A COMMENT ON MARTIN'S RELATION

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ABSTRACT In the limit of slowly varying synaptic conductance changes, a quantity proportional to the quantal content of a synaptic potential is provided by Martin's formula: $1/(V_o/V_p - 1)$, where V_p is the peak amplitude of the synaptic potential and V_o is the synaptic equilibrium potential. If the synaptic conductance change is not slowly varying on the time scale of the postsynaptic cell's membrane time constant, Martin's formula overestimates the effects of nonlinear summation and provides an upper limit for the actual quantal content. In the limit of rapidly varying synaptic conductance changes the quantity $\ln(1/[1 - V_p/V_o])$ is proportional to the quantal content. This formula underestimates the effects of nonlinear summation and gives a lower limit for the quantal content for cases in which the synaptic conductance is not rapidly varying. These two formulas used together provide upper and lower bounds to the correction for nonlinear summation of postsynaptic potentials.

Martin's correction for the nonlinear summation of quantal contributions to a synaptic potential has been important and widely used since its introduction in 1955 (1). Although this correction is known to be only approximately accurate (1, 2), its use has continued because a more precise relationship is not available and because errors made by using Martin's original formulation are usually felt to be not large.

To correct synaptic potentials for nonlinear summation, Martin proposed that the peak postsynaptic voltage change V_p be divided by the quantity $(V_o - V_p)$, where V_o is the equilibrium potential; voltages here are represented as differences from resting potential and depolarizations are positive. The ratio $V_p/(V_o - V_p)$ then gives the relative quantal content m; that is, $V_p/(V_o - V_p)$ is proportional to m. Specifically, Martin's relation (1) is

$$V_p/(V_o - V_p) = mg_p/G, \tag{1}$$

where g_p is the peak synaptic conductance change and G is the conductance of the resting cell.

Discussions of Martin's relation have suffered from two main difficulties. First, the nerve or muscle cell under consideration has been treated as being electrically equivalent to a simple parallel resistor-capacitor circuit, whereas most real cells have more complicated equivalent circuits. Second, although Martin's relation is known to overestimate the quantal content (2), the size of the errors in estimation are generally unknown.

The purpose of this communication is first, to present a derivation of Martin's relation that does not assume a specific equivalent circuit for the cell under investigation, and second, to provide a new relation that supplements Martin's original equation. The supplementary equation gives an alternative correction for nonlinear summation and permits bounds to be placed on the errors made in estimating quantal contents.

A synaptic region small enough to be isopotential injects a current into a cell that is proportional to the synaptic conductance change and the driving potential:

$$i(t) = mg(t)[V_o - V(t)],$$

where $i(t)$ is the current injected through the synaptic region at time t, $g(t)$ is the synaptic conductance increase due to one quantum, m is the number of quanta, $V(t)$ is the deviation of the membrane potential from its resting level, and V_o is the synaptic equilibrium potential (measured as deviation from the resting potential). Provided that the cell in which the synaptic current flows may be represented as a time invariant linear system, the voltage change $V(t)$ produced by synaptic action is given by the integral equation

$$V(t) = \int_0^t K(t - \tau)\, i(\tau)\, \mathrm{d}\tau = m \int_0^t K(t - \tau)\, g(\tau)(V_o - V(\tau))\, \mathrm{d}\tau. \quad (2)$$

$K(t)$ is the impulse response of the cell in question, that is, the voltage change produced by a delta function application of current. Two limiting cases—very slowly and very rapidly varying $g(t)$—will yield Martin's relationship and a new equation for estimating relative quantal content. Martin's relation, then, will be exact in the limit of very slowly varying conductance changes; the new relation will be appropriate for the limit of conductance changes that are rapid on the time scale set by the $K(t)$ relaxation. These two relations turn out to provide upper and lower bounds on the relative quantal contents for intermediate cases.

Suppose, as Martin (1) originally did, that the synaptic conductance change $g(t)$ is slowly varying on the time scale set by the passive membrane (and cable) properties of the nerve or muscle cell. In that limit $K(t)$ acts like a delta function, so that the membrane potential change produced by synaptic activation is given by

$$V(t) = mg(t)[V_o - V(t)] \int_0^\infty K(\tau)\, \mathrm{d}\tau.$$

This may be rearranged to give a version of Martin's relation

$$V_p/(V_o - V_p) = m\left[g(t_p) \int_0^\infty K(\tau)\, \mathrm{d}\tau\right] \quad (3)$$

where V_p is the peak voltage change produced by synaptic action and the peak occurs at time t_p. Since voltage follows conductance exactly in the limit of slowly varying $g(t)$, $g(t_p)$ is a constant.

If $g(t)$ is rapidly varying the synaptic current acts like a delta function to give

$$V(t) = mK(t) \int_0^t g(\tau)(V_o - V(\tau))\,\mathrm{d}\tau \tag{4}$$

Note that, in the limit of rapidly varying $g(t)$, an integral equation again results because $V(t)$ will in general not be slowly varying during the period of synaptic current flow even if $K(t)$ is.

Fortunately this type of integral equation is easily solved. Write Eq. 4 as

$$V(t) = mK(t)I(t), \tag{5}$$

where $I(t)$ is

$$I(t) = \int_0^t g(\tau)(V_o - V(\tau))\,\mathrm{d}\tau$$

The derivative of I is

$$\mathrm{d}I/\mathrm{d}t = g(t)(V_o - V(t)) = g(t)\,V_o - g(t)\,mK(t)\,I(t).$$

This differential equation for $I(t)$ is solved to give

$$I(t) = V_o \int_0^t g(\tau) \exp\left[-\int_\tau^t mK(x)g(x)\,\mathrm{d}x\right]\mathrm{d}\tau,$$

which may be substituted back into Eq. 5 to provide the solution

$$V(t) = \mathrm{m}\,V_o\,K(t) \int_0^t g(\tau) \exp\left[-\int_\tau m\,K(x)\,g(x)\,\mathrm{d}x\right]\mathrm{d}\tau.$$

Since the conductance change occurs, by assumption, so rapidly that $K(t)$ has no chance to relax from its initial value during the $g(t)$ transient, V_p is thus given by

$$\begin{aligned} V_p &= m\,K(0)\,V_o \int_0^\infty g(\tau) \exp\left[-\,m\,K(0) \int_\tau^\infty g(x)\,\mathrm{d}x\right]\mathrm{d}\tau \\ &= V_o\left(1 - \exp\left[-\,m\,K(0) \int_0^\infty g(x)\,\mathrm{d}x\right]\right). \end{aligned}$$

The integral has been done by change of variable. Rearranging this last relationship and taking logarithms, one obtains the final relationship for nonlinear summation of synaptic events that holds in the limit of rapid changes in conductance:

$$\ln[V_o/(V_o - V_p)] = m\left[K(0) \int_0^\infty g(\tau)\,\mathrm{d}\tau\right]. \tag{6}$$

For small synaptic potentials, that is for small values of V_p/V_o, both relationships reduce approximately to V_p, so that synaptic potential amplitude is simply proportional to quantal content. Thus both relationships predict, as they should, linear summation of synaptic potentials far from the equilibrium potential. As V_p approaches V_o

both equations approach infinity, but Martin's relationship grows much more rapidly than does Eq. 6 because of the compressing effect of the logarithm. The Eq. 6 correction is always less than or equal to Martin's correction, and the difference between the two grows larger as V_p approaches V_o.

Straightforward arguments starting from Eq. 2 confirm what one would expect intuitively: when the synaptic conductance change is intermediate between the two limiting cases, Eq. 6 undercorrects in estimating quantal content and Martin's relation overcorrects. For synapses such as the neuromuscular junction at which the conductance change is considerably more rapid than the membrane time constant (3), Eq. 6 would provide a more accurate estimate. Martin's relation is preferable when the conductance change is slowly varying as occurs at certain central synapses (e.g. see ref. 4). Since precise limits on the accuracy of estimates cannot be made without detailed knowledge of the cell's impulse response, the most favorable situation is one in which Martin's correction is not very different from the Eq. 6 result.

Although Martin's relation and Eq. 6 gives bounds on the correction for nonlinear summation, the actual correction may not be contained within the bounds set because assumptions made in the derivation may not be met. First, the synaptic region must be isopotential for the relationships derived above to hold, but this condition does not always occur in practice. The frog neuromuscular junction, a preparation to which Martin's correction is frequently applied, can have a synaptic region that stretches for a significant fraction of the DC space constant, and for an even larger fraction of the frequency-dependent space constant more applicable to the rapidly changing synaptic potential (5). Second, the function $g(t)$ that describes the time course of conductance changes produced by a single quantum is assumed to be voltage independent. As first shown by Kordas (6), however, neurotransmitter produced conductance changes may have time courses that depend significantly on membrane potential. Third, the synaptic equilibrium potential V_o is assumed to be constant, but ion accumulations in some instances may cause significant deviations. Fourth, the impulse response $K(t)$ must be voltage independent for the equations above to hold, but voltage-activated conductances and rectification occur so commonly that this assumption is seldom exactly true. Finally, the above treatment assumes that the synaptic potentials are recorded at the site of their generation, and errors result if this is not the case.

Because actual situations depart significantly from the idealization represented in Martin's relation and Eq. 6, it is much better to estimate a quantal content under voltage clamp conditions. When voltage clamp experiments are for some reason impossible or inconvenient to carry out, Eq. 6 in conjunction with Martin's relation should prove helpful in correcting for nonlinear summation.

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