Supplementary Information

This document contains supplementary information related to the following paper:

> Rudolph M and Destexhe A. On the use of analytic expressions for the voltage distribution to analyze intracellular recordings. *Neural Computation* **18**: 2917-2922, 2006.

Synopsis

This paper provided a comparison of different analytic expressions for the steady-state membrane potential (V_m) distribution of neurons subject to conductance-based synaptic noise. The model used consists of a passive membrane subject to two conductances (excitatory, inhibitory), each described by an Ornstein-Uhlenbeck stochastic process (Destexhe et al., 2001). The subthreshold V_m distribution can be obtained analytically using different approximations (Rudolph & Destexhe, 2003; Richardson, 2004; Rudolph & Destexhe, 2005; Lindner & Longtin, 2006). These different approximations are respectively:

- RD2003: Original analytic expression of Rudolph & Destexhe (2003);
- RD2005: An "extended" analytic expression based on *RD2003*, where the time constants have been corrected to account for larger ranges of parameters (Rudolph & Destexhe, 2005);
- RD2005*: A Gaussian approximation of the extended expression *RD2005* (Rudolph & Destexhe, 2005);
- R2004: An effective time constant approximation (Richardson, 2004), which is equivalent to a current-based approximation and is also Gaussian;
- LL2006: An analytically-exact white-noise approximation (limit of time constants $\rightarrow 0$; Lindner & Longtin, 2006);
- LL2006*: An analytically-exact static-noise approximation (limit of time constants $\rightarrow \infty$; Lindner & Longtin, 2006).

Figure 1A-D of the companion paper shows a scan of 10,000 parameter values, randomly chosen within reasonable bounds (larger than physiological values). For each parameter set, 100 sec of activity was simulated and the V_m distribution was computed numerically. This numerical estimate was then compared to each of the six expressions outlined above. In this scan, *RD2005* was the best estimate in about 80 % of the cases, while the second-best estimate was *R2004* in about 60 % of the cases.

Additional analyses and scans of parameters

In this supplementary information, we provide more examples of parameter scans (using the same procedure as described in the paper), as well as illustrate some typical situations. As a first example, we scanned 10,000 parameter sets within strictly "physiological" values. Those values were obtained from a recent study (Rudolph et al., 2005), in which the synaptic noise was analyzed from intracellular recordings of neurons in cat parietal cortex *in vivo*. This analysis used both classic conductance analysis methods, the extended expression *RD2005*, as well as direct matching of compartmental models to the recordings (see details in Rudolph et al., 2005). Both up/down states (Ketamine-Xylazine anesthesia) and EEG-activated states were used for the analysis (n=12 cells). The minimal and maximal values for the conductances and variances obtained in those measurements were used as bounds for choosing the 10,000 parameters. The results of these simulations are shown in Fig. S-1A. Similar to Fig. 1 of the companion paper, *RD2005* was the most accurate estimate for about 86 % of the cases, followed by the *R2004* approximation. Because including two expressions biases the analysis against *RD2005*, we also repeated the same analysis by removing the Gaussian approximation *RD2005**, as shown in Fig. S-1B. In this case, *RD2005* was the best estimate for about 95% of the parameter sets.

Manual examination of the cases for which *RD2005* was not the best estimate revealed that this happened when both time constants were slow ("slow synapses"; decay time constants $>$50 ms). An example of such distribution is shown in Fig. S-2. In this case, the static-noise limit *LL2006** was the best estimate, followed by *RD2005*.

To explore this region of parameters, we performed two additional runs of 5,000 randomly selected values of parameters, contrasting a region of parameter with fast time constants with the same region with slow time constants. When time constants were fast, *RD2005*, *RD2005** and *M2004* accounted for the best performance (Fig. S-3A), in agreement with above. However, for slow time constants, the most accurate estimate was obtained by using the static noise limit (Fig. S-3B; identical run as Fig. 1F of the paper). The performance of static noise limit is not surprising since this expression is specific for systems with infinitely large noise time constants.

A last run was realized using a wider parameter range (Fig. S-4), that included physiological values, as well as slow synapses and strong conductances. The parameter space scanned included all regions of parameters scanned in all preceding runs. Based on a set of 10,000 parameter values randomly chosen within this parameter space, the *RD2005* expression still provided the largest number of best estimates (about 50% of the cases), followed by the static-noise limit *LL2006** (37%). Similar values were obtained by removing *RD2005** from the analysis (Fig. S-4B).

Based on these runs, we conclude that, for physiologically-relevant parameter values, the extended expression *RD2005* is the most accurate for about 80-90% of the cases. Outside of this range, however, the situation is different. The static noise limit can be a better approximation for systems with large noise time constants ("slow synapses"), and should be used in such cases.

NEURON Code

All simulations above and in the paper were done under the NEURON simulation environment (Hines & Carnevale, 1997). The NEURON source code that was used for the simulations shown here, as well as the code for data analysis and drawings, can be found at the following location:
http://cns.iaf.cnrs-gif.fr/files/Note2006_demo.zip
This code contains two parts. First, a scanning program runs the numeric simulations for the 10,000 parameters, and writes the results to a data file. Second, an analysis/drawing program reads this data file and creates the histograms shown in Fig. 1. The user can easily change the parameters and verify the simulations shown here, or perform scans in unexplored parameter ranges, and thereby contribute to a more rich analysis of how the different analytic expressions fit numeric simulations.

Note that, contrary to the previous papers (Rudolph & Destexhe, 2003, 2005), no boundary conditions were used here, and the codes provided allow the conductance to go negative. Similar results were obtained when boundary conditions were used (this is easy to modify in the code provided).

Experimental tests and analysis of experimental data

Finally, another test of the analytic expressions is by comparing them directly to experimental data. The *RD2005* expression is the basis of a recently proposed method to analyze intracellular recordings by fitting experimental distributions, yielding estimates of parameters of the real synaptic noise, such as the mean and variance of excitatory and inhibitory conductances (Rudolph et al., 2004). This method is presently used by several laboratories around the world. Related to the present paper, the *RD2005* expression was tested against experimental data, in different ways. First, the conductances obtained by using the *RD2005*-based method were compared to other methods for conductance analysis, as well as to the direct matching of computational models to experimental data. These different methods yielded consistent results for activated states recorded intracellularly in cat parietal cortex *in vivo* (see Rudolph et al., 2005), suggesting that *RD2005* is accurate for the parameters corresponding to this type of synaptic noise in cortical neurons *in vivo* (indeed those are the parameters shown in Fig. S-1).

A second test, more severe, was realized using the dynamic-clamp technique. The synaptic noise produced spontaneously in ferret cortical slices ("up-states") was analyzed using *RD2005*, yielding estimates of the conductance parameters. An artificial synaptic noise was then generated using the estimated parameters, and was re-injected in the *same neuron* during quiescent activity using dynamic-clamp. This yields a "recreated" state that can be compared to the "natural" state. This procedure was successful, as shown by the matching of the natural and artificial V_m distributions (see Fig. 7 and Fig. 8A in Rudolph et al., 2004). Another test, equally severe, was to first inject synaptic noise with known parameters, and then compare the V_m distribution obtained in the real neuron with the analytic prediction of *RD2005*. This procedure also yielded consistent estimates (Fig. 8B in Rudolph et al., 2004).

These experiments and analyses show that the extended expression *RD2005* can provide a very useful analysis tool for extracting conductances from experimental data, and that the accuracy of this analysis is acceptable. Other expressions could possibly be used in similar paradigms, but this has not been done yet. Future experiments should be designed to address the respective accuracy of the different expressions using similar procedures, which would constitute a further test of their respective accuracy in physiological conditions.

Resources

Electronic (PDF) copies of the paper and supplementary information are available at:
http://cns.iaf.cnrs-gif.fr/files/Note2006.pdf
http://cns.iaf.cnrs-gif.fr/files/Note2006_suppl.pdf

The NEURON code corresponding to the simulations is available at:
http://cns.iaf.cnrs-gif.fr/files/Note2006_demo.zip

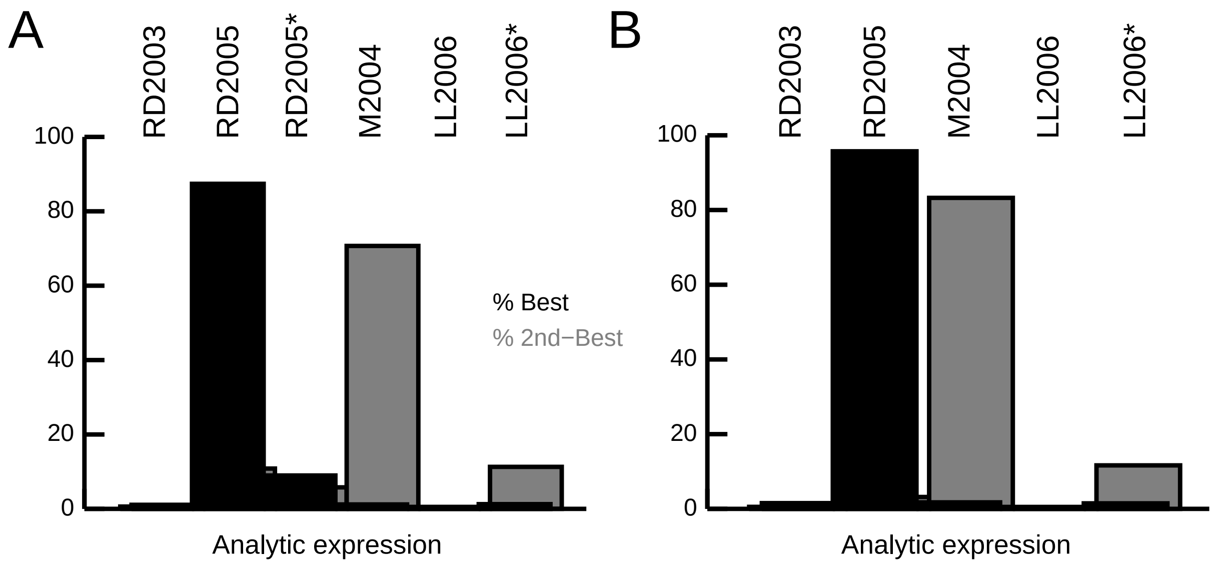

Fig. S-1: Histogram of best estimates for physiological values of parameters. **A.** Additional scan of 10,000 runs of parameters using randomly-chosen parameter (same procedure as in Fig. 1 of the accompanying article) within the following range: membrane area a = 5,000–50,000 μm^2, mean excitatory conductance g_{e0} = 1–96 nS, mean inhibitory conductance g_{i0} = 20–200 nS, correlation times τ_e = 1–5 ms and τ_i = 5–20 ms. The red dashed histograms show the second best estimates. The extended expression (*RD2005*) had the smallest mean-square error for about 86% of the cases. **B**. Same set of simulations, but the histogram was calculated by removing *RD2005**. In this case, *RD2005* was the most accurate for about 95% of the cases.

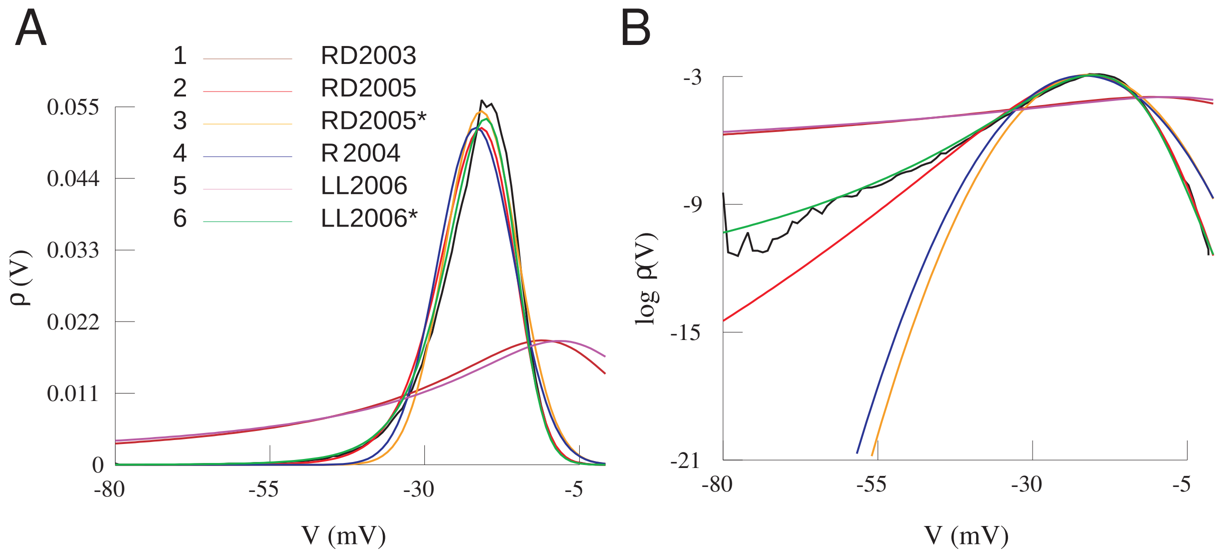

Fig. S-2: Example of V_m distribution for parameters where the static noise limit is the best approximation. The V_m distributions are shown using a similar layout as Fig. 1A-B of the accompanying article (left: linear scale, right: log-scale; color code in inset). The best fit was in this case the static noise limit (*LL2006**, green), while *RD2005* was second best (red). Parameters: membrane area a = 37286 μm^2, excitatory conductance g_{e0} = 400 nS, σ_e = 130 nS, mean inhibitory conductance g_{i0} = 141 nS, σ_i = 39 nS, correlation times τ_e = 35.4 ms and τ_i = 20.8 ms.

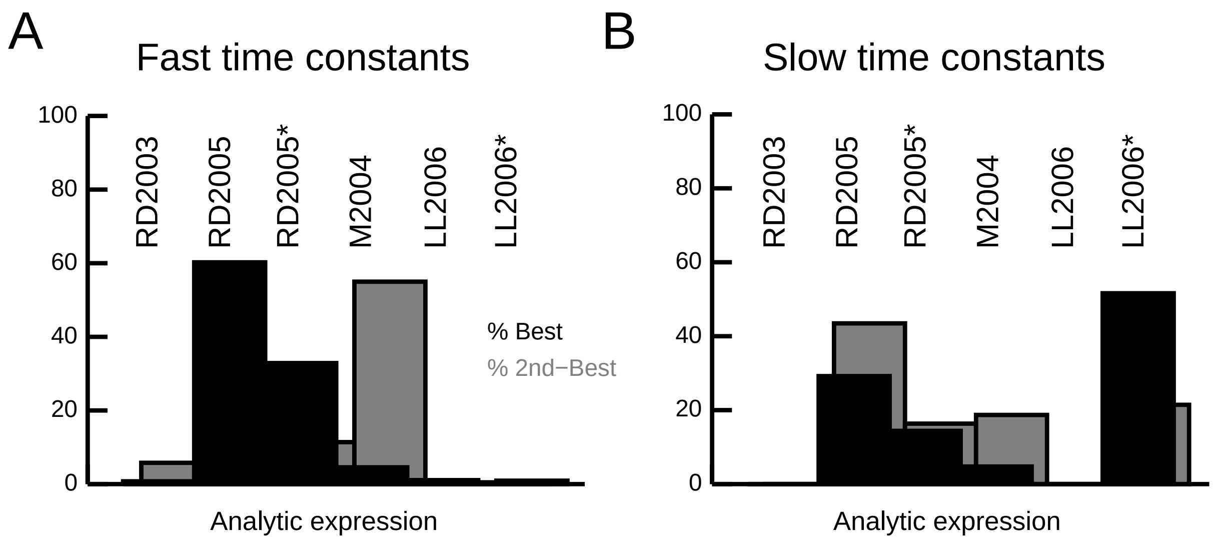

Fig. S-3: Histogram of best estimates for fast and slow time constants. Two additional scans of 5,000 parameters each are shown in **A** and **B**, using the same procedure as in Fig. 1 of the accompanying article. The same parameters were used in both scans (a = 5,000–50,000 μm^2; g_{e0} = 1–50 nS, g_{i0} = 1–50 nS), except for the time constants (τ_e = 1–5 ms and τ_i = 5–20 ms in **A**; τ_e and τ_i = 50–200 ms in **B**). The red dashed histograms show the second best estimates. For fast time constants, *RD2005* was the most accurate estimate for about 60% of the cases, whereas for slow time constants, *LL2006** was more accurate for about 50% of the runs.

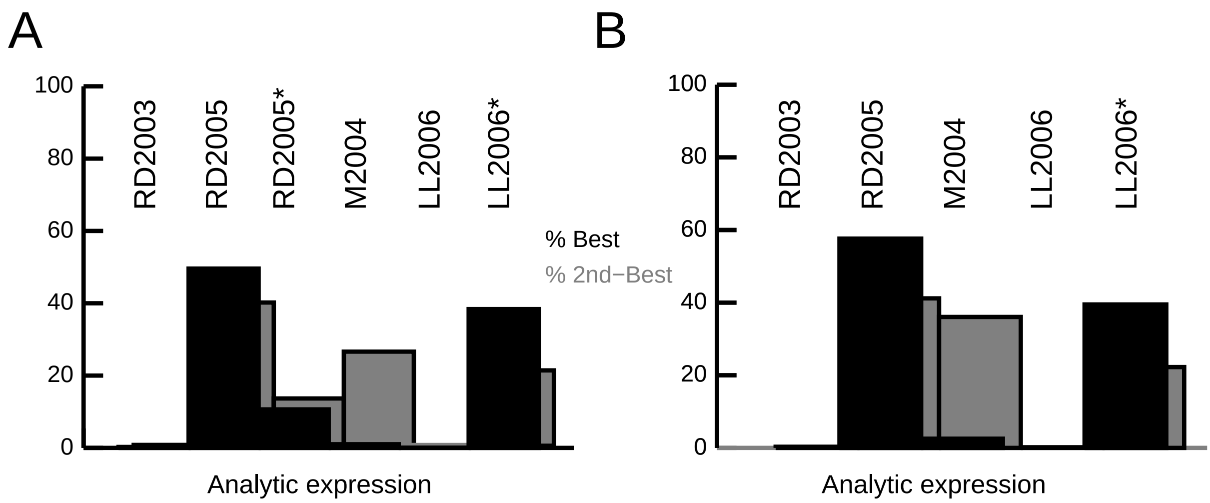

Fig. S-4: Histogram of best estimates for scans within a wide range of parameter values. **A.** Additional scan of 10,000 runs of parameters using randomly-chosen parameters (same procedure as in Fig. 1 of the accompanying article) within the following range: a = 1,000–100,000 μm^2, g_{e0} = 1–300 nS, g_{i0} = 1–300 nS, τ_e = 1–200 ms and τ_i = 1–200 ms. The red dashed histograms show the second best estimates. The extended expression (*RD2005*) had smallest mean-square error for about 50% of the cases. **B**. Same set of simulations, but the histograms were calculated by removing *RD2005**. In this case, *RD2005* was the most performant for about 57% of the cases.

References

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