Interaction of Sub-threshold Oscillations with Synaptic Input in the Cortex.

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Introduction:

Nerons communicate amongst each other via synaptic transmission. Post-synaptic potentials in the cortex in vivo encounter membrane potentials that are strongly fluctuating due to massive synaptic input from other sources (Destexhe et al., 2003) and/or intrinsic membrane properties (Klink&Alonso, 1993). We investigated the interaction of inhibitory post-synaptic potentials (IPSPs) with intrinsic subthreshold oscillations, emphasizing the effect IPSPs have on the phase of these oscillation.

Experimental Methods:

We recorded with the patch-clamp technique from layer II/III pyramidal neurons and interneurons in the slices of the mouse (P28 to P35) visual and prefrontal cortex. We then evoked subthreshold oscillations in these cells by injecting long (2 to 6 sec.) positive current pulses to depolarize the cell to around firing threshold. An initial zero to six spikes were followed by episodes of subthreshold oscillations. Traces with additional spikes interrupting these oscillations were discarted. During the oscillations we either evoked an IPSP by monopolar extracellular stimulation or injected a short (20 to 60msec) hyperpolariyzing current pulse, mimicking an IPSP. During the majority of experiments excitatory synaptic transmission was blocked by DNQX (20µM) and APV (50µM).

Data Analysis:

To determine the phase of the oscillations as a function of time we first band-pass filtered the voltage signal (Fig.1A), subtracted from it a fit to the IPSP or the voltage response to the current pulse (Fig.1B), and then plotted it against it´s Hilbert transformation (Fig.1C). The cumulative angle (Φ) in this plot represents the cumulative phase of the oscillation and was plotted as a function of time (Fig.1D). To determine the phase progression of the voltage signal containing the IPSP or I-pulse we averaged the phase during the 300msec before and after the pulse and subtracted them (ΔΦ). We plotted ΔΦ as a function of a number of properties of the oscillation, such as voltage average and fluctuation, power in the 1 to 5Hz and 5 to 15Hz bands as well as Φ at the onset of the IPSP or I-pulse.

In addition we averaged all individual plots of Φ vs. time and V_m vs. time of every cell (temporally alligned at the beginning of the IPSP/I-pulse). We extrapolated a linear fit to the 300 msec before the IPSP/pulse of both averages to see how long it takes either of them to cross that extrapolation (and thus return to baseline).

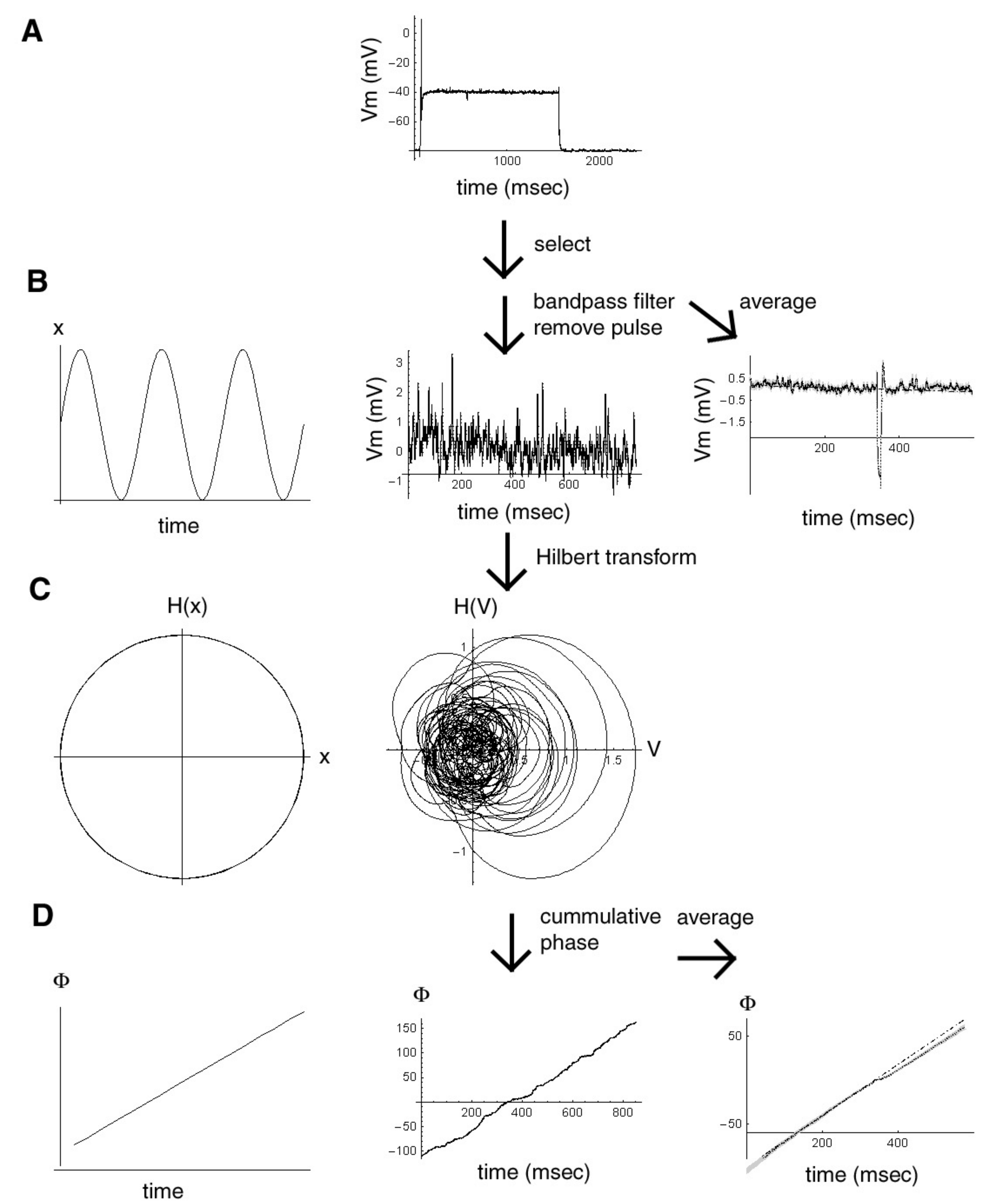
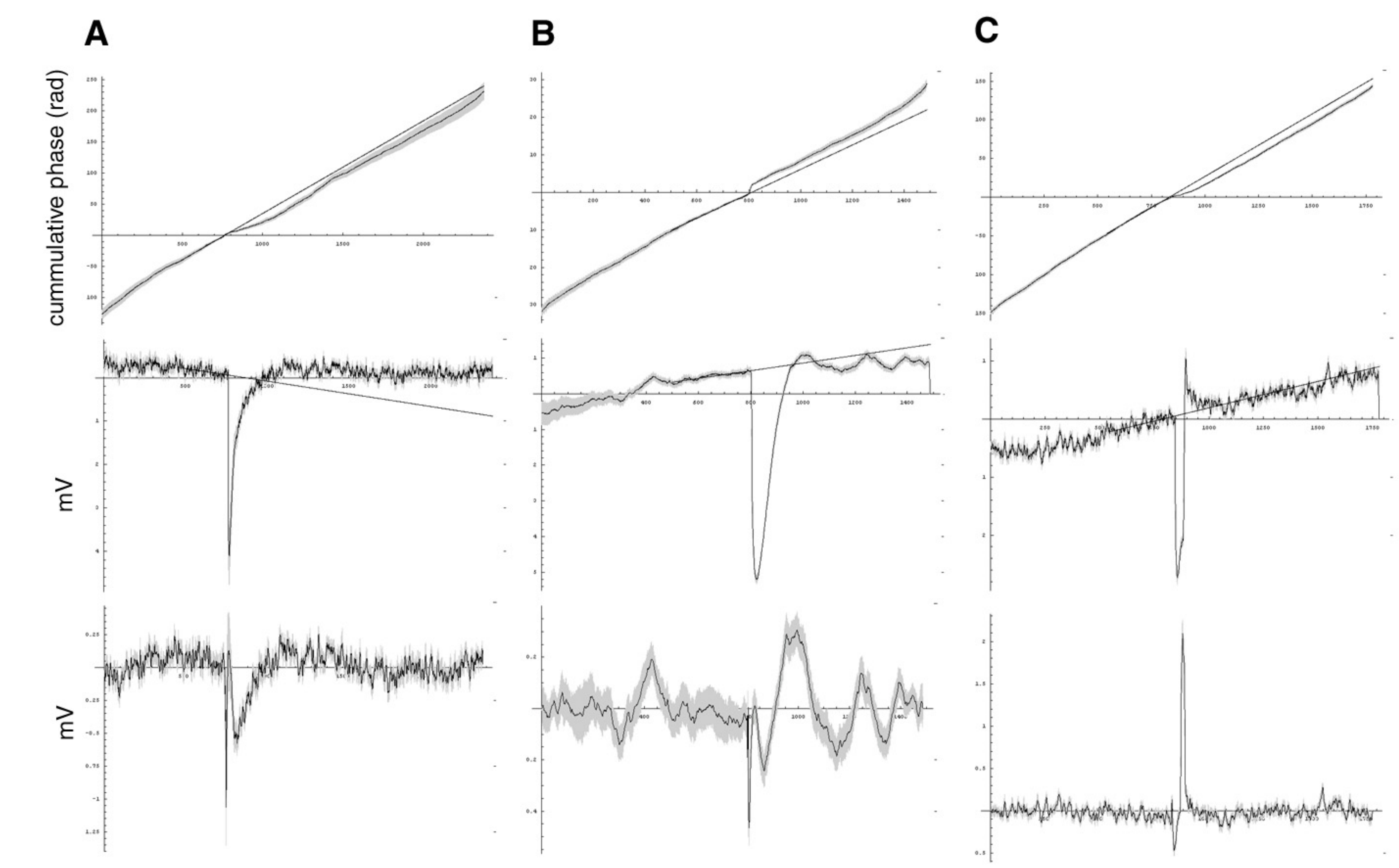


Figure 1 (left): Phase determination: left column: example, middle column: actual data, right column: averages. A: Raw data. A subthreshold part of the voltage trace before and after the pulse is selected. B: Data after the pulse is fit by two exponentials and subtracted and band pass filtering. C: Plot of the Hilbert transform of (B) against itself. D: The cumulative phase angle of (C), representing the phase of the oscillation, plotted as a function of time.

Figure 2 (below): Example data. Each trace is the mean +- s.e.m. over all sweeps in one cell. Top: Cumulative phase of the subthreshold oscillation Middle: Voltage. Bottom: Voltage after subtraction of the fit of the IPSP/I-pulse and band-pass filtering. A, B: Experiments conducted with IPSPs, C: Experiment conducted with I-pulses.



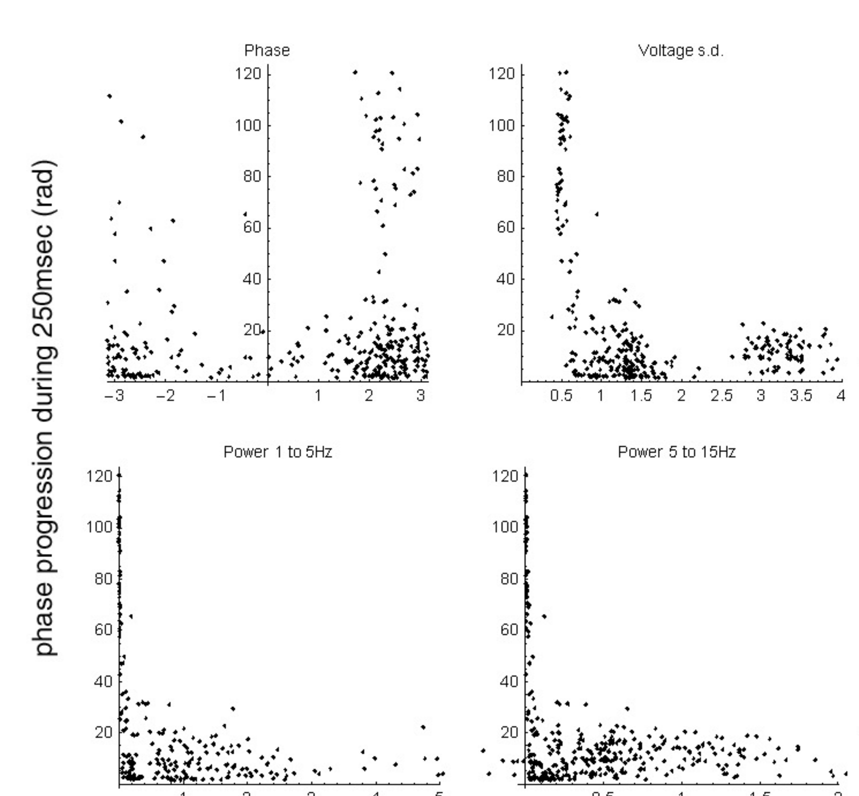


Figure 3: The Phase shift is dependent on the phase of the IPSP and the power of the oscillation. Scatter plots of the phase shift as a function of phase of the IPSP (A), standard deviation of the voltage during the oscillations (B), power in the 1Hz to 5Hz band (C) and the 5Hz to 15Hz band of the oscillations. Pooled data from 4 pyramids and 2 interneurons.

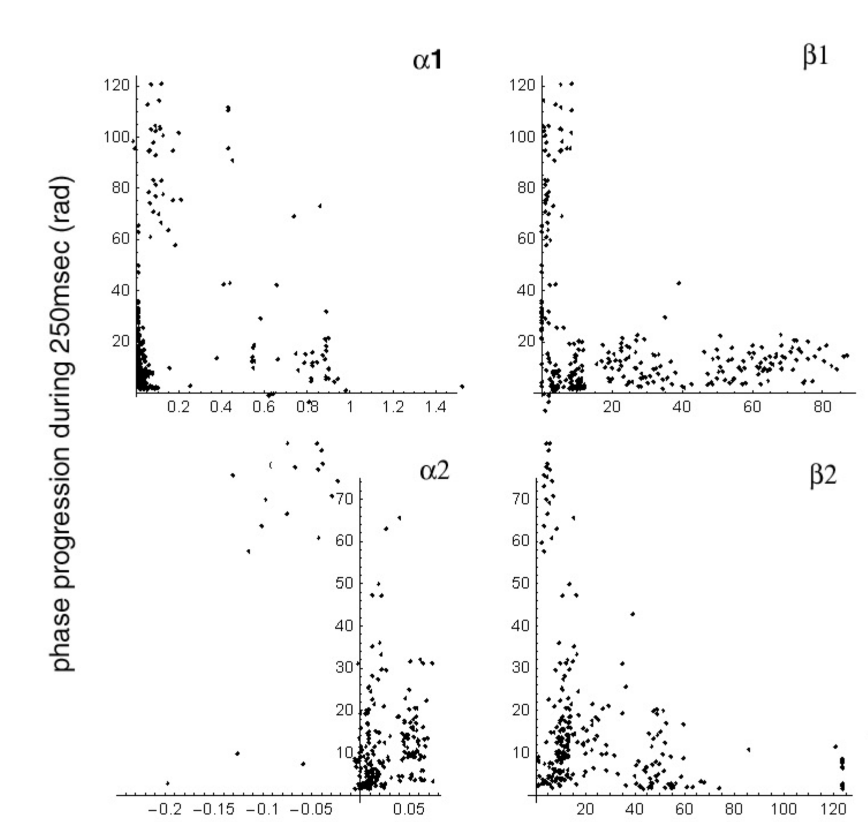


Figure 4: The shape of the IPSP is not correlated with the phase-shift. Fit-parameters (to $V(t)= \alpha_1\, t\, e^{-t/\beta_1} - \alpha_2\, t\, e^{-t/\beta_2}$) as a function of the phase shift. Pooled data from 4 pyramids and 2 interneurons.

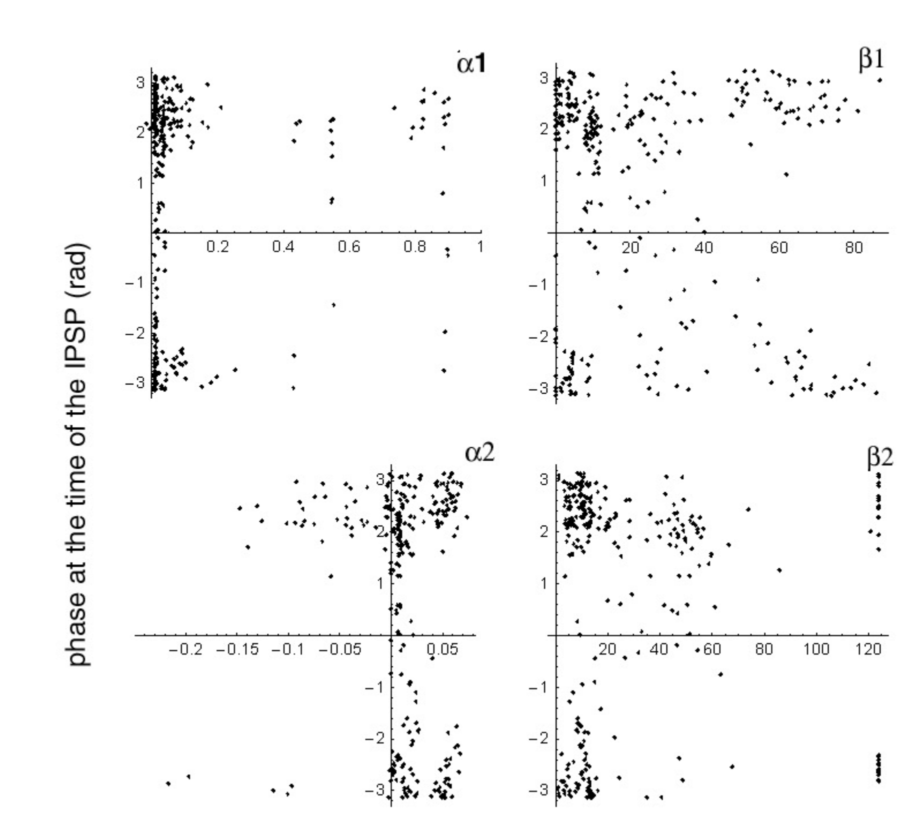


Figure 5: The shape of the IPSP is dependent on the phase of the oscillation. Fit-parameters (to $V(t)= \alpha_1\, t\, e^{-t/\beta_1} - \alpha_2\, t\, e^{-t/\beta_2}$) as a function of the phase of the oscillation at the onset of the IPSP. Pooled data from 4 pyramids and 2 interneurons.

Results:

1. Phase deflections can persist for extended time spans.
In 2 out of 6 experiments conducted with IPSPs, the average phase shift persisted untill the end of the sweep (avg. 1150 msec). In the remaining 4 experiments, the phase intersected with the extrapolation of the linear fit to the 300 msec before the pulse on average after 887 msec. The experiments in which the IPSP was subsitituted with a negative current pulse, mirror the results of the experiments with IPSPs. In 3 out of 5 cells phase averages did not intersect with the extrapolation (in the remaining two cells the pulse failed to cause a phase-shift).

2. Voltage deflections persist for much shorter time spans.
In contrast, the voltage average intersected with the extrapolation in all but one cases, on average 212 msec after the onset of the IPSP (Fig.2). In the experiments with I-pulses, the voltage average intersected with the extrapolation in all cases, on average 46 msec after the onset of the pulse (Fig.2).

3. Dependence of the phase shift on parameters of the oscillation and dependence of the shape of the IPSP on the phase.
The phase shift was negatively correlated with the standard deviation of the voltage during the oscillations and the power of the oscillations in the 1Hz to 5Hz and 5 to 15Hz bands (Fig.3). The shape of the IPSP waveform was uncorrelated to the phaseshift (Fig.4) but showed a dependence on the phase at which the IPSP occurred (Fig.5). We fit the IPSP with a sum of two β-functions ($V(t)= \alpha_1\, t\, e^{-t/\beta_1} - \alpha_2\, t\, e^{-t/\beta_2}$). The parameters α_1 and α_2 thus correspond to the amplitude, β_1 and β_2 to the time constants of the IPSP.

Conclusions:

Changes in the phase of subthreshold oscillations can persist much longer than voltage deflections causing them. Neurons with a rich repertoire of intrinsic properties can store information in them for extended time spans.

References:

Destexhe, A., Rudolph, M. and Paré, D. The high-conductance state of cortical neurons in vivo. *Nature Reviews Neuroscience* 4: 739-751, 2003.

Klink R., Alonso A., Ionic mechanisms for the subthreshold oscillations and differential electroresponsiveness of medial entorhinal cortex layer II neurons., *J Neurophysiol*. Jul;70(1):144-57, 1993.

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