**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 neuronal complexity, including 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 (Bernader et al. 1991; Destexhe and Paë 1999; Hő and Destexhe 2000; Paë 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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