Congenital nystagmus: Hypotheses for its genesis and complex waveforms within a behavioral ocular motor system model

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Attempts to simulate dysfunction within ocular motor system (OMS) models capable of exhibiting known ocular motor behavior have provided valuable insight into the structure of the OMS required for normal visual function. The pendular waveforms of congenital nystagmus (CN) appear to be quite complex, composed of a sustained sinusoidal oscillation punctuated by braking saccades and foveating saccades followed by periods of extended foveation. Previously, we verified that these quick phases are generated by the same mechanism as voluntary saccades. We propose a computer model of the ocular motor system that simulates the responses of individuals with pendular CN (including its variable waveforms) based on the instability exhibited by the normal pursuit subsystem and its interaction with other components of the normal ocular motor control system. Fixation data from subjects with CN using both infrared and magnetic search coil oculography were used as templates for our simulations. Our OMS model simulates data from individuals with CN during fixation and in response to complex stimuli. The use of position and velocity efference copy to suppress oscillopsia is the key element in allowing for normal ocular motor behavior. The model's responses to target steps, pulse-steps, ramps, and step-ramps support the hypothetical explanation for the conditions that result in sustained pendular oscillation and the rules for the corrective saccadic responses that shape this underlying oscillation into the well-known family of pendular CN waveforms: pendular (P), pseudopendular (PP), pendular with foveating saccades (P_{fs}), and pseudopendular with foveating saccades (PP_{fs}). Position error determined the saccadic amplitudes of foveating saccades, whereas stereotypical braking saccades were not dependent on visual information. Additionally, we propose a structure and method of operation for the fixation subsystem, and use it to prolong the low-velocity intervals immediately following foveating saccades. The model's robustness supports the hypothesis that the pendular nystagmus seen in CN is due to a loss of damping of the normal pursuit-system velocity oscillation (functionally, it is *pursuit-system* nystagmus—PSN).

Keywords: congenital nystagmus, model, extended foveation, saccades, smooth pursuit

Introduction

Congenital nystagmus (CN) consists of involuntary oscillations of the eyes toward and away from an attempted point of fixation. CN waveforms can be variations of either pendular or jerk waveforms, and the slow phases are increasing velocity (or "runaway") exponentials, though approximately linear slow phases account for some less common waveforms, such as triangular, bidirectional jerk, and some pure jerk (Dell'Osso & Daroff, 1997). The slow-phase characteristics differentiate most CN waveforms from other types of nystagmus, such as latent/manifest latent nystagmus (LMLN) that has a linear or *decreasing* velocity slow phase, or vestibular nystagmus, with its linear slow phase. CN is predominantly horizontal, with some torsional and, rarely, vertical motion. Despite the oscillation, individuals with CN exhibit normal visual function unless additional afferent deficits are present. Because of that, behavioral models of the ocular motor system of individuals with CN can provide valuable insight into the mechanisms by which the ocular motor system ensures good visual function.

There are additional characteristics of CN that help to distinguish it from the many other types of nystagmus (e.g., the failure of saccades to damp the underlying pendular oscillation, the intervals of extended foveation imposed on the oscillation, the ability to accurately foveate new targets, and the ability to accurately pursue moving targets). They serve as the underlying fundamentals of attempts to de-

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velop a realistic control-system model of CN. Such a model should be capable of reproducing these basic behaviors to be considered biologically relevant. CN is conjugate, affecting both eyes similarly, even in the additional presence of strabismus. Although the amplitude of the oscillations may not be equal, the frequency is and the eyes are phase locked; in contrast, the eyes move in and out of phase in spasmus nutans (Weissman, Dell'Osso, Abel, & Leigh, 1987).

Many of the ocular motor subsystems have been suggested as the origin of CN, or at least to be severely deficient, including the optokinetic subsystem (Kommerell & Mehdorn, 1982; Yee, Baloh, & Honrubia, 1980), the saccadic subsystem (Abadi & Worfolk, 1989; Dell'Osso, Gauthier, Liberman, & Stark, 1972), and the smooth pursuit (SP) or vestibular subsystems (Kommerell & Mehdorn, 1982; St. John, Fisk, Timney, & Goodale, 1984; Yamazaki, 1979). However, careful observation and study of most of these candidate systems led us to rule them out as the source of the more common CN waveforms.

The smooth pursuit gain is normal in CN (Dell'Osso, 1986; Dell'Osso, Van der Steen, Steinman, & Collewijn, 1992b; Kurzan & Büttner, 1989). For many years it had been believed that CN was due to a deficit of smooth pursuit, and that pursuit could even be reversed, (i.e., the eyes would move in the direction *opposite* to that of the target) (Lueck, Tanyeri, Mossman, Crawford, & Kennard, 1989). This arose from a failure to adhere to the definition of "gain," namely that it can be calculated only during those intervals when the output is a direct result of the input. The vestibulo-ocular gain is also normal (Dell'Osso, Van der Steen, Steinman, & Collewijn, 1992c). There is experimental evidence (Abadi & Dickinson, 1985; Abadi, Dickinson, & Lomas, 1982; Shallo-Hoffmann, Wolsley, Acheson, & Bronstein, 1998) that the optokinetic subsystem does in fact behave properly. Also, personal observations by one of the authors (LFD) of optokinetic-induced circularvection and the "waterfall effect" have always supported his belief that the optokinetic subsystem also functioned normally.

Similarly, individuals with CN make accurate saccades that compare favorably with those made by normal subjects. During foveation periods, they can maintain fixation almost as accurately (*SD* within 13 arcmin for CN vs. 6 arcmin for normals) (Dell'Osso, Van der Steen, Steinman, & Collewijn, 1992a). Finally, CN waveforms may coexist with failure of the common neural integrator (NI) to maintain eccentric eye position (Dell'Osso, Weissman, Leigh, Abel, & Sheth, 1993); the foundations of several prior models of CN appear to be inconsistent with this finding (see "Discussion"). Thus, despite the omnipresent underlying oscillation of CN, all ocular motor subsystems have been shown to perform their designated functions accurately — we conclude from this that they *function* normally despite the clearly abnormal oscillation contained in each response.

The absence of oscillopsia is paramount to good visual function. Oscillopsia *only rarely* accompanies CN, and in the minority of those who have experienced it, oscillopsia occurred only under specific circumstances (Abadi & Bjerre, 2002; Abadi & Dickinson, 1986; Abel, Williams, & Levi, 1991; Leigh, Dell'Osso, Yaniglos, & Thurston, 1988). This has critical implications for modeling because it constrains the origin of the oscillations to be within the efference copy loop where they are properly accounted for when calculating the reconstructed target velocity (Dell'Osso, Averbuch-Heller, & Leigh, 1997). The brain cannot correctly interpret retinal image motion without knowledge of expected eye motion (derived from efference copy of motor commands). Other forms of nystagmus, whose origins appear outside of this compensating mechanism, sometimes result in a debilitating global sense of movement. A realistic ocular motor system model capable of simulating CN requires mechanisms and signals that identify the perceived target position and velocity appropriately, whether it is simulating the responses of a normal individual or one with CN (i.e., the model must *not* have oscillopsia if the individual being simulated does not). Once the model simulates the vast majority of CN without oscillopsia, some oscillopsia can be added to the model by simply diminishing the effectiveness of the efference copy mechanism subject to the idiosyncratic condition causing some oscillopsia in the individual being modeled.

What, then, is the origin of CN? CN is driven by attempts at fixation or pursuit, regardless of whether the target is real or imaginary, and can therefore exist in total darkness, absent of any physical target (Dell'Osso, 1973a). It is exacerbated by stress, anxiety, and other psychological inputs. Conversely, it may damp (or even disappear) when the subject is inattentive. These facts suggested that a variable gain modulates CN (Dell'Osso, 1973b). We propose that for the pendular waveforms of CN, this gain resides in the smooth pursuit (SP) subsystem, but it is a gain *internal* to the subsystem, *not* the overall pursuit gain. Thus, we hypothesize that the underlying cause for CN is an inborn, or developmental, failure of this portion of the smooth pursuit system to calibrate this internal gain; it is *not* due to the normally present efference-copy loops or to feedback loops associated with the neural integrator. This explanation is compatible with the wide variety of afferent visual system abnormalities (ranging from none to the total absence of an optic chiasm) that are known to be associated with CN. Each could easily facilitate the failure to calibrate a subsystem that is already borders on instability (i.e., oscillatory behavior) in normal humans.

Braking saccades are small, automatic (i.e., non-visually triggered), stereotyped fast phases that appear in some CN waveforms — pseudopendular (PP), pseudopendular with foveating saccades (PP_{fs}), triangular (T), pseudojerk (PJ), bidirectional jerk (BDJ), and pseudocycloid (PC) (Dell'Osso & Daroff, 1975). Braking saccades act to oppose the runaway slow phases, slowing the eyes, and in some cases reversing their direction (Dell'Osso & Daroff, 1976; Jacobs,

Dell'Osso, & Erchul, 1999). They, like normal corrective saccades, are triggered automatically by extraretinal velocity efference signals; once the eye's velocity motor command exceeds some critical velocity, there is reason to attempt to arrest the eye's runaway (e.g., a 4°/s eye movement would produce a retinal slip velocity that decreases visual acuity).

It is our hypothesis that apparently complex pendular CN waveforms are created by a simple sinusoidal oscillation already present (but damped) in the normal smooth pursuit subsystem and shaped by the interposition of braking and foveating saccades. In some infants, CN may be almost purely slow-phase pendular or triangular movements initially (Reinecke, Suqin, & Goldstein, 1988) and, as the ocular motor system develops, saccades begin to appear and establish familiar CN waveforms. However, recordings of most infants document adult waveforms, already containing braking and foveating saccades (Hertle & Dell'Osso, 1999); further development of the ocular motor system serves to increase the accuracy and duration of foveation periods.

This model was designed as a proof of concept for the above hypothesis. Although a model of horizontal control, it can be extended for other planes of motion. The ocular motor data collected from individuals with CN constrains the model to be normal in all respects save the underlying oscillation itself. In this model for eye movements with a fixed head and no confounding optokinetic inputs (corresponding to the conditions under which most of our CN data have been taken), both the saccadic and smooth pursuit subsystems must function and interact normally, despite the underlying oscillation. We have taken a top-down approach to modeling this complex system rather than the bottom-up approach usually employed in modeling specific subsections of it. The details of subsystem boxes (functional blocks) are less important in this type of interaction (they are largely unknown and often controversial), requiring us to concentrate on the overall system and its behavioral responses to well-studied inputs.

Methods

Recording and protocol

The ocular motility recordings of approximately 750 subjects and patients with CN made in our laboratory over the past 35 years, as either part of a clinical evaluation or specific research protocol, are the foundation for the model presented in this work. Over that time period, we used three methods: infrared reflection, a phase-detecting revolving magnetic field, and most recently, high-speed (500 Hz) video. Details of the respective equipment, methods, and protocols used may be found in the referenced studies. Written consent was obtained from subjects before the testing.

Analysis

Data analysis (and filtering, if required), statistical computation of means and standard deviations, and graphical presentations were performed using custom software written in MATLAB (The MathWorks, Natick MA), a development environment for scientific computing.

Computer simulation

The ocular motor system (OMS) model was designed and implemented using the Simulink component of MATLAB, a control systems simulation package capable of performing simulations in both continuous and discrete time. As the block diagram of Figure 1 shows, the model is of modular, hierarchical design, consisting of the functional building blocks thought to be required for accurate ocular motor control. Modular design allows for easy substitution of any block by an equivalent block, based on new data, personal preference, or to demonstrate other possibilities. It also facilitates expansion of the model to include additional subsystems (e.g., the vestibuloocular and optokinetic subsystems) and preserves the separation of functions required to produce the wide variety of ocular motor responses exhibited by humans, both normal subjects and those with specific dysfunction. In addition to modularity, the model contains lumped delays, distributed in the afferent and efferent portions of model, that simulate the smaller delays shown to be distributed throughout the OMS by neurophysiological studies (Figure 2); their exact placement or values are not meant to imply anatomical correspondence to actual delays. The components of the smooth pursuit (SP) and saccadic subsystems are shown along with the fixation subsystem and neural integrator hold circuitry (see below).

At the simplest level, our OMS model consists of SP and saccadic subsystems whose behaviors are coordinated by an "Internal Monitor" (IM) that receives inputs from the retina (afferent) and both subsystems (position and velocity efference copy) and sends motor control signals back to the motor subsystems, including fixation. The model is of unilateral, bidirectional architecture (Dell'Osso, 1994), that is, both sides of the brain stem are combined into one model capable of both positive and negative signals that drive one — the fixating — eye. Provision also exists to drive a second, non-fixating eye for studies of conditions where the eyes are unyoked due to strabismus or paresis. This model architecture suffices for the simulation and study of most disorders that result in conjugate oscillations of the eyes, such as CN.

Based on the recorded saccadic and pursuit responses of the CN subjects described above, we concluded that their ocular motor systems are *not* dramatically different from normals. Thus, our model's subsystems (SP and saccadic) should be capable of normal behavior, as well as being able to also simulate many common clinical dysfunctions and their effects on fixation, saccadic refixation, and pursuit.

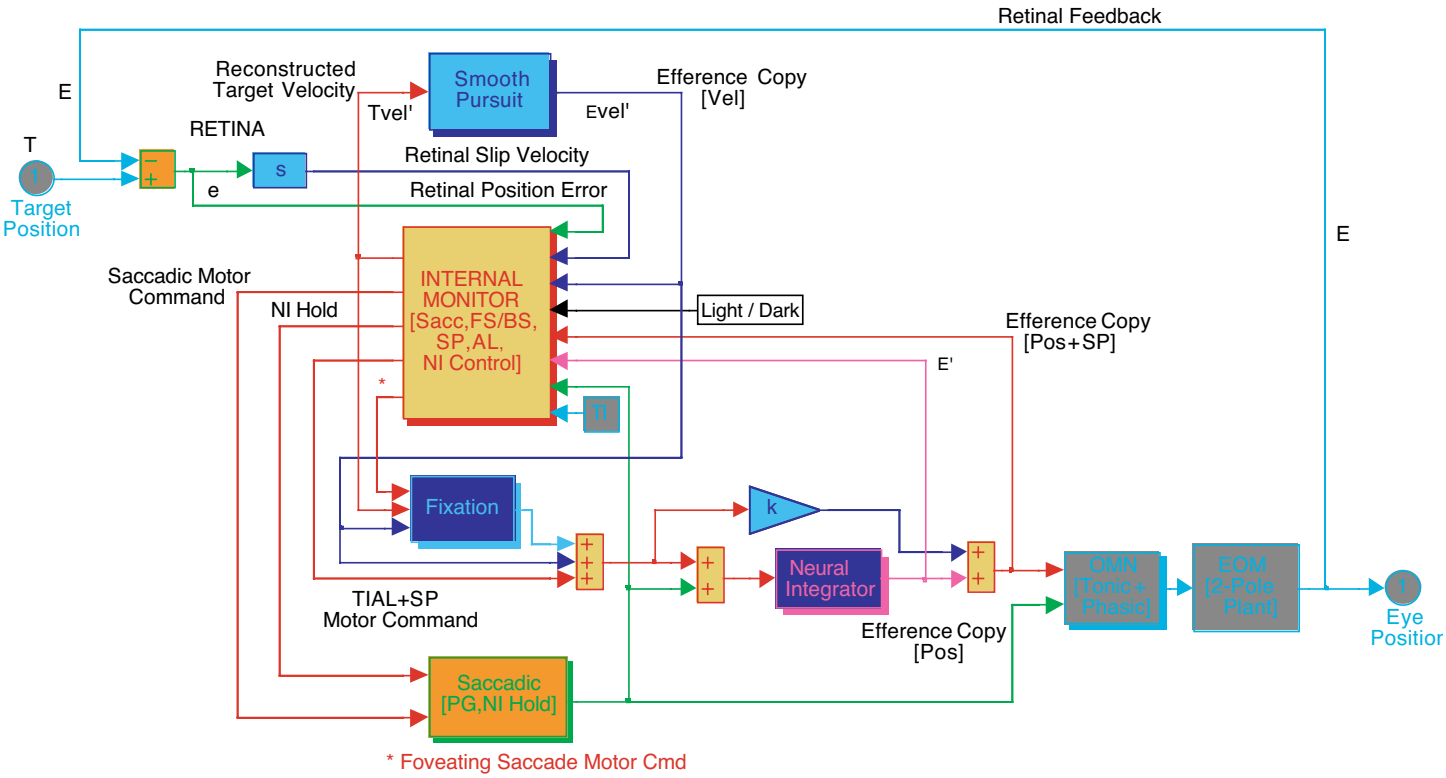

Figure 1. A functional block diagram of the ocular motor system (OMS) model showing the basic organization of subsystems and major components: saccadic, smooth pursuit, fixation, internal monitor, final common neural integrator (NI), ocular motor neurons (OMN), and extraocular muscles and globe (plant) (EOM). In this and the following figures, T = target; E = eye; e = retinal error; Tvel' = reconstructed (perceived) target velocity; Evel' = eye-velocity motor command; E' = eye-position motor command; PG = pulse generator; Sacc = saccadic, SP = smooth pursuit, TI = tonic imbalance, AL = Alexander's law, TIAL = tonic imbalance modulated by Alexander's law, and NI control = neural integrator control functional blocks (respectively) in the internal monitor; and other symbols within square brackets are signals used by other blocks. Transfer functions of various blocks are shown in their Laplace notation within the block. Drop shadows on a functional block indicate that other functional blocks are contained within. In this and Figures 2-4, different colors indicate specific ocular motor signals and pathways, including timing and decision-making signals and pathways.

OMS model subsystems

Smooth pursuit subsystem

We constructed several published models of the SP subsystem (Krauzlis & Lisberger, 1989; Krauzlis & Miles, 1996; Robinson, Gordon, & Gordon, 1986) and evaluated their suitability for inclusion in our model. We selected the Robinson model because of its simplicity of design that nonetheless yields realistic results. However, with a few minor modifications, we could substitute other SP models in its place.

A defining feature of Robinson's model is the damped oscillation (ringing) that occurs with the onset of pursuit. This ringing affects only *initial* pursuit, not steady-state performance, for the oscillation dies away within a few cycles. The source of this ringing is in the pre-motor circuitry (PMC) sub-block. The frequency of the oscillation depends on the length of the delay (τ_3) in the feedback branch of this block. As τ_3 is increased from its default value of 30 ms, the frequency of the oscillation decreases and the amplitude increases; decreasing τ_3 has the opposite effect.

The modified PMC sub-block (PMC+) is shown in Figure 2. To induce the model into *sustained* oscillation of around 3 Hz (the exact frequency depending on the PMC+ parameter settings), the internal PMC+ gain must be raised above its original value of 1.1. (This parameter is *separate* from the *steady-state* overall gain for SP, set to 0.95.) As the PMC+ gain is increased, both the magnitude of the velocity of the oscillation and the time constant of its damping increases accordingly. Above 1.3, the oscillation becomes sustained, and its peak velocity increases with PMC+ gain. As the gain surpasses 3.9 the oscillation increases exponentially. Initially, as a tradeoff between amplitude of the velocity oscillation and time to reach steady state, we chose a value 3.025 for the model. This value is no longer so restricted because we can decrease the required time to steady state with an initiating impulse as described immediately below.

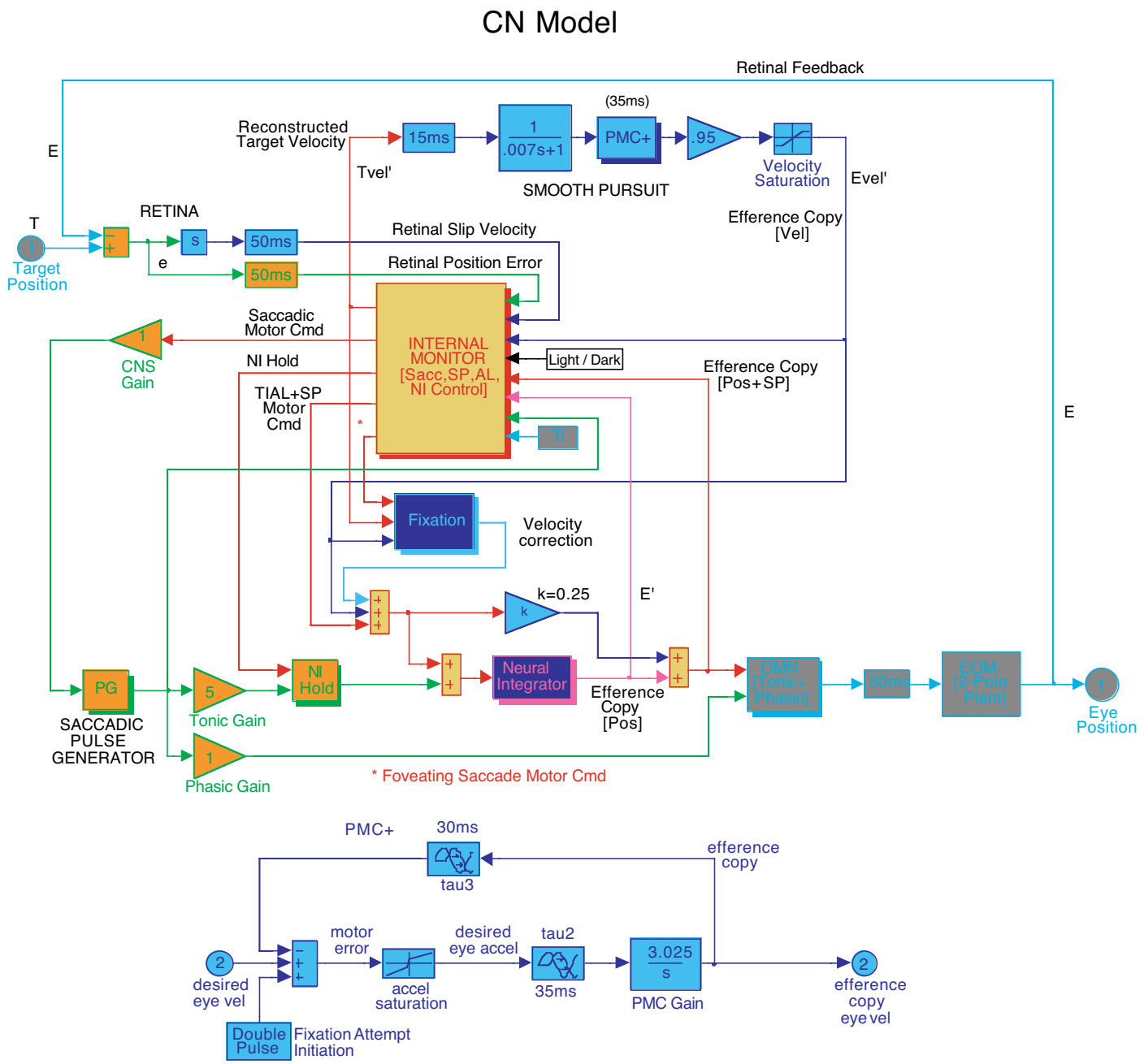

Figure 2. Ocular motor system (OMS) model showing distributed delays, pursuit subsystem components, pulse generator and neural integrator hold. The PMC+ circuitry is shown below.

Because even an unstable system requires an inducement to begin oscillating, we initially added a low-energy velocity noise source to the feedback junction. This small disturbance insured continuous oscillation of the system even in the absence of a pursuit signal. However, the model required more than two seconds before the oscillation achieved its steady-state amplitude. When we substituted a very short duration, biphasic pulse for the noise source, the output reached full amplitude in under a second; this latter stimulus simulates the abrupt onset of effort to use or direct the eyes (*fixation attempt*), which has been shown to be necessary for the CN oscillation to become manifest (Dell'Osso, 1973a). A biphasic pulse is the bidirectional equivalent to unidirectional pulses to each side of a more anatomically correct bilateral model (i.e., two unidirectional models connected in push-pull). Physiologically, this abrupt onset may be caused by the sudden increase of an internal gain in the smooth pursuit system; this will be explored in future versions of the model by examining patient data during known transitions from inattention to fixation attempt.

To incorporate the Robinson SP subsystem in our OMS model, we changed the plant dynamics from a single pole (time constant 15 ms) to a double pole (time constants

7 ms and 180 ms). This achieved more realistic eye trajectories when combined with the saccadic portion of the model. Although a two-pole, one-zero plant would be more physiologically correct, this extra degree of complexity (including the concommitant change of the motor signal to the ocular motor neurons [see below] to a pulse-slide-step mechanism [see below]) would provide no additional insight into overall system behavior beyond saccadic trajectories (Jacobs, 2001).

It was also necessary to convert the Robinson SP subsystem from one that operated as a velocity-in, velocity-out model to one that could operate within a position-in, position-out OMS model to facilitate interaction with the saccadic subsystem. There is evidence that both position and velocity are afferent signals to the brain, encoded by signals present in the optic nerve, with the velocity created by calculations between retinal ganglion cells (Korth, Rix, & Sembritzki, 2000), although most motion processing may take place cortically (Bach & Hoffmann, 2000). This was accomplished in our model by adding a differentiator following the retinal summing junction at the input, converting the position error signal into velocity error signal (retinal slip velocity). The common neural integrator converts the pursuit subsystem's velocity output signals back into position signals. Because the eye must be driven by a *step-ramp* signal if it is to pursue constant-velocity targets (ramps), we then added the pursuit subsystem's output to the direct pathway that sums with the integrated one at the ocular motor neurons.

These last two modifications required further changes to the SP portion of the IM where target velocity is reconstructed (i.e., to its virtual plant that transforms the efference signal that is fed back to the input summing junction of the model). First, we added a second pole to match the one added to the actual plant. Second, we added a zero to account for the integrator/direct path added before the final motor pathway.

Saccadic subsystem

We built a saccadic subsystem composed of a pulse generator, saccadic internal monitor, and ocular motor neuron and connected it to the two-pole plant used in the SP subsystem. The pulse generator was based on a resettable neural integrator (RNI) (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. The RNI is part of the circuit that determines saccade duration; the output of the RNI is compared to a piece-wise linear function. When the output surpasses the function-value, the RNI resets, ending the saccade. The saccadic durations are based on a combination of published physiological data (Yarbus, 1967; Zuber & Stark, 1965) and data analyses performed in this lab over three decades. Pulse amplitude was set by an exponentially shaped nonlinearity determined by an adaptive algorithm that varied the magnitude of the pulse applied to the two-pole plant until the steady-state amplitude of the eye matched the intended target position. An exponential function was then fit to these magnitudes and used as the amplitude nonlinearity in the pulse generator.

The common neural integrator

Because a pulse-step is required to drive the two-pole plant with a saccadic trajectory, it is necessary to take the signal from the pulse generator and integrate it (analogous to the above discussion of position and velocity signals and smooth pursuit) in preparation for combination with the original pulse with the step. The integration is performed by the common neural integrator shown in Figures 1 and 2, which consists of a leaky integrator (time constant equal to the normal dark-drift time constant of 25 s) around which is a positive feedback gain to offset that leak and produce a non-leaky integrator. Provision was also made to include two such elements to simulate gaze-evoked nystagmus caused by a leak in a subpopulation of the neural integrator cells (Abel et al., 1978).

The ocular motor neurons

The combining of the pulse and the step is done by the ocular motor neurons (OMN). This combination of signals is *not* a simple addition of the pulse and the step, for that would not yield a true pulse-step, as the integrated signal is ramping up during the pulse and does not attain its final height until the pulse has concluded. Physiological data do not show such a ramping up during the burst. Instead, the signal from the pulse generator is passed to the output at the moment when the pulse starts (summed with any constant offset already present at the output of the common NI). Upon termination of the pulse, the integrated step from the common NI is then passed to the output, yielding a pulse-step motor command; essentially, the pulse inhibits the OMN from responding to the step. When no pulse is present, the OMN simply sums all signals in the direct and integrator pathways. An alternative OMN model to the inhibition mechanism would have a saturation nonlinearity to limit the firing frequency during the burst or use presynaptic inhibition controlled by the burst signal.

Internal monitor

The IM is the "brains" of this model, performing all the computation necessary to ensure proper smooth pursuit velocities, saccades and neural integrator control, among other functions. The IM has a long pre-history in models of ocular motor function in the presence of dysfunction (Abel et al., 1978; Dell'Osso, 1968; Dell'Osso & Daroff, 1981; Dell'Osso, Troost, & Daroff, 1975; Doslak, Dell'Osso, & Daroff, 1979, 1982; Weber & Daroff, 1972). What emerges with this model is the realization that the IM is also necessary for the *normal* operation of the OM system and for normal visual function. The IM makes use of visual signals from the *moving oculocentric coordinate system* (i.e., the retina), as well as position and velocity efference signals recorded in the *moving or stationary craniocentric space* (i.e.,

the brainstem). Using this information, delayed appropriately, it is possible to reconstruct target position and velocity in *stationary, earth-centric space* independent of any confounding "noise" (e.g., CN or LMLN oscillations). The model can then respond appropriately to target changes, providing proper commands to the SP and saccadic subsystems based on these reconstructed "perceived" signals. The equivalences of these reconstructed signals, whether the model is simulating normal responses or those made during CN, is itself a simulation of the absence of oscillopsia in CN.

Due to the complexity of tasks that the IM is required to perform, it was designed in a modular fashion, facilitating testing of each function before adding it to the IM, and allowing for simpler debugging of the module after incorporating it into the IM. Each functional block makes use of a combination of afferent and efferent signals to achieve its goal of providing needed signals to either other internal monitor blocks or to external functional subsystems. Working together, these logic and signal-reconstruction blocks allow the ocular motor system to properly differentiate target position/velocity from eye position/velocity and make appropriate, timely decisions to generate accurate, responsive eye movements.

As the number of behaviors the IM was required to simulate increased, there was an associated increase in the number of *interconnections* between its internal blocks but *no additional blocks* were required; compare Figure 3A with Figure 3 of the LMLN model (Dell'Osso & Jacobs, 2001). This is intuitively pleasing, for by analogy, a biological brain's interconnectedness greatly increases with its degree of sophistication. Although additional blocks may be required as the model's behavioral repertoire is increased, the IM's initial configuration has been sufficient for all of the current behavioral simulations. Because they were performing similar functions, the Sampled Target and Sampled Error Reconstruction blocks were combined into one, as were the Target Velocity and Slip Velocity Reconstruction blocks.

Examination of the structure of the IM in Figure 3A only hints at its complexity. The drop shadows on functional blocks indicate that they, too, contain functional blocks. For example, the block labeled "Saccade Enable" in Figure 3B determines whether a corrective saccade is to be made based on visual feedback or efference copy information. Even this block is further composed of sub-blocks. Space does not permit a detailed description of each block in the model, a matter of small importance in a top-down model. At the most basic level, all the building blocks are composed of elemental operations that simulate functions (e.g., timing or summation) that could be reproduced easily by analog methods (e.g., RC simulation of membrane time constants) or by neural networks. As a result, any departures from known neuroanatomical structures (or their *presumed* functions) do not detract from the model's functional accuracy. Detailed descriptions of the operating principles of the IM's functional sub-blocks have been published previously (Dell'Osso & Jacobs, 2001) and all of the details for each sub-block are also available (Jacobs, 2001).

Two of the IM's most important functions are to ensure both a level of separation between the SP and saccadic subsystems (so that they respond only to their appropriate input signals) and their synergistic operation. For example, it is crucial that when saccades are made, the SP subsystem does not act upon them and attempt to pursue, but instead ignores perceived movement until the saccade has ended. To accomplish this, the IM blanks out saccades so that SP doesn't see and try to react to their large velocity changes. The complexity of these tasks is greatly increased by the presence of internal oscillations. Similarly, the saccadic subsystem must allow for eye movement produced by slow eye movements (SP or an internal oscillation) when calculating the size of a required saccade.

Braking/foveating saccade logic

Braking saccades are automatically generated to brake runaway eye velocities. Inspection of the PP_{fs} waveform suggests the logic necessary to decide whether a saccade will be braking or foveating. 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. 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 calculated by the predicting where the eye will be 60 ms later (default value based on current distribution of internal delays), when the saccade will occur. This is consistent with the definition of a braking saccade (Dell'Osso & Daroff, 1976; Jacobs et al., 1999); it should *oppose* the slow phase. The foveating saccade is also a braking saccade (although a special case) because it, too, acts to brake the slow phase at the time of its execution. We hypothesize that these reflex saccades originate in the fast-phase mechanism underlying the generation of both vestibular and optokinetic nystagmus; thus, no new system functions are required to produce complex CN waveforms from their simple sinusoidal beginnings.

Fixation subsystem

Stable fixation periods are necessary for normal visual function. The fixation subsystem is a velocity-limiting system aimed at reducing retinal slip velocity (Epelboim & Kowler, 1993). Fixation is most effective when the target image falls within the fovea, and the slip velocity is relatively low. These, therefore, are the activation conditions for the model's fixation subsystem. A further condition is that fixation follows foveating (including volitional) saccades. These criteria are based on data from CN subjects, who do not show extended foveation in the absence of

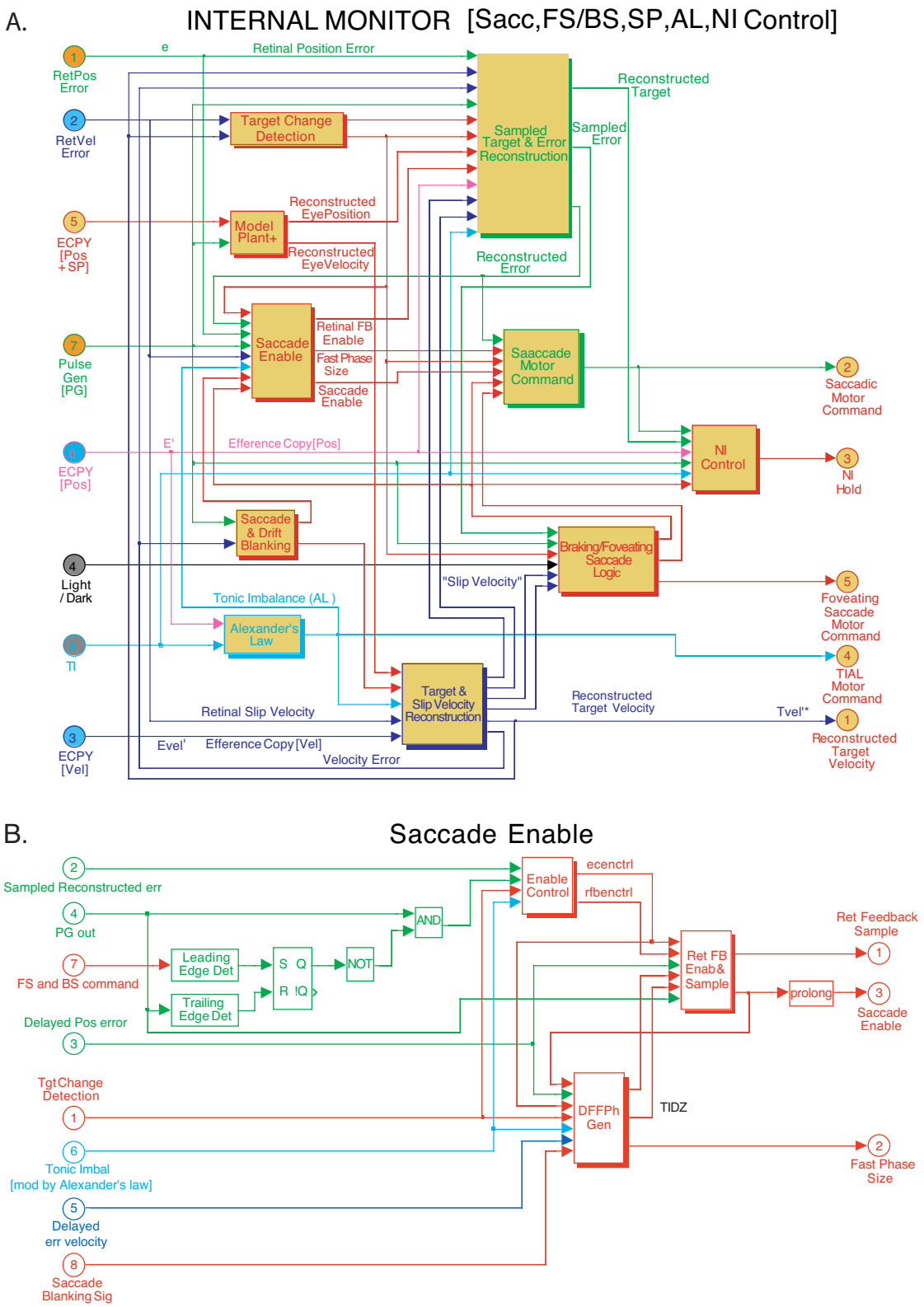

Figure 3. A. The arrangement and interconnections of the functional blocks contained within the internal monitor. The major functions of the internal monitor are detecting target changes, reconstructing target position and velocity, controlling the neural integrator, and determining the timing and amplitudes of saccades and fast phases of nystagmus. The input, output, and other signal labels are consistent with those shown in Figures 1, 2, and 4. B. The arrangement and interconnections within one of the major functional blocks within the internal monitor, the saccade enable and timing block. As the drop shadows indicate, each of these functional blocks contains additional functional blocks within.

saccades or after braking saccades. We initially created position- and velocity-sensitivity functions that approximated the general sensitivity of the visual system. They exhibited high sensitivity (scale factor = 1) for the central portion of the fovea and for lower velocities, with approximately exponentially decreasing sensitivity at increasing distance from the center of the fovea or for higher velocities. Position and velocity errors were passed through these functions and multiplied by a signal that corresponds to the presence of a foveating saccade, to create a "quality of foveation" signal that ranges from 0 to 1. We found that the position component was, at best, redundant and eliminated it in this simulation. This is supported by observations of actual CN data that show the presence of apparent "extended foveation" even following improperly programmed foveating saccades that did not achieve target foveation.

We initially modeled fixation using two distinct approaches: first (Figure 4), to provide a counter-signal equal and opposite to the nystagmus velocity (the difference between the reconstructed target and eye velocities) to cancel out a portion of that oscillation; and second, to use a variable gain to modulate the velocity signal that is fed to the input of the NI and its associated linear gain pathway. The counter-signal approach is derived from the method employed to cancel the nystagmus motor signal from the retinal error signal in the first behavioral model of a normal OMS capable of simulating CN (Dell'Osso, 1968). In the present case, however, the subtraction is a velocity signal and is limited to periods following a foveating saccade, corresponding to the time when the target image would be in the foveal area. It is the product of the aforementioned foveation-quality signal, the nystagmus velocity, and an additional constant factor of 4 (to compensate for the 0.25 gain of the velocity signal that is passed to the ocular motor neurons). The resulting product is subtracted from the velocity signal just before the input to the NI.

In the variable-gain method, the quality signal is subtracted from 1 to create an overall gain. When foveation is poor, this gain is 1, allowing the velocity signal to pass unimpeded. When foveation criteria are met, the total gain drops towards zero, passing less of the velocity signal, thereby slowing the eye. The present OMS model utilizes the first approach in its simulation of the fixation subsystem.

Evolution

As we added features to the model to broaden its range of simulations, each addition triggered extensive retesting of all previous simulations to ensure that no loss of function had occurred. Attempts that failed to accomplish their goal or compromised existing functions were discarded and those that worked were retained and refined. In this manner we interactively *evolved* the model over a period of several years. Finally, the OMS model contains internal-monitor features required by our recent model of LMLN (Dell'Osso & Jacobs, 2001) that, although not necessary for CN simulations, were retained and did not interfere with them. Our experience in building this model leads us to conclude that definitive testing of a total OMS model for biological relevance requires that *all* functions in the system remain active, not just those needed to demonstrate a particular response. We consider this to be a major shortcoming of simpler models that lack "unnecessary" functions.

Results

Because we propose that the ocular motor system in subjects with CN is essentially normal, it is necessary to demonstrate that the model can perform the behaviors demonstrated by normals as well as those with pathologies, such as saccadic dysmetrias, NI dysfunction, and muscle paresis. Furthermore, the presence of nystagmus should not interfere with the goal-directed operation of the system; it does not in individuals with CN.

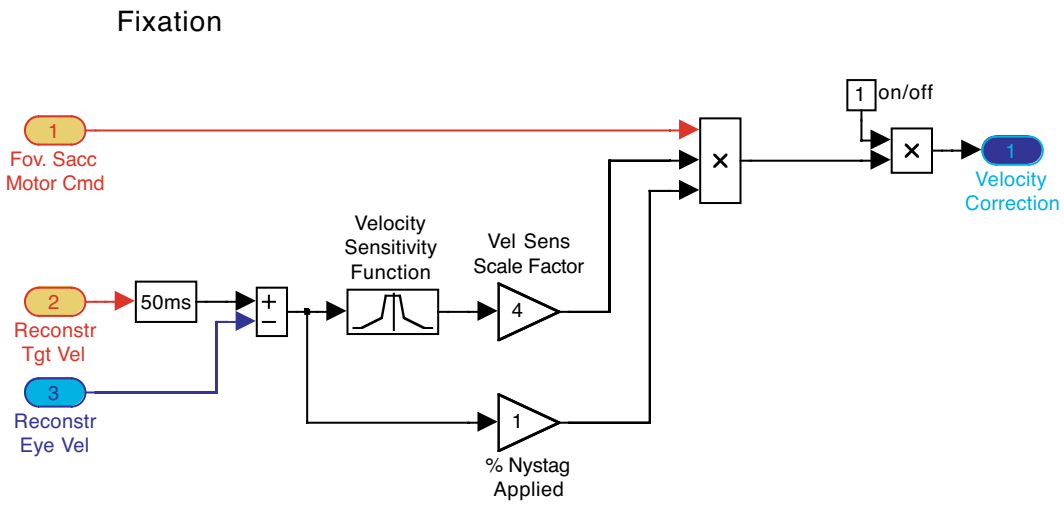

Figure 4. Fixation subsystem using the counter-signal approach. The velocity sensitivity function is a piecewise approximation of a Gaussian function.

Normal behavior

This model shares a common development path with our LMLN model (Dell'Osso & Jacobs, 2001) that is incorporated into it. Therefore it reproduces the same range of normal behaviors, such as the ability to make orthometric saccades over a wide range (<1° to >±50°), and it can also reproduce several common ocular motor dysfunctions, such as saccadic dysmetria and macrosaccadic oscillation, gaze-evoked nystagmus, and the muscle paresis of myasthenia gravis (Dell'Osso & Jacobs, 2001) (Figures 5-7). In addition, as will be shown below, the current model reproduces accurate responses to more complex stimuli. Comparison of the Internal Monitor of the present model with that of its predecessor, demonstrates how it is the more complex *interconnections* of functional blocks that allows this new behavior, not the addition of new functional blocks.

Evolution of CN waveforms

The panels in Figure 5 show the progression of CN from the initial underlying pendular SP *velocity* oscillation (panel A) that straddles the intended fixation point at 0°. In panel B, only braking saccades have been enabled (using the criteria described above) resulting in the pseudopendular (PP) waveform. Because braking saccades have fixed amplitude and do not attempt to achieve foveation, the oscillation remains symmetric around the fixation point at 0°. However, braking saccades do reduce the peak-to-peak amplitude of the CN. Note that in both of these waveforms, the fovea spends a bare minimum of time on the target, therefore neither is conducive to good acuity and both are seen only transiently in individuals with CN as they shift between more visually useful waveforms.

In panel C, only foveating saccades have been enabled (also as described above); braking saccades have been disabled. This resulting P_{fs} waveform no longer straddles the fixation point. The foveating saccades make use of reconstructed eye-position error to foveate the target, effectively *shifting* the waveform ("bias shift") so it is no longer symmetric about the target (Dell'Osso, 1973a). The periods following the foveating saccades can now make a useful contribution to visual acuity, as they are both within the fovea (defined by the dot-dashed lines) and of low retinal slip velocity. In panel D, braking and foveating saccades are both active, resulting in the complex-appearing PP_{fs} waveform. Important features in panels C and E are the spontaneous reversals of foveating saccade direction. This is known as *bias reversal*; it is commonly seen in CN and was not specifically designed into the model — it is an emergent property.

In panels B and D, the braking saccades appear to be less than 1°, despite their 1° programmed magnitude, reflected in the size of the motor command sent to the plant. This effect has been discussed previously (Jacobs, 2001; Jacobs & Dell'Osso, 1997; Jacobs, Dell'Osso, & Leigh, 2003), and can be explained by the mechanical interaction between the fast and slow phases, as the saccades must overcome the opposing velocity of the slow phase; this does not rule out neural interaction between the SP and saccadic subsystems.

Finally, in panels E and F, the effect of the fixation subsystem upon the oscillation is shown, decreasing the effect of the oscillation when the conditions specified above ("Fixation Subsystem") are met. The distinct flattening of the waveform immediately following the foveating saccades is *extended foveation*, a prolonging of the low-velocity, on-target period to maximize visual acuity. Thus, the model makes use of a normal ocular motor function (fixation) to compensate for dysfunction elsewhere (e.g., smooth pursuit). The small variation in the position of successive foveation periods (jitter) duplicates known CN fixation behavior and affects visual acuity. It is an emergent property of the model. In panels C and D, eye position continues sinusoidally after the saccade, reflecting the ongoing drive of

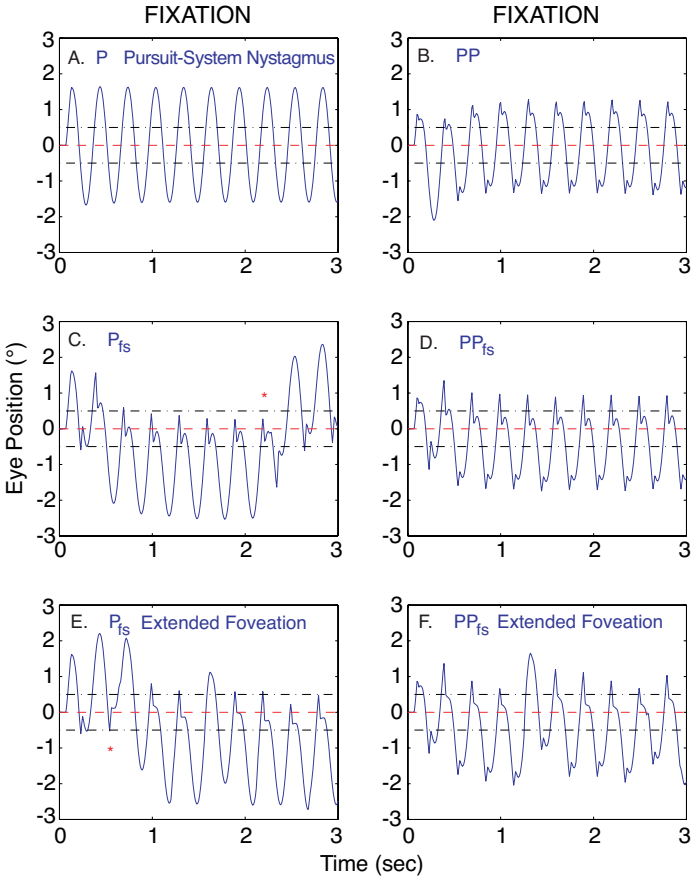

Figure 5. Evolution of pendular waveform of *pursuit-system* nystagmus. A. Pendular (P) oscillation about the fixation point caused by the underlying velocity instability. B. Braking saccades of the pseudopendular (PP) waveform damp the oscillation but do not alter its position. Foveating saccades, alone in the pendular with foveating saccade (P_{fs}) waveform (C and E) or with braking saccades in the pseudopendular with foveating saccade (PP_{fs}) waveform (D and F), shift the eye position to allow target foveation at one peak or the other. E. and F. The fixation subsystem extends foveation, allowing increased visual acuity. Dash-dotted lines indicate the foveal extent.

the nystagmus signal. Even though the target falls on the fovea, its velocity relative to the fovea is higher than the case when foveation has been extended; therefore visual acuity will be reduced. The prevalence of one type of waveform over another is idiosyncratic and the model's parameters can be set to simulate an individual's waveforms and, in later versions of the model, the variation of waveforms and amplitudes with gaze angle or pursuit, vestibuloocular, or optokinetic eye velocity.

Figure 6 shows the PP_{fs} waveform of our model (panel A; Movie 6A [high bw (high-bandwidth)/low bw (low-bandwidth)]) and a CN patient (panel B; Movie 6B [high bw/low bw]). Both exhibit braking and foveating saccades as well as periods of extended foveation. In panel C (Movie 6C [high bw/low bw]), we include the eye-movement response (gaze = eye in space) to vestibular input (rapid head shaking) of a patient with multiple sclerosis and low VOR gain. Note the presence of "braking saccades" in this adult with an *acquired* condition.

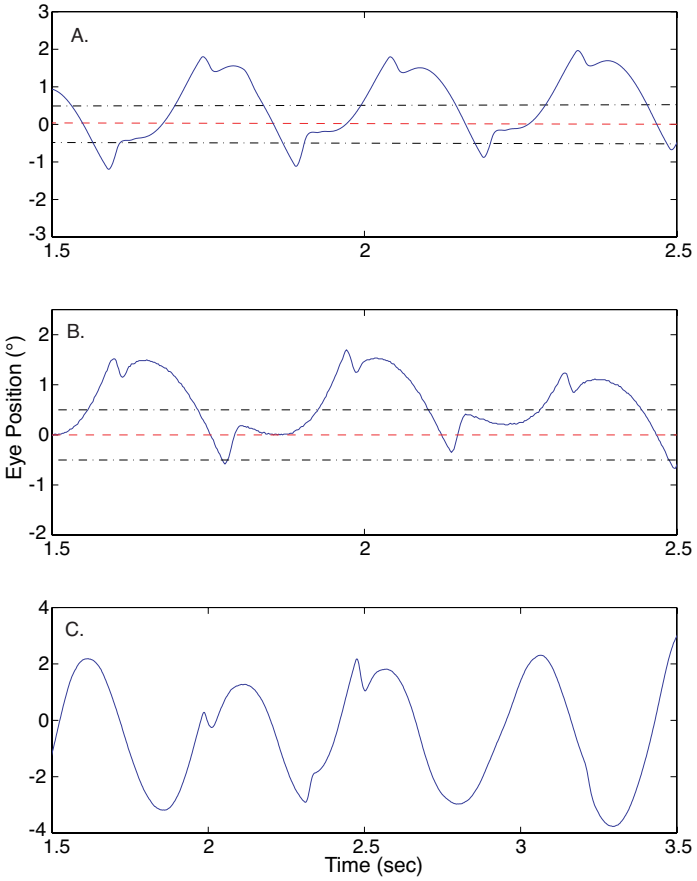

Figure 6. Examples of a PP_{fs} waveform generated by (A) the OMS model and (B) a patient with CN. (C). The response of a patient with multiple sclerosis to vestibular input (see text). The trace in C is gaze, which is eye in space and would be a straight line if the VOR gain was normal. Dash-dotted lines indicate the foveal extent, except in C where the patient's attempted point of fixation is unknown.

Responses to step, pulse-step, ramp, and step-ramp stimuli: normal and with CN

In the first recordings of the responses of an individual with CN to step, pulse-step, ramp, and step-ramp changes in target position, it was found that, despite the ongoing oscillation, the responses to each of these stimuli were normal in both accuracy and timing (Dell'Osso, 1968). All of the LMLN model's previously demonstrated responses (Dell'Osso & Jacobs, 2001) are properly executed by the present evolution of the model — even when CN oscillations, and their attendant foveating and braking saccades are present. Figures 7-11 show the model's responses to various target stimuli in the presence of both P_{fs} and PP_{fs} waveforms, analogous to the responses from our LMLN model.

Figure 7 (Movie 7A [high bw/low bw] and Movie 7B [high bw/low bw]) shows normal saccades made over the range of 1–30°. Saccades up to 17° are accurate, whereas larger ones require an additional, corrective saccade (after a 130-ms latency) to reach the target; this is commonly seen in normal subjects. This and subsequent figures demonstrate that the presence of nystagmus quick phases does *not* interfere with voluntary refixations. If two saccadic commands compete for control of the saccadic pulse generator, the first one to arrive will be programmed, and the other will be executed after the saccadic refractory period. Individuals with CN duplicate this behavior. The responses made during both the P_{fs} and PP_{fs} waveforms are accurate (falling within the dot-dashed lines) and foveation may oc-

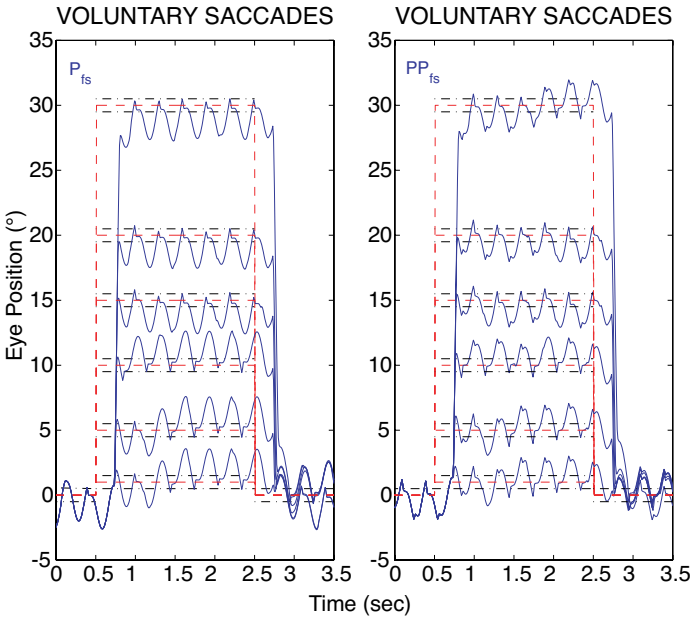

Figure 7. Accurate voluntary saccades made to target step changes in position (1-30°) made despite the presence of either P_{fs} or PP_{fs} nystagmus waveforms. Note the periods of extended foveation and spontaneous *bias shifts* about the fixation point. In this and Figures 9-11, dash-dotted lines around the target stimuli indicate the foveal extent.

cur at either peak of the oscillation. Occasional bias reversals occur when a foveating or braking saccade is not made. The amplitudes of the foveating saccades vary but foveation is maintained. The responses to a 30°-step change in target position during both P_{fs} and PP_{fs} contain short-latency corrective saccades followed by foveating saccades that quickly establish target foveation at the rightmost peaks of the oscillation. The return saccades from 30° do not contain corrective saccades; instead, the slow phases of the nystagmus are extended to reach the target. After return to primary position, foveation may occur at either peak of the oscillation. These emergent behaviors of the model duplicate recorded responses from individuals with CN.

For the responses shown in the left column of Figure 8, the model is simulating "normal" responses (i.e., the internal parameters of the PMC+ block are set to their default values) (Movie 8A [high bw/low bw], Movie 8B [high bw/low bw], Movie 8C [high bw/low bw]). Responses to pulse-step stimuli properly ignore pulses shorter than 50 ms, responding only to the second step (Becker & Jürgens, 1979; Carlow, Dell'Osso, Troost, Daroff, & Birkett, 1975). A pulse longer than 50 ms will trigger a saccade to that location, followed (200 ms later) by a second saccade in response to the step. These responses duplicate those of normal individuals, who when given appropriate instructions can decrease the probability that they will ignore short pulses in target position. Changing a model parameter or including a probability function based on pulse width accomplishes this. In the middle and right columns of Figure 8, the responses in the presence of P_{fs} and PP_{fs} CN are shown, respectively (Movie 8D [high bw/low bw], Movie 8E [high bw/low bw], and Movie 8F [high bw/low bw]). Again, the responses are normal, with the addition of the CN waveforms, and they duplicate those of individuals with CN.

Figure 9 (left) shows that the model (when simulating a "normal") accurately pursues rightward or leftward ramps ranging from very low (e.g., 1°/s, not shown) to moderately high velocities (30°/s) (Movie 9A [high bw/low bw] and Movie 9B [high bw/low bw]). The initial pursuit latency is 130 ms. The eye, although off-target, almost immediately matches the target's velocity, and 100 ms later (at 230 ms) a catch-up saccade is generated that puts the eye onto the target. At high stimulus speeds, the initial catch-up saccade may be followed by a 130 ms-latency corrective saccade. Also, because the overall SP gain is 0.95, more catch-up saccades are required; catch-up saccades increase in amplitude and frequency as target velocity increases. In Figure 9 (right), the responses to step-ramp (or Rashbass) changes in target position are shown (Movie 9C [high bw/low bw] and

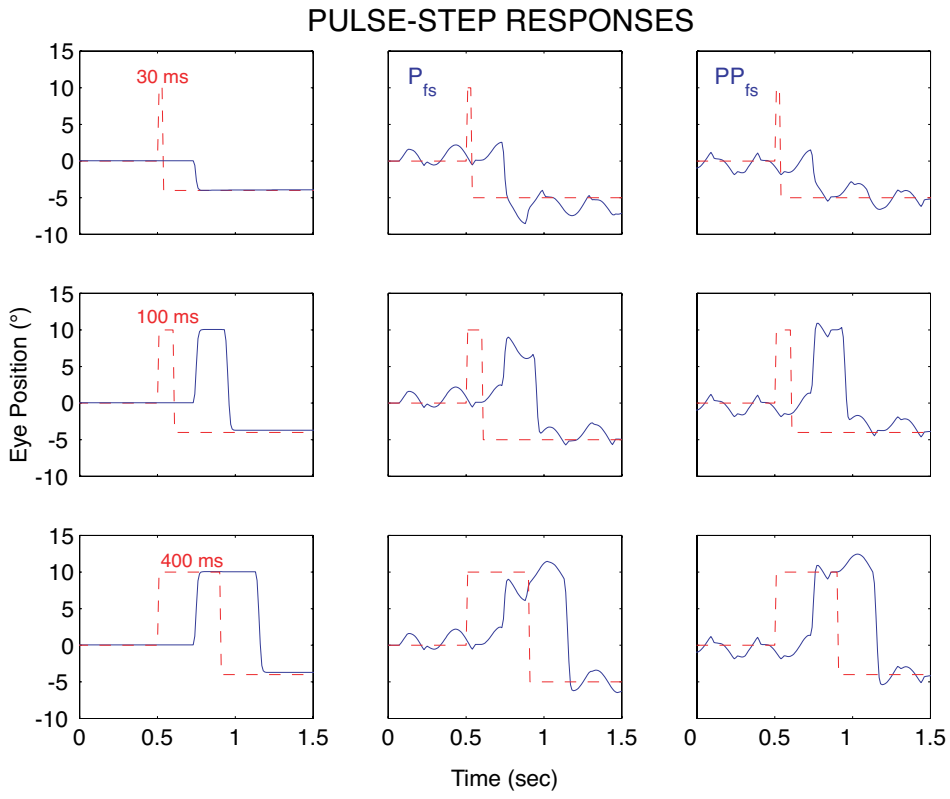

Figure 8. Accurate responses to pulse-step changes in target position made under normal conditions and despite either P_{fs} or PP_{fs} nystagmus waveforms. In all cases, short pulse widths (<50 ms) are ignored and a response is made to the second step after the appropriate saccadic latency. Longer pulse widths (>50 and <200 ms) result in a two-saccade response with an intersaccadic interval of 200 ms. Pulse widths >200 ms are responded to as individual step responses, each after the normal saccadic latency.

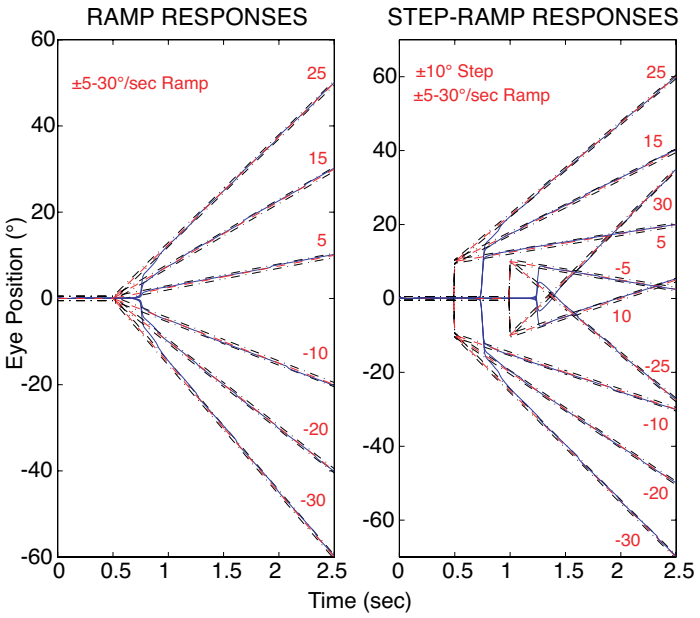

Figure 9. Accurate responses to ramp and step-ramp changes in target position made by the normal model. In both types of response, the pursuit subsystem responds first and is followed by either a catch-up saccade (ramps) or a modified refixation saccade (step-ramps). Note the corrective saccade following large initial saccades and the increased occurrence of catch-up saccades at the higher ramp velocities. Ramp velocities are indicated in this and Figures 10 and 11.

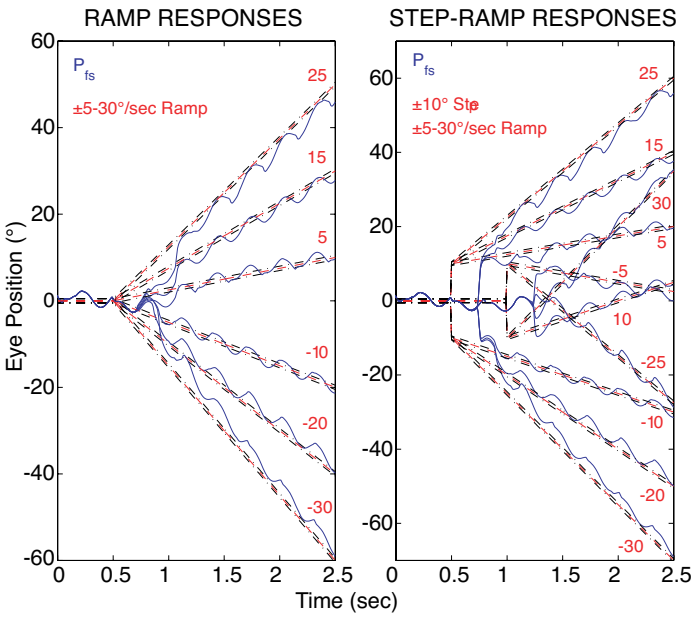

Figure 10. Accurate responses to ramp and step-ramp changes in target position made despite the presence of the P_{fs} nystagmus waveform. In this and Figure 11, note the presence of corrective saccades after larger initial saccades and the distortion of the underlying waveforms during pursuit at higher velocities, due to the required catch-up saccades. Pursuit during the periods of extended foveation is accurate.

Movie 9D [high bw/low bw]). The initial steps can be to either the right or the left and are followed by a ramp that either continues in the same direction, or goes against the initial step. The same behavior of initial and catch-up saccades described for ramp responses is exhibited in step-ramp responses.

In addition to these normal behaviors that demonstrate both the separate and synergistic functioning of the SP and saccadic subsystems, the model also simulates accurate responses to ramp and step-ramp stimuli, despite the presence of nystagmus. Figure 10 shows the model's responses in the presence of P_{fs} to both ramp and step-ramp changes in target position. Pursuit accuracy is indicated by the location of the foveation periods within the dot-dashed lines indicating the fovea. The initial catch-up saccades for ramp stimuli are diminished by the ongoing nystagmus slow phases, an emergent behavior. Similarly, for step-ramp stimuli, the initial saccade is diminished by the nystagmus slow phase and corrective saccades may be replaced by the slow phase. For high-velocity target motion, the eye falls behind more quickly and more, larger, catch-up saccades are needed. This distorts the waveform from that exhibited during fixation of a static target. Each of the above emergent behaviors duplicates responses of individuals with CN.

In Figure 11, the model's responses to both ramp and step-ramp changes in target position in the presence of PP_{fs} nystagmus are shown (Movie 11A [high bw/low bw], Movie 11B [high bw/low bw], Movie 11C [high bw/low bw], and Movie 11D [high bw/low bw]). The accuracies, observations, and emergent behaviors discussed above for P_{fs} also apply to the responses made during PP_{fs} nystagmus.

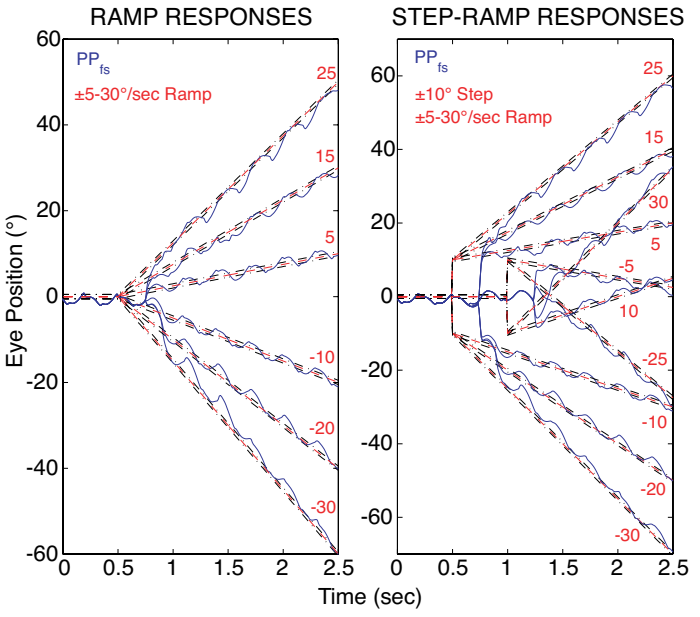

Figure 11. Accurate responses to ramp and step-ramp changes in target position made despite the presence of the PP_{fs} nystagmus waveform.

Discussion

Significant efferent factors affect real-world visual function. They include accuracy of target acquisition; time to target acquisition; stability of target foveation; and perception of target position and velocity (i.e., the absence of oscillopsia). These are the very factors whose hypothetical mechanisms are simulated in our ocular motor system (OMS) model. Even small oscillations of the eyes can result in significant deterioration of visual function. The model demonstrates how even in the presence of severe oscillations, good visual function may be preserved (extended foveation) and oscillopsia eliminated (efference copy). Without good foveation and absent oscillopsia, useful visual function is severely compromised, even if the whole afferent system from cornea to cortex were perfectly normal. We constructed a computer model of the normal OMS that simulates normal saccadic, pursuit, and saccade-pursuit combination responses, saccadic dysfunctions, gaze-evoked nystagmus, myasthenia gravis, and the dual-mode waveforms of LMLN (Dell'Osso & Jacobs, 2001). To it, we have added the ability to simulate the pendular-CN responses during fixation, saccades, pursuit, and combinations of the latter two, based on the following philosophy, conceptual bases, and foundations.

Philosophy behind the model

The philosophy that guided the development of this OMS model (and those that preceded it) is based on the premise that studying the ocular motor system during *dysfunction* would uncover hidden abilities and mechanisms required for *normal function* that might never be appreciated from study limited to the latter. Furthermore, the control-systems approach has historically demonstrated success in elucidating the complex mechanisms involved in the system-level decision-making required for the exquisitely accurate and rapid responses of the ocular motor system. Complex behaviors are dependent on the interconnections and feedback pathways between specific sites — the nature of feedback control systems. To understand how each response is generated, requires understanding *what* functions need to be performed and how they *interact.* The details of exactly how or where each is performed by the brain are secondary in this approach; however, the latter is a vital medical consideration and is of intense interest to all OMS researchers. The control-system decisions made in the design of the functional blocks within the model, especially their interconnections, were consistent with known neurophysiological data and eye-movement responses to a variety of targets.

Despite the importance of neuroanatomical studies of specific cell populations in elucidating how individual functions are performed by the brain, control-systems analysis is more suited to provide insights into complex, overall system behavior. Each functional block or interconnection of the control system model is a specific hypothesis, and is open for study and modification or replacement as neuroanatomical studies suggest specific, local mechanisms. Substitution of a "new and improved" block for an existing one should not substantially change the system's overall performance if each does the same job, albeit in different ways—that, too, is the stabilizing nature of a feedback control system. New functional blocks will continue to come from the single-cell researchers, who have made great strides in the past two decades in identifying and exploring the local brain circuitry responsible for specific neurophysiological functions and dysfunctions. Added to these will be advances made using the newer techniques of fMRI, PET, TMS, and high-resolution, event-related potentials; each approach adds insight at different levels.

We developed this model to fill the role of a "digital animal" model of CN, because at present there are vanishingly few animal models of CN, as well as a more complete model of the normal ocular motor system. Though several have been proposed, the animals appeared *not* to have CN, but rather LMLN or an acquired nystagmus. At present, there are only two verified animal models, a family of Belgian Sheepdogs with a mutation that affects the optic chiasm (Dell'Osso, 1994; Dell'Osso & Williams, 1995; Williams & Dell'Osso, 1993; Williams, Garraghty, & Goldowitz, 1991) and RPE65-deficicent canines (Acland et al., 2001). In the most extreme case in the Belgian model, *achiasma*, the chiasm is totally eliminated and visual input remains ipsilateral from retina to visual cortex. There is a lesser form, *hemichiasma,* that causes partial, unequal decussation so that a much smaller fraction of the axons cross over from each eye to the contralateral lateral geniculate nucleus (Hogan & Williams, 1995). Unfortunately, the mutation has been found only in this one pedigree, and severe fertility problems and limited understanding of the genetics of the defect have endangered the line's survival. In this light and because of the absence of any robust, behavioral models of ocular motility, a reliable, easily accessible OMS model capable of simulating CN may prove invaluable.

Most ocular motor models put forth in the past 30 years have been restricted to small portions of specific subsystems or models whose main purpose was to demonstrate how a specific waveform of nystagmus might be generated; we are unaware of any attempts to assess the effects of these mechanisms on the behavior of the ocular motor system. Without such demonstrations, the hypothetical mechanisms generating such waveforms remain speculative. One use to which a robust, behavioral model of the ocular motor system may be put is to test such mechanisms by integrating them into the model and determining the effects they have on all known responses. Another use of a behavioral model is to suggest and test hypothetical mechanisms responsible for observed deviations from normal behavior exhibited by those with specific disorders.

The history of ocular motor system investigation has, for the past half-century, been one of control-system-based prediction of function followed, often after many years, by

localization within the brain and partial models limited to their hypothetical function. Examples are the common neural integrator and the local resettable integrator within the saccadic pulse generator, the latter, originally hypothesized in our Lab in 1972 and published in a model of gaze-evoked nystagmus (Abel et al., 1978). Apparently unaware that control-systems analysis of ocular motor dysfunction had recognized the necessity for a local, resettable signal a decade earlier, Scudder described its use in the pulse generator (Scudder, 1984). In the ensuing years several groups have put forth differing and conflicting hypotheses for the site, function, and even the existence of the resettable integrator (Fukushima, Kaneko, & Fuchs, 1992; Kaneko, 1996; Munoz & Wurtz, 1995a, 1995b; Optican, 1994; Optican, 1995; Optican & Zee, 1984; Waitzman, Ma, Optican, & Wurtz, 1988). Thus, 30 years after its prediction and despite the Herculean efforts of the above groups, a universally accepted location and model for the resettable integrator (a small part of only one subsystem) or some other mechanism to perform the same function, remains undecided. What the control-system approach suggests is that this function is required, by neural circuitry that either approximates mathematical integration or achieves the same transformation in another way; it does not suggest either an anatomical location (e.g., the function might be distributed) or an identifiable separate entity (e.g., the integration may be combined with some other necessary function). It is impossible to avoid physics; we have velocity information and we need position information to direct and hold the eyes.

A top-down model is invaluable in conceptualization of how the overall system works and how it might fail in the face of specific types of dysfunction. Given the long time intervals required for the bottom-up approach to modeling to arrive at universally agreed upon anatomic sites or structural models for small portions of subsystems, the expectation that it is likely to produce a total, behavioral model of ocular motility in the near future is problematic. Taken to its limit, the requirement that all models be anatomically and neurophysiologically accurate at the neuronal or cellular level, leads to a model of the size and complexity approaching that of the brain itself, a task requiring computer power not yet available. Therefore, we regard the development and use of top-down, behavioral models (consistent with known neurophysiological functions) as imperative to continued progress in studying ocular motor function and dysfunction; we are unaware of a reliable alternative.

Conceptual bases for the model

We hypothesized that within the OMS, an internal monitor makes use of afferent retinal errors (position and velocity) and efferent motor information (position and velocity) to detect changes in target position and velocity and to accurately reconstruct target and error (position and velocity). This allows the OMS to differentiate this important input information from internally generated eye position and velocity signals, such as those resulting from CN oscillations. We further hypothesized that these oscillations are merely an extension of the damped ringing observed in the normal SP subsystem at the onset of pursuit. By a small gain change to reduce the damping, we allowed the ringing to continue, rather than decay exponentially. Thus, our hypothetical source for pendular CN is an otherwise normal SP subsystem acting within a normal ocular motor system. The OMS model uses the abilities necessary for *normal* operation to react to the pendular velocity oscillation, inserting foveating and braking saccades, and most importantly, using efference copy to properly reconstruct a stable percept of the outside world (i.e., one without oscillopsia). Furthermore, this reconstruction effort does not diminish the model's ability to respond to complex stimuli with the appropriate accuracy and latency. In the model, less-than-perfect reconstruction produces some oscillopsia, simulating that seen in CN under specific circumstances. The underlying pendular nystagmus is, therefore, a *pursuit-system* nystagmus (PSN), and the resulting waveforms (some pathognomonic for CN) and eye repositioning are generated by normal saccadic responses.

Since the initial behavioral model of CN (Dell'Osso, 1968), several models limited to simulating some CN waveforms have been proposed; four in particular deserve attention. Three (Harris, 1995; Optican & Zee, 1984; Tusa, Zee, Hain, & Simonsz, 1992) are all based on the same mechanism, namely a large, inappropriate positive feedback around the neural integrator (NI) that leads to the runaway slow phases (Dell'Osso & Daroff, 1981; Zee, Leigh, & Mathieu-Millaire, 1980). The fourth (Broomhead et al., 2000) starts from a different premise, that the responsible mechanism can be traced to insufficiencies in the saccadic subsystem. This is based on an earlier suggestion (Dell'Osso et al., 1972) and a conclusion from an earlier study (Abadi & Worfolk, 1989) that found the peak velocities of saccades made by CN subjects appear to be slower than those made by controls. For the reasons enumerated below, we believe the two hypotheses proposed in these models are unsupported by CN data.

The underlying hypothesis of the first three models is that the gain around the common neural integrator is excessive. However, CN has been demonstrated in members of family with gaze-evoked nystagmus (GEN) (Dell'Osso et al., 1993). The centripetal slow phases of GEN have been shown to be due to a *leaky* (i.e., low-gain) neural integrator (Abel et al., 1978; Cannon & Robinson, 1987). The gain cannot simultaneously be too high (causing CN) and too low (causing GEN), disproving the fundamental hypothesis of these models. Also, many individuals with CN exhibit long periods of extended foveation (several hundred milliseconds) before the eye accelerates off target, suggesting a stable neural integrator. Additional problems with this hypothesis are that it could not generate sustained pendular nystagmus (unlike many with CN); it produced two null regions (there is at most *one* null in CN); it was applied to patients whose characteristics did not match those of CN;

it led to the postulation of an abnormal loop providing extra positive feedback to the neural integrator and suggested a midline defect due to inappropriate decussation of axonal fibers carrying velocity information, something that has not, as of yet, been found in anyone with CN and has been ruled out in others (Shallo-Hoffmann & Apkarian, 1993); it suggested that pulse-step mismatches were an ignition source for initial generation of CN. Such mismatches are not seen in those with CN, whose nystagmus is a function of gaze angle, regardless of how that position was achieved (e.g., large and small saccades, slow pursuit, or slow VOR). The hypothesis led to the postulation of a maladaptation to early visual deprivation; this does not address the etiology of those whose CN was present at birth or who have no afferent visual deficits (i.e., patients with idiopathic or hereditary CN). Finally, the hypothesis also led to the postulation of excessive, overall smooth pursuit gain, contradicting known CN behavior, where the SP gain has been shown to be normal (Dell'Osso, 1986; Dell'Osso et al., 1972; Dell'Osso et al., 1992b; Kurzan & Büttner, 1989).

The second hypothesis, the basis for the fourth model (Broomhead et al., 2000), was a putative deficit in the saccadic subsystem, plus the presumption that CN saccades were slower than normal (the latter may not be a necessary accompaniment to this hypothesis). It has been shown elsewhere (Jacobs, 2001; Jacobs & Dell'Osso, 1997; Jacobs et al., 2003) that apparent differences in peak velocities are due to artifacts of measuring techniques and simple mechanical summation-cancellation of the saccadic and slow-phase or smooth-pursuit signals. No attempt was made, using this hypothetical saccadic deficit, to reproduce the saccadic accuracy demonstrated by individuals with CN when changing fixation to new targets. Published and unpublished ocular motor data from hundreds of CN patients recorded in our laboratory (Averbuch-Heller, Dell'Osso, Leigh, Jacobs, & Stahl, 2002; Dell'Osso, 1973b, 1985; Dell'Osso et al., 1997; Dell'Osso & Daroff, 1975, 1976; Dell'Osso, Ellenberger, Abel, & Flynn, 1983; Dell'Osso, Flynn, & Daroff, 1974; Dell'Osso et al., 1972; Dell'Osso & Leigh, 1990; Dell'Osso, Schmidt, & Daroff, 1979; Dell'Osso et al., 1975; Dell'Osso et al., 1992c; Jacobs et al., 1999), especially studies of target foveation (Dell'Osso, 1973a; Dell'Osso & Jacobs, 2002; Sheth, Dell'Osso, Leigh, Van Doren, & Peckham, 1995), plus CN data published by others during the past four decades (Abadi & Dickinson, 1986; Abadi, Pascal, Whittle, & Worfolk, 1989; Abadi & Worfolk, 1989; Bedell & Currie, 1993; Bedell, White, & Abplanalp, 1989; Chung & Bedell, 1995, 1996; Hertle & Dell'Osso, 1999; Hertle, Maldanado, Maybodi, & Yang, 2002; Reinecke et al., 1988) led us to conclude that the causes of the oscillation are slow eye movements (slow phases), not saccades.

CN slow phases begin in the absence of (and do not depend on the size of) preceding saccades; therefore, models whose generation of slow phases depends on prior saccades (as all four of these models do in different ways) appear to be inconsistent with CN data. Any saccades present in CN waveforms are *always* corrective in nature and result from a normal saccadic subsystem attempting to either brake the runaway eye movements or to additionally refoveate the target; the OMS model is consistent with these observations. We have outlined the problems and limitations of the hypotheses embodied in the above models of CN waveform simulation; detailed discussions have been published elsewhere (Broomhead et al., 2000; Dell'Osso, 1988; Harris, 1995; Jacobs et al., 2003). We regard limitations in the simulation of ocular motor behavior of either normals or individuals with CN as restricting a model's usefulness and undermining its fundamental hypotheses. The current OMS model provides a different approach and alternative hypotheses supported by more robust behavior; it does not disprove prior attempts, but we believe it provides a more biologically relevant standard by which future models should be judged.

Fixation subsystem

The hypothesis that fixation is active during pursuit is supported by normal pursuit responses to ramp stimuli, during which eye velocity is transiently greater than target velocity after the catch-up saccade that brings the target image into the foveal area. This allows the fixation subsystem to bring the target image to the center of the fovea where the pursuit system can maintain eye velocity just below target velocity (i.e., pursuit gain is slightly less than 1). Although fixation complements pursuit, it is a separate subsystem (Luebke & Robinson, 1988). Figures 9 and 10 demonstrate that SP gain is normal during the extended foveation periods, as has been shown for individuals with CN (Dell'Osso, 1986; Dell'Osso et al., 1992b; Kurzan & Büttner, 1989).

Foundations of the model

This model of ocular motor function (and dysfunction) evolved from models that were built on basic foundations stemming from years of observation and analysis of normal and abnormal eye movement data; wherever applicable, adherence to demonstrated neurophysiological structure was maintained. This approach helped ensure that the model would be "robust" in its behavior, meaning that (1) it would respond realistically to a broad range of inputs, simulating a broad range of behaviors; and (2) in the more classical control-systems definition of the term, it would recover from internal errors in a realistic manner, rather than simply failing or yielding wildly uncontrolled outputs. A thorough treatment of the preceding models is available elsewhere (Dell'Osso, 2002).

We are *not* proposing a discrete anatomical structure that we purport to be the "Internal Monitor," but, consistent with the top-down, engineering-based approach, the disparate signals and functions proposed for the IM are grouped in one block for clarity. Interestingly, recent work has uncovered the presence of many of these signals in the paramedian tract (PMT) (Nakamagoe, Iwamoto, & Yo-

shida, 2000) and, at the cellular level, climbing fiber activity has been shown to predict interval times allowing neurons to work as timers, such as those used in the IM to make logical decisions regarding visually guided, corrective, and braking saccades (Durstewitz, 2003). Similarly, we do not speculate on possible anatomical sites for each functional block (e.g., fixation and the superior colliculus) or discuss the putative roles of specific neurons (e.g., omnipause and burst cells) known to play a part in ocular motor control. In fact, we do not even claim that the specific functions identified separately in the model are necessarily anatomically distinct. Individual functional blocks aid in our understanding their respective roles in ocular motor control. Therefore, we made no effort to streamline the model by combining functions; we remain mindful of how prior attempts to use the final common NI to perform too many tasks limited those models' capabilities and rendered them unable to simulate dysfunction (see below) (Abel et al., 1978). Although we named blocks for their functions in this model, we believe each is present in the normal OMS (e.g., the Braking/Foveating Saccade Logic block is probably the same mechanism used to program fast phases of vestibular and optokinetic nystagmus; the common stimuli for all are eye motion and retinal slip). Data supporting the common origin of fast phases and braking saccades appear in Figure 6C. Shown are vestibular fast phases in the response of a subject with a low-gain VOR secondary to multiple sclerosis. These braking saccades (up to two per VOR cycle) were generated despite the hi-frequency head oscillation. This suggests an innate ability for the ocular motor system to generate braking saccades in response to vestibular input. Thus, their common appearance in CN waveforms does not represent a newly developed, adaptive skill but rather, an *exaptation* (i.e., performance of a new function) (Gould, 1991) of the normal fast-phase mechanism. Until such time as neurophysiologists sort out all of the relevant anatomical sites, we prefer to err on the side of redundancy and separation of function, a more instructive and physiological approach.

Development of the model

Although it is possible to learn much from simpler models, they tend to be incapable of performing beyond their imposed limitations. Models designed to simulate *only* normal ocular motor control may succeed when tested against a small repertoire of behaviors, but they usually fail when challenged by injury to their structure, or inputs beyond their intended range. This is often due to oversimplifications in both their design (the parsimonious false economy of "engineering elegance") and assumptions about the operation of the ocular motor system based solely on normal data. A model that can adequately reproduce a large range of normal functions is more likely to be able to also simulate dysfunctions, as each new insult to the system suggests a possible set of remedies that might be used both in nature and in the model. Because of this approach, our simulation makes extensive use of efference copy of motor output signals (the *internal monitor*), as first required in a model of CN (Dell'Osso, 1968), later in a study of normal corrective saccades (Weber & Daroff, 1972), and in models of square-wave pulses (originally designated "macro square-wave jerks") (Dell'Osso et al., 1975), gaze-evoked nystagmus (Abel et al., 1978), and myasthenia gravis (Abel et al., 1980). The pulse generator also contains a resettable neural integrator (Abel et al., 1978; Abel et al., 1980) that is distinct from the common neural integrator responsible for maintaining eye position, and it utilizes feedback control of the saccadic pulse input to the common neural integrator ("NI Control" and "NI Hold"), as first required by the gaze-evoked nystagmus model (Abel et al., 1978). Most models of normal ocular motor control presume (incorrectly, we contend) that the pulse is totally and *always* integrated by the NI.

The model presented is consistent with CN data thus far published and demonstrates the ease with which our hypothesis for the generation of the most complex CN waveforms can be realized by a functionally normal OMS without diminishing the responses to a broad variety of stimuli. Other features will be implemented in future versions. General OMS model development includes the addition of vestibulo-ocular and optokinetic subsystems (a preliminary model is currently being tested), and the expansion of the model from a unilateral, bidirectional form to a more anatomically realistic bilateral, unidirectional form. This will allow us to implement CN damping as the eyes converge and include other characteristics of the vergence subsystem. There remain features of CN that are not yet implemented, such as simulation of jerk CN waveforms by a mechanism other than the disproved neural integrator dysfunction mechanism. Although jerk CN is the simplest waveform to simulate using any of several methods (as the models discussed above show), it is not clear exactly how it transitions so easily with pendular waveforms when gaze is shifted or even if a separate mechanism is required. We have not added a mechanism for jerk waveforms to the current version of the OMS model because we are experimenting with methods consistent with CN data. We will incorporate changes in waveform around the null angle due to Alexander's law for changes in gaze angle, and shifting of the null angle due to pursuit. We also intend to further integrate LMLN and CN function so that both can coexist simultaneously (some individuals have both types of nystagmus), and the CN can also have a latent component (i.e., produce CN waveforms that change as a function of which eye is fixating). Finally, the fixation subsystem will be further refined, allowing even greater extension of the low-velocity intervals following foveating saccades.

Emergent behavior

The origin of bias reversals had been hypothesized to be due to a mildly unstable null making small shifts. However, the model's behavior is due to small variations in the

timing of braking/foveating saccade generation. In panel C of Figure 5 (P_{fs}), a second foveating saccade occurs shortly after the marked (*) foveating saccade rather than waiting for the cycle to complete. This is most probably due to conditions at the time of the second saccade's programming that still favor a foveating saccade, for the effect of the first foveating saccade may not have been predicted to be sufficient. In panel E, the bias reversal occurs for a different reason; here the foveating saccade expected to follow the marked (*) foveating saccade failed to be generated and the oscillation completed a turn-around before conditions again favored the programming of a foveating saccade. This occurred because the times when both the velocity and acceleration criteria were satisfied did not overlap long enough for a saccade to be programmed. Thus, the model's emergent property suggested new hypotheses for bias reversals. Panel E also demonstrates another effect of failure to make a foveating saccade (for reasons described above). The resulting oscillation is larger and straddles the fixation point until the next foveating saccade re-establishes target foveation and waveform bias.

The OMS model exhibited the following emergent behavior that was neither designed into it nor predicted a priori:

- The size of voluntary saccades was modulated by the CN slow phases and not equal to that of the target step.
- The normal saccadic subsystem alone automatically transformed a velocity-induced oscillation that straddled the fixation point into one biased to allow foveation at one peak of the oscillation. There was no need to postulate a "biasing" mechanism, as we had anticipated.
- Occasional suppression of braking or foveating saccades led to increased nystagmus amplitude and decreased frequency. Therefore, braking saccades were shown to damp CN.
- Spontaneous bias reversals were caused automatically by occasional, small voluntary saccades serving to correct accumulated position error.
- CN slow phases could suppress required corrective saccades following hypometric voluntary saccades and accomplish target acquisition.
- The variability in the magnitude of foveating saccades was produced by minor (<0.075°) variations in motor commands.
- The magnitudes of braking and foveating saccades were affected by slow-phase velocity.
- Initial catch-up saccades during ramp and step-ramp pursuit were diminished by the CN slow phases.
- The catch-up saccades needed during high-speed pursuit distorted the classic CN waveforms.

It is important to note that all of these behaviors are consistent with — and provide explanations for — recorded human data; their emergence provides support for the basic ocular motor mechanisms and their interconnections built into the model.

An important insight from this model is that complex-appearing behavior arises from the interaction of many simpler interconnected subsystems, as is seen in nature. In addition to expanding the range of normal responses and adding those with pendular CN, this model retains the capability of simulating normal eye movements and, with proper settings (i.e., "lesions"), the other neurological conditions of its predecessors (e.g., gaze-evoked nystagmus, myasthenia gravis, and latent/manifest latent nystagmus). It represents a major step in our goal to marry previous models of ocular motor dysfunction into a unitary ocular motor control system model that can be used to study, simulate, and predict many of the behaviors exhibited by both normal individuals and those with specific ocular motor dysfunction. The model has already predicted responses of individuals with CN to smooth-pursuit targets and provided testable hypotheses that are the foundation for a study of smooth pursuit and CN that is now underway. It has also provided a simulation and hypothetical mechanism for a newly discovered saccadic instability, "staircase saccadic intrusions" (Garbutt, Dell'Osso, & Jacobs, 2003). In addition to its usefulness in research, the model's pedagogical potential is broad.

The new CEMAS nomenclature

In an attempt to arrive at a more acceptable and consistent nomenclature for strabismus, nystagmus, and saccadic intrusions and oscillations, a new classification system has recently been adopted by the Committee on Eye Movement Abnormalities and Strabismus, sponsored by the National Eye Institute (CEMAS Working Group, 2001). To ease the transition to this new nomenclature, it will be necessary to link the *old* with the *new*. Thus, the hypothetical nystagmus that is the subject of this work falls under the "Infant Nystagmus Syndrome—INS" that includes the various types of specific nystagmus waveforms previously documented as "CN." Thus, PSN would fall into that syndrome as one of several underlying types of nystagmus commonly seen in the INS, and P, P_{fs}, PP, and PP_{fs} represent the specific waveforms of PSN. Additionally, LMLN, will be replaced by "Fusion Maldevelopment Nystagmus Syndrome—FMNS."

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