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INTEGRATING WITH NEURONS

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INTRODUCTION

Integration has two meanings in neurophysiology: One indicates some vaguely specified combination as in ". . . an integration of visual and vestibular signals may lead to a perception of . . ."; the other comes from calculus. If $x(t)$ is one variable in time and $y(t)$ another, then

$$y(t) = \int_0^t x(\tau)\, d\tau \qquad 1.$$

says that y is the time integral of x. This mathematical operation occurs in the central nervous system and is the subject of this review. The review concentrates on the integrator of the vestibulo-ocular reflex as a prominent example, offers a model of how integration might be done by neurons, and speculates about the extent to which neural integrators occur elsewhere in motor control.

Integration describes physical processes all around us: The volume of a fluid (blood) in a container (ventricle) is the integral of the inflow (venous return); the position of the shaft of a d.c. motor is the integral of the current applied to its armature. These examples, however, are just statements of physics. They are not examples of devices deliberately constructed by nature or technology to integrate a signal to achieve some desired end. Such devices are not very visible in our world. One exception is attached to the back of our houses, it measures the energy we use by integrating our power consumption, but most integrators hide in boxes that operate cranes, fly airplanes, orient satellites, and so on.

In these examples, the integrators are usually located in negative feedback control systems. Their value there, to oversimplify, is that integrators have very large gains at low frequencies, making controllers very accurate

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in the steady state. On the other hand, integrators have low gains at high frequencies, helping to prevent oscillations. If a control system does not contain an integrator naturally (such as a motor), the design engineer will probably add one, if not two, to the system to get the desired performance.

Consequently, when engineers became interested in biological control systems, they took it for granted that integrators were everywhere—how else could all these control systems possibly work? The oculomotor system offers an especially clear example: The retina senses the error between the eye (fovea) and the target, and the system turns the eye until the error is zero—a simple negative feedback scheme (e.g. Young & Stark 1963). Moreover, when the goal is reached, a constant eye deviation (output) is maintained while the error (input) is zero. But that is just what an integrator does—it holds signals in the absence of new information. Indeed, the only way its output can be constant is if the input error is zero—the desired condition. So obviously the oculomotor system had an integrator and to the bioengineer this idea was so obvious as to be trivial.

To the neurophysiologist a neural integrator seemed exotic, but, so long as it only appeared in top-down, black-box models, it could be relegated to "higher centers" and ignored. This was not, however, the case for the vestibulo-ocular reflex. By the early 1960s, it was clear that the signal from the semicircular canals, coded in the rate modulation of the primary afferents, was head velocity. The discharge rate of motoneurons, on the other hand, largely determined eye position. If a constant head velocity is to make the eyes move at a constant velocity, the motoneurons must respond to the time integral of the canal signal. This integrator was not hidden under a feedback loop—it was the major signal-processing element in a short, well-defined, pontine reflex. It could not be ignored without also ignoring the main function of the reflex.

Still, it was not until 1968 that this obvious observation first appeared, however briefly, in print (Robinson 1968). Soon thereafter neurophysiological evidence appeared. Cohen & Komatsuzaki (1972) found that electrical stimulation of the reticular formation caused the eyes of monkeys to move at a constant velocity—the time integral of the step of excitation. We know now that they were stimulating an input to the integrator (from saccadic burst neurons), not the integrator itself, but no matter; integration was clearly occurring. It was also confirmed that motoneurons were responsible for determining the position of the eye (Robinson 1970), and by recording from them during sinusoidal rotations of monkeys we demonstrated the requisite 90 deg phase lag between vestibular and oculomotor motoneurons created by the integrator (Skavenski & Robinson 1973).

Although the integrator's existence was not open to question simply on theoretical grounds, these findings lent a sort of respectability to the idea and helped in making clear the integrator's essential role. The concept was readily accepted in neuro-ophthalmology; after all, it is the neural integrator that generates the slow phases of nystagmus and holds the eye eccentrically after a saccade. Disorders of these basic operations could now be attributed to the integrator.

THE NEURAL INTEGRATOR IN THE VESTIBULO-OCULAR REFLEX

Figure 1 shows the signal processing involved in the reflex. On the right, the canal produces, in the frequency range of physiological head movements, a signal proportional to head velocity, $\dot{H}(t)$, coded in the discharge-rate modulation, R_{vl}, of primary vestibular afferents. The background rate (90 spikes/sec) and sensitivity [0.4 (spikes/sec)/(deg/sec)] are taken from Fernandez & Goldberg (1971). On the left is shown the well-established relationship between the modulation of motoneuron discharge rate, ΔR_m

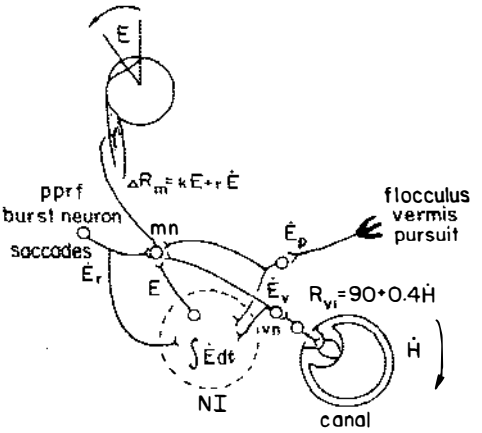

Figure 1 The final common integrator. On the *right* the canals transduce head velocity, $\dot{H}$, and report it, coded as the modulation of the discharge rate, R_{vl}, of primary vestibular afferents to the vestibular nucleus, vn. This signal becomes an eye velocity command for vestibular movements, $\dot{E}_v$, which is sent directly to the motoneurons, mn, and to the neural integrator, NI, to provide the needed position signal E. These signals provide those needed by the motoneurons modulating by ΔR_m. The pursuit and saccadic signals also arrive as eye velocity commands, $\dot{E}_p$ and $\dot{E}_r$, from the cerebellum (flocculus, vermis) and paramedian pontine reticular formation (pprf), respectively, and are also sent to the motoneurons and the neural integrator. The latter is contained in the nucleus prepositus hypoglossi and the vestibular nuclei (*dashed lines*).

(around a background rate of typically 100 spikes/sec), and eye position and velocity. The coefficient k is the neural reflection of the elasticity of the orbital tissues while r represents orbital viscosity. Typical values are 4 (spikes/sec)/deg and 1.0 (spikes/sec)/(deg/sec), respectively.

For a vestibular command, the motoneurons need a signal proportional to desired eye velocity ($\dot{E}_v$ in this case) and desired eye position $E(t)$. The former can obviously be obtained directly from the vestibular nucleus by the direct path shown. This agrees, fortunately, with the anatomical fact that the neurons in the vestibular nucleus project directly to the motoneurons to form the well-known three-neuron arc.

The signal E, on the other hand, is the integral of $\dot{E}$, and, no matter how it is done, the process can be given its mathematical name: integration, labeled NI in Figure 1. Since this operation occurs in the dark when no other sense modality can help, it would appear that a network of neurons in the pons must perform this mathematical operation.

Interestingly, bioengineers themselves felt uncomfortable with the idea of integrating just with neurons and suggested an alternative familiar to engineers—velocity feedback. If the output of a control system is differentiated before being fed back, the overall system behaves like an integrator. So it was proposed that velocity feedback from muscle proprioception could do the trick (e.g. Fender & Nye 1961). We were able to eliminate this hypothesis by showing that there was no mono- or paucisynaptic stretch reflex for the eye muscles of the rhesus monkey (Keller & Robinson 1971). This indicated that integration was done somehow by a network of neurons.

Figure 1 is greatly simplified to emphasize the signal processing. The integrator must be a bilateral structure with its halves coupled across the midline. It receives a push-pull signal from a pair of canals, one canal modulation decreasing the other increasing. It sends a push-pull signal to the motoneurons to modulate the agonist and antagonist muscles in reciprocal innervation.

The integrator does its job well. Figure 1 shows, as discussed below, that a single integrator is shared by all the conjugate oculomotor subsystems. When, for example, the burst neurons create a saccade by sending a pulse of activity directly to the motoneurons, the eye is held in its new position by the step of innervation produced by integrating the pulse. The integrator is not perfect; it leaks and, in the dark, the eye begins sliding back toward the center with a time constant, T_n, of about 25 sec (Becker & Klein 1973). This is so much longer than the interval between most normal eye movements that this imperfection can be largely ignored. Lesions can greatly decrease T_n and create a failure of gaze-holding called gaze-paretic nystagmus.

LOCATION OF THE INTEGRATOR

For a long time the neural integrator was thought to lie in the paramedian pontine reticular formation because lesions there affected eye movements profoundly and the reticular formation seemed a good place for anything mysterious. This idea was finally disproved when Henn and his colleagues made neurotoxin lesions there. Ipsilateral saccades were abolished but not gaze holding (Henn et al 1984). The cerebellum is important in minimizing leak rate. Total cerebellectomy (Robinson 1974), ablation of the flocculus in particular (Zee et al 1981), reduces the time constant T_n to about 1.3 sec. This might tempt one to put the integrator entirely in the cerebellum (Carpenter 1972) except that 1.3 sec is not negligible. During vestibular nystagmus, the integrator need only integrate well from one quick phase to the next (roughly ●.3 sec), and even after total cerebellectomy only close examination will detect such leakiness in nystagmus recordings. Moreover, during ice-water stimulation of one ear, simulating a vestibular lesion, T_n in humans is deliberately decreased to about 2.4 sec within 80 sec of the onset of the inappropriate nystagmus (Robinson et al 1984). The cerebellum may well be responsible for parametric adjustments with this time scale. It is shown below that lesions of the vestibulo-prepositus complex abolish *all* integrator action, so the current thinking is that the integrator is basically in this complex, but the cerebellum has a powerful influence in adjusting its time constant.

Studies of cells in the vestibular nuclei of alert monkeys discovered that a large proportion of cells in the superior and rostral-medial subdivisions carried, among others, the eye position signal E. Many cells are purely oculomotor in that their activity reflects eye movements whether or not of vestibular origin. Thus, significant subdivisions of these nuclei form an eye-movement nucleus. This led Tomlinson & Robinson (1984) to propose this region as the site of the neural integrator. Meanwhile, the nucleus prepositus hypoglossi, right next door, had also been suggested because its cells also carried the eye-position signal and projected directly to motoneurons. Finally, Cheron et al (1986) showed integrator failure after electrolytic lesions of either region in the cat, and Cannon & Robinson (1987) showed in the monkey total loss of the neural integrator after bilateral neurotoxin lesions of both the prepositus and medial vestibular nuclei.

The latter study showed that, as one would predict from Figure 1, without the integrator the eye velocity commands would pass directly to the motoneurons and produce an eye *position* that was proportional to desired eye *velocity*. For a step of head velocity, for example, the step of $\dot{E}_v$, in the absence of the ramp normally generated by the integrator, simply causes a step change in eye position without the usual slow phases of

nystagmus. Similar results occurred with pursuit and optokinetic stimulation. For the saccadic pulse, the eyes moved quickly to one side but, without the usual step from the integrator, the eyes returned rapidly to straight ahead with the time constant of the orbital mechanics (about 200 msec). Consequently, the time constant of the integrator, if any, was significantly less than 0.2 sec. Thus, in addition to locating the integrator, this study showed, as had long been proposed, that a single integrator was used by all conjugate oculomotor systems.

MODELS OF NEURAL INTEGRATORS

If an engineer wants to build an integrator, either rate feedback, mentioned above, or positive feedback are the two usual choices. The former is risky: It requires large gains around the feedback loop so that if, by a lesion, the loop is broken, the output would try to rise to very large values. Positive feedback is more failsafe. One starts with a very leaky integrator with a time constant τ. Positive feedback of gain k around it raises the effective time constant to $\tau/(1-k)$. The integrator becomes perfect when k is 1.0; no large gains are involved, and if feedback is lost, the integrator simply returns to being very leaky. Put another way, if cells excite their neighbors and are excited by them, then cells excite themselves and this perseverates activity, once started, by a "system of reverberating collaterals." To date, this has been the only model seriously considered.

On the other hand, one could, for example, hypothesize a neurotransmitter we could call integratide. When released into the subsynaptic cleft, it binds to the subsynaptic cell membrane and depolarizes it (so the cell fires faster) indefinitely until integratase is released into the cleft to inactivate the integratide and decrease depolarization and firing rate, again indefinitely, until a new signal comes along. One cannot object to this idea because the time constant of the neural integrator can be decreased from 25 to 2.4 sec within 80 sec of caloric stimulation; one need only hypothesize another neuromodulator that breaks down both integratide and integratase with the same suitable rate constant. Unfortunately, such neuromodulatory behavior has not yet been observed. Long-term synaptic changes have been observed in *Aplysia* (Frost et al 1985) but these are changes in sensitivity or gain, a multiplicative operation, quite unlike the linear operation of integration.

Returning to reverberating collaterals or positive feedback, we find two problems arising. The first is that all the signals to be integrated (except the saccadic pulse) ride on a background discharge rate. From Figure 1, the vestibular background rate is 90 spikes/sec. Recordings from other neurons in the region of the integrator (e.g. Tomlinson & Robinson 1984)

show that 100 spikes/sec is typical. We don't want to integrate this background rate, that would be disastrous, just the modulation riding on it. Shamma & Cannon hit upon lateral inhibition as an exceedingly simple way to solve this problem (Cannon et al 1983). In Figure 2A, each neuron inhibits its neighbor with strength w and is inhibited by it. Thus, each cell excites itself by disinhibition—positive feedback. In this scheme, the initial lag τ is the membrane time constant of an individual neuron, about 5 msec. Analysis shows that when both inputs, $u_1(t)$ and $u_2(t)$, change together, the outputs, $x_1(t)$ and $x_2(t)$, respond with a time constant of $\tau/(1+w)$ or, since w is close to 1.0, about 2.5 msec. Thus, the background rates are simply passed through the system unchanged, as shown initially in Figure 2A. But when u_1 and u_2 change in push-pull, by Δu in Figure 2A, x_1 and x_2 differ, the feedback loop starts to operate, and the cells respond with a time constant of $\tau/(1-w)$. If w is very close to 1.0, this time constant can be very large, and integration takes place. It is remarkable that lateral inhibition, a work horse of neural network modelers, solves this problem as well.

The second problem is that to increase the time constant from 5 msec to 20 sec, the value of w must be 0.99975. Of course, if the membrane time constant of these particular neurons was 50 instead of 5 msec, the value of w becomes 0.9975, but this is still hardly robust. On the other hand, no one supposes that two neurons are adequate. Cannon et al (1983) examined a ring of 32 neurons connected as in Figure 2B. Figure 2C shows that the Bode diagram (log gain vs log frequency, ω, if the input were a sinusoid) depends on the spatial frequency, P, of the inputs. If all the cells received the same signal (e.g. the background rate), its spatial frequency would be zero and the network would act like a wide-band, low-gain system with a time constant of 2.5 msec (*front edge* in Figure 2C). If the inputs from left and right canals (or pursuit cells or saccadic burst neurons) are interleaved as shown, one has the highest spatial frequency ($\pi/2$ or one half cycle/neuron), and the system has the Bode diagram of an integrator with a time constant of 20 sec (*back edge* in Figure 2C).

We were able to show that adding spatial noise to such a model (changing synaptic strengths randomly throughout) did little to perturb its integrating behavior. Nothing depended heavily on only a few synapses. Killing one cell (out of 32, 3%) caused the impulse response (a saccade) to drift back quickly by about 15%, because the dead neuron broke local feedback loops with nearby cells, but then to recover and drift toward zero at a rate appropriate to a 20 sec time constant. This result indicated that the major property of the network did not depend critically on any one parameter in the model. The model was robust.

Integration still requires a critical adjustment in a global sense. If $X(s, P)$

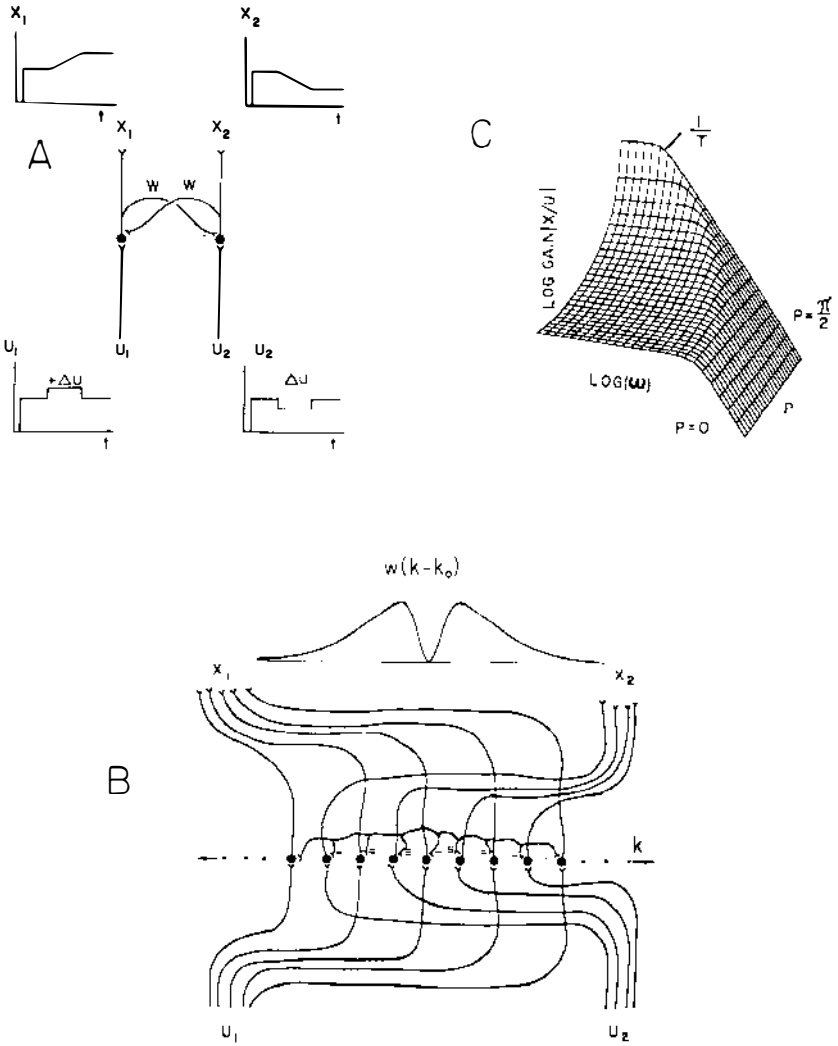

Figure 2 A model of the neural integrator. A: Lateral inhibition. Each cell excites itself (positive feedback) by self-disinhibition through its neighbor. A common input, u_1 and u_2, is not integrated but is simply repeated by the outputs x_1 and x_2. A differential input, on the other hand, such as Δu, is integrated as shown. B: A fuller model with 32 neurons. The spatial variable k runs from 1 to 32. The neuron at k_0 inhibits itself and neighboring cells with the strength $w(k-k_0)$ shown by the double Gaussian curve at the *top*. The inputs enter from push-pull sources and alternate on the neurons to achieve the highest spatial frequency: $\pi/2$ or one half cycle per neuron. C: The Bode diagram of the gain X/U of this network with the spatial frequency of the input P as a third dimension. As P approaches $\pi/2$, the system behaves like an integrator with a time constant T of 20 sec.

and $U(s, P)$ are the transforms of the outputs and inputs, where s is the Laplace transform frequency in the temporal frequency domain and P is the Fourier transform frequency in the spatial frequency domain, then

$$\frac{X(s, P)}{U(s, P)} = \frac{1}{s\tau + [1 - W(P)]} \qquad 2.$$

where $W(P)$ is the Fourier transform of the spatial function of the pattern of lateral inhibition $w(k - k_0)$ shown in Figure 2B. The effective network time constant is $\tau/[1 - W(P)]$ when P is near the highest spatial frequency of one half cycle/neuron. Thus, $W(P)$, encompassing hundreds of cells and hundreds of thousands of synapses, must have a global value of 0.99975.

Of course, any network must be able to have its function monitored and its parameters adjusted. In the case of this integrator one thinks of the cerebellum. Integrator failure results in eye motion during attempted, eccentric fixation. The resulting image motion is sensed by the retina and reported to the inferior olive by way of brainstem visual pathways via the nucleus of the optic tract. The olive reports this signal to the cerebellum, particularly the flocculus, via climbing fibers. The flocculus in turn is well connected to the prepositus-vestibular complex and is known to be involved in several ways in decreasing retinal image motion (Zee et al 1981). Thus, a reasonable hypothesis is that the flocculus monitors the error (retinal slip) and adjusts the connectivity of the integrator network to fine tune its ability to hold eye position. How the latter might be done is quite unknown. The main point here is that in the model of Figure 2, such visual feedback and parametric adaptation should be able to adjust and maintain the time constant of the integrator. Note that moderate changes of many individual synapses still contribute only infinitesimal changes in the global property $W(P)$.

The model in Figure 2B is, of course, much too simple. All the neurons are identical and inhibitory and all the inputs are identical. To show that these conditions could be relaxed, Cannon & Robinson (1985) extended the model. The background discharge rates of the incoming fibers and cells of the network could be allowed to vary over the population in a realistic manner. Most important is that almost all the cells in the prepositus-vestibular complex carry not just the eye position signal E but a variety of combinations of $\dot{E}_r$, $\dot{E}_v$, and $\dot{E}_p$ as well (Figure 1). The model in Figure 2 is not dynamically rich enough to do this; it integrates too well and all the cells just carry E. To provide velocity terms, we used a double-layer model; a row of excitatory and a row of inhibitory cells that talk, in certain ways, to both types of neighbors. This is, of course, a minimal step in the right direction since the integrator output to downstream cells,

especially the motoneurons, must be excitatory as well as inhibitory. Finally, we showed that the integrated signal could spread almost instantly through the whole network, even if the velocity input entered only part of it, so that neurons could carry E while carrying $\dot{E}_r$, $\dot{E}_v$, and $\dot{E}_p$ at quite different strengths, as observed experimentally.

The time is ripe, now that we know the location of the integrator, to test the hypothesis in Figure 2 and to modify it or replace it with a better one. For example, it depends heavily on fibers crossing between the bilateral prepositus-vestibular complexes, similar to a proposal by Galiana & Outerbridge (1984). Preliminary results by T. J. Anastasio and myself, trying to make midline lesions to interrupt these fibers, have met with peculiar results. In only one monkey so far, electrolytic lesions in the midline, in the region 0 to 4 mm caudal to the abducens nuclei and 4 mm deep, did decrease the integrator time constant to 0.6 sec after each lesion, but recovery was significant in just a few hours and more so after two days. Two nagging questions arise: What is the anatomical course of these crossing fibers—did we interrupt them? What pathways and mechanisms mediate this incredible capacity for repeated recuperation?

Equally important, new models should be proposed by theoreticians to provoke further experimental tests. The operation we are considering is not trivial.

INTEGRATORS ELSEWHERE

The integrator we have considered so far is for horizontal, conjugate eye movements. Vertical eye movements are probably combinations of movements created by two integrators, in part in the caudal mesencephalon, with planes of action near those of the vertical semicircular canals and the vertical recti and oblique muscles. Current findings in the vergence system suggest another integrator there (Mays et al 1986). That's four. Current models of gaze saccades suggest integrating the head velocity signal, $\dot{H}$, to obtain head position, H, needed for internal calculations of eye in space, as opposed to eye in head (e.g. Laurutis & Robinson 1986). That could add three more, one for each degree of freedom. Thus, in the oculomotor system, we can see that there is nothing special about the integrator shown in Figure 1; integrators crop up everywhere.

Can we then conclude that integrators are everywhere in motor control? Before extrapolating too quickly, it is important to appreciate some unusual features of the oculomotor system. Phylogenetically, the vestibulo-ocular reflex has dominated its development. In lateral-eyed, afoveate animals, this reflex and its visual extension, the optokinetic system, rep-

resent almost their entire oculomotor capability. In frontal-eyed, foveate animals, the saccadic, pursuit, and vergence systems were added. The vestibulo-ocular reflex is dominated by the semicircular canals, which are unique sense organs. Although each contains a sheet of sensory neurons (the hair cells), all the receptors report the same signal to the brainstem—that component of the head rotation vector that is perpendicular to the plane of that canal. There are no maps as in the visual, auditory, and somatosensory systems—the signal is entirely one-dimensional. Moreover, the canal signal rides on a high, stable, resting background rate so that modulation both up and down, in push-pull, can occur, thereby avoiding the most severe nonlinearity in the nervous system: Discharge rate cannot be negative. The result is linearity. It has also been shown that the canals have even imposed their planes upon the pulling directions of the extraocular muscles, even in frontal-eyed animals. Thus, the canals have imposed on the oculomotor system (*a*) the pulling directions of the muscles, (*b*) a high background discharge rate, (*c*) push-pull operation (expressed at the motor end by strict reciprocal innervation), (*d*) linearity. These features are exhibited not only by the motoneurons (Figure 1) but by all the interneurons in this reflex.

In the spinal cord, on the other hand, high background rates, reciprocal innervation, and especially linearity, are not the order of the day. Because of cocontraction and the need to handle a wide variety of loads utilizing proprioceptive feedback (unnecessary and not found in the eye), one would not even hope to write an equation, as in Figure 1, between motoneuron discharge rate and load position that was even unique, let alone linear. Nevertheless, this does not mean that it is too soon to think about integrators in the spinal cord. If I point straight ahead with extended arm and hand, what keeps my arm from succumbing to gravity? To say that "tonic signals" form "higher centers" are responsible is simply to avoid the question.

In the cord one can, of course, use position feedback via proprioception to hold a limb still, turning it on only during limb fixation. This is, however, not an integrator; a tonic, central signal is still needed, if only to the γ motoneurons, and where does that come from? One could try to build an integrator by proprioceptive rate feedback, as mentioned above. The major problem with all these speculations is that because recording from single units in the spinal cords of alert, behaving animals is technically difficult, we have almost no idea of the signal processing that goes on there. Working out anatomical pathways and some properties of basic spinal reflexes in immobile animals helps almost not at all in fathoming what the cord does to the signals we see descending from the cerebellum and motor cortex before they reach the motoneurons. Without seeing the signals in the

incredibly rich internuncial networks in the cord, it is difficult to even guess about premotor signal processing.

In the saccadic system, the signal most often seen in supramesencephalic structures is transient, indicating an impending change in eye position, more resembling movement velocity than position. Only when these signals descend to the caudal pons (for horizontal movements) are they converted by an immediately premotor network—the integrator—from velocity to position commands. Similarly, the majority of intracranial signals related to limb movements also seem to be phasic or velocity-related, although this is certainly not always so. If there is any analogy to the saccadic (and pursuit system as well), these phasic signals would be converted to limb position commands at the last minute, namely in the cord close to the motor nuclei. Of course, identification of such a process will be considerably complicated by the wealth of proprioceptive feedback signals, but for those who see value in the bottom-up approach, we will never even start to unravel such mysteries unless we record from premotor neurons in behaving animals and find out what they are telling the motoneurons.

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