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# Sequences and their shuffling may crucially impact coordinated reset stimulation – A theoretical study

*Dear Editor,*

Deep brain stimulation (DBS) is a well-established treatment for medically refractory Parkinson's disease (PD) [1]. While highly effective in adequately selected PD patients, DBS delivered to the subthalamic nucleus (STN) or globus pallidus internus is not effective for all symptoms and may cause relevant side effects [1]. Also, PD symptoms return shortly after cessation of DBS [2].

A theory-based stimulation technique, coordinated reset stimulation (CRS), aims at long-lasting desynchronization that persists after stimulation ceases [3,4]. As shown computationally, in neural networks with synaptic plasticity, CRS-induced desynchronization of PD-related neuronal synchrony [5] may cause an unlearning of abnormal synaptic connectivity and related neuronal synchrony [4]. In this way CRS moves networks from strongly connected synchronized states (SCSS) to weakly connected desynchronized states (WCDS), ultimately inducing effects outlasting stimulation. Corresponding long-lasting desynchronization and therapeutic effects were observed in preclinical studies [6–8], and in PD patients [9].

CRS is a multisite stimulation technique during which phase-shifted stimuli are delivered to separate neuronal subpopulations. Stimuli are sequentially delivered to the different stimulation sites, forming a *CR sequence* (Fig. 1F, H, and 1J). CRS is delivered in cycles. Each stimulation site is activated exactly once per cycle. The CR sequence is typically shuffled after a shuffle period, $T_{shuffle}$, (Fig. 1J). A recent preclinical study found that shuffled CRS outperforms non-shuffled CRS regarding long-lasting therapeutic aftereffects in PD monkeys [8].

In this letter, we computationally analyse why shuffling may improve long-lasting effects of CRS. We uncover that the effect of non-shuffled CRS depends on the selected CR sequence: "Favourable" CR sequences may drive the network into a WCDS; conversely, "unfavourable" sequences may induce an SCSS (Fig. 1B). We show that long-lasting aftereffects of CRS with long shuffle periods depend on the timing at which stimulation is turned off, whereas short shuffle periods led to consistent long-lasting effects after sufficient stimulation duration (Fig. 1C–E).

We simulated CRS for two types of networks of excitatory leaky integrate-and-fire neurons with spike-timing-dependent plasticity (STDP): an inhomogeneous network in which the probability for a synaptic connection depended on the neurons' locations (Fig. 1A) and a homogeneous network where the connection probability was the same for all neuron pairs (Fig. 1A') [10]. For both networks, stable abnormal (SCSS) and stable physiological (WCDS) model states coexisted (see Fig. 1 in Ref. [10]).

We delivered CRS and determined the evolving mean synaptic weight. In the inhomogeneous network, the long-lasting outcome of non-shuffled CRS varied depending on the employed CR sequence (Fig. 1B) and the mean synaptic weight stabilized either at low values (WCDS) or high values (SCSS). In contrast, no such differences were observed in the biologically unrealistic homogeneous network (Fig. 1B').

In general, two aspects are critical for the effect of a CR sequence on the mean synaptic weight: (i) Based on STDP, the time lags between stimuli administered to different sites and, hence, different subpopulations, determine to which extent the synapses between them strengthen or weaken [11]. (ii) How many synapses interconnect these subpopulations determines the overall strength of this plasticity modulating effects. A strong reduction of many synapses cannot be achieved if the stimulated subpopulations are only sparsely interconnected. Conversely, to minimize the mean synaptic weight and achieve a WCDS, stimuli have to affect densely interconnected subpopulations at time lags that cause a reduction of the synaptic weights.

In preclinical and clinical studies, CR sequences were typically shuffled [6,8,9]. In Fig. 1B–E and 1B′-1E′, we show computational results for different $T_{shuffle}$. In the inhomogeneous network and for $T_{shuffle}$ long compared to the time scale of STDP, the mean synaptic weight slowly oscillates between the stationary values attained for different CR sequences during non-shuffled CRS (compare $T_{shuffle} = 30\,min$ and non-shuffled CRS in Fig. 1E and B). Cessation of stimulation while the network is close to stationary states induced by unfavourable CR sequences led to unfavourable long-lasting aftereffects, i.e., strong synchronization (blue trajectory in Fig. 1E, bottom). In contrast, $T_{shuffle}$ short compared to the STDP time scale, e.g., $T_{shuffle} = 100\,ms$ (Fig. 1C and J), led to more robust long-lasting outcome and to even lower mean synaptic weights than non-shuffled CRS with favourable sequences (Fig. 1B–C) as it avoids stimulation-induced reverberations in the network dynamics and the resulting formation of strongly connected clusters. These results hold for different degrees of network heterogeneity (Fig. 1L–O). Note that the degree of acute synchrony was lower for longer shuffle periods.

The performance of non-shuffled CRS in inhomogeneous networks crucially depends on the selected CR sequence. Our computational results suggest that this effect is most pronounced in inhomogeneous networks, likely reflecting biologically more realistic conditions. CRS with unfavourable sequences may perform poorly by supporting the formation of strongly connected clusters. In contrast, non-shuffled CRS with specific CR sequences may strongly reduce the overall synaptic weight. However, so far, it is unclear how to determine these favourable sequences and deliver them to a small structure like the STN as knowledge of the structure, connectome, and plasticity mechanisms is incomplete. Computationally, long shuffle periods induce the risk of turning stimulation off at the "wrong" time when the network undergoes an SCSS. In contrast, rapidly shuffled CR avoids reverberation of

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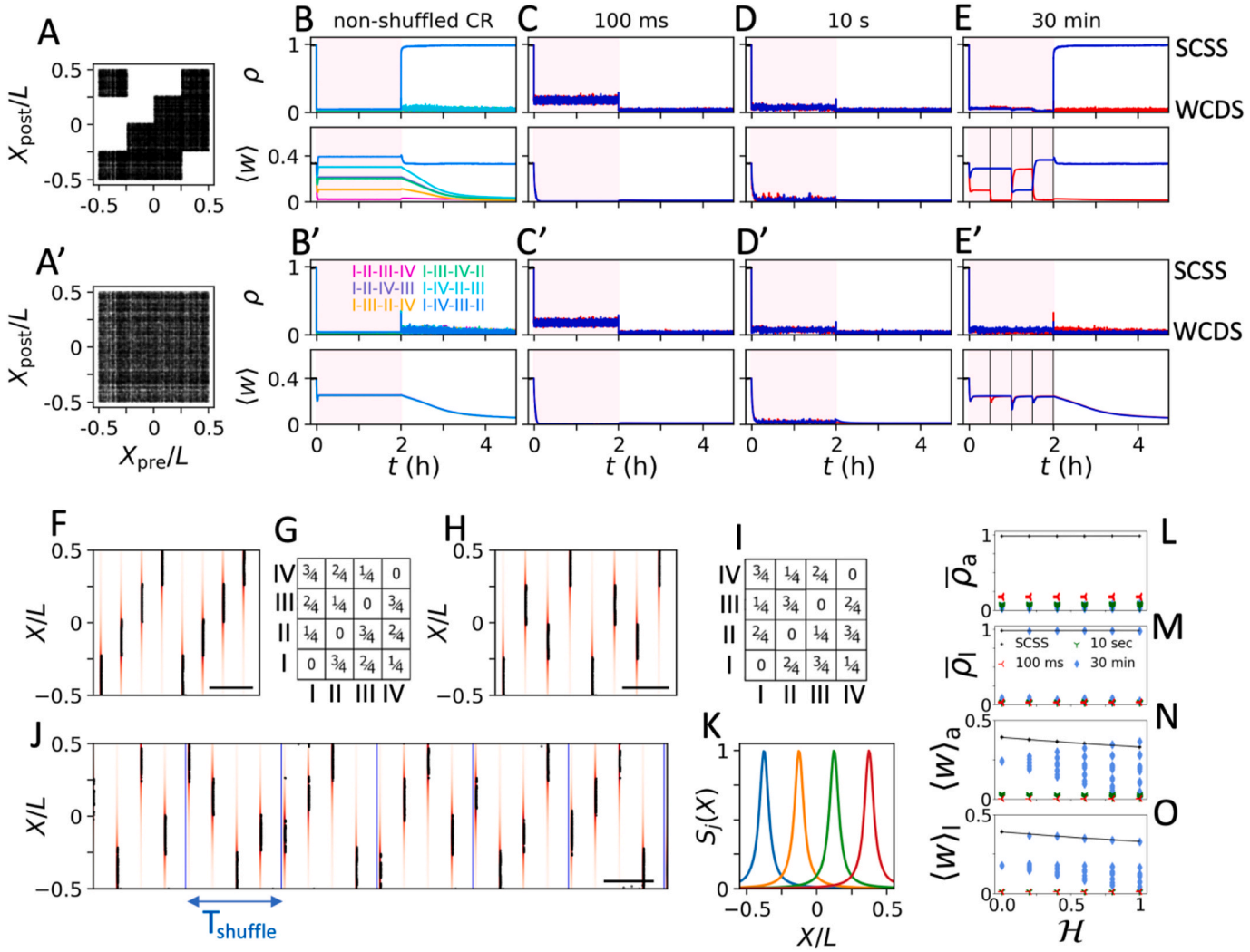


**Fig. 1. CRS of inhomogeneous and homogeneous networks.** A: Synaptic connectivity of an inhomogeneous network. Black dots mark connections between presynaptic neurons at locations $X_{pre}$ and postsynaptic neurons at locations $X_{post}$, in units of the system's length scale, L. B-E: Trajectories of the Kuramoto order parameter, measuring the degree of synchrony, averaged over 10 sec time windows, ρ, (top) and the mean synaptic weight, ⟨w⟩, before, during (light rose), and after CRS with non-shuffled sequences (B) and shuffled sequences for different shuffle periods, $T_{shuffle}$, (C-E), respectively. Large, $\rho \approx 1$ indicates in-phase synchronized spiking activity. Colours correspond to different CR sequences (see labels in B′). After cessation of stimulation the network approaches either the stable strongly connected synchronized state (SCSS) or the stable weakly connected desynchronized state (WCDS). A′ and B′-E': Same as A and B-E but for a homogeneous network. F: Raster plot of neuronal spiking activity (black dots) for neurons at different locations, X, during delivery of non-shuffled CR with CR sequence I-II-III-IV. Red colours show the intensity of the spatial stimulus profile (see also panel K). The horizontal black bar marks a 50 *ms* time interval. G: Corresponding time lags between stimuli delivered to sites I-IV in units of $1/f_{CR}$. The CR frequency was set to $f_{CR} = 10$ *Hz*. H and I: Same as F and G but for the CR sequence I-III-II-IV. J: Raster plot for CRS with rapidly shuffled sequence, so-called rapidly varying sequences (RVS) CRS, with $T_{shuffle} = 100$ ms. K: Illustration of the spatial stimulus profiles used to model the four stimulation sites located at $X_I = -\frac{3}{8}L$ (blue), $X_{II} = -\frac{1}{8}L$ (orange), $X_{III} = \frac{1}{8}L$ (green), $X_{IV} = \frac{3}{8}L$ (red). L-O show effects of CRS for increasing network heterogeneity, *H*. $H = 0$ corresponds to homogeneous networks (A′) and $H = 1$ to inhomogeneous networks (A). Panels L and M show Kuramoto order parameter time-averaged over the last 18 sec of CRS, quantifying acute effects, $\overline{\rho}_a$, and time-averaged over a corresponding time window 2000 sec after cessation of stimulation, quantifying long-lasting effects, $\overline{\rho}_l$, respectively. N and O: Corresponding snapshots of the mean synaptic weight. Symbols show results of simulations for shuffled CRS with randomly selected CR sequences for the indicated shuffle periods. Note that the spread of mean synaptic weights increases with network heterogeneity for $T_{shuffle} = 30$ min resulting in CR sequence-dependent long-lasting outcome of such CRS (panel M). Contrastingly, CRS with shorter $T_{shuffle}$ reliably causes long-lasting desynchronization (M). See Kromer and Tass [10] for more details regarding model and stimulation parameters and further statistical analysis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

"unfavourable" sequences, which may be the reason why non-shuffled CRS was inferior to shuffled CRS delivered to the STN in monkeys rendered Parkinsonian by MPTP [6–8]. According to our results, rapid shuffling may overcome the need for selecting favourable CR sequences for non-shuffled CRS. We conclude that shuffling after individual cycles is advantageous for CRS. Our results, obtained in a comparably simple, yet clearly understandable network model, provide hypotheses for more detailed and computation time-demanding computational modelling studies as well as pre-clinical and clinical studies.

## Data availability

The original contributions presented in the study are included in the article and the data manuscript Kromer and Tass [10]. Further inquiries can be directed to the corresponding author.

## CRediT authorship contribution statement

**Justus A. Kromer:** Conceptualization, Data curation, Formal

analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Peter A. Tass:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Justus A. Kromer and Peter A. Tass filed a Stanford-owned provisional patent related to the presented results. Peter A. Tass reports a past relationship with Boston Scientific Neuromodulation that includes: consulting or advisory and funding grants. Peter A. Tass is part of the editorial board of Brain Stimulation.

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