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# A Mechanism for Eye Position Effects on Spontaneous Nystagmus*

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*Abstract*— **In acute stages of unilateral vestibular deficit, the imbalanced tonic activity on vestibular afferents evokes spontaneous nystagmus. The slow-phase velocity of this nystagmus varies with eye position, such that it is smaller when looking in the direction of slow-phases. The neural mechanism for this behavior is still not understood. Here, using a simple control system model, we show that plausible changes in the neural responses within the central vestibulo-ocular reflex pathway are adequate to cause eye position dependent effects in the nystagmus pattern. The proposed transformations in population response functions could happen immediately following a lesion and can be useful to stabilize gaze in part of the gaze field.**

## I. Introduction

In order to maintain clear vision, movements of the head are compensated for by involuntary counter rotation of the eyes, such that the direction of gaze in space remains stable. Such involuntary eye movements evoked by head motion are called the vestibulo-ocular reflex (VOR). Head movements are detected by inertial sensors in the inner ear, namely semicircular canals (SCC) and otolith organs, which detect angular and linear acceleration of the head, respectively. Their signals are conveyed mainly to the vestibular nuclei (VN) of the brainstem via primary vestibular afferents. Here we focus on the semicircular canals.

There are three roughly orthogonal SCC's in each ear (lateral, anterior, and posterior), which are maximally excited/inhibited by head rotations in their respective plane. The coplanar SCC's on either side of the head function in a push-pull manner; when the head turns towards one side, the ipsilateral vestibular nerve increases its activity above its resting discharge while the contralateral nerve lowers its firing by the same amount (reciprocal innervation). In the case of a unilateral vestibular deficit (UVD), the tonic activity of ipsi-lesional afferents dramatically decreases or becomes absent. This induces vertigo attacks caused by a sensation of being constantly rotated towards the healthy side, evoking compensatory eye movements with a saw-tooth pattern, called nystagmus (Fig. 1). Vestibular nystagmus consists of low velocity eye movements towards the lesioned side (i.e. slow-phases), interspersed by quick reorienting movements that bring the eyes back to the fixation point (fast-phases). Pathological spontaneous nystagmus (SN) due to canal imbalance is one of the most common seen in clinical practice.

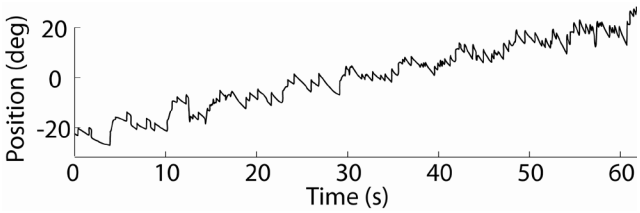


**Figure 1**– A typical nystagmus record from a patient with left side vestibular deficit. The velocity of slow-phases increase as the patient looks further towards the right side (the intact side). Adapted from [5].

A well-known characteristic of SN is that its intensity (i.e. the velocity of slow-phases) varies with eye position [1,2,4]. Eye velocity is smaller when looking in the direction of slow-phases and larger in the direction of fast-phases. This phenomenon is well known by clinicians as "Alexander's Law". Such behavior is absent during normal VOR evoked by sinusoidal or head impulse stimuli [2,3], suggesting that visco-elastic properties of the eye plant (i.e. extraocular muscles, eye ball, and the orbital tissue collectively) are not responsible for such effects.

The two theories that explain this behavior are from Robinson et al. [2] and Doslak et al. [4]. Robinson et al. [2] proposed that as an adaptation mechanism, the neural integrator of the ocular motor system reduces its time constant in response to prolonged unnatural stimulation. The neural integrator is a neural network that presumably performs mathematical integration of eye velocity commands to obtain proper drive to apply to the eye plant. If the integration is not perfect (i.e. integrator has a small time constant), then a desired eye position cannot be held in darkness and the eye drifts to a null position over time because of the visco-elastic properties of the plant. Such a drift towards the null position counteracts the spontaneous eye movement when the patient looks in the slow-phase direction and hence is desired during SN. However it adds to spontaneous eye velocity when looking in the fast-phase direction. Therefore, at least in one part of the visual field, the gaze could be stable.

Doslak et al. [4] proposed that in UVD, a gaze-dependent command is added to the total VOR drive, which after passing through an intact neural integrator produces an eye position dependent velocity that is larger in the direction of fast-phases and decreases linearly as eye is directed towards the slow-phase direction. They postulated that a presynaptic inhibition gates the gaze-dependent signals in normal VOR.

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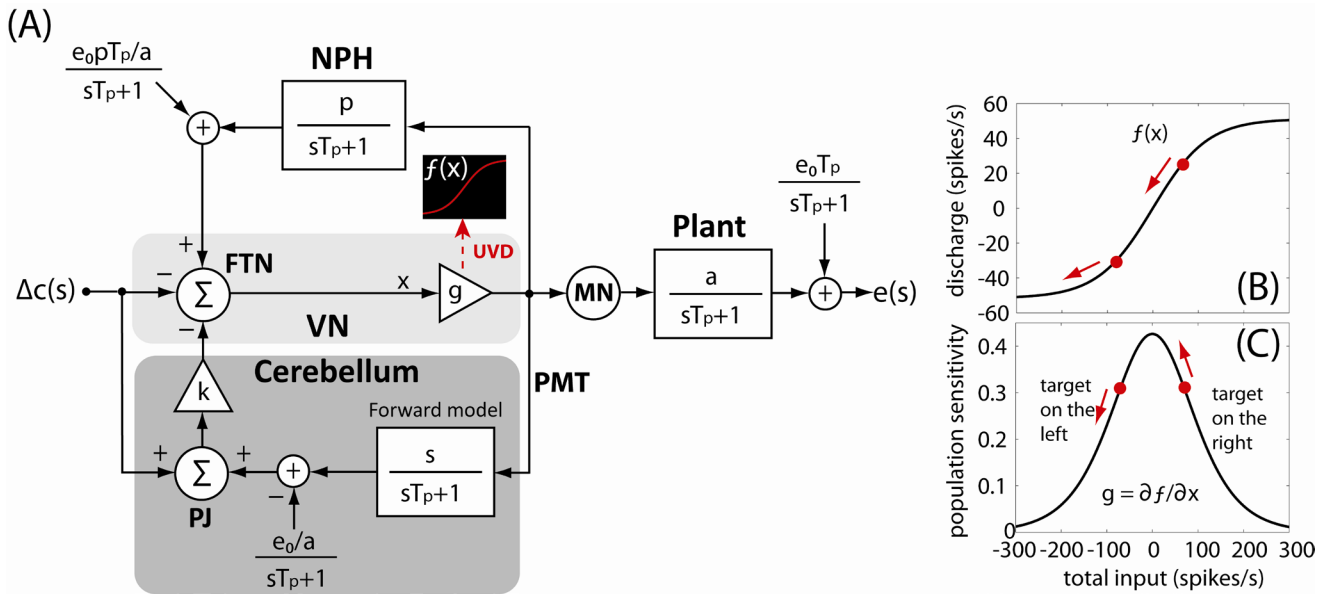


**Figure 2– (A)** Model structure for the horizontal canal driven VOR during slow-phases. Small letter 's' is the complex Laplace variable. Δc is the difference between right and left canal signals and e is the conjugate eye position. $e_0$ is the initial eye position at the start of each slow-phase. The effect of initial condition are added explicitly to the output of each filter. For a healthy system, the population response of the VN can be approximated with a linear function with constant gain '*g*'. In case of a UVD (unilateral vestibular deficit), this response function is no longer linear. A sigmoidal function *f(x)* is proposed to replace the linear function. VN: vestibular nuclei; FTN: flocculus target neurons; PJ: Purkinje neurons; NPH: nucleus Prepositus Hypoglossi; PMT: paramedian tract; MN: motor nuclei. $T_p$ is the time constant of the plant; p is the gain of the low-pass filter at the NPH; k is the projection gain of PJ neurons; *g* is the gain of the VN. Numerical values are given in Table 1. **(B)** The suggested population response function for the VN, following a UVD is plotted with parameters given in Table 1. **(C)** The bell-shaped function is the derivative of the sigmoidal function *f(x)* in (B). Arrows show the direction of slow-phase eye movement for a *left-side* UVD. When the fixation point is on the right (i.e. in the fast-phase direction) slow-phases move the eye in a direction that increases the VN gain. While for a fixation point on the left, slow-phases move the eye such that the VN gain decreases.

This presynaptic inhibition is itself inhibited by a pathologic vestibular imbalance, hence allowing the gaze-dependent signals to pass through to the VOR circuit. This mechanism affects the output of the VOR system without altering the neural integrator properties.

Robinson's and Doslak's theories both account for this eye position dependent behavior, but through different mechanisms. Nevertheless they are both unclear about the underlying neural mechanism used by the vestibular system. In Robinson's theory, the neural mechanism to trigger and to reduce the time constant of the neural integrator is left unexplained. In Doslak's theory, the origin of the proposed gating inhibitory signal and the gaze-dependent drive is unclear. In addition, neither is able to explain the recent findings that in UVD patients the velocity of slow-phases does not vary linearly with eye position [5, 10].

Here we use a control system model for the VOR to show that a physiologically plausible transformation in the population response of the secondary vestibular neurons in the VN is sufficient to cause the eye position dependent vestibular nystagmus. We propose that this response transformation from quasi-linear to a sigmoidal function could be a direct consequence of the UVD without having to resort to extra triggering or guiding neural signals from higher order brain structures.

## II. Model Description

The model used here is a commonly accepted feedback structure for the canal driven conjugate horizontal VOR (Fig. 2(A)). The model simulates only the slow-phases of nystagmus. The input to the model is the difference in discharge between right and left vestibular primary afferents: $\Delta c(s) = c_R(s) - c_L(s)$. The output e(s) is conjugate eye position defined as the mean right and left eye positions. Rightward movements and positions are considered positive.

The primary vestibular afferents carry canal signals directly to the VN. The VN integrate (i.e. sum) several converging control signals and project to the motor nuclei (MN), which in turn drive the eye plant. The mathematical integration of the VOR velocity commands is accomplished through a distributed network of neurons in the VN, Nucleus prepositus hypoglossi (NPH), and the vestibular cerebellum (here: Flocculus/ventral Paraflocculus) [6]. The effect of this network is to augment the time constant of the VOR response above the 200 ms time constant of the eye plant. This is achieved by two feedback loops around the VN: a positive position feedback through the NPH and, a negative velocity feedback through the Flocculus. The NPH performs the first integration in the brainstem. Here the NPH is modeled as a first order low-pass system (i.e. a leaky integrator) whose dynamics are set equal to those of the eye plant for simplicity of analyses. If the dynamics of the NPH low-pass filter do not exactly match those of the eye plant, the positive feedback will not cancel the eye plant dynamics but will only

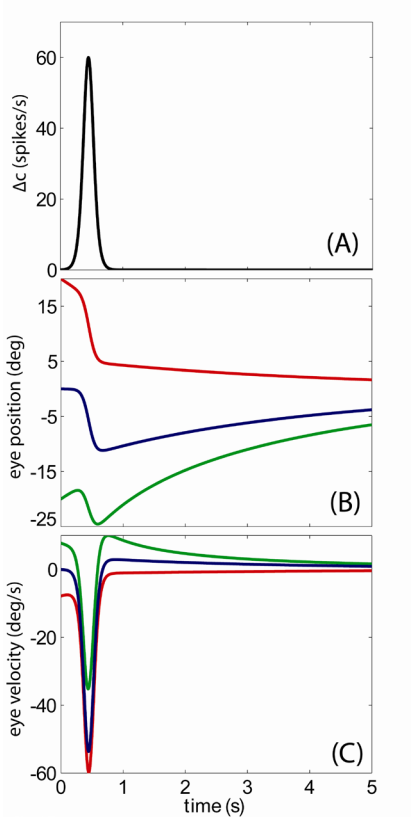


**Figure3**– Simulation results are provided for a pulse input to the model as shown in (A). The positive pulse causes a leftward eye movement (i.e. slow-phase is to the left). The resulting change in position (shown in B) and velocity (in C) are compared for three cases: when the eye is initially deviated 20°to the right (in red), at null position (in blue), and 20° to the left (in green). The velocity is larger when the eye is deviated to the right compared to the left.

lengthen the dominant time constant of the response. A second integration is done through the Flocculus/ventral Paraflocculus of the cerebellum. The Flocculus receives a copy of the motor neuron drive from the paramedian tract (PMT) neurons in the brainstem via mossy fibers [7]. It is believed that the Flocculus constructs an efference copy of eye velocity using a stored forward model of plant dynamics (see [9] for a review). The Flocculus also receives vestibular signals, perhaps from Floccular projecting neurons in the VN. In turn, Floccular gaze-velocity Purkinje neurons (PJ) make inhibitory projections to the Flocculus target neurons (FTN) in the VN [8], closing the negative feedback loop around the VN.

In a healthy system, the population response of the VN could be approximated by a linear function, with a constant sensitivity (i.e. gain, parameter $g$ in the model) to the incoming activity over a wide operating range. Indeed a large population of on-off elements (i.e. individual neurons) with different on-thresholds behaves like a sigmoidal function with a large, quasi-linear operating range between total saturation and cut-off. However, if the incoming baseline activity is not enough to push individual neurons into their operating range, then the population response can no longer be approximated by a linear function.

For a balanced healthy system, the eye position, e(s), and velocity, e′(s), from the model are given by:

$$e(s) = -\frac{ag(1+k)}{s(T_P+gk)+1-gp}\Delta c(s) + \frac{T_P+gk}{s(T_P+gk)+1-gp}e_0 \quad (1\text{-a})$$

$$e'(s) = -\frac{s\,a\,g(1+k)}{s(T_P+g\,k)+1-g\,p}\Delta\, c(s) - \frac{1-g\,p}{s(T_P+g\,k)+1-g\,p}e_0 \quad (1\text{-b})$$

The first component of (1-a,b) presents the forced system response to the vestibular stimulus and the second component is the transient response to initial conditions. From (1), the time constant and high frequency gain of the response are derived as:

$$\tau = \frac{T_P+gk}{1-gp} \quad (2)$$

$$\varphi = \left.\frac{e'(s)}{\Delta c(s)}\right|_{s\to\infty} = -\frac{ag(1+k)}{T_P+gk} \quad (3)$$

The effect of feedback loop gains on enhancing the time constant of the response above the eye plant time constant, $T_P$, can be seen from (2). Note that to maintain system stability the term $1-gp$ should be positive. Model parameters (Table 1) are chosen such that for a healthy system the response gain is unity and the time constant is 17 s, similar to what is seen in real data. Using Eqs. (2,3), it can be shown that a larger $g$ results in a larger response gain, φ, as well as a larger time constant, τ .

Since following a UVD many of the ipsi-lesional VN units turn-off because of insufficient incoming baseline activity on the primary afferents, then it is plausible to assume that the VN response function deviates from a linear approximation. We hypothesize that a sigmoidal function would replace the linear function (with the slope of $g$) in the model in case of UVD. Eq. (4) presents a generalized analytical form for the sigmoidal function that is used in simulations (see also Fig. 2B):

$$f(x) = \alpha + \beta\left(1+\lambda\exp\left(-\gamma\left(x-\mu\right)\right)\right)^{-\frac{1}{\lambda}} \quad (4)$$

with parameters given in Table 1. The local derivative of this function (i.e. $g = \partial f/\partial x$, shown in Fig. 2C) defines the sensitivity of the population to the incoming activity and Eqs. (1-3) hold for local small signal stimulations.

To qualitatively explain the effect of nonlinearity, consider a left side UVD, which evokes a SN with slow-phases that move the eyes leftward. As shown in Fig. 2(C), when looking to the right, slow-phases move the eyes towards the null position, increasing VN gain (and hence φ and τ) as the eye travels along the curve. But for a fixation point on the left, slow-phases move the eye away from the

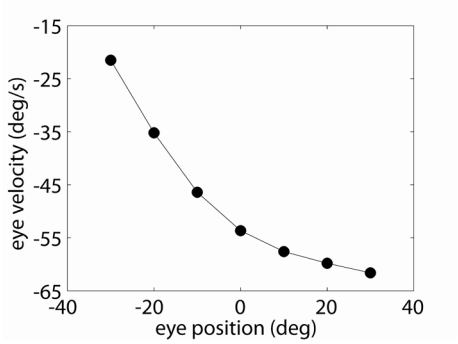


**Figure 4**– The amplitude of eye velocity is plotted as a function of eye position, for a rightward pulse of 60 spikes/s. With the mechanism suggested here, the velocity-vs-position curve is not necessarily linear.

null position, decreasing VN gain, *g*. Therefore for a fixation point on the left side, the forced response in (1) will be smaller (i.e. a smaller φ). Plus, for this fixation point, the time constant is also smaller (since *g* is smaller), causing a larger drift velocity towards the null position. Hence the small forced response will be counteracted by an even larger transient response in the opposite direction, resulting in an overall smaller velocity.

## III. Simulations

The model was simulated in MATLAB SIMULINK (The MathWorks Inc., MA, USA). An example of simulation results is provided in Fig. (3). The model was stimulated with a rightward pulse (resembling a left-side UVD), causing an eye movement towards the left. The response of the model is largest for initial eye position at 20° to the right (red curve) and smallest for eye position 20° to the left (i.e. the slow-phase direction). Note that there is a transient response because of the initial conditions that equals ~ +8°/s for eye position on the left and –8°/s for the eye position on the right. In addition, the forced response (i.e. the amplitude of the output pulse) is also larger for the rightward eye position. These two factors both contribute to the larger response when eye position is initially on the right, compared to the left.

It can also be shown that the resulting eye velocity is not necessarily a linear function of eye position as would result from Robinson's and Doslak's theories [2,4]. For instance, Fig. (4) presents a plot of eye velocity as a function of fixation position that results from stimulating the model with

TABLE I. Model Parameters

| **Parameter** | α | β | γ | λ | μ | $T_p$ | *k* | *p* | *a* | *g* |
|---|---|---|---|---|---|---|---|---|---|---|
| **Value** | –51.6 | 102.8 | 0.017 | 1.02 | 0 | 0.2 | 1 | 2 | 0.7 | 0.48 |

a rightward pulse of 60 spikes/s. The figure shows that the rate of change in velocity with position is not constant, but declines in the fast-phase direction. A similar effect has also been reported in patient studies [5, 10].

## IV. Conclusion

We propose a new mechanism for the effects of eye position on spontaneous nystagmus during acute UVD. We hypothesize that the population response function of central vestibular neurons becomes nonlinear following a UVD since many individual VN units are forced into cut-off region. In this case, a change in eye position shifts the operating point of the VN along this sigmoidal nonlinearity, changing the average sensitivity of VN to the incoming neural activity. Since such a change happens within the neural integrator network for the VOR, both the time constant and gain of the response are affected. We also showed that with this mechanism, the eye position dependent effect is not necessarily linear across the oculomotor range, an observation that has also been reported by experimental studies [5, 10]. It is also reported that the shape of the velocity-vs-position plot depends on individual UVD patients. The model also has the flexibility to produce different velocity-position profiles by changing the parameters of the sigmoidal function. For example, changes in the parameter μ will shift the point of maximum sensitivity from $x = 0$ to the right or left, at $x = \mu$ (see Eq. (4) and Fig 2C). Also changes in the parameter λ will affect the symmetry of the sigmoidal function around the point $x = \mu$. Furthermore, with this mechanism another factor that affects the shape of the velocity-vs-position curve is the amplitude of the stimulus that depends on canal asymmetry, Δc. This is because Δc directly affects the total drive to the nonlinear function.

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