CHAPTER 2

NEURAL INTEGRATION IN OCULAR MOTILITY*

L. F. DELL'OSSO**

If we accept the hypothesis that the main purpose of eye movements is to guarantee a clear and stable view of the world and since visual acuity is degraded by image slip across the retina exceeding 2-3°/sec, we can conclude that maintenance of stable gaze is a paramount requirement of the ocular motor system. Holding a desired eye position requires that a neural signal proportional to eye position be provided to the ocular motor neurons and extraocular muscles. Such a signal is necessary to maintain eccentric gaze after a saccade; smooth pursuit of a moving target; and gaze in the presence of head movements. How is this "eye-position" signal generated? What are the input signals used in the generation of an eye-position signal? Does the same neural network generate the eye-position signals for the various subsystems (saccadic, pursuit and vestibulo-ocular) or are they generated by different networks? As mentioned in Chapter 1, a *neural integrator* is the network that provides the eye-position signal.

Defining neural integration

In neurophysiology, the term "neural integration" is used in two different contexts. First, neural integration describes the summing of several neural input signals to produce an output signal that is some desired function of those inputs. Secondly, neural integration is used in its literal, mathematical sense to describe, as a time integral, the relationship between the output of a neural network and its input.

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** From the Ocular Motor Neurophysiology Laboratory, Veterans Administration Medical Center; and the Departments of Neurology, Case Western Reserve University and University Hospitals of Cleveland; Cleveland, Ohio.

That is, the output firing frequency is the integral with respect to time of the input firing frequency:

$$f_{out}(t) = \int_0^t f_{in}(t)\, dt$$

It is in this second, more exact, sense that the term will be used in this Chapter. Thus, if the input to the neural integrator (NI) is the eye-velocity signal, $\dot{E}$, the output will be the eye-position signal, $\hat{E}$.

The need for neural integration

In 1968 Robinson observed that the proper functioning of the vestibulo-ocular reflex (VOR) required a neural network performing mathematical integration of the afferent signal on the eighth nerve (1). It had been known for several years before that time that the signal coming from the semicircular canals on the eight nerve was coded in head velocity and that the discharge rate of ocular motoneurons was predominantly coded in eye position. If the VOR is to move the eyes at a velocity equal and opposite to the head velocity, the motoneurons require a signal that is the integral with respect to time of the afferent head-velocity signal. Therefore, the integrator plays a major role in the forward path of the VOR. After its existence was predicted, based on this simple mathematical analysis of the signals involved, neurophysiological supporting evidence for the integrator began to appear. A step of electrical stimulation applied to the reticular formation resulted in constant-velocity eye movements in monkeys (2) (i.e., the ramp of eye position vs. time was the integral of the step of excitation). Also found was a 90° phase lag between vestibular and ocular motoneurons during sinusoidal rotation of monkeys (3). Mathematically, an integrator exhibits a 90° phase lag between its input and output.

In addition to the VOR, another important slow eye movement (SEM) is smooth pursuit. The purpose of the smooth pursuit subsystem is to move the eyes with a velocity equal to that of a moving target. The input to the smooth pursuit subsystem is retinal error (slip) velocity and its output to the motoneurons must also be an eye-position signal. As is the case for the VOR, a velocity signal must be transformed into a position signal; neural integration is also needed by the smooth pursuit subsystem. The optokinetic subsystem similarly requires integration of retinal slip velocity signals.

Studies of the ocular motor plant (the globe, muscles and supporting tissue) show it to be a highly overdamped system (4). That is, it is slow and sluggish to respond to changes in innervation. Despite this, the eyes are moved extremely rapidly when fixation is changed from one target to another. These fast eye movements (FEM) are called saccades. Burst cells in the pontine paramedian reticular formation (PPRF) create a pulse of high frequency that is relayed through the motoneurons to the extraocular muscles creating saccades (5). To complete the saccade and hold the eye in its new position, the burst of activity must be followed by a constant step change in activity of the motoneurons. Since the burst cell activity (the pulse) can be considered an eye-velocity command (6), the required eye-position command (the step) can be achieved by integration of the pulse. The saccadic subsystem requires neural integration for the same reasons that the SEM subsystems do.

Thus, each of three ocular motor subsystems requires neural integration. Are there three NI's or can one do the job for all subsystems? Neurophysiological evidence supports the common NI solution (7). All ocular motoneurons carry an eye-position signal that is independent of the type of movement involved. The NI integrates all the velocity commands to produce a single, composite eye-position command at its output. Figure 1 is a simple block diagram illustrating the common NI reponding to saccadic (FEM), pursuit (SEM) and vestibulo-ocular (VEST) velocity commands. The direct pathway around the NI provides the velocity information that is also carried by ocular motoneurons. Both the FEM and SEM subsystems are enclosed by the negative feedback of vision at the retina but the VOR is open loop (i.e., there is no feedback).

Ocular motility models incorporating neural integrators

Early models of the ocular motor control systems contained integrators (8, 9). These engineering models took advantage of the qualities of integrators in negative feedback control systems; they provide high steady-state accuracy and help prevent system oscillation. Since the ocular motor control system was required to accurately direct the eye with little or no instability in the resulting position signal, it was natural for bioengineers to include integrators in the feedback models. This inclusion NI's in models preceded evidence of their neurophysiological existence. In addition to normal ocular motility, control system

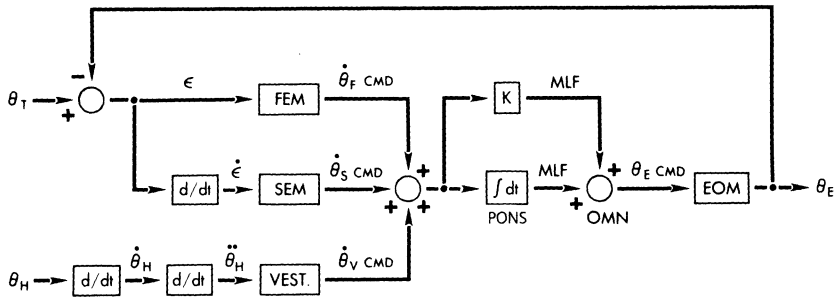

Fig. 1. – Block diagram of the dual-mode version subsystems with vestibular input illustrates the difference between the closed-loop FEM and SEM mechanisms and the open-loop vestibulo-ocular apparatus (VEST). The velocity commands of the FEM ($\dot{\theta}_F$ CMD), SEM ($\dot{\theta}_S$ CMD), and VEST ($\dot{\theta}_V$ CMD) subsystems are shown summing and utilizing the final common integrator ($\int$ dt). Its output and the velocity outputs travel to the oculomotor nuclei (OMN) via the medial longitudinal fasciculus (MLF). The eye position command (θ_E CMD) is sent to the extraocular muscle (EOM) to effect the required eye position (θ_E). θ_T is the target position. In this way, the position error, $\varepsilon = \theta_T - \theta_E$, and the velocity error, $\dot{\varepsilon} = d/dt\,(\theta_T - \theta_E)$, are driven to zero; there is no feedback to the vestibular system, which responds to head acceleration ($\ddot{\theta}_H$). Head position (θ_H) and velocity ($\dot{\theta}_H$) and also are shown along with their relationship to $\ddot{\theta}_H$. (Reprinted with permission from Dell'Osso and Daroff, 1988).

models were used to study ocular motor dysfunction. The first such model, used to investigate saccadic and pursuit responses in a subject with congenital nystagmus, also contained NI's (10).

In his "bang-bang" model of saccadic generation, Robinson used a NI to feed back a signal that turned off the burst neurons (11). Figure 2 is a model of this pulse generator (PG). A perceived position error causes a velocity pulse output, shaped by the non-linearity shown, whose width is determined by the output of the NI shown. Since a NI was needed for the eye-position signal, *its* output was used as the source for the signal needed by the PG. While efficient in terms of the number of elements required to do the job, this assumption reduced the flexibility of the model for the study of normal variability and plasticity and also limited its use for studying dysfunction. If the same NI determines both the pulse width and the final eye position, then altering its gain (deg/(spikes/sec) for eye position) could change both the initial trajectory and the final position of a saccade. Studies of plasticity have shown these to be under independent control (12-14). Also, there are types of nystagmus, caused by NI dysfunction, where the slow- phase waveforms but not those of the saccadic fast phases are determined by the NI dysfunction; a single NI would affect both.

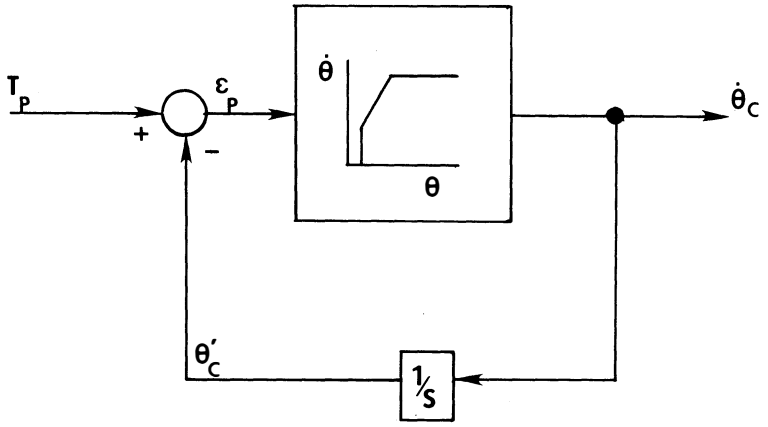

Fig. 2. — A model of the pulse generator. T_p is perceived target position, θ_p is perceived retinal error position, $\dot{\theta}_c$ is the eye velocity command and $\hat{\theta}_c$ is an approximation of the eye position command. (Reprinted with permission from Dell'Osso and Daroff, 1981).

Figure 3 illustrates the slow-phase waveforms produced by NI time constants that are either too high or too low. The normal NI has a "leaky" time constant of about 25sec. in the dark (15); in the light, it is improved by cerebellar feedback (16). Too low a time constant produces decreasing-velocity slow phases and too high a time constant produces increasing-velocity slow phases. Slow phase waveforms are diagnostic of certain types of nystagmus.

The computer models of the ocular motor system destined for use in our laboratory in the early 1970's were deliberately designed to be both flexible and as physiologically accurate as possible. Since they were intended to aid in the study of a variety of neurological conditions exhibiting ocular motor dysfunction that was both undefined and unpredictable, they were bilateral in architecture (mimicing

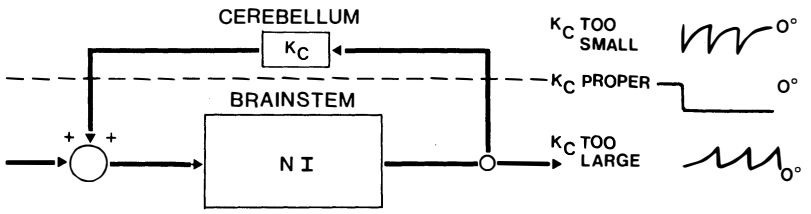

Fig. 3. — Block diagram of the cerebellar positive feedback path with gain (K_c) around the leaky neural integrator (NI). (Reprinted with permission from Dell'Osso and Daroff, 1988).

the brain stem) and contained separate functional "boxes" for different ocular motor tasks. The "local" NI of the saccadic PG, needed to convert the pulse to a step, was distinct from the common NI shared by the various subsystems. These considerations: provided the flexibility to make changes in one function without altering another; allowed for normal (and abnormal) plasticity adjustments; restricted all signals to be greater than or equal to zero (as are neural firing frequencies); allowed study of unilateral dysfunction reflecting deficits on one side of the brain stem; and duplicated the "push-pull" nature of the interconnections across the midline. This last characteristic yielded models that acted differently on common signals, such as resting firing rates (tone), than they did on differential signals from each side of the brain stem. For studies where some of these factors were not important, the models were consolidated into simpler models that shared elements or were unilateral.

The study of gaze-evoked nystagmus (GEN) produced an early model of NI nystagmus (17). Here, as is shown in figure 4, the NI was "lesioned" in two ways to produce GEN. It was either made leaky (meaning its time constant was reduced) or was made to saturate to

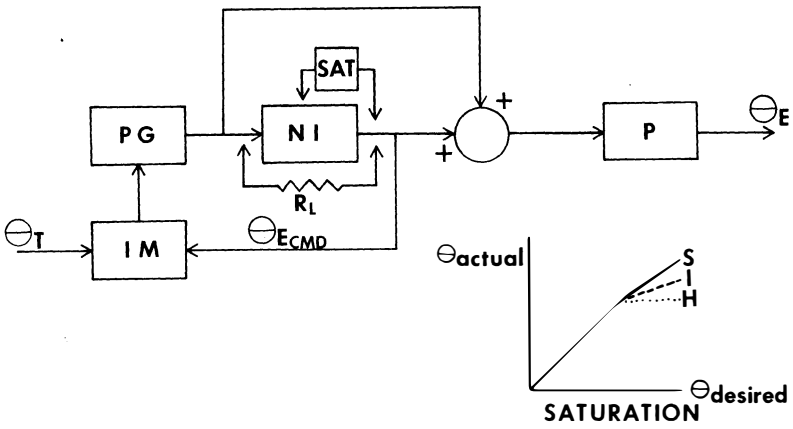

Fig. 4. — Block diagram of the model used to simulate gaze-evoked nystagmus. The input target position (θ_T) is compared by the internal monitor (IM) to the eye position command ($\hat{\theta}_{ECMD}$) and the necessary saccade initiated in the pulse generator (PG). The IM contains an error threshold below which no correction is called for. It also is prevented by a refractory circuit from calling for a correction during a saccade. The PG contains nonlinearities that reproduce the physiological variations in pulse height and duration. The output of the PG is integrated in the neural integrator (NI). The pulse and step are summed, with the resulting innervation used to drive the plant (P) to produce the desired eye position (θ_E). Both a leaky NI (R_L) and saturating NI (SAT) are indicated as ways to produce gaze-evoked nystagmus. The inset shows typical saturation characteristics used (soft, S; intermediate, I; hard, H).

varying degrees. Recognizing the distributed nature of a real NI, we divided the model's NI into two parts, each representing a portion of those neurons reponsible for integrating velocity command into position commands. In this way, a portion of the neuronal pool could be lesioned and the resulting GEN studied. With such a partial deficit, the model produced a GEN that decayed to a non-primary position gaze angle. In figure 4, the NI shown is the *common* NI, shared by the saccadic, pursuit and VOR subsystems; the *local* NI for saccades is contained within the PG. The internal monitor (IM) used the eye-position command to determine if a corrective saccade was needed. The IM did *not* alter the pulse width of the saccade; the local NI within the PG accomplished that. In addition to GEN, the model predicted different effects on saccadic trajectories dependent on the particular NI defect used. Leaky NI's produced overshooting saccades whereas saturating NI's produced normal saccades in the region before the saturation took effect.

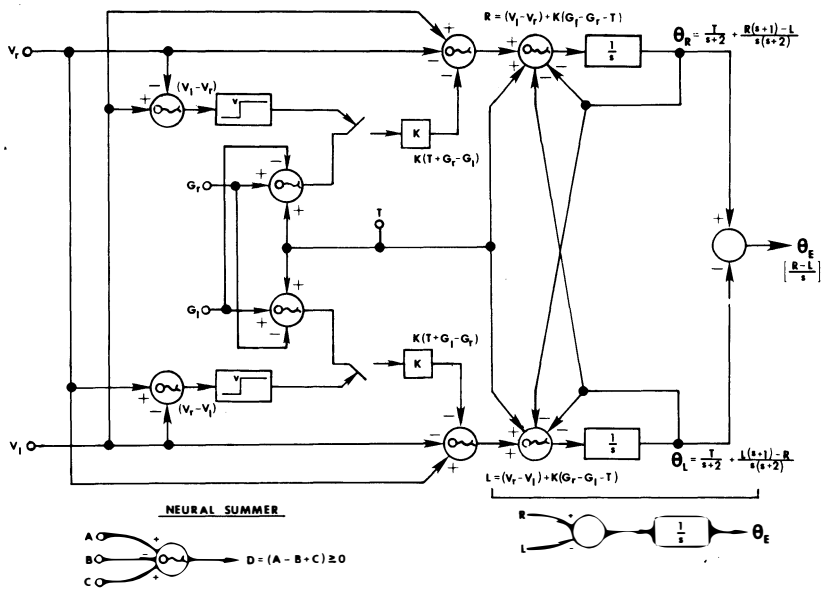

Fig. 5. — Signal flow diagram of a model for the Alexander's law variation of vestibular nystagmus containing the necessary quantitative interaction among signals. Mathematical relationships utilize Laplace notation where applicable. The push-pull interconnected neural integrators (1/s) integrate differential inputs and pass common tone (T) signals. Neural summers can have only positive outputs. (Reprinted with permission from Doslak *et al.*, 1979).

Although we were able to use a unilateral model of the ocular motor system for the above study, a bilateral model was necessary for studying the Alexander's law variation of vestibular nystagmus (18). It was an extension of an earlier model (1974) made in our laboratory and featured bilateral NI's connected in a push-pull fashion. Figure 5 is the signal flow diagram for this model; we will concentrate only on the NI interconnections. As is shown, all neural summers were restricted to outputs greater than or equal to zero (simulating neurons). Since there is a tonic firing rate on each vestibular input and a tonic output to each motoneuron and muscle (even during fixation at primary position), the NI's were interconnected in a manner that resulted in both the integration of the differential input (left vs. right) and the simple relaying of the common tonic inputs to the motoneurons. The lower right-hand equivalent diagram for the two interconnected NI's shows that eye position is a function of only the differential input while the equations for each NI output show the existing tonic signal. A bilateral model with connections across the midline is necessary for illustrating both these phenomena and the importance of the crossing fibers; these features would be lost if a unilateral model were used. This reciprocal inhibition of NI's was to be used in later models of the NI itself (see the Models of Neural Integration section of this chapter).

The common brain stem NI also played a role in a study of a peripheral deficit, myasthenia gravis (MG) (19). For this study, we used an expanded version of the unilateral GEN model discussed above. The GEN model was designed to produce only unidirectional eye movements and could not simulate corrective saccades based on deficits that occurred in the periphery. To study MG, the model had to be expanded to produce both bidirectional eye movements and bidirectional corrective saccades (caused by peripheral deficits) and it required two eyes instead of the single eye modeled for GEN. Figure 6 is a block diagram of the MG model. Although the deficits introduced were peripheral and in either the right or left eye (the viewing eye was chosen by a switch in the model that is indicated in figure 6), it was the *central* increase in gain resulting from the ocular motor system's plasticity that reproduced the eye movements seen in patients. That is, to overcome the peripheral deficit in MG, the central nervous system increases the innervation necessary to make a saccade; the higher innervation drives the deficient ocular motor plant to the desired fixation angle. Thus, in the model, the signals to the PG and NI were

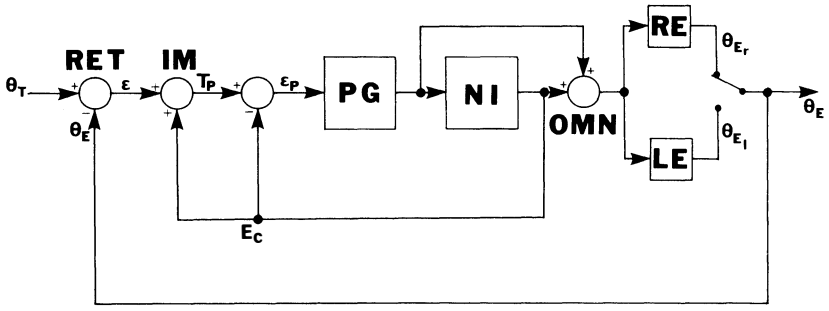

Fig. 6. — Block diagram of model used to simulate the saccadic eye movements of patients with myasthenia gravis. The target angle (θ_T) is compared to the angle of the eye (θ_E) at the retina (RET) generating the error signal (ε). The internal monitor (IM) compares ε with a copy of the eye position command (E_c) producing perceived target position (T_p) which drives the pulse generator (PG) to produce the pulse of neural activity necessary for a saccade. The neural integrator (NI) produces the step of activity required to hold eye position and the sum of the pulse and step drive the ocular motor neurons (OMN) of each eye (LE and RE). The choice of which will be the viewing eye is made by the switch which chooses θ_{E_r} or θ_{E_l}. (Reprinted with permission from Abel *et al.*, 1980).

increased to a higher level than normal. The model produced eye movements similar to those seen in patients with MG. It was also able to produce the changes in eye movements seen when MG patients are injected with edrophonium chloride (Tensilon). Tensilon transiently removes the deficit from the plant. This was illustrated by the simulation after removing the deficit from the plant and observing the saccadic outputs produced by the model with its higher internal gains and normal plant. The two-part NI of the GEN model was retained for this model to simulate two neuronal pools that might be differently affected. The deficits introduced in the ocular motor plant were similar to those used in the NI of the GEN model (i.e., leaks and saturations were incorporated into the dynamics).

The final model of NI dysfunction that I will discuss was used in a study of the variable waveforms in downbeat nystagmus (20). This model, functionally equivalent to an earlier model of downbeat nystagmus (21), was a bilateral model whose input was the velocity pulse from the PG and output was the eye-position command; a neural tone signal was also included (see figure 7). As was discussed above, a NI deficit can cause the slow phase of nystagmus to be either increasing or decreasing in velocity. In the horizontal plane, increasing-velocity slow phases have only been observed in congenital nystagmus (22), but in the vertical plane they have also been observed in downbeat nystagmus (23, 24). Based on the recordings of a patient

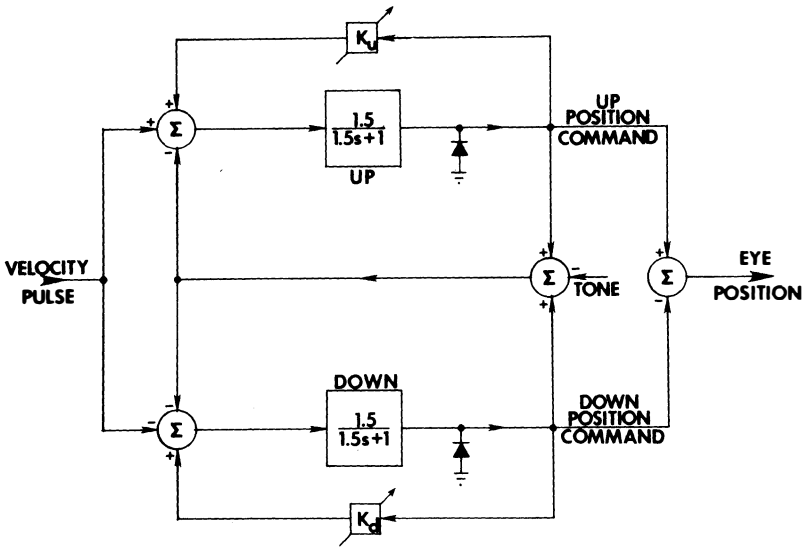

Fig. 7. — Block diagram of the computer-simulated up and down brainstem leaky integrators and their cerebellar compensatory feedback loops (K_u and K_d, respectively). (Redrawn from Zee *et al.*, 1981 and reprinted with permission from Abel *et al.*, 1983).

with downbeat nystagmus subsequent to ankylosing spondylitis, a model was constructed in which the nature of the NI deficit could be varied in an attempt to reproduce the slow-phase waveforms seen. Both increasing- and decreasing-velocity slow phases as well as linear slow phases were duplicated by this model. Slow phases that varied on an intrabeat basis between the various types were also simulated by the model. This was achieved by allowing the cerebellar compensation around the leaky brainstem NI's to vary in gain on a short-term basis. However, the best simulation of the patient's waveforms resulted from varying the inherent leakiness (gain) of the NI rather than the gain of the cerebellar positive feedback loop. ~~Linear waveforms were produced by allowing the cerebellar positive feedback loop.~~ Linear waveforms were produced by allowing the cerebellar feedback to produce an increasing-velocity exponential slow phase with a very long time constant; this produced a slow phase that looked linear for its few hundred milliseconds duration before a fast phase reset the eye position. This mechanism for producing linear slow phases had been suggested by the previous study on GEN (17). The bilateral NI model provided the hypothesis that nystagmus with all three types of slow phases could be produced by one basic defect: short-term gain changes in the NI.

Searching for the neural integrator

Despite the presence of NI's in early bioengineering models of the ocular motor system, neurophysiologists were not actively looking for such an entity; models were viewed as mathematical abstractions that did not necessarily have any basis in reality. However, after the observation that a neural network perfoming mathematical integration was necessary for the proper functioning of the VOR, neurophysiologists became interested in where it might be located in the brain stem. That search lasted 20 years during which time the models discussed above, and others, were being used in the study of normal and pathological ocular motility; models continue to be a valuable tool in such studies. The difficulty in locating the NI might have been due in part to the suggestion, implicit in lumped black-box models, that neural integration might be accomplished by neurons whose inputs were velocity signals and outputs were position signals. Neurophysiologists began to look for such neurons despite the realization by some that neural integration would require a distributed process involving many neurons and feedback pathways (as discussed for the GEN and MG models).

Initially the NI was thought to reside in the PPRF because lesions there could abolish all horizontal eye movements. Step changes in electrical stimulation of the PPRF produced ramp changes (the integral of the step) in eye position (2). Early block diagrams of the ocular motor system usually contained the letters "PPRF" near the NI. However, lesion studies in the PPRF showed that although ipsilateral saccades were abolished, gaze holding was not (25). The time constant of the NI was severely altered by cerebellar lesions, particularly in the flocculus (26, 27). The cerebellum became the next likely place where the NI might reside (28). However, although cerebellar lesions significantly effected its time constant, the NI was still functioning. This made it unlikely that the NI neurons were totally in the cerebellum. The cerebellum seemed to be more involved in parametric adjustments of the NI time constant than in where the NI resided. The next regions to be implicated were the nucleus prepositus hypoglossi (NPH) and the vestibular nuclei (VN). Cells in the NPH carried eye-position signals and projected directly to ocular motoneurons. Lesions of the NPH or VN in the cat resulted in failure of the NI (29, 30). Thus, the NI was shown to reside predominantly in the NPH and VN with extensive connections to the cerebellum.

Furthermore, after ablation of NPH and the medial VN, NI deficit was shown in response to vestibular, pursuit and optokinetic stimulations. The hypothesis that a single NI was used by all conjugate ocular motor subsystems was therefore, proved. Additionally, because the saccadic trajectories were *not* affected by loss of the NI, the additional hypothesis that the PG used its own local NI to modulate pulse width and did not use signals from the common NI, was supported by this work.

Models of neural integration

We have seen that four NI's are required for horizontal eye movements (two on each side of the brain stem). If the same number are required for vertical and torsional eye movements, the NI count rises to twelve. Add two more, possibly needed for vergence, and three more, to make gaze saccades by integrating head velocity, and it is obvious that the NI is not rare in the brain stem. Nor is the idea of neurons performing integration a new one; it is the progression from vague descriptions of networks using "reverberating collaterals" (31) (positive feedback) to the construction of neuronal models that has brought the NI from mathematical abstraction to realizable physiology.

One of the earliest models of neural integration itself suggested that it was accomplished by feeding back a velocity signal around a forward gain element (32). Such a combination behaves like an integrator without requiring a neural network to actually integrate; it was suggested that the velocity feedback came from muscle proprioception. This hypothesis was eliminated by the demonstration that there was no monosynaptic stretch reflex for the eye muscles (33). The configuration shown in figure 3, where a leaky neural integrator (a first-order lag element) is enclosed within a positive feedback loop to increase its time constant, is a more reasonable model since it functions as an ideal integrator without the high gains needed by the former method. Furthermore, loss of the feedback merely results in a leaky integrator.

Rosen proposed a theoretical neural-network model for the NI (34). The neurons in his network could either fire maximally or remain silent; this behavior has not been seen in ocular motor areas of the brain stem. Kamath and Keller proposed a neural network that contained lateral excitation of homogeneous neurons in a dense

population (35). Their model was very sensitive to gain values in the feedback pathways. Neither of the above models allowed tonic firing rates in addition to the eye-velocity signal inputs; all cells that have been studied carrying such inputs also have appreciable background firing levels. Cannon *et al.* presented a neural network consisting of lateral inhibition of linear neurons to accomplish neural integration (36). Their network functions as a leaky integrator and has independent control for DC gains (tonic levels) and modulated components of the input (velocity signals). This was achieved by utilizing the push-pull interconnections developed by Doslak *et al.* (18) for NI's themselves, within the building block of the half integrators. In a simulation using 32 neurons they showed that a partial lesion of their network would reproduce the GEN simulated by the Abel *et al.* model (17) when its NI neuronal pool was partially lesioned. Thus, the prediction made by the Abel *et al.* model that GEN, where the slow phases decayed to a non-primary position gaze angle, could be caused by a partial deficit in the total neuronal pool responsible for neural integration was confirmed by this neural-network model. The model was later improved to make the individual neurons a more realistic representation of those seen in the ocular motor system (eye-velocity and eye-position signals are present in these neurons) (37). This improved, more complicated, model contains afferents with non-uniform background firing rates and a double-layer network consisting of inhibitory and excitatory cells. The model does an excellent job of simulating the behavior of neurons thought to be part of the NI.

Summary

The NI is an important part of the ocular motor system; one that determines both normal and certain pathological eye movements. As this chapter has chronicled, bioengineers have played the major role in developing this concept. Early models predicted its use by the ocular motor system for accuracy and stability. Required velocity-to-position signal conversions (i.e., mathematical integration) necessitated its existence in the brain stem. Each type of conjugate eye movement used integration to convert premotor velocity commands into the required position commands. Successful synergistic operation of all subsystems was best served by one common NI but the flexibility and observed independence of certain functions suggested a local NI for the PG. The very nature of integration resulted in the realization that one

neuron could not perform this mathematical operation and therefore, the NI was likely to be distributed in several brain stem locations. Finally, the creation of neural network models that accomplish the task of mathematical integration demonstrated the need for reciprocal inhibition. Although the theoretical grounds for some of the hypotheses of bioengineers were not always based in neurophysiology, many of the resulting conclusions are supported by later neurophysiological evidence.

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Reprint requests and correspondence to: L.F. Dell'Osso, Ocular Motor Neurophysiology Laboratory, Veterans Administration Medical Center (127A) 10701 East Boulevard, Cleveland, OH 44106 USA. Telephone (216) 421-3224.

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