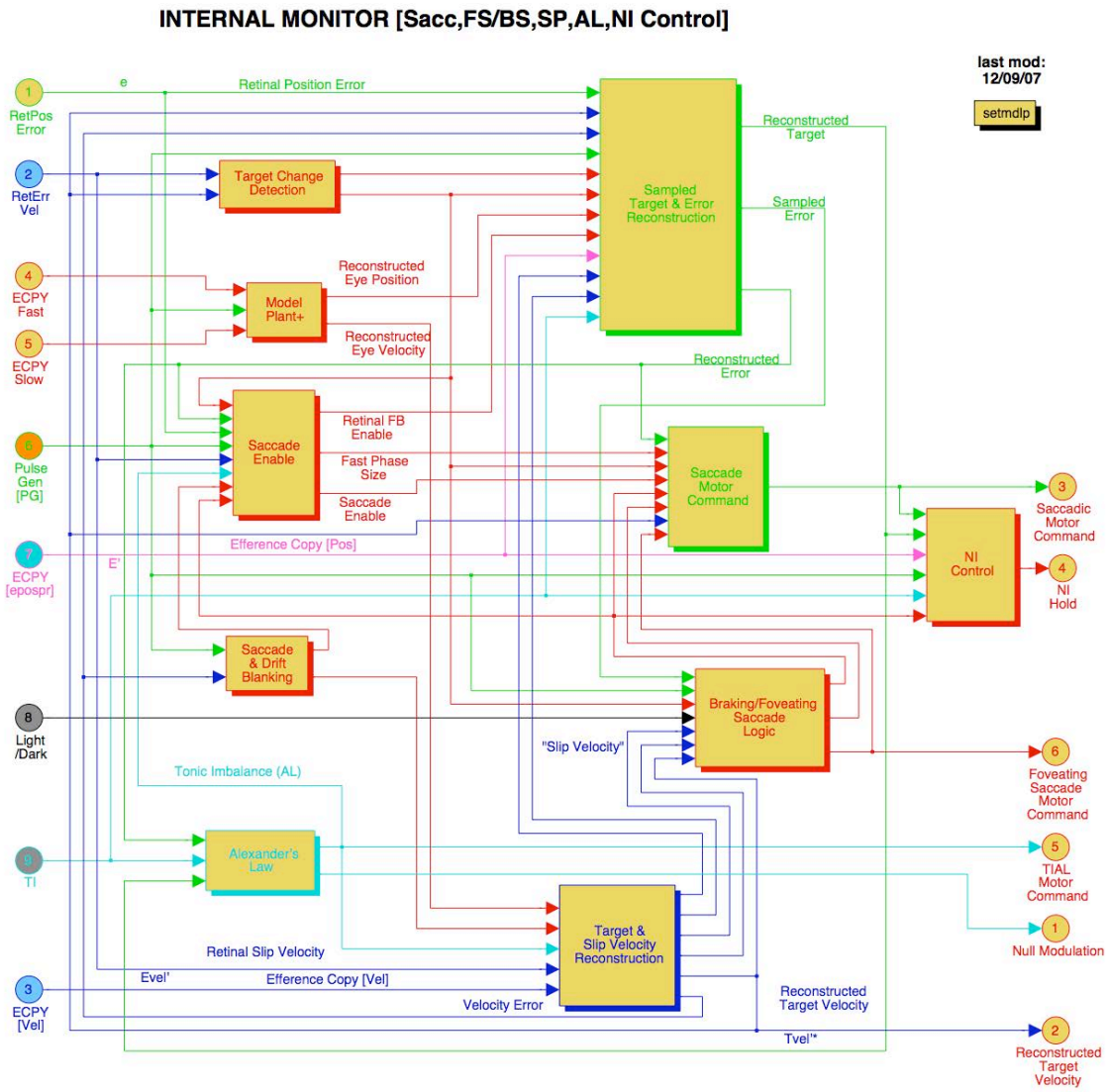

Figure A-3. The updated Internal Monitor.

Model Plant+

This block is part of the Internal Monitor. It is an estimation of the current plant output; the circuit should correspond to the OMN and plant layout. Therefore, the changes we made for the dual OMN paradigm should also be reflected here. Figure A-4 shows the updated Model Plant+ block.

Saccade Motor Command

This block is part of the Internal Monitor. Its function is to pass either voluntary saccade command or bs/fs command to the pulse generator. The "Corrective Sacc Inhibition" block was added to ensure no corrective saccade is generated during the foveation periods of a pendular waveform. The "IF prolong" logic ensures every voluntary saccade command is seen and sampled. The other parts remain unchanged from v1.0. This block is shown in Figure A-5.

Braking/Foveating Saccade Logic

This block is part of the Internal Monitor. It is only in function for INS simulations. It uses sampled, reconstructed retinal position error, sampled, reconstructed retinal slip velocity, and desired eye velocity to determine whether to generate a bs or a fs. In this version (v1_4) we added reconstructed target velocity ("tvpr") as an input to allow more accurate foveating saccades during smooth pursuit. This is done by either adding or subtracting from the prior calculation depending on the relative directions of the pursuit and the foveating saccade. This block is shown in Figure A-6.

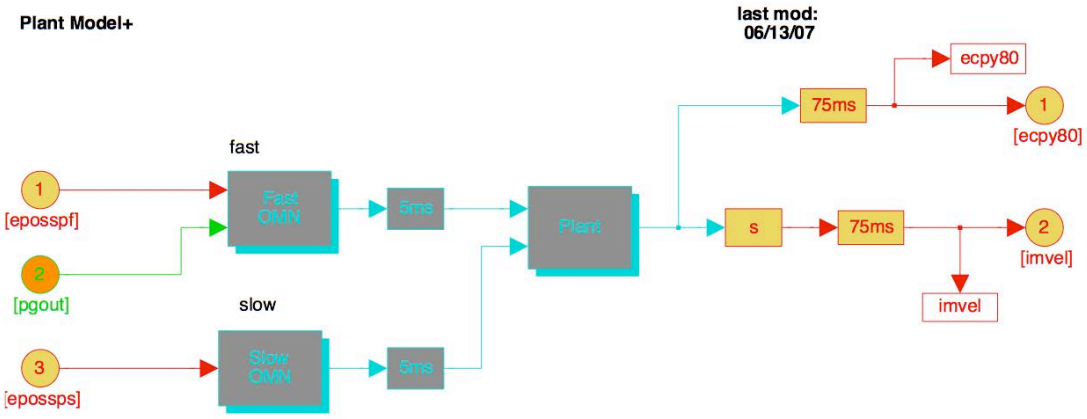

Figure A-4. The updated Model Plant+ block.

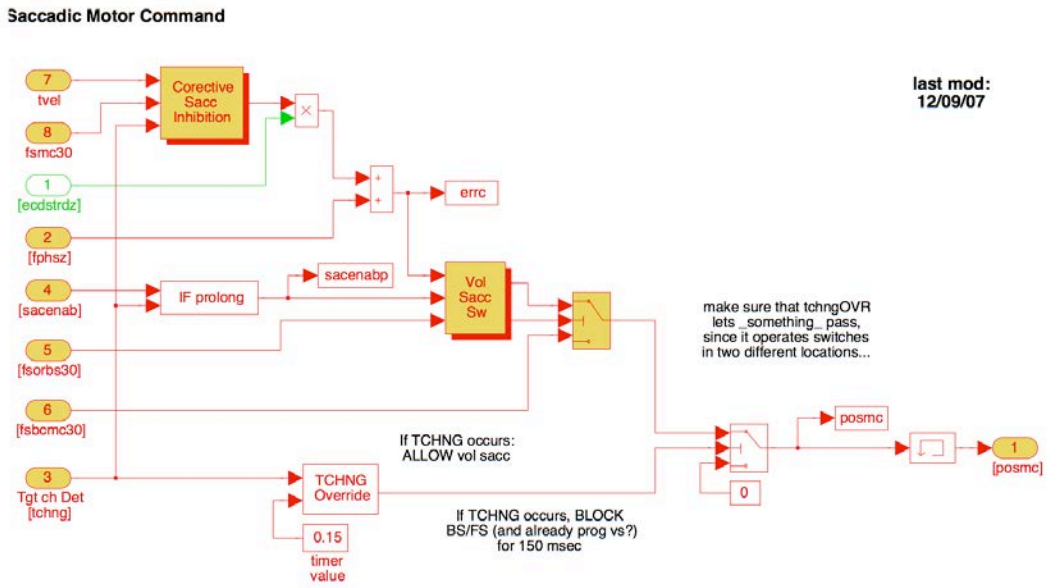

Figure A-5. The updated Saccadic Motor Command block.

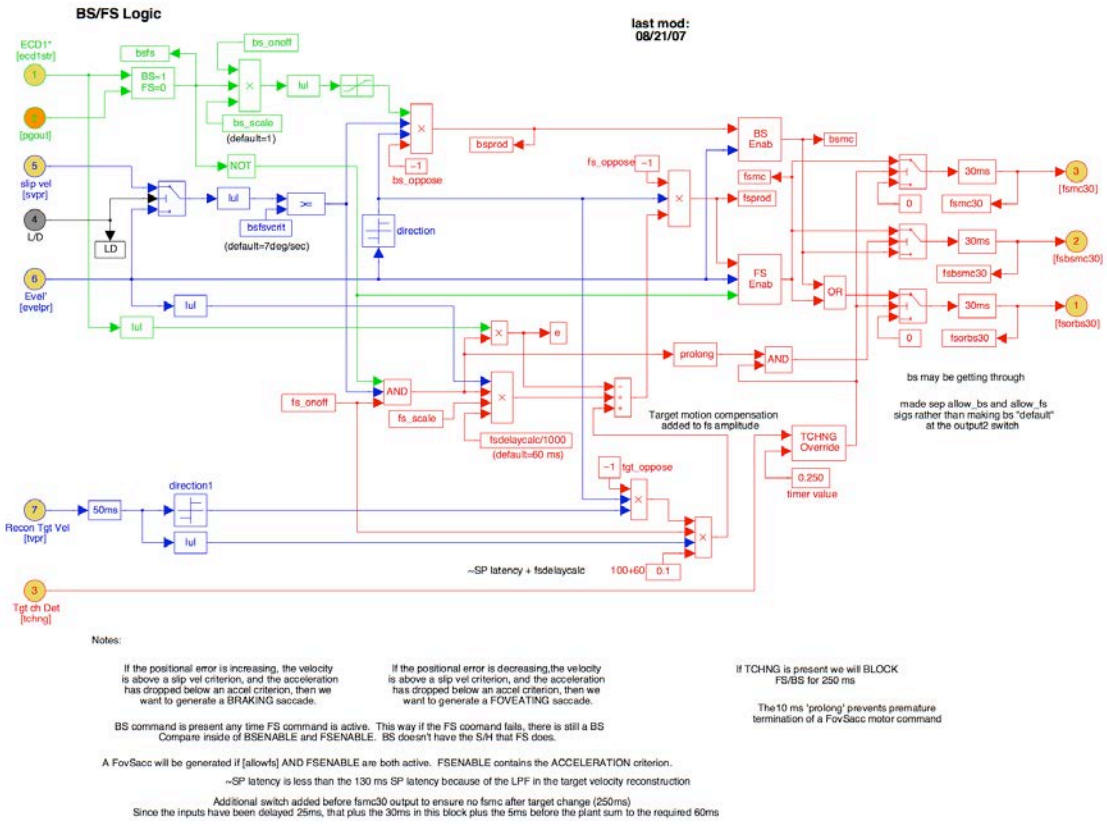

Figure A-6. The updated BS/FS Logic block.

A.4 References

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Appendix B

The Modified Pulse-height Table

```
% Written by:  Jonathan Jacobs
%              October 1998 - February 1999 (last mod: 02/18/99)
% Revised by:  Zhong Wang (last mod: 12/10/07)


function out = PHfn_ss(in);

sgn = sign(in);
in = abs(in);

if in > 50
  in = 50;
end

% teeny tiny saccades -- 0.05 to 0.09 degrees
smallmag = [0.6366    0.7635    0.8903    1.0170    1.1438];
if in < 0.05, out = 0; return; end
if (in >= 0.05) & (in < 0.1)
  ind = fix((in-0.04)*100);
  if ind==0; ind=1;end
  out = smallmag(ind)*sgn;
  return
end

% we go by 2.5 degree increments so that we only have to load
% small (25 element) matrices.  If we had to load in values for
% all fifty degrees at once, it would make the model unbearably slow.
%%% this seems to be the best tradeoff between speed and partitioning effort
if (in >= 0.1) & (in < 2.55)
  mag = [...
     1.2732    2.5449    3.8155    5.0852    6.3542 ...  %% 0.1 - 0.5
     7.6228    8.8910   10.1590   11.4269   12.6946 ...  %% 0.6 - 1
    13.9623   15.2300   16.4977   17.7654   19.0331 ...  %% 1.1 - 1.5
    20.3009   21.5688   22.8366   24.1046   25.3725 ...  %% 1.6 - 2
    26.6406   27.9086   29.1767   30.4449   31.7131 ...  %% 2.1 - 2.5
   ];
  ind = round(in*10);
  out = mag(ind)*sgn;
  return
```

```
end


if (in > 2.5) & (in < 5.05)
  mag = [...
    32.9813   34.2495   35.5177   36.7860   38.0543 ...  %% 2.6 - 3
    39.3226   40.5910   41.8593   43.1277   44.3961 ...  %% 3.1 - 3.5
    45.6644   46.9328   48.2012   49.4696   50.7380 ...  %% 3.6 - 4
    52.0064   53.2749   54.5433   55.8117   57.0801 ...  %% 4.1 - 4.5
    58.3486   59.6170   60.8854   62.1538   63.4223 ...  %% 4.6 - 5
   ];
  ind = round((in-2.5)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 5) & (in < 7.55)
  mag = [...
    64.6907   65.9592   67.2276   68.4960   69.7645 ...  %% 5.1 - 5.5
    71.0329   72.3014   69.2340   70.3865   71.5447 ...  %% 5.6 - 6
    72.7076   73.8747   75.0451   76.2185   77.3944 ...  %% 6.1 - 6.5
    78.5724   79.7522   76.4592   77.5283   78.6059 ...  %% 6.6 - 7
    79.6905   80.7809   81.8763   82.9757   84.0786 ...  %% 7.1 - 7.5
   ];
  ind = round((in-5)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end

if (in > 7.5) & (in < 10.05)
  mag = [...
    85.1843   86.2924   82.8469   83.8477   84.8586 ...  %% 7.6 - 8
    85.8779   86.9042   87.9361   88.9727   90.0131 ...  %% 8.1 - 8.5
    91.0566   92.1028   88.5749   89.5126   90.4626 ...  %% 8.6 - 9
    91.4226   92.3907   93.3654   94.3455   95.3298 ...  %% 9.1 - 9.5
    96.3176   97.3083   93.6681   94.5619   95.4677 ...  %% 9.6 - 10
   ];
  ind = round((in-7.5)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end
```

```
if (in > 10) & (in < 12.55)
   mag = [...
      96.3829   97.3057   98.2346   94.7130   95.5548 ...  %% 10.1 - 10.5
      96.4106   97.2775   98.1530   94.8065   95.5987 ...  %% 10.6 - 11
      96.4076   97.2295   98.0613   94.8181   95.5822 ...  %% 11.1 - 11.5
      96.3616   97.1527   97.9528   94.8341   95.5726 ...  %% 11.6 - 12
      96.3249   97.0877   97.8583   94.9234   95.6205 ...  %% 12.1 - 12.5
    ];
   ind = round((in-10)*10);
   if ind==0; ind=1;end
   out = mag(ind)*sgn;
   return
end

if (in > 12.5) & (in < 15.05)
   mag = [...
      96.3345   97.0612   97.7973   94.9418   95.6175 ...  %% 12.6 - 13
      96.3089   97.0117   97.7229   94.9630   95.6190 ...  %% 13.1 - 13.5
      96.2892   96.9698   97.6577   95.0522   95.6710 ...  %% 13.6 - 14
      96.3081   96.9581   97.6175   95.0731   95.6755 ...  %% 14.1 - 14.5
      96.2948   96.9259   97.5654   95.0959   95.6831 ...  %% 14.6 - 15
    ];
   ind = round((in-12.5)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 15) & (in < 17.55)
   mag = [...
      96.2857   96.8990   97.5197   95.1874   95.7388 ...  %% 15.1 - 15.5
      96.3112   96.8978   97.4940   95.2086   95.7475 ...  %% 15.6 - 16
      96.3058   96.8771   97.4572   95.2310   95.7583 ...  %% 16.1 - 16.5
      96.3034   96.8603   97.4250   95.2555   95.7715 ...  %% 16.6 - 17
      96.3039   96.8470   97.3971   95.2816   95.7868 ...  %% 17.1 - 17.5
    ];
   ind = round((in-15.0)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end

if (in > 17.5) & (in < 20.05)
   mag = [...
```

```
    96.3070   96.8370   97.3730   95.3693   95.8416 ...  %% 17.6 - 18
    96.3361   96.8445   97.3617   95.3926   95.8562 ...  %% 18.1 - 18.5
    96.3406   96.8377   97.3426   95.4167   95.8722 ...  %% 18.6 - 19
    96.3468   96.8331   97.3264   95.4421   95.8896 ...  %% 19.1 - 19.5
    96.3549   96.8307   97.3128   95.4685   95.9083 ...  %% 19.6 - 20
   ];
  ind = round((in-17.5)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 20) & (in < 22.55)
  mag = [...
    96.3645   96.8302   97.3016   95.4958   95.9282 ...  %% 20.1 - 20.5
    96.3755   96.8315   97.2925   95.5239   95.9489 ...  %% 20.6 - 21
    96.3877   96.8343   97.2853   95.6043   95.9992 ...  %% 21.1 - 21.5
    96.4169   96.8473   97.2848   95.6291   96.0185 ...  %% 21.6 - 22
    96.4292   96.8516   97.2802   95.6544   96.0386 ...  %% 22.1 - 22.5
   ];
  ind = round((in-20.0)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 22.5) & (in < 25.05)
  mag = [...
    96.4425   96.8571   97.2772   95.6805   96.0594 ...  %% 22.6 - 23
    96.4568   96.8637   97.2757   95.7071   96.0810 ...  %% 23.1 - 23.5
    96.4718   96.8714   97.2754   95.7343   96.1031 ...  %% 23.6 - 24
    96.4877   96.8800   97.2763   95.7619   96.1258 ...  %% 24.1 - 24.5
    96.5041   96.8895   97.2784   95.7899   96.1489 ...  %% 24.6 - 25
   ];
  ind = round((in-22.5)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 25) & (in < 27.55)
  mag = [...
    96.5212   96.8998   97.2814   95.8182   96.1724 ...  %% 25.1 - 25.5
```

```
    96.5388   96.9108   97.2854   95.8914   96.2169 ...  %% 25.6 - 26
    96.5663   96.9267   97.2923   95.9165   96.2388 ...  %% 26.1 - 26.5
    96.5836   96.9383   97.2976   95.9418   96.2612 ...  %% 26.6 - 27
    96.6013   96.9505   97.3038   95.9676   96.2840 ...  %% 27.1 - 27.5
   ];
  ind = round((in-25.0)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 27.5) & (in < 30.05)
  mag = [...
    96.6195   96.9633   97.3106   95.9937   96.3071 ...  %% 27.6 - 28
    96.6381   96.9766   97.3182   96.0202   96.3304 ...  %% 28.1 - 28.5
    96.6570   96.9903   97.3264   96.0469   96.3541 ...  %% 28.6 - 29
    96.6763   97.0045   97.3351   96.0738   96.3780 ...  %% 29.1 - 29.5
    96.6959   97.0191   97.3445   96.1010   96.4021 ...  %% 29.6 - 30
   ];
  ind = round((in-27.5)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 30) & (in < 32.55)
  mag = [...
    96.7157   97.0341   97.3543   96.1283   96.4263 ...  %% 30.1 - 30.5
    96.7358   97.0494   97.3646   96.1558   96.4507 ...  %% 30.6 - 31
    96.7560   97.0650   97.3754   96.1834   96.4752 ...  %% 31.1 - 31.5
    96.7764   97.0809   97.3866   96.2110   96.4998 ...  %% 31.6 - 32
    96.7970   97.0971   97.3982   96.2388   96.5245 ...  %% 32.1 - 32.5
   ];
  ind = round((in-30.0)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 32.5) & (in < 35.05)
  mag = [...
    96.8178   97.1135   97.4101   96.2981   96.5592 ...  %% 32.6 - 33
    96.8418   97.1312   97.4227   96.3230   96.5827 ...  %% 33.1 - 33.5
```

```
    96.8623   97.1478   97.4353   96.3481   96.6064 ...  %% 33.6 - 34
    96.8829   97.1647   97.4482   96.3734   96.6303 ...  %% 34.1 - 34.5
    96.9037   97.1818   97.4613   96.3988   96.6542 ...  %% 34.6 - 35
   ];
  ind = round((in-32.5)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 35) & (in < 37.55)
  mag = [...
    96.9246   97.1991   97.4748   96.4245   96.6782 ...  %% 35.1 - 35.5
    96.9456   97.2166   97.4885   96.4502   96.7023 ...  %% 35.6 - 36
    96.9667   97.2342   97.5025   96.4761   96.7264 ...  %% 36.1 - 36.5
    96.9878   97.2519   97.5167   96.5020   96.7506 ...  %% 36.6 - 37
    97.0091   97.2698   97.5311   96.5281   96.7749 ...  %% 37.1 - 37.5
   ];
  ind = round((in-35.0)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 37.5) & (in < 40.05)
  mag = [...
    97.0304   97.2879   97.5458   96.5542   96.7991 ...  %% 37.6 - 38
    97.0517   97.3060   97.5606   96.5804   96.8234 ...  %% 38.1 - 38.5
    97.0731   97.3242   97.5756   96.6066   96.8476 ...  %% 38.6 - 39
    97.0945   97.3426   97.5908   96.6328   96.8719 ...  %% 39.1 - 39.5
    97.1160   97.3610   97.6062   96.6591   96.8961 ...  %% 39.6 - 40
   ];
  ind = round((in-37.5)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 40) & (in < 42.55)
  mag = [...
    97.1374   97.3795   97.6217   96.6854   96.9203 ...  %% 40.1 - 40.5
    97.1589   97.3981   97.6374   96.7117   96.9445 ...  %% 40.6 - 41
    97.1804   97.4168   97.6532   96.7380   96.9687 ...  %% 41.1 - 41.5
```

```
    97.2019   97.4355   97.6691   96.7642   96.9928 ...  %% 41.6 - 42
    97.2234   97.4543   97.6852   96.7904   97.0168 ...  %% 42.1 - 42.5
   ];
  ind = round((in-40.0)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 42.5) & (in < 45.05)
  mag = [...
    97.2449   97.4731   97.7014   96.8166   97.0408 ...  %% 42.6 - 43
    97.2664   97.4920   97.7177   96.8428   97.0648 ...  %% 43.1 - 43.5
    97.2878   97.5109   97.7341   96.8775   97.0895 ...  %% 43.6 - 44
    97.3094   97.5299   97.7506   96.9018   97.1131 ...  %% 44.1 - 44.5
    97.3308   97.5490   97.7672   96.9262   97.1367 ...  %% 44.6 - 45
   ];
  ind = round((in-42.5)*10);
  out = mag(ind)*sgn;
  return
end


if (in > 45) & (in <= 47.55)
  mag = [...
    97.3522   97.5680   97.7839   96.9507   97.1603 ...  %% 45.1 - 45.5
    97.3736   97.5871   97.8006   96.9754   97.1838 ...  %% 45.6 - 46
    97.3949   97.6062   97.8175   97.0001   97.2073 ...  %% 46.1 - 46.5
    97.4163   97.6253   97.8344   97.0250   97.2308 ...  %% 46.6 - 47
    97.4376   97.6445   97.8514   97.0500   97.2542 ...  %% 47.1 - 47.5
   ];
  ind = round((in-45.0)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end


if (in > 47.5) & (in < 50.05)
  mag = [...
    97.4589   97.6637   97.8684   97.0751   97.2776 ...  %% 47.6 - 48
    97.4802   97.6829   97.8855   97.1002   97.3008 ...  %% 48.1 - 48.5
    97.5015   97.7021   97.9027   97.1255   97.3241 ...  %% 48.6 - 49
    97.5227   97.7213   97.9199   97.1508   97.3472 ...  %% 49.1 - 49.5
    97.5439   97.7405   97.9372   97.1763   97.3703 ...  %% 49.6 - 50
```

```
    ];
  ind = round((in-47.5)*10);
  if ind==0; ind=1;end
  out = mag(ind)*sgn;
  return
end
```

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