Mathematical modelling of oscillatory basal ganglia activity in normal and Parkinsonian condition

Roman Borisyuk,

Robert Merrison-Hort

Plymouth University

Nada Yousif

Imperial College London

Outline

- Introduction: brain modelling
- Introduction: the Basal Ganglia (BG) and movement control
- Interactive Channel Model of the Basal Ganglia
- Deep Brain Stimulation (DBS) modelling

Brain modelling

Usually, two scales of neuronal activity are considered for modelling:

- **Meso-scopic** scale (level) of modelling where the average activity of neuronal **populations** is studied. We use this approach in multi-channel model of the BG.
- **Microscopic** level of modelling where the **spiking** activity of individual cells is considered. We use detailed model of spiking activity for DBS study.

Population activity

Very popular model: Wilson-Cowan (1972, 1973)

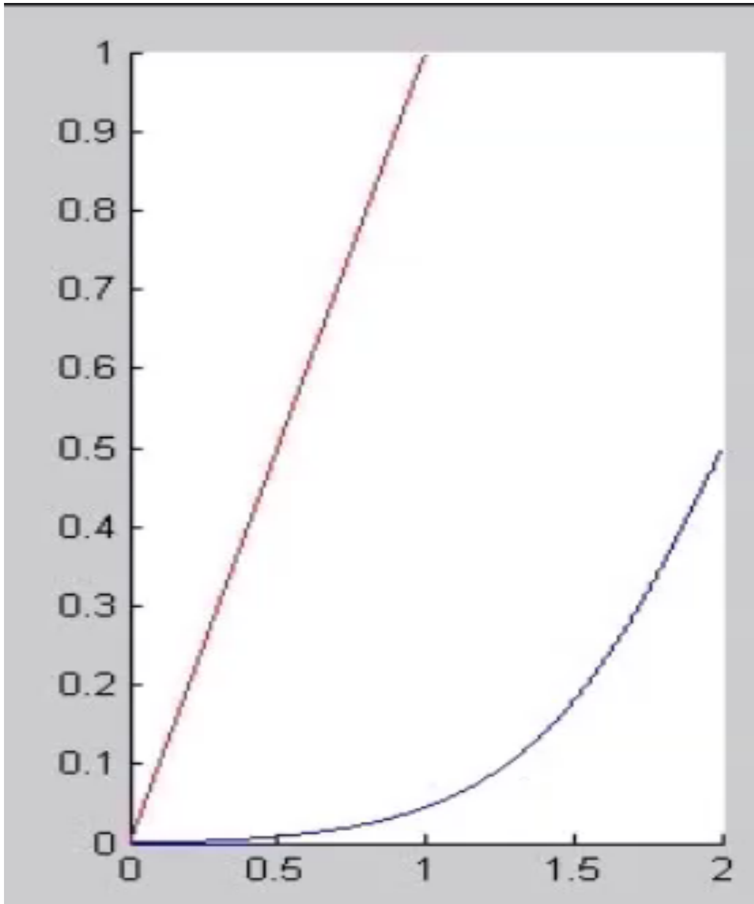
$$\dot{x} = -x + Z(ax + I)$$

$x(t)$ is the average activity of neuronal population

$Z(.)$ is the sigmoid function

a is the connectivity parameter

I is an external input to the population



Connection strength increases:
One stable fixed point (low level of population activity)

Fold bifurcation

Multistability: Three fixed points: two are stable (low and high activity levels, one is unstable

Hysteresis

Population activity

Two interactive W-C populations can oscillate

$$dx/dt = -x + Z(ax - by + Ix)$$

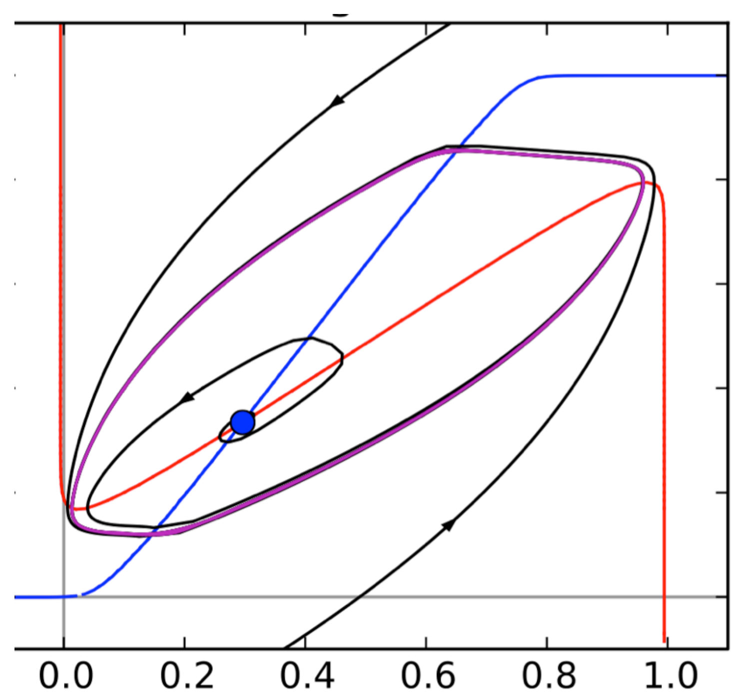
$$dy/dt = -y + Zy(cx - dy + Iy)$$

$x(t), y(t)$ are the average activities of excitatory and inhibitory neuronal populations recpectively

$Zx(.), Zy(.)$ are the sigmoid functions

a, b, c, d are the connectivity parameters

Ix, Iy are the external inputs to excitatory and inhibitory population respectively



Brain modelling

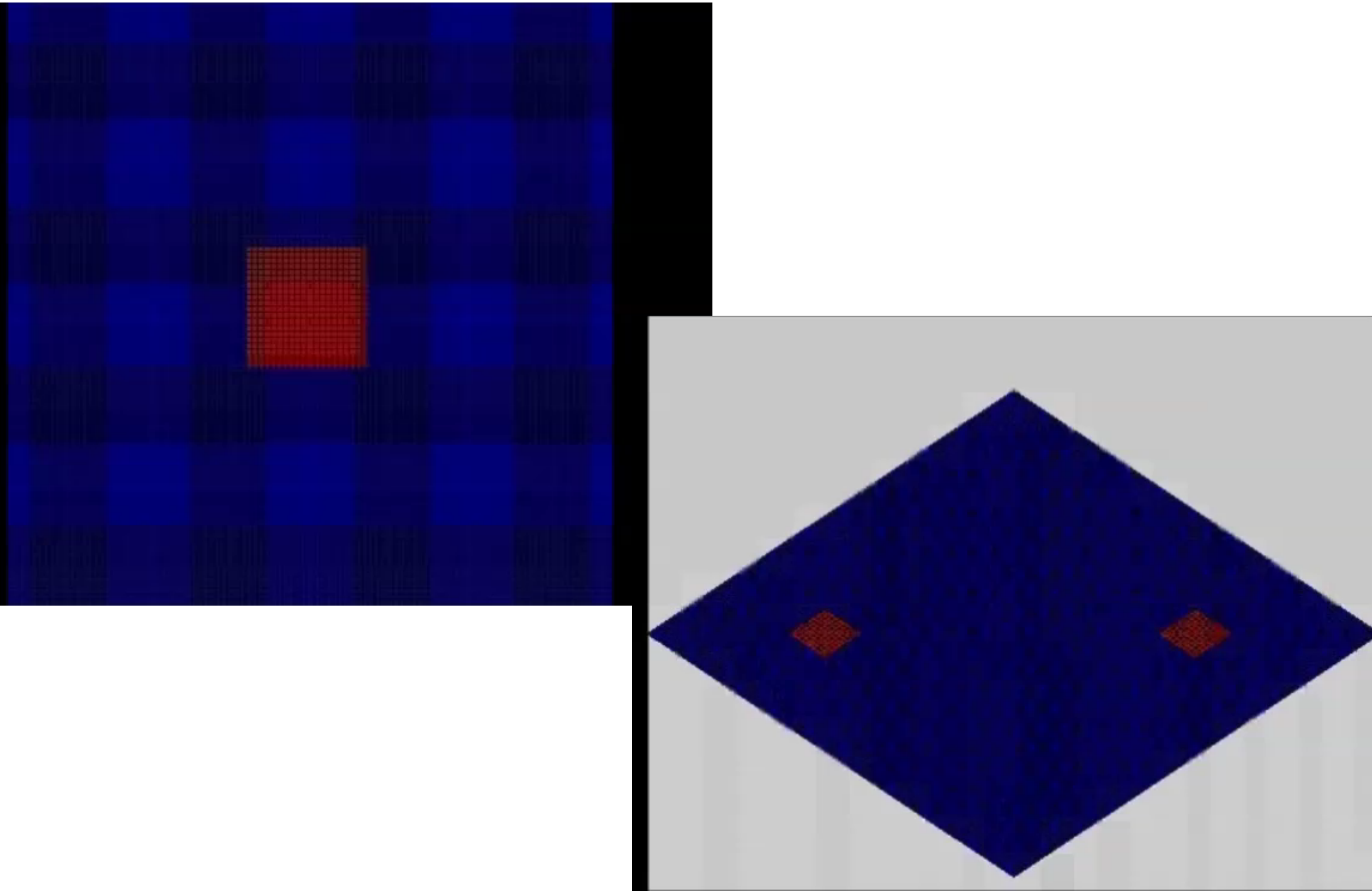
- In many cases brain modelling deals with patterns of neuronal activity either on microscopic or meso-scopic scale

- From recent Connectionist discussion on “How the brain works”:

  Steven Pinker (Psychology, Harvard University) was asked to describe in 5 words how the brain works:

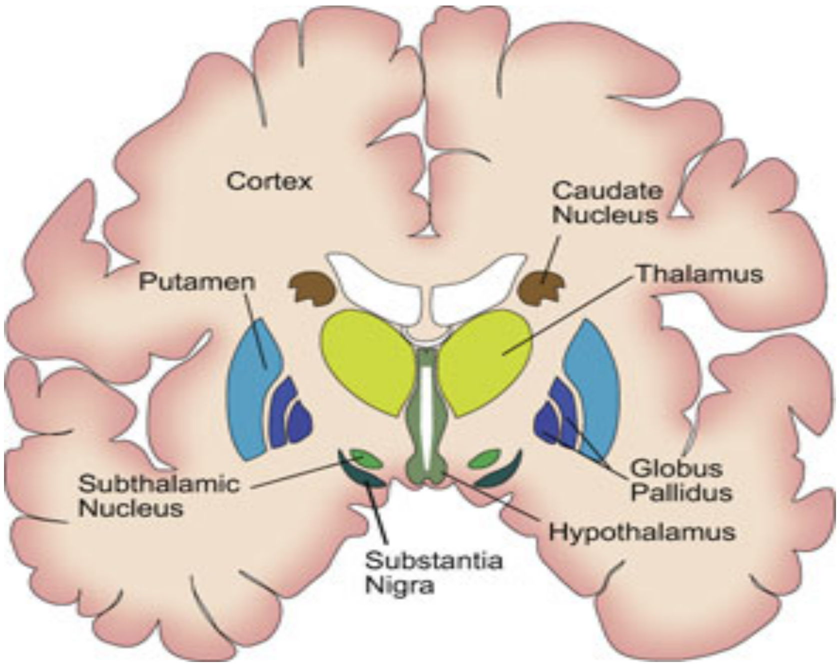
"Brain cells fire in patterns“

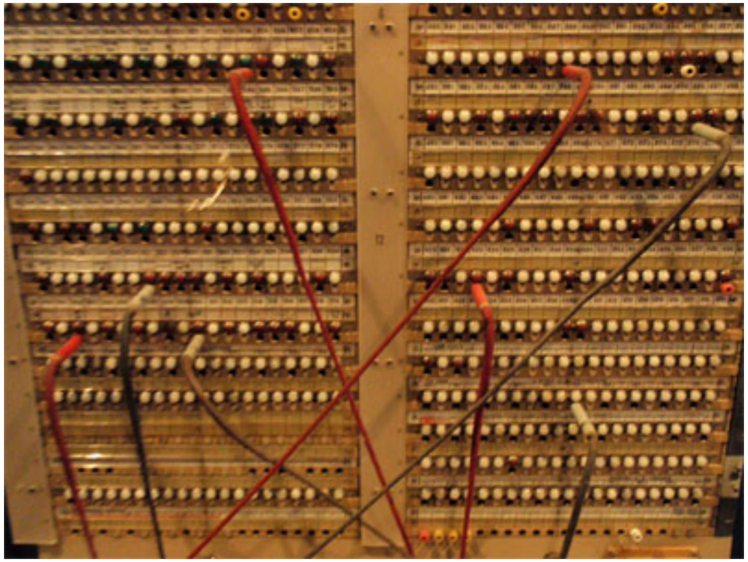
“Brain cells fire in patterns”



Introduction: The Basal Ganglia

- The Basal Ganglia (BG) comprise multiple subcortical nuclei
- Current hypothesis implicate the BG primarily in action selection: “behaviour (channel) switching” in BG is influenced by signals from the cortex

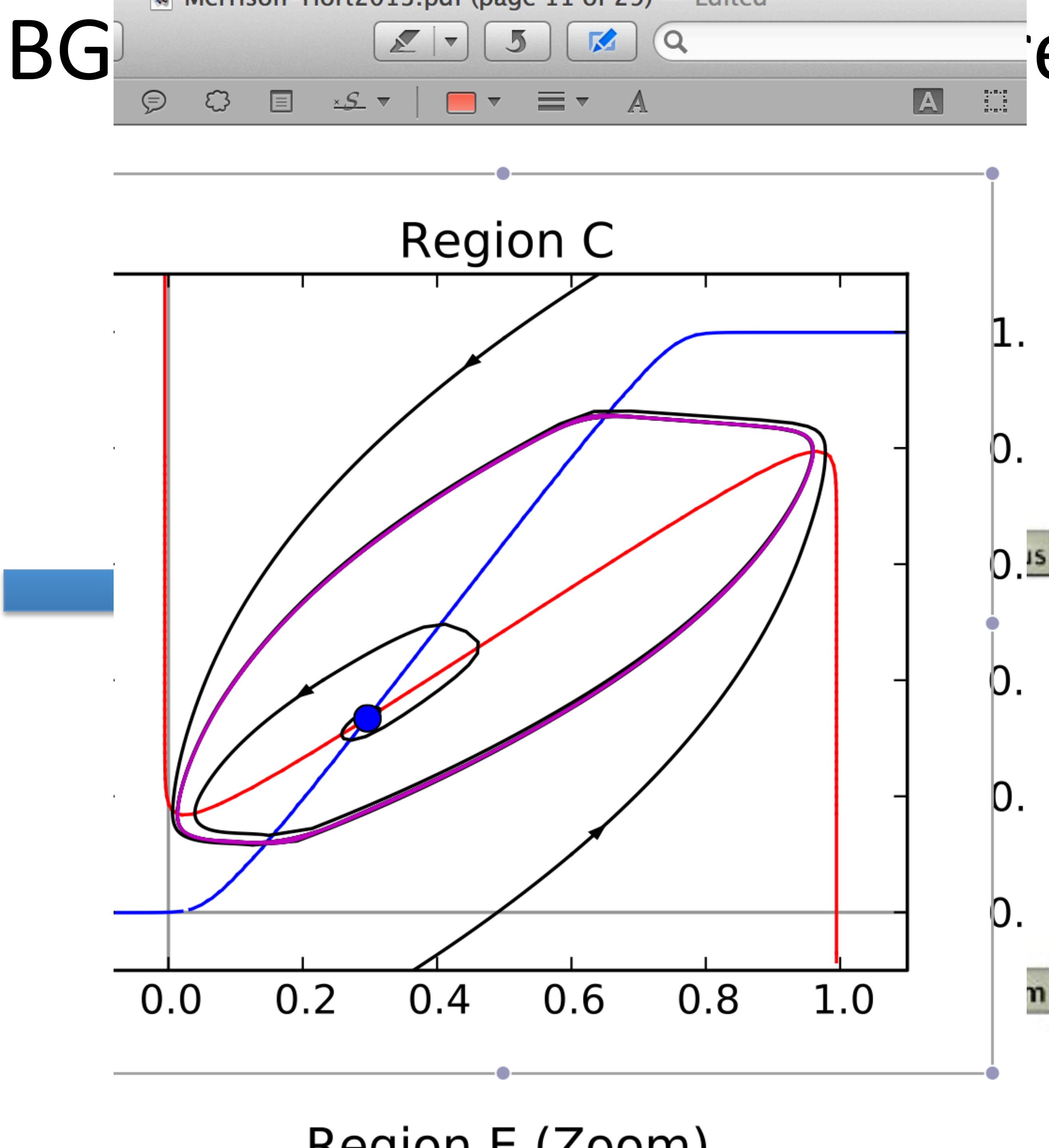




BG and Parkinson's Disease (PD)

- BG exert an inhibition to the motor system and the release from inhibition permits a motor system to become active
- PD is primarily a disease of BG which relates to the death of neurons and decrease of dopamine
- The population activity in Parkinsonian BG is oscillatory in beta-range

BG ... ect

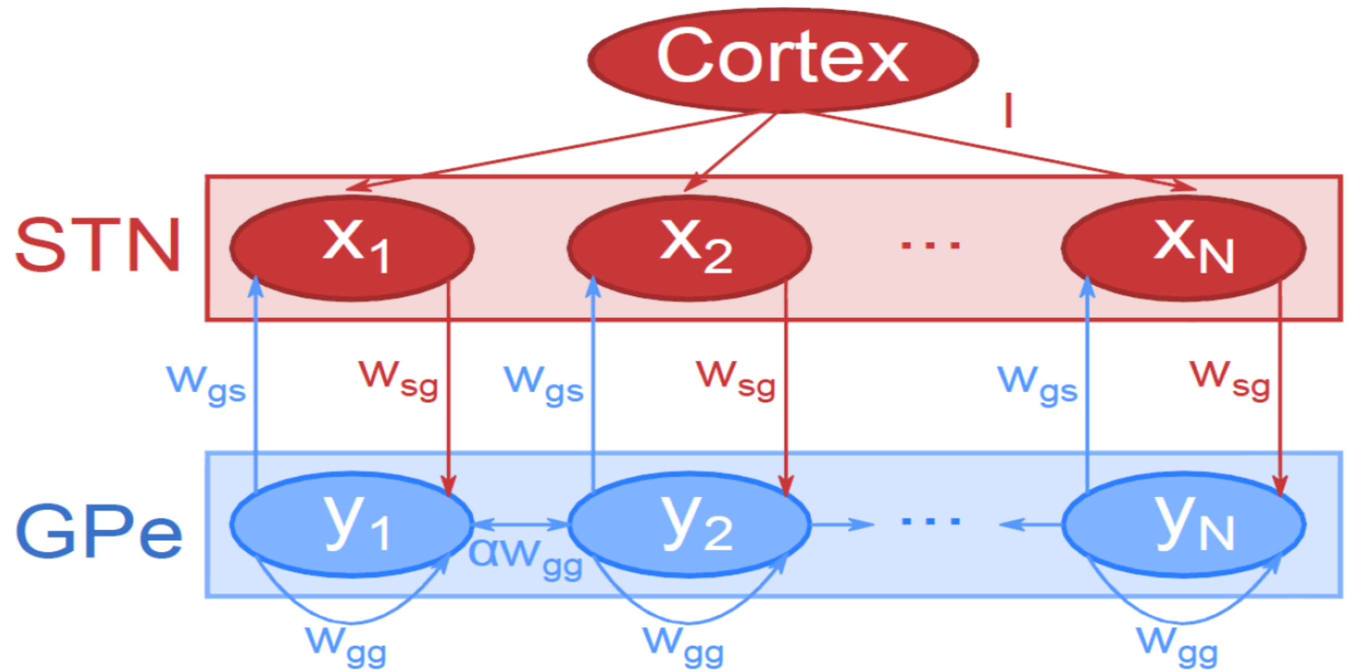


Wilson-Cowan model of BG

$$\tau_s \dot{x}_i = -x_i + Z_s(w_{ss} x_i - \boxed{w_{gs}} y_i + I) \quad (1)$$

$$\tau_g \dot{y}_i = -y_i + Z_g\left(-\boxed{w_{gg}} y_i + w_{sg} x_i - \alpha w_{gg} \sum_{j \in L_i} y_j\right), \quad i = 1, 2, \ldots, N \quad (2)$$

$$Z_j(x) = \frac{1}{1 + \exp(-a_j(x - \theta_j))} - \frac{1}{1 + \exp(a_j \theta_j)}$$



Merrison-Hort et al. (2013) J Math Neurosci

Parameter values

Selection of parameter values of the Wilson-Cowan model has been inspired by the recent model:

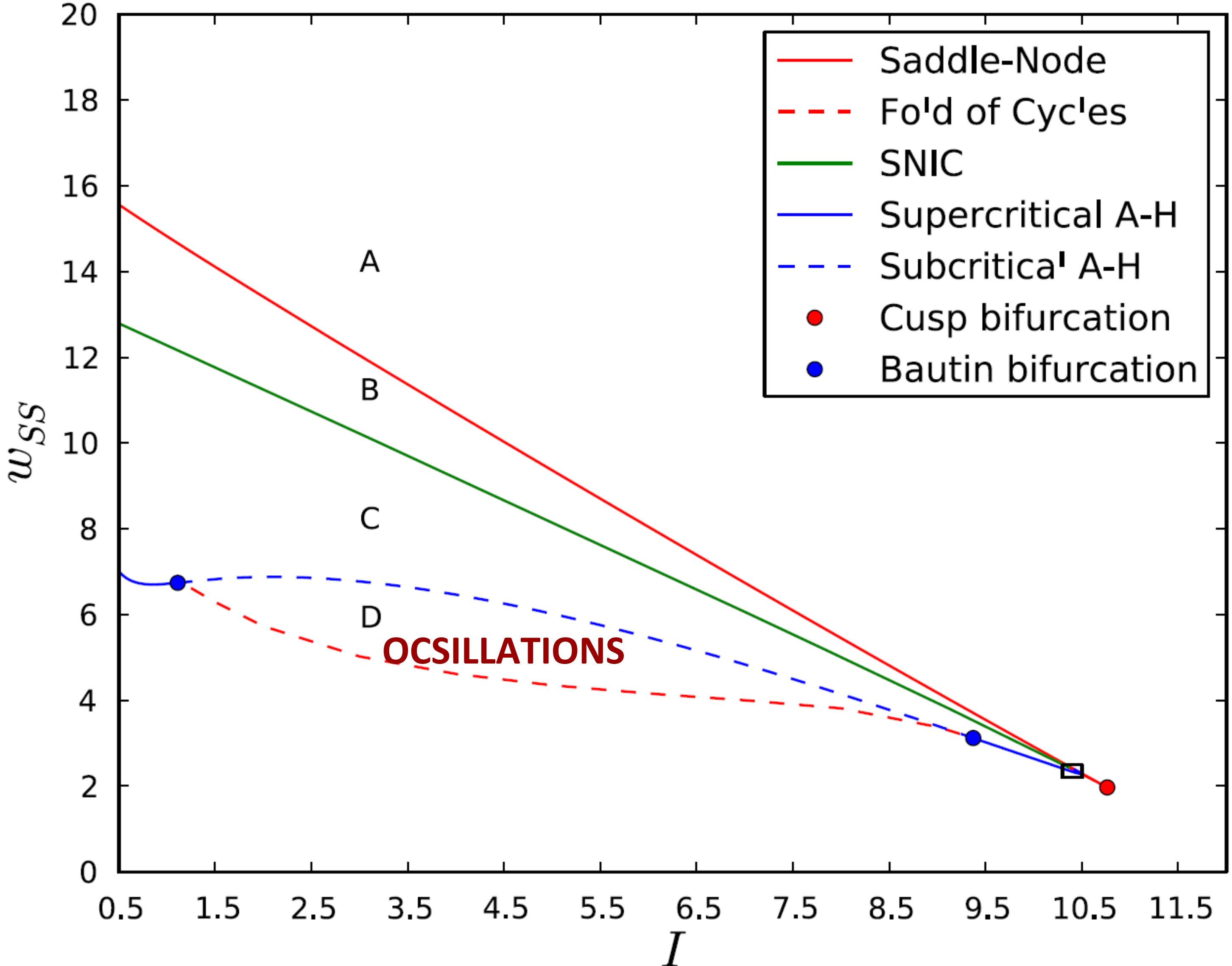
Holgado AJN, Terry JR, Bogacz R: **Conditions for the generation of beta oscillations in the subthalamic nucleus-globus pallidus network**. *J Neurosci* 2010, **30**(37):12340-12352.

	Healthy		Parkinsonian
w_{gg}	6.6		12.3
w_{gs}	1.12		10.7
w_{sg}	19.0		20.0
τ_s		6 ms	
τ_g		14 ms	
a_s		4	
θ_s		1.3	
a_g		3.7	
θ_g		2	

In Parkinsonian case parameter values of inhibitory connections are significantly larger than in healthy case

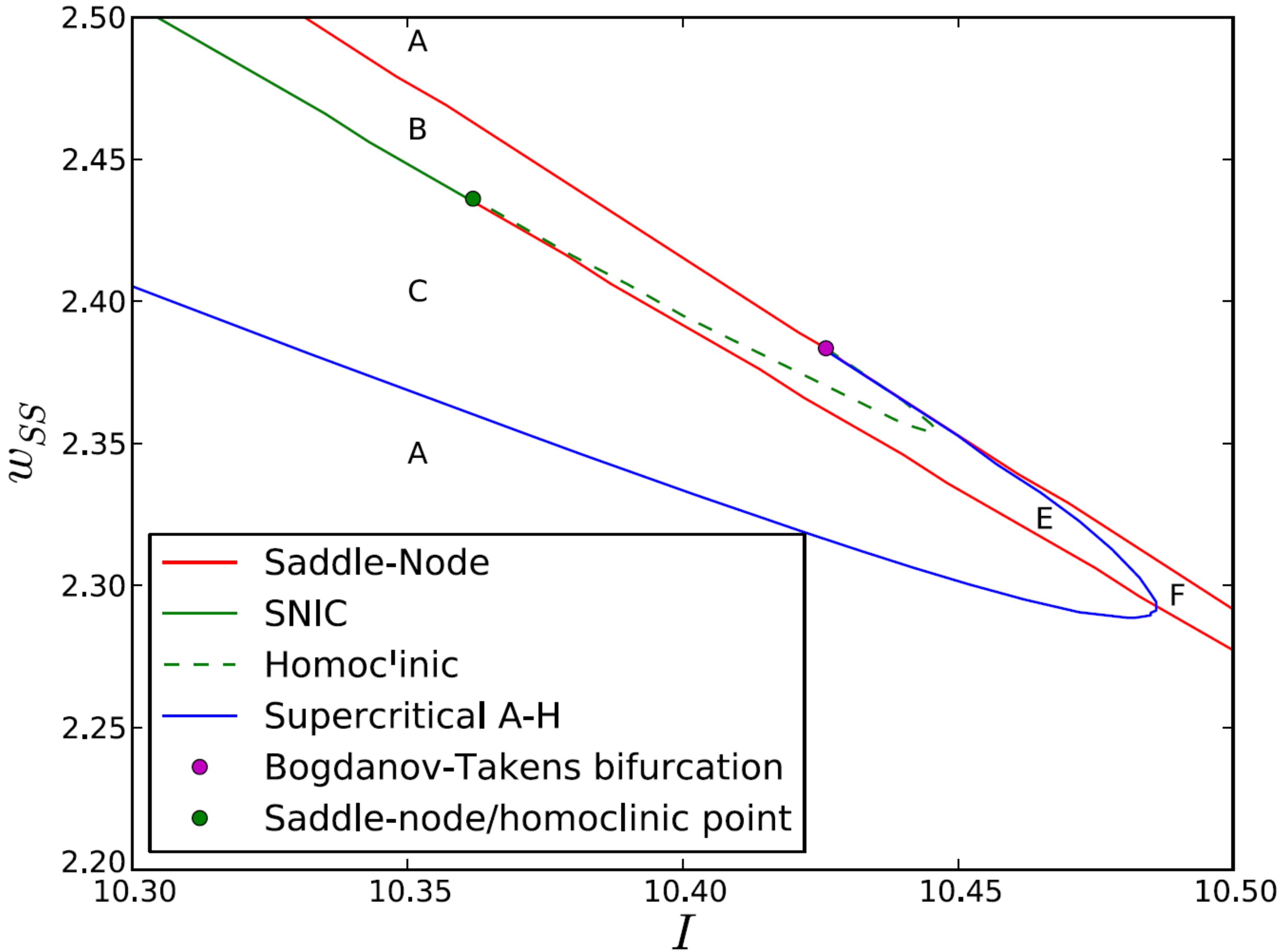
Merrison-Hort et al. (2013) J Math Neurosci

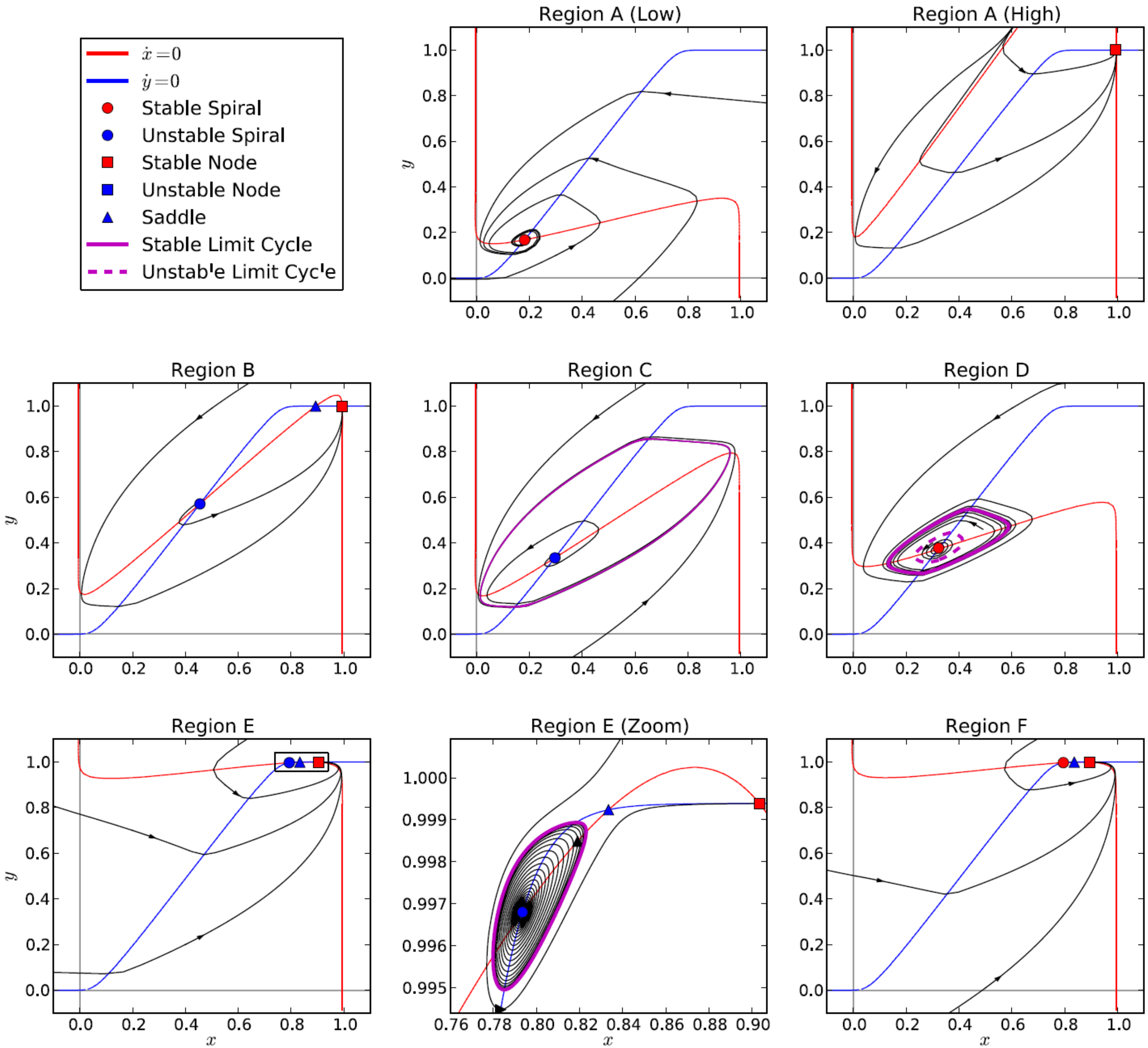
Bifurcation diagram in PD case



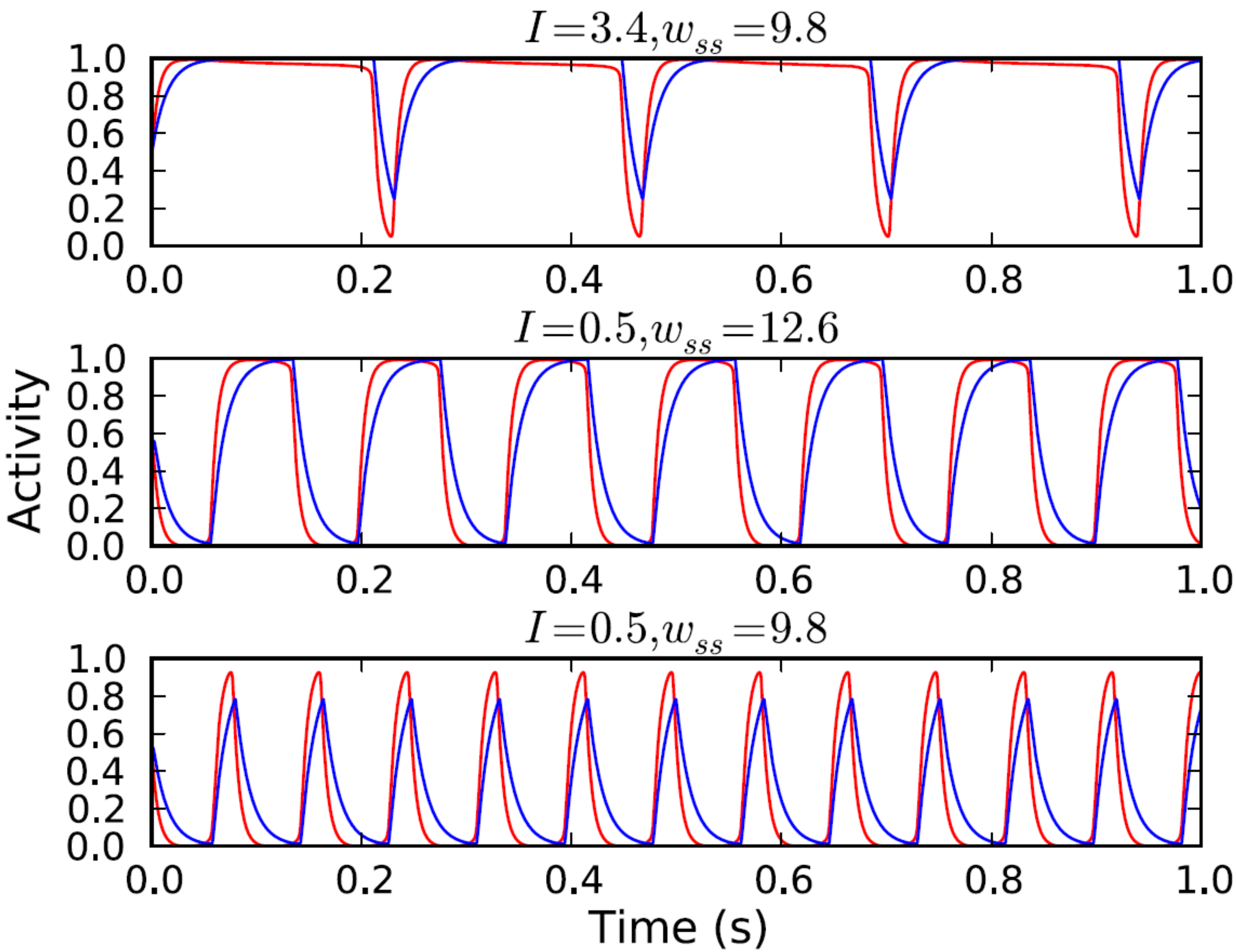
Merrison-Hort et al. (2013) J Math Neurosci

Zoom of the bifurcation diagram

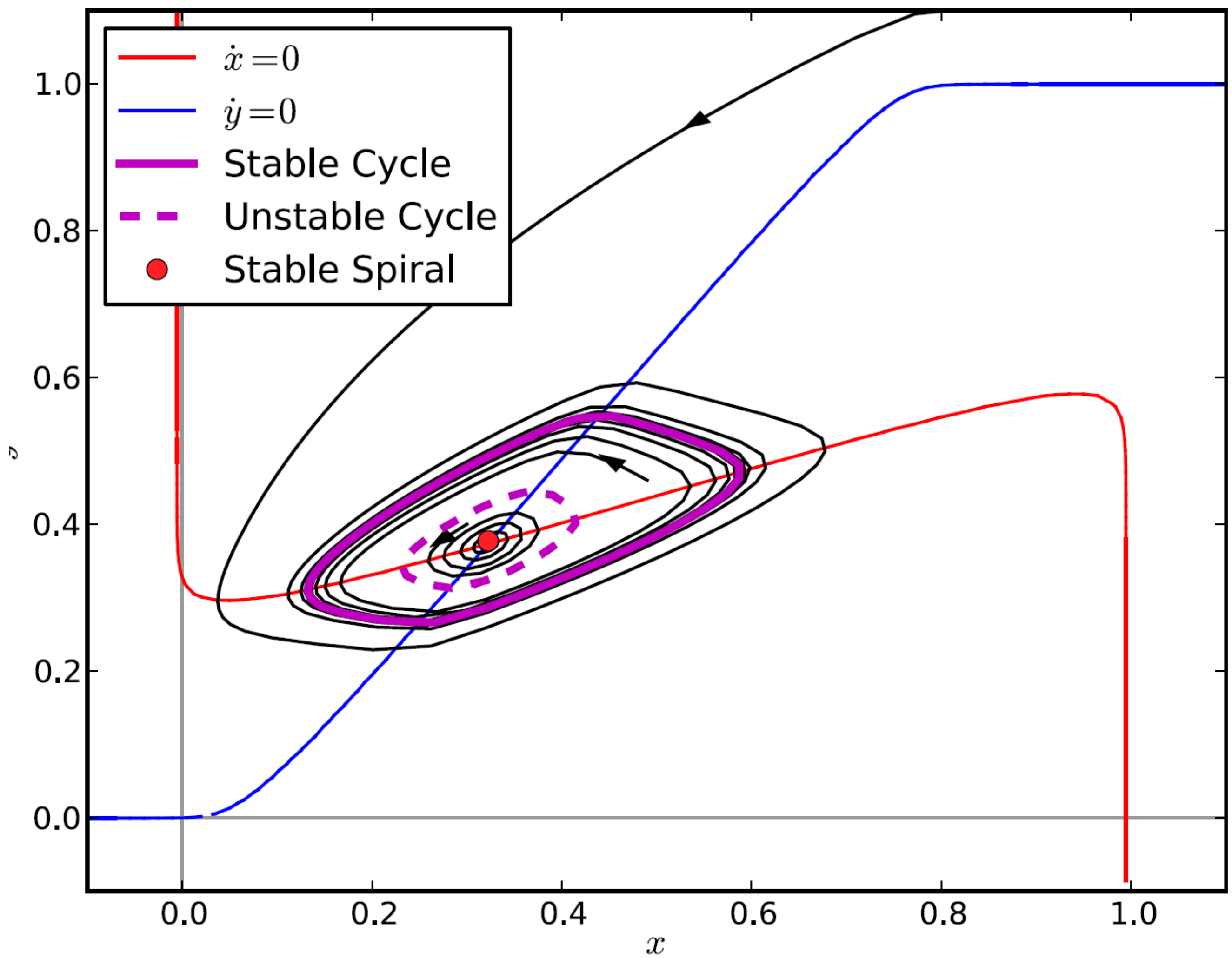



$\dot{x}=0$
$\dot{y}=0$
Stable Spiral
Unstable Spiral
Stable Node
Unstable Node
Saddle
Stable Limit Cycle
Unstable Limit Cycle
Region A (Low)
Region A (High)
Region B
Region C
Region D
Region E
Region E (Zoom)
Region F
x
y

Oscillatory activity in region (c)



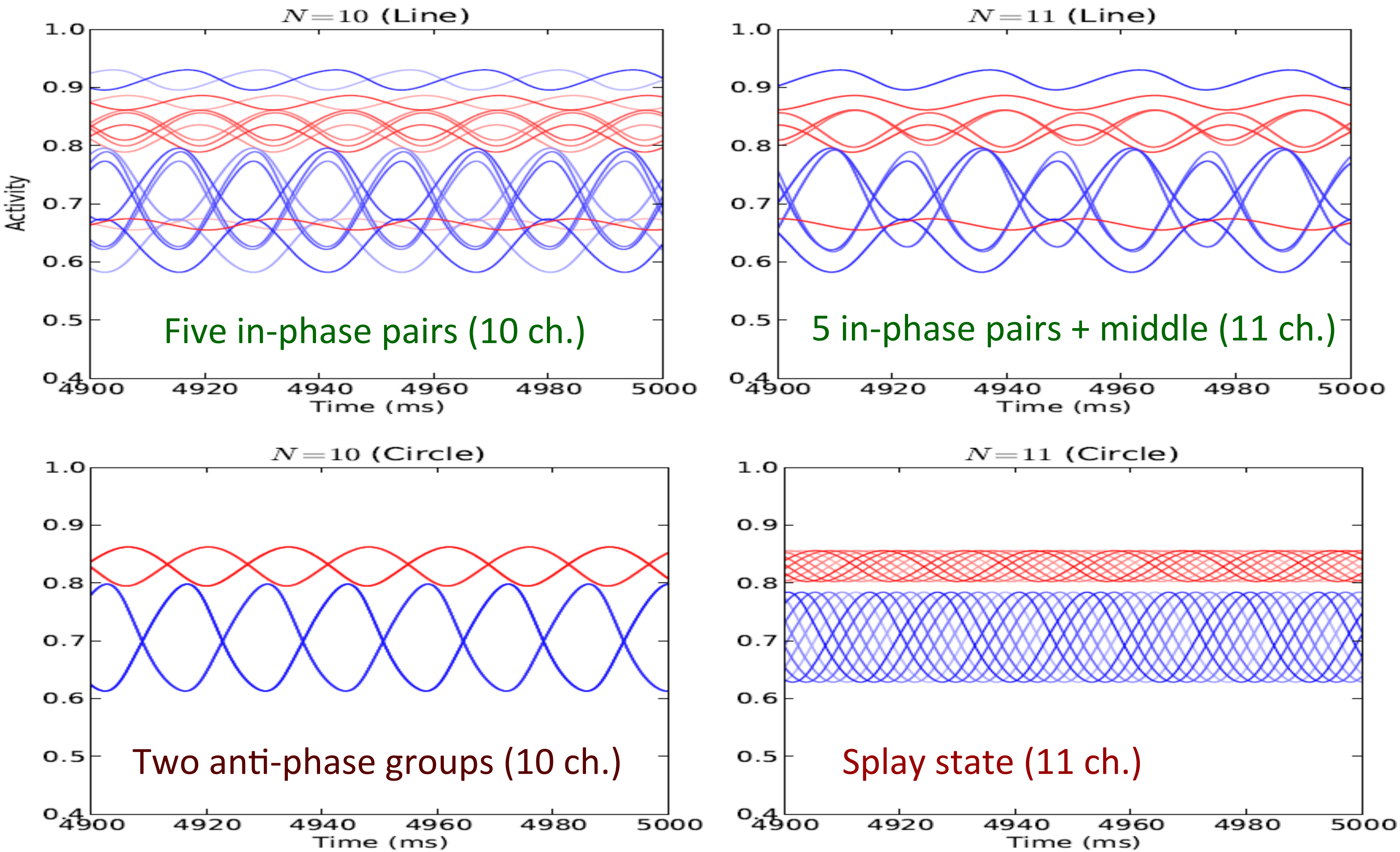
Bistability in Parkinsonian case: region (D)



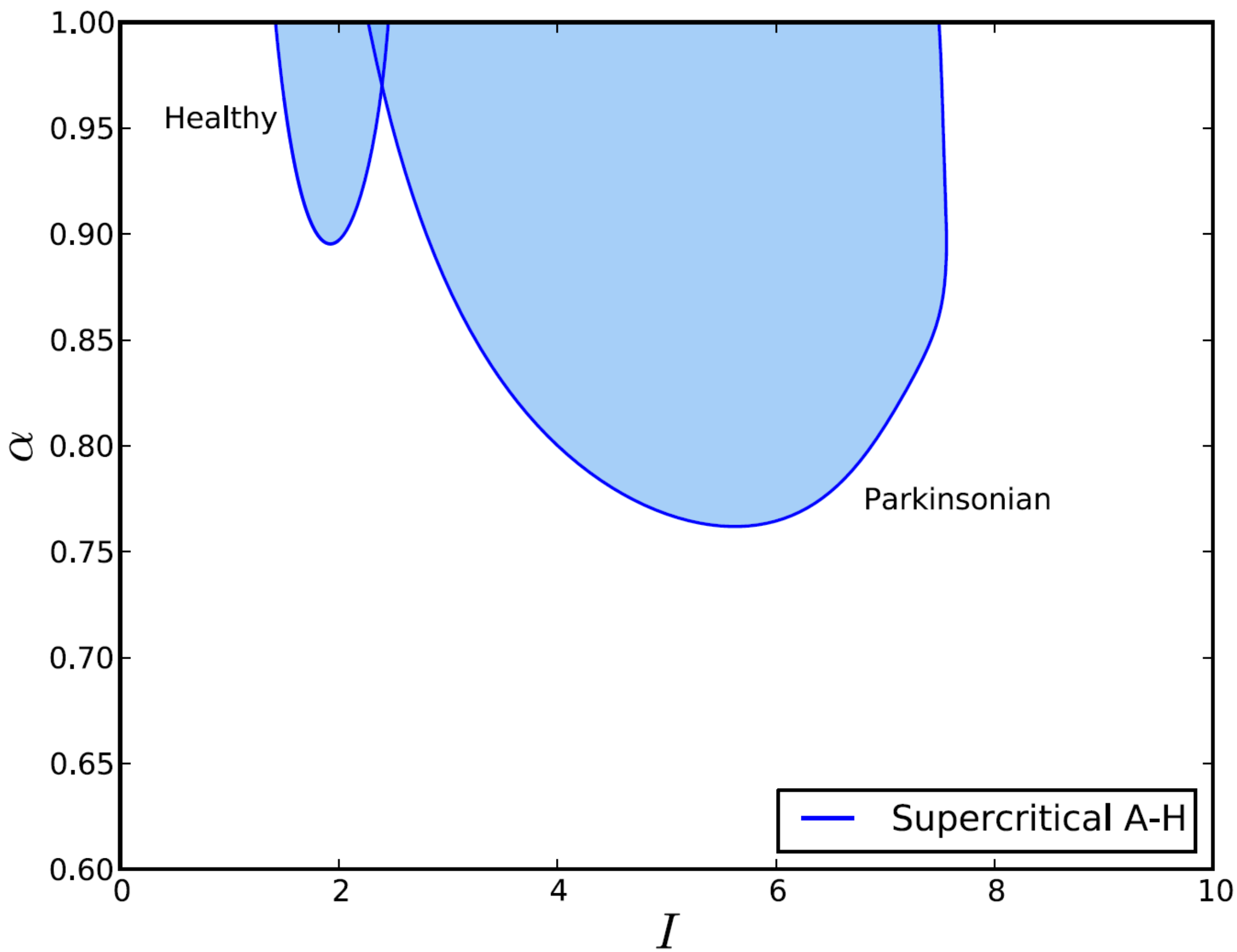
Isolated STN-GPe Channel: Effects of slowly increasing STN self-excitation

Oscillatory activity of coupled channels

on **a line** and on **a circle** (**STN is RED**, **GP is BLUE**)



Oscillations in Healthy and PD cases

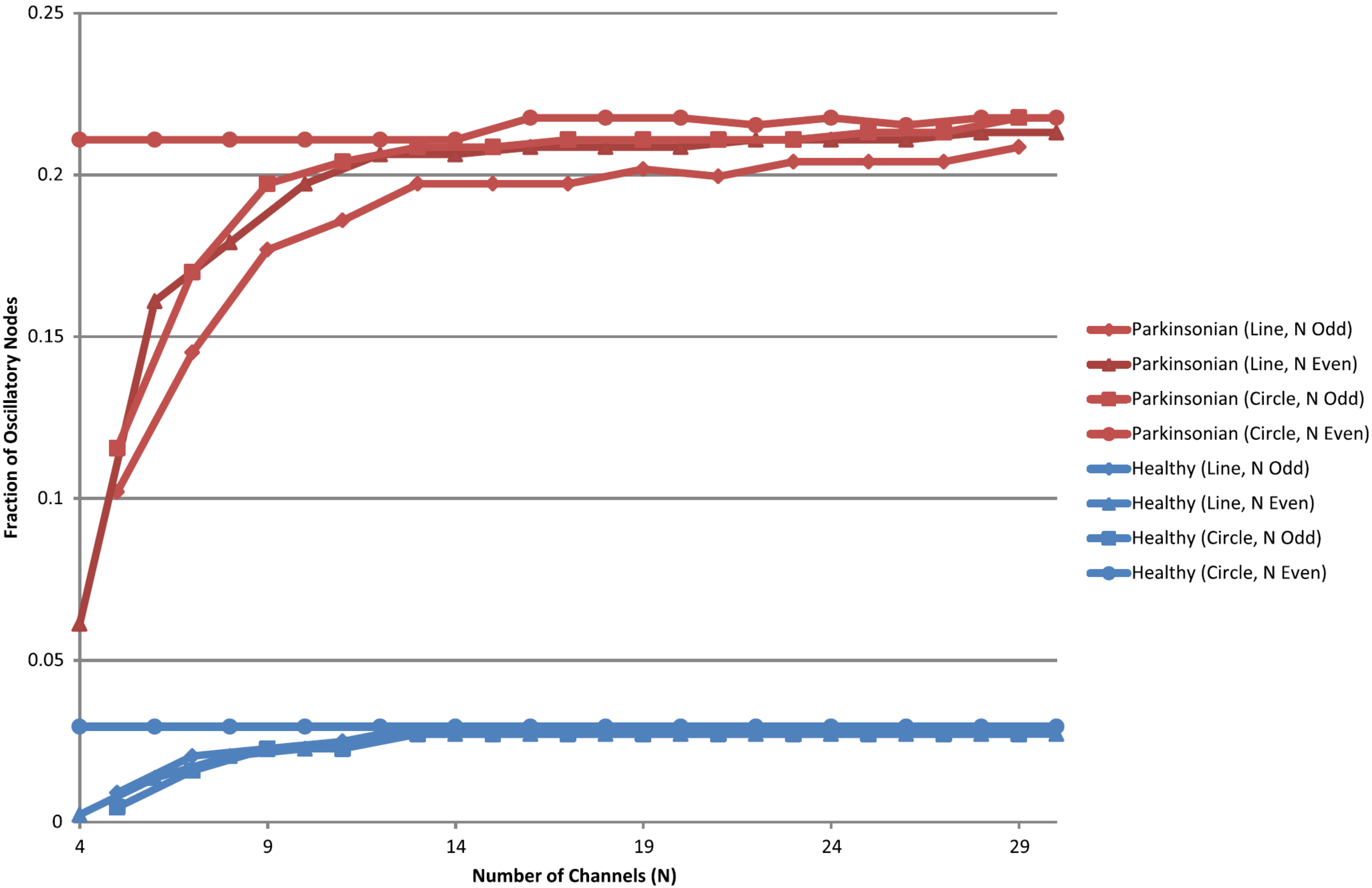


A-H bifurcation curves for 5 channels in a line model for healthy and Parkinsonian cases.

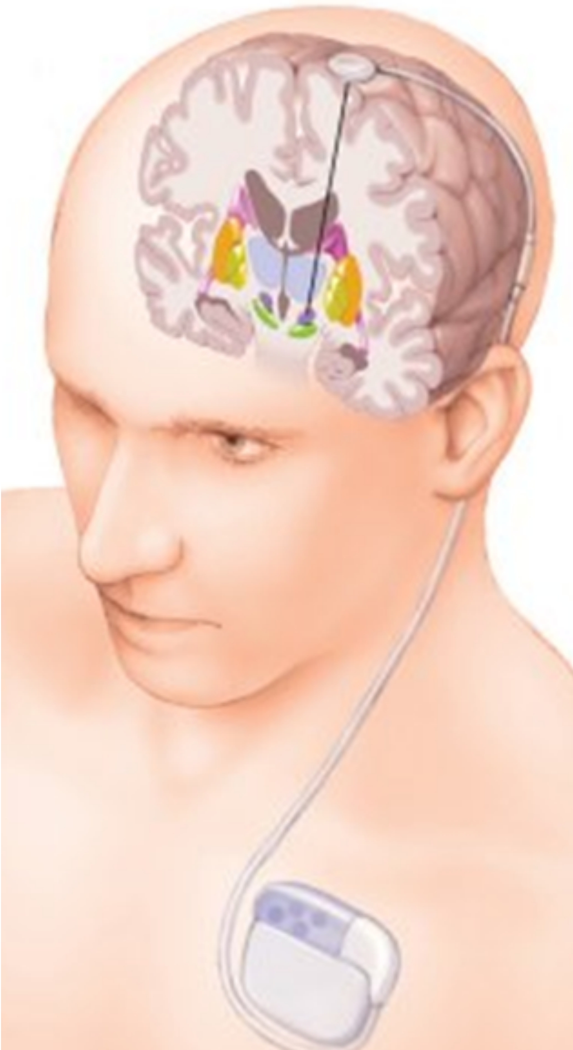
Parameter α is a strength of inhibitory coupling between GP populations of different channels. I is cortical input to STN.

Merrison-Hort et al. (2013) J Math Neurosci

Area of oscillatory region in parameter space



Deep-Brain-Stimulation (DBS)

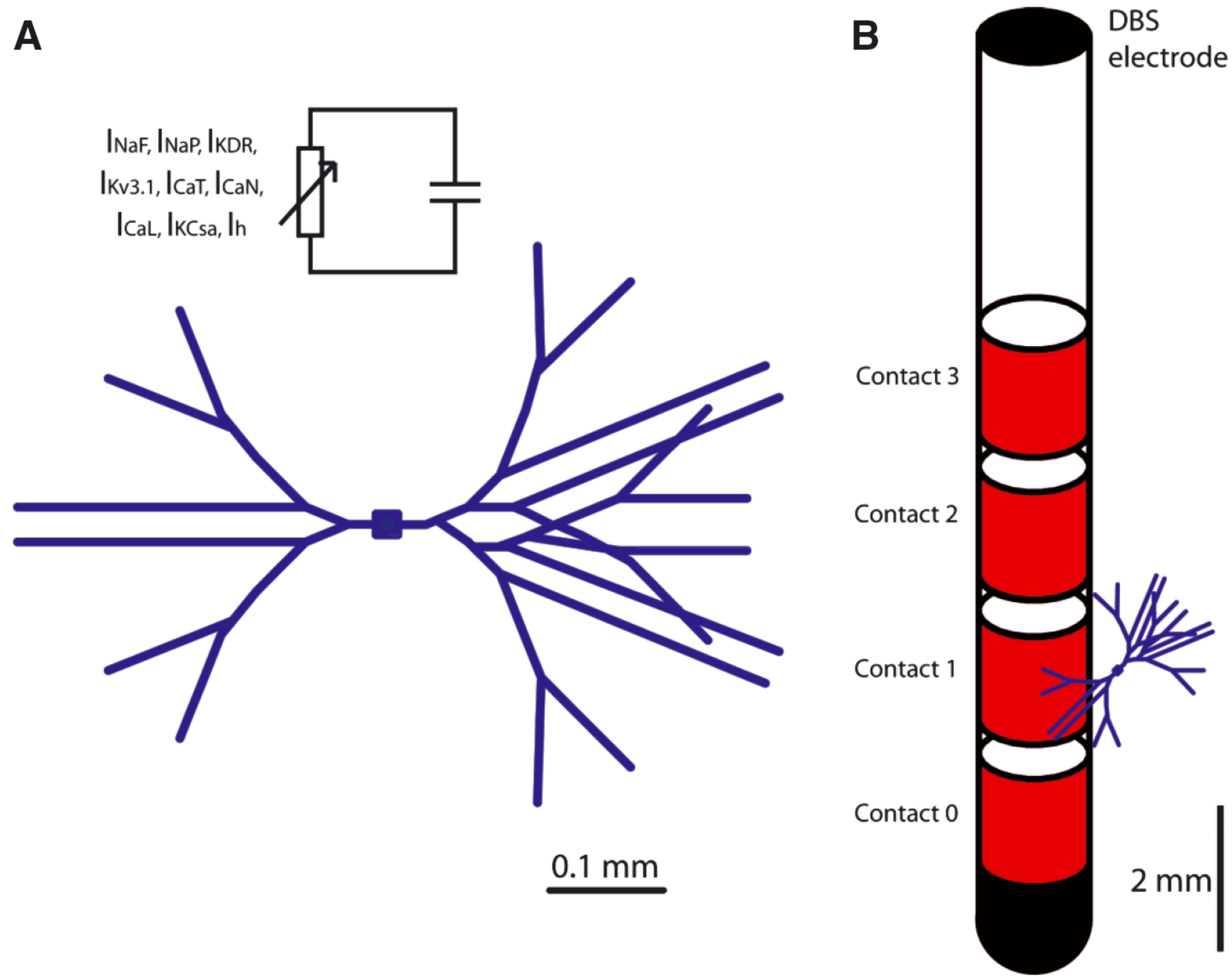


DBS is a successful surgical therapy which involves the chronic stimulation of disorder-specific nuclei.
The implanted electrode sends pulses of high frequency and amplitude to a specific part of the brain. In case of PD, the electrode is often implanted to the STN region.

Borisyuk R, Yousif N (2007) International symposium: theory and neuroinformatics in research related to deep brain stimulation. *Expert Review of Medical Devices*, Vol:4, Pages: 587-589

http://neurowiki2013.wikidot.com/individual:deep-brain-stimulation-dbs-treatment

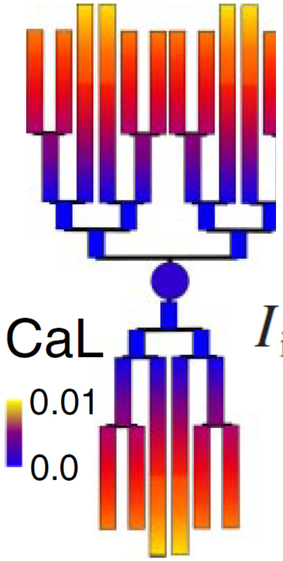
STN neuron under DBS stimulation



Yousif, Borisyuk, et al. (2012) European J Neurosci

Compartmental model

- To model the STN projection neuron we use a compartmental spiking model of Hodgkin-Huxley type which was developed by Gillies & Willshaw (J Neurophysiol, 2006, 95:2352-65)
- Equations for each compartment (*j*) include interactions with the nearest compartments (*j-1*) and (*j+1*), 9 ionic currents and an external input:



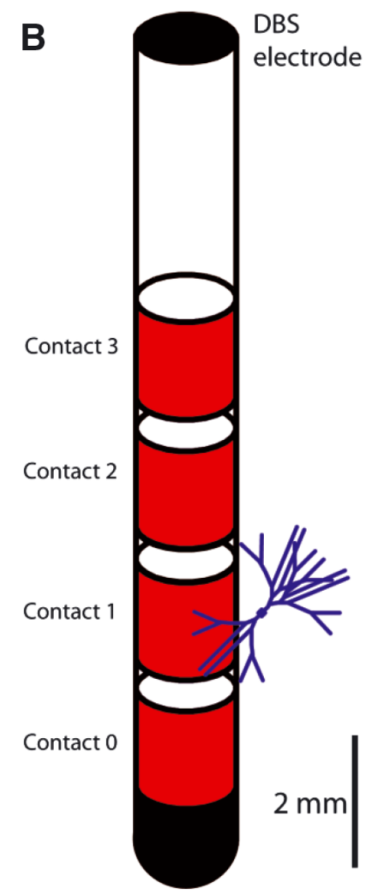
$$c_{mj}\frac{dv_j}{dt} = \frac{v_{j-1} - v_j}{r_{j-1,j}} - \frac{v_j - v_{j+1}}{r_{j,j+1}} - I_{\mathrm{ion}j} - I_{sj}$$

$$I_{\mathrm{ion}j} = I_{\mathrm{Na}j} + I_{\mathrm{KDR}j} + I_{\mathrm{Kv31}j} + I_{\mathrm{sKCa}j} + I_{\mathrm{h}j} + I_{\mathrm{CaT}j} + I_{\mathrm{CaL}j} + I_{\mathrm{CaN}j} + I_{\mathrm{L}j}$$

Electrical potential near the electrode

- The finite element method (FEM) was used to describe geometry of the DBS electrode (3D cylinder surrounded by the homogeneous brain tissue)
- The distribution of electric potential in 3D space induced by stimulation was described the Laplace equation:

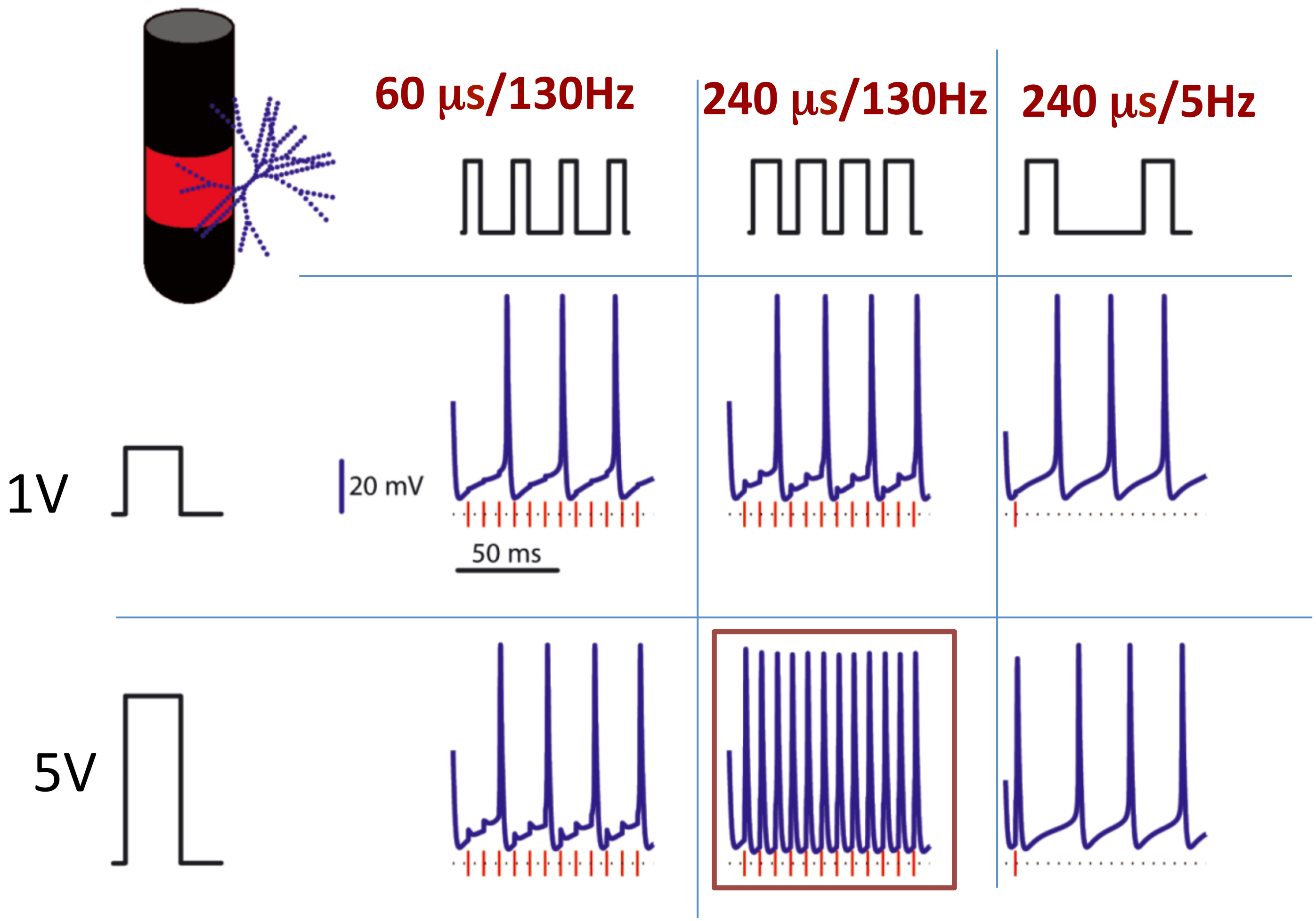
$$\nabla.(\sigma \nabla V) = 0$$



Yousif, Borisyuk, et al. (2012) European J Neurosci

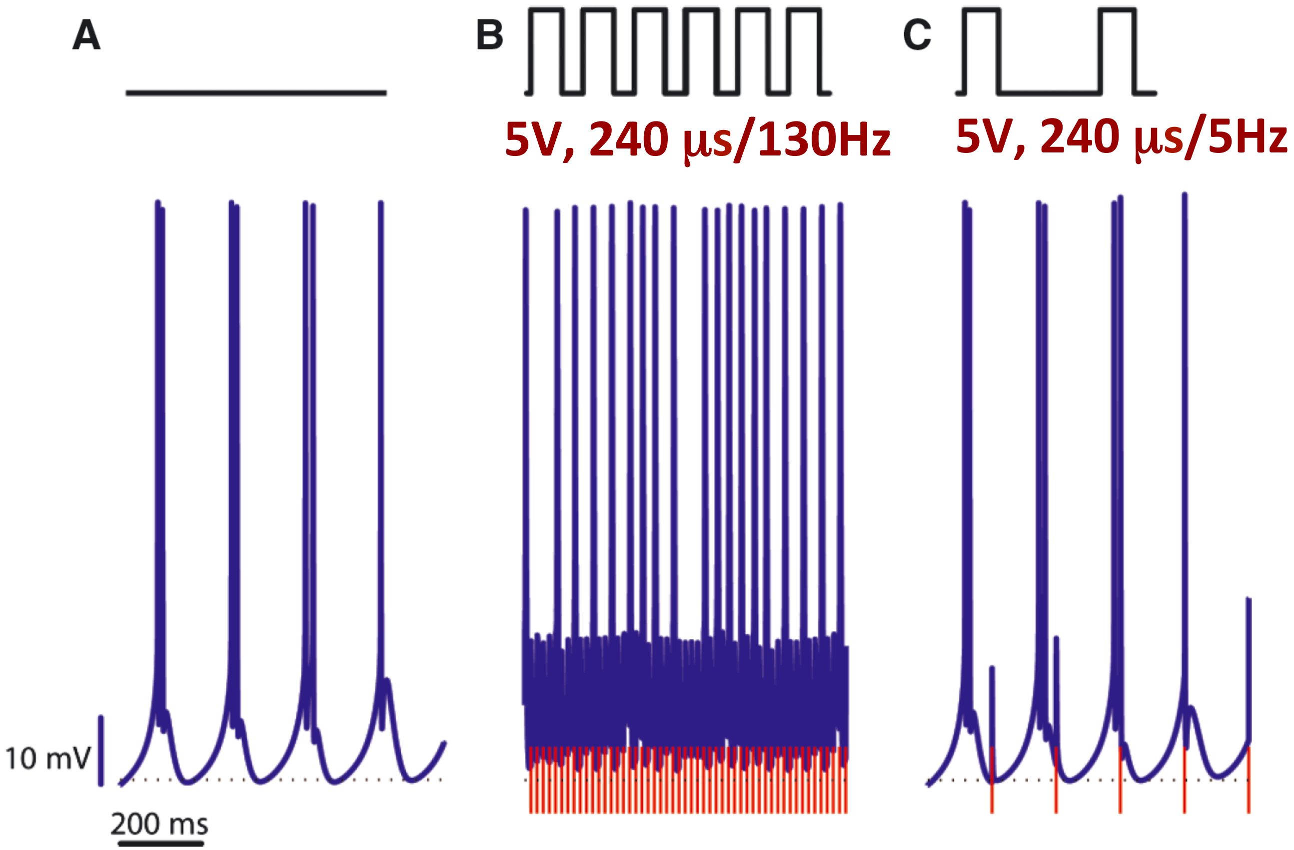
The response of the tonically firing STN cell to DBS pulses

Neuron spontaneously firing at 37 Hz is stimulated by the train of pulses



The response of the bursting STN cell to DBS pulses

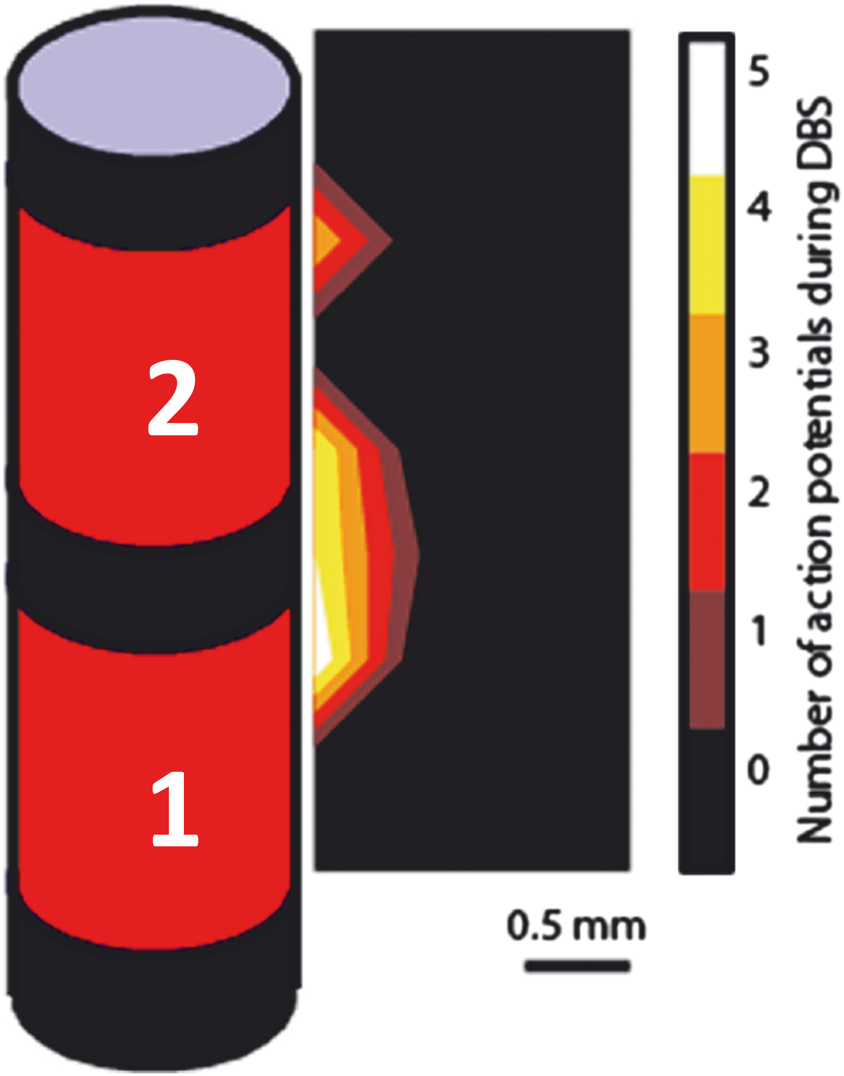
- Burst firing is increased in the Parkinsonian case
- Increase of maximum conductance of T-type calcium channel leads to the bursting activity (2-3 spikes per burst, 4.4 Hz)



Under high-frequency simulation the STN cell fires single spikes with frequency of 53Hz

Low-frequency stimulation does not drastically change the spiking pattern

Spatiotemporal view of DBS stimulation

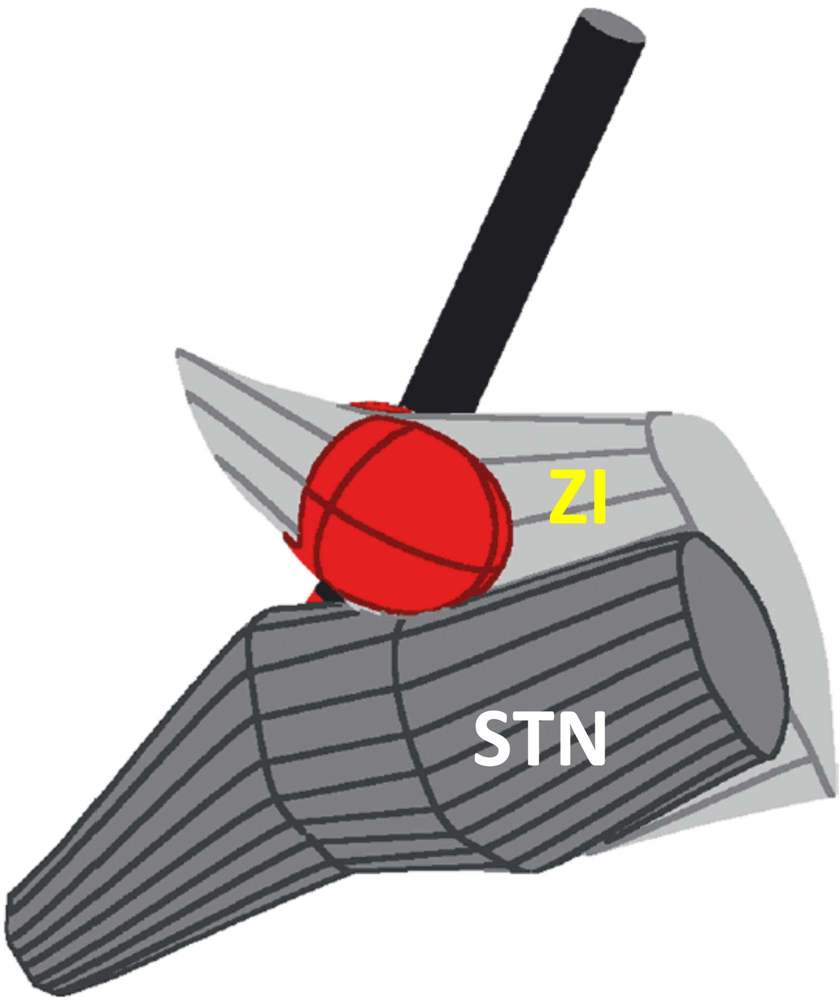


- DBS electric field with a clinical set of parameters (3.8V, 60 μs/ 130Hz, contact 1– negative, contact 2 - positive) is applied on 10x4 array of STN neurons

- The plot shows changes in the number of spikes: the centre of **the main region of firing rate change** corresponds to the upper edge of contact 1 and another region at the edge of contact 2.

Yousif, Borisyuk, et al. (2012) European J Neurosci

Anatomical reconstruction



- Anatomical model (using patient's data) represents STN by dark grey), the Zona Incerta (ZI) by light grey, and DBS electrode by black.
- The main region of firing rate change (according to our array of STN cell modelling) is shown by red.
- This region at the dorsolateral border of the STN and ZI perfectly correlates with a clinically identified optimal region of electrode for treating Parkinsonian symptoms.

Conclusions

- We study dynamics of STN and GP population activity in the BG multichannel model using bifurcation analysis and simulations
- Although, without STN self-excitation a single channel cannot generate oscillations, our results show that the interactive channels with strong enough lateral coupling demonstrate robust oscillations
- It is shown that under Parkinsonian condition the region of oscillations in parameter space is much wider than under healthy conditions
- The DBS electric potential model was combined with the multi-compartmental STN spiking cell model to study the influence of DBS on activity pattern of STN neurons
- Our simulations show that the bursting STN cell exhibits behaviour observed in experimental and clinical studies
- We show that in a patient-specific anatomical model, the region of affected tissue is consistent with clinical observations of the optimal DBS site.

END