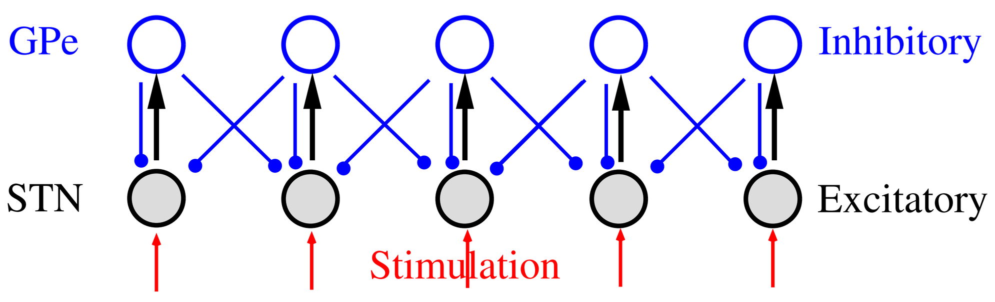
Delayed feedback approach for desynchronizing closed-loop DBS

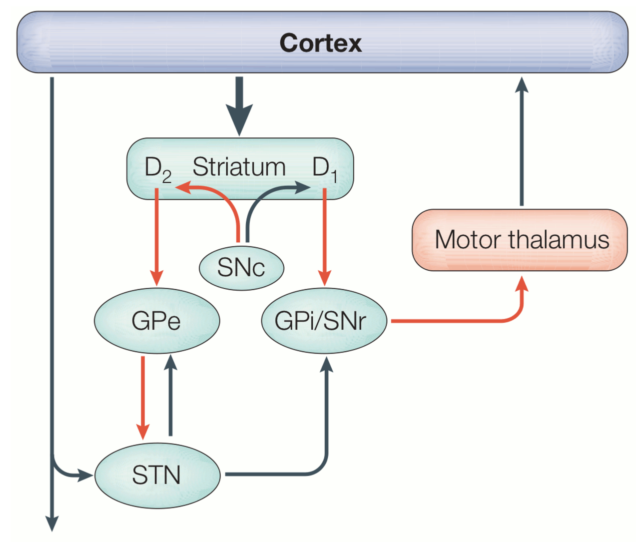
Oleksandr V. Popovych[1,2], Borys Lysyansky[1] and Peter A. Tass[3]

[1] Institute of Neuroscience and Medicine - Brain & Behaviour (INM-7), Research Centre Jülich, Jülich, Germany
[2] Institute for Systems Neuroscience, Medical Faculty, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany
[3]Department of Neurosurgery, Stanford University, Stanford, CA, USA

Closed-loop adaptive deep brain stimulation (DBS) is a novel and promising approach for the treatment of Parkinson's disease (PD), where the stimulation is administered to the extent and when necessary, for example, based on the ongoing neuronal activity as reflected by dynamics of the local field potential (LFP). The closed-loop stimulation setup is naturally realized by intrinsically demand-controlled delayed feedback methods designed for desynchronization of abnormal neuronal synchronization characteristic for PD, epilepsy, tinnitus and other neurological disorders. We computationally adapt and test delayed feedback methods for pulsatile electrical brain stimulation, where smooth feedback signal is used to modulate the amplitude of biphasic charge-balanced electrical pulses constituting the stimulation signal of pulsatile delayed feedback stimulation appropriate for electrical stimulation of the neuronal tissue. Linear and nonlinear pulsatile delayed feedback methods are tested and compared to the high-frequency (HF) DBS on physiologically motivated model network comprising neurons from subthalamic nucleus (STN) and external globus pallidus (GPe). We show that pulsatile delayed feedback methods can effectively desynchronize the STN-GPe network of model neurons, and an interphase gap introduced between the recharging phases of the pulses can significantly improve the stimulation-induced desynchronization and reduce the amount of the administered stimulation. We show that pulsatile nonlinear delayed feedback can require less stimulation current as compared to pulsatile linear delayed feedback, and all considered delayed feedback methods are much more efficient in counteracting abnormal neuronal activity than conventional HF DBS. The pulsatile feedback stimulation techniques can be suggested for pre-clinical and clinical tests for effective and efficient desynchronizing DBS, which may be of clinical relevance.

I. STN-GPe model network





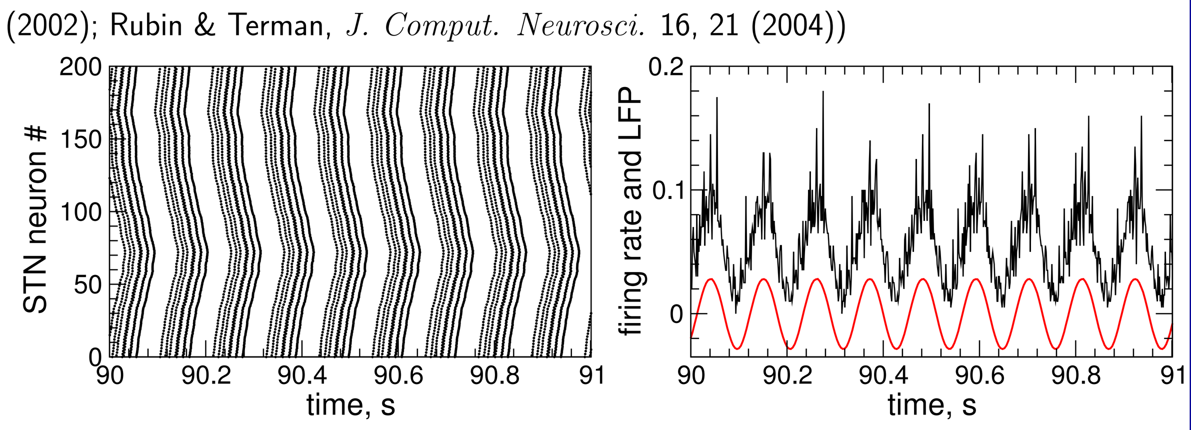
(Schnitzler & Gross, *Nat.Rev.Neurosci.* **6**, 285 (2005))

Conductance-based model of STN and GPe neurons:

$$C\dot{V}_j = -I_{\mathrm{L}} - I_{\mathrm{K}} - I_{\mathrm{Na}} - I_{\mathrm{T}} - I_{\mathrm{Ca}} - I_{\mathrm{AHP}} + I_{\mathrm{app}} + I_{\mathrm{syn}} + I_{\mathrm{stim}}$$

(Terman *et al.*, *J. Neurosci.* **22**, 2963 (2002); Rubin & Terman, *J. Comput. Neurosci.* 16, 21 (2004))

In PD, STN neurons change to burst-firing mode, and a pronounced increase of local field potential (LFP) oscillations is observed.

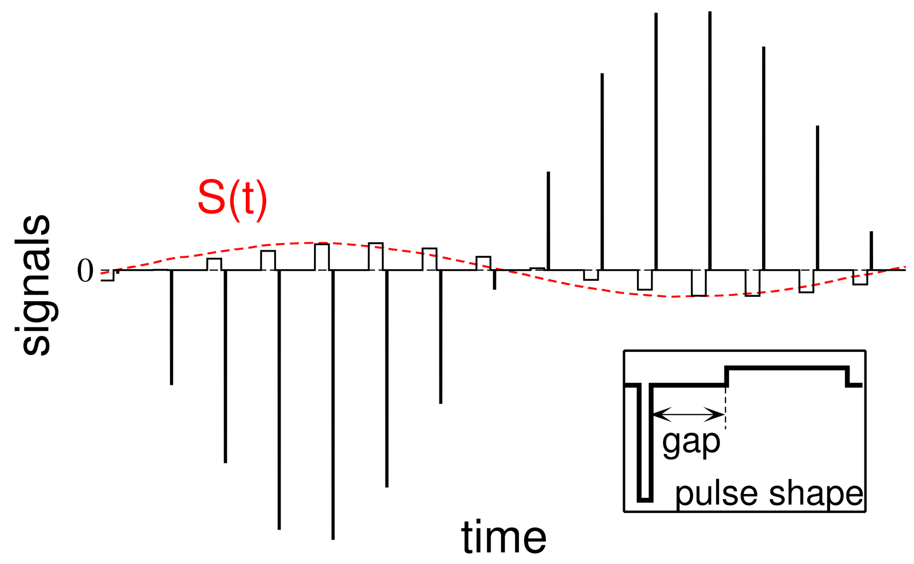


Linear delayed feedback: $S(t) = K(x(t-\tau) - x(t))$, $x(t)$ - filtered LFP

Nonlinear delayed feedback: Mean field is considered as a complex analytic signal $Z(t) = x(t) + \mathrm{i}y(t)$. Feedback signal: $S_z(t) = KZ^2(t)Z^*(t-\tau)$. We use only the real part for stimulation $S(t) = Kx(t-\tau)\left(x^2(t) - y^2(t)\right) + 2Kx(t)y(t)y(t-\tau)$

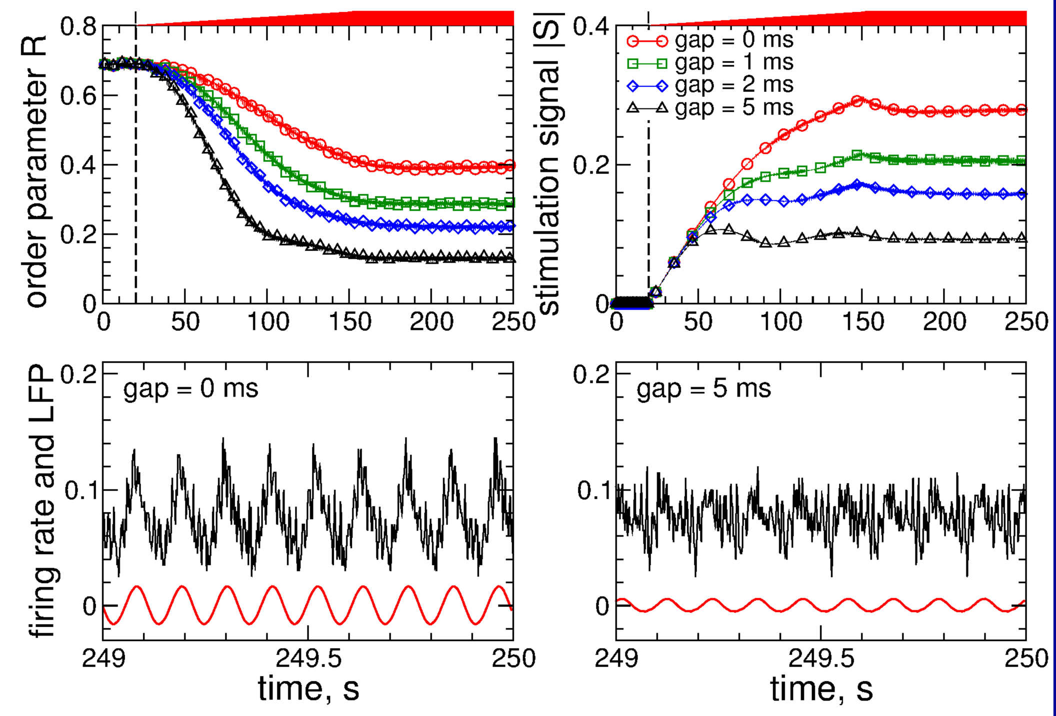
II. Pulsatile delayed feedback

- Electrical stimulation by slowly oscillating smooth signal may cause an irreversible and damaging charge deposit into the neuronal tissue.
- We suggest to modulate the amplitude of the high-frequency train of charge-balanced pulses used by the standard HF DBS by feedback signal - *pulsatile feedback stimulation*
- We also consider an *interphase gap* between the recharging phases of the pulses

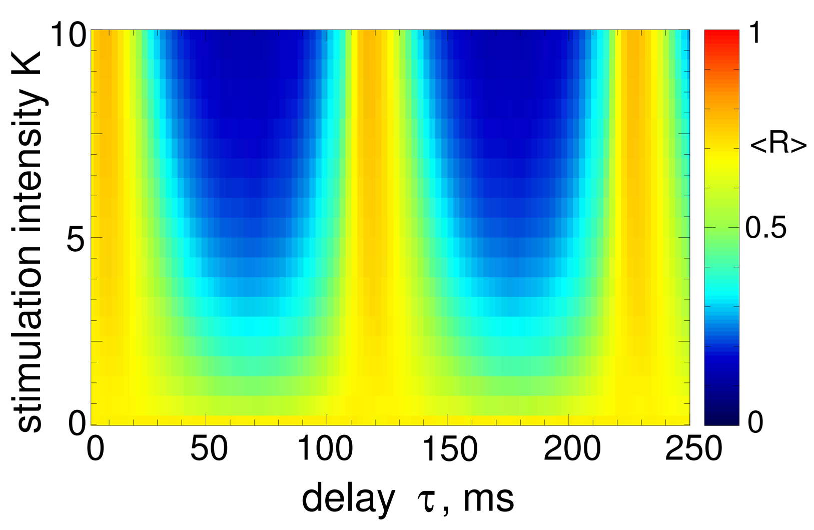


Introducing an interphase gap can lead to

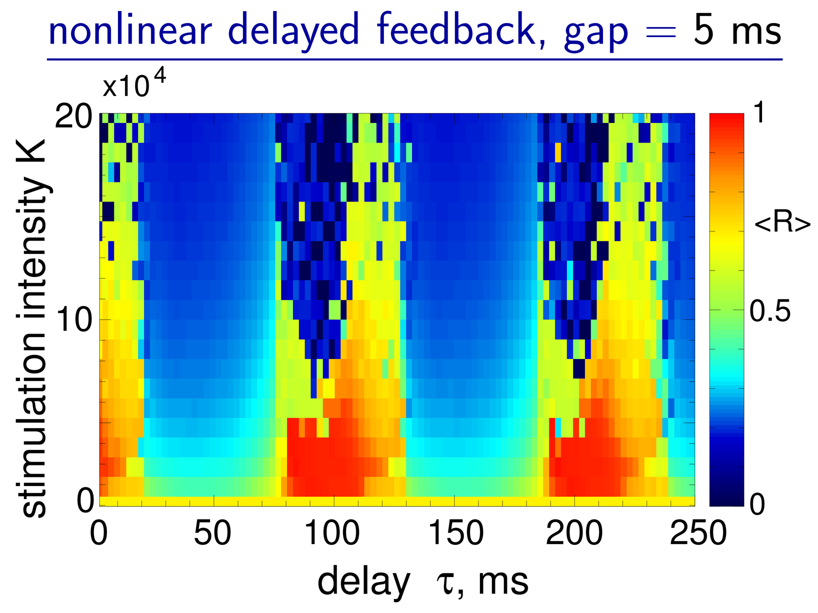
- improvement of the stimulation-induced desynchronization
- reduction of the amount of administered stimulation
- these effects can further be enhanced for larger interphase gap



linear delayed feedback, gap = 5 ms

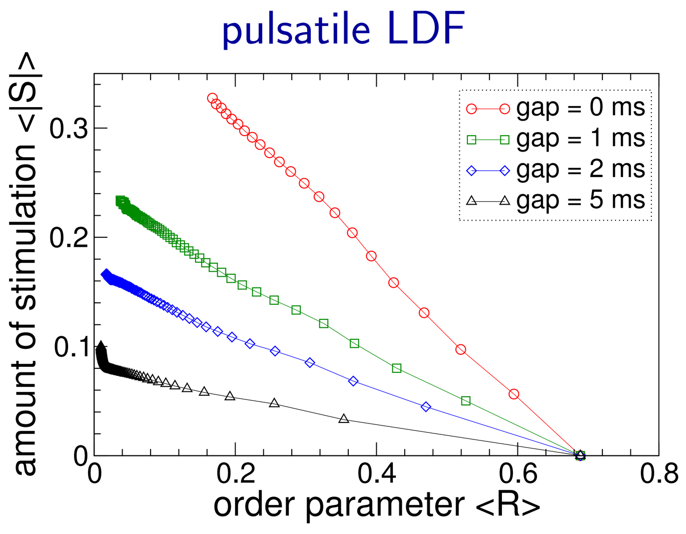


nonlinear delayed feedback, gap = 5 ms

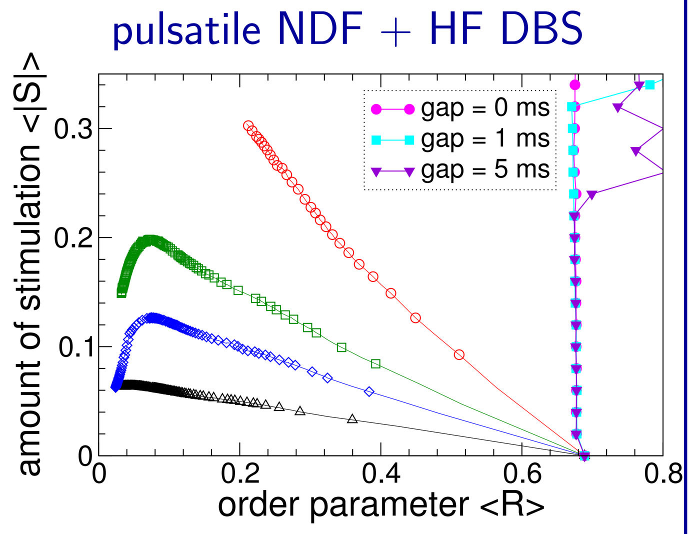


Efficacy of the pulsatile delayed feedback: amount of stimulation vs. extent of induced desynchronization

pulsatile LDF

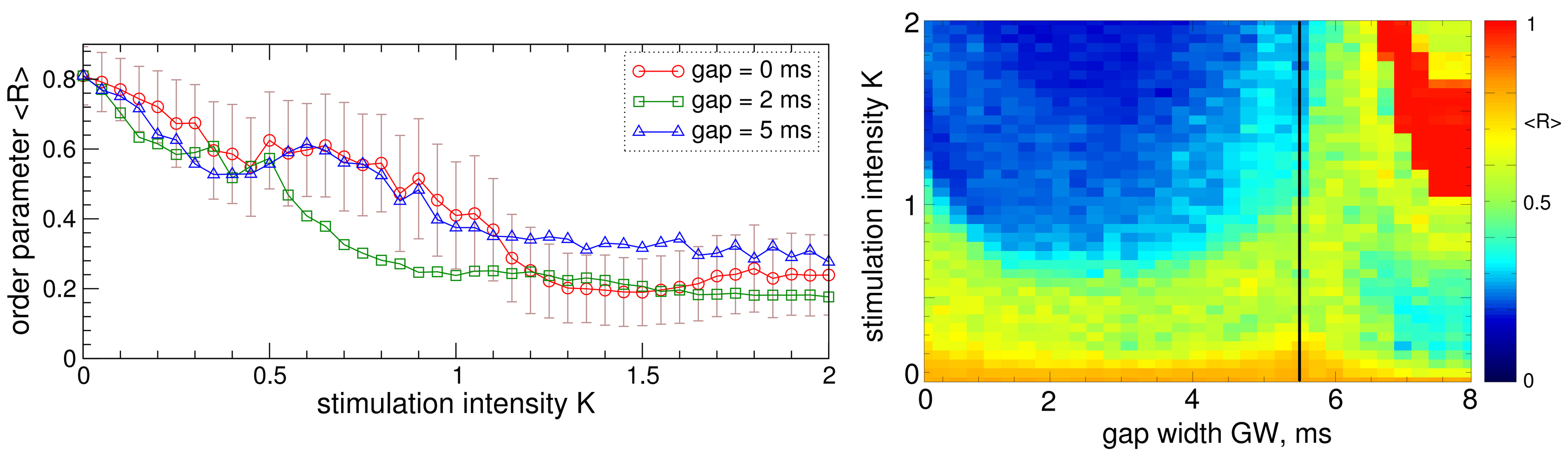


pulsatile NDF + HF DBS

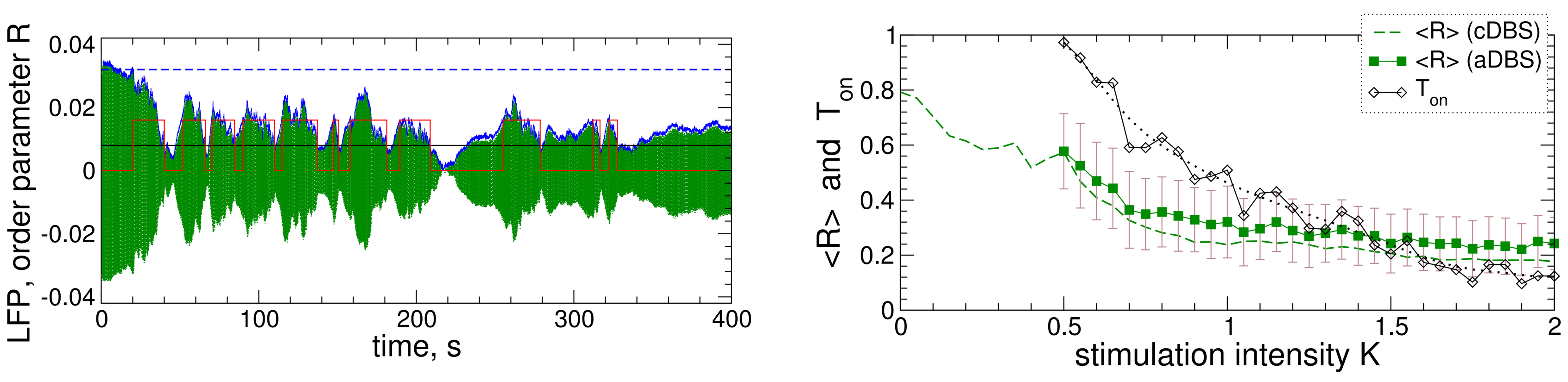


III. Adaptive delivery of stimulation

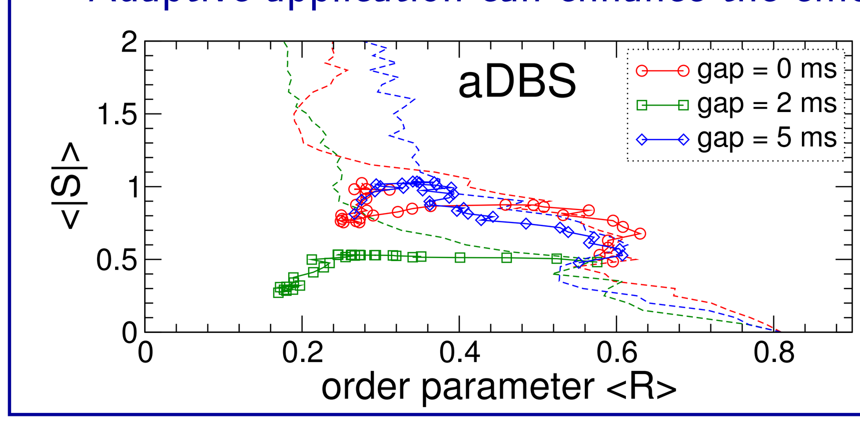
- Conventional continuous HF DBS (cDBS) can optimally suppress synchronization for an interphase gap of an intermediate width

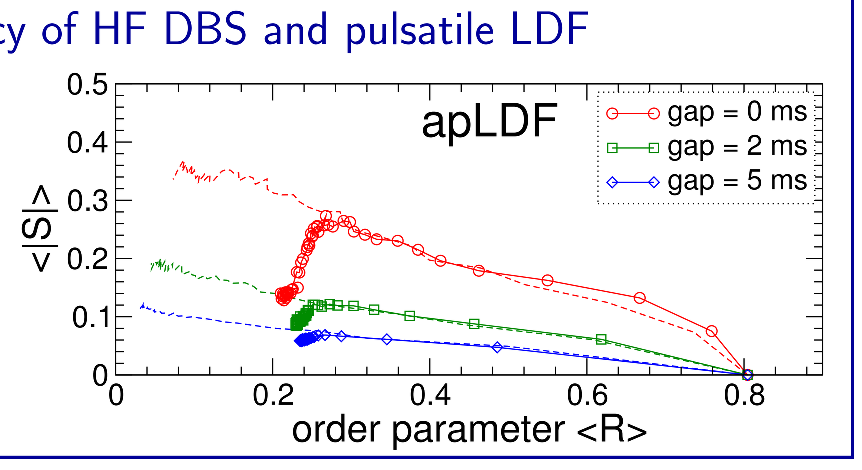


- Adaptive HF DBS (aDBS) can suppress synchronization for much less stimulation time



- Adaptive application can enhance the efficacy of HF DBS and pulsatile LDF





References

1. Popovych, O. V., Lysyansky, B., Rosenblum, M., Pikovsky, A., Tass, P. A. (2017) Pulsatile desynchronizing delayed feedback for closed-loop deep brain stimulation. *PLoS ONE* **12**, e0173363.
2. Popovych, O. V., Lysyansky, B., Tass, P. A. (2017) Closed-loop deep brain stimulation by pulsatile delayed feedback with increased gap between pulse phases. *Sci. Rep.* **7**, 1033.
3. Popovych, O. V. & Tass, P. A. (2018) Multisite delayed feedback for electrical brain stimulation. *Front. Physiol.* **9**, 46.
4. Popovych, O. V. & Tass, P. A. (2018) Adaptive delivery of continuous and delayed feedback deep brain stimulation - a computational study. *Sci. Rep.* (under review).