WHAT CAN NEURONS DO TO SERVE AS INTEGRATING DEVICES?

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Abstract

This communication describes several ways that markedly enhance the classical view of the nerve cell as an integrating unit, and make understanding it much harder.

The first section (I) refers to the morphological variety under the light microscope of neurons and synapses. The second (II) concerns action potentials (AP's); it stresses the restricted validity of the all-or-nothing law violated by pervasive changes (e.g., in amplitude, shape, velocity and threshold) when either reaching non-cylindrical regions (e.g., initial segment, soma, dendrites, branch points, terminals) or when the membrane's properties shift. It describes also how excitability after an AP can fluctuate down and up, reflect several firings and follow different cycles in axon, soma, etc. AP's with special shapes and neurons that do not spike are mentioned. In section III the great variety of PSP's is stressed, in general and from the viewpoint of those elicited in or by a particular neuron. Some reasons for this variability are multiple transmitters, dissimilar terminals, and heterogeneous postsynaptic susceptibilities. The polyphasic nature of even the simplest PSP rate effects is noted, as are the complex, often counterintuitive consequences of presynaptic rate modulations. Section III also describes how synaptic events leave traces that modify subsequent ones causing durable non-stationarities (e.g., facilitation, reduction, etc.). Section IV describes intrinsic mechanisms sufficient for neurons to fire regularly, as pacemakers or in bursts. Section V calls attention to a broad category of neuronal interactions that imply cross-effects between axons, somata, and/or dendrites, including primary afferent depolarization, the dorsal root reflex, presynaptic inhibition, heterosynaptic facilitation and counter-current influences. Section VI describes electrical synapses, i.e., interneuronal pathways of low electrical resistance commonly embodied by dendro-dendritic nexuses. Finally, section VII lists the possible consequences of such factors as electric fields, cyclic nucleotides and second messengers, etc.

Not all dimensions have the same generality and importance: some (e.g., the morphological heterogeneity, the distribution of AP's and their not-all-or-

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nothing nature, the PSP features and the variety of neuronal interactions) have well recognized significance; others await final judgments. In any case, their joint reiteration seems opportune as a reminder that the CNS is not simple, as an aid to better understanding of its operation, and as an overall context against which the manipulations at the more basic levels become meaningful.

"Integration", as used by neurophysiologists, refers to the transformation, mapping, or coding across a neural entity (neuron, circuit, nucleus, etc.) from the influences acting upon it to its own manifestations, i.e., to its input-output relation. To describe the neuron as an integrating device, our starting point is the legitimate though simplistic view that a neuron has four functional components: first, a dendrosomatic input pole where it is influenced by other cells; next, a decision-making element at the trigger zone in the initial axon where, on the basis of whether PSPs have carried the membrane potential MP beyond threshold, the alternative is resolved between firing or not firing an action potential AP. Third, the axon provides an active somatofugal conductor of AP's. Finally, axonic terminals constitute an output pole through which it acts upon other cells. This is but a first approximation, however, and it is indispensable to consider other mechanisms (several are described here). Their power and pervasiveness justify the realistic statement by Bullock, Orkand and Grinnell (1977) that, "The neuron is like a miniature person — having a personality, having an array of unlike parts, having actions both spontaneous and upon stimulation. Its actions depend on the convergence of steady states, transient events, built-in weighting factors and intrinsic tendencies; it speaks finally with one voice, which integrates all that went before." One might differ with the notion of a single voice, but certainly not with the rest.

The goal is not to list all, or even the most important, dimensions of neuronal integration. Indeed, this would be a hopeless task because of its magnitude and inevitable out-of-date nature. Moreover, not all phenomena presented have the same generality or importance: some, such as the heterogeneous morphology, the AP distribution over the neuron, the PSP features and the variety of other neuronal interactions, have well demonstrated functional significance; others still await a final judgment. The references included are restricted to the essential minimum illustrating phenomena or identifying figure sources.

This joint reiteration and review of certain dimensions appears opportune, nevertheless, in the hope of contributing to their diffusion, and as a warning against oversimplified and/or misleading explanations of how the central nervous system (CNS) works. Furthermore, this current opportunity for translation to such a level of understanding is useful to explain many spectacular manipulations such as, for example, those achieved by molecular biologists.

1. Morphological heterogeneity of nerve cells and synapses

Neurons exhibit under the light microscope a huge variety of shapes, departing substantially and frequently from forms such as the long-axon neuron (Fig. 1A) with arborized dendrites and a remotely-projecting axon. Similarly, axo-somatic and axo-dendritic synapses exhibit many departures from the conical bouton (Fig. 2A) whose base is applied to the postsynaptic surface. These, though common, often are mistakenly attributed excessive generality.

Fig. 1 shows some neuronal prototypes. A "monopolar" neuron (B) has a single axon-like process (a) that emits collaterals to, say, the periphery and motor neurons. C is a "bipolar" neuron whose soma provides a dendrite with distal branches and an axon that proceeds towards the CNS. D is a "Purkinje" cell with at one end several dendritic trunks branching profusely and at the other the axon. E is a "short axon cell", common in striate body and cerebral or cerebellar cortices, whose axon does not exceed the dendritic domain: it raises the issue of the relation between axon length, space constant, and the extent of propagation of each AP. Axonless "amacrine" cells (F), described by classical histologists with few comments (e.g., Retzius, 1893), have been identified widely (retina, olfactory bulb, thalamus, cerebral cortex, etc.).

The presynaptic fiber, near its ending, usually divides and again into branches of diminishing diameters that may exhibit varicosities, narrowings, thickenings, etc., and vary enormously from one fiber to another. In some (Fig. 2B), the axon forms a
sparse brush of knotty branches that contact few cells. In others (C), it forms an abundant scaffolding that holds several cells. Yet others form "glomeruli", complex knots wherein converge axonic and dendritic branches whose intermingling suggests multiple interactions.

The extreme endings or terminals apply themselves upon other cells — neuron, receptor, effector — adopting different shapes, in spite of their relative ultrastructural uniformity. Some (in skin or motor endplate) exhibit large lateral thickenings. In the oto-lateral system, certain fibers (D) form a single enlargement or "chalyx" that, as a hand, holds one or more postsynaptic cells covering much of their surface: perforated, it allows the passage of other converging axons or of the innervated cell's neurites. Some fibers make staggered contacts starting far from the ending proper. It is possible also that a neuron contacts itself ("autosynapse", E), as that in a posterior column nucleus whose axon collateral contacts its dendrites: if functional, autosynapses could cause recurrent excitation and/or inhibition.


This description was restricted to vertebrates. In an arrangement frequent in invertebrates (Fig. 2F), the arriving fiber branches, and its terminals contact those of a monopolar neuron whose eccentrically located soma lacks synapses and whose axon emerges downwards.

2. Action potentials

A. Character and distribution over the neuron

The AP generated by a particular cell is all-or-nothing and propagates as such under certain circumstances only, and not under many others. Certainly, a particular membrane patch will always generate the same AP if its properties and the stimulus do not change, and the all-or-nothing rule will hold for propagations along similar patches concatenated with the invariant geometry of a cylindrical process. This statement implies constraints, however, that restrict the all-or-nothing law to only part of the time and to just parts of the neuron that, though not unimportant, certainly are not the preeminent ones. This section will survey evidence showing that a single patch generates different kinds of AP's when its properties vary, and that more complex morphologies alter AP propagation. These conditions hold in many important physiological situations, and include major integrating regions such as dendrites, soma, branch points, and terminals.

Numerous experimental observations reveal exceptions to uniform all-or-nothing conduction. In crab nerves, for instance, AP's in one fiber modify the excitability and conduction of adjacent ones, as if these were responding to the local currents in the former, an influence called "ephaptic" (e.g., Arvanitaki, 1942). Moreover, a decrease in the excitability of an individual fiber may lead to what is referred to as "decremental conduction" (e.g., Lorente de Nó and Honrubia, 1958). The individual AP, as it propagates, gradually loses amplitude and velocity, and finally may die out. There is, in addition, an increase in threshold and a decrease in the AP's spatial extent. The response becomes a function of the stimulus strength. Very intense ones cause large AP's that propagate undiminished; weaker stimuli cause responses with lesser amplitude, conduction velocity, and range; very weak stimuli cause the so-called "local responses", active depolarizations that, small and slowly varying, propagate only electrotonically. If a decrementally conducted signal reaches a fully excitable area, it may recover its initial properties, a process referred to as "incremental conduction". In the ionic model membrane conductances are continuous functions of the potential, as they appear to be in nature, and stimuli just below threshold for the usual AP provoke smaller responses with decremental conduction or just local responses: the domain of intensities where this happens is, however, small and hard to encounter in living, cylindrical, and non-modified axons.

Fig. 3 (Decima and Bryant, unpublished) shows decremental conduction in depressed Aplysia axons. Experiments involved recording at two or more points after stimulating either end. In A, with intra-axonic records, the left column corresponds to distal stimulation and distal-proximal AP sequences; the right one, to proximal stimulation and proximal-distal sequences. The upper row is the control in normal
saline (the difference between proximal and distal APs is simply a matter of recordings). The lower one in the depressed axon (in low Na+) shows that, regardless of the propagation sense, the farther from the stimulus (i.e., the later) potential is smaller than the closer (i.e., the earlier) one. In B, with extracellular recordings, stimulations are distal. The AP close to the stimulus (upper record) and that far from

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**Fig. 3. Decremental conduction of APs.** Aplysia axon, recording intra- (A) or extracellular (B) in artificial sea water, 35, 40% Na+ (percentage of normal concentration). (Décima and Bryant, unpublished)

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it (lower) are smaller after depression (b, c, d) than in the control (a). The treated records illustrate also the influence of stimulus magnitude: indeed, intense ones (b) cause large, propagating acceptably AP's; intermediate ones (c), intermediate AP's; weak ones (d), small distal responses that don’t make it to the proximal site. The greater separations between successive AP’s in treated axons (A, B) reveal the diminished conduction velocities.

The significant question of AP propagation through non-cylindrical regions must be posed practically throughout for the dendritic tree and the soma, and at the initial segment, branch points, and terminals for the axon: i.e., for a widespread portion of the neuron that is large and where much of importance goes on. A significant contribution has come from mathematical models and computer simulations (e.g., Goldstein and Rall, 1974; Ramón, Joyner and Moore, 1975): the membrane potential is described by partial differential equations as function of time and place in different regions with pre-specified geometries. This model assumes a uniform membrane, an isopotential extracellular milieu, and long processes with circular cross-sections. Some of the major conclusions follow.

i. Process with a step-like decrease in diameter (Fig. 4)

The AP arrives along the heavy portion H, passes the step S without problems, and continues along the thin portion T at lower velocity. The dotted AP’s are those that would occur were the diameter uniform throughout; the continuous AP’s are those that do occur, that at S preceding, and that at T following, the dotted one. Far from S, the shape of the local AP is practically the same at either side (H, T). Near S and on the heavy side, the current circulating ahead of the AP is opposed by a higher longitudinal resistance in the thin side, and more will circulate across the adjacent membrane; hence, the AP has a faster depolarizing phase and is larger. Fig. 4B, with distance from S on the abscissa and the local voltage on the ordinate, shows how the spatial extent of the AP shifts: initially (1), when the AP is entirely in H, it occupies a larger area than when finally (7) it is in T; when it straddles the step, it shows deformation and notches. The time between AP’s (1) and (2) and that between (6) and (7) are identical, but the 1–2 spatial separation is greater because of the faster propagation. This difference is accentuated around S because just prior to it propagation is faster than along H, and just after it is slower than along T.

ii. Process with a step-like increase in diameter.

There are three possible behaviors that depend on the ratio \(d_2/d_1\) of the diameters \(d_2\) in the heavy portion \(H\) and \(d_1\) in the thin one \(T\). If, at one extreme, \(H\) is barely thicker than \(T - d_2/d_1\) is just over 1 — the AP crosses \(S\) without problems and settles to a higher velocity along \(H\). If, at the other extreme, \(H\) exceeds \(T\) by a lot — \(d_2/d_1\) is large — the AP is blocked at \(S\). Though not reaching threshold, it still will cause some electrotonic depolarization of \(H\), however: a subsequent AP, arriving after one or more blocked ones, may cross \(S\) by taking advantage of such lingering subliminal contributions. The passage of only some AP’s implies that the arriving sequence is
converted into a subsequence, or "filtered": if, say, the former has evenly spaced doublets, the latter could just have evenly spaced AP's.

If \( \frac{d}{dt} \) has intermediate values, the AP on reaching S will cross it and advance along H. In certain cases it will also recede back along T, or "rebound": this happens when the AP crosses S so sluggishly that the immediate wake recovers in time to be re-excited by the hesitating AP at S, and thus initiates an AP rebounding back along T. Fig. 4C shows records from successive, equidistant points along a process whose diameter increases by a step at \( X_0 \). An AP arriving at the .0 point on T passes forward at acceptable velocities through points .6 (AP 2) and 1.2 (3), is delayed and protracted on reaching and straddling point \( X_0 \) at 4, continues along H at higher velocity, and eventually reaches point 7.2 (12). Point 1.2, recovered from its first AP (3), is excited by the delayed, protracted AP (4) in S, and generates its second AP (3') that rebounds along T passing in reverse through .6 (2'), etc. If the recovery of point 1.2 is not complete, the AP may rebound decrementally and simply fade. Regardless of whether it is decremental, the rebounding AP may meet with a subsequent descending AP, and the respective refractory wakes wipe each other out: this, called "collision", also leads to filtering. If a thin segment is interposed between two heavy ones, it is possible that a single AP may rebound from one end to another uneasingly: since, conceivably, it can propagate out through one or both ends, that region may be a generator of evenly spaced AP's.

iii. Process with a gradual reduction in diameter

The sharper the taper, the more this resembles the step reduction (case i). The velocity increase prior to the tapering portion persists in the first part of the latter, decays as the diameter diminishes, finally reaching the value corresponding to the thin end.

iv. Process with a gradual increase in diameter

This case resembles ii: the velocity evolution is opposite to that for iii. When the flare is very sharp and the diameter increase marked, AP's may be blocked.

v. Branch points

Precise mathematical considerations support the intuitive notion that propagation at a branch point where \( n + 1 \) branches meet depends on the relation between their diameters. Specifically, propagation of an AP depends on the quantity

\[
R = (d_o)^{-3/2} \sum_{j=1}^{n} d_j^{3/2},
\]

where \( d_o \) is the diameter of the branch along which an AP arrives; the \( d_j \) are those of the \( n \) remaining branches. There are three cases. If \( R \) is close to 1, the arriving AP changes only slightly in shape and velocity around the branch point, and continues along all other processes; if small, the AP behaves roughly as in a step decrease: if large, the AP behaves as in a step increase.
There are interesting possibilities if AP's arrive almost simultaneously along several branches ($d_{3/2}$ should be replaced by the sum of the $3/2$ powers of the corresponding diameters). If, for example, the first AP passes into all other branches, it collides with the subsequent arrivals; if, on the other hand, it is blocked, its electrotonic repercussions will still interplay with the others. None of these simulations showed selective blocks at certain branches and not others.

Several model behaviors are found in living preparations (e.g., Ramón, Joyner and Moore, 1975). In giant axons of cockroaches, the diameter of an intermediate region is about 75% of that of the rest (Fig. 5, Spira, Yarom and Parnas, 1976). A is the experimental set-up with the axon traversing two thoracic and one abdominal ganglia (T2, T3, A5): the stimulating electrode (ST) initiates AP's, and electrodes R1 and R2 record the potential at the ends of the thin portion. In B, sweeps with the first four AP's of successive 50/s bursts are superimposed: in R2, closer to the stimulus, the AP's arriving at the thin portion are invariant; in R1, at the other end, there are slight amplitude reductions with latency increases in the first and second responses of the burst; they are substituted by small wavelets, sporadic and variable in the third, and

**METATHORACIC GANGL.**

**SYN. INFL.**

**AXON**

**ST**

**R1**

**R2**

**T2**

**T3**

**A5**

**Fig. 5. Step increase in diameter. I. Selective, not all-or-none blockings. Metathoracic ganglion T3, cockroach. A, anatomical diagram showing stimulating (ST) and recording (R) electrodes. B, superimposed sweeps with first four AP's of successive bursts elicited by electrical stimulation through ST 2. (Spira, Yarom and Parnas, 1976)**

constant in the fourth. These wavelets are the repercussions of AP's whose propagation, either all-or-nothing or decremental, is blocked somewhere between R1 and R2.

**Membrane modifications in a particular patch or on passing from one patch to another is another influential issue.** The step increase in diameter is, of course, a factor in the changes illustrated in Fig. 5, but cannot suffice, since the early ones are not blocked; other factors, such as the consequences of the early firings, must participate. The cockroach axon (Fig. 5A) has lateral arbor subject to chemical synaptic effects that, by reducing the membrane's resistance, diminish the safety factor for conduction. Fig. 6A (Spira, Yarom and Parnas, 1976) shows the reliable passage of all AP's in a control low-rate burst; B shows the block of all AP's immediately following a synaptic barrage; C (40 s later) and D (50 s later) are recovery stages where one every two and one every three, respectively, are blocked.

**Fig. 6. Step increase in diameter. II. Blockings induced by synaptic influences. Metathoracic ganglion, cockroach. Bursts as in R2 Fig. 5 prior to (A) and after, B (immediately), C (40 s later), D (45 s) synaptic activation. (Spira, Yarom and Parnas, 1976)**

At a bifurcation in crayfish motoneurons, passage to one daughter branch can be blocked selectively. Fig. 7 (Parnas, 1972) shows the intracellularly recorded EPSP's caused by a single motor axon in the lateral L and median M fibers of an abdominal muscle: EPSP's occur in both at low (40/s), but only in the lateral one at high (50/s) rates. With extracellular recordings close to the median terminal, both arriving AP's (arrow) and EPSP's are identified at 5/s as negative-going deflections; both disappear
at high rates (e.g., 50/s), suggesting that the absence of the EPSP is due to an AP block at the bifurcation.

Fig. 7. Branch point. Selective AP block. Neuromuscular preparation, crayfish. Above, intracellular recordings of EPSP’s in median M and lateral L muscle fibers with stimuli to the single motoneuron at 40/s and 50/s. Cal. 25 ms. Below, extracellular recordings close to the terminals on a median fiber at 5/s (left) and at 50/s (right): the AP’s (arrow) and the EPSP’s are present in the former but not in the latter. (Parnas, 1972).

Careful intra- and extracellular studies have demonstrated that the dendrites of cerebellar Purkinje cells generate AP’s (Llinás and Sugimori, 1980). Fig. 8b shows simultaneous intracellular records from a dendrite D and the soma S of the Purkinje neuron in a slice and under direct microscopic control as illustrated by 8a. Rectangular depolarizing currents injected at the soma trigger two categories of AP’s. One, typified by the very first (horizontal arrow), are large in the soma and small in the dendrites; these AP’s have the standard features, start at the TZ in the initial axon, and are associated with inward Na⁺ currents. The other category, typified by the later ones (oblique arrows), are small in the soma and large in the dendrites; they start at additional trigger zones in the dendrites, and are associated with Ca²⁺ currents. The Purkinje dendritic tree thus has several trigger zones. The AP initiated in a particular dendrite could result from a PSP or from repercuission (active, electrotonic) of a neighboring AP. Fig. 8c (Llinás and Sugimori, 1979) is a hypothetical diagram of a Purkinje cell with TZ’s in black and conceivable AP trajectories of all-or-nothing, continuous or saltatory, decremental or incremental propagation indicated by arrows. Electrical properties favor dendritic propagation towards the soma, but do not preclude the opposite one.

The neuron of crustacean stretch-receptor organs (SRO’s) allows controlled placement of microelectrodes in several of the cell’s regions, thus permitting precise identification of the portions invaded actively by each AP, as well as the temporal profiles of the latter (Fischer, Fischer and David, 1980; Grampp, 1966). This confirmed and extended rigorously conclusions suggested in less favorable preparations such as vertebrate motoneurons.

Fig. 8. Dendritic vs. somatic AP’s in a single neuron. Purkinje cerebellar cell in a slice, guinea pig. a. Experimental set-up. b. AP’s triggered by a depolarizing current step delivered at the soma. c. Hypothetical trigger zones (in black) and AP trajectories (arrows). (a, b, Llinás and Sugimori, 1980; c, Llinás and Sugimori, 1979)

In any region of the SRO neuron (Fig. 9 center, Fisher, Fischer and David, 1980), the intracellular record shows large AP’s; in many, the extracellular one shows the negative deflections that reveal active participation of the subjacent membrane. The wave chronology in different regions reveals the trajectory over the neuron. Fig. 9 (Grampp, 1966) shows antidromic AP’s initiated by shocks to the axon that proceed towards the soma: several sweeps triggered by the stimulus are superimposed. On the left, records are intracellular, axonic (Ax), somatic (S) or dendritic (D). The temporal profile shifts between regions: axonic AP’s have faster ascent and descent and are sharper, higher, and briefer than the others; dendritic ones are the smallest and most protracted; somatic ones are intermediate. The axonic, TZ, and somatic extracellularly recorded AP’s (right) are triphasic with positive-negative-positive phases revealing, respectively, the antidromic AP approaching from the distal axon, its passage under the electrode, and its final progression through to the dendrites. The
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Dendritic extracellular AP is biphasic positive-negative, revealing an AP that approaches from axon and soma and dies out in the dendrites at about 100µm from the soma. There is temporal coincidence, i.e., of the active inward axonic current (negative deflection) with the early passive outward somatic one (positive), and ii. of the inward dendritic current with the late outward somatic one. The dendritic genesis of the last wave is confirmed by its absence after local application of xylazine (Fig. 10, Grampp, 1966).

Spontaneous AP’s in SRO’s basically have the same shapes, localization, and relations as the antidromic ones. They do reveal, however, that their site of origin, i.e., the TZ where the extracellular AP is biphasic negative-positive, is a narrow portion, about 50µm long, located at about 300µm from the initiation of the axon. Fig. 9B — SPONT shows somatic and dendritic AP’s (that trigger sweeps).

Localized stimulation of the axon or soma of the SRO neuron can trigger AP’s. The threshold (measured, say, by the intensity of brief cathodal currents) is minimal at the hillock TZ, intermediate on the axon and high on the soma, with usually no response from the dendrites. Fig. 11 (Ringham, 1971) shows soma, axon, and the identified TZ.

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**Fig. 9. Distribution and regional characteristics of AP’s in a particular neuron.** In Figs. 9, 10 and 11, neuron in the stretch-receptor organ SRO, lobster or crayfish. The central drawing depicts an actual neuron (Fischer, Fischer and David, 1980). Left, intracelluar recordings from axon Ax, soma S and dendrite D. Right, extracellular recordings from soma S and dendrite D. AP’s are initiated by shocks to the axon, except for B-spont where they appear spontaneously. (Grampp, 1966)

**Fig. 10. Dendritic origin of the late positive deflection recorded extracellularly at somatic level.** Elimination by xylazine delivery to the dendrites. (Grampp, 1966)

**Fig. 11. Trigger zone (TZ) in the initial axon (Ax) as it meets the soma (S).** Distance from 3 to 4 68 µm. (Ringham, 1971)
axonic or dendritic), it poses special problems (suggested by the broken arrows) according to the properties of the membrane and the geometry. Moreover, there may be additional trigger zones (small asterisks) at, say, dendritic sites. Individual neurons may comply with all of this general scheme much of the time, or only with parts of it; some in fact may not generate AP's at all (see later).

A basic functional classification of neuronal processes is the following: on the one hand, those that, as appreciable portions of axons, are cylindrical and relatively isolated from other neurons, and whose AP's usually propagate in an all-or-nothing manner; on the other hand, those as dendrites and axon terminals, that are non-uniform geometrically, suffer influences from other neurons and whose AP's usually are not all-or-nothing. The sense of AP propagation — to or from the soma — is only of secondary interest in this electrophysiological classification: in dorsal root ganglion cells, since both branches of the single T-like process are cylindrical, subjected to the few influences and generate all-or-none AP's, both are axons even though one conducts somatopetally. The propagation sense is, of course, necessary to understand the functional role of the neuron: it need not always be the same at a particular cell, however (see V-A).

In short, it is important to remember: (i) that the membrane's properties change because of environmental or synaptic influences, or just because having fired; (ii) that non-cylindrical regions have their own dynamics; and (iii) that parts (or even all) of a

**Fig. 12. Trajectory over the neuron of an AP initiated at a trigger zone (TZ) in the initial axon. General case. (Ax) axon, (S) soma, (D) dendrites, (T) terminals, (BP) branch points. All-or-nothing character predominant only in the white portions of the axon trunks. Dotted arrows imply questionable extent of invasion. Asterisks, large or small, indicate, respectively, the main or the possible additional TZ's.**

**Fig. 13. The recovery of the excitability in a neuron after firing an AP involves both decreases and increases and depends on the timing of several recent firings. A. Giant cell, Aplysia. The cell's excitability is evaluated with a test EPSP that triggers an AP either 50% (open circles) or 100% of the times (black circles); the latter cannot reveal excitability increases. The conditioning stimulus causes the cell to fire, either one AP (A) or a pair of them separated by either 2 s (B, triangles) or 5 s (C, squares). The vertical lines indicate 6 s (broken) or 11 s (dotted) after the first AP of the pair. (Segundo, Moore, Stensaas and Bullock, 1963)**
the excitability of an Aplysia neuron is evaluated by the proportion of times it responds with an AP to a test EPSP. The latter (elicited by stimulating a multifibered connective trunk) is adjusted so that the resting neuron responds with an AP at a particular proportion of times. In A, excitability is followed after a single conditioning AP at time zero. The black symbols resulted from a moderately (50%) effective test EPSP; the excitability becomes successively lower (0%), higher (100%), and lower (20%) than the control (50%); hence, after a single AP, excitability may fluctuate both down and up.

The white symbols resulted from a very (100%) effective test which can reveal only excitability reductions. In B, C, excitability is followed after a pair of conditioning APs, one at time 0, the other earlier (at $-2$ s or $-5$ s). All white symbol graphs (A, B, C) follow successively lower, normal, and lower than the control (100%) values. Coincidences are exclusively qualitative, however, and quantitative discrepancies are substantial. For example, in C, the first recovery and the second drop occur earlier, and the latter is more durable, than those in A and B. Thus, the excitability fluctuations that follow the AP at time 0 depend on whether it stands alone (A) or is preceded by others (B, C), and in the latter case on when they happened (e.g., at $-2$ or $-5$ s). B and C show that, if the test (happening at the times indicated by discontinuous vertical lines) arrives at a particular interval after the first AP of the conditioning pair, its outcome depends on the trio's pattern. Indeed, if the interval is 6 s, the test will not trigger if the second AP of the pair is close to the first (and far from the test) as in B, but will if it is far from the first (and close to the test) as in C.

The same conclusions are reached in a computer simulation based upon the ionic model with squid axon values (Perkel and Segundo, unpublished), and allowing the analysis of membrane potentials (MP's), permeabilities, etc. After an AP, excitability decreases and then increases before returning to normal; the recovery changes if there have been other recent AP's and with their timing. In Fig. 14, the first AP was caused by the stimulus magnitude 250 (arbitrary units) in the lower record; subsequent stimuli were adjusted to cause practically the same MP changes (PA's included) as the first. So as to elicit an AP, a second stimulus required 500 at 4 ms (a, c) and 200 at 8 ms (b, d). Furthermore, and in spite of a more intense stimulus in the first case and a weaker one in the second, the maximum Na+ conductance was less in the former (c) and more in the latter (d). The third stimulus arrived 12 ms after the first, at 8 ms from the second in a, c and at 4 ms in b, d. In a, c a 200 intensity sufficed and caused a greater increase than in b, d with 500. The K+ conductance varied little.

The role played by the EPSP's or the stimuli in Figs. 13, 14 can be played at any synapse by several successive PSP's (forming a "word", Segundo, 1984); its capacity to trigger an AP (or, in the same jargon, be a "password") thus depends on the extant postsynaptic excitability whose value is conditioned by earlier firings. Excitability fluctuations need not be identical at different regions of the same cell, i.e., in TZ, soma, dendrites, and axon (e.g., Gramp, 1966).

When a system is subjected to a step stimulus, its response may reach a maximum almost immediately and then decay gradually toward a practically stationary status. The reduction of the response during the invariant stimulus is called "adaptation". The notion, often applied after step increases at sensory receptors, can be extended without distortion to after shifts in either sense and in any system. If a transmembrane current step is imposed, the discharge changes quickly to then adapt and become acceptably stationary. Fig. 15 (Granit, Kertmess and Shortess, 1963) shows the discharge of a motoneuron submitted to current steps: the heavy graph reflects the current, whose levels are indicated. When depolarizing or hyperpolarizing shifts occur (represented downward from, say, 8.2 to 10.1 or upward from 12.8 to 10.1, respectively), responses exhibit overshoot or undershoot, adaptation and stabilization, as revealed by...
naked-eye evaluation of successive interspike intervals. The relation between the current and the rate in the stationary condition is (beyond threshold) increasing: it also is proportionate, but only locally, because the slope is high close to threshold and low later. Moreover, comparison of stationary portions at 10.1 shows tighter packing of AP's in the right-hand side when the previous current was 8.2 than in the left one when it had been 12.8: this illustrates that the discharge depends not only on the present current intensity, but also on how it was reached, i.e., illustrates hysteresis. When the cell is depolarized and Na⁺ accumulates, adaptation has been attributed partly to an electric pump that hyperpolarizes, in favor is that it is suppressed by metabolic poisons.

Accommodation is the threshold increase (i.e., its positive-wards displacement) during a slowly depolarizing stimulus. It implies that the decision to fire depends not only on the potential level, but also on its rate of change. It has been attributed to a smaller increase in Na⁺ and a greater increase in K⁺ permeability during slowly changing depolarizations. The MP level at which the stimulus takes off is yet another influential issue, as demonstrated by post-anodal excitation.

C. Plateau and hyperpolarizing AP's. Non-spiking neurons

Additional forms of regenerative AP's are observed in, say, smooth muscle fibers. Fig. 16 (Del Castillo and Morales, 1967) is an intracellular record from an esophageal fiber subjected to successive electrical stimuli: while 1 and 2 cause conventional depolarizing, brief AP's, 3 causes a depolarizing plateau AP that can last up to one minute and 4 a hyperpolarizing AP.

![Fig. 16. Different types of AP: regular (1, 2), plateau (3, 5), hyperpolarizing (4). Smooth esophageal muscle, Acaena umbrosoides. (Del Castillo and Morales, 1967)](image)

Certain neurons play their parts without firing AP's. For example, in the motor systems of invertebrates (Fig. 17, Pearson and Fourtner, 1975), the naked eye reveals correlations between the interneuronal polarization levels and motoneuronal discharges. The mechanism, that could be through either electrical or chemical synapses, is as yet unknown. Other examples are the horizontal and bipolar cells of the vertebrate retina.

![Fig. 17. Non-spiking neurons. Cockroach. The slow fluctuations of a non-spiking interneuron correlate with the AP discharge of motoneurons. (Pearson and Fourtner, 1975)](image)

3. Postsynaptic potentials (PSPs)

Neurophysiologists often operate as if convinced, i. that there are exclusively two PSP categories, excitatory and inhibitory, ii. that each causes pure accelerations and slowings, respectively, iii. that their consequences are stationary, and iv. that they become more apparent as the presynaptic discharge becomes more intense. The following strongly qualifies such excessively simplistic views.

A. Non-stationarity and complexity of synaptic effects

The synaptic effects of stationary presynaptic discharges often are non-stationary, and what holds for one portion may not for another. Fig. 18B (Bittner, 1968) displays the amplitudes of PSP's elicited by the single motoneuron in the crayfish claw-opener (A, anatomical diagram), simultaneously in a distal (broken graph) and in a proximal muscle fiber along a 10,000 AP train: stationarity, clear-cut and quite contrasted in much of a 10/s and a 30/s case, is mostly inadmissible elsewhere. The upper graph of 18C (Bittner, 1968) shows EPSP's elicited in a central fiber by AP's that arrive along the excitatory motoneuron at intervals that become shorter and shorter, so that rates are swept up to 100/s: the EPSP, practically invisible initially, increases almost uninterruptedly. The lower graph shows the EPSP's elicited simultaneously in a distal fiber: they are large from the very beginning, and decay slightly. A second axon innervates the same muscle fibers but elicits IPSP's: these too vary as the rate increases and do so in a manner parallel to that of the corresponding EPSP's: D (Atwood and Bittner, 1971) contrasts sizes at 1/s (with 6× greater gain) and other rates.

The non-stationarity of the consequences of stationary presynaptic discharges is illustrated also by Fig. 19 (Kohn, Freitas da Rocha and Segundo, 1981) where the inhibitory axon in the SRO fires during the bar, causing a marked initial postsynaptic slowing, followed by an adaptation up to a stationary period, and at the off, a marked rebound to beyond the prestimulation level with a final adaptation down to about the latter level.
The synaptic influence upon the rate is at least biphasic, slowing-acceleration if involving IPSP's and acceleration-slowing if involving EPSP's. The point is made in Fig. 20 (Segundo, 1984), either (A) with superimposed sweeps showing pre- and postsynaptic discharges and centered on presynaptic spikes, or (B, C) with cross-correlation histograms. The relative magnitude of the phases depends on such factors as the background postsynaptic discharge; e.g., if there is none, the acceleratory effects of E or IPSP's may predominate.

When the presynaptic discharge that elicits IPSP's becomes more intense, the postsynaptic one may become either less or more so. Fig. 21 offers examples of both effects, plotting postsynaptic vs. presynaptic rates: in A, rates are averaged over stationary epochs of pacemaker cells; in B, cycle histograms during periodic presynaptic modulation are displayed in a Lissajous manner (Kohn, Freitas da Rocha and Segundo, 1981; Segundo, 1984).

Adaptation after the end of the synaptic barrage would lead to about the control level, but not quite, because the stationary level at which the postsynaptic discharge...
finally settles at each of a sequence of step presynaptic rate changes depends not only on the present presynaptic discharge but also on how it was achieved, i.e., exhibits hysteresis (see below). Hysteresis under dynamic conditions, illustrated by the loops in Fig. 21B, happens when the presynaptic inhibitory rate is modulated periodically; it exhibits different features according to the latter (e.g., as frequency 1/60 vs. 2/s). It was predicted (Matthysse, 1976) on the basis of thermodynamic and other considerations concerning the relation (Fig. 21C) between GABA concentrations (that reflect presynaptic discharges) and postsynaptic conductances.

Fig. 21. Synaptic rate-effects. II. Slowings and accelerations at a synapse with IPSP's. Post- vs. presynaptic average rates, A, stationary epochs (horizontal arrows in Fig. 19, B, Lissajous displays of cycle histograms, C, Hysteresis in the conductance vs. GABA concentration curve. (A, Kohn Freitas da Rocha and Segundo, 1981, B, Segundo, Tolkmunov and Wolfe, 1976, C, Matthysse, 1976)

B. Variety of PSP types

Contemporary neurophysiology has revealed an impressive variety of PSP's, in which de- and hyperpolarizing phases combine in many patterns. This supports the view (Teorell, 1971) that PSP's are damped oscillations. Those in Fig. 22 (Shimahara and Tauc, 1975) are found in the Aplysia giant cell R2, with de- or hyperpolarizing phases referred to as E or I, respectively, in chronological sequence; besides conventional EPSP's and IPSP's, there are a slow EPSP and several polyphasic ones with fast and slow components, called EIPSP, IEPSP, and IIIPSP. The unitary character, i.e., their reflecting an AP in a single terminal, and the chemical nature of each are practically certain (except for the last representing an electric synapse, see later). The possibility of numerous PSP categories in one single neuron is self-evident.

Fig. 22. Different types of unitary PSP's in a single neuron. Giant cell, Aplysia. (Shimahara and Tauc, 1975)

In certain neuronal pairs of molluscan ganglia, a presynaptic AP causes a double PSP with a brief initial hyperpolarization similar to current IPSP's, and a prolonged one called "inhibition of long duration" (ILD) (Kehoe, 1968): the postsynaptic cells
Fig. 23. AJPSP. HILDA neuron, Apysia. A, C, a presynaptic burst elicits two types of IPSP's. B, only the early and fast IPSP's remain after the late and protracted one has been blocked by TEA. D, only the late IPSP remains after the early ones were blocked by curare. Cal. 20 s, 20 mV, 5 mV. E, ACh electrophoretic injections elicit similar double effects. The early IPSP reverses at -60 mV, the late one at -80 mV. (Kehoe, 1968)

are designated HILDA. Fig. 23A, C shows a short presynaptic AP burst that elicits a postsynaptic sawtooth that reflects the temporal summation of fast IPSP's followed by the slow ILD wave. When the neuron is hyperpolarized, all become depolarizing as genuine chemical PSP's; inversions occur at different levels, the IPSP near the Cl⁻ equilibrium, and the ILD near the K⁺ equilibrium. The upper record of E shows that an electrophoretic application of acetylcholine (ACh) also causes an early brief hyperpolarization followed by a late, protracted one. As the cell is hyperpolarized from -45 to -100 mV, both waves are converted to depolarizations, the initial one at -60 and the other at -80 mV. This plus ionic substitutions and physiological manipulations suggest cholinergic mediations of both effects and that they are associated with changes in Cl⁻ and K⁺ permeabilities, respectively. They differ pharmacologically, since most anti-cholinergic substances block one but not the other.

Fig. 24. EJPSP. Giant cell, Apysia. It is elicited by the AP in another neuron (lower record). (Shimahara and Tauc, 1975)
block the early IPSP's without affecting the ILD (D), itself blocked by TEA that does not modify the other (B).

The giant cell responds with the EIPSP in the upper record to the presynaptic AP in the lower one in Fig. 24 (Shimahara and Tauc, 1975): cells that exhibit such PSP's are called "DILDA". The EPSP component may be mediated by ACh, and the ILD component by dopamine, perhaps with the participation of an electric pump. In vertebrate sympathetic ganglie, preganglionic stimulation causes an EEPSP and, sometimes an EIEPSP: it is thought that both EPSP's are cholinergic — the early one nicotinic, the other muscarinic — but the transmitter for the IPSP is as yet unknown.

The variety of PSP's has many causes, as for example the multiplicity of transmitters and of contact placements and morphologies; contributory also is the fact that different neurons or even separate (but not necessarily remote) points on one neuron may exhibit different chemical susceptibilities. A particular neuron may in fact show receptors whose specificities differ, involving different substances or different responses to the same substance — examples of the former are DILDA cells (ACh, dopamine), and of

the latter the HILDA cells with ACh, as well as others with dopamine or serotonin.

Fig. 25 (Wachtel and Kandel, 1971) has simultaneous records of a presynaptic neuron L10 and a postsynaptic one L7: when the former fires weakly with widely separated AP's, as at both ends of A, it elicits EPSP's; when it fires intensely with tightly packed AP's, as in A's central portion and in B, EPSP's become smaller and soon are substituted by IPSP's. This duality is attributed to differently sensitive ACh receptors upon L7: some mediate EPSP's and soon desensitize if used excessively; others mediate IPSP's and, though not too responsive at rest, sensitize dramatically at high rates.

The temporal profile of a PSP as recorded at a particular site depends simultaneously on the synaptic current that creates it and on the electrical behavior of the membrane, particularly that between the synapse and the recording site (Rall, 1977). This behavior depends jointly on the cell's geometry and on the membrane's properties. On the basis of exclusively passive properties, the observed PSP becomes smaller and takes longer to achieve its peak when the recording site is farther from the synapse: a large PSP with rapid initial phase is one generated by a powerful terminal close to the electrode; a small one, by a remote terminal if slow or and by a close weak terminal if fast. Except for special cases, intracellular recordings are from the soma or large processes. Hence, electrotonic repercussions along processes create another situation where mathematical and computer modeling are justified: conclusions from such efforts are compatible with observations in several living cases. Models imply that the membrane is a simple uniform electrical circuit, that the potential is the same over the entire external surface, and that it is the same over the entire inner surface of the soma. They concentrate on the passive behavior of the process. The active behavior introduces additional issues, of course.

Even though a single membrane patch (or an equipotential soma) and a process (or a predominantly dendritic neuron) can be represented acceptably by simple electrical models (Junge, 1981), the question of how synaptic currents circulate along a dendritic tree with numerous contacts is a difficult one, giving the multiplicity of possible shapes. However, under certain conditions the entire tree can be considered as equivalent to a single cylindrical process (Rall, 1977; Jack, Noble and Tsien, 1975). The condition is that at each branch point, the total diameter of the branches not differ too much from that of the parent one. Expressed precisely:

$$\sum_{k=1}^{m} d_{k}^{2} = D^{2}$$

d_{k} is the diameter of the kth branch, D that of the parent, and m the number of daughters. This conditions is not too restrictive, holding for neurons with tapering dendrites. Fig. 26 (Jack, Noble and Tsien, 1975) shows two stages of this equivalence, first the "neuron" to "a sphere (soma) with several cylindrical neurites (axon, dendrites)", and then that of the latter to "a sphere with a single cylindrical neurite". The basic parameters are the membrane's time constant, the cylinder's length and the ratio of the somatic to the cylinder's resistances. The difficulty of calculations relating to impressed currents of different shapes, particularly if the space and time constants
change along the tree, or when the forcing functions instead of the currents are, say, the conductances submitted to synaptic control, are simplified by breaking up the tree into separate cylindrical compartments.

Some conclusions follow. i. PSP attenuation along the dendrites and towards the soma is less than what might be assumed. ii. Although the attenuation of certain PSP's can be substantially greater (about 95%), their influence is by no means negligible. In fact, weak PSP's become quite significant when they pertain to a set of numerous converging terminals. The degree of correlation between them is crucial: if uncorrelated, they provide a DC-like bias that depends only on their average rate and not on the precise patterns of the individual arrivals (e.g., irregular, in bursts, etc.); contrarily, if tending to fire synchronously, subtle pattern-dependent influences are imposed. iii. The PSP caused in the soma by a synaptic current of a particular magnitude depends exclusively on the synapses-to-soma distance, and not on the number and identity of the affected dendrites. iv. PSP summation often is non-linear (see later). For instance, spatial summation of synapses staggered along a dendrite is more effective when activation starts distally and moves successively to the more proximal ones.

C. Influence of synaptic events upon subsequent ones

The influence of an AP in a presynaptic terminal upon the postsynaptic element may be modified if there have been other recent AP's in that terminal (or even in others): this is reflected by changes in the elicited PSP's. When PSP's are larger than the isolated control, it is said that there is "augmentation, facilitation, or potentiation"; when they are smaller, the terms are "depression, attenuation, anti-facilitation". The influence is called "homsynaptic" or "homologous" if all AP's arrive along the same axon, "heterologous" or "heterosynaptic" otherwise.

A single conditioning AP often suffices for the effect of the test one to be modified. The squid giant synapse (Fig. 27, Charlton and Bittner, 1978) shows the facilitation of the second EPSP caused by a pair of presynaptic AP's (A), and that along a burst (B). In the frog neuromuscular junction (in excess Mg²⁺), a conditioning AP increases the test response (Fig. 28, Hubbard, 1963): the upper records show EPSP pairs; below is the time course of facilitation, together with the roughly parallel increase in the rate of

![Fig. 26. Equivalence neuron-sphere with several cylindrical processes-sphere with single cylindrical process. (Jack, Noble and Tsien, 1975)](image-url)

![Fig. 27. PSP facilitation I. Giant synapse, squid. EPSP's and corresponding presynaptic AP's. A. Pair. B, Burst. Cal 2 mV, 2 ms. (Charlton and Bittner, 1978)](image-url)

![Fig. 28. PSP facilitation II. Neuromuscular preparation (high Mg²⁺), rat. Above: EPSP's pairs at different intervals. Below: EPSP amplitude and minipotential rate as functions of the pair](image-url)
spontaneous mini-potentials. IPSP's attenuate in the SRO neuron (Fig. 29, Jansen, Nå, Ormstad and Walløe, 1971): the first one involves a larger hyperpolarization than any of the later ones (that take off from more negative levels). PSP attenuation can occur at low rates: in Fig. 30 (Castellucci and Kandel, 1974) a sensory Aplysia neuron is stimulated at .1/s and each successive EPSP is smaller than the preceding ones.

Fig. 29. PSP depression I. Neuron in stretch-receptor organ, crayfish. Presynaptic AP's above, PSP's below. (Jansen, Nå, Ormstad and Walløe, 1971)

Fig. 30. PSP depression II. Aplysia ganglion (low Ca$^{2+}$, high Mg$^{2+}$). EPSP's elicited in SN every 10 s by direct stimulation of the presynaptic neuron L7. A illustrates the experimental set-up. (Castellucci

Effects are more marked and lasting when instead of a single conditioning AP there are several. Their influence depends on the number and timing. For instance, when they arrive evenly spaced and very close to each other, constituting a tetanus, their marked and durable consequences are called post-tetanic potentiation PTP. Fig. 31 (Hubbard, 1963) illustrates this in the neuromuscular synapse: graphs show the increase in the test EPSP (and the concomitant mini-potential acceleration). When the tetanus is prolonged, the increase is more durable: nevertheless, potentiation seems to depend less on the total number of conditioning AP's than on their rate.

Fig. 31. PSP facilitation III. Neuromuscular preparation (high Mg$^{2+}$). Rat. Presynaptic bursts at from 20 to 200/s. Above: EPSP burst and (at arrow) test. Below: test EPSP amplitude (block dots) and MP rate as functions of time from conditioning burst. (Hubbard, 1963)

Fig. 32. Post-tetanic potentiation PTP. EPSP amplitude. Biceps-semimembranosus motoneuron (intra-
Fig. 32 (Curtis and Eccles, 1960) shows that in a monosynaptic reflex arc, an afferent tetanus of 3,000 AP's at 400/s (occurring in the hatched portion) causes a potentiation of × 1.8 the control for about 2 m (the black circles are on a different time scale). It may be followed by a depression.

Several factors contribute to modify the PSP elicited by a particular AP. Presynaptic factors act through the transmitter's release. Facilitations, for example, may reflect that an AP increases availability of transmitter. "Availability" is a useful concept estimating how much is released by the test PSP. The changes in the terminal's membrane potential caused by the AP's arrival are important: they evolve in time and extend in space, depending on whether the AP invades, how far it invades, how widespread is its electrotonic repercussion, variables that reflect also the geometry and characteristics of the membrane. In some cases, EPSP facilitation is associated with an AP enlargement: the latter per se is not sufficient, however, because, as shown by Fig. 278 (Charlton and Bittner, 1978), there can be progressive facilitation without AP changes. This contrast suggests that probably mechanisms associated with the most influential currents (i.e., Na⁺, K⁺) have little to do with facilitation, an opinion supported by other results as its persistence after TTX that blocks inward Na⁺ currents. A plausible hypothesis is that facilitation is associated with minor currents, as that of Ca²⁺ for instance, whose changes affect AP's little. Furthermore, Ca²⁺ currents and facilitation have very similar susceptibilities to several manipulations. Hence, a Ca²⁺ related mechanism deserves strong consideration as a facilitating factor: it might involve free Ca²⁺ increases due, for example, to saturation of processes that renew it in the mitochondria or the endoplasmic reticulum, or increases in Ca²⁺ current.

Other factors affect postsynaptic susceptibility. One, very obvious, arises simply from the PSP dependence on the postsynaptic MP (e.g., Fig. 29): a first PSP displaces the MP towards the reversal potential, so a second one soon after will inevitably take off from a level at which it will be smaller. Moreover, the transmitter itself may increase or reduce that susceptibility, effects called "sensitization" and "desensitization", respectively. Responsibility for the late depression after PTT has been assigned to desensitization.

The fact that the PSP's caused by a particular terminal depend on earlier AP's implies that neither the results of summation, temporal if one terminal is involved or spatial if more, can be deduced easily from the single PSP; it cannot be predicted by adding or subtracting the PSP, neither as is nor scaled by a constant factor, i.e., PSP summation is essentially non-linear. Fig. 33A (Segundo, Moore, Stensaas and Bullock, 1963) illustrates the simplest situation, i.e., the homologous pair, with summation. The first EPSP is seen at the beginning of the sweep and along the broken line: its maximum is P1. The second EPSP is recognized by the excess over the first; its maximum is P2, whose relation to P1 is an index of interaction, facilitation if greater and depression if smaller. The distance to the resting level indicates the total contribution: its maximum T2 is an index of temporal summation and depends on both individual contributions — one the tail of the first, the other conditioned by interactions. The efficacy of this pair, judged by whether threshold is achieved and an
may be because selective blocks at branch points determine different trains arriving at separate terminals, as illustrated in Fig. 7. The second cause is the existence of terminals with different properties. Indeed, a neuron may release different amounts of transmitter at separate terminals: an AP in a primary spindle afferent causes EPSP’s worth several mV in DSCT neurons but much smaller in motoneurons. Besides, PSP’s may change differently along the same train, as in crayfish neuromuscular preparations (Fig. 18). Many years ago (Potter, Furshpan and Landis, 1981), Dale cautiously stated that the identity of the transmitter at one terminal of a neuron served as a hint as to that of another of the same cell; years later this was transformed into “Dale’s principle” that claimed that all terminals of a particular neuron used the same transmitter. This opinion, apart from not reflecting Dale’s assertions, is not borne out by the facts, since, for instance, cultivated sympathetic neurons are simultaneously adrenergic and cholinergic at an intermediate development stage; furthermore, it seems highly likely that certain parasympathetic neurons release both ACh and active peptides.

Another cause is that separate postsynaptic elements may react differently to the same transmitter, e.g., that separate neurons have different receptors. An early observation was that ACh depolarizes certain neurons and hyperpolarizes others, categories referred to, respectively, as “D” and “H”. This is illustrated in Fig. 34-A (Gerschenfeld and Tauc, 1961) where a brief electrophoretic injection of ACh (at arrows) depolarizes neuron “D” and hyperpolarizes “H”; 5-HT can have similar effects causing conventional EPSP’s (B) or slow IPSP’s (C) by increasing, respectively, Na⁺ or K⁺ conductances (Gerschenfeld and Stefani, 1966; Paupardin-Tritsch and Gerschenfeld, 1974; Stefani and Gerschenfeld, 1969). A subsequent observation (D, Koester, Mayeri, Liebeswahr and Kandel, 1974), showed that neuron L10 (Aplya) causes IPSP’s in certain cells (e.g., L3) and EPSP’s in others (R19); cholinergic transmission is likely in all contacts. The operational possibilities of such dissimilar diverging connections are many.

4. Intrinsic mechanisms for pacemaker and bursting discharges

It goes without saying that important in a cell’s discharge are the extrinsic influences that impinge upon it. In addition, however, many cells have an intrinsic mechanism that makes them fire.

Some cells produce AP’s at relatively invariant intervals. Both the cells and the discharges are referred to as “regular”, “periodic”, or “pacemaker”. Fig. 35 shows pacemaker records, intracellular in A (Aplya, Junge and Moore, 1965) and extracellular in B (utricule, cat; Vidal, Jeannerod, Lifschitz, Levitan, Rosenberg and Segundo, 1971). There is, of course, some variability from one interval to another, but it is small. Measured, say, by the coefficient of variation (cv), values of .030, and even of around .001, are not rare; measured by the interspike interval histogram, practically all fall into bins tightly packed around a particular value (e.g., 14 ms in Fig. 35B).
In Fig. 35B several superimposed sweeps are triggered by an AP. Regularity reveals itself by the coincidence across all sweeps of equidistant instants where AP’s occur and of the epochs without AP’s: the pacemaker tends to fire “naturally” with an interval N, i.e., a rate 1/N.

It constitutes a representation to the naked eye of how the firing probability varies after an AP. This is quantified by an estimator of that probability, the autocorrelation histogram ACH. As expected, the ACH of a pacemaker (right) is characterized by very high values around a time N from the origin and around its multiples 2N, 3N, ..., and by very low values interposed, characteristics that attenuate as one moves away from the origin. Knowing when an AP occurs and the ACH, it is possible to predict with acceptable precision when other AP’s occurred, particularly those close to the known one.

Fig. 35C includes a very different discharge. When (left) several sweeps are superimposed, the distribution of the AP’s is almost uniform, with little indication of which is the first after the beginning, which is second, etc. Starting at an AP, there practically is no instant where it would be more likely to find another, nor one where it would be less likely; i.e., after an AP, the probability of another is almost constant (as in a Poisson process). The ACH (right) is practically invariant; knowing when an AP occurred says little as to when another will or will not.

The intracellular record in a pacemaker (Fig. 38A) shows that a slow and stereotyped depolarization carries the MP from the undershoot at the end of an AP to threshold and another AP; this depolarization is called “pacemaker potential”. Certain invertebrate pacemakers have been examined with voltage clamp and ionic substitutions (Junge, 1981): the usual Na⁺ (and/or Ca²⁺) and K⁺ currents increase just prior to each AP; in addition, an outward current associated with K⁺ is very intense just after the AP and decays afterwards, first slowly and then rapidly just prior to the next AP.

Other neurons have intrinsic mechanisms that make them fire in bursts. Fig. 36 (Vibert, unpublished) shows such neurons in the respiratory center; their discharge involves short intra-burst and long inter-burst intervals, leading to a bimodal histogram. Usually bursts occur at regular intervals. The intracellular record shows a hyperpolarizing wave during the inter-burst interval. These cells in Aplysia (Junge, 1981) exhibit two relatively invariant currents (one is outward and associated with Na⁺ and Ca²⁺ perhaps intensifying somewhat just prior to the bursts, the other generated by an electrogenic pump) as well as an outward K⁺ current maximum just after the burst. Bursting does not disappear when the pump is blocked, indicating that it is not indispensable; TTX suppresses the AP’s but not the hyperpolarizing wave, which thus uses special Na⁺ channels.

Pacemaker and bursting discharges require certain additional comments. i. All discharges — pacemaker, bursting, or any other, no matter how irregular they appear — exhibit some degree of periodicity, since only the physically unrealizable Poisson process is totally aperiodic. ii. The pacemaker-bursting separation is not cutting, since each pacemaker AP could be considered a burst with one AP. This comment is not just conceptual, since the shift from one discharge to the other is common. iii. Some pacemaker or bursting patterns are determined not by intrinsic mechanisms, but by extrinsic ones, as regularly arriving large PSP’s, many weak independent EPSP’s, or recurrent excitation. iv. The regularity of certain discharges is associated with the periodicity of functions such as respiration, mastication, walking, etc. v. Finally, the interaction between oscillators implies unexpected, even anti-intuitive complexities (e.g., Fig. 22).

5. Other interactions involving somata, dendrites, and/or axons

Invertebrates and vertebrates present dendro-dendritic, dendro-somatic, somato-somatic, and axo-axonic contacts whose closeness is of the order of that in the axo-dendritic and axo-somatic synapses accepted as operational. On the basis of abundant optic and electron microscopic evidence, Clemente Estable (1962) called attention to this, concluding that it was likely that dendrites, somata, and axons received, conducted, and exerted interneuronal influences that could be “reversible” in the sense of acting both ways: hence, he recommended that their functional role should be explored. Examples of the accuracy of this prediction are reviewed below. Fig. 37 (Estable, 1962) illustrates the point: in A, cerebellar granules (Gr) interlace dendritic branches as fingers in dendro-dendritic contacts (Dd. syn.); in B, two horizontal retinal cells converge upon a third, forming dendro-somatic contacts (Ds. syn.). M. E. Scheibel and collaborators insisted on the pervasiveness of bundles where dendrites were so close that a lack of functional role was hardly conceivable: C (Scheibel, Davies and Scheibel, 1973) is a horizontal section of the medulla where dendritic bundles form a veritable net crossed by perpendicular axonic bundles. The overwhelming abundance of thin unmyelinated fibers in close contact with each other in numerous portions of the CNS must alert neuroscientists to the possibility of close interactions in as yet poorly understood roles.

A. Primary afferent depolarization. Dorsal root reflex.

When an interneuron acts upon the terminals of a presynaptic neuron by way of an axo-axonic contact, it can influence the latter’s synaptic efficacy. AP discharges in
certain primary afferents, on arrival to their intra-spinal terminals, depolarize also the terminals of other afferents in the same or neighboring roots: this "primary afferent depolarization" (PAD) is large, and its electrotonic repercussion exceeds the cord and is recorded on the dorsal roots. Introducing a microelectrode into an afferent fiber from the triceps just after it enters the cord (Fig. 38A, Eccles, Magni and Willis, 1962), it is possible to see how one, two or four shocks to the biceps-semimembranosus nerve cause such depolarizations (B).

**Fig. 38.** Axo-axonic effects at terminals in the cord. 1. Primary afferents. Cat. A, set-up and B, depolarizations elicited by 1, 2, and 4 shocks. C, primary afferent depolarizations (PAD) recorded on the surface of the dorsal root: the first upwards deflection coincides with the dorsal root reflex (DRR). Parallel evolutions of PAD and the excitability (increasing upwards). (A, B, Eccles, Magni and Willis, 1962; C, Wall, 1958)

*PAD is associated with increased excitability in the sensory terminals.* As a consequence, AP's are generated in some that, propagating from cord to periphery, i.e., opposite to sensory-elicted AP's, constitute what is referred to as "dorsal root reflex" (C, DRR, see counter-current effects). If an excitatory current is passed through an extracellular micropipette at terminal level, the hyperexcitability of the population is reflected either by a larger number of fibers responding by an AP to a particular stimulus, or by a weaker stimulus sufficing to activate a particular number of fibers. In C, right (Wall, 1958) the record is of the responses elicited in a dorsal root by a particular stimulus applied repetitively: the height of each reflects the number of fibers that respond. A shock applied to a neighboring dorsal root at the arrow, provokes the hyperexcitability revealed by the height increase, whose profile is similar to that of the corresponding PAD.

Fig. 39 (Rudomin, Enberg, Jankowska and Jimenez, 1980) plots, as function of time, the intensity of a stimulus sufficing to activate a particular number of fibers: a shows that for triceps' afferents it is less during the conditioning stimulation of biceps-semimembranosus afferents (BST that do not affect rubrospinal terminals E). A slight hyperexcitability of the rubrospinal terminals (RS) is conditioned by cutaneous

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**Fig. 37.** Variety of interneuronal contacts. A, dendro-dendritic (cerebellar granules), B, dendro-somatic (retina). C, dendritic bundles (a) crossing axon bundles (b) (reticular nucleus). (A, B, Estable, 1961; C, Scheibel, Davies and Scheibel, 1973)
peroneal stimuli (SP). When GABA is applied iontophoretically to the triceps terminals (C), their excitability changes in the same sense as with BST; GABA either does not affect rubro spinal excitability, or it shifts it in a sense opposite to SP (D).

**B. Presynaptic inhibition**

PAD and the concomitant afferent terminal hyperexcitability are accompanied by a reduction of reflex responses called "presynaptic inhibition".

Fig. 40A (Rudomin and Dutton, 1969) shows the electrophysiology of the monosynaptic stretch reflex; a brief shock to the triceps sensory fibers causes a synchronous AP barrage that, through the dorsal root (whose neurogram is in the upper record), reaches the spinal cord; the sensory fibers elicit EPSP's in the homologous motoneurons and the reflex AP's of the latter course along the ventral root (whose neurogram is in the lower record). Several sweeps (triggered by the shocks) are superimposed: they illustrate the practically constant arriving barrage and the slightly variable outgoing one. B and C graph the magnitudes of successive reflex responses, respectively, control and conditioned by a peroneal nerve stimulation. The latter causes an amplitude reduction, or inhibition, revealed by a downward displacement of points, whose average ordinate (indicated by arrows) drops by about 40%; this would be translated by a drop in the contraction of calf muscles. The second result is a remarkable decrease in variability revealed by the smaller vertical dispersion of points. This is not due to the amplitude change because, as shown by D, with average on the abscissa and variability on the ordinate, the conditioned graph (black circles) is below the control at all amplitudes.

The influences that cause PAD, hyperexcitability and presynaptic inhibition in a neuronal pool act rather specifically, and not in an indiscriminate and uniform manner. Indeed (Figs. 39A, E), impulses from the biceps-semimembranosus BST, arriving at the triceps motoneuronal pool, act upon afferents from the triceps but not on rubro-spinal RS fibers, in turn susceptible to cutaneous inputs SP.

Recording intracellularly from motoneurons, M. G. F. Fuortes and collaborators called attention to this type of influence, where there was a decrease in EPSP magnitude without evidence of other effects (e.g., IPSP's). They sensibly posed the not mutually excluding possibilities that such inhibition was due either to currents so remote on the dendritic tree that their electrotonic repercussion was undetectable, or to mechanisms acting upon the presynaptic terminal. The second possibility is compatible with the following facts. The terminals from the triceps are depolarized by fibers from the biceps-semimembranosus complex, thus PAD is associated with hyperexcitability. Simultaneously, AP's in the terminals are reduced in size which in turn should lower the amount of transmitter released, i.e., decrease synaptic efficacy. The specificity of such effects suggests that they happen by way of interneurons excited by biceps-semimembranosus fibers that have axo-axonic contacts with afferents from the
A GABAergic chemical synapse seems likely. The possibility that the conditioning afferent activity accumulates K⁺ in the extracellular milieu leading to depolarization, has been proposed, but it is hard to envisage how this could be so specific.

The neuromuscular organization in crayfish where a single excitatory and a single inhibitory nerve fiber with axo-axonic connections converge upon single muscular fibers, allows a more straightforward analysis. The mechanism here also reduces the presynaptic AP, thus the amount of transmitter released. Fig. 41 (Baxter and Bittner, 1981) illustrates that the EPSP (lower record) caused by the excitatory fiber is smaller during activation of the inhibitory fiber (B) than without it (A). The mechanism revealed by impalements is that the inhibitory fiber elicits in the excitatory fiber an IPSP (C, D) with all the features of chemically mediated ones, including its dependence on the postsynaptic membrane level. The important issue is not the potential shift, however, but the drop in the membrane resistance that reduces the AP height. GABA, the likely transmitter, would increase the conductance to Ca²⁺.

C. Heterosynaptic facilitation

Aplysia neurons behave in a way suggestive of an heterosynaptic or presynaptic facilitation, whereby one pathway increases the efficacy of another simply because both have been active simultaneously. The probably unitary EPSP in Fig. 42 (Kandel and Tauc, 1965) increased significantly relative to the control and remained so for several minutes after repetitive stimulation of a connection trunk. The increase does not require high rate bursts (thus PTP cannot be invoked), and is not associated with detectable postsynaptic changes. It is hard to believe that this would be due to postsynaptic sensitization to the transmitter, since the latter has not been observed in the preparation. Since application of 5HT close to the synaptic region augments the EPSP in a similar manner, it is hypothesized that a third neuron with serotonergic terminals modulates the release of the synaptic transmitter (probably ACh). It has been suggested also that 5HT triggers successive increases of cAMP, inwardly moving Ca²⁺, and transmitter release.

D. Counter-current effects

Fig. 43 (Décima and Goldberg, 1970) illustrates somato-dendro-axonic excitation in a cat spinal cord. D is the set-up where recording is from a thin dorsal root filament and stimuli are delivered to the rest of the dorsal root (or on neighboring ones) and/or a thin ventral root filament (VR). A shows that the test stimulus (T-st) to the ventral filament that causes antidromic AP invasion of the motoneuronal soma has no visible dorsal filament effect. B shows that the conditioning stimulus (C-st) to the dorsal root causes, via the dorsal root reflex, a short latency discharge of small AP’s in the filament. C shows that, when preceded by the conditioning stimulus, the test stimulus triggers also a longer latency large AP. The ventral root stimulus is conditioned similarly by natural stimuli such as pinching the skin.

It is reasonable to attribute this centrifugal antidromic discharge to the sum at the activated terminal of subliminal excitations due to other terminals on the one hand and to the motoneurons on the other. The latter excitation (whose precise mechanism is as yet unknown) reflects an interneuronal influence that goes from soma and dendrites to axon, and that classical physiology would call “counter-current”. While stimulations of certain ventral root filaments do not elicit counter-current events when conditioned by any of several dorsal root stimuli, others do, sometimes even without conditioning: this suggests that connections are selective. Counter-current effects relate to PAD, but the recording conditions differ for Fig. 38 (thick filament, close to the cord, preferential recording of lower frequencies) and Fig. 43 (very thin filament, far from the cord, preferential recording of higher frequencies) and do not detect the same events.

![Fig. 41. Presynaptic inhibition II. Neuromuscular preparation, crayfish. EPSP caused by the excitatory motoneuron without (A) and with (B) conditioning by the inhibitory motoneuron. C. IPSP caused by the inhibitory motoneuron in the excitatory terminal at different MP's (-75, -69 mV) in the latter. (Baxter and Bittner, 1981)](image-url)
6. Electrical synapses

In contacts called "electrical synapses", interneuronal communication is by way of low resistance paths that allow easy current flow from one cell to another. Even small membrane potential MP fluctuations in one have close-cut repercussions in the other.

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Fig. 42. Heterosynaptic facilitation. Aplysia. The EPSP evoked by a shock to the right connective trunk prior to (a), and after (b, c) a stimulus to the siphon nerve during its facilitation. Below: temporal evolution. (Kandel and Tauc, 1965)

Fig. 43. Counter-current effects. Spinal cord, cat D, experimental set-up: recording far from cord on thin dorsal root filament; test stimulus (TS) to the corresponding ventral root (VR); conditioning stimulus (CS) to rest of dorsal root (DR). A, test alone; B, conditioning alone; C, conditioning-test pairing. (Saima and Goldfarb, 1970)
Conditions favorable for between-cell communication (Fig. 44) are that the resistance (depicted horizontally) through the contact CC be much smaller than those (vertical) to the rest of the intercellular milieu O, either across the membranes or from the contact (S). The condition that the resistance of one cell exceed that of the other favors flow from it and hinders the opposite one. The flow of current in these synapses does not differ substantially from that along neurites.

The equivalent circuit is a “low-pass filter” that transmits low frequencies up to a cut-off value beyond which attenuation increases markedly. Subthreshold MP fluctuations have lower frequency components than the AP and thus are attenuated less. There is also a certain delay in the sense that if, say, sinusoids are used, the output peaks later than the input. Electrotonic propagation is instantaneous in the sense that the repercussion is initiated at the same instant as the imposed current; it is not in the sense that the maximum at a remote point may occur with delays that may be considerable, even greater than those it would take for an AP to arrive.

The anatomical substrate underlying electrical synapses is referred to as “gap-junction” or “nexus”. They abound in practically all tissues: in the CNS and skeletal muscle they appear to be less frequent and distributed less uniformly. Fig. 45A (Sotelo, Llinás and Baker, 1976) shows a nexus from the cat inferior olive: it is a flattish contact where the membranes are about 3 nm apart; if the section is along the contact’s plane, particles of about 9 nm in diameter become visible. In B (Cantino and Mugnaini, 1975) the scanning EM and cryo-fracture method show the distribution of those particles in the chick ciliary ganglion. Dense substances (like lanthanum) penetrate the gap as well as between particles, revealing that the latter have an hexagonal outline and perhaps a central pore of about 2 nm. Fig. 44 (Loewenstein,
Fig. 45. Nexus II. A, EM of a dendro-dendritic nexus (inferior olive, cat). B, scanning EM (ciliary ganglion, chick). (A, Soto, Liná, and Baker, 1974; Cantino and Mugnaini, 1975)

1980) includes a diagram. Some electrical connections in crustacean cardiac ganglia are allowed by cytoplasmic bridges.

The critical experiment for demonstrating that a synapse is electrical is to pass current through one cell, thus changing its MP, and see what happens to the MP of the other: if the ratio between the imposed MP change in the second cell to that in the first is high and close to 1, i.e., attenuation is low, the interposed resistance is low, i.e., there is an electrical synapse. Fig. 46A shows the parallelism between subthreshold MP fluctuations in two leech "colossal" neurons (Hagiwara and Morita, 1962). AP's, on the other hand, are attenuated markedly; however, even the small depolarization they cause may trigger AP's in the second cell, which in turn may make the first one fire again, thus leading to AP clusters (extreme right). B displays how the frequency-dependent attenuation is weak at low frequencies (on right of the graph) and the attenuation marked with high ones.

Fig. 47 (Bennett, 1966) illustrates an electrical synapse in the puffer-fish. The two lower records correspond to the MP's of the participating neurons and reveal the clear correlations when hyperpolarizing current rectangles (upper record) are delivered to either one cell (left) or the other (right): profiles are quite similar in both cells, and the ratio is of about 0.5 (gains differ in the two records). Influences are essentially symmetric in these leech and puffer-fish synapses.

In Aplysia (Meunier and Tauc, 1973), an AP in the right giant cell CGG (Fig. 48, left) causes a biphasic wave in the left giant CGG, where an initial depolarization corresponds to the AP and a late hyperpolarization to the undershoot and afterpotentials. The impaled soma is several space constants away from the contact, so the critical experimental test that the connection is electrical inevitably would be
inconclusive; conclusive evidence has been obtained in rare specimens where both somata are close to the contact. The circuit on the right (with appropriate components) reproduces the contact’s behavior.

The electrical connection between the lateral and the motor giant fibers in crayfish conducts asymmetrically, i.e., rectifies. It was studied as shown in Fig. 49A (Furshpan and Potter, 1959). Transmission in motor acts is from lateral to motor, referred to as pre- and postsynaptic, respectively. An AP in the lateral has a large repercussion in the motor (C); one in the motor leads at most to a less than 1 mV depolarization in the lateral (B). Using subthreshold depolarizing steps into the lateral (D-a) the motor responded with small attenuations (ratio .30); hyperpolarizing steps had practically no repercussions (ratio .00). Contrastingly, if currents were injected into the motor (D-b), while depolarizations had no repercussions, hyperpolarizations did. This electrical synapse thus is a rectifier passing positive current from lateral to motor, and negative in the opposite sense: approximate resistance estimates are 55 and 400 ohm/cm² (close to that from the cell to the milieu), respectively. Hence, it transmits excitatory influences orthodromically and inhibitory ones antidromically. This synapse has a narrow cleft but no hexagonal structure.

Electrical synapses exhibit temporal and spatial summations (Fig. 50, Bennett, 1972). It is possible that the latter reflect an increase in the size of the presynaptic AP’s whose electrotonic repercussions are the depolarizing PSP’s, or a more thorough invasion of the contact area.

In general, an electrical synapse implies shorter latencies, greater firing synchronicity, and the possibility of two-way effects, i.e., reversibility, though not necessarily symmetry. These are advantageous biologically in, say, withdrawal reflexes, escape reactions, or when the simultaneous discharge of several neurons is desirable (e.g., swallowing, inspiration). A chemical synapse, on the other hand, would allow more plasticity and asymmetry.

There are cases where two neurons are connected by both chemical and electrical synapses. In the chick ciliary ganglion, for instance, the postsynaptic record in Fig. 51 (Pilar, unpublished) shows a double depolarizing response, the early brief one electrical, and the late protracted one chemical (the neuron is hyperpolarized so as to prevent firing). When a second presynaptic AP follows a conditioning one, the electrical potential remains the same, and the other is clearly modified: hence, the relative rigidity of the electrical synapse contrasts with the plasticity of the chemical one.

The labeling of a synapse as chemical or electrical can be based on several criteria. It should be chemical if the EM shows a gap with a certain width, a dense material and vesicles, if the electrical resistance between the neurons is high, if there is a detectable delay, if PSP’s are influenced (reversed even) by postsynaptic polarizations and are susceptible to certain ionic and pharmacological manipulations or to repetition. A synapse is likely to be electrical if it has a narrow gap and particles, if the electrical resistance is low, and if it has no delay nor is particularly susceptible. None of these
7. Other features

Electrical fields created by currents generated physiologically probably modulate neuronal operations. Significant discharge changes have been observed in stretch-receptor neurons by minuscule gradients that may well be even smaller close to the TZ. An influence likely to be of this kind has been seen in the large Mauthner cells of the fish brain. The region close to the initial axon is surrounded by a mesh of several terminals, including collaterals from the contralateral cell. An antidromic invasion of the soma by an AP triggered from its axon can be blocked by stimuli such as that from the stato-acoustic nerve or from the other Mauthner cell. Fig. 52 (Furukawa and Furshpan, 1963) includes extracellular records from the initial axon. A stimulus to the stato-acoustic nerve triggers a positive deflection (a); the axonic stimulus causes the

criteria is absolute or tested easily: for example, certain synapses are electrical but exhibit vesicles, the electrical coupling may be difficult to evaluate, etc.

A nexus is a pathway for intercellular electrical communication (De Robertis and De Robertis, 1980); this obviously implies the passage of ions (e.g., Na⁺, Cl⁻). They also allow passage of small molecules such as nucleotides and vitamins (but not that of macromolecules or enzymes), thus constituting a pathway for metabolic communication as well. The size of the channels can be estimated using, in addition to morphologic criteria, the diffusion of molecules of different sizes: in salivary glands, the passage of fluorescent peptides of up to 1,900 daltons suggests pores of about 1.4 nm diameter. In any tissue including the NS, the permeability of these channels decreases as the intracellular Ca²⁺ concentration increases. The Ca²⁺ level depends on several factors as its extracellular concentration, its capture and retention by mitochondriae, phosphorylizations, etc. Inhibiting cellular metabolism (by cyanide, for instance) would cause an increase in intracellular Ca²⁺ and consequently that of intercellular resistance.
antidromic AP seen as a fast negative deflection (b); if the stimulus to the stato-acoustic nerve precedes the axonic one (MSA–M), the active AP invasion of the soma is blocked. Intracellular recordings reveal that the positive extracellular fluctuation in a corresponds to an intracellular hyperpolarizing swing, and that the most powerful block occurs at its peak. A likely explanation is that the APs along the terminals in the mesh do not quite reach their very ends so that these become extracellular anodes; the Mauthner cell therefore is hyperpolarized and prevented from firing, as in fact it can be with a microelectrode in the mesh used as anode.

Neuromodulators are substances which affect several neurons, particularly modifying their response to other influences in a rather protracted manner (Bullock, Orkand and Grinnell, 1977). They differ, then, from neurotransmitters whose effects are more localized and brief. Prostaglandins, for example, are fatty acids to which smooth muscle fibers are very sensitive: they are present in the CNS of higher vertebrates, and their electrophoretic application causes a variety of changes. Their precise physiological roles are uncertain.

The cyclic nucleotides cAMP and cGMP, present in vertebrate and invertebrate neurons, affect their general metabolism and in particular the properties of the membrane including its electrophysiological behavior. cAMP, for instance, influences Ca$^{2+}$ regulation, transmitter release, and MP in the neuromuscular junctions, increases neurally-induced release of nor-epinephrine by the adrenals, and reproduces the influence of catecholamines in neurons in locus coeruleus or caudate. Perhaps they act presynaptically on enzymes involved in either synthesizing the transmitter or transporting Ca$^{2+}$, and/or postsynaptically on certain channels. Their own synthesis is stimulated by several alleged transmitters and thus may be a second messenger for synaptic influences. Though study of this dimension dates only from recent years, it is not too soon to state that it has opened a special and important perspective of neural dynamics.

Other components of the intercellular milieu that may be influential are the ionic concentrations, including the pH of course, and the O$_2$ and CO$_2$ tensions. Endocrinology offers numerous examples of hormonal influences on the CNS, even though much remains to be learned of the basic mechanisms involved. Mechanical influences are another dimension about which we know little, but that may well be crucial if, as is likely, the electrokinetic model (Teorell, 1976) holds beyond mechano-receptors and if the unceasing movements revealed by slow motion cinematography in tissue cultures persist in the natural situations.

To finish, then, the title’s question can be answered, at the same time exhaustively, briefly and vaguely, by saying, “a lot, a lot, a lot”.

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What can neurons do to serve as integrating devices?


