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A Model of Excitatory Synaptic Interactions Between Pacemakers. Its Reality, its Generality, and the Principles Involved*

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Abstract. This is a model of the steady-state influence of one pacemaker neuron upon another across a synapse with EPSP's. Its *postulates* require firstly the spontaneous regularity of both cells, whose intervals are E and N, respectively. In addition, they require a special shortening or negative "delay" of the interspike interval by one or more EPSP's, with a V-shaped dependence of the delay on the position or "phase" of the EPSP's in the interval; the minimum of the delay function corresponds to the earliest EPSP arrival phase (λ) that triggers a spike immediately. Finally, they impose on the variables certain bounds. The model's *behavior* has two main features. The first is a zig-zag relationship with an overall increasing trend between the steady-state pre- and post-synaptic discharge intensities (Fig. 7). The zig-zag is formed predominantly, if not exclusively, by segments with positive slopes that are rational fractions. Passage from one such segment to others is negatively-sloped ("paradoxical"), involving staggered positively-sloped segments whose details are unclear for weak presynaptic discharges and discontinuities for intense discharges. The same postsynaptic intensity may result from several presynaptic ones; the maximum postsynaptic intensity may reflect refractoriness, or the earliest instants of immediate triggering. The second main feature is the "locking" of the discharges in an invariant forward and backward temporal relation. With at most one EPSP per postsynaptic spike, locking is always present. If the presynaptic interval E is in the closed $\{rN+\lambda,(r+1)N\}$ range, locking is $1:r+1$, either stable at a greater-than-λ phase or unstable at a smaller one; arrivals at integral multiples of N do not affect the postsynaptic intensity. If E is in $\{rN, rN+\lambda\}$ ($r>0$), locking is at other ratios (e.g., $2:3$) and less apparent. With more than one EPSP per spike, when E is below bounds that depend on the interspike interval and the point of earliest triggering, locking happens in the simple $s':1$ ratio ($s'=2, 3, \ldots$) and is stable; when E is above those bounds, there are E ranges where locking is in other ratios (e.g., $3:2$) and ranges where behavior is unclear. The validity of any model is based jointly upon an *a priori* judgment as to whether postulates depart reasonably little from nature, and upon an *a posteriori* experimental comparison of modelled and real behaviors. The model's domain of applicability depends on the specific embodiment, each of the latter tolerating characteristically each departure. The present model will be evaluated in the crayfish stretch-receptor neuron (Diez-Martínez et al., in preparation). The model is applicable to any physical system that complies with its postulates, and evidence compatible with this notion is available in many disparate fields. It illustrates the modelling path to a scientific proposition, other paths being inference from experimentation, or deduction from premises acceptable at other approach levels (in this case, for example, from that of synaptic mechanisms). The periodicity postulates set this model within the category of those for oscillators. The notion of an oscillator has a far broader applicability than appears at first sight, since all physically realizable systems have some predominant output frequency, i.e., to a certain extent are oscillators.

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Introduction

The present communication has two main purposes. One is to extend to an excitatory synapse a model of the stationary effects of PSPs that impinge regularly upon a pacemaker neuron; the counterpart for an inhibitory junction is described elsewhere (Kohn,

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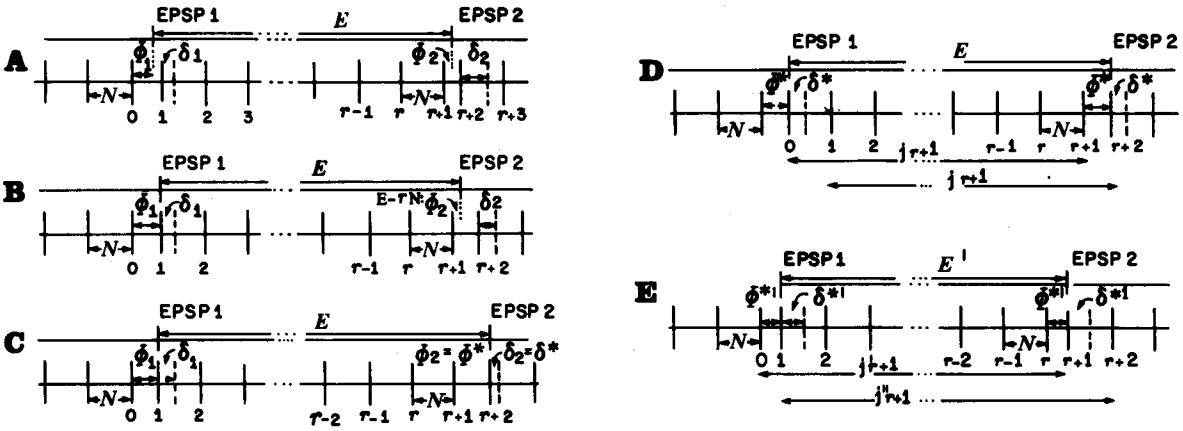

Fig. 1A–E. *Discharges with at least one postsynaptic spike between two EPSPs* (Situation I). Here, as in Fig. 5: upper record, presynaptic or EPSP discharge; lower record, postsynaptic discharge. An EPSP arriving at an interval, or "phase" ϕ, from the previous spike shortens the interspike interval by an amount or "delay" δ, as illustrated in Fig. 2A. **A–C** Beginning of EPSP discharge: initial phase ϕ_1 smaller (A; Case I-A) or larger (B, C; Case I-B) than λ; presynaptic interval E smaller (B; Case I-B-a) or larger (I; Case I-B-b) than $rN \pm \lambda$. **D and E** Locked discharges: at $1:r+1$ (**D**) or $1:r$ (**E**)

1980; Kohn et al., 1981; Segundo, 1979). The other is to discuss certain issues inherent in modelling efforts in general, and particularly in those of interacting oscillators.

Description

Postulate i requires that the pre- and post-synaptic cells, if undisturbed, fire at invariant intervals E and N, respectively (e.g., Fig. 1). Other postulates will be presented as they become necessary. Two situations, differing in the relative firing intensities, will be examined: namely that (I) where there is at most one presynaptic spike or EPSP for each postsynaptic spike, and that (II) where there is more than one presynaptic spike or EPSP between two postsynaptic ones. The term "intensity" is given a special meaning here, referring to a feature inherent in our intuition of a point process, namely, to whether points are few and far between, or close and tightly packed: it thus implies jointly numbers and intervals, i.e., the counting and interval descriptions of any point process (Cox and Lewis, 1966).

I. At Most, One EPSP for Each Postsynaptic Spike

Additional postulates are required. *Postulate ii:* The EPSP elicited by the presynaptic spike shortens the interval separating the postsynaptic spikes between which it falls, thus advancing the next spike (it does not affect other intervals). *Postulate iii:* The advance, or negative "delay", δ is a *V*-shaped function of the position, or "phase" ϕ, of the EPSP with respect to the last postsynaptic spike. The "delay function" is thus piece-wise linear with two straight segments (Fig. 2A):

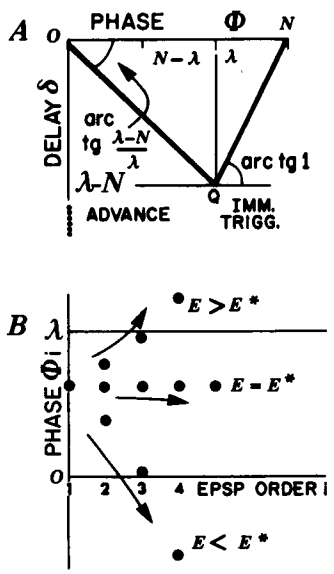

Fig. 2. A *Delay function.* On the abscissa, the position of the EPSP with respect to the last preceding spike, or "phase" ϕ; on the ordinate, corresponding shortening or "delay" δ. The relation has two linear segments: $0Q$ through the origin and decreasing with slope $\frac{\lambda-N}{\lambda}$; QN with slope 1 and through point $\{N,0\}$. Their intersection corresponds to the earliest phase where an EPSP arrival causes immediate firing. **B** *Phases that follow a particular initial phase ϕ_1 if the presynaptic intervals E differ* (Situation 1). Depending on whether E is greater than, equal to, or smaller than E^* (5), phases increase surpassing λ, remain invariant (locked), or decrease becoming negative, respectively

the first $0Q$ corresponds to phases from 0 to λ ($0<\phi<\lambda$) starts at the origin and has a negative slope $\frac{\lambda-N}{\lambda}=1-\frac{N}{\lambda}<0$; the second QN corresponds to phases from λ to N ($\lambda \leqq \phi \leqq N$), intersects the abscissa

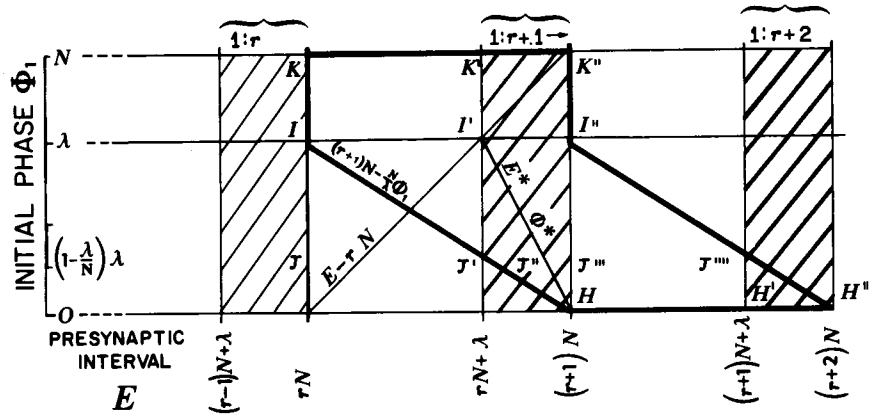

Fig. 3. *Initial phase ϕ_1 (on vertical axis), presynaptic interval E (on horizontal axis), and pacemaker interactions* (Situation I). Hatched areas correspond from left to right to lockings $1:r$, $1:r+1$, and $1:r+2$. See text

at N, has a positive slope of 1, and implies that EPSPs arriving at or after λ immediately trigger a spike. λ is a characteristic of the synapse, and must be between 0 and N ($0<\lambda\leqq N$).

Two variables (represented in Fig. 3) must be considered: they are the phase of the first EPSP, or "initial" phase ϕ_1, and the presynaptic interval E. Indeed, both the instant when a presynaptic cell starts firing, i.e., the initial phase, and its average intensity have biological significance. Behavior can be analyzed by fixing any one of them at representative values and then examining what happens when the other is modified systematically. In the present communication, we first fix ϕ_1 and modify E; subsequently, the alternate approach (confirmatory of the first) is used to explain conclusions of general interest. Figure 3 is crucial for clarification of the argument of either approach.

When the initial phase is fixed, the argument is contingent upon ϕ_1 being larger or smaller than λ; two general cases will be considered. Figures 1A–D illustrate the convention that the first EPSP occurs no earlier than postsynaptic spike number 0 and no later than 1, and that the second one relates similarly to $r+1$ and $r+2$; $r+1$ is the number of spikes between EPSP's 1 and 2, and therefore cannot be 0 in case I (i.e., $r=0,1,2,\ldots$).

(A) $0<\phi_1<\lambda$ (lower band in Fig. 3, segment $0Q$ in Fig. 2A). In this case the delay is expressed by:

$$\delta=\frac{\lambda-N}{\lambda}\phi=\left(1-\frac{N}{\lambda}\right)\phi \qquad (\lambda-N<\delta<0). \tag{1}$$

These definitions imply that E must be between $(N+\delta_1-\phi_1)+rN$ and $(N+\delta_1-\phi_1)+(r+1)N$ which, substituting δ_1 by its value as a function of ϕ_1, means that:

$$(r+1)N-\frac{N}{\lambda}\phi_1<E<(r+2)N-\frac{N}{\lambda}\phi_1. \tag{2}$$

Range (2) is between $\{rN,(r+1)N\}$ and $\{(r+1)N,(r+2)N\}$ when ϕ_1 is between 0 and λ (Fig. 3).

Figure 1A justifies the following equality since both sides represent the time from spike 0 to the second EPSP:

$$\phi_1+E=N+\delta_1+rN+\phi_2 \tag{3}$$

substituting δ_1:

$$\phi_2=\frac{N}{\lambda}\phi_1+E-(r+1)N. \tag{4}$$

An identical expression with ϕ_{i+1} and ϕ_i instead of ϕ_2 and ϕ_1, respectively, gives the "new" phase as a function of the "old" one at a given E: Fig. 4 represents ϕ_2 for all ϕ_1 and for three E's. ϕ_2 is a meaningful value only if $0<\phi_2\leqq N$, and this happens in I under conditions (2).

From (4) one deduces also that the next phase will be greater than, equal to, or smaller than the present phase, depending on E being greater than, equal to, or smaller than, respectively, a value E^* [within range (2)]:

$$E^*=(r+1)N+\left(1-\frac{N}{\lambda}\right)\phi_1. \tag{5}$$

Three conclusions are to be drawn (Fig. 2B). Firstly, that if E equals E^*, all succeeding phases will equal ϕ_1. This situation is called "locked" and E^* "locking interval" (see below; Kohn, 1980; Segundo, 1979): the locked delay will be $\left(1-\frac{N}{\lambda}\right)\phi_1$, and the first spike after each EPSP follows the latter by $N+\left(1-\frac{N}{\lambda}\right)\phi_1$ $=\left(1-\frac{\phi_1}{\lambda}\right)N$. E^* is in the range $\{rN+\lambda,(r+1)N\}$ (Fig. 3). Secondly, that when E is smaller or greater than E^*, the successive phases $\phi_1,\phi_2,\phi_3,\ldots$ will constitute a monotonic series, either decreasing until a value becomes negative, or increasing until a value

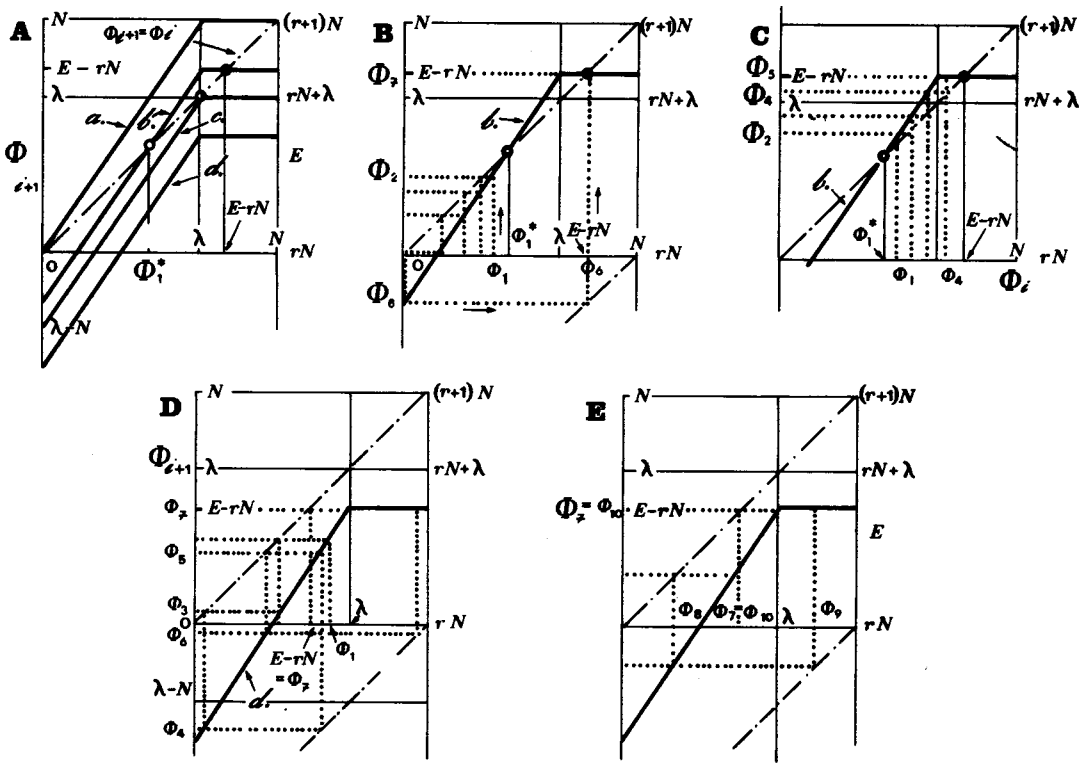

Fig. 4A–E. *Successive phases and locked phases (stable or unstable) for different presynaptic intervals* (Situation I). **A** "Old" phase ϕ_1 on abscissae; "new" phase ϕ_{i+1} on ordinate at left; presynaptic interval E on ordinate at right. Each heavily traced curve corresponds to the particular E at its intersection with the rightmost axis; a locked condition ($\phi_{i+1}=\phi_i$, circles) exists if and where a curve intersects the 45° line (dot and dash). Curve *b* for $rN+\lambda<E<(r+1)N$ has two intersections with the 45° line: one (black circle) with slope 0 and therefore stable, and another (open circle, ϕ^*) with slope $\frac{N}{N-\lambda}>1$ and therefore unstable; *a* for $E=(r+1)N$, has one that is stable to its left; *c* for $E=rN+\lambda$, has one that is stable to its right and unstable to its left; *d* for $rN<E<rN+\lambda$, has none. **B** Successive phases for Curve *b* $rN+\lambda<E<(r+1)N$, decreasing when $\phi_1<\phi_1^*$ or increasing when $\phi_1>\phi_1^*$ **C** and in either case arriving at a $1:r+1$ locking. **D and E.** Successive phases for Curve *d*, $rN<E<rN+\lambda$, early ones, **D**, and those in a three-EPSP cycle **E**

surpasses λ, respectively. A locked phase is "unstable" relative to E when even the slightest modification of E will be followed by phases that diverge from it. Thirdly, that there will be at most a single unstable locked phase. As explained when it is E that is fixed, the range

$$rN+\lambda<E<(r+1)N \tag{6}$$

is characterized by two meaningful locked phases, an unstable one ϕ^* (11) less than λ achieved only if the initial phase ϕ_1 happened to equal it, and a stable one $E-rN$ larger than λ achieved when ϕ_1 was no smaller than λ. The relation of these bounds to those in (2) depends on ϕ_1. The difference between the lower ones is:

$$(rN+\lambda)-\left\{(r+1)N-\frac{N}{\lambda}\phi_1\right\}=\frac{\lambda^2-N\lambda+N\phi_1}{\lambda}$$

whose sign is that of the numerator. Hence, the lower bound in (6) will be larger than that in (2) only when $\phi_1>\left(1-\frac{\lambda}{N}\right)\lambda$. The upper bound $(r+1)N$ in (6) is always similar than that $(r+2)N-\frac{N}{\lambda}\phi_1$ in (2) because, subtracting the latter from the former, gives a negative number $-N\left(1-\frac{\phi_1}{\lambda}\right)$, and is always larger than the lower bound which it exceeds by $\frac{N}{\lambda}\phi_1$. Consequently, range (2) for E when ϕ_1 is fixed always contains a range wherein there would be meaningful values of ϕ_1^* were it E that was fixed. Moreover, the E that preserves the fixed initial phase, i.e., E^* (5) is within range (6); indeed, the difference between E^* and the lower bound $rN+\lambda$ has the sign of the positive quantity $(N+\phi_1)^2$, and that between E^* and $(r+1)N$ is a negative quantity.

(B) $\lambda\leqq\phi_1\leqq N$ (upper band in Fig. 3). In this case (segment QN in Fig. 2A) δ is expressed by:

$$\delta=\phi-N \quad (\lambda-N\leqq\delta\leqq 0).$$

The first EPSP (Fig. 1B, C) triggers spike 1, and the next one arives later than $r+1$ and no later than $r+2$.

These conventions imply that:

$$rN < E \leqq (r+1)N \tag{7}$$

with $r=0,1,\ldots$. In addition, and so as to have at least one spike per EPSP when $r=0$, E cannot be smaller than λ. Figure 1B justifies the equality:

$$\phi_1 + E = N + \delta_1 + rN + \phi_2 .$$

Substituting δ_1:

$$\phi_2 = E - rN \tag{8}$$

that, because of (7), will necessarily be between the required values of 0 and N. The second phase ϕ_2 will be greater, equal to, or smaller than λ, depending on whether:

$$E \gtreqless rN + \lambda . \tag{9}$$

(C) *Different Cases.* In the following paragraphs cases I-A and I-B where ϕ_1 was fixed shall be broken up into partial cases contingent on where E falls in its inevitable ranges. The E range for I-A, with ϕ_1 fixed between 0 and λ, is $\left\{(r+1)N - \frac{N}{\lambda}\phi_1,\ (r+2)N - \frac{N}{\lambda}\phi_1\right\}$ [(2), rhomboid II *"H" H* in Fig. 3]. *Case I-A-a* (triangle *II'H*) involves

$$(r+1)N - \frac{N}{\lambda}\phi_1 \leqq E < (r+1)N + \left(1 - \frac{N}{\lambda}\right)\phi_1 = E^* . \tag{10}$$

Throughout (10) E will be less than E^*, i.e., to the left of line *I'H*. Therefore, phases will form a decreasing series (see above) $\varphi_1 > \varphi_2 > \ldots$: this means that eventually, after $i-1$ EPSP's with positive phases, an ith EPSP will arrive with a negative phase ϕ_i (Fig. 2B, lower arrow). The ith EPSP will precede the $(r+1)$th spike, since phases are measured with respect to it: it will, however, follow the rth spike because E exceeds rN [see bounds (1)]. The positive phase with respect to the rth spike is called ϕ_i' ($\phi_i' = \mathrm{N} - \phi_i$). E exceeds the E^* for this situation that is in the $\{(r-1)N+\lambda, rN\}$ range: hence, either ϕ_i or a subsequent phase surpasses λ, with a *switch to Case I-B* (i.e., a jump across segment *II"*). The boundary $rN+\lambda$ between the two I-B partial cases will be to the left of range (10) or within it, i.e., $rN+\lambda$ will be no greater or greater, respectively, than $(r+1)N - \frac{N}{\lambda}\phi_1$, depending on whether $\phi_1 \leqq \left(1 - \frac{\lambda}{N}\right)\lambda$, or $\phi_1 > \left(1 - \frac{\lambda}{N}\right)\lambda$, respectively. If $\phi_1 \leqq \left(1 - \frac{\lambda}{N}\right)\lambda$ (Case *I-A-a-i*, triangle *J'J"H*, I-A-a-i switches to I-B-b which (see below) implies a $1:r+1$ *locking*.

In the alternate case (trapeze *II'J"J'*), ϕ_1 exceeds $\left(1 - \frac{\lambda}{N}\right)\lambda$, and $rN+\lambda$ separates (10) into two portions (triangles *II'J'*, *I'J"J'*). When $E < rN+\lambda$ (triangle *I'J"J'*, also called Case I-A-a-i), the switch is to I-B-b which implies a $1:r+1$ *locking*. When $E \geqq rN+\lambda$ (triangle *II'J*, Case I-A-a-ii). *The switch is first to I-B-a and then back to I-A-a-i.*

If $E = (r+1) + \left(1 - \frac{N}{\lambda}\right)\phi_1 = E^*$ (5) (segment *I'H*), there is *immediate* $1:r+1$ *locking* at phase ϕ_1 (Case *I-A-b*). Case *I-A-c* involves $(r+1)N + \left(1 - \frac{N}{\lambda}\right)\phi_1 < E \leqq (r+1)N$ (triangle *I'I"H*). E being larger than E^* (see above), successive phases increase and eventually surpass λ, passing to Case I-B in range $\{rN, (r+1)N\}$ (see below). Since

$$(r+1)N + \left(1 - \frac{N}{\lambda}\right)\phi_1 > (r+1)N + \left(1 - \frac{N}{\lambda}\right)\lambda = rN + \lambda ,$$

I-A-c *switches to I-B-b with* $1:r+1$ *locking.*

Case *I-A-d* involves $(r+1)N < E < (r+2)N - \frac{N}{\lambda}\phi_1$ (triangle *I"H"H*). E exceeds E^*, so successive phases increase and eventually surpass λ, with the ith EPSP triggering immediately (Fig. 2A); calling this spike 1, the next one arrives E, and therefore more than $(r+1)N$, time units later ($r=0,1,2,\ldots$). It will fall therefore between spikes $r+2$ and $r+3$: this is a *switch to I-B* within the range $\{(r+1)N, (r+2)\}$ where the boundary $(r+1)N+\lambda$ separates partial Cases a and b. Two possibilities depend on whether ϕ_1 exceeds or does not exceed $\left(1 - \frac{\lambda}{N}\right)\lambda$. When $\phi_1 > \left(1 - \frac{\lambda}{N}\right)\lambda$ (Case *I-A-d-i*, triangle *I"J""J"'*), the upper bound $(r+2)N - \frac{N}{\lambda}\phi_1$ is less than the boundary: therefore, this case *switches to I-A-a* (in the corresponding range). When $\phi_1 \leqq \left(1 - \frac{\lambda}{N}\right)\lambda$ (trapeze *J"'J""H"H*), the upper bound surpasses the boundary. If, then $(r+1)N < E < (r+1)N+\lambda$ (Case *I-A-d-i*, rectangle *J"'J""H'H*), there is a *switch to I-B-a.* If, however, $(r+1)N+\lambda \leqq E < (r+2)N - \frac{N}{\lambda}\phi_1$ (*Case I-A-d-ii* triangle *J""H'*), there is a *switch to I-B-b with* $1:r+2$ *locking.*

When ϕ_1 was neither smaller than λ nor greater than N (Case I-B), the range for E was $\{rN, (r+1)N\}$ (rectangle *KK"I"I*), with the first EPSP triggering immediately spike 1 and the next one not arriving earlier than spike $r+1$ nor later than $r+2$ ($r=0,1,\ldots$). If, on the one hand (*Case I-B-a*, Fig. 1B) $rN < E < rN+\lambda$ (rectangle *KK'I'I*), the second EPSP will arrive with a phase ϕ_2 between 0 and λ, implying a switch to I-A with $\phi_2 = E - rN$ now playing the role of initial phase ϕ_1. When E is within the rightmost

portion $\left\{rN+\frac{N\lambda}{N+\lambda}, rN+\lambda\right\}$ of its range, there is a switch to *I-A-a-ii* (triangle $II'J'$) which will switch back to I-B-a and so on; when in the left leftmost portion $\left\{rN, rN+\frac{N\lambda}{N+\lambda}\right\}$ the *switch is to I-A-d-i*, this time in the range $\{rN,(r+1)N\}$ (triangle $IJ'J$)}: *either case in turn switches back to I-B-a.* This is true regardless of the relation of ϕ_2 to $\left(1-\frac{\lambda}{N}\right)\lambda$, since E does not exceed $rN+\lambda$. If, on the other hand (Case *I-B-b*, square $K'K''I''I'$, Fig. 1C), $rN+\lambda \leqq E \leqq (r+1)N$, the second phase is no smaller than λ. Consequently, ϕ_3 and all successive phases will be identical to ϕ_2, implying a $1:r+1$ *locking* with:

$$\phi^* = E - rN \qquad \delta^* = E-(r+1)N. \tag{11}$$

This locking is "stable" relative to E because it is re-established after any sufficiently small change of E, i.e., one within range $\{rN+\lambda,(r+1)N\}$. The first spike following an EPSP will be at an interval N from it.

Graphical Analysis. Expression (4) and (8) compose *non-linear, piecewise-linear difference equations of first order in* ϕ_i ($i=1,2,\ldots$). Figure 4 plots the next phase ϕ_{i+1} or ϕ_2 as function of the present one ϕ_i or ϕ_1. The elaboration above indicated that for the first segment $0Q$ this graph is oblique with slope $\frac{N}{\lambda}>1$, and for the second one QN it is horizontal at $E-rN$. The vertical position of each curve depends on E. This is reflected by two intercepts: that on the ordinate, i.e. ϕ_{i+1} for $\phi_i=0$ equals the difference $E-(r+1)N$ which can be either positive or negative; that on the vertical axis on the right, i.e., ϕ_{i+1} for $\phi_i=N$ equals the value at which E was fixed. Points (depicted as circles) where the graph for a fixed E intersects the dotted $\phi_{i+1}=\phi_i$ diagonal line identify "locked" or "equilibrium" phases ϕ^*. A locked phase is achieved after starting at a particular initial phase ϕ_1. When, starting in the close vicinity of ϕ_1, ϕ^* is still achieved it is called "asymptotically stable relative to ϕ_1'' but, if successive phases diverge from it, ϕ^* is called "unstable". The condition of asymptotic stability of a ϕ^* in a first-order difference equation (Bernussou, 1977) is that the absolute value of the derivative at the point be no greater than 1:

$$\left|\frac{\partial\phi_{i+1}}{\partial\phi_i}\right|_{\phi^*} \leqq 1.$$

Curves *a* and *c* in Fig. 4 are at the extremes of, and *b* is within, a range where graphs intersect twice the diagonal. The horizontal segment provides one locked phase at $E-rN$ (black circles), stable because of the 0 slope. The oblique segment provides another locking phase ϕ_1^*, unstable because of the greater-than-1 slope. ϕ_1^* derives from (4) after making

$$\phi_1=\phi_2=\phi_1^*: \qquad \phi_1^* = \frac{E-(r+1)N}{1-N/\lambda}. \tag{11A}$$

When E is fixed, there will be at most one ϕ_1^*. This value, which always exists since $1-\frac{N}{\lambda}\neq 0$, is meaningful within the present context, i.e., between 0 and λ, only when E is within the range $\{rN+\lambda,(r+1)N\}$ identical to (6) (segment HI' in Fig. 3). There is a reciprocal relation between E^* (5) and ϕ_1^* (11), in the sense that each guarantees locking if the other is fixed. Curve *b* is within this range: the dotted trajectories in Fig. 4B illustrates that after fixing E if the initial phase is smaller than ϕ_1^*, successive phases decrease and eventually ϕ_6 achieves a negative value. The trajectory goes successively from ϕ_1 on the abscissa up to the graph, horizontally to the corresponding ϕ_2 and, by way of the 45° line back to the abscissa; likewise from ϕ_2 to ϕ_3; and so on. Trajectories in Fig. 4C illustrate that if $\phi_1>\phi_1^*$, phases increase and eventually surpass λ. The corresponding arithmetic consists in calculating the successive differences between phases and ϕ_1^*. $\phi_2-\phi_1^*$, by substituting the expressions (4) and (11), can be shown to equal $\frac{N}{\lambda}(\phi_1-\phi_1^*)$; hence, $\phi_3-\phi_1^* = \left(\frac{N}{\lambda}\right)^2(\phi_1-\phi_1^*)$; and eventually:

$$\phi_{i+1}-\phi_1^* = \left(\frac{N}{\lambda}\right)^i(\phi_1-\phi_1^*).$$

As i increases, this expression increases preserving the sign of the first difference. Hence, $1:r+1$ locking occurs exclusively with E in range (6). Curve *d* is in a range with no locking phase. Figure 4D illustrates the phases from an arbitrary ϕ_1 to $\phi_6>\lambda$ (with immediate triggering) and $\phi_7=E-rN$. Figure 4E illustrates that starting at ϕ_7 a full cycle of 3 EPSP's returns to $E-rN$ at ϕ_{10}, the locking ratio being $3:3r+2$.

"Locking" refers to the invariance of the timings of EPSP's and spikes relative to each other, i.e., to the fact that the individual EPSP is always preceded and followed by spikes at characteristic intervals. The probabilistic aspects of the "locking" concept are discussed by Kohn (1980). The stable $1:r+1$ locking in Case I-B-b where E is in the closed range $\{rN+\lambda, (r+1)N\}$, is arrived at either directly after fixing $\lambda \leqq \phi_1 \leqq N$ or indirectly after fixing $0<\phi_1<\lambda$. Hence the relation between the pre- and postsynaptic intensities, i.e., E and N, is the crucial issue. Such locking is represented in Fig. 1D, which illustrates that there is a single kind of postsynaptic $(r+1)$-order interval J_{r+1} formed by one shortened first-order interval following,

preceding, or inserted among r natural ones. All j_{r+1} thus equal $(N+\delta^*)+rN=(r+1)N+\delta^*$, and so does their average J_{r+1}. Substitution of δ^* by its value in (11), or Fig. 1D, shows that

$$J_{r+1}=j_{r+1}=E \tag{12}$$

and therefore $J_1=E/r+1$. After a small decrease of E that remains no smaller than $rN+\lambda$ another, still $1:r+1$, locking is established with a new $(r+1)$-order average interval $J'_{r+1}=E'<E=J_{r+1}$: there is, therefore, a monotonic discharge intensification within the segment. A certain decrease will carry E to E' in the range $\{(r-1)N+\lambda, rN\}$ and to a $1:r$ locking (Fig. 1E), with $J'_r=E'$ and $J'_1=E/r$. The shortening from the smallest E with $1:r+1$ locking to the longest with $1:r$, i.e., from $rN+\lambda$ to rN, implies an increase in the first order interval from $\dfrac{rN+\lambda}{r+1}=N-\dfrac{N-\lambda}{r+1}$ to N. Hence there is a "*paradoxical*" *intensity decrease on passing from one segment to the next*, i.e., from $1:r+1$ to $1:r$.

A $1:r+1$ stable locking occurs when E in the $\{N+\lambda,(r+1)N\}$ range: the corresponding postsynaptic average interval of first order J_1 is in the $\left\{N-\dfrac{N-\lambda}{r+1}, N\right\}$ range. This means that *EPSP's arriving at integral multiples of* N, *i.e.*, N, $2N$, ..., *will not affect the postsynaptic intensity.* As r tends to infinity *when the presynaptic discharge intensity decreases, the postsynaptic upper bound tends to* N, i.e., effects are smaller and smaller; on the other hand, *when the EPSP intensity increases,* r *becomes* 0 *and locking is* $1:1$ within pre- and postsynaptic bounds λ and N. *An EPSP interval shortening from the lower bound* $rN+\lambda$ *in the* $1:r+1$ *segment to the upper bound of any one of the lower order segments leads to a postsynaptic interval lengthening* from $N-\dfrac{N-\lambda}{r+1}$ to N. Figure 7 displays the corresponding average rates with presynaptic on the abscissae and postsynaptic on the ordinates.

The pre- vs. postsynaptic intensity graph regions with negative overall slopes and without overt locking are referred to as "*interposed segments*", as they were in the case with IPSPs (e.g. Kohn, 1980; Segundo, 1979). Contrary to that case, however, it is they that exhibit the intensity relation that, opposing the general trend and a naive intuition, are called "paradoxical". Such segments occur with E within the $\{rN, rN+\lambda\}$ ranges $(r\geqq 1)$, independently of ϕ_1. This means that between two successive EPSPs there will be at least r and at most $r+1$ spikes: in turn, this implies that all phases measured with respect to the $(r+1)$th spike are within a range that although unspecified is bounded, since it must be contained in the $\{-N, N\}$ interval. There being an endless number of phases, either they are distributed uniformly, or some are more frequent thus implying some degree of locking. Rescigno (1978) demonstrated that regardless of the periods involved a regular input to, and the output from, a certain class of oscillators will inevitably either lock or approach locking. Glass and Mackey (1979) discuss the issues relevant to the phase-locking observed in a system (where "activity" increases linearly with time and is reset to 0 as soon as a threshold is achieved) when the threshold is modulated sinusoidally. Numerical studies based upon analytical considerations showed that two critical parameters reflected ratios, one of amplitude (threshold modulation to its average) and the other of frequencies (that of the oscillator were the threshold constant to that of the modulation). When their product was high, stable phase-locked patterns occurred practically always: many areas represented simple modulation-to-oscillator frequency ratios, but between them areas with more complex ratios were found. When their product was low, few lockings appeared. These results agreed with their topological considerations which also predicted the existence of irregular, hard-to-describe dynamics in a Cantor set of measure 0 and therefore unobservable in simulations. Glass and Mackey (1979) further point out that, since any real system must have some noise, the latter should expand this domain and it should be possible to encounter the irregular dynamics: this may well be the case in, for example, crayfish stretch receptor neurons (Kohn et al., 1981).

The following considerations constitute an application and elaboration of their conclusions to the present compatible model. All situations described above as without locking imply first E within the $\{rN, rN+\lambda\}$ range, and second a passage in their evolution through Case I-B-a, i.e., imply some EPSP with a phase ϕ_i between λ and N: this holds for I-B-a itself, as well as for I-A-a-ii and I-A-d-i. Consequently, the EPSP that follows the ith will necessarily have the phase $E-rN$ (see above); this, in turn, means that every switch into I-B-a creates an invariant (for each E) situation, that therefore will be followed by a sequence of pre- and postsynaptic firings that are invariant also, extending from one entry into I-B-a to the next. The main conclusion to be drawn is that, since only that phase sequence and no other will occur, it is legitimate to say that *locking is present always* (using the locking criterion discussed by Kohn et al., 1981). The between-discharge correlation will exhibit a periodicity that depends solely on E, N, and λ. Since the numbers of EPSPs and of spikes in each period are integers, *the ratio of the corresponding intensities will always be rational*, and there will be a countable number of them.

The "reference", i.e., the start and end, point in the cycle will be the EPSP at phase $E-rN$ referred to as ϕ_0

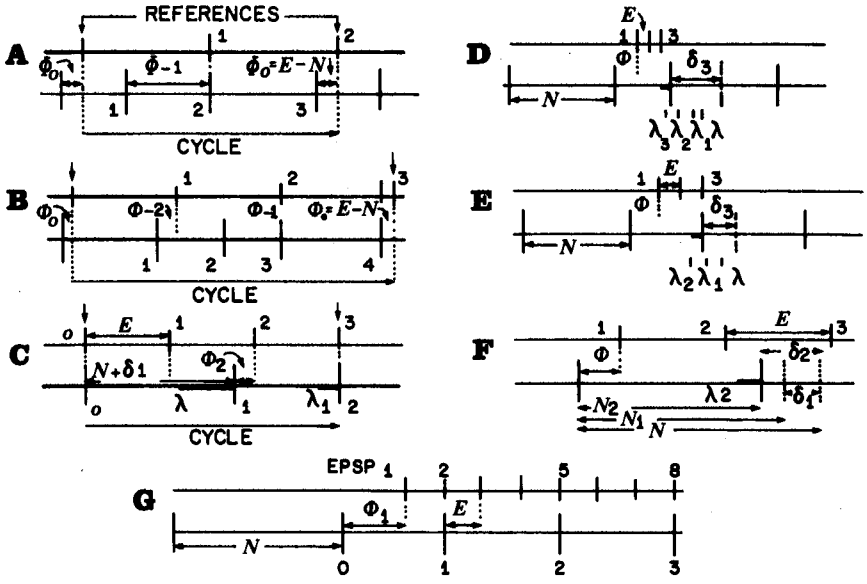

Fig. 5A–F. *Pre- and postsynaptic discharges.* **A–C.** *Higher-order lockings.* See text. **A**, 2:3; **B**, 3:4; **C**, 3:2. Cycles are indicated by horizontal arrows. **D and E** *EPSP triplets.* Delays and shortenings. **F** *Initiation of an intense presynaptic discharge with initial phase* ϕ_1 (Situation II)

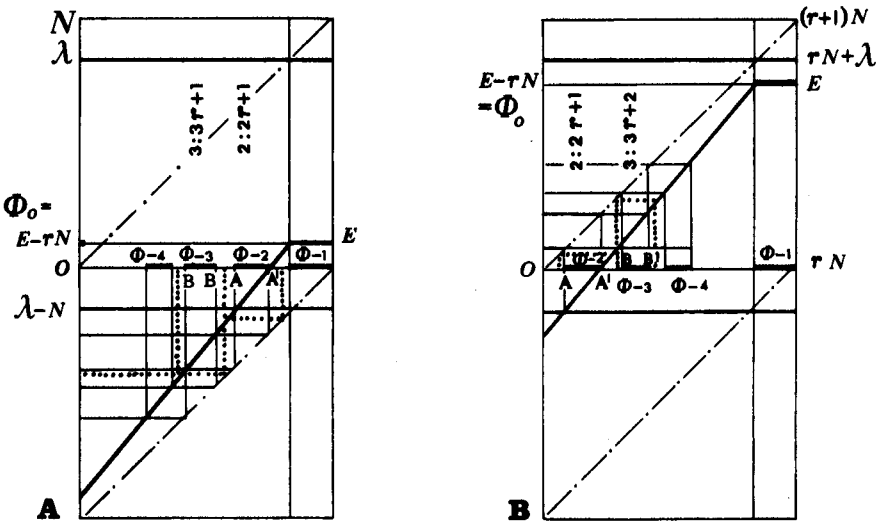

Fig. 6A–B. *Successive phases and higher-order lockings with* $rN<E<rN+\lambda$ (Situation I). **A** E close to rN $(2:2r+1, 3:3r+1)$. **B** E close to $rN+\lambda$ $(2:2r+1, 3:3r+2)$. Mappings go successively through ϕ_{-4}, ϕ_{-3}, ϕ_{-2}, and ϕ_{-1}

(Fig. 5). Preceding it necessarily will be one whose phase ϕ_{-1} is within the immediate triggering range represented as $\{\lambda-N, 0\}$ in Figs. 4A and 6. This inevitable pair brackets r spikes, not counting the triggered one (Figs. 1B and 5A). Phase ϕ_{-1} must be preceded by the phase ranges ϕ_{-2}, ϕ_{-3} in Table 1, as calculated on the basis of (4). Each E determines a reference phase $\phi_0=E-rN$, and a set of bounds. ϕ_0 can never be in the immediate triggering range because $rN<E<rN+\lambda$; it can be, however, in other ranges, and under each bound in Table 1 is the E whose ϕ_0 corresponds to it.

If ϕ_0 is in the ϕ_{-2} range, the cycle that follows consists exclusively of the inevitable pair, namely the triggering one in the ϕ_{-1} range and that at ϕ_0 closing the cycle. The number of spikes in the cycle is $r+1$ (including the triggered one) up to the first EPSP, plus r between the latter and the last EPSP (see above): i.e., $2r+1$, so locking will be in the $2:2r+1$ ratio. The pre- vs. postsynaptic intensity graphs (Fig. 7) will present a positively sloped segment whose ranges are (13) in Table 1 for the abscissa, and the appropriate proportion for the ordinate. The upper bound of the ϕ_{-2} range is the X-intercept A' in Fig. 6. The bounds for the extreme E values are $\left\{\frac{\lambda^2}{N}, \lambda\right\}$ and $\left\{0, \lambda\frac{N-\lambda}{\lambda}\right\}$. For $E=rN+\frac{\lambda}{N+\lambda}$, the upper bound equals the X-intercept. The width of the ϕ_{-2} range is $\lambda-\frac{\lambda^2}{N}$, independent of E: it tends to 0 when λ approaches its

Table 1

	Lower bound	Upper bound	
ϕ_{-1}	$N-\lambda$	N	
ϕ_{-2}	$-(E-rN-\lambda)\frac{\lambda}{N}$	$-(E-rN)\frac{\lambda}{N}+\lambda$	(13)
E	$(rN+\lambda)\frac{\lambda}{N+\lambda}$	$(rN+N)\frac{\lambda}{N+\lambda}$	
ϕ_{-3}	$-\left\{(E-rN)\frac{N+\lambda}{\lambda}-\frac{N^2+\lambda^2}{N}\right\}\frac{\lambda}{N}$	$-(E-rN)\frac{N+\lambda}{N}+N+\lambda$	(14)
E	$rN+\frac{\lambda(N^2+\lambda^2)}{N^2+N\lambda+\lambda^2}$	$rN+\lambda\frac{N^2+N\lambda}{N^2+N\lambda+\lambda^2}$	

possible limits 0 and N, because the bounds both converge to 0 and N, respectively.

If ϕ_0 is within the ϕ_{-3} range (14) in Table 1, the cycle consists of 3 EPSPs (Fig. 5A), one with a phase in the ϕ_{-2} range, plus the inevitable pair. If, on the one hand, E is close to rN (Fig. 6A), the ϕ_{-3} range is to the left of the ϕ_{-2} range, in the region of negative phases. Hence, there will be r spikes up to the next EPSP at ϕ_{-2}, while from the latter to the end of the cycle, there will be $2r+1$ (see above): locking is $3:3r+1$. If, on the other hand, E is close to $rN+\lambda$ (Fig. 6B), the ϕ_{-3} range is to the right in the region of positive phases. Hence, there will be $r+1$ spikes up to the next EPSP at ϕ_{-2}, and $2r+1$ thereafter: locking is $3:3r+2$ (Fig. 5B).

We chose to not pursue this further, partly because the algebra became cumbersome, and partly because of the difficulties in resolving the detailed behavior, as well as the relations it implied between N, λ, and E. *Important issues remain to be clarified:* for example, the bounds of several ranges, their relative positions, the λ and E values for which they are meaningful, the presence or absence of a monotonicity with E of the slopes, etc. Partial answers that were derived suggest certain comments.

The ϕ_{-2} and ϕ_{-3} ranges have no common point (Fig. 6), leaving a space ($B'A$, or $A'B$) between them. This implies that when E moves by small steps from an E that determines a locking initiated at ϕ_{-2}, i.e., $2:2r+1$ to one initiated at ϕ_{-3}, say $3:3r+1$, other lockings must intervene. Moreover, a trajectory (dotted lines) that, corresponding to a particular E, passes through $B'A$ or through AB', comes from that between the ϕ_{-4} and ϕ_{-3} ranges, and proceeds by skipping to the other side of the AA' ϕ_{-2} range. There is an endless number of fractions of the form $\frac{p}{pr+q}$ $(q<p)$ between

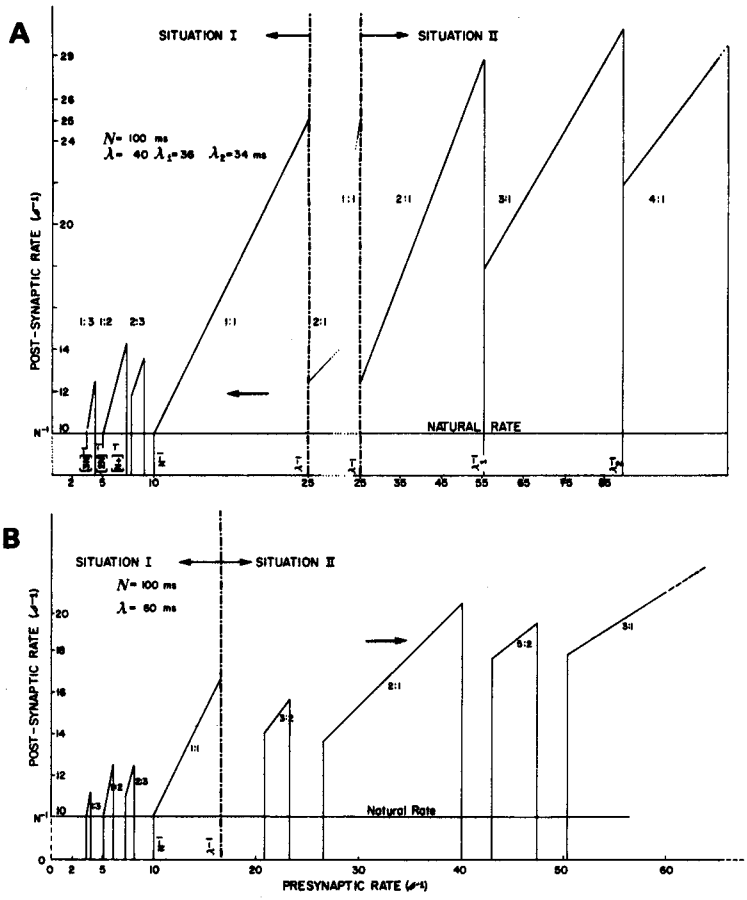

Fig. 7. *Presynaptic vs. postsynaptic steady-state intensities.* Presynaptic mean rate on abscissa, and corresponding postsynaptic rate on ordinate. The upper graph corresponds to $N=100$ ms, $\lambda=40$ ms, $\lambda_1=36$ ms, $\lambda_2=34$ ms: only Case II-A is possible because λ is smaller than $N/2$. The lower graph corresponds to a simulation in an electronic neuromime $N=100$ ms, $\lambda=60$ ms, (with other parameters undetermined): both Cases II-A and II-B exist

$2:2r+1$ and $3:3r+1$. It is unclear to us which ratios are swept on passing from the E with $1:r$ locking to that with $1:r+1$, as well as which are their order and corresponding E ranges. If all fractions are swept, some must have vanishingly small ranges. If only some are, i.e., if there was a bound on the number of EPSPs per cycle, different sets would imply different properties: the set $\left\{\frac{p}{pr+q},\ q=1,\ldots,p-1\right\}$, for example, where p is a large even number with several prime factors, and where fractions with extreme q's exhibit small ranges, would sweep with decreasing slopes practically from $1:r$ to $1:r+1$.

II. More than One EPSP for Each Postsynaptic Spike

It is opportune to stress here two important points, even though both are discussed elsewhere (Diez-Martínez et al., in preparation; Kohn, 1980): both imply that modelling of situation II is more complex, and inevitably will be less firmly grounded upon reality, than that of I. The first is that the parameters involved (see below), influenced in each case by the PSP's in the interval, are joint functions of the latter's phase, number and timing (i.e., span, rate and pattern in the sense of Segundo et al., 1966), and there is scant experimental evidence as to what actually happens: postulates are then based on educated guesses or simply made for convenience. The second point is that in nature the influence of PSP's in one interspike interval, and particularly when there are several of them, extends into the following ones (e.g., Kohn, 1980; Kohn et al., 1981; Schulman, 1969).

The upper bound for E is λ (see above). When a sequence of s closely equispaced EPSPs is delivered, their effects depend on how the successive arrivals on the one hand change the earliest instant where the arrival of an additional EPSP will trigger immediately a spike, and on the other advance (delay negatively) the projected firing. After a non-triggering sequence of EPSPs, the instants (measured from the last spike) of earliest triggering, and projected firing, will be referred to as λ_s, and N_s, respectively; λ and N corresponded to $s=0$. *Postulate iv* demands first that a set of s EPSPs ($s\geqq 1$) that does not trigger shortens the interval preserving the V-shaped delay function and advances the point of immediate triggering, i.e., $N_s<N$ and $\lambda_s<\lambda$; and additional $(s+1)$th EPSP shortens and advances more, i.e., $N_{s+1}<N_s$ and $\lambda_{s+1}<\lambda_s$. Secondly, it demands that, for given phase and s, the shortening and the advance be greater for more tightly packed EPSPs: i.e., $\lambda_s<\lambda_s^1$ if the corresponding E intervals are similarly related. Thirdly, we accept that as E decreases and s increases, λ_s, N_s, and $N_s-\lambda_s$ (always smaller than $N-\lambda$) tend in a monotonically decreasing manner to limits M, N_m, and N_m-M, respectively.

In general, in the course of a sequence of EPSPs evenly spaced at E, that started at a phase ϕ, the "next" postsynaptic spike will be one triggered immediately if and when an EPSP arrives that complies jointly with two conditions: firstly, that each of the s earlier EPSPs $(1,2,\ldots,s)$ arrives at intervals from the last spike [ϕ, $\phi+E,\ldots,\phi+(s-1)E$, respectively], smaller than the extant λ ($\lambda,\lambda_1,\ldots,\lambda_{s-1}$, respectively) determined by the EPSP set that preceded it (none, 1, 1 and $2,\ldots,1$ to $s-1$, respectively); second, that the interval $\phi+(s-1)E$ from the last spike to it be no smaller than the λ_s determined by the s earlier EPSPs $(1,\ldots,s)$ and no greater than the extant time to the projected firing $(N,N_1,\ldots,N_s)$. Figure 5-E illustrates this for $s=2$. The "next" spike will not be one triggered immediately by EPSP $s+1$ under either one of two circumstances. Firstly, when EPSP $s+1$ also precedes the extant λ_s, i.e., $E<\lambda_s-\{\phi+(s-1)E\}$ implying $E<\frac{\lambda_s-\phi}{s}$. Secondly, when E is long enough so that the "λ_s to N_s" interval is clear of EPSPs and EPSP $s+1$ follows the next spike, i.e., $Ns-\{\phi+(s-1)E\}<E$ implying $\frac{N_s-\phi}{s}<E$. For the interval to be clear, it is necessary that $E>Ns-\lambda_s$ (as illustrated for $s=2$ in Fig. 5F).

Postulate iv demands also that, given a sequence of s EPSPs where the last one triggers immediately, there always will be a value of E such that, if shortened by little to $E-\Delta E$, s EPSPs will not longer trigger, even though λ_s is reduced. Finally, *postulate v* sets lower bounds for interspike intervals that reflect the respective refractoriness: postsynaptically, intervals cannot be less than a value U between 0 and λ; presynaptically, E cannot be less than some value which we take smaller than U, so as to be more general.

There are two separate cases. One referred to as *Case II-A* involves $E<N_s-\lambda_s$, where N_s and λ_s are conditional on ϕ and s (only regular arrivals are considered). For the larger s, this case *will exist always for the shortest presynaptic intervals*, providing their lower bound $U\leqq N_m-M$. Under those circumstances, an EPSP sequence II-A will inevitably trigger immediately regardless of its phase at some EPSP, say the sth. The $(s+1)$th will arrive with phase E, and eventually the $(s+s')$th will trigger immediately; the $(s+s'+1)$th will arrive with phase E, the $(s+2s')$th will trigger immediately, and so on. There is, therefore, an $s':1$ locking, with an average postsynaptic interval $s'E$.

If, starting at an $s':1$ locking, the presynaptic discharge were intensified slightly passing to $E-\Delta E$, the s'th EPSP would still trigger and the $s':1$ locking would be maintained: this implies a segment with

slope $1/s'$ (Fig. 7). When, however, the shortening ΔE were that (see postulate *iv*) where the locking shifts to $s'+1:1$, the average interval will jump from $s'E$ to $(s'+1)(E-\Delta E)=(s'+1)E-(s'+1)\Delta E$, which at any given s' implies a weakening of the postsynaptic discharge for sufficiently small ΔE. *Paradoxical slowings* thus occur on passing from one locking to the next, and are in the form of discontinuities. Case II-a can, in fact, be the only case (Fig. 7, upper graph) if the upper bound for E in situation II, i.e., λ, is smaller than $N_s-\lambda_s$ for all s, i.s., $\lambda \leqq N_m - M < N-\lambda$, implying $\lambda < \frac{N}{2}$.

Necessary for this $s':1$ locking (see above) is that the first $s'-1$ not trigger but that the sth trigger: i.e., $(s'-1)E<\lambda_{s'-2}$ and $\lambda_{s'-1}<s'E$. Interval bounds are, presynaptically: $\frac{\lambda_{s'-1}}{s'} \leqq E < \frac{\lambda_{s'-2}}{s'-1}$; postsynaptically $\lambda_{s'-1}$ and $\frac{s'}{s'-1}\lambda_{s'-2}$. Because λ_s has a minimum M, as E shortens and s increases: *i* the presynaptic range of the $s':1$ locking becomes small for intervals and large for rates; and *ii* the postsynaptic intensity $s'E$ tends to a plateau where the interval is M and the rate M^{-1}, a bound whose meaning differs from that set by refractoriness and relating to U. Figure 7 illustrates the relationship between the mean rates in a synapse where only II-A exists (upper graph) and in one with both *A* and *B* (lower graph): among other features, it shows that one same postsynaptic rate (e.g., $12s^{-1}$ at arrow) may correspond to several presynaptic ones.

Case II-B involves $E>N_s-\lambda_s$. This is possible only (see above) for the larger λ, i.e. $\lambda > \frac{N}{2}$. For those large λ, it can occur only for an s such that $N_s-\lambda_s$ is less than the larger E's. We have not been able to analyze this case exhaustively, and will restrict conclusions to the following. Immediate triggering by the first spike depends on the initial phase, some (smaller, equal to, or larger than λ) determining it: hence, the initial phase may influence the subsequent steady-state. Certain combinations of initial phase and of E lead to $s':1$ locking: for example, $\phi_1>\lambda$ and E such that a certain EPSP falls in the immediate triggering region. It is not clear which are the boundaries, nor whether other combinations lead to locking, or do not. Hence, as of now, we accept for II-B interposed segments where behavior is unclear: they should be analyzed in computer or electronically simulated models (Kohn, 1980; Kohn and Segundo, in preparation).

Discussions

The model is relatively simple, as was its counterpart for IPSPs (Kohn, 1980; Kohn et al., 1981; Segundo, 1979). Its postulates are few and straightforward, referring to pre- and postsynaptic regularities to a *V*-shaped delay function whose vertex is the earliest point where an EPSP will trigger immediately, to how several EPSP's affect the latter, and to limits in the firing intensities. Its mathematics are not particularly complex, at times bordering on high-school algebra and everyday logic. Its behavior is characterized by two outstanding features: namely, a zigzag rate relationship with an overall increasing trend (Fig. 7), and the pervasive fact of locking between the pre- and postsynaptic discharges.

In the first place, as the steady-state presynaptic discharge passes from weak to strong, the postsynaptic excited intensity passes from natural to maximum values: the route from one extreme to the other is increasing, as expected. It is increasing only in a general and special way, however. Indeed, a just as apparent feature is that the trajectory from one extreme to the other is formed very predominantly, and perhaps exclusively, by segments whose slopes are positive fractions s/r that decrease with increasing presynaptic intensities, and are broader when the sum of s and r is small (e.g., 1:1, 1:2, 2:1) than when it is large. The passage from one $1:r$ or $s:1$ positively-sloped segment to others is negatively sloped (paradoxical) involving for the more intense presynaptic discharges (i.e., $s \gg 1$) discontinuities, and for weak ones other staggered positively sloped segments whose features (e.g., number, breadths) are unclear. The same postsynaptic intensity may correspond to several presynaptic ones. The highest postsynaptic intensity achieved may reflect how early in the interval the spike can be triggered immediately, as well as pre- or postsynaptic refractorinesses.

The second outstanding feature is the "locking" of the discharges, i.e., the invariant forward and backward temporal relation between pre- and postsynaptic spikes. When the presynaptic firing intensity is weak and there is at least one spike per EPSP, locking is present regardless of the initial phase ϕ_1, or of the presynaptic interval E. It occurs in the simple $1:r+1$ ratio ($r \geqq 0$) if E is in the $\{rN+\lambda,(r+1)N\}$ range, being either stable with E and ϕ_1 at a phase $E-rN$, or unstable at a phase ϕ_1^*. It occurs in other ratios $(2:3,3:4,\ldots)$ if E is in the $\{rN,rN+\lambda\}$ range ($r>0$). EPSP's arriving at integral multiples of N do not change the postsynaptic intensity. When the presynaptic intensity is strong and there is more than one EPSP per spike, locking occurs in the simple $s':1$ ratio ($s' \geqq 2$) and is stable if E is in ranges that depend on the earlist instants for immediate triggering (15). This may be the only possibility when the earliest instant for immediate triggering is very close to the preceding spike. When the earliest instant is far from the preceding spike,

there are ranges of larger E's where locking occurs in other ratios (e.g., 3:2), or may not occur at all, behavior being unclear.

The rest of this section will be framed around three main questions.

First Question. How does one test the validity of a model? A model must be judged against standards provided by the reality of the living entity it is designed to represent. There are two complementary criteria. The first is an *a priori* judgement as to whether the postulates depart reasonably little from nature. This implies deciding, on the one hand, that the relations stipulated between the parameters are realistic, and on the other that important influential issues have not been ignored. Some departure is inevitable, and unknown issues can never be discarded. The second criterion arises *a posteriori* from an experimental examination of whether the natural behavior, in spite of departures and/or other issues, is still compatible with the model's behavior. What this examination tells us is in essence how behavior is modified when conditions depart from those stipulated rigorously in a model, and the domain over which the model is applicable in an admissible way. The expressions "reasonably little", "is still compatible with" and "in an admissible way" are attended with some degree of vagueness and ambiguity. These are less marked than they appear at first sight, however, since many parameters can be evaluated by statistical tests in which the nature and extent of the uncertainty can be expressed precisely. Judging the usefulness of a model, in terms for instance providing insights as to mechanisms (e.g. Kawato and Suzuki, 1980), or predicting behavior patterns, is a somewhat separate issue that will not be discussed here.

Each physical system that is a putative embodiment of the model tolerates departures from the postulates in its own characteristics manner, whose determination ultimately is an empirical question. Though an extensive evaluation of the present model will be presented by Diez-Martínez et al. (in preparation), a preliminary summary follows. Living pacemakers violate postulate *i* about perfect regularity by exhibiting interval coefficients of variation of 1–5% (e.g., Firth, 1966; Kohn, 1980). EPSP's in *Aplysia* neurons shorten postsynaptic intervals, and the shortening depends on the phase in a way close to a V-shaped curve, as required in postulates *ii* and *iii*, respectively (e.g., Fig. 172 in Segundo and Perkel, 1969): they violate *iii*, however, because of some scatter around the best-fitted lines, and because of the practically 0 delays for small phases. PSP's are not instantaneous events: this is particularly true in centrally placed neurons where a powerful compound PSP can be elicited jointly by several synchronized weak synapses. A totally synchronous discharge of several cells would be equivalent to the unitary PSP in the model: the gradual breaking up of a powerful PSP into several less synchronous ones is yet another natural departure to be analyzed, one particularly relevant to central networks.

Insofar as behavior is concerned, the little evidence available is compatible with the notion that some neuronal performances are mimicked fairly well by this model; indeed, locking occurs in *Aplysia* ganglia (Fig. 159 in Segundo and Perkel, 1969) and computer-simulated synapses exhibit zigzag rate relations (Moore et al., 1963; Perkel et al., 1964; Segundo and Perkel, 1969). Furthermore, Hartline (1976) obtained approximately V-shaped delay functions using brief depolarizing current pulses in the tonic stretch receptor neuron of crayfish, noting also that larger pulses led to smaller values. His "active pacemaker model", that includes processes representing an active component that adds to a passive pacemaker potential as well as electrogenic pumping, resembled the living preparation better, and therefore was a better embodiment and justification of postulate *iii*, than an "integrate and fire" model.

This and similar models (e.g., Segundo, 1979) ignore the remarkable experimental finding of hysteresis, i.e., of the fact that estimates of curves as those in Fig. 7 are translated to the right or to the left (and thus "cycles" appear), depending on whether presynaptic rates tested at short intervals are in increasing or decreasing order, respectively (e.g., Kohn et al., 1981; Vibert et al., in preparation). Within the present context hysteresis would imply a change in parameters (e.g., A, B in Segundo, 1979, or λ here). Kawato and Susuki (1980) explain the hysteresis (as well as other behavior) of a circadian pacemaker by assuming it to be composed of two identical oscillators coupled weakly and symmetrically, and subjected to some environmental parameter: stable solutions are only in-phase or only out-of-phase at extreme values of this parameter, but at intermediate ones will be one or the other depending on previous history. Even without hysteresis, the quantitative analysis of periodic stimuli acting upon non-linear oscillations is, as pointed out by Glass and Mackey (1979), extremely complex.

Second Question. Is the model applicable to other systems with periodic manifestations, i.e. to other oscillators? The answer must be affirmative. Indeed, the crucial assertions remain true though the specifics of the language are valid only for synapses with EPSP's. The postulates, on the one hand, demand only certain behaviors (e.g., periodicity, delaying effects, maximum intensities); neither the nature of the entities studied,

nor the underlying mechanisms (in, say, synapse or membrane), nor the role being played in a larger network ever become issues. The logical skeleton of the argument, on the other hand, subsists even if the neurophysiological labels are substituted by different ones. Experimental observations performed in several preparations, though not exhaustive, are entirely compatible with an affirmative answer: the interacting variables have been temperature pulses – Drosophila ecclosion, light-circadian rhythms, lung inflation-phrenic discharge, vagal outflow-heart beat, oxygen concentration-yeast glucose consumption, as well as others (Vibert et al., in preparation; Winfree, 1980). Particularly relevant to neurophysiologists is that where the variables are periodic sensory stimuli and afferent spike discharges.

This question implies the more general one of the possible paths followed by the scientific process that lead to accepting a particular assertion. An example of such an assertion is the first paragraph of this Discussion, from "The behavior of this model ..." to "... postsynaptic discharges". This assertion can be accepted on the basis of any one of the following actions. *i.* By inferring it from experimentation; in other words, by proposing it after observing what actually does happen when living pacemaker neurons interact trans-synaptically, and noting that results are those to be expected were the assertion justified and unlikely were it false. This path, which in fact is essentially the only way that new knowledge can be generated, constitutes the ultimate test. *ii.* By deducing the assertion from general rules that have been accepted at a different level of approach. For example, by taking as premises current notions about basic synaptic mechanisms (transmitter, membrane, thermodynamic), and then passing to the conclusions that are judged necessary in terms of the trans-synaptic relation between spike trains. Or, alternatively, by taking as premises current notions about the operation of a network that includes a synapse with EPSP's, and then passing to the conclusions that are judged necessary in terms of the trans-synaptic relation in that particular component. *iii.* By deducing the assertion from the behavior of some model. For example, if a model of the synapse (the present one; Hartline, 1976; Kohn, 1980; Kohn and Segundo, 1981; Moore et al., 1963; Perkel et al., 1964; Segundo, 1979) performs in a certain manner then we deduce that living ones will too.

A "model" of a system is another system (mechanical, electrical, computer-simulated, mathematical, etc.) that resembles, copies or mimics the first more or less closely. The usefulness of models arises ultimately from the fact that what at first sight simply are fundamental geometrical concepts in space have a broad and ever-increasing domain of application, that can reach numerous fields of logical thought. Because of this, questions posed in fields that superficially appear as quite different have a common core, and therefore are subject to similar answers. This notion has been analyzed and discussed extensively precisely a propos of oscillators (Winfree, 1980). Though the analysis of such fundamental issues often loses much immediate intuitiveness and may become obscure to non-specialists, neurophysiologists cannot avoid recognizing that they are always implicit in their work.

Third Question. How broad is the domain within which the rules of oscillator behavior can be applied legitimately? The answer is contingent on the definition of oscillator. An "oscillator" is an entity (mathematical, physical) whose output shows a periodic variation. At an intuitive level, most would agree that a system such as a perfect clock, where given a manifestation right now one knows exactly from the beginning to the end of time the precise times of past and future manifestations, is an oscillator. Most would agree too that a system, such as a "generator" of white noise or of a Poisson process, where given a manifestation right now one knows absolutely nothing about when past and future manifestations occur, is not an oscillator. Likewise, there would be little disagreement as to the oscillator or non-oscillator character of systems that deviate little from the above; i.e., a system where other manifestations are extremely likely around integral multiples of a certain period and extremely unlikely elsewhere is an oscillator, and one where other manifestations are more likely in broad areas around integral multiples of a certain period and barely less likely elsewhere is not. Separating oscillators from non-oscillators in less extreme cases requires the choice of a "threshold" along a continuum (where spectra provide an appropriate quantification): hence, any system can be accepted, or rejected, as an oscillator providing that the threshold criterion is sufficiently lax, or stringent, respectively. Excepted from the above are only the perfect clock and the white noise or Poisson generator that always will be accepted, or rejected, respectively. Since neither is physically realizable, it is necessary for any real system to ask in which measure it abides by the rules that control oscillator behaviors.

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