

## Noise in the Foreground. Focus on “A Method to Estimate Synaptic Conductances From Membrane Potential Fluctuations”

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How does one measure synaptic conductances? Textbooks tell us to perform a voltage-clamp experiment: clamp the cell at several potentials, measure the amplitude of the synaptic current, plot the current-voltage relationship and obtain the conductance from the slope, and the reversal potential from the intercept. In practice, due to space-clamp problems, one rarely has true voltage control over the synapse in question even if it is close to the soma. In addition, series resistance further attenuates and filters the current. Now try to repeat this experiment *in vivo* under massive synaptic bombardment. This is no longer trivial. In an elegant paper appearing in this issue of the *Journal of Neurophysiology* (p. 2884–2896) Rudolph et al. (2004) address this problem by presenting a new method for the estimation of synaptic conductances from fluctuations in the membrane potential, proving again that the road less traveled may be the more interesting.

To fully appreciate the paper by Rudolph and colleagues (2004) one really should first read their earlier publication (Rudolph and Destexhe 2003) in which they derive, using stochastic calculus, an analytic expression for the steady-state distribution of  $V_m$  measured under conditions of intense network activity. They now take this analytic expression one step further, by deriving a simple expression linking the means and SDs of two subthreshold  $V_m$  distributions (measured at two different constant levels of current injected via the recording electrode in current-clamp mode) to the mean excitatory and inhibitory synaptic conductances and to their variances. A simple experiment to carry out: measure subthreshold activity in the high-conductance state, generate the amplitude histogram from the recordings, fit the histograms to a Gaussian distribution, obtain the means and SDs, plug them into the simple equation derived by Rudolph and colleagues and get the mean excitatory and inhibitory conductances. The method was tested on a series of numerical models of increasing complexity to show that it was reasonably accurate even in the face of nonlinear dendritic synaptic integration. It is important to note that the method is currently applicable to a mixture of AMPA and GABA<sub>A</sub> conductances with known reversal potentials. The effects of NMDA and GABA<sub>B</sub> have yet to be investigated. The authors also acknowledge that their method for estimating the leak conductance may be a potential source of error especially for *in vivo* recordings.

Using dynamic-clamp, Rudolph and colleagues (2004) apply their conductance estimation method to an excited slice preparation (Sanchez-Vives and McCormick 2000) and show that in the high-conductance state the estimated inhibitory synaptic conductance parameters were twice as large as those of excitatory conductance. This conductance ratio was then used to recreate high-conductance states using the dynamic-clamp configuration. Their results touch a sore point that most of us suppress when examin-

ing brain slices. Background synaptic activity in brain slices is low. This leads to a higher membrane resistance ( $R_m$ ) and consequently to a slower membrane time constant ( $\tau$ ) and longer passive space constant ( $\lambda$ ) as compared with that observed *in vivo*. Therefore synaptic integration in brain slices displaying low background synaptic activity is different from *in vivo* (Bernander et al. 1991; Destexhe and Pa e 1999; H o and Destexhe 2000; Pa e et al. 1998). This problem raises several important questions. To what extent can we learn from results obtained *in vitro* about synaptic integration *in vivo*? Is it enough to scale membrane properties in cellular models obtained *in vitro* to reliably simulate *in vivo* properties? Isn't it more likely that increased synaptic activity will lead to nonlinear changes in synaptic integration? This can be the result of morphological characteristics of the dendritic tree, changes in the activation or inactivation states of voltage-gated ion channels, and modulation by metabotropic receptors activated by neurotransmitter spillover.

The paper by Rudolph et al. (2004) brings to the forefront important aspects of the investigation of synaptic integration. First, this new technique opens possibilities for investigations of synaptic integration both *in vitro* and *in vivo*. Personally, I am looking forward to the combination of this methodology with dendritic recordings of  $V_m$  so that we may learn how dendrites transform information under synaptic bombardment. Second, high-conductance states are fragile and respond badly to the standard pharmacological toolkit of the electrophysiologist. The proposed methodology should direct us to developing more tools that will be able to extract information from a highly noisy neuron. Finally, we who investigate synaptic integration in the quiescent slice preparation should start exploring the transformation of information in a neuron that is really doing what it is supposed to do, integrating many synaptic inputs simultaneously.

### REFERENCES

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