# 4

# Waveforms in Infantile Nystagmus: Mechanisms Yield the Best Classification

**L.F. Dell'Osso**[1,2,3]

*[1]Daroff–Dell'Osso Ocular Motility Laboratory, Louis Stokes Cleveland Department of Veterans Affairs Medical Center and CASE Medical School, Cleveland, Ohio, USA*
*[2]Department of Neurology and [3]Department of Biomedical Engineering, Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, Ohio, USA*

## 4.1 Introduction

With the possible exception of the original name "congenital nystagmus," the determination of the *cause* of infantile nystagmus syndrome (INS) (CEMAS Working Group 2001) has produced the most heated (and unenlightening – entropic) debate. Attempts were made to find simple explanations for the ubiquitous appearance of INS in infants who had many different and *unrelated* afferent visual disorders, and in those with no such disorders. The terms "sensory-defect," "motor-defect," and "idiopathic" (for those that could not be forced into either of the first two putative categories) nystagmus became common in the medical literature. To support such claims, the resulting INS waveforms were said to have a significant difference (i.e. "sensory" = pendular and "motor" = jerk waveforms). This erroneous and simplistic picture containing multiple "causes" of INS was supported by the misinterpretation of the work of David Cogan (Dell'Osso *et al.* 2007). Interestingly, no model has ever been put forth delineating exactly how any of the many putative sensory "causes" of INS (most of which have no predominant plane of action) could produce this predominantly horizontal oscillation with its complex assortment of waveforms that easily transitioned from one to another. Its proponents also either ignored or refused to acknowledge documented cases of

*The Challenge of Nystagmus*. Edited by Chris Harris, Irene Gottlob and John Sanders.

INS present at birth (uncommon, but more so in families with a genetic predisposition for INS); such patients negate claims that INS is directly caused by sensory deficits in the developing infant.

In this paper, I will attempt to put forth conditions that all putative "causes" must be meet plus the requirement for a specific mechanism, or mechanisms, demonstrating how all INS waveforms result from that "cause." Using those preconditions, I will argue that only one of the putative "causes" found in the literature meets those conditions. I will also argue that the words "sensory," "motor," and "idiopathic" should never be used as adjectives preceding the term, "INS." After identifying the cause(s) of INS, I will present a mechanism-based waveform classification and a model-based demonstration of how a *single ocular motor cause* is responsible for most of the pathognomonic INS waveforms and another ocular motor cause produces the less-often-seen, linear-slow-phase waveforms.

## 4.2 Methods

### 4.2.1 Recording

Eye-movement data were taken using state-of-the-art recording systems including infrared reflection, magnetic search coil, and high-speed digital video. Calibration was always monocular while the fellow eye was occluded to obtain accurate position information and to document small tropias and phorias hidden by the nystagmus.

### 4.2.2 Protocol

Written consent was obtained from subjects before the testing. All test procedures were carefully explained to the subject before experiments began, and were reinforced with verbal commands during the trials. Subjects were seated in a chair with headrest and either a bite board or a chin stabilizer, far enough from an arc of red light-emitting diodes (LEDs) to prevent convergence effects (>5 feet). At this distance the LED subtended less than 0.1° of visual angle. The room light could be adjusted from dim down to blackout to minimize extraneous visual stimuli. Experiments consisted of from one to ten trials, each lasting under a minute with time allowed between trials for the subject to rest. Trials were kept this short to guard against boredom because INS intensity and foveation accuracy are known to decrease with inattention.

### 4.2.3 Analysis

Analyses were performed in MATLAB using specially developed "OMtools" software available for download at www.omlab.org. Simulations were performed in Simulink using a behavioral ocular motor system (OMS) model.

## 4.3 Results

### 4.3.1 Causality

The search for causality in INS is, in essence, a search for its *direct cause*. By that, I mean the condition that must be present in *all* cases of INS and without which, no INS results. That is, *if-and-only-if* the direct cause, INS results. Having identified the direct cause, a mechanism must be described by which the specific waveforms and characteristics of INS are achieved. I refer to the former as the SNIFF test (subject the putative nystagmus cause to the if-and-only-if test) and the latter, the BULLSEYE test (produce a mechanism or model of one that reproduces INS in all its complexity).

First, let us consider the myriad of so-called "sensory" causes of INS. The following problems become evident on even cursory examination: (1) they may have no plane or be uni- or multiplanar but INS is essentially uniplanar (horizontal); (2) no connections to specific ocular motor mechanisms have ever been identified that would produce the complex waveforms of INS; (3) INS occurs in patients with no known sensory deficit; and (4) INS has been documented to occur in some *at birth* thereby preventing any subsequent sensory deficit to have a detrimental effect on the OMS which is, in the final analysis, the system that must be unstable and produce INS. What of genetic causes? The same problems arise. Finally, what of channelopathy, which has also been suggested as a cause of INS? Channelopathy has been suggested to cause congenital stationary night blindness (CSNB) (Bech-Hansen *et al.* 1998). However, the same problems listed above for sensory deficits apply and none of the associated conditions/symptoms expected to accompany this cellular disorder are found in INS patients without CSNB.

To those who would propose that, in different patients, different causes for INS exist, that argument lost its credibility when accurate ocular motor data proved that all INS was essentially the same in waveforms, characteristics, and ocular motor responses. Besides, accepting multiple "causes" for INS is equivalent to an admission that the single direct cause has not been identified.

Rather than being distracted by the numerous afferent visual conditions associated with INS, I undertook the task of identifying the single ocular motor condition that might be responsible. I successively hypothesized and later disproved that disorders of the saccadic, fixation, and neural integrator subsystems were responsible for INS (Dell'Osso 2006). The only remaining subsystem was smooth pursuit, a subsystem I had originally thought to be involved (Dell'Osso 1968). One of the unique features of smooth pursuit is its semi-oscillatory nature in *normals*. That is, smooth pursuit exhibits underdamped responses to changes in target velocity. The transition between an underdamped (transient, diminishing oscillation) and an undamped (continuous oscillation) system is both predictable and easily made. This putative cause is consistent with the slow-phase genesis of INS (saccades are

always corrective) and the ubiquitous nature of INS (all normal OMSs have this propensity to oscillate).

### 4.3.2 Waveforms

The most incisive method of classifying INS waveforms is by their underlying ocular motor mechanism. A sinusoidal velocity oscillation in the smooth pursuit subsystem is hypothesized to be responsible for most of the pathognomonic INS waveforms (pendular with foveating saccades, pseudo-pendular, pseudo-pendular with foveating saccades, jerk, jerk with extended foveation, pseudo-cycloid, and pseudo-jerk; see Figure 4.1) (Dell'Osso & Daroff 1975). The slow phases of all

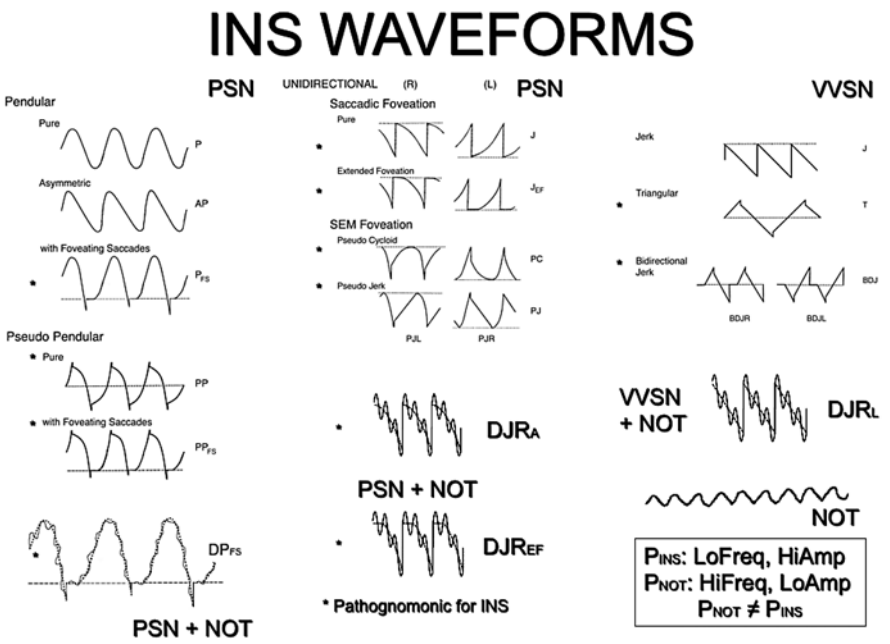


**Figure 4.1** Waveforms of INS arranged according to their underlying mechanism(s). PSN, pursuit system nystagmus; VVSN, vestibular, visual system nystagmus; NOT, nucleus of the optic tract; P, pendular; AP, asymmetric pendular; Pfs, pendular with foveating saccades; PP, pseudopendular; PPfs, pseudopendular with foveating saccades; J, jerk; Jef, jerk with extended foveation; PC, pseudocycloid; PJ, pseudojerk; T, triangular; BDJ, bidirectional jerk; DJ, dual jerk; DP, dual pendular; R, right; L, left; A, accelerating; L, linear; Lo, low; Hi, high; Amp, amplitude; Freq, frequency.

these waveforms are initially accelerating. A sinusoidal velocity oscillation can also result in the non-pathognomonic, pure pendular and asymmetric pendular waveforms. When the low-amplitude, high-frequency pendular oscillation secondary to the nucleus of the optic tract (NOT) (Tusa *et al.* 2002) is added, the dual-jerk, dual-jerk with extended foveation, and dual-pendular waveforms are produced. The only remaining INS waveforms are jerk with a linear slow phase, triangular, and bidirectional jerk; the last two are rare but pathognomonic. Again, combined with NOT nystagmus, dual-jerk with linear slow phases results. Thus, nine of twelve pure INS waveforms plus three of the four INS-plus-NOT waveforms can be caused by the *same* ocular motor disorder; these mostly pathognomonic waveforms are also the most commonly seen in INS. Only the less common linear-slow-phase jerk waveform and the rare triangular and bidirectional jerk waveforms require postulating a second causal mechanism. That mechanism has already been demonstrated to be an imbalance in the visual – vestibular (vestibular – optokinetic) subsystem and produces vestibular, optokinetic, and fusion maldevelopment nystagmus.

### 4.3.3 Mechanisms

If the above hypothesis is correct, we should be able to simulate it in a computer model of the OMS. To be acceptable and robust, the simulation must do the following: (1) simulate INS waveforms during steady fixation with appropriately accurate foveation periods every cycle; (2) repeat "(1)" while exhibiting normal ocular motor responses to common target inputs; (3) exhibit the amplitude changes and waveform transitions with changing gaze angle common to INS; (4) predict ocular motor responses seen in INS patients; (5) simulate known, and predict new, post-therapy, visual function improvements; and (6) exhibit emergent properties not designed into the model. Our OMS model (see Figure 4.2) has done all of the above (Jacobs 2001; Jacobs & Dell'Osso 2004). It is the only OMS model that simulates the waveforms (Wang 2008; Wang *et al.* 2008) foveation periods, and behavioral responses (Wang & Dell'Osso 2007) of INS (and many other ocular motor disorders) and predicts therapeutic improvements (Wang *et al.* 2006a, b, 2007; Wang & Dell'Osso 2008) INS characteristics, such as the position and sharpness of an INS "null," may be simulated (Figure 4.3a) as well as the automatic, seamless transitions to different waveforms at lateral gaze angles (Figure 4.3b). Figure 4.3a demonstrates how the INS increases as gaze is directed away from the null in either direction. Similarly in Figure 4.3b, as the INS increases as gaze is directed away from the null in either direction, it transitions from pseudopendular with foveating saccades (PPfs) to jerk with extended foveation (Jef) with accelerating, centripetal slow phases.

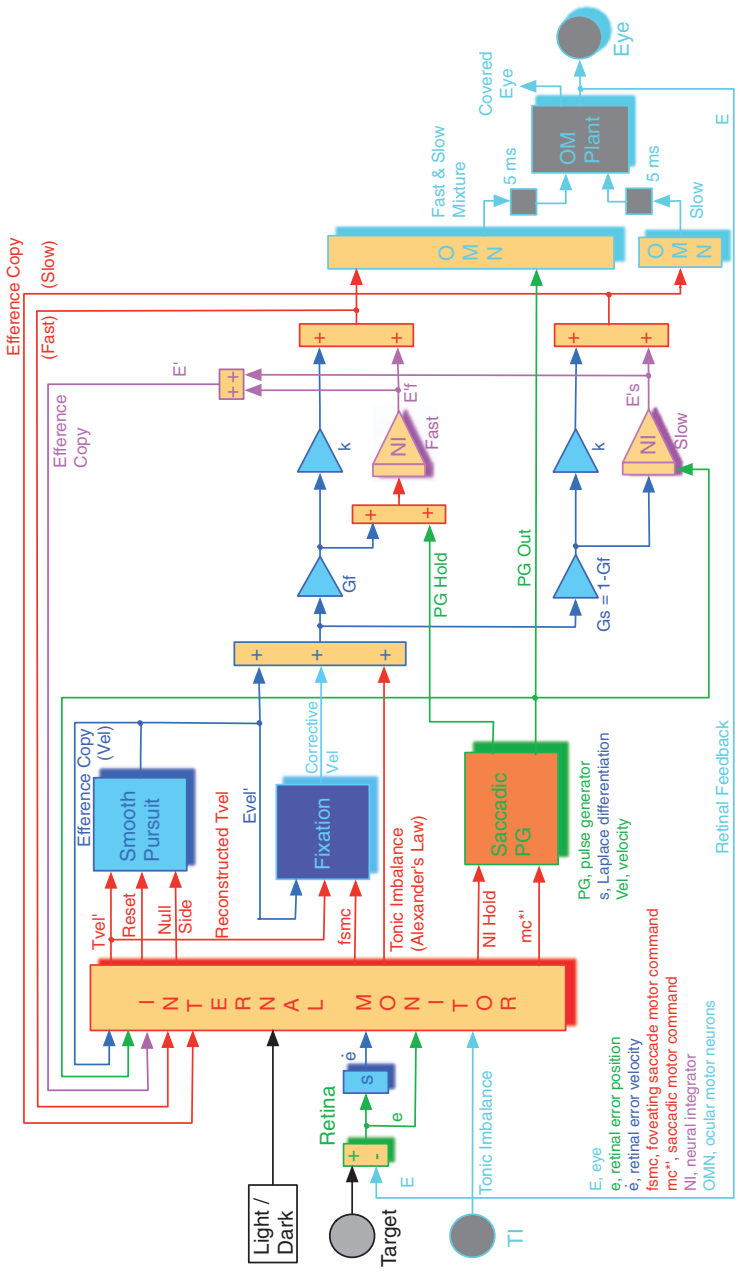


**Figure 4.2** Block diagram of a behavioral ocular motor system model capable of simulating the waveforms, characteristics, and responses of INS.

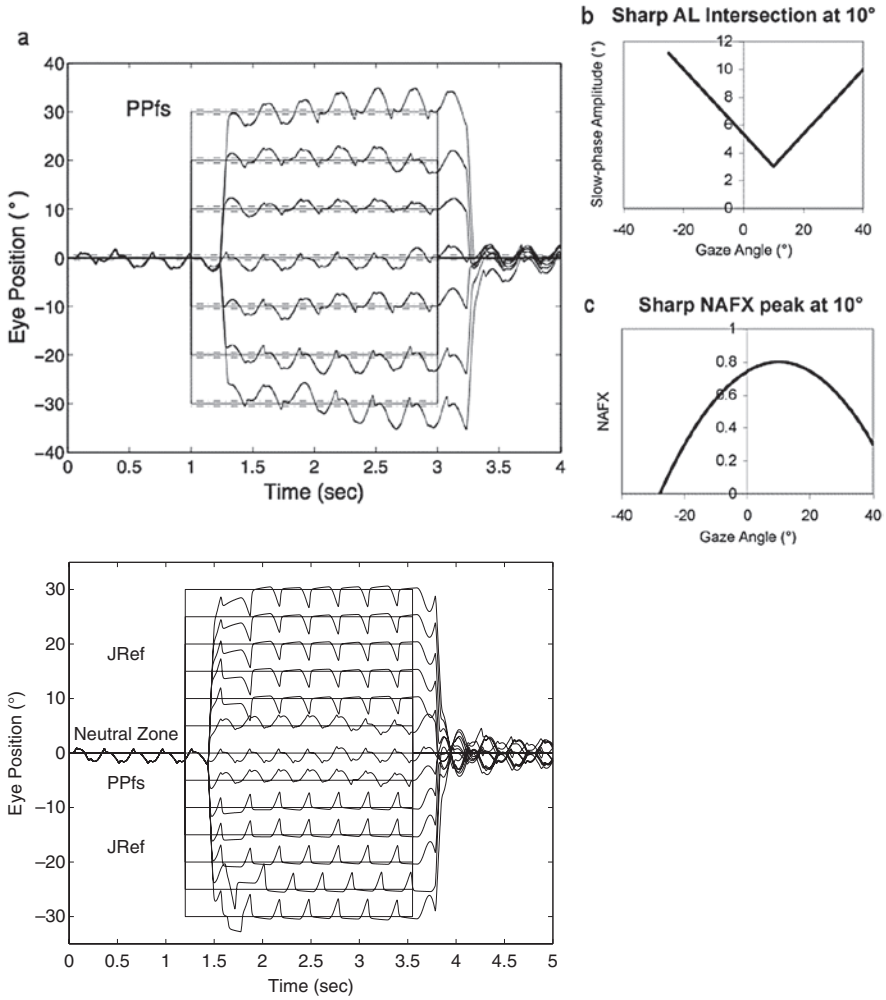


**Figure 4.3** (Top) Saccades to and fixation of targets at different gaze angles showing the PPfs waveform changes dictated by the intersection (here, 10° right gaze) and slopes (here, sharp) of the Alexander's law curves; also shown is the NAFX versus Gaze Angle curve. (Bottom) Saccades to and fixation of targets at different gaze angles showing the PPfs waveform changes and transitions in lateral gaze to Jef dictated by the intersection (here, 0°) and slopes (here, medium) of the Alexander's law curves. PP, pseudopendular; PPfs, pseudopendular with foveating saccades; Jef, jerk with extended foveation; R, right; L, left; NAFX, expanded nystagmus acuity function.

## 4.5 Discussion

The hypothesis that INS is predominantly caused by an undamped smooth pursuit subsystem passes the SNIFF test because all normals have an underdamped smooth pursuit subsystem, underdamped systems are prone to becoming undamped if not accurately calibrated, and all other possible ocular motor subsystems have been eliminated by ocular motor data. Thus, although one cannot prove a hypothesis, these factors support it. The hypothesis also passes the BULLS EYE test because the behavioral OMS model with an undamped smooth pursuit subsystem provides the mechanisms for the most common INS waveforms, the gaze-angle variation of INS, and waveform transitions. The model also predicted the effects of target onset time on acquisition time and the therapeutic effects of the tenotomy and reattachment procedure (i.e. damping of only slow phases, improvement of foveation periods, broadening of the range of high-acuity waveforms, and reduction of target acquisition times). The additional hypothesis that the few linear waveforms of INS are caused by an imbalance in the visual – vestibular subsystem has already been demonstrated when simulating fusion maldevelopment nystagmus syndrome (Dell'Osso & Jacobs 2001).

Because a direct cause for INS has been hypothesized and strongly supported by a model and its predictions, the use of "idiopathic" is both erroneous and misleading, as it implies that multiple "causes" for INS associated with sensory deficits are known, different from each other, and different from the so-called "motor" type. The past 45 years of ocular motor research into INS have demonstrated that the INS common to all patients is predominantly (all of the common, pathognomonic waveforms) due to a single cause. The undamped-smooth-pursuit hypothesis is the most parsimonious explanation for INS, and provides a reason why so many unrelated afferent visual and genetic abnormalities predispose the pursuit system's continuous oscillation (i.e. by interfering in different ways with the necessary precise calibration of smooth-pursuit damping). Productive discussions will be problematic unless we cease referring to those abnormalities as "causes" of INS and cease referring to INS in the absence of these precipitous abnormalities as "idiopathic" INS.

Finally, INS = INS = INS; just as there is no "idiopathic INS," there is no "ocular albinism infantile nystagmus;" a patient with the latter phenotype has INS plus ocular albinism. The medical need to diagnose ocular albinism for possible genetic counseling does not justify calling the *same* INS something different or failing to provide the *same* INS treatments to all with INS, independent of afferent visual deficits. The visual prognosis, in terms of percentage improvement, is the same for all INS patients with the same pre-surgical expanded nystagmus acuity function (see Chapter 21).

## Acknowledgments

This work was supported in part by the Office of Research and Development, Medical Research Service, Department of Veterans Affairs.

## References

Bech-Hansen NT, Naylor MJ, Maybaum TA, et al. (1998) Loss-of-function mutations in a calcium-channel α1-subunit gene in Xp11.23 cause incomplete X-linked congenital stationary night blindness. *Nature Genetics* **19**: 264–267.

CEMAS Working Group (2001) A National Eye Institute Sponsored Workshop and Publication on The Classification of Eye Movement Abnormalities and Strabismus (CEMAS). In The National Eye Institute Publications (www.nei.nih.gov). Bethesda, MD: National Institutes of Health, National Eye Institute.

Dell'Osso LF (1968) A dual-mode model for the normal eye tracking system and the system with nystagmus. PhD dissertation. Laramie: Electrical Engineering (Biomedical), University of Wyoming.

Dell'Osso LF (2006) Biologically relevant models of infantile nystagmus syndrome: the requirement for behavioral ocular motor system models. *Seminars in Ophthalmology* **21**: 71–77.

Dell'Osso LF, Daroff RB (1975) Congenital nystagmus waveforms and foveation strategy. *Documenta Ophthalmologica* **39**: 155–182.

Dell'Osso LF, Hertle RW, Daroff RB (2007) "Sensory" and "motor" nystagmus: erroneous and misleading terminology based on misinterpretation of David Cogan's observations. *Archives of Ophthalmology* **125**: 1559–1561.

Dell'Osso LF, Jacobs JB (2001) A normal ocular motor system model that simulates the dual-mode fast phases of latent/manifest latent nystagmus. *Biological Cybernetics* **85**: 459–471.

Jacobs JB (2001) An ocular motor system model that simulates congenital nystagmus, including braking and foveating saccades. PhD dissertation. Cleveland: Biomedical Engineering, Case Western Reserve University.

Jacobs JB, Dell'Osso LF (2004) Congenital nystagmus: hypothesis for its genesis and complex waveforms within a behavioral ocular motor system model. *Journal of Vision* **4**: 604–625.

Tusa RJ, Mustari MJ, Das VE, Boothe RG (2002) Animal models for visual deprivation-induced strabismus and nystagmus. *Annals of the New York Academy of Sciences* **956**: 346–360.

Wang Z, Dell'Osso LF, Jacobs JB, Burnstine RA, Tomsak RL (2006a) Effects of tenotomy on patients with infantile nystagmus syndrome: foveation improvement over a broadened visual field. *Journal of the American Academy of Pediatric Ophthalmology and Strabismus* **10**: 552–560.

Wang Z, Dell'Osso LF, Zhang Z, Leigh RJ, Jacobs JB (2006b) Tenotomy does not affect saccadic velocities: support for the "small-signal" gain hypothesis. *Vision Research* **46**: 2259–2267.

Wang ZI (2008) A unifying hypothesis for the multiple waveforms of infantile nystagmus and their idiosyncratic variation with gaze angle and therapy. PhD dissertation. Cleveland: Biomedical Engineering, Case Western Reserve University.

Wang ZI, Dell'Osso LF (2007) Being "slow to see" is a dynamic visual function consequence of infantile nystagmus syndrome: Model predictions and patient data identify stimulus timing as its cause. *Vision Research* **47**: 1550–1560.

Wang ZI, Dell'Osso LF (2008) Tenotomy procedure alleviates the "slow to see" phenomenon in infantile nystagmus syndrome: model prediction and patient data. *Vision Research* **48**: 1409–1419.

Wang ZI, Dell'Osso LF, Jacobs JB (2008) Expanding the original behavioral infantile nystagmus syndrome model to jerk waveforms and gaze-angle variations. In Leigh RJ, Devereaux MW (eds) *Advances in Understanding Mechanisms and Treatment of Congenital Forms of Nystagmus.* New York: Oxford University Press, pp. 139–142.

Wang ZI, Dell'Osso LF, Tomsak RL, Jacobs JB (2007) Combining recessions (nystagmus and strabismus) with tenotomy improved visual function and decreased oscillopsia and diplopia in acquired downbeat nystagmus and in horizontal infantile nystagmus syndrome. *Journal of the American Academy of Pediatric Ophthalmology and Strabismus* **11**: 135–141.