

On the Use of Analytical Expressions for the Voltage Distribution to Analyze Intracellular Recordings

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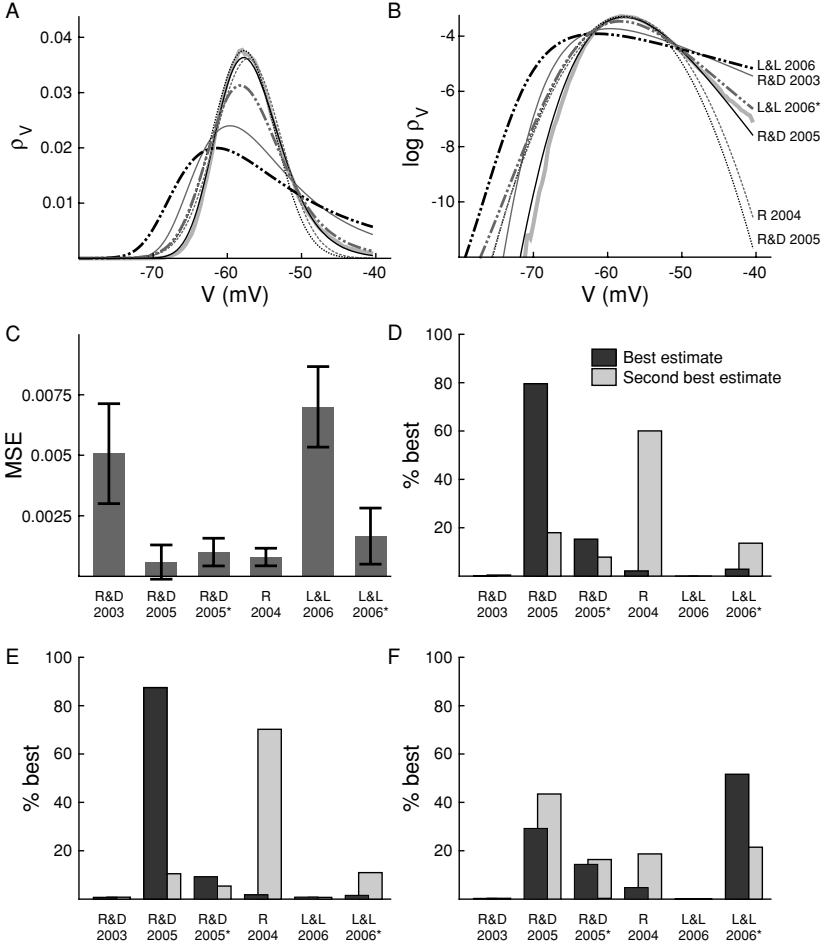
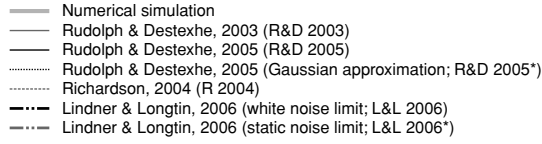
Different analytical expressions for the membrane potential distribution of membranes subject to synaptic noise have been proposed and can be very helpful in analyzing experimental data. However, all of these expressions are either approximations or limit cases, and it is not clear how they compare and which expression should be used in a given situation. In this note, we provide a comparison of the different approximations available, with an aim of delineating which expression is most suitable for analyzing experimental data.

Synaptic noise can be modeled by fluctuating conductances described by Ornstein-Uhlenbeck stochastic processes (Destexhe, Rudolph, Fellous, & Sejnowski, 2001). This system was investigated by using stochastic calculus to obtain analytical expressions for the steady-state membrane potential (V_m) distribution (Rudolph & Destexhe, 2003, 2005). Analytical expressions can also be obtained for the moments of the underlying three-dimensional Fokker-Planck equation (FPE) (Richardson, 2004) or by considering this equation under different limit cases (Lindner & Longtin, 2006). One of the greatest promises of such analytical expressions is that they can be used to deduce the characteristics of conductance fluctuations from intracellular recordings *in vivo* (Rudolph, Piwkowska, Badoual, & Destexhe, 2004; Rudolph, Pelletier, Paré, & Destexhe, 2005).

A recent article (Lindner & Longtin, 2006) provided an in-depth analysis of some of these expressions, as well as different analytically exact limit cases. One of the conclusions of this analysis was that the original expression provided by Rudolph and Destexhe (2003) was derived using steps that were incorrect for colored noise and that the expression obtained matches numerical simulations only for restricted ranges of parameters. The latter conclusion was in agreement with the analysis provided in Rudolph and Destexhe (2005). Another conclusion was that the “extended expression” proposed by Rudolph and Destexhe (2005), although providing an excellent fit to V_m distributions in general, does not match for some parameter values

and, in particular, does not agree with the analytically exact static noise limit. This extended expression is therefore not an exact solution of the system either. Since several analytical expressions were provided for the steady-state V_m distribution (Rudolph & Destexhe, 2003; Richardson, 2004; Rudolph & Destexhe, 2005; Lindner & Longtin, 2006), and since all of these expressions are either approximations or limit cases, it is not clear how they compare and which expression should be used in a given situation. In particular, it is unclear which expression should be used to analyze experimental recordings. In this note, we attempt to answer these questions by clarifying a number of points about some of the previous expressions and providing a detailed comparison of the different expressions available in the literature.

Figure 1: Comparison of the accuracy of different analytical expressions for the V_m distributions of membranes subject to colored conductance noise. (A) Example of V_m distribution calculated numerically (thick gray trace; model from Destexhe et al., 2001, simulated during 100 s), compared to different analytical expressions (see legend). (B) Same as in A in log scale. (C) Mean square error obtained for each expression by scanning a plausible parameter space spanned by seven parameters. Ten thousand runs similar to A were performed, using randomly chosen (uniformly distributed) parameter values. For each run, the mean square error was computed between the numerical solution and each expression. Parameters varied and range of values: membrane area $a = 5000\text{--}50,000 \mu\text{m}^2$, mean excitatory conductance $g_{e0} = 10\text{--}40 \text{ nS}$, mean inhibitory conductance $g_{i0} = 10\text{--}100 \text{ nS}$, correlation times $\tau_e = 1\text{--}20 \text{ ms}$, and $\tau_i = 1\text{--}50 \text{ ms}$. The standard deviations (σ_e , σ_i) were randomized between 20% and 33% of the mean conductance values to limit the occurrence of negative conductances (in which case, some analytical expressions would not apply). Fixed parameters: leak conductance density $g_L = 0.0452 \text{ mS cm}^{-2}$ and reversal potential $E_L = -80 \text{ mV}$, specific membrane capacitance $C_m = 1 \mu\text{F cm}^{-2}$, and reversal potentials for excitation and inhibition: $E_e = 0 \text{ mV}$ and $E_i = -75 \text{ mV}$, respectively. (D) Histogram of best estimates (black) and second best estimates (gray; both expressed in percentage of the 10,000 runs in B). The extended expression (Rudolph & Destexhe, 2005) had the smallest mean square error for about 80% of the cases. The expression of Richardson (2004) was the second best estimate, for about 60% of the cases. (E) Similar scan of parameters restricted to physiological values (taken from Rudolph et al., 2005; $g_{e0} = 1\text{--}96 \text{ nS}$, $g_{i0} = 20\text{--}200 \text{ nS}$, $\tau_e = 1\text{--}5 \text{ ms}$, and $\tau_i = 5\text{--}20 \text{ ms}$). In this case, Rudolph and Destexhe (2005) was the most performant for about 86% of the cases. (F) Scan using strong conductances and slow time constants ($g_{e0} = \text{and } g_{i0} = 50\text{--}400 \text{ nS}$, τ_e and $\tau_i = 20\text{--}50 \text{ ms}$). In this case, the static noise limit Lindner & Lung was the most performant for about 50% of the cases. All simulations were performed using the NEURON simulation environment (Hines & Carnevale, 1997). See the supplementary information for additional scans and the NEURON code of these simulations.



First, we would like to clarify a number of misleading statements we made in the original article (Rudolph & Destexhe, 2003) that may have led to confusion. The goal of the article was to obtain an analytical expression for the steady-state V_m distribution of membranes subject to conductance-based colored noise sources. To obtain this, we considered the full system under a $t \rightarrow \infty$ limit. In this limit, we noted that the noise time constants become infinitesimally small compared to the time over which the system is considered, and this property allowed us to treat the system as for white noise. Our main assumption was that this procedure would allow us to obtain the correct steady-state properties like the V_m distribution. Our approach was to obtain a simplified FPE that gives the same steady-state solutions as the FPE describing the full system. These assumptions were stated in the Results section of Rudolph and Destexhe (2003), but were not clearly stated in the abstract and Discussion, and it could be understood that we claimed to provide an FPE valid for the full system. We clarify here that the treatment followed in that article did not intend to describe the full system but was restricted to steady-state solutions.

Unlike the original expression (Rudolph & Destexhe, 2003), which matches only for a restricted range of parameters, the extended expression (Rudolph & Destexhe, 2005) matches for several orders of magnitude of the parameters (see also the supplementary information of Rudolph and Destexhe, 2005, at <http://cns.iaf.cnrs-gif.fr>). Why the extended expression matches so well, although it is not an exact solution of the system (Lindner & Longtin, 2006), is currently unknown. It is not due to the presence of boundary conditions, which could compensate for mismatches by chance. Simulations with and without boundary conditions gave equally good fits for the parameters considered here (see the NEURON code in supplementary information). Our interpretation (Rudolph & Destexhe, 2005) is that the $t \rightarrow \infty$ limit altered the spectral structure of the stochastic process (filtering), and one can recover a better spectral structure by following the same approximation for a system that is solvable (e.g., that of Richardson, 2004) and correct it accordingly. Thus, as also found by Lindner and Longtin (2006), the extended expression is a very good approximation of the steady-state V_m distribution. Other expressions have been proposed under different approximations (Richardson, 2004; see also Moreno-Bote & Parga, 2005) or limit cases (Lindner & Longtin, 2006) and also match well the simulations for the applicable range of parameters.

Since different expressions were proposed corresponding to different approximations (Rudolph & Destexhe, 2003, 2005; Richardson, 2004; Lindner & Longtin, 2006), we investigated which expression must be used in practical situations. We have considered an extended range of parameters and tested all expressions by running the model for 10,000 randomly selected values within this parameter space. The results of this procedure are shown in Figures 1A to 1D. The smallest error between analytical expressions and numerical simulations was found for the extended expression of Rudolph

and Destexhe (2005), followed by gaussian approximations of the same authors and that of Richardson (2004). The fourth best approximation was the static noise limit by Lindner and Longtin (2006). By scanning only within physiologically relevant values based on conductance measurements in cats in vivo (Rudolph et al., 2005), the same ranking was observed (see Figure 1E), with even more drastic differences (up to 95%; see the supplementary information). Manual examination of the different parameter sets where the extended expression was not the best estimate revealed that this happened when both time constants were slow ("slow synapses"; decay time constants > 50 ms). Indeed, performing parameter scans restricted to this region of parameters showed that the extended expression, while still providing good fits to the simulations, ranked first for less than 30% of the cases, while the static noise limit was the best estimate for almost 50% of parameter sets (see Figure 1F; see the details in the supplementary information). Scanning parameters within a wider range of values including fast and slow synapses and weak and strong conductances showed that the extended expression was still the best estimate (about 47%), followed by the static noise limit (37%; see the supplementary information).

In conclusion, we have clarified here two main points. First, we clarified the assumptions and approximations that were too ambiguously stated in Rudolph and Destexhe (2003). Second, we provided a comparison of the different expressions available so far in the literature. This comparison showed that for physiologically relevant parameter values, the extended expression of Rudolph and Destexhe (2005) is the most accurate for about 80% to 90% of the cases. Outside this range, however, the situation may be different. In systems driven by slow noisy synaptic activity, the static noise limit performed better. We therefore conclude that for practical situations of realistic conductance values and synaptic time constants, the extended expression provides the most accurate alternative available. This is also supported by the fact that the extended expression was successfully tested in real neurons (Rudolph et al., 2004), which is perhaps the strongest evidence that this approach provides a powerful tool to analyze intracellular recordings.

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