combination (*45*). Abelson MuLV, like MSV, originated by recombination of Moloney MuLV with a mouse cell-derived transforming gene (*46*). Surprisingly, during the generation of Abelson MuLV and MSV, the Moloney MuLV genome appears to have undergone recombination at the same point with two different cell-derived genes (*47*). These findings suggest that "hot spots" for recombination exist within the retrovirus genome and have also played a crucial role in their evolution.

Our sequence data here demonstrate that recombination between c-*mos* and helper viral sequences has occurred in the middle of two functional codons of the c-*mos* gene. Hence v-*mos* lacks regulatory signals for its transcription and translation. To render such an incomplete gene biologically active, the helper virus has provided this gene with transcriptional promoter and terminator signals as well as the initiating and terminating codons for translation. Recent findings have shown that molecularly cloned c-*mos* can be rendered biologically active as a transforming gene by the addition of the helper virus LTR (*3*). Detailed structural comparisons of v-*mos* and c-*mos*, as well as analysis of c-*mos* flanking sequences, may provide insights as to how c-*mos* might be transcriptionally activated in naturally occurring tumors.

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An Efference Copy Which is Modified by Reafferent Input

Abstract. *In electric fish of the mormyrid family, an efference copy is present in the brain region that receives afferent input from ampullary electroreceptors. The efference copy is elicited by the motor command to fire the electric organ. Its effect is always opposite that of ampullary afferents responding to the electric organ discharge, and it changes to match variations in this afferent input. It probably reduces the central effects of activity in ampullary receptors evoked by the electric organ discharge.*

The motor behavior of an animal will normally elicit activity in its own receptors and sensory afferents. This self-induced sensory input was termed reafference by von Holst and Mittelstaedt (*1*). An animal must always distinguish between such reafferent input and sensory input from external sources. Behavioral experiments of von Holst and Mittelstaedt (*1*) and Sperry (*2*) suggested that the problem is solved by signals from motor centers to sensory receiving areas; these signals prepare such areas for the expected reafference. Such signals were termed "efference copies" by von Holst and Mittelstaedt and "corollary discharges" by Sperry. Effects of motor commands on sensory centers have since been seen physiologically in a variety of preparations (*3–6*).

In many sensory-motor systems, reafferent input must be nullified to prevent inappropriate reflexes or interference with detection of external sources of stimulation. In the lateral line system of fish and amphibia (*4*), the crayfish escape response (*3*), or the knollenorgan electroreceptor afferents in mormyrids (*5*), the motor command briefly inhibits the expected reafference. Such a simple inhibition does not seem functionally useful, however, when the effects of the motor act are complex and of long duration. Von Holst and Mittelstaedt (*1*) and Sperry (*2*) argued that the inhibition of the reafference during voluntary movement could not explain their results. They inferred instead that a kind of negative image of the expected reafference is conveyed to the sensory centers. Such an image could be excitatory, inhibitory, or both. When summed with the actual sensory input, the result is a nulling or reduction of the effect of the reafference. This report describes an efference copy of the latter type in electric fish.

There are three distinct types of electroreceptors in mormyrids: mormyromasts, knollenorgans, and ampullary receptors (*7*). All three types respond, with different time courses, to the electric organ discharge (EOD). However, only the responses of mormyromasts seem to be involved in measuring object-induced distortions in the electric field created by the EOD, that is, in active electrolocation (*7–9*). Knollenorgans probably assist in detecting the EOD's of other fish, that is, in communication. Ampullary receptors in mormyrids, like similar receptors in catfish or sharks, measure the low-frequency external electric fields generated by other aquatic animals (*10*). Afferents from the three types of electrore-

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ceptors terminate centrally in different parts of the posterior lateral line lobe (PLLL), a large medullary roof structure.

Curare blocks the synapse between motoneurons and the electric organ, but a synchronized volley in these motoneurons, which would normally elicit an EOD, can still be recorded from the surface of the tail. This volley, or command signal, is the final stage of the motor command which evokes the EOD. It can be used to trigger electrical pulses in the water, mimicking some aspects of the EOD. The waveform of such pulses, as well as their delay with respect to the command signal, can be varied. Using this method, Zipser and Bennett (*5*) showed that the EOD motor command affects both mormyromast and knollenorgan receiving cells in PLLL at the time when EOD-evoked activity in the primary afferents would normally arrive at these cells. Most mormyromast responses are facilitated, whereas knollenorgan ones are inhibited. Such effects are functionally appropriate since mormyromast responses evoked by the fish's own EOD inform it about external conductances, whereas self-induced knollenorgan responses convey little information and could disrupt the detection of the EOD's of other fish. Responses of ampullary afferents to the EOD also seem to convey little information (*9*) and could interfere with sensing the external signals to which ampullary receptors are particularly sensitive. In this report I show that the motor command in the ampullary receiving area reduces the effect of EOD responses by generating an efference copy, which is opposite in sign to the primary afferent response to the EOD. Furthermore, this efference copy changes to match variations in the afferent input evoked at the time of the EOD.

Fifteen fish of the mormyrid species *Gnathonemus petersii* were studied. Fish were anesthetized [Triaine (MS-222), 1:20,000] and held against a wax block with the dorsal surface of the head above the water. The brain was exposed posteriorly and the valvula cerebelli reflected forward. Curare (0.1 mg) was then injected intramuscularly. The fish was respired with a constant flow of fresh, aerated water to remove the anesthetic. The command signal was recorded with a wire placed over the electric organ (Fig. 1). Cells were recorded extracellularly in the ventral lateral zone of the PLLL, where ampullary afferents project (*11*), with metal-filled platinum blacked glass electrodes. Whole-body stimulation was delivered between a silver wire along the wall of the chamber

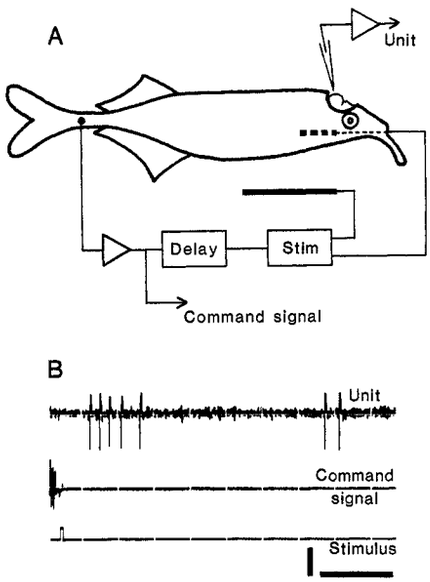

Fig. 1. (A) Experimental arrangement. (B) Recording of a single unit in the ampullary receiving area of PLLL discharging in relation to the command signal and a paired stimulus. Vertical scale bar, 300 μV for the top trace and 150 μV for the middle trace. Horizontal scale bar, 40 msec.

and a silver ball placed in the stomach by means of a wire through the mouth. Long duration (200 to 400 msec) outside positive or outside negative stimuli were used to identify ampullary cells and to determine which polarity activated them. Brief pulses (0.5 to 2 msec) of both polarities were used to mimic the effect of the EOD. Such pulses were usually given at the time when the EOD would have occurred in the absence of curare (1.5 msec after the command signal) (Fig. 1). Controls were also run with pulses at delays of 60 msec to 1 second by means of a digital delay line. The digital delay line made it possible to trigger a stimulus with every command signal, even at delays much longer than the intercommand signal intervals. Stimuli were constant current pulses in the range of 1 to 10 μA. In some cases, local stimuli were delivered to the skin with a pair of chlorided silver balls 3 mm apart.

Like primary ampullary afferents, the secondary ampullary cells are tonically active. Two types of cells are seen, "outside positive" and "outside negative" (*12*). The discharge rate of outside positive cells is accelerated by stimuli of long duration when the outside electrode is positive and slowed when the outside electrode is negative. This response polarity is the same as that of primary afferents (*10*). Outside negative cells respond in a manner opposite that of outside positive cells and primary afferents. Like primary afferents, the central cells of both types show OFF responses on the cessation of long duration stimuli. OFF responses are opposite to the effect during the stimulus. The effect of brief pulses (or of the EOD) on primary afferents or central cells combines the effect of the stimulus itself and the OFF response. Thus, an outside positive pulse causes an acceleration-deceleration sequence in primary afferents (*9*) and in outside positive cells, but a deceleration-acceleration sequence in outside negative cells (Fig. 2B). In each case, an outside negative pulse has opposite effects (Fig. 2G). A previous study (*9*) showed that in most primary afferents the EOD had the same effect as an outside positive pulse—an acceleration-deceleration—but that in a few afferents it evoked an opposite response.

The responses of most cells (31/36) to the command alone depended on the recent history of stimulation; that is, they showed plasticity. When no electrical stimulus had been given for 10 minutes or more, discharge rates were generally unaffected by the command alone (Fig. 2, A, F, and J). Immediately after 2 to 10 minutes of pairing a stimulus pulse with the command at a delay of 1.5 msec, however, there was a clear effect of the command on the cell (Fig. 2, D and I). This poststimulatory effect of command alone then declined over a period of 2 minutes or more in the continued absence of evoked afferent activity (Fig. 2, E and J). In every case, the poststimulatory influence of the command was similar in duration but opposite in effect to that of the stimulus. For example, if the stimulus evoked an acceleration-deceleration sequence, the command alone evoked a deceleration-acceleration sequence after cessation of the paired stimulus (Fig. 2I). This was true for outside positive and outside negative cells and for both stimulus polarities. The same cell could show opposite responses to the command alone depending on the polarity of the stimulus pulse that had just been paired with the command (compare Fig. 2D and Fig. 2I). Of the 21 cells that showed plasticity and that were tested with both stimulus polarities, all but two showed plasticity in both directions. In most cells, the effect of command plus stimulus was greater initially than after a few minutes of pairing (compare Fig. 2B with Fig. 2C and Fig. 2G with Fig. 2H). This result could be expected since command alone had little effect initially but a clear effect, opposite that of the stimulus, after pairing. Indeed, this reduction of the effect of the stimulus, normally the EOD, on the secondary cells can be suggested as a func-

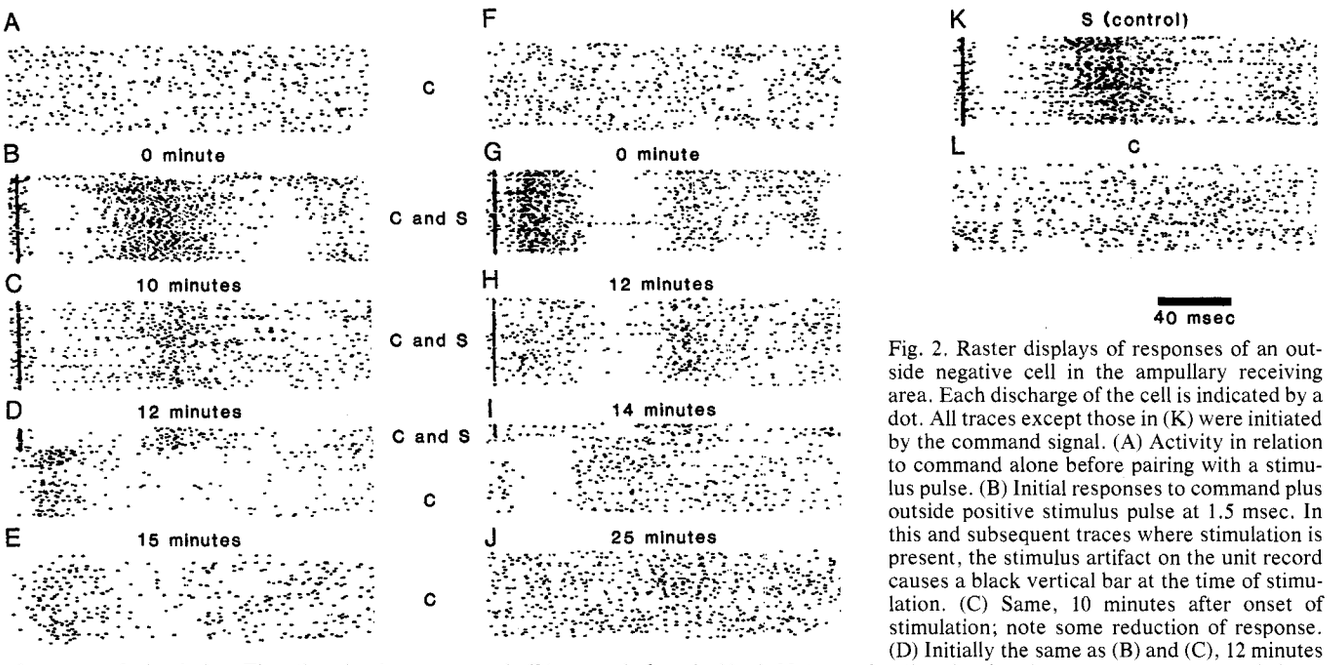

Fig. 2. Raster displays of responses of an outside negative cell in the ampullary receiving area. Each discharge of the cell is indicated by a dot. All traces except those in (K) were initiated by the command signal. (A) Activity in relation to command alone before pairing with a stimulus pulse. (B) Initial responses to command plus outside positive stimulus pulse at 1.5 msec. In this and subsequent traces where stimulation is present, the stimulus artifact on the unit record causes a black vertical bar at the time of stimulation. (C) Same, 10 minutes after onset of stimulation; note some reduction of response. (D) Initially the same as (B) and (C), 12 minutes after onset of stimulation. Then the stimulus was turned off (note end of vertical bar). Note acceleration-deceleration response to command alone. (E) Same, 1 minute after end of (D); response to command alone is present but less prominent. (F) Activity in relation to command (*C*) alone before pairing with outside negative pulse. Traces in (F) were taken 16 minutes after those in (E); command no longer elicits a response. (G) Initial responses to command plus outside negative pulse. (H) Some 12 minutes after onset of pairing; note reduction of response. (I) Initially same as (G) and (H), 14 minutes after stimulus (*S*) onset, then stimulus turned off. Response to command alone is a pause followed by a slight acceleration. (J) Activity in relation to command alone 9 minutes after end of (I). Response to command alone is gone. (K) Sweep initiated just before stimulus. Stimulus is outside positive pulse with same intensity as in (B), but given 600 msec after command signal. Responses similar to those in (B). (L) Responses to command alone immediately after 10 minutes of stimulation as in (K). Compare with (D); note lack of response.

tion of the efference copy. The lack of effect of command alone after several minutes without stimulation is consistent with this suggestion in that an absence of stimulation is equivalent in the normal animal to an absence of a response to the EOD in ampullary receptors. The latter has been seen at low water resistivities (*9*).

The effect of pairing the command with a stimulus on subsequent responses to the command alone depends on close temporal proximity to the command; it is not due to a nonspecific cause such as sensitization or dishabituation. The fact that the effect of command alone can reverse, depending on the stimulus with which it is paired, argues against nonspecificity. In addition, controls were run in which the stimulus was given at either a fixed rate (three per second), similar to the spontaneous rate of the command, or at long fixed delays after the command. Because of the variability in rate of the spontaneously generated command, stimuli given at fixed delays of 600 msec or more seem to occur randomly with respect to the most recent command signal. Controls were run in 16 of the cells which showed plasticity—4 with stimuli with fixed rate and 12 with stimuli with fixed delay. The control stimulation period lasted 3 to 10 minutes, as in the experimental series. No effects of the command alone were seen at the end of the stimulus period with either fixed rate or with fixed delay at delays greater than 500 msec (13 cells) (Fig. 2, K and L). Slight effects were seen in some cases with shorter delays of 60, 120, or 140 msec (three cells).

It is unlikely that the command exerts it effects by way of the primary afferents since electroreceptors, and in particular ampullary receptors, do not seem to receive efferents (*13*). Nevertheless, this possibility was tested by recording from 16 primary ampullary afferents. Afferents were recorded at their terminals in PLLL, 200 to 300 μm deep to the layer where cells were recorded. They were confirmed to be afferents by briefly recording simultaneously from the terminal and from the receptor pore on the skin (*7*). None of the primary afferents responded to the command alone, in spite of 10 to 15 minutes of pairing at the appropriate delay of 1.5 msec. Both negative and positive pulses were tested with each afferent. Thus, the command exerts its effects by a central pathway. Whether the changes that are seen are occurring in PLLL or some other center remains to be seen.

An adaptive efference copy in the ampullary region is useful in minimizing unwanted reafference because the responses of primary ampullary afferents to the EOD can change. This will occur with changes in water resistivity (*9*) or with proximity of nonconducting boundaries. An efference copy that depends on the sensory consequences of an associated motor act could also be useful in more common sensory-motor systems. The EOD is an unusual motor act, however, in that the brief volley from motoneurons to electric organ is always the same. Thus, changes in the efference copy can be due only to a change in reafference and not to a change in motoneuronal activity. It would be more difficult to make such a conclusion in ordinary motor systems, however, where the output is graded and complex.

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A New Laser Scanning System for Measuring Action Potential Propagation in the Heart

Abstract. *A rapid laser scanning system was developed to map the spread of excitation in amphibian and mammalian hearts stained with fluorescent dye. Isochronic maps of conduction were constructed by timing the upstroke of the optical action potential; 128 sites could be scanned in 4 milliseconds. The accuracy of this technique was verified by recording simultaneously from 16 unipolar electrodes placed in different areas of the heart. Conducted action potentials in normal frog heart propagated at 0.1 meter per second. Propagation of action potentials was also monitored in ischemic cat heart, in which both driven and arrhythmic action potential upstrokes could be tracked. The results suggest that this system is capable of scanning the normal and abnormal spread of electrical activity in the heart.*

Voltage-sensitive fluorescent and absorption dyes are regularly used to measure action potentials in a variety of excitable tissues (*1–7*). Previously we suggested (*8*) that optical scanning of electrical activity in the heart would be possible if the signal-to-noise ratios of the voltage-sensitive dyes were improved and a sufficiently rapid and versatile scanning system were developed. We now describe a new laser scanning system for mapping the spread of electrical activity in the heart. The system is capable of monitoring changes in membrane potential from 128 to 512 locations in 4 to 16 msec. Amphibian atrium and ventricle and mammalian whole ventricles were scanned optically for the action potential upstroke, and activation maps were constructed. Simultaneous measurements from a grid of 16 Ag-AgCl electrodes and suppression of contraction by using Ca antagonist (Diltiazem, Marion Laboratories) or no Ca^{2+} suggest that the laser scanning system measures the propagation of action potential upstrokes rapidly and reliably, with good spatial and temporal resolution.

The heart of a bullfrog (*Rana catesbeiana*) was removed and perfused through the sinus venosus with Ringer solution containing 116 m*M* NaCl, 3 m*M* KCl, 2 m*M* $NaHCO_3$, and 1 m*M* $CaCl_2$. Ringer solution containing 0.1 mg of WW-781 dye (*9*) per milliliter was admitted to the heart and withdrawn after 5 minutes. The change in fluorescence produced by a single action potential was about 10 percent for the wavelengths collected above 645 nm. In some experiments the intact heart was optically scanned. In experiments that required preparation of a ventricular flap, the ventricle was freed of the atria and opened by incisions along both sides. Numerous fibers crisscrossing the inside of the heart were cut to permit spreading of the ventricular flaps. Such a preparation was pinned onto the Sylgard bottom of a black Perspex dish. Protruding through the dish and flush with the exposed Sylgard surface were 16 Ag-AgCl electrodes (diameter, 500 μm), which were used to record unipolar electrograms or to deliver electrical shocks to the heart. The dish was positioned under the photodetector optics, allowing the laser scanning beam to impinge on the tissue at a small angle from the perpendicular. The He-Ne laser beam was focused to a 130-μm spot with an incident intensity of about 7 mW.

The laser (Jodon HN-20) provides a monochromatic beam of 20 mW at a wavelength of 632.8 nm, with < 0.5 percent (root-mean-square) noise from 120 Hz to 100 kHz. The rapid positioning of the laser beam was achieved by a pair of acousto-optical devices (Intra Action Corp.) (*10, 11*). It was possible to point the laser spot randomly at any part of the heart on a 128-point grid within 5 μsec. The fluorescence elicited from dye-stained tissue was collected and focused through a cut-on filter (Schott RG 645) onto a photodiode (UDT Pin-10). The photodiode signal was processed by a high-bandwidth amplifier (settling time, 25 μsec). Each acousto-optic device deflects the laser beam along one of the perpendicular scan axes to an extent determined by the control signals. The control signals are generated by the scan controller interface under the supervision of programs running within the computer. The actual scan is performed by repeatedly cycling through a list of coordinates, pausing at each site to digitize a fluorescence level and store the reading. Each coordinate corresponds to a site

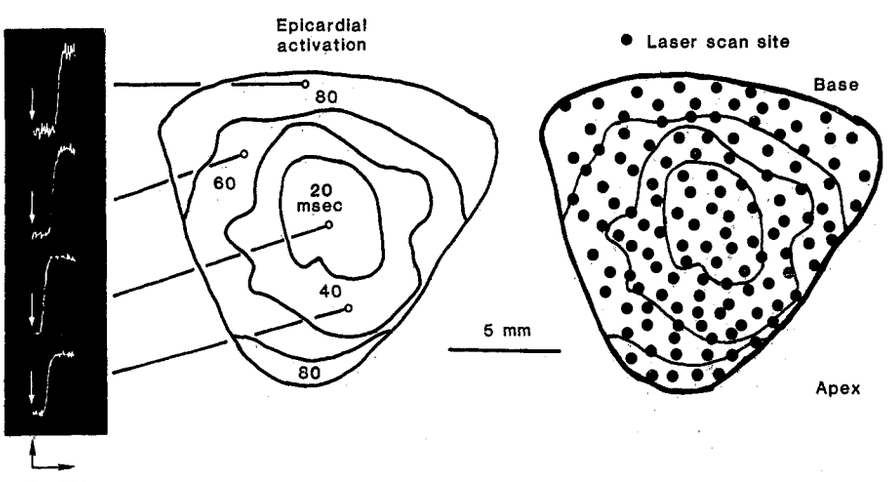

Fig. 1. Epicardial activation in an atrially paced bullfrog ventricle. The map in the center shows contours of activation moments, or isochrones, for action potentials monitored on the epicardial surface of an intact, continuously perfused heart in a Langendorff-type setup. All action potentials occurring 20 msec before the labeled time or sooner are included in a given zone. On the right the same isochrones are shown with dots indicating the 128 sites where action potential upstrokes were recorded and from which the map was constructed. On the left are action potential upstrokes obtained from the sites indicated by open circles and shown as starting at time 0 (white arrows) and continuing for 250 msec. Activation moments were timed as the midpoint of the upstroke of the action potential. Concentration of calcium in the perfusate was 1.0 m*M*; temperature, 20°C.

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