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A Distal Model of Congenital Nystagmus as Nonlinear Adaptive Oscillations

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Abstract. Congenital nystagmus (CN) is an incurable pathological spontaneous oscillation of the eyes with an onset in the first few months of life. The pathophysiology of CN is mysterious. There is no consistent neurological abnormality, but the majority of patients have a wide range of unrelated congenital visual abnormalities affecting either the cornea, lens, retina or optic nerve. In this theoretical study, we show that these eye oscillations could develop as an adaptive response to maximize visual contrast with poor foveal function in the infant visuomotor system, at a time of peak neural plasticity. We argue that in a visual system with abnormally poor high spatial frequency sensitivity, image contrast is not only maintained by keeping the image on the fovea (or its remnant) but also by some degree of image motion. Using the calculus of variations, we show that the optimal trade-off between these conflicting goals is to generate oscillatory eye movements with increasing velocity waveforms, as seen in real CN. When we include a stochastic component to the start of each epoch (quick-phase inaccuracy) various observed waveforms (including pseudo-cycloid) emerge as optimal strategies. Using the delay embedding technique, we find a low fractional dimension as reported in real data. We further show that, if a velocity command-based pre-motor circuitry (neural integrator) is harnessed to generate these waveforms, the emergence of a null region is inevitable. We conclude that CN could emerge paradoxically as an ‘optimal’ adaptive response in the infant visual system during an early critical period. This can explain why CN does not emerge later in life and why CN is so refractory to treatment. It also implies that any therapeutic intervention would need to be very early in life.

Key words: adaptive control, chaos, distal model, early onset nystagmus, eye movements, human development, infant, infantile nystagmus

1. Introduction

Congenital nystagmus (CN) is a pathological spontaneous oscillation of the eyes in humans with an onset within the first few months of life. CN is almost always persistent and life-long, and there is no cure. The cause of CN is unknown, but in about 90% of cases there is a range of underlying visual disorders [1]. The range is remarkably wide, however, and includes such disparate conditions as albinism and isolated foveal hypoplasia, cataract, congenital stationary night blindness, aniridia, cone dysfunction and many other conditions. CN may even occur after acquired damage to the corneas at birth [2]. Because of these wide associations, it is difficult to argue that CN is caused by any single neural or visual abnormality or any single genetic mutation. Instead it seems that almost any congenital sensory abnormality (whether inherited or not) affecting the central retina can lead to CN. In contrast, onset of a visual disorder after a few months of age (e.g., cataracts) does not lead to CN. Thus, CN emerges only in early infancy, a time of peak visuomotor plasticity when there is development of the visual system (especially the formation of the fovea and visual cortex) and the development of eye movement systems, notably the smooth pursuit system. It seems plausible that CN arises because of some abnormality during this time of plasticity.

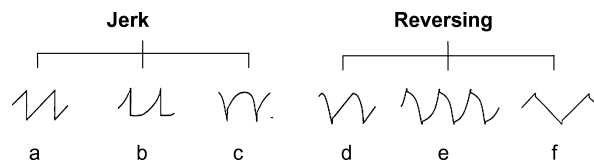


Figure 1. Typical observed CN waveforms. Jerk nystagmus: (a) pure, (b) extended foveation, (c) pseudo-cycloid. Reversing: (d) pseudo-jerk, (e) pseudo-pendular, (f) triangular; based on [3].

We propose that CN occurs as the result of normal adaptation to an abnormal visual environment in infancy. Our tenet is that ‘normal’ eye movements are not all hardwired from birth, nor inevitably predetermined by postnatal maturation of the brain. Instead, some eye movement strategies, including gaze holding and smooth pursuit, develop postnatally which, we propose, also depend on the visual environment. Pre-motor neural networks develop their connectivity to support vision, which in the vast majority of normal human infants results in so-called ‘normal’ eye movements. After infancy the plasticity decreases considerably to prevent unlearning of the strategies, but still enough to allow some modification to respond to continued growth and disease. Our argument is that these same pre-motor networks may develop an abnormal connectivity in order to organise an eye movement strategy (CN) to support abnormal vision, but only during early infancy. Once formed, they also remain for life.

CN oscillations have some unique properties that require explaining by any useful model. The oscillations have waveforms (trajectories) that are not usually observed in other types of acquired nystagmus. The most common is an increasing velocity slow phase followed by a resetting quick phase (saccade) (see Figure 1). Variants on this basic shape can be observed, most notably the pseudo-cycloid waveform [3]. There also is usually a ‘null region’ or ‘null point’. The amplitude of the oscillations usually varies with the direction of viewing (direction of eyes relative to the head), being minimal in one viewing direction (the null region) and increasing when the eyes point either side of the null region. In most patients the waveform also changes with direction, becoming pseudo-cycloid away from the null.

Although there have been numerous attempts to model *how* the oculomotor system might generate these unique waveforms (*proximal models*, see [4–9]), there has been no explanation for *why* CN might emerge in the first place (*distal model*). Taking our plasticity argument one stage further, how could these peculiar oscillations result from an adaptive process, or equivalently, what is the control objective of infant eye movement development?

2. Non-Veridical Velocity Tuning

Neural representations of physical objects are not *intrinsically* veridical. For example, it is well established in the visual system that neural assemblies are tuned along different features (or dimensions) such as object form, colour and motion. Particularly, there is no mathematical relationship between neural populations that are tuned to object position and object velocity. There is no intrinsic reason for neural representations to follow the physically veridical relationships.

$$v(t) = \frac{dx(t)}{dt}, \quad (1a)$$

$$x(t_2) = x(t_1) + \int_{t_1}^{t_2} v(t) dt. \quad (1b)$$

Separation between position and velocity tuning occurs early in the visual system. A retinal ganglion cell (RGC) has a receptive field that is tuned to position by virtue of its coordinates in the retina and its retinotopic projection to the visual cortex. Receptive fields are also tuned in the spatial frequency and temporal frequency domains, yielding a velocity tuning. Psychophysics has demonstrated that sensitivity to a spatial frequency is maximal at some non-zero image speed, where the optimal speed varies inversely with spatial frequency. Thus, high spatial frequencies (as mediated via the central retina) require very low drift speeds, whereas low spatial frequencies require more moderate speeds to induce maximal visual contrast [10–12].

In the normal visual system, spatial frequency resolution is maximal at the fovea due to the high concentration of small receptive fields, and the optimal image motion is therefore very low. In this case, the veridical relationship in Equation (1) very nearly maximizes visual contrast of an object. The fixation and smooth pursuit eye movement systems have presumably evolved to maintain this contrast when there is relative motion of the object.

When there is compromised foveal function, whether due to malformation (e.g., foveal hypoplasia) or poor optics (e.g., cataracts, myopia) high spatial frequency resolution will be reduced. Consequently, the optimal image motion should move to a higher speed (which we will denote by p). The question is how to maximize visual contrast, since maintaining optimal image motion will inevitably cause the image to fall off the fovea (or its remnant). Conversely, maintaining position would require a suboptimal zero velocity. Mathematically, constant position and non-zero velocity could be achieved simultaneously if the image oscillated with a saw-tooth waveform with infinite frequency and infinitesimal amplitude. However, the visual system has low-pass temporal characteristics, the visual ‘integration time’, which we will denote by T . This causes visual contrast to fall when images oscillate at high frequencies. Thus, the algebraic maximum requires positional and velocity tuning that cannot be achieved [cannot obey Equation (1)].

The question is what real (and hence veridical) image motion maximizes the response of such a visual system? To answer this we cast the problem as a minimization problem in which we attribute costs when the image falls off the fovea or moves at speed other than p . This allows us to find the optimal image motion in the least squares sense. Real eye movement control has limitations (speed of response, timing, accuracy), and therefore, we ask how these limitations would affect the generation of the ideal image motion.

3. Optimal Image Motion

Image motion on the retina is determined by gaze (eye + head) movements and the motion of the object. We only consider the one-dimensional problem and denote the position of the image relative to the central fovea by $y(t)$ where $y = 0$ when the image is on the central fovea. Image velocity is given by $\dot{y} \equiv dy/dt$. Image position is given by

$$y(t) = o(t) - e(t) - h(t), \tag{2}$$

where $h(t)$ is the position of the head and $e(t)$ is the position of the eye relative to the head, and $o(t)$ is the actual position of the object’s image on retina due to object motion relative to the body (see Figure 2). Positional cost $F_y(t)$ is minimal when the image is on the central fovea, and assumed to be quadratic in the vicinity of the fovea

$$F_y(t) = c_1 + ay^2(t), \tag{3}$$

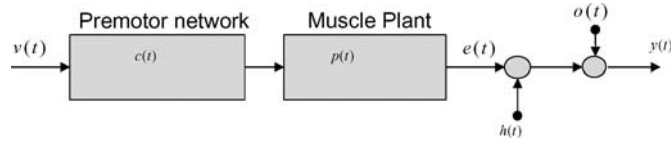


Figure 2. Linear lumped model of oculomotor control of image motion. Image position relative to the fovea, $y(t)$, is determined by the actual object position $o(t)$, head position, $h(t)$, and eye position $e(t)$. We only elaborate the eye movement system. Eye movement position is determined by the filtering action of the muscle dynamics, $m(t)$, a pre-motor compensator network, $c(t)$, driven by a velocity command, $v(t)$.

where a is a positive constant of proportionality describing the steepness of the minimum, and c_1 is the cost at the fovea. Similarly, velocity cost $F_{\dot{y}}(t)$ is minimal when the image is moving at speed, p , which in general could depend on the position of the image, y . However, in this treatment, we shall assume that changes in p are negligible. $F_{\dot{y}}(t)$ is also assumed quadratic when image velocity is in the vicinity of p

$$F_{\dot{y}}(t) = c_2 + b[\dot{y}(t) - p]^2, \tag{4}$$

where c_2 and b are also positive constants. Assuming total cost to be additive

$$F(t, y, \dot{y}) = F_{\dot{y}}(t) + F_y(t), \tag{5}$$

total cost over the time interval $(0, T)$ is given by the integral

$$J = \int_0^T F(t, y, \dot{y}) dt = \int_0^T [c_1 + c_2 + ay^2(t) + b[\dot{y}(t) - p]^2] dt. \tag{6}$$

Our goal is to find the optimal trajectory of the image

$$y^*(t): \min_{y(t)} J. \tag{7}$$

We assume that $y(t)$ is sufficiently smooth to take a standard variational approach.

The Euler–Lagrange equation for the functional in Equation (6) is

$$2ay - \frac{d}{dt}[2b(\dot{y} - p)] = ay - b\ddot{y} = 0 \tag{8}$$

which has the general solution

$$y = Ae^{-t/\tau} + Be^{t/\tau} \tag{9}$$

where $\tau = \pm\sqrt{b/a}$. The Weierstrassian condition is met since

$$\partial^2 F(t, y, q) / \partial q^2 = 2b > 0,$$

for arbitrary q , indicating a strong minimum. Substituting Equation (9) into Equation (6) and setting the partial derivatives $\partial J/\partial A$ and $\partial J/\partial B$ to zero yields the optimal coefficient values

$$A^* = -\frac{p\alpha e^{T/\tau}}{e^{T/\tau} + 1}, \quad B^* = \frac{p\alpha}{e^{T/\tau} + 1} \tag{10}$$

and the optimal motion is

$$y^* = A^* e^{-t/\tau} + B^* e^{t/\tau}. \tag{11}$$

The effect of p is only to scale the trajectory without changing its shape. The shape is dependent on the ratio T/τ , and different optimal trajectories and their phase plots are shown in Figure 3.

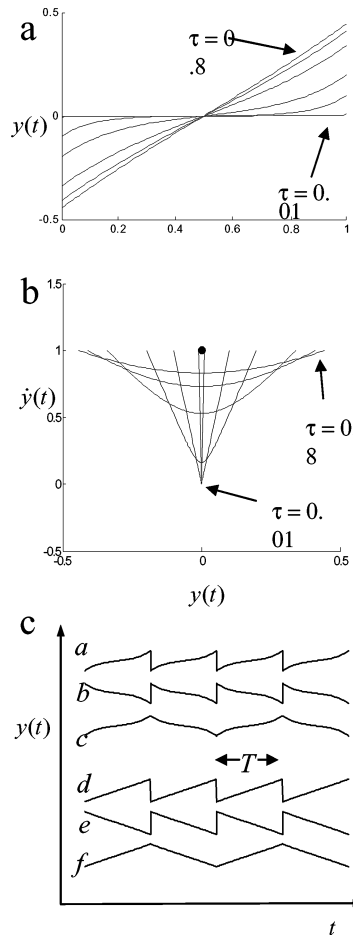


Figure 3. Optimal trajectories. (a) Optimal trajectories from Equation (10) for $\tau = 0.01, 0.1, 0.2, 0.4, 0.6, 0.8$ with $Y = 1$ and $p = +1$. Note trajectories become linear with large τ . (b) Phase plots of the trajectories with target shown by large dot. Reset is not shown but would be a large negative velocity excursion. (c) Over an extended time period, the optimal trajectory is cyclical as illustrated here for $\tau = 0.2$ (a,b,c) and $\tau = 0.8$ (d, e, f), with $p = +1$ (a, d) with $p = -1$ (b, e), and when p alternates after each cycle (c, f) (see text).

Clearly, the optimal image motion requires net shift in position from one side of the fovea to the other. The cost of the optimal trajectory is

$$J^* = \frac{p^2 \tau^2 (T e^{T/\tau} - \tau e^{T/\tau} + 2\tau + T)}{e^{T/\tau} + 1}, \quad (12)$$

which always increases with T (for a fixed τ) since

$$\frac{\partial J^*}{\partial T} = \frac{p^2 \tau^2 (e^{T/\tau} - 1)^2}{(e^{2T/\tau} + 1)^2} \geq 0, \quad (13)$$

and therefore it pays to make T as small as possible.

We conclude that over an extended period of time, the optimal trajectory is oscillatory with each epoch given by $y^*(t)$. We note that this applies even if the object is moving, so that an underlying ‘smooth pursuit’ system would be needed to track the object motion. If the sign of p is changed, trajectories may be inverted. If p can change sign on each epoch then reversed cycles will occur [Figure 3(c)]. Overall cost is minimized by increasing the frequency as high as possible. As described above, there are biological limitations on the effectiveness in reducing T , since the visual system has a low-pass temporal filtering action, so that contrast is reduced for high-frequency image oscillations.

Real CN sometimes shows waveforms similar to the global optimum waveform predicted by Equations (10) and (11) (e.g., [13]), but it is not the most common. More realism emerges when we consider the limitations imposed by the eye movement system, which we now outline.

4. Oculomotor Constraints

To generate the desired image motion, the nervous system must innervate the extraocular muscles and the neck and body muscles with appropriate motor commands. For simplicity, we will assume that the head and body are still, so that image position is controlled only by the oculomotor system. It is well established that the oculomotor system is controlled via a pre-motor network that compensates for the muscle plant. This network receives the motor command which is the desired velocity (see Figure 2). For the normal oculomotor system the velocity command is used to control eye velocity and position (via the Neural Integrator) dynamically, and the viscoelastic forces of the muscles are compensated by the pre-motor network. This pre-motor network has evolved to cope with normal vision (i.e., $p \approx 0$), rather than with generating precise oscillatory image motion. We now briefly look at the effects of limitations of eye movement control.

4.1. THE FIELD OF EXTREMALS FOR INITIAL POSITION

Rapid resetting of eye position at the end of an epoch can only be achieved by saccadic eye movements. Saccades are driven by brief intense velocity pulses, but they are not instantaneous steps. They are not perfectly accurate, and their timing is quite variable. We first consider the effect of inaccuracy.

Visually guided saccades (i.e., saccades to a small visual target) are not perfectly accurate. The end-point standard deviation is about 5–10% of the amplitude of the saccade. There is also a tendency for saccades to undershoot the target by 5–10% (the undershoot bias). cursory observation indicates that the end-points of nystagmus resetting quick phases are also quite variable. Since the end-point of one cycle is the initial position of the next cycle, it means that the desired starting position of the optimal

trajectory, $y^*(0)$, cannot always be determined. Given uncertainty in initial position, the ideal strategy would be to generate the i th cycle trajectory based on the actual i th initial position. We therefore need to find the optimal trajectory given $y_i(0)$.

Specifying $y_i(0)$ places a constraint on A_i and B_i since $B = y(0) - A$. Substituting this into Equation (6) gives

$$\begin{aligned}
 J = & -A^2\tau e^{-2T/\tau} + \tau[y(0) - A]^2 e^{2T/\tau} - 2pA\tau^2 e^{-T/\tau} \\
 & - 2\tau^2 p(y(0) - A)e^{T/\tau} + \tau^2 p^2 T - \tau y^2(0) \\
 & + 2\tau Ay(0) + 2\tau^2 py(0)
 \end{aligned} \tag{14}$$

and solving $\partial J/\partial A = 0$ yields the optimal coefficients given $y(0)$

$$A_i = \frac{y_i(0)e^{2T/\tau} - p\tau e^{T/\tau}}{e^{2T/\tau} + 1}, \tag{15a}$$

$$B_i = \frac{y_i(0) + p\tau e^{T/\tau}}{e^{2T/\tau} + 1}. \tag{15b}$$

Substituting into (9) yields a field of extremals depending on $y_i(0)$

$$y_i(t) = A_i e^{-t/\tau} + B_i e^{t/\tau}, \tag{16}$$

and some illustrative examples are shown in Figure 4. The divergence of these extremals is given by the derivative

$$\frac{d}{dt} \left(\frac{dy_i}{dy_0} \right) = \frac{e^{t/\tau} - e^{-2T/\tau} e^{-t/\tau}}{\tau(e^{2T/\tau} + 1)}. \tag{17}$$

Clearly the extremals always converge for $t < T$, and diverge for $t > T$ and are always parallel at $t = T$.

A second possibility is that the system minimizes expected cost over many cycles. Denote the mean and standard deviation of $y(0)$ by \bar{y} and σ . Then from Equation (14), the expected cost is

$$\begin{aligned}
 E\{J\} = & -A^2\tau e^{-2T/\tau} + (\sigma_x^2 + (\bar{y} - A)^2)\tau e^{2T/\tau} - 2pA\tau^2 e^{-T/\tau} \\
 & - 2\tau^2 p(\bar{y} - A)e^{T/\tau} + \tau^2 p^2 T - \tau(\sigma_x^2 + \bar{y}^2) \\
 & + 2\tau A\bar{y} + 2\tau^2 p\bar{y}.
 \end{aligned} \tag{18}$$

The partial derivative $\partial E\{J\}/\partial A$ is independent of σ and is the same as in Equation (14) with $y(0)$ replaced by \bar{y} , and the optimal trajectory belongs to the same field of extremals as in the deterministic case [Equation (16)]. The actual optimal trajectory will depend on the precise value of σ . If, as we expect, σ depends on the distance between the start of the epoch and the end-point of the previous $(i-1)$ th epoch, $\sigma = k|y_{i-1}(T) - y_i(0)|$, where k is a constant of proportionality, then the shape of optimal trajectory will depend on the amplitude of the optimal trajectory. Whether such oscillations are stochastically stationary or not will depend on the divergence of extremal field.

Clearly, depending on the initial condition of an epoch, a wide range of waveforms may be optimal, ranging from the global optimum (Figure 3), through simple accelerative slow phases, to the pseudo-cycloid waveform [Figure 4(c)], and all can be seen in real data [Figure 1(a)-(c)]. If we allow p to

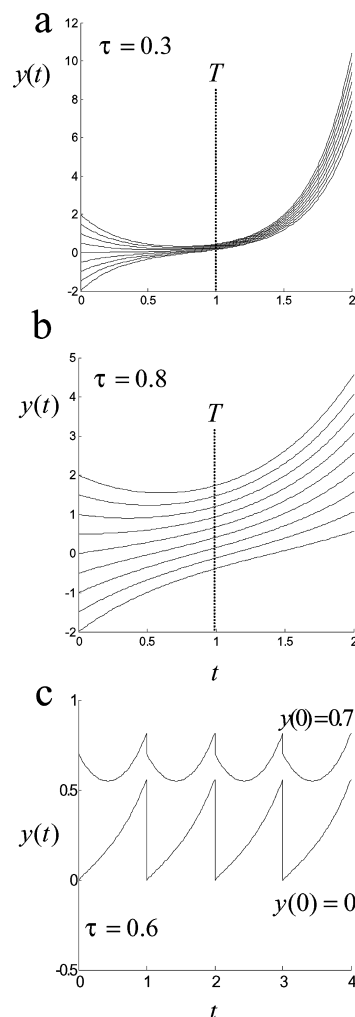


Figure 4. Fields of extremals. (a) Each curve is the optimal trajectory over $(0, T)$ for a given starting position, $-2 \leq y(0) \leq 2$, with $\tau = 0.3$, $T = 1$, $p = 1$. Note convergence of trajectories for $t < T$. When extremals are extended for $t > T$ divergence occurs and there is rapid acceleration. (b) Same as (a) except $\tau = 0.8$. Note less convergence and less acceleration in the extended period. (c) (*bottom curve*) examples of waveform for $\tau = 0.6$ with $y(0) = 0$, showing accelerative slow phase that is typical of CN; (*top curve*) waveform for $y(0) = 0.7$ illustrating the typical pseudo-cycloid waveform of CN.

change sign between epochs, then reversals can occur and are sometimes observed as well [Figure 1(e) and (f)]. Moreover, if p can be anisotropic (see Section 5) then reversals may occur with different profiles [e.g., Figure 1(d)], but empirically these are rarer. Reversals require instantaneous changes in velocity. For the normal oculomotor system this cannot be achieved without a saccade (assuming there is no external stimulus). Therefore, a small saccade would be needed to enable a reversal, which again is empirically observed [Figure 1(d)–(f)].

4.2. TIMING LIMITATIONS AND EXTENDED EXTREMALS

Observation of CN (or any other type of jerk nystagmus) reveals that the timing of quick phases is highly variable. In infants (when CN begins), quick phases occur much less frequently than in adults.

The mechanism of triggering quick phases is very poorly understood, and for infants, it seems that they cannot be generated much faster than about 2–3 per second [14]. Although empirical data are needed, it seems most likely that there are limitations on how soon a reset at the end of an epoch could occur, both in terms of mean and standard deviation. Let us denote the time when a reset occurs by D (D_i for the duration of the i th epoch). Clearly, if a reset does not occur until D , the trajectory will continue. If the waveform were ideally maintained during $0 < t \leq T$, then the trajectory would follow the extended extremal for $t > T$ (the extremals are analytic functions). In reality, we might expect deviations from the extended extremal, but this could only occur relatively slowly due to improper compensation and the low-pass nature of the muscle plant (see later). Extended extremals are divergent [Equation (17)] and will cause the eye position to accelerate rapidly, and subsequent large resetting quick phases will be needed (see Figure 4). Thus, slow phase velocities may far exceed p depending on the extremal acceleration.

Assuming quick phases behave similarly to saccades, larger amplitudes will be associated with larger σ and possible undershoot. This will influence the next cycle either directly or stochastically, adding to the complexity of the sequence of cycles. The possibility that CN may be a nonlinear dynamical system has been explored empirically by Abadi and colleagues, who have reported low dimensionality and determinism for real CN data taken from a female subject with typical idiopathic congenital nystagmus [13]. Using a similar approach based on the use of delay embedding techniques, we quantified the dynamics of simulated cycles in the region of foveation. Eye position trajectories were assumed to be perfect extended extremals—with perfect plant compensation assumed. A cycle was reset by a simulated saccade using a minimum jerk profile [15]. The three-dimensional projection of the reconstructed phase space trajectory, calculated using Matlab's Tstool toolbox [16], shows a similar profile as observed empirically [13] [Figure 5(c) and (d)].

4.3. PLANT COMPENSATION AND THE NULL REGION

The muscle plant has strong viscoelastic forces that tend to restore eye position to an equilibrium position. For normal eye movements it is necessary for the pre-motor networks to compensate for the muscle plant and to integrate the velocity command to a positional signal (the famous 'neural integrator'). When correctly compensated, a velocity command will drive the eyes at the desired velocity in all eye positions, and a saccadic velocity pulse will move the eyes rapidly to the new position and remain steady due to the tonic signal generated by the integrator [17].

A key question is how CN waveforms could be generated. In principle it would be possible to devise a network that could generate $y^*(t)$ at all eye eccentricities. For example, a velocity signal representing $\dot{y}^*(t)$ could be added to the ongoing velocity command in the normal system (although a problematic reset would be needed on every cycle, see [7]). However, such a system does not exist in the normal primate genotype/phenotype. Therefore, we consider the possibility that the normal pre-motor plant compensation network could be adapted to generate each cycle of $\dot{y}^*(t)$.

Modelling the control as a linear system, we denote the transfer function of the muscle plant by $m(t)$ and the transfer function of the pre-motor network by $c(t)$ (see Figure 2). The motor command is denoted by $u(t)$. Assuming a linear lumped model, we can take Laplace transforms to yield the transform of the image motion

$$Y(s) = H(s) + M(s)C(s)U(s) - O(s). \quad (19)$$

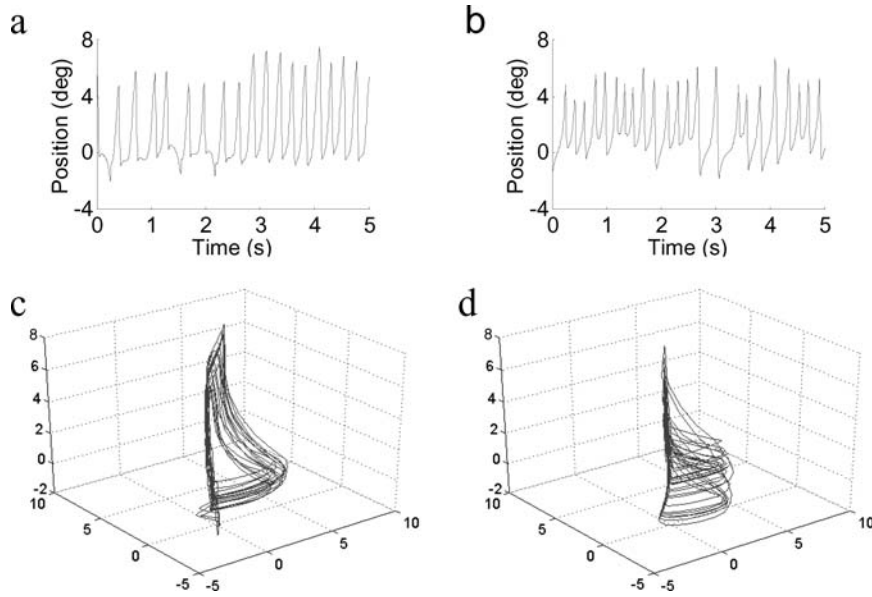


Figure 5. Comparison of 5-s sequence of empirical data taken from a female subject with typical idiopathic congenital nystagmus [13]. (a) with simulated data generated by the model (b) ($T = 0.05$, $p = 13.5$, $\tau = 0.0025$). Saccades were modeled using a minimum jerk velocity profile. (c, d) Comparison of associated three-dimensional projections of the reconstructed phase space trajectories; in both, an embedding dimension of 3 and a delay of 4 was used. Even though the model contains several random processes, the correlation dimensions were finite and of similar values (empirical data: correlation dimension, $D_2 = 1.404$; model data: correlation dimension, $D_2 = 1.423$).

For a desired image motion $Y^*(s)$, we have

$$C(s) = \frac{Y^*(s) + O(s) - H(s)}{M(s)P(s)U(s)}. \quad (20)$$

Consider the simplest case where the object is stationary at some visual angle E so that $O(s) = E/s$, with the head pointing straight ahead and stationary, i.e., $H(s) = 0$. We denote the command to shift gaze to E by $u_E(t)$. The ideal compensator is then

$$C(s) = \frac{Y^*(s) + E/s}{M(s)U_E(s)}. \quad (21)$$

For the *normal* visual system, $p \approx 0$, the optimal trajectory would be to keep the image on (or very close to) the fovea, or $Y^*(s) = 0$, and the ideal compensator becomes

$$C(s) = \frac{1}{sM(s)} \frac{E}{U_E(s)}. \quad (22)$$

The ideal command is therefore proportional to E . If $u_E(t)$ is a velocity command, then it should be a delta function of strength $U_E(s) = E$, and the compensator will be $C(s) = 1/sM(s)$ which is a perfect plant compensator and a perfect integrator (the eye position ‘neural integrator’). This is now well established in the field of oculomotor physiology (see [17]). In reality, the velocity pulse is not a delta function so the compensation should be considered up to some high frequency.

For the *abnormal* case, $p > 0$. The optimal trajectory is given by repeated extremals from Equation (9). The Laplace transform of an extended extremal (without reset) is

$$Y^*(s) = \frac{A(y_0)\tau}{(s\tau + 1)} + \frac{B(y_0)\tau}{s\tau - 1} \quad (23)$$

and clearly $Y^*(s) \neq 0$. From Equation (21), we see that there is no single function that can transfer a velocity delta function command into an optimal image motion for *all* object eccentricities. However, it is possible to construct a compensator, C_0 , for a single eccentricity, E_0 , say

$$C_0(s) = \frac{sY^*(s) + E_0}{sP(s)U_0(s)}, \quad (24)$$

where $u_0(t)$ is the velocity command for eccentricity E_0 . Substituting this into Equation (19), we have the general Laplacian equation for the optimal eye movement given perfect compensation at E_0

$$Y(s) = \frac{U_E(s)}{U_0(s)}Y^*(s) + \left[\frac{E_0U_E(s)}{U_0(s)} - E \right] \frac{1}{s}. \quad (25)$$

There are two components, a scaled waveform and an offset error. Clearly, there is no command that can provide simultaneously a unity scale [$U_E(s) = U_0(s)$] and eliminate the offset [$E_0U_E(s) = EU_0(s)$]. A compromise between scaling and offset errors is needed, and since patients with CN do indeed shift gaze, we must conclude that scaling must increase with target eccentricity. Some kind of ‘null point’ (a point of least amplitude) is inevitable. One way round this problem would be to use independent head movements to control one of the components in Equation (25). Thus, shifting head position towards the target eccentricity will eliminate the offset error and allow the desired waveform to be achieved with unity gain. This strategy is adopted by most patients with CN. Head movement is much slower than a saccade, thus it is not an ideal strategy although it may be the best available (there is little research on the issue).

5. Discussion

Previous models of CN have attempted to describe *how* the nervous system might generate such oscillations (actually simplified models of the oculomotor circuitry) [4–9]. Although ingenious, these are proximal models and cannot offer any explanation as to why CN might develop in the first place. They are not testable and have not had any impact on the management of CN. Instead, we have attempted to model *why* CN might develop. Understanding the causal mechanisms opens up the possibility of meaningful intervention, but also provides testable predictions.

There is no evidence to indicate that the normal adaptive processes for regulating eye movements have been damaged in CN, and the obvious question is why do these oscillations persist throughout life? Why are they not suppressed, or gradually ‘adapted out’? We deduce that the oscillations may be actively maintained by adaptive mechanism, possibly because the teaching signals that drive normal adaptive control are abnormal. This is appealing as it provides a possible explanation of why abnormal sensory processes (which occurs in most patients with CN) could lead to an abnormal motor behaviour. Our argument is based on three key premises.

First, we propose that the objective of the developing visuomotor system is to develop a control network that generates an eye movement strategy to maximize visual contrast. At this stage we make no

comment on the anatomical substrate for this plasticity, other than it involves at least the connectivity in the pre-motor oculomotor circuits. For most infants, who are born with typical sensory processes this development results in behaviours which we label as ‘normal’ eye movements, such as steady fixation and smooth pursuit. However, this is not a foregone conclusion. If the sensory processes are atypical, a different eye movement strategy may develop, which we label as ‘abnormal’. Thus, we argue that CN is a developmental strategy, albeit anomalous. This is in stark contrast to the implicit medical model, which assumes CN to be caused by a ‘lesion’ (as in acquired nystagmus, for example).

Second, we propose that the abnormal sensory process is an abnormal reduction in high spatial frequency sensitivity from birth (relative to a healthy infant) due to any of a wide range of abnormalities in the eye or optic nerve (which may or may not be inherited). This leads to a strategy to attempt to maximize visual contrast by maintaining positional registration with the fovea (or its remnant) but also maintaining some optimal image speed over the visual integration time. This task is impossible and the best compromise is to generate oscillatory eye movements, which we call ‘nystagmus’. If the saccadic system can be harnessed to reset eye position after each epoch, then jerk nystagmus with increasing velocity slow phases is optimal as described here.

Our final premise is that plasticity is not omnipotent. Oculomotor control is limited and performance is not perfect, leading to additional constraints. Poor saccade (quick phase) timing delays the epoch reset so that slow phases may reach much higher velocities and amplitudes than the optimum due to their high acceleration. Reset inaccuracies lead to uncertainty in the starting position of an epoch, which may lead to complex nonlinear sequences. As we have briefly outlined, a purely velocity command driven pre-motor circuit cannot generate the desired waveform at all eccentricities, and a null region seems inevitable. The consequences of this (including head movements) need to be explored further, but there is qualitative agreement with observations. We have focussed on epochs with only saccadic resets (jerk nystagmus) and have not examined pendular nystagmus. Although sinusoidal oscillations are more costly than the global optimum, we can show that they may sometimes be less costly than jerk nystagmus when we take into account the extra cost of saccade inaccuracy and timing. Space limitations prevents us from demonstrating this, but pendular nystagmus may be an alternative oscillatory strategy and could require different circuitry, such as anomalous smooth pursuit (see [7]).

An important aspect of the distal approach is that this model makes predictions that are *in principle* testable (although we acknowledge this will be difficult). According to this model, the waveform should be related to the underlying profile of contrast sensitivity which ultimately determines the two key parameters: The optimal image speed p , and the relative cost of velocity to positional error τ . Both will depend on the degree of foveal dysfunction in infancy (which may not be the same in the adult nystagmas because of maturational and amblyogenic factors).

The parameter $\tau = +\sqrt{b/a}$ describes the trade-off between cost of the image moving at a speed different from p and the cost of the image being off the fovea. It is the critical factor in determining the shape of the optimal trajectory. τ is not a directly measurable physiological quantity but could be inferred from observed trajectory shapes (given that other parameters are known). Nevertheless, we can make qualitative predictions. For an increasingly sharply defined fovea, positional control becomes more important and τ decreases. The optimal trajectory therefore becomes more curvilinear and accelerative. On the other hand, for a poorly defined fovea positional control becomes less important, thus increasing τ and leading to more linear slow phases with less acceleration (Figure 3). Interestingly, large amplitude linear slow phases are often seen in young infants with CN, and could reflect a lack of need for good positional control (see later).

Although a non-zero p is a key requirement of this model, it only scales the optimal slow phase profile. In the normal adult visual system, contrast sensitivity to a moving bar is maximized at $p \approx 3$ deg/s for

a bar width of 1 degree, but this increases to $p \approx 10$ deg/s for a width of 3 degrees [10]. For low spatial frequency gratings (0.75 cyc/deg), [11] reported a considerable increase in p with foveal eccentricity from ~ 8 deg/s at the fovea to ~ 20 deg/s at 7.5 deg. Thus, substantial values for p are not improbable, but it is difficult to ‘guesstimate’ p for an abnormal visual system (and in infancy!). The spatial contrast sensitivity function (CSF) has been measured in adult albinos (the most common sensory defect in CN), but unfortunately not at very low spatial frequencies. However, [18] reported CSFs down to 0.4 cyc/deg for horizontal and vertical gratings. They clearly showed a relative enhancement for vertical gratings below about 1 cyc/deg, implying that image motion caused by nystagmus does increase sensitivity to low spatial frequencies even in the albino retina. However, temporal sensitivity needs to be measured directly to find p .

The question of isotropy in p and τ also arises. Directional differences in cost will lead to a preference to oscillate in one or more meridians. This may explain why CN is usually horizontal after early infancy. There may also be left–right differences due to naso-temporal asymmetries in monocular viewing in infants or older patients with strabismus. This may bias p and τ towards one direction and/or lead to asymmetric reversal waveforms. This is a complicated problem that requires further theoretical and empirical investigation.

An important aspect of this model is that it is *not* possible to proscribe a ‘foveation period’, at least when defined as a period when the eye position and velocity are within some limits (a rectangle in state space; [19]). The cost depends on the trajectory through state space and will vary between individuals depending on their spatio-temporal contrast sensitivity functions. If we knew p we could define a period when the eye speed is below p (which in any case would be greater than the value of 4 deg/s as typically proscribed for a foveation period), but this would not take into account the full cost. Instead we need to integrate cost over time according to Equation (6). Clearly it would be an interesting experiment to explore the relationship between cost and visual acuity to test this model.

A persistent conundrum has been why so few infants develop CN. Foveal development is protracted over the postnatal period [20] so why do not all infants develop CN? We propose that in the normal visual system, eye movement development occurs slowly in order not to outpace foveal maturation. After normal development, this will leave the infant with a functioning fovea and the optimal eye movement strategy, namely steady fixation and smooth pursuit. If foveal development were delayed/inhibited (or eye movement development were precocious), oscillations would develop and CN would ensue. Such oscillations might even prevent further visual development (i.e., amblyogenic), thus further delaying foveal vision. Once the period of peak plasticity is over (critical period), the strategy becomes irreversible. Clearly this is a complex issue, but it can explain why CN only occurs in infancy. It may also explain some idiopathic cases (where no underlying visual anomaly can be detected), since a transient mismatch between sensory and motor development could lead to permanent CN without any trace of an underlying abnormality later in life. We note that according to this model, a pre-requisite for CN is an eye movement system that is capable of developing steady fixation and smooth pursuit. Thus, we would not expect CN to develop in species without such eye movement systems.

This is an initial outline of a distal model. We have only considered the one-dimensional scenario and we have not explored the interaction between plant compensation and waveform. In particular, how important are head movements in developing CN waveforms and the null region? We have assumed quadratic minima and have had to make ‘guesses’ about quick phase metrics, as there is little data on the subject. Nor have we discussed pendular CN as an alternative locally optimal strategy. Furthermore, how an eye movement strategy is learnt and whether ‘normal’ brainstem circuitry might be harnessed for oscillations need to be revisited. These many issues need further exploration. In spite of these obvious limitations, remarkably, this model captures many of the unique waveforms associated with CN, the

low fractional dimensionality, and even predicts a null region. A conservative conclusion is that a non-veridical conflict between velocity and positional tuning is a sufficient condition for CN to develop in a plastic nervous system. It seems plausible that this tuning is related to underlying visual defects present at birth. We urge that CN should be viewed as a developmental strategy that needs to be redirected, not as pathology to be 'cured'. Indeed, Congenital Nystagmus may be as permanent and as 'incurable' as normal eye movements in a normally sighted individual.

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