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Biologically Relevant Models of Infantile Nystagmus Syndrome: The Requirement for Behavioral Ocular Motor System Models

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ABSTRACT Infantile nystagmus syndrome (INS) is a combination of several types of nystagmus, each representing dysfunction in one subsystem of the ocular motor system (OMS) and having characteristic waveforms. Eye-movement recordings are the only certain way to identify IN and differentiate it from other types. The waveform classification scheme in use for 30 years is both accurate, inclusive, and suggests the underlying subsystem instabilities. In different individuals, they may appear at birth (hard wired) or in early infancy (developmental). The *primary subsystem instability* in IN is hypothesized to lie in the normally underdamped smooth pursuit system; vestibular dysfunction (imbalance) may also be present. Less often, the nucleus of the optic tract may be involved. Ocular motility studies over the past 40 years have demonstrated that saccades and gaze holding are normal in the INS and saccades contained within IN waveforms are always corrective; i.e., they *cannot* be the initiating movement responsible for IN. Because there are an infinite number of solutions to simulating specific waveforms, models that merely generate waveforms that resemble IN in isolation are of little use, either clinically or to increase our understanding of the underlying mechanisms of IN. A biologically relevant model of the INS should be part of, and operate within, a complete OMS model, capable of reproducing the normal ocular motor *behavior* of these individuals while still oscillating; i.e., the model, like the patient, must not have oscillopsia and be able to respond correctly to various target inputs.

KEYWORDS infantile nystagmus syndrome, functional causes, models

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INTRODUCTION

In this paper I will present our hypotheses for the underlying mechanisms of the various specific nystagmus types (i.e., waveforms) found in the infantile nystagmus syndrome (INS).[1] These hypotheses and conclusions are based on observations and analyses of the ocular motility recordings (on approximately 1000 individuals with INS) we, and others, have made over a span of 40 years using a control-systems approach and "top-down" modelling.

CAUSES AND CHARACTERISTICS OF INS

The INS may be present in individuals with no visual sensory deficits and in those with such deficits. Being neither necessary nor sufficient, afferent deficits cannot be the *direct* cause of INS. From a control-systems perspective, the direct cause is simply an excessive gain in a feedback control system or a tonic imbalance; the specific ocular motor subsystem responsible may be inferred from the nystagmus waveform and other characteristics. Although medically important, associated visual deficits and the exact time-of-onset of IN are essentially irrelevant in determining the direct causes of the distinct types of IN. The original name of this condition, "congenital nystagmus," and the erroneous hypothesis that IN is a "fixation" nystagmus (only developing as the fixation system developed) fuel ongoing debates, adding heat but no light. Although many cases of IN develop in early infancy, some advocates of this hypothesis ignore the many documented cases of IN documented *at birth* by both concerned parents and physicians (which debunk the "fixation-system" hypothesis) and falsely claim IN is *never* present at birth. In normal ocular motor systems, some subsystems have evolved to a point where they are on the brink of instability and require careful calibration. A visual defect associated with IN may act as a facilitator or trigger for oscillations in these subsystems, whose stability is determined by initial calibration, early in development, and maintained by the plasticity of important gain settings within the involved control systems. Put another way, *IN is a disorder waiting to happen* in all humans; its common occurrence with any of a wide variety of visual deficits or in the absence of any afferent deficits supports this conclusion. Furthermore, hypothetical causes of IN must conform to these epidemiological facts. Before identifying what I regard as the functional causes of IN, it will be helpful to review what we know about the characteristics of both IN and the ocular motor system in general.

First, IN becomes manifest only when the affected individual attempts to use his ocular motor system to acquire, pursue, or maintain fixation of a target or to direct the eyes; it slows and eventually ceases with inattention or sleep. The term "fixation attempt" has been used to describe this precondition for IN, despite the fact that an actual fixation target is not necessary for IN to appear; it can occur behind closed lids or in complete darkness. Even momentary lapses in visual attention will cause the initiating slow phase to continue for a longer time than during active fixation, delaying the corrective fast phase. After a few such lengthened cycles, simple verbal or visual prompting will cause corrective fast phases to return and the IN cycles to resume their prior, short-duration, clock-like appearance. Thus, the first indication of a waning of fixation attempt is delayed corrective fast phases (either braking saccades or foveating saccades); this results in larger amplitude, lower frequency cycles of IN and may change its waveform.

Second, if stress in introduced, the IN becomes more intense, diminishing visual acuity. In most individuals, increasing the difficulty in resolving a target does not, of itself, exacerbate the IN. It appears to be the stress caused by such difficulty that results in increased nystagmus and diminished acuity.[2] This suggests that the key parameters in the feedback control systems responsible for IN are under active control that may either damp the nystagmus or exacerbate it. The effects of stress on IN are idiosyncratic, ranging from barely detectable (although recordable) to easily observed clinically.

There are three main classes of IN waveforms: pendular (with variations dependent on the nature of corrective saccades inserted into the waveform by the normal saccadic system); jerk with accelerating slow phases; and jerk with linear slow phases. An additional class, the dual jerk (DJ) waveform, consists of one of the IN waveforms (usually jerk) plus a low-amplitude, higher frequency pendular (Plahf) oscillation superimposed on it. We have documented one instance of "dual pendular" (DP) IN where the Plahf oscillation is superimposed on the lower frequency pendular nystagmus waveform common in IN (Figure 1). This is the first new IN waveform discovered since the original 12 were described in 1975[3] and provides strong support for the hypothesis that the Plahf nystagmus of DJ and DP nystagmus is not from the same source as the well-documented pendular IN waveforms. Pendular oscillations arise from unstable feedback loops whose gain is too high. Accelerating (runaway) slow phases were initially thought to arise from positive feedback around the common neural integrator[4] and linear slow phases from a tonic imbalance in the push-pull circuitry of the ocular motor system. Most individuals with INS exhibit several types (waveforms) of nystagmus whose appearance and amplitude depends on gaze angle. That suggests that more

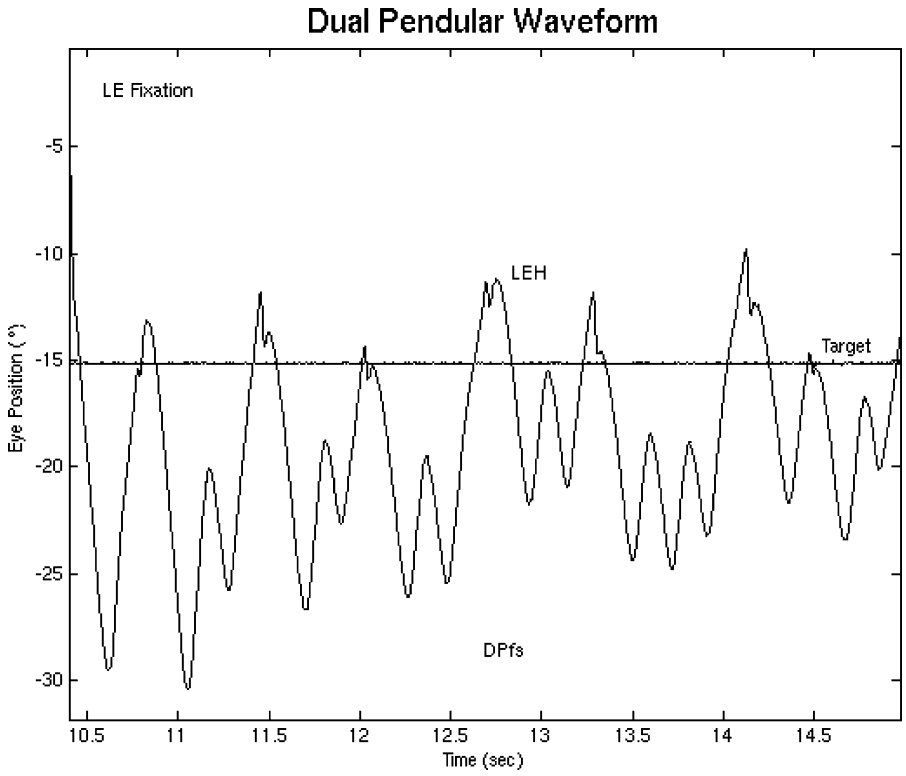

FIGURE 1 **An example of the "dual pendular" (DP) waveform of infantile nystagmus (IN). It consists of a high-frequency (4–5 Hz), lower-amplitude (2–5° p-p) pendular nystagmus superimposed on the more common lower frequency (1–2 Hz) and higher amplitude (11–18° p-p) pendular IN.**

than one instability is responsible and the waveform exhibited at a particular gaze angle will depend on the relative contributions of each (i.e., there is more than one *cause* for IN). Although IN waveform variation is idiosyncratic, it is repeatable in recordings made throughout the life of the individual. In some individuals, the magnitude and type of IN waveform varies with time as well as gaze angle. This time variation is usually neither symmetrical (i.e., duration of the jerk-left phase is not equal to that of the jerk-right phase) nor periodic. Time-variable IN is accurately described as Asymmetric Periodic Alternating Nystagmus (APAN). Recognition of the complexity of these often overlapping waveforms and their different causes prompted the change in terminology from CN to INS.

Properly (monocularly) calibrated eye-movement recordings utilize small stationary targets at known locations and only the *foveation periods* of each IN cycle. Such recordings document that the voluntary saccades of individuals with INS are normal[5] and saccades contained within IN waveforms are *always corrective* in direction (braking and foveating) and accurate (foveating). Braking and foveating saccades follow the initial slow eye movement, taking the eyes off target, and reduce the amplitude of the IN. The latter allow target foveation, a requirement for good visual acuity. Also, the waveform and intensity of IN is dependent on gaze but *not* on the saccade used to achieve that gaze angle. That is, IN at 20° right aze is the same whether preceded by a 1° saccade or a 40° saccade. It is also the same if that gaze angle is achieved by slow rotation of the head or pursuit of a slowly moving target *with no saccade at all*. The latter eye movements must be slow because the IN null position is also dependent on eye velocity as well as position. Finally, when inattention damps the IN completely and attention slowly returns, the slow phase precedes any saccades that may be present in the waveform. Thus, saccades play no part in the *generation* of IN and are not part of the problem; rather, they are part of the brain's solution.

MODELS OF INS

An early hypothesis for the generation of the accelerating slow phases of jerk IN was that the positive feedback around the eye-position maintaining neural integrator (NI) was greater than needed to offset its inherent leakiness.[4] However, a study of members of a

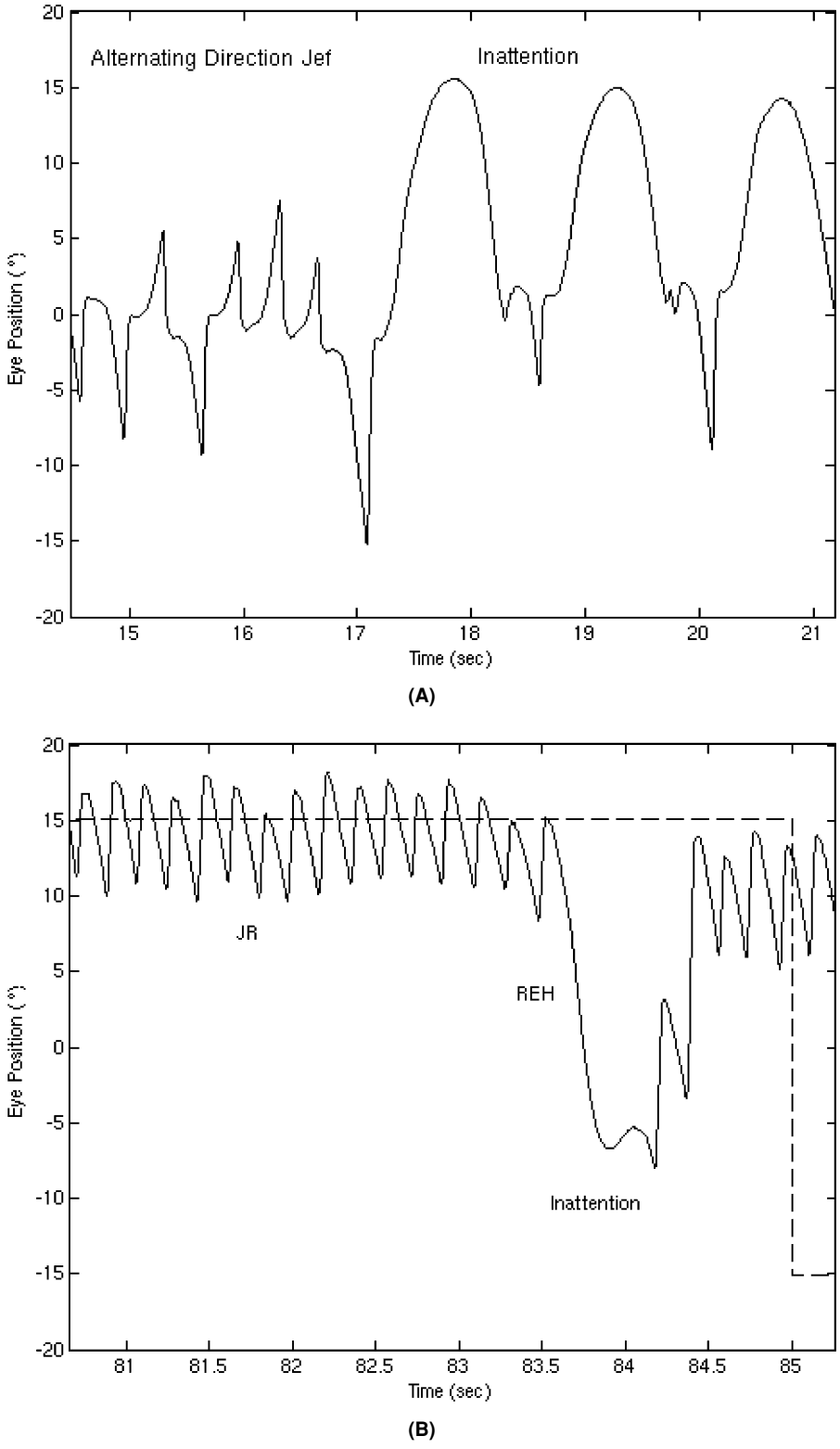

FIGURE 2 **Fixation in primary position with alternating direction jerk IN waveforms whose slow phases become pendular when inattention suppresses the fast phases (A). Fixation at 15° right gaze with jerk right IN degenerating to pendular IN with inattention (B). Dashed line in B is the target trace.**

family whose children had both INS and gaze-holding failure demonstrated that the *centripetally* (with respect to the IN null position) accelerating slow phases of their IN coexisted with the centripetally (with respect to primary position) decelerating eye position (due to the leaky NI); that disproved the hypothesis by counterexample (in this family, many).[6] The final common neural integrator functions normally in most INS patients and

is not the source of the nystagmus. Nevertheless, there have been several attempts to simulate accelerating slow phases resembling IN using variations of the above hypothesis. These "neural integrator" models did not accurately simulate either characteristic ocular motor behavior or the waveforms of individuals with IN. Also, those waveform models produced *centrifugal* acceleration corrected by centripetal fast phases (with respect to primary position) whereas the jerk waveforms of IN actually contain *centripetally* accelerating slow phases and *centrifugal* fast phases (with respect to the null angle). Thus, accurately calibrated ocular motor data have provided strong evidence eliminating both the saccadic subsystem and the NI from consideration as possible sources of the instabilities exhibited in the INS. In contrast, some investigators who were inexperienced in recording or analyzing IN data (e.g., they could not differentiate IN from latent nystagmus) failed to properly, monocularly calibrate IN data or detect and eliminate from analysis changes in the fixating eye, inattention, or blinks. The resulting in two studies were devoid of both sound methodology and meaningful conclusions[7]—but did increase entropy. The authors' rude, *ad hominem* non-response (a plethora of erroneous statements and baseless inferences) does not merit citation in a scientific paper.

Individuals with INS may pursue high-frequency, sinusoidally moving targets more accurately than normal subjects[8] The normal smooth pursuit subsystem is underdamped; velocity step responses of normal smooth pursuit show a damped velocity oscillation. I hypothesized that the source of pendular types of IN could be due to a miscalibration in the internal loop gain governing the damping of the pursuit subsystem. The result would be an undamped pendular velocity oscillation present whenever the pursuit system was activated. Because the loop with the excessive gain was internal, it would not affect the overall pursuit gain, which has been shown to be normal in IN.[9–11] This hypothesis is consistent with the observations that IN appears in many individuals, with and without afferent deficits, and no lesion has ever been found to cause IN.

The first behavioral OMS model containing a simulated IN demonstrated that the use of efference copy

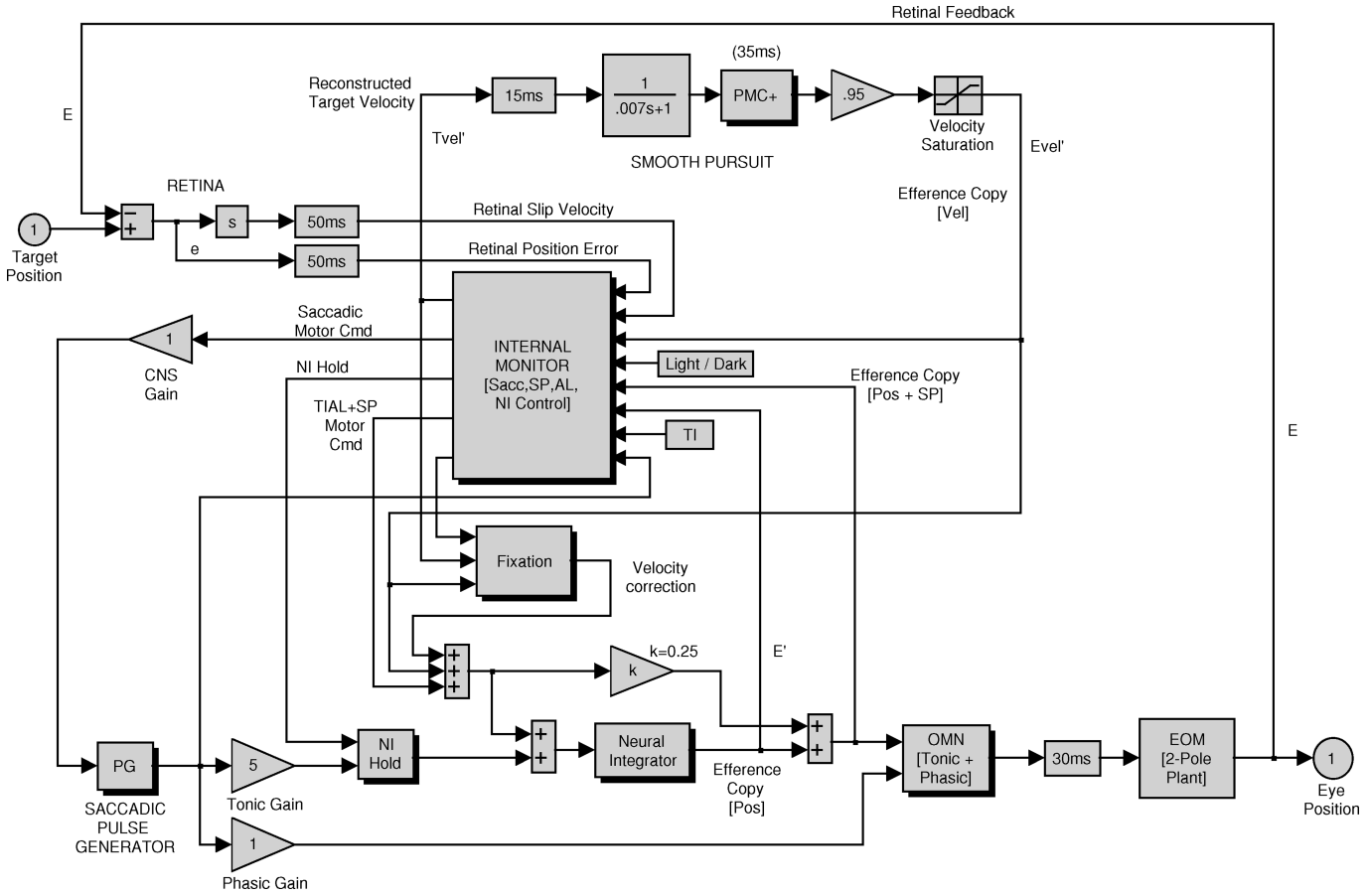

FIGURE 3 **A block diagram of the OMS behavioral model capable of simulating the ocular motor behavior of normals, those with IN, and those with a variety of other ocular motor disturbances.**

was essential if the OMS was to differentiate true target position and velocity from retinal position and motion.[12] Thus, a realistic OMS model must use efference copy to reconstruct target position and velocity; these are the signals that drive the saccadic and pursuit systems, respectively. Recently embodied in a behavioral model of the ocular motor system (OMS), the pursuit-system hypothesis was 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) [13,14] As Figure 3 shows, the model contains only functional blocks known to be part of the OMS; the same is true for those within the IM block. In addition, 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. One of the most important was the demonstration of how the *normal* saccadic and fast-phase mechanisms acted to shift the velocity oscillation allowing target foveation at one peak of the sinusoidal nystagmus, exactly as patients do to achieve good visual acuity. In its original version, this model simulated all of the complex pendular nystagmus types seen in INS during each of the above ocular motor tasks.

The accelerating slow phases of most jerk IN actually appear to be the same sinusoidal signal underlying the pendular waveforms. Eye movement data from individuals with jerk IN show that, with inattention, the foveating fast phase is delayed and the accelerating slow phase actually decelerates (i.e., there is a point of inflection) before the fast phase resets the fovea on target (Figure 2). Thus, this type of instability is not due to excessive positive feedback but its underlying mechanism is the same as for the pendular waveforms–jerk IN, like pendular IN, appears to be a *pursuit-system* nystagmus. Our OMS model simulated the linear slow phases of fusion maldevelopment nystagmus (FMN) based on a tonic imbalance, presumably from the optokinetic portion of the vestibular-optokinetic subsystem. In IN, linear slow phases would be similarly generated by the same type of imbalance from the vestibular portion. Finally, the Plahf oscillation present in the dual jerk waveforms of both IN and FMN and in the DP waveform of IN are probably due to instability in the lateral geniculate pathways.[15,16] At present we are incorporating these jerk, DJ, and DP types of IN into our OMS model.

THE NEED FOR PROPRIOCEPTION IN THE PLANT

Recent ocular motor studies demonstrated that four-muscle tenotomy was sufficient to damp both IN[17,18] and acquired pendular nystagmus *but not saccades*.[19,20] This supports the hypothesis that its mode of action is to interfere with proprioceptive control of the resting tension of the extraocular muscles.[21] Recent neuroanatomical studies also support this hypothesis.[22–24] Thus, newer models of the plant need to incorporate proprioceptive tension control in the form of differential gains for small (nystagmus slow phases) and large (saccades) signals.

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