Improving long lasting anti-kindling effects via coordinated reset stimulation frequency mild modulation

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Several brain diseases are characterized by abnormally strong neuronal synchrony. Coordinated Reset (CR) stimulation [1,2] was computationally designed to specifically counteract abnormal neuronal synchronization processes by desynchronization. In the presence of spike timing-dependent plasticity (STDP) [3] this leads to a decrease of synaptic weights and ultimately to an anti-kindling [4], i.e. unlearning of abnormal synaptic connectivity and abnormal neuronal synchrony. The long-lasting desynchronizing impact of CR stimulation has been verified in pre-clinical and clinical proof of concept studies (e.g. [5]). However, as yet it is unclear how to optimally choose the CR stimulation frequency, i.e. the repetition rate at which the CR stimuli are delivered. We have chosen a certain range of stimulation durations, where we were able to achieve a reasonable success rate (i.e. anti-kindling) at least for suitable stimulation frequencies. For this purpose, CR stimulation was applied with Rapidly Varying Sequences (RVS) [4] and Slowly Varying Sequences (SVS) [6] in a wide range of stimulation frequencies and intensities. The RVS turn out to be more robust against stimulation frequencies; however, the SVS can obtain stronger anti-kindling effects [7]. In cases where the initial combination of CR intensity and frequency did not perform efficiently, we implement three plausible therapy-like stimulation protocols, which aim to ameliorate the long-lasting effects. The first one prolongs the CR on period before ceasing it completely, the second one consists of repetition of CR on/off trial-periods with the same fixed CR frequency while the third one incorporates a control mechanism monitoring the degree of synchronization at the end of the CR off period and adjust CR's period for the following trials via a mild modulation. The last one manages both to induce global desynchronization and to show very good robustness among different signals and network dependent variations [8]. These findings can be implemented into stimulation protocols for first in man and proof of concept studies aiming at further improvement of CR stimulation.

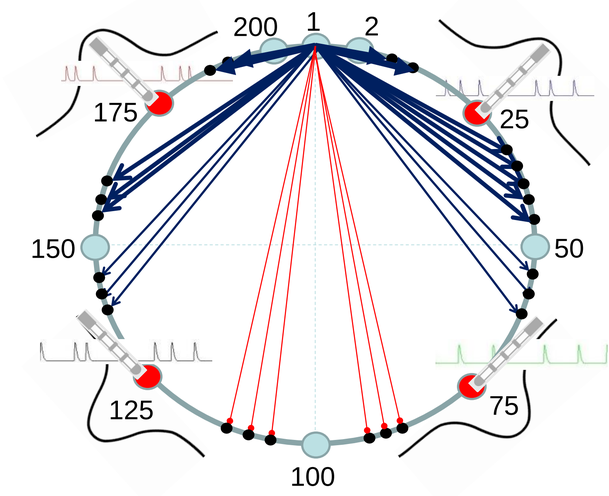
MODELS – METHODS

The Hodgkin-Huxley model

$$
\begin{cases}
C\dfrac{dV_i}{dt} = I_i - g_{Na}m_i^3h_i(V_i - V_{Na}) - g_K n_i^4(V_i - V_K) - g_l(V_i - V_l) + \underbrace{N^{-1}\sum_{j=1}^{N}(V_{r,j} - V_i)c_{ij}|M_{ij}|s_j}_{\text{internal synaptic input/coupling term}} + \overbrace{F_i}^{\text{external CR stimulation}} \\
\dfrac{dm_i}{dt} = \alpha_m(V_i)(1 - m_i) - \beta_m(V_i)m_i \\
\dfrac{dh_i}{dt} = \alpha_h(V_i)(1 - h_i) - \beta_h(V_i)h_i \\
\dfrac{dn_i}{dt} = \alpha_n(V_i)(1 - n_i) - \beta_n(V_i)n_i \\
\dfrac{ds_j}{dt} = \dfrac{0.5(1 - s_j)}{1 + exp\left[-(V_j + 5)/12\right]} - 2s_j
\end{cases}
$$

$$M_{ij} = \left(1 - d_{ij}^2/\sigma_1^2\right) exp\left(-d_{ij}^2/(2\sigma_2^2)\right) : \textit{Mexican hat}$$

$$\alpha_m(V) = \frac{0.1V + 4}{[1 - exp(-0.1V - 4)]}, \quad \beta_m(V) = 4\exp\left[\frac{-V - 65}{18}\right],$$
$$\alpha_h(V) = 0.07\exp\left[\frac{-V - 65}{20}\right], \quad \beta_h(V) = \frac{1}{[1 + \exp(-0.1V - 3.5)]},$$
$$\alpha_n(V) = \frac{0.01V + 0.55}{[1 - \exp(-0.1V - 5.5)]}, \quad \beta_n(V) = 0.125\exp\left[\frac{-V - 65}{80}\right].$$



Spike timing-dependent plasticity (STDP) rule

$$\Delta c_{ij} = \begin{cases} \beta_1 e^{\frac{-\Delta t_{ij}}{\gamma_1 \tau}}, & \Delta t_{ij} \geq 0 \\ \beta_2 \dfrac{\Delta t_{ij}}{\tau} e^{\frac{\Delta t_{ij}}{\gamma_2 \tau}}, & \Delta t_{ij} < 0 \end{cases},$$

Each single synaptic weight c_{ij} is updated in an event-like manner, i.e. we ***add*** or ***subtract*** an increment $\delta \cdot \Delta c_{ij}$ for ***excitatory*** or ***inhibitory*** connections respectively, with ***learning rate*** $\delta > 0$ **every time a neuron spikes**. Furthermore, we restrict the values of c_{ij} on the interval [0,1] mS/cm^2 for both excitatory and inhibitory synapses, ensuring in this way that their strengthening or weakening remains bounded.

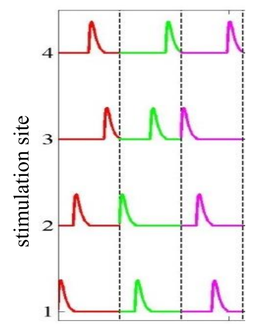
Coordinated Reset (CR)

$$F_i = [V_r - V_i(t)] \cdot K \sum_{k=1}^{N_s} D(i, x_k)\rho_k(t)G_{stim}(t)$$

The stimulation signals → single brief **excitatory post-synaptic currents**. The evoked time-dependent normalized conductances of the postsynaptic membranes are represented by ***α*-functions**:

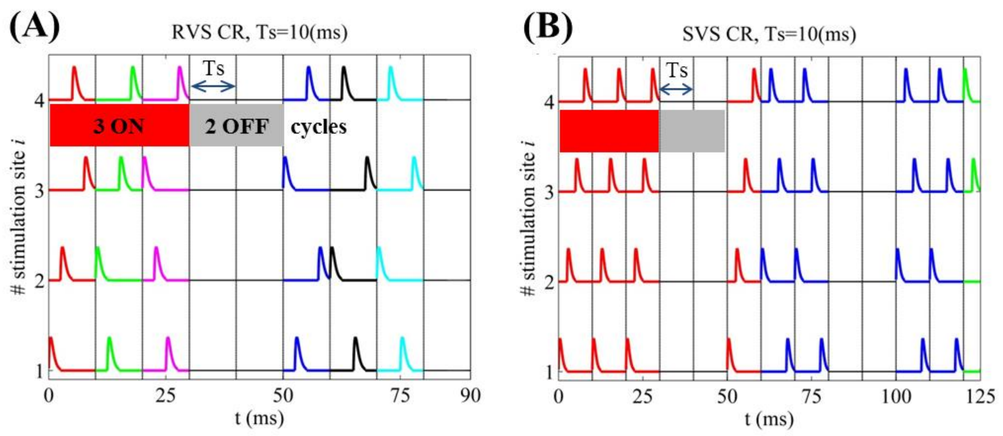
$$G_{stim}(t) = \frac{t - t_k}{\tau_{stim}} e^{-(t - t_k)/\tau}, \qquad t_k \leq t \leq t_{k+1}.$$

$\tau_{stim} = T_s/(6Ns)$: the time-to-peak of G_{stim}, and t_k is the onset of the k^{th} activation of the stimulation site. K: stimulation intensity.

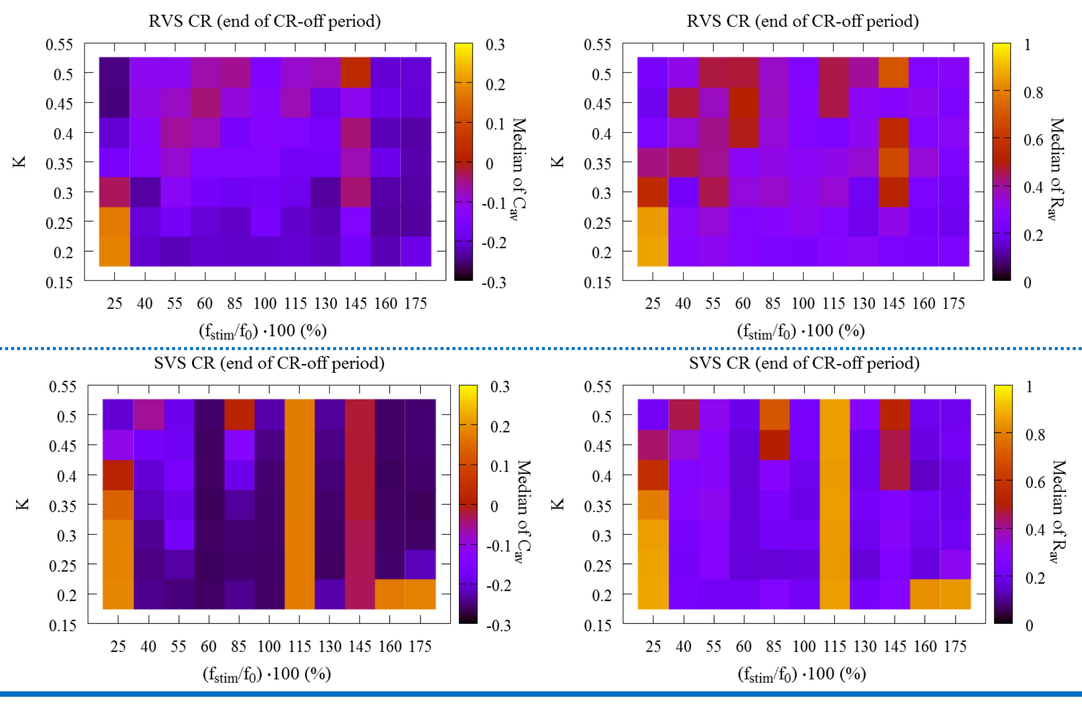


RESULTS

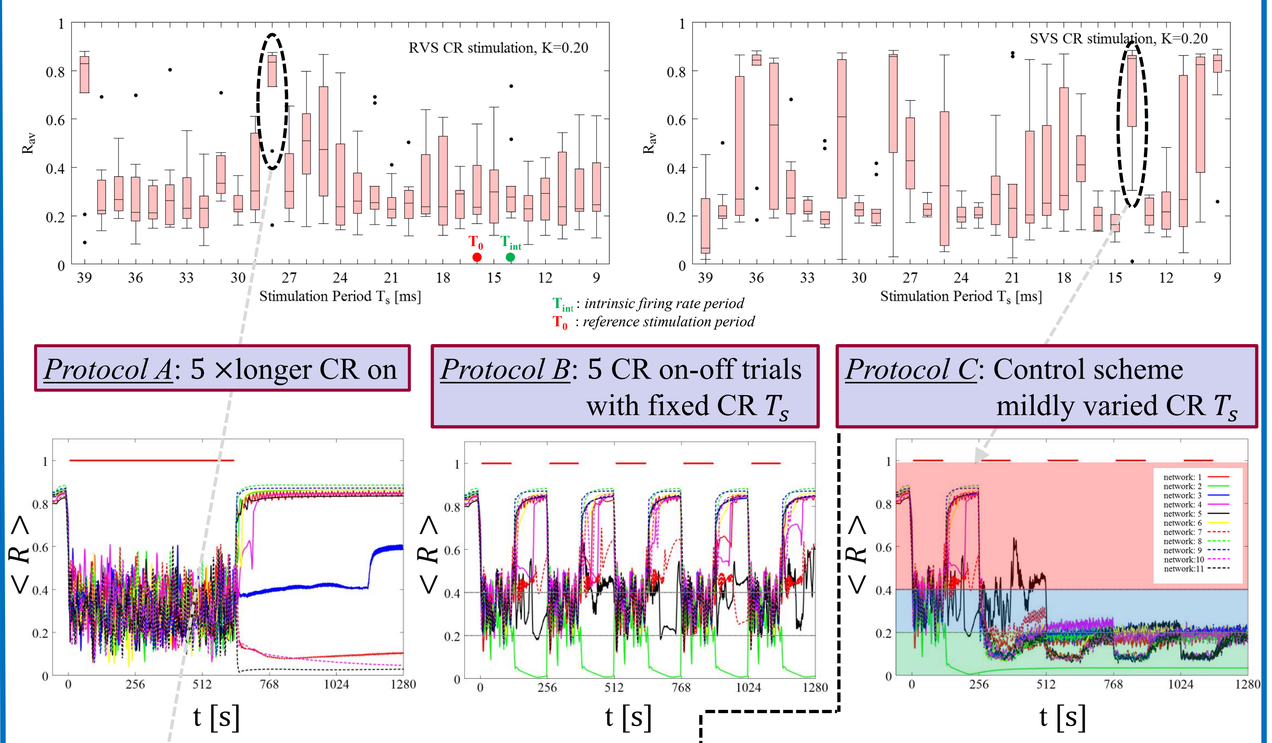
Time evolution of CR stimulation signals



C_{av} (average synaptic connectivity) and R_{av} (1st order parmeter) at the end of CR-off period as a function of stimulation intensity K and stimulation frequency f_{stim}



Finer T_s −period grid analysis for the RVS CR stimulation intensity $K = 0.20$



- If $R_{av} > 0.4$ → $T_s = T_s - 1$ ms
- If $0.2 \leq R_{av} \leq 0.4$ → keep same T_s
- If $0 < R_{av} \leq 0.2$ → cease CR

- If $R_{av} > 0.4$ → $rnd\ T_s \in [T_0 - 4\text{ms}, T_0 + 4\text{ms}]$
- If $0.2 \leq R_{av} \leq 0.4$ → keep the same T_s
- If $0 < R_{av} \leq 0.2$ → cease CR

Testing these *Protocols* for both RVS & SVS CR stimulation and many (K, T_s) −pairs, it turns out that ***Protocol C and varied C*** **perform better** than *A* and *B*

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[8] Manos, T., Zeitler, M., and Tass, P.A. (2017) Improving long lasting anti-kindling effects via coordinated reset stimulation frequency mild modulation. *To be submitted*