brief communication

Applicability of the coefficient of variation method for analyzing synaptic plasticity

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ABSTRACT The classical coefficient of variation method for "quantal" analysis of synaptic responses allows unambiguous identification of pre- and postsynaptic loci underlying synaptic plasticity only when extensive simplifying restrictions are made. They include invariance of quantal parameters and the assumption that a single afferent produces the evoked potentials or currents. More general theoretical formulations and simulations demonstrate that the standard criteria do not always provide useful guidelines because when the other sources of physiological variance are included, putative pre- and postsynaptic domains may overlap. For example, data typically interpreted as indicating modifications at both sites can be due to a mechanism localized to only one of the two, if parameter variances are taken into consideration in the case of a single input cell, or if there are multiple inputs and the stimulus does not activate all of them reliably. With this perspective, other physiologically realistic hypotheses relevant to the expression of synaptic plasticity, such as that during long-term potentiation, can be envisioned.

INTRODUCTION

Neurotransmitters are released from nerve endings in quantal packets, that is, as integer multiples of a minimal unit called a quantum. This notion is largely based on the use of statistical models to describe fluctuations in synaptic transmission at single connections having a number of specialized release sites apposed, in turn, to receptor-channel complexes. The mathematical models incorporate two presynaptic terms, namely p, the probability of evoked release of a quantum and n, the number of available units (del Castillo and Katz, 1954*a*). The latter has more recently been correlated with the number of morphologically identified release sites or active zones (Korn et al., 1981, 1982; Korn and Faber, 1987). In addition, whereas the size of the quantum, q, depends upon both pre- and postsynaptic factors, such as the number of molecules issued by a packet, and the availability of receptors, it is generally treated as a postsynaptic indicator. It follows that a complete quantal analysis (i.e., determination of n, p and q) would permit specification of the locus (pre or post) at which synaptic modifications are expressed in various conditions of plasticity, as, for example, with repetitive stimulation or during long-term potentiation (LTP) and depression (LTD). However, in the central nervous system, experimental limitations, particularly the inability to resolve a quantum, often necessitate indirect approaches centered around changes in the coefficient of variation (CV) of composite evoked synaptic events.

The apparent advantage of the CV method is that if quantal parameters are assumed to be invariant, and a simple binomial description is adopted, $CV = \sigma/M = [(1-p)/np]^{1/2}$, where σ is the standard deviation and $M = npq$ is the mean synaptic response. Consequently, CV is independent of quantal size (see also Martin, 1966; McLachlan, 1978). Then, when synaptic efficacy changes, two extreme cases can be met, depending on whether the pre- or postsynaptic side of the junction is implicated. In the first case, $(CV)^{-2}$ increases or decreases at least as much as M. In the second, $(CV)^{-2}$ is unaffected. These conditions are illustrated (Fig. 1) with the aid of two terms,

$$r = CV^2 \text{ before}/CV^2 \text{ after} \quad \text{and}$$

$$\pi = M \text{ after}/M \text{ before},$$

with π being equivalent to the potentiation factor f, used for studies of LTP (Bekkers and Stevens, 1990), but noncommital here. Specifically, for potentiation the mechanism is postsynaptic when the CV^2 ratio is 1 (i.e., when experimental values are on line I of Fig. 1) and presynaptic if it is on or above the diagonal (points in region designated II), whereas both sites are involved if the ratio is between these two limits (indicated as III). Analogous domains exist with depression.

This reduced framework can mask alternative interpretations because it ignores both intrinsic variations of the individual parameters, regardless of whether one or more connections to the postsynaptic cell are considered, and additional weighting factors associated with intermittent activation of multiple inputs to a polyinnervated neuron. The last point is relevant to the technique

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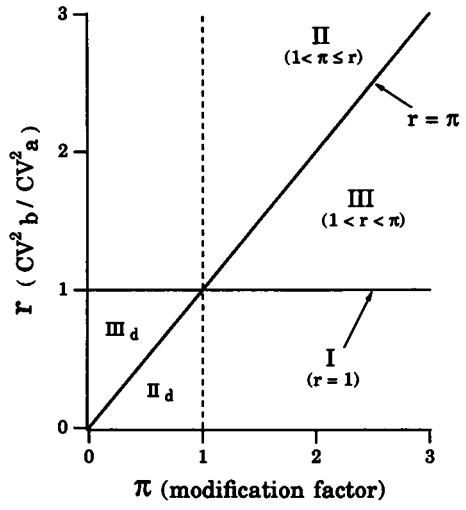

FIGURE 1 Domains of the plot relating the ratio of the coefficients of variation squared (CV_b^2/CV_a^2) to the modification factor (π). Regions I (*horizontal line*), II, and III are to the right of the vertical dashed line and therefore are for potentiation ($\pi > 1$). According to classical interpretations, data in those areas signify that for a single cell the locus for potentiation is postsynaptic when on horizontal line (I), presynaptic when above the identity line (II) or both when between (III). It has been suggested that for multiple inputs with quantal variance, zone III is postsynaptic (Bekkers and Stevens, 1990). Note that there are analogous domains for depression (*d*), corresponding to $\pi < 1$. Subscripts *a* and *b* are as in text.

of minimal intracellular stimulation commonly used to study LTP in hippocampal slice preparations (McNaughton, et al., 1981; Bekkers and Stevens, 1990; Malinow and Tsien, 1990). We consider here the effects of these additional factors on the interpretation of data obtained with the CV method.

METHODS AND RESULTS

Expanded expressions for multiple inputs

The derivations below assume a simple binomial model of release, as has been the case when the CV method has been applied to experimental data (Johnson and Wernig, 1971; Kuno and Weakly, 1972; Lin and Faber, 1988; Bekkers and Stevens, 1990; Malinow and Tsien, 1990). That is, a given presynaptic cell, i, has two release parameters, n_i, the number of release sites, and p_i, the average probability of release per site. Then, when several (N) cells with different parameter sets are activated together the distribution of the postsynaptic responses is no longer a binomial, but becomes the sum of the individual binomials, and the probability that a response consists of a certain number of quanta is expressed by a convolution integral, incorporating all possible combinations producing that outcome.

Including the possibility that all cells are not activated reliably,

$$M = \sum_{i=1}^{N} q_i n_i p_i (1 - pf_i), \tag{1}$$

which is the sum of the different cell's means, with pf_i being the probability of failure of impulse initiation for an afferent. Furthermore, the standard deviation,

$$\sigma = \left[\sum_{i=1}^{N} q_i^2 n_i p_i [1 - p_i + pf_i n_i p_i + c_q^2 - c_p^2(p_i/q_i^2) + c_n^2 n_i p_i](1 - pf_i)\right]^{1/2}, \tag{2}$$

where c_q, c_p, and c_n are the coefficients of variation of the corresponding variables, and are taken to be the same for all connections onto the target cell. Eq. 2 simply states that the total variance, σ^2, is the sum of the variances associated with each presynaptic cell. Despite the complexity of this equation, it can already be appreciated that CV (σ/M) is only independent of quantal size if q_i is the same for all cells (which is hard to conceive for distributed synapses, particularly if a conditioning paradigm has uneven effects on them) and if c_p^2 is zero. This raises the question of whether the clear boundaries illustrated in Fig. 1 for distinguishing pre- versus postsynaptic mechanisms remain valid, and if any domain is unambiguously the "province" of a specific synaptic side. The approach taken here was to determine if postsynaptic changes can generate data in area II, and if incursion into region III can be linked to one parameter alone. That is, can the classical designations be invalidated, under physiologically realistic conditions? The results are presented for facilitation, although analogous conclusions hold for depression. The mathematical expressions delineating each zone are found in Fig. 1.

The r-π relationship for a single input

In this section we consider the effects of c_q, c_p, and c_n separately at a connection reliably stimulated, as in the case of paired intracellular recording. The logic underlying the calculations was to first establish the general expression for r, the ratio of $(\sigma/M)^2$ before (b) to that after (a) a given modification. Replacing M and σ by Eqs. 2 and 3 with $i = 1$, and $pf_1 = 0$ yields the generalized expression,

$$r = \frac{1 - p_b + c_q^2 - c_p^2(p_b/q_b^2) + c_n^2 n_b p_b}{1 - p_a + c_q^2 - c_p^2(p_a/q_a^2) + c_n^2 n_a p_a} \cdot \frac{n_a p_a}{n_b p_b}. \tag{3}$$

Second, only one variance was allowed to be nonzero, to establish its influence on the structure of Fig. 1, with n,

p, or q being the plastic term. For example, to assess the effect of c_p (which represents variations in the release probability from one site to the next) when q was enhanced, Eq. 3 became:

$$r = \left[\frac{(1 - p_b)q_b - c_p^2(p_b/q_b)}{(1 - p_a)q_a - c_p^2(p_a/q_a)} \cdot \frac{n_a p_a q_a}{n_b p_b q_b}\right]$$

because $p_a = p_b$ and $n_a = n_b$. In this case r is always ≤ 1, thereby matching the classical prediction.

Similar derivations were done by selecting c_p, c_q, or c_n and allowing only p, q, or n to facilitate. The results were essentially as predicted in Fig. 1 for the outer sectors. More specifically, area I relates to postsynaptic changes and can be expanded below the line (i.e., $r \leq 1$), and data in area II always indicate a presynaptic mechanism.

In contrast, values in III did not always force composite explanations. For example, they could result from, (*a*) a purely presynaptic process, namely an increase in n, with the constraint that $c_n^2 n_b > 1$, and (*b*) only an increase in q if accompanied by a change in c_q^2. The requirement for the latter condition is

$$\Delta c_q^2 < (1 - p_b + c_{qb}^2)(\pi - 1)/\pi,$$

with $\Delta c_q^2 = c_{qa}^2 - c_{qb}^2$, and it is always met if c_q^2 decreases. One must ask whether these conditions might occur physiologically.

The first case can be achieved if a presynaptic impulse intermittently fails to invade some terminal arborizations (Lüscher et al., 1979), particularly when n is relatively large, and if potentiation relieves that block. The second is more novel: it corresponds to an increase in q associated with a decrease of its variance. This may happen if the cluster of functional postsynaptic receptors is somewhat labile in control conditions (i.e., significant variance) and if potentiation both enhances the availability of the receptors and maintains them in a responsive state.

The r-π relationship for multiple inputs

The qualifications described above also pertain when more than one afferent is excited. Therefore, we focus here on situations where some pf_is are nonzero. The corresponding experimental condition is when an extracellular electrode is placed within a bundle of fibers projecting to the recorded target cell. Then even if one attempts to activate a single afferent consistently, using a "minimal stimulation paradigm" (McNaughton et al., 1981), the stimulus strength might well straddle threshold for more than one axon. Obviously this adds another source of uncertainty in addition to that inherent to release. Simplifying Eq. 2 by eliminating parametric variances yields

$$\frac{\sigma}{M} = \frac{\sum_{i=1}^{N} q_i^2 n_i p_i[1 - p_i + pf_i n_i p_i](1 - pf_i)}{\sum_{i=1}^{N} q_i n_i p_i(1 - pf_i)}. \quad (4)$$

Despite the fact that CV now depends upon quantal size, computations based on Eq. 4 show that regardless of the values assigned to q_i, n_i, p_i, pf_i, this coefficient remains constant if the only effect of potentiation is to elevate all q_is by the same factor. Then $r = 1$, as in the case of a single cell. Similarly, if the presynaptic parameters n_i and/or p_i are each enhanced uniformly, r is $\geq \pi$. However, because some forms of synaptic plasticity, such as LTP, are activity dependent, it is critical to consider the likelihood that one of these parameters undergoes a Hebbianlike adjustment. That is, its increment should be scaled as a function of $1 - pf_i$.

Effect of distributed postsynaptic changes

To simulate a nonlinear modulation of q_i for different degrees of potentiation, the expression used was

$$q_{i,a} = q_{i,b}[1 + \lambda(1 - pf_i)^x] \quad (5)$$

with $x > 1$ and λ representing the proportional increase in quantal size when a cell is activated all the time. Thus, constant increments in λ produce progressively greater amounts of potentiation of each connection. The resulting dependency of q_a on the power function $(1 - pf_i)^x$, which accounts for activity related potentiation, is illustrated for $x = 2$ and two values of λ in Fig. 2 (*left*). The relationship becomes even more nonlinear for larger values of x.

Diverse $r - \pi$ plots could be generated by combining Eqs. 4 and 5 to calculate CV^2 before and after different levels of potentiation, by varying λ systematically. The most interesting outcome was that, as shown in Fig. 2 (*right*), data points could be in region II of the $r - \pi$ space in Fig. 1, despite the absence of presynaptic involvement. The inequality delineating the lower boundary of this region ($r \geq \pi$) is

$$\sigma_b^2 \cdot Ma \geq \sigma_a^2 \cdot Mb. \quad (6)$$

It can be satisfied by a variety of conditions which are difficult to generalize, given all the independent variables, including the number of cells, N, their probability of not being excited (pf_i), the mean quantal contents, $n_i \cdot p_i$, and the order x taken for the power function; increasing any one of these factors extends the range over which the classical rule is untenable. The examples shown were obtained with a few afferents and moderate

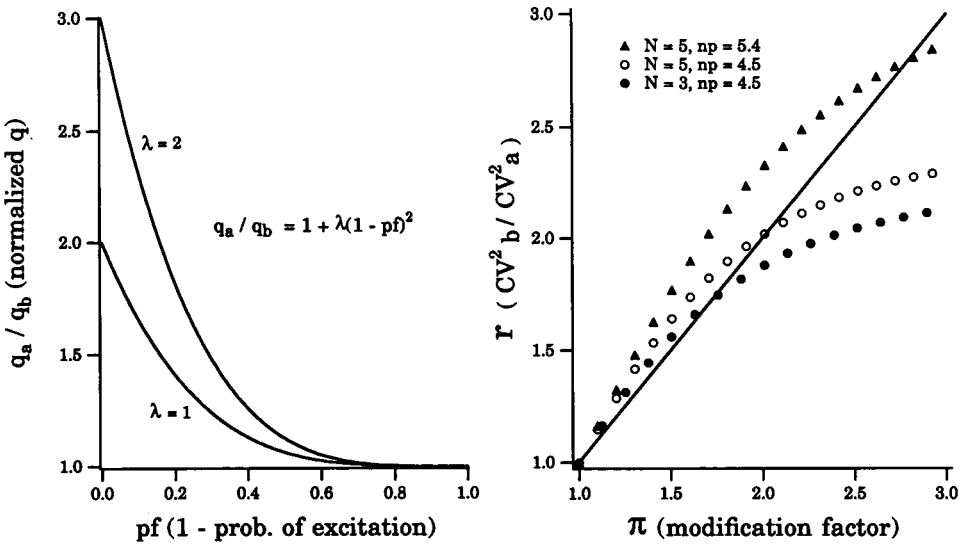

FIGURE 2 Invasion of the presynaptic domain with uneven potentiations of quantal size. (*Left*) Algorithm used to scale quantal amplitudes nonlinearly as a function of *pf*, which is the probability that stimulation fails to evoke an afferent impulse. For simulations λ, the incremental potentiation for a cell always excited, was systematically increased from 0 to 3.8 (▲, ○) or 3.2 (●), with a step size of 0.2; curves are shown for two values of this parameter. (*Right*) Relation between changes in synaptic efficacy (π) and the reduction of the CVs squared (ordinates) after potentiation of several cells (N), assuming an increase of q alone, according to the equation indicated in the accompanying graph. For this and subsequent simulations, initial values of all qs were 1. Parametric values were: N, as indicated, all $n_s = 9$; $p = 0.5$ (●, ○) and 0.6 (▲), $pf_1 = 0$ for reliable activation of one cell, $pf_2 = 0.6$; $pf_3 = 0.8$; $pf_4 = 0.7$; $pf_5 = 0.9$. Note that incursion into region II is greater as either N or the mean quantal content increase.

quantal contents, to match likely experimental conditions, in slice or intact brain preparations. They all indicate a tendency for the CV^2 ratio to cross over into region III as potentiation increases.

As already mentioned (Korn et al., 1991), predicted values in region II cover a broader range if the neurons have relatively large *np* products or more cells are involved. Also, although q is the concerned variable, it was interesting to find that this range could be very sensitive to the release probability of the cell excited most reliably, as shown in Fig. 3.

Influence of presynaptic modifications

The limitations of the CV method are amplified by the outcome that when the presynaptic term p is scaled nonlinearly, the CV^2 ratio can be $< \pi$ and may even reach the value of 1 that is classically used to establish a postsynaptic locus. The basic formulation used is

$$p_{i,a} = p_{i,b} + (p_{max} - p_{i,b})(1 - e^{-\kappa(1-pf_i)x}), \quad (7)$$

where p_{max} is the upper limit reached by the probability of release, and κ is a variable scale factor for p which is analogous to λ for q and allows different degrees of synaptic efficacy to be reached. This is exemplified in Fig. 4 (*left*) for three values of this term. The equation incorporates an exponential scaling term, as opposed to the simpler formulation used for quantal size, because of the constraint that p_i have an upper bound of 1 or less.

Plots obtained by combining Eqs. 4 and 7 for different κs are in Fig. 4 (*right*). A variety of parametric sets could generate data in region III when only p was changed, although the necessary conditions were not explored systematically. Comparison of the computer generated curves does suggest, however, that there is a greater tendency for points to remain on the diagonal before crossing from II to III when there is more room for p to increment, for example, when it is initially low. It should be noted that the conditions which produced r values approaching 1 (i.e., the "postsynaptic domain") for significant potentiations, namely an inverse relationship between p_i and pf_i (see table in Fig. 4 legend), may not be physiological.

DISCUSSION

The coefficient of variation method is an indirect one, typically invoked when single quanta cannot be resolved. Generally this situation occurs when the quantal unit of interest is too close in magnitude to that of the back-

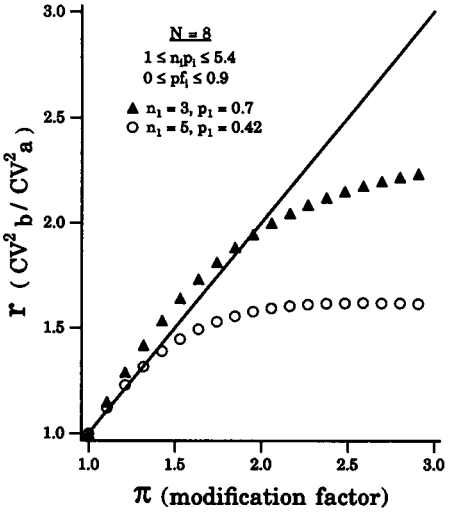

FIGURE 3 Effect of different np combinations on the $r - \pi$ plot obtained with nonlinear scaling of quantal size. Same protocol as for Fig. 2, with λ varying from 0 to 5.4 in increments of 0.3. A population of eight cells, each having different quantal contents ($n_i p_i$) and probabilities of being excited ($1 - pf_i$), was selected. Parameters were, for *o*:

Cell	1	2	3	4	5	6	7	8
n	5	3	2	5	8	3	4	7
p_b	0.42	0.6	0.5	0.6	0.5	0.5	0.5	0.5
p_f	0	0.2	0.3	0.5	0.7	0.8	0.9	0.9

The only change for curve (▲) was $n_1 = 3$ and $p_1 = 0.7$. That is, p was larger but the quantal content remained the same. This single alteration significantly increased r for comparable levels of potentiation, with a consequent shift of the curve into region II.

ground noise, (even in patch clamp), is variable and/or cannot be distinguished from events due to activity in other inputs. In turn, these complications introduce large intrinsic standard errors that make it difficult to interpret changes in CV, as already stressed by others (Martin, 1966; McLachlan, 1978). For example CV^2 must be corrected for the variance of the background (instrumental) noise, using the relation $\sigma^2 = \sigma^2_{measured} - \sigma^2_{noise}$, a calculation only reliable when the sample size is very large; it is not surprising that when determined with this technique, the mean quantal content has often been greater than when obtained differently (e.g., Foster and McNaughton, 1991). Also, the interpretation of the computed results depends upon assumptions about the release process, the parametric variances and, for extracellular stimulations, N and pf_i. Indeed, data on hippocampal LTP falling in region III of Fig. 1 has been taken as indicating a presynaptic locus according to one set of assumptions (single cell stimulation, $c_q^2 = 0$; Malinow and Tsien, 1990), but would have been indicative of a postsynaptic one according to another set (multiple inputs, $c_q^2 > 0, pf_i = 0$; Bekkers and Stevens, 1990).

The general equations used here (1 and 2) are for multiple inputs with different release parameters, assuming a simple binomial model, for reasons noted above. But, they also apply to conditions where the probability of release varies significantly from site to site, i.e., to a compound binomial, for one or more inputs. Then, p_i would refer to the release probability at individual sites and n_i to the number of synapses having the same p value. Clearly, the CV method has minimal utility, if any, in this situation as well. It would also be further compromised if parametric variances were not the same for all inputs and/or all sites.

Most attempts to fit amplitude distribution histograms at single connections have found that a binomial model, whether simple or compound, is superior to a Poisson (reviewed in Korn and Faber, 1987; Redman, 1990). That is, p and n are finite, the last term having a physical counterpart (Korn et al., 1981, 1982; Triller and Korn, 1982). Yet, data from the hippocampal slice preparation with minimal extracellular stimulation were fit better with a Poisson (Bekkers and Stevens, 1990). This raises the question of whether a convolution of binomials may approximate a Poissonlike probability density function. For the latter, $(\sigma/M)^2 \cdot M = 1$ (because the variance equals the mean); thus Eq. 4 yields

$$1 = \frac{\sum_{i=1}^{N} q_i^2 n_i p_i [1 - p_i + pf_i n_i p_i](1 - pf_i)}{\sum_{i=1}^{N} q_i n_i p_i (1 - pf_i)},$$

and computer simulations demonstrate that this condition can be satisfied by a variety of conditions for a few cells as long as pf_i is nonzero for some of them. In these cases, the Poisson fit can be better than or at least as good as the optimal binomial and may even more closely approximate the rate of failures. For example, the prob- ability p_o of failures when all $pf_i = 0$ is $\prod_i (1 - p_i)^{n_i}$ because all cells are active synchronously. The corresponding term when $pf_i > 0$ is

$$p'_o = \prod_i [pf_i + (1 - pf_i)(1 - p_i)^{n_i}],$$

the two internal terms representing failures to excite a cell, and for this cell to not release when activated, respectively. It is obvious that in all cases, $p'_o > p_o$. High overall failure rates, which is the condition where a Poisson is most likely to be superior to the binomial, thus could reflect either (*a*) the release property of a single cell, with a low p, or (*b*) unreliable stimulation of a few, with no indication about their release characteristics.

Our formulations stress instances where the classical

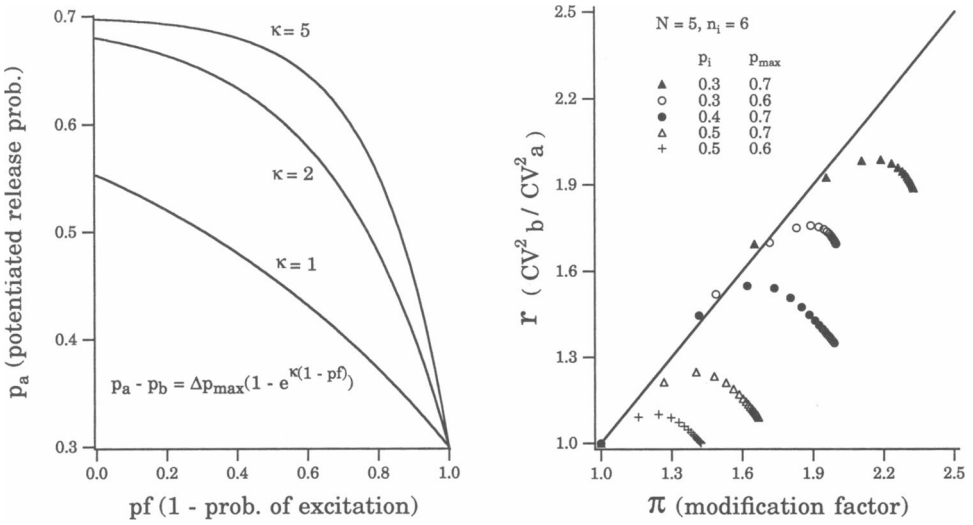

FIGURE 4 Extension of presynaptic modifications into area III. (*Left*) Hypothetical activity-dependent augmentation of the release probability, according to the indicated relationship, where subscripts *a* and *b* refer to after and before modification, respectively, Δp_{max} is the maximum increase in p to its upper limit and κ is used to obtain different degrees of potentiation. For the illustrated curves, $p_b = 0.3$, $\Delta p_{max} = 0.4$. (*Right*) Simulated $r - \pi$ plots for a population of five cells, with six release sites each, and different combinations of initial p_i, pf_i and p_{max}. Each curve was obtained by incrementing κ in steps of 1.0, from 0 to upper values ranging between 20 and 35. From bottom to top, the release parameters were,

	p_1	p_2	p_3	p_4	p_5	pf_1	pf_2	pf_3	pf_4	pf_5	p_{max}
+	0.5	0.4	0.3	0.3	0.3	0	0.5	0.7	0.8	0.9	0.6
Δ	0.5	0.4	0.3	0.3	0.3	0	0.5	0.7	0.8	0.9	0.7
●	0.4	0.3	0.3	0.3	0.3	0	0.6	0.7	0.8	0.9	0.7
○	0.3	0.3	0.3	0.3	0.3	0	0.3	0.5	0.7	0.9	0.6
▲	0.3	0.3	0.3	0.3	0.3	0	0.3	0.5	0.7	0.9	0.7

Note that as the range over which p can be enhanced (Δp_{max}) expands, data values remain in region III for larger potentiations.

use of the CV may be misleading in absence of further information, specifically knowledge of the quantal size and of its variability. Lacking these essentials, which have not been clarified in most central structures, such as the hippocampus, despite enormous attention, an alternative approach could be to compare the rate of failure before and after potentiation (del Castillo and Katz, 1954*b*; Kuno, 1974; Kuno and Weakly, 1972). However, this measurement is also compromised by the inability to assess the quantum, and, therefore, a failure. If as considered here, LTP increases q at some connections, there could be an apparent decrease of p'_0 in the absence of presynaptic changes, particularly if the signal to noise ratio is low, due to a small initial q.

Two of the exceptions to the standard interpretations of changes in CV^2 described in this report involve an uneven enhancement of q and/or a reduction of its variance. Both are physiologically realistic, as may be other solutions embedded in the most general formulations, but not addressed here.

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