Propagation of parkinsonian activity patterns and the effects of deep brain stimulation

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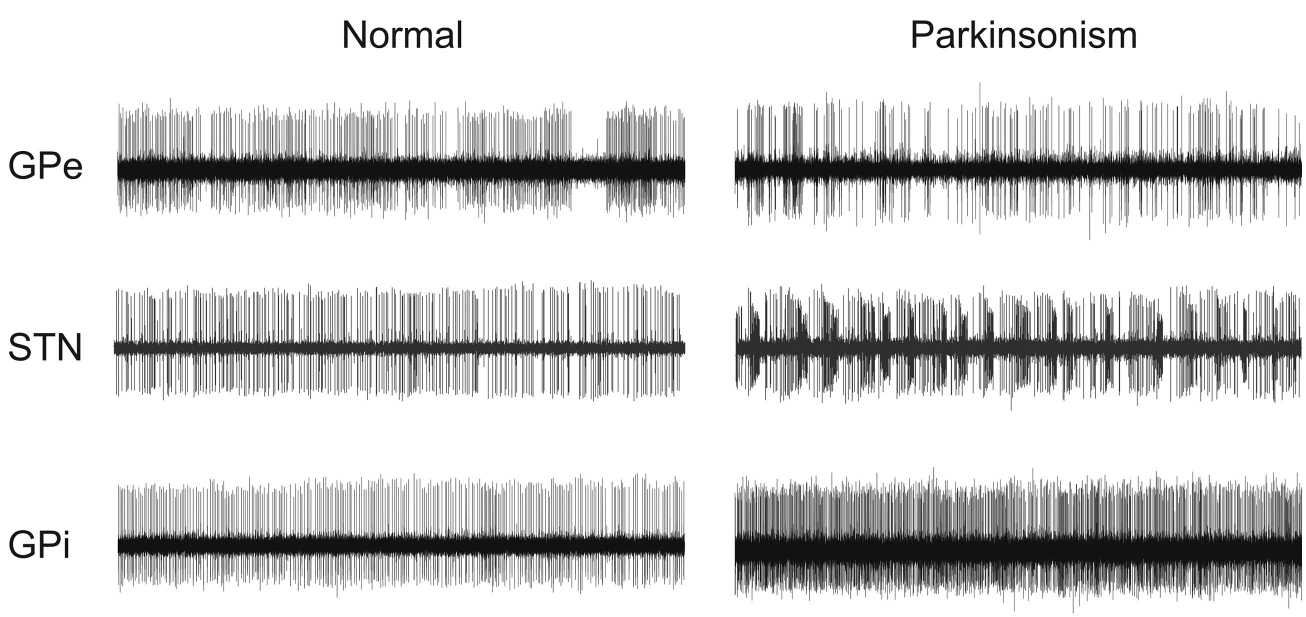
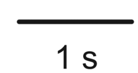
altered basal ganglia activity patterns in parkinsonism

- *changes in firing rates*
- *increased oscillations*
- *increased burstiness*

Magnin et al., *Neuroscience*, 2000

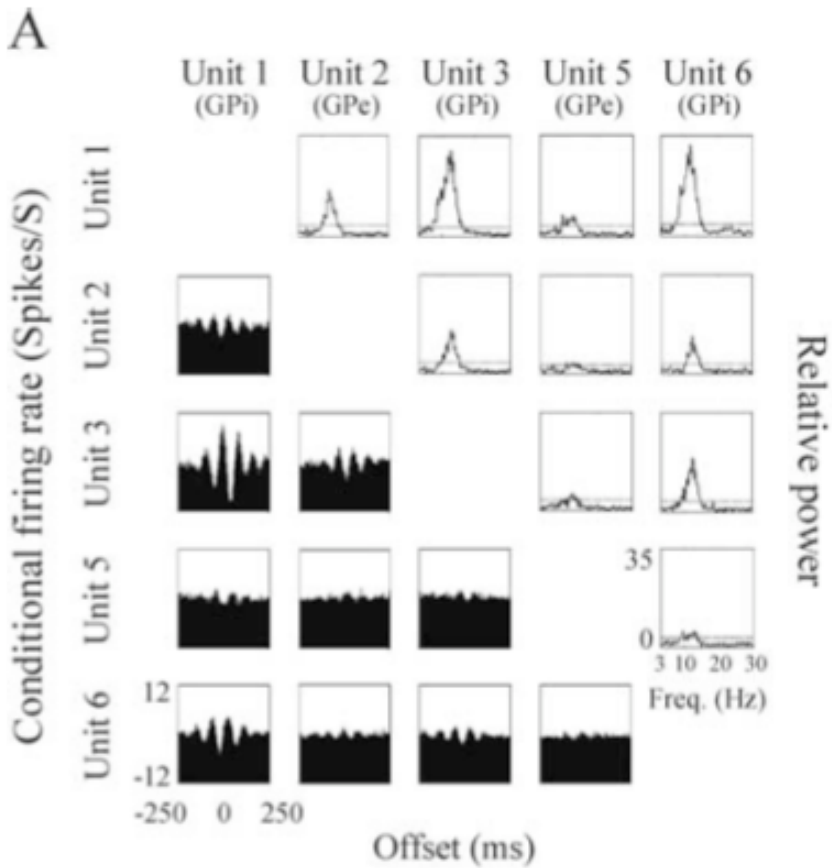




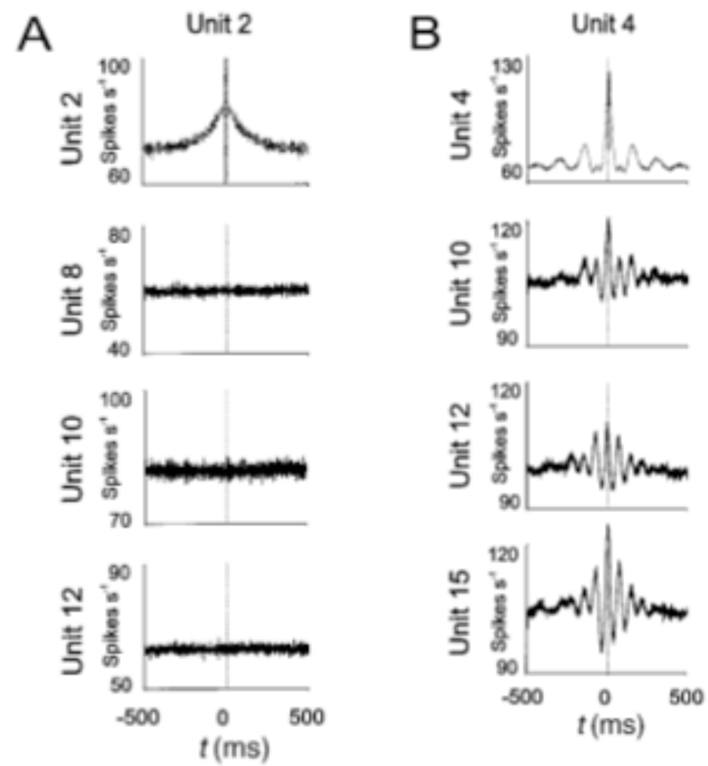
Galvan & Wichmann, *Clin. Neurophysiol.*, 2008

altered basal ganglia activity patterns in parkinsonism

- *loss of specificity/increased correlations*



Heimer et al., *J. Neurosci.*, 2006



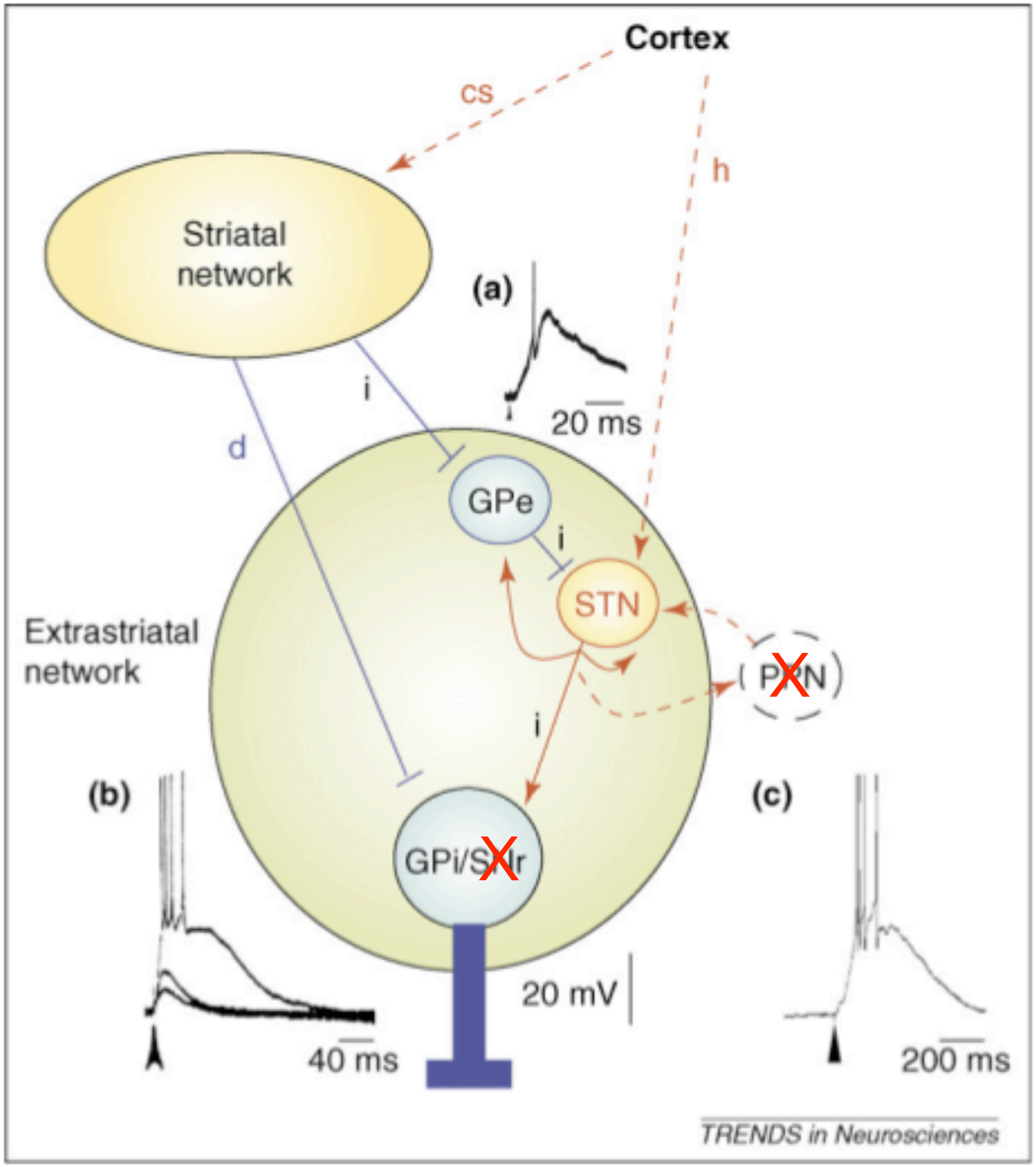
normal MPTP

Bergman et al., *TINS*, 1998; globus pallidus recordings

How do parkinsonian activity patterns lead to parkinsonian motor signs?

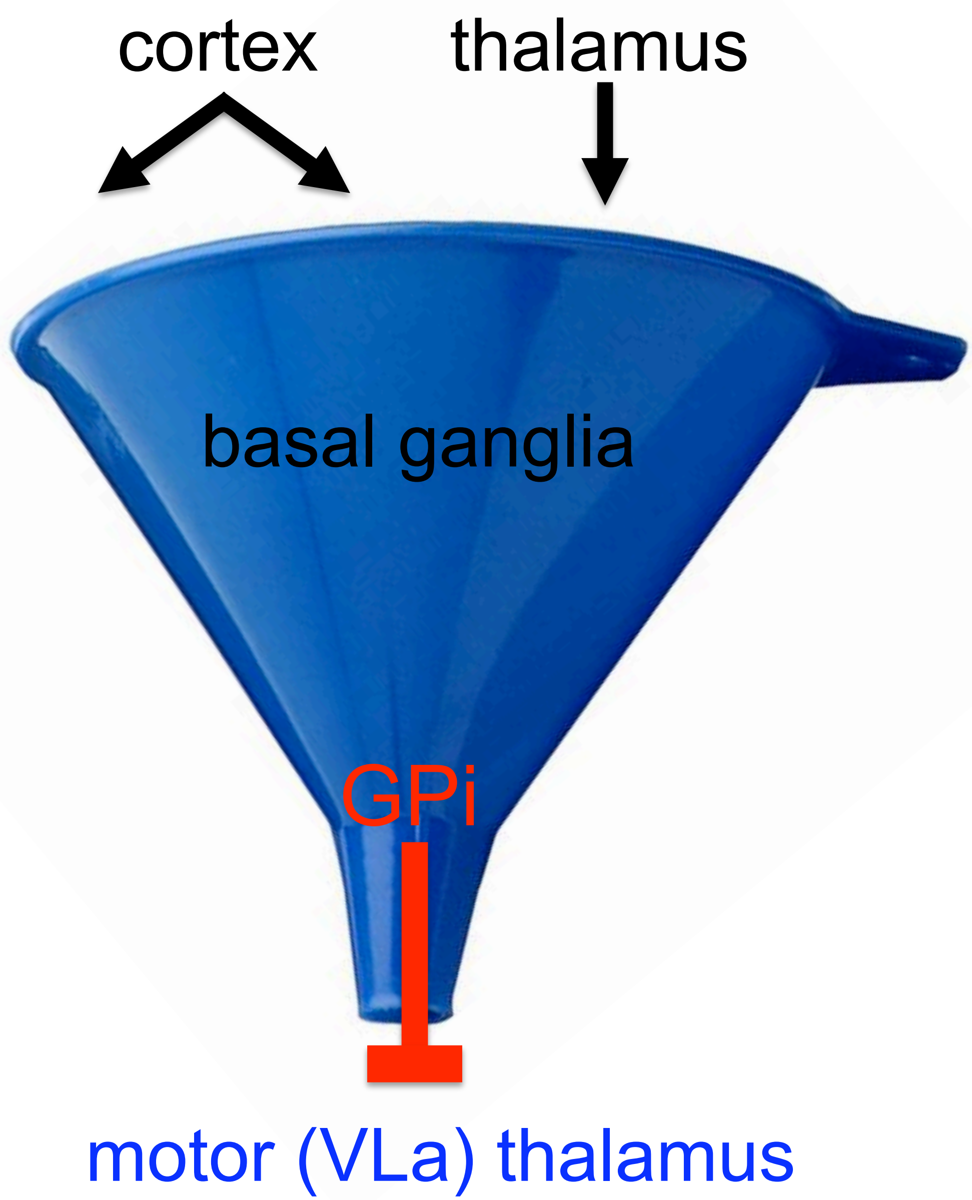
How do effects of deep brain stimulation (DBS) on the former help to improve the latter?

motor pathway wiring diagram



Hammond et al., *TINS.*, 2007

motor pathway wiring diagram



How do parkinsonian activity patterns lead to parkinsonian motor signs?

omission

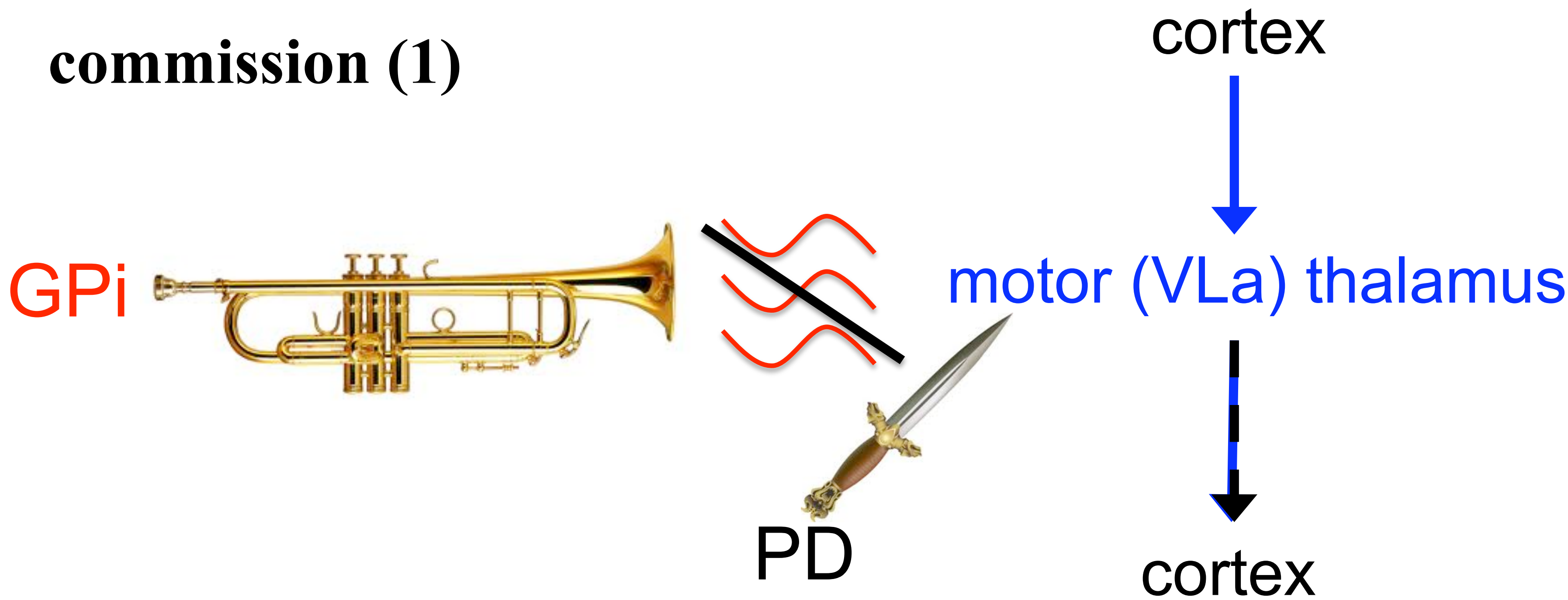
GPi  ~~! ! ! ! !~~ motor (VLa) thalamus

PD

but what is ! ! ! ! ! ?

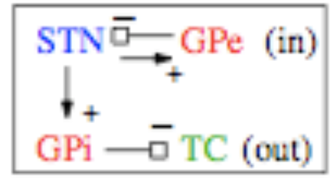
How do parkinsonian activity patterns lead to parkinsonian motor signs?

commission (1)



test using biophysical basal-ganglia-TC network model

Individual TC cell equations:



$$\begin{aligned}
C_m v' &= -I_L - I_{Na} - I_K - I_T - I_{GPi\to TC} - I_{signal} \\
h_T' &= (h_{T\infty}(v) - h_T)/\tau_{h_T}(v) \\
h' &= (h_\infty(v) - h)/\tau_h(v) \\
s' &= \alpha(1-s)exc(t) - \beta s, \quad exc(t) = \Sigma H(t - t_{on})(1 - H(t - t_{off}))
\end{aligned}$$

$$\begin{aligned}
I_L &= g_L(v - v_L) & I_T &= g_T m_{T\infty}^2(v) h_T (v - v_{Ca}) \\
I_{Na} &= g_{Na} m_\infty^3(v) h (v - v_{Na}) & I_{GPi\to TC} &= g_{GPi}(v - v_{inh})\Sigma_j (s_{GPi})_j \\
I_K &= g_K n^4 (v - v_K) & I_{signal} &= g_{signal} s (v - v_{exc})
\end{aligned}$$

$$X_\infty(v) = (1 + \exp(v - \theta_X)/\sigma_X)^{-1}; \quad X \in \{m, h, m_T, h_T\}$$

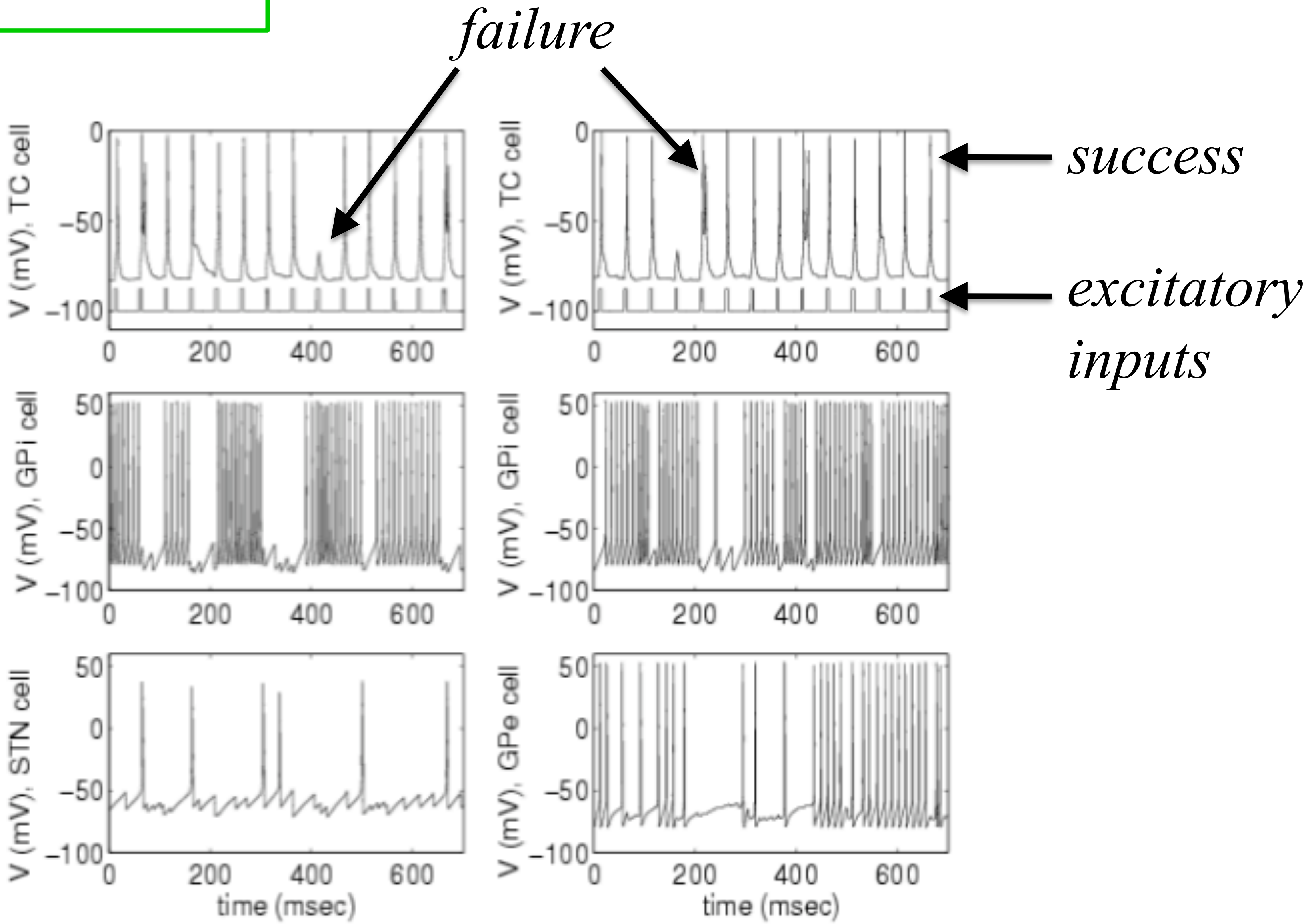
STN voltage equation:

$$C_m v'_{STN} = -I_L - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{GPe\to STN} + DBS$$

GPe voltage and synaptic equations (GPi is similar):

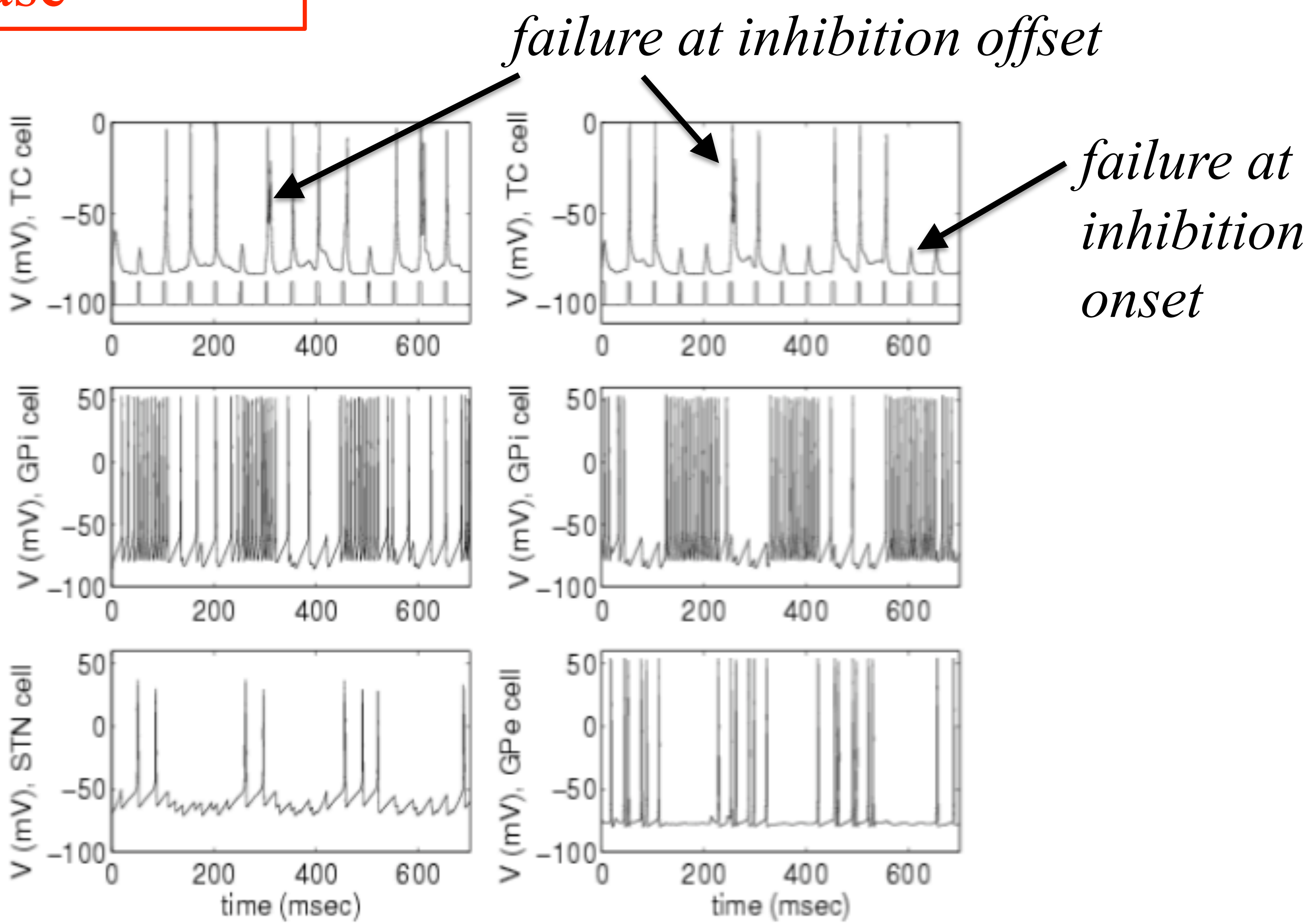
$$\begin{aligned}
C_m v'_{GPe} &= -I_L - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{STN\to GPe} - I_{GPe\to GPe} \\
s'_{GPe} &= \alpha_{GPe}(1 - s_{GPe}) inh(v_{GPe}, t) - \beta_{GPe} s_{GPe}
\end{aligned}$$

Rubin & Terman, *J. Comp. Neurosci.*, 2004 normal case


failure
success
excitatory
inputs
V (mV), TC cell
V (mV), GPi cell
V (mV), STN cell
V (mV), GPe cell
time (msec)
0
−50
−100
50
200
400
600

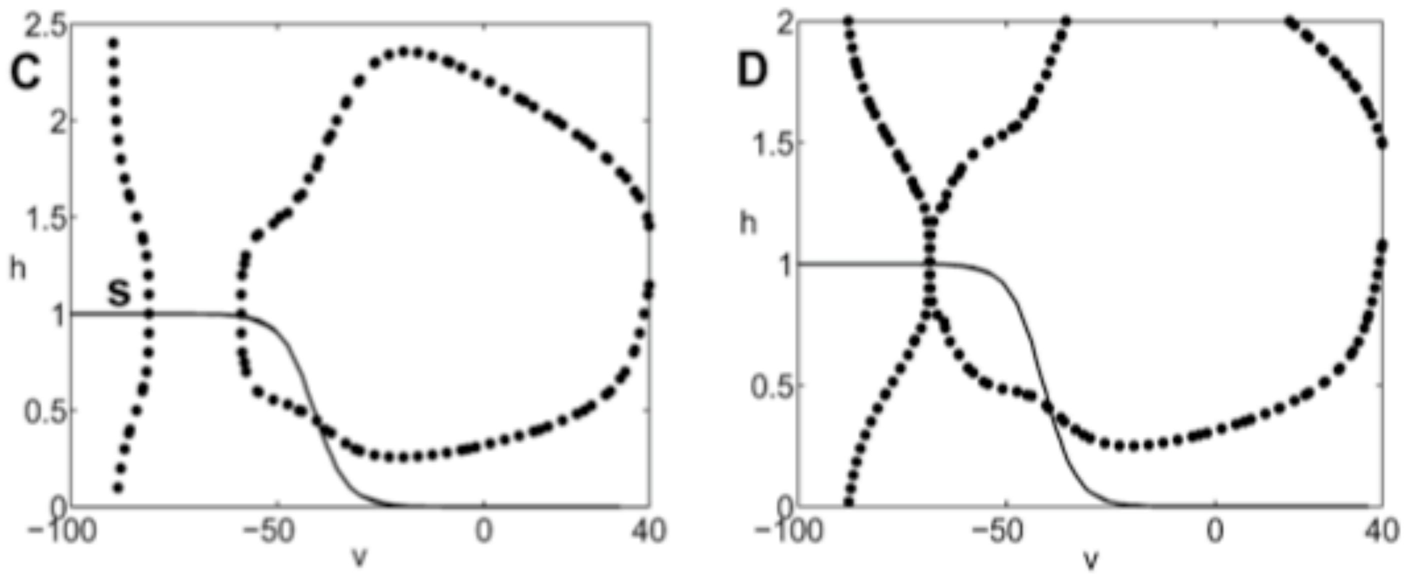
parkinsonian case

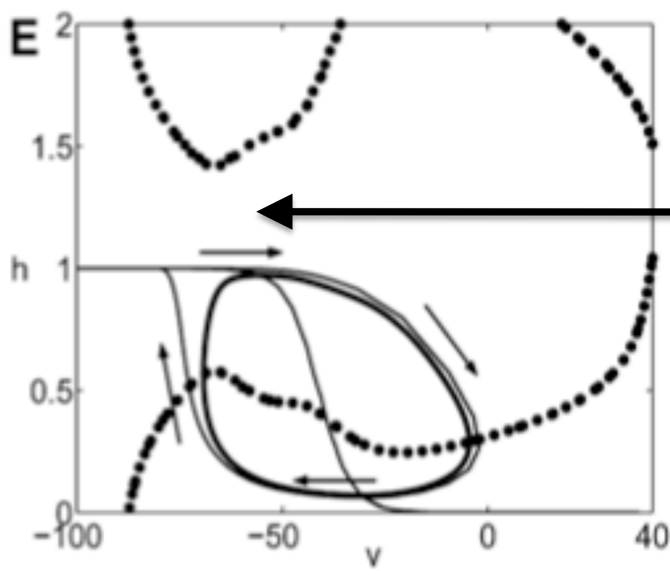
GPi bursts → thalamic relay failure



normal case

thalamic model phase plane

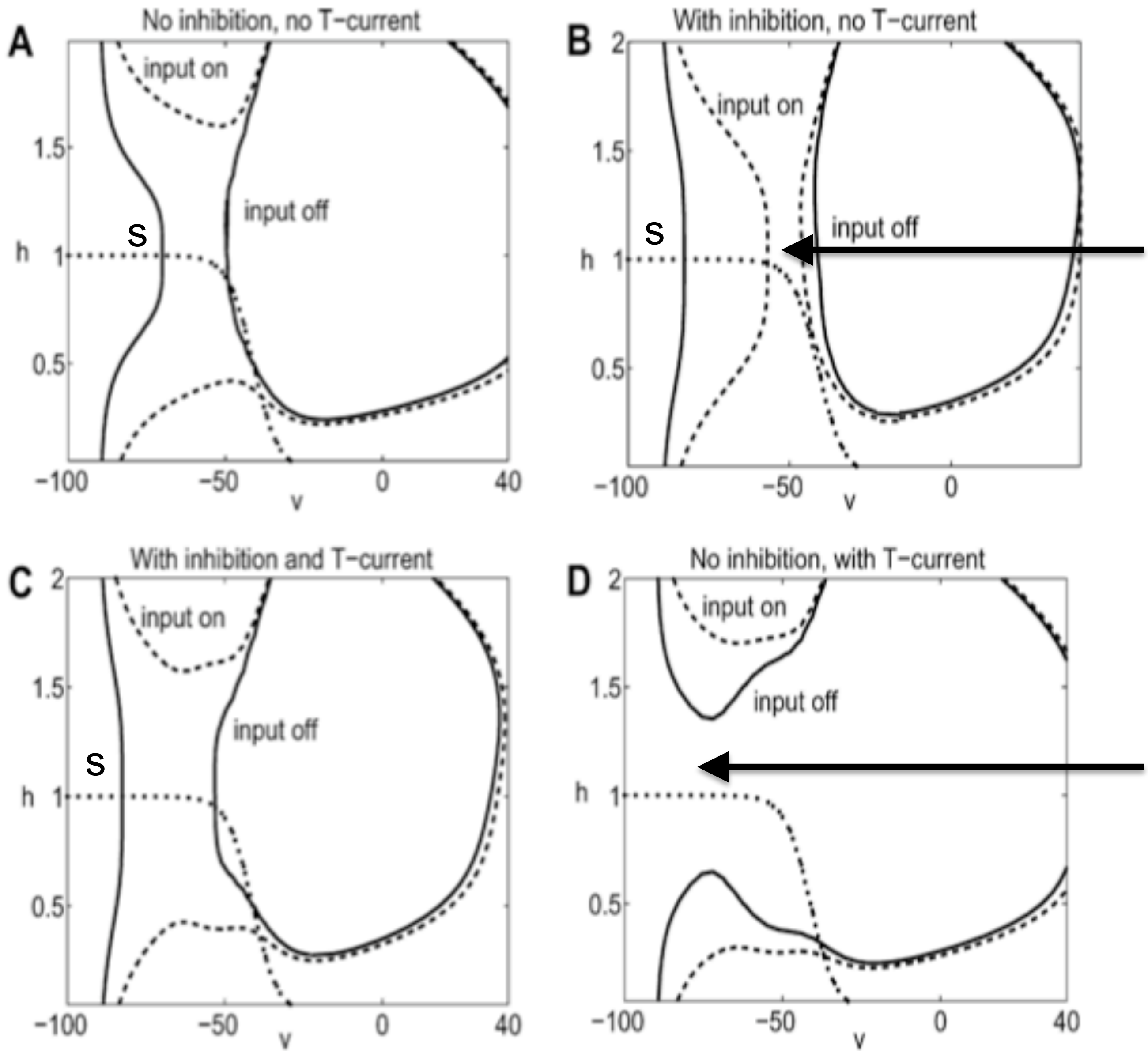




C to D to E: increase synaptic excitation

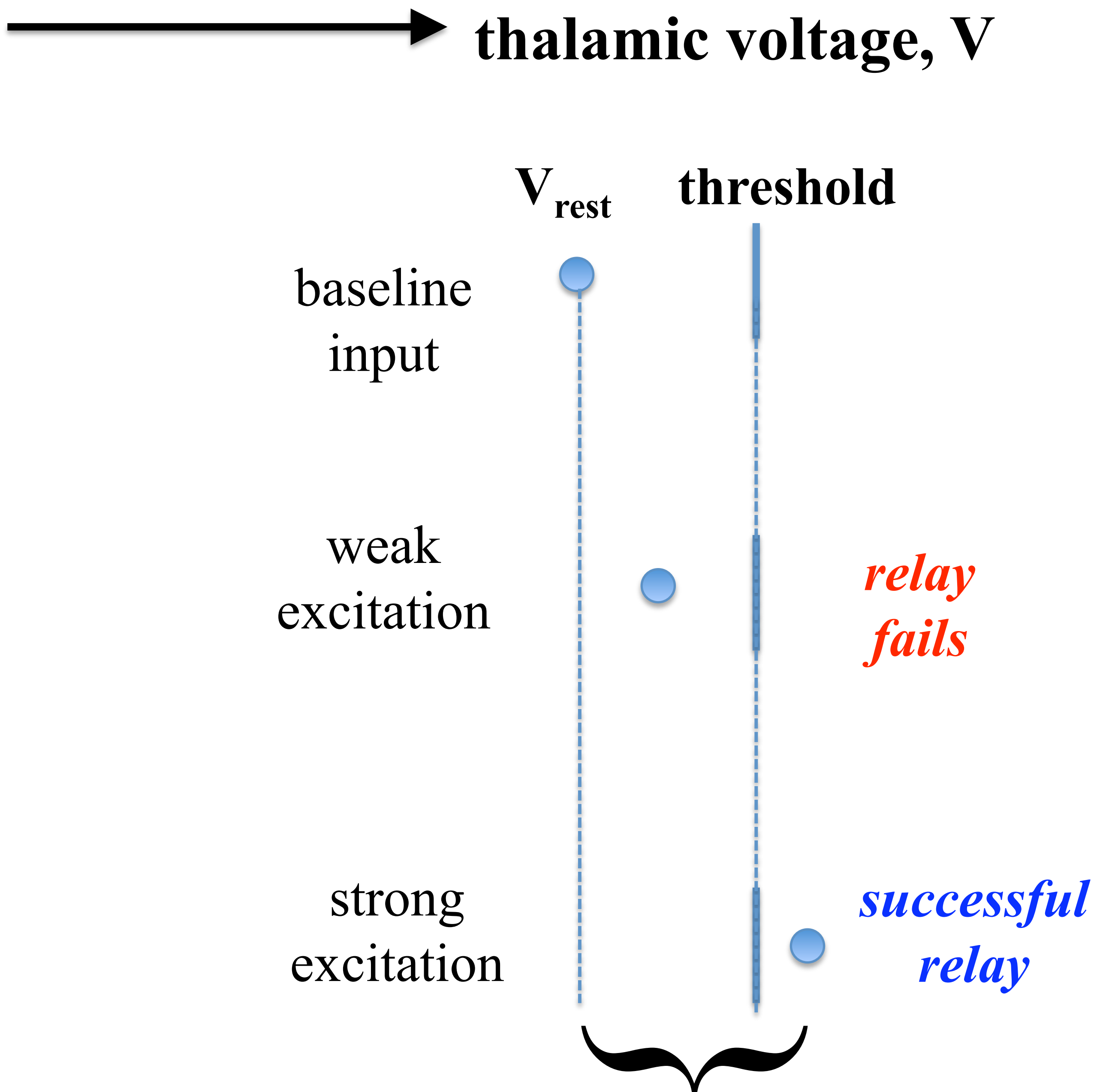
with low inhibition, suff. strong excitation opens a channel parkinsonian case

thalamic model phase plane

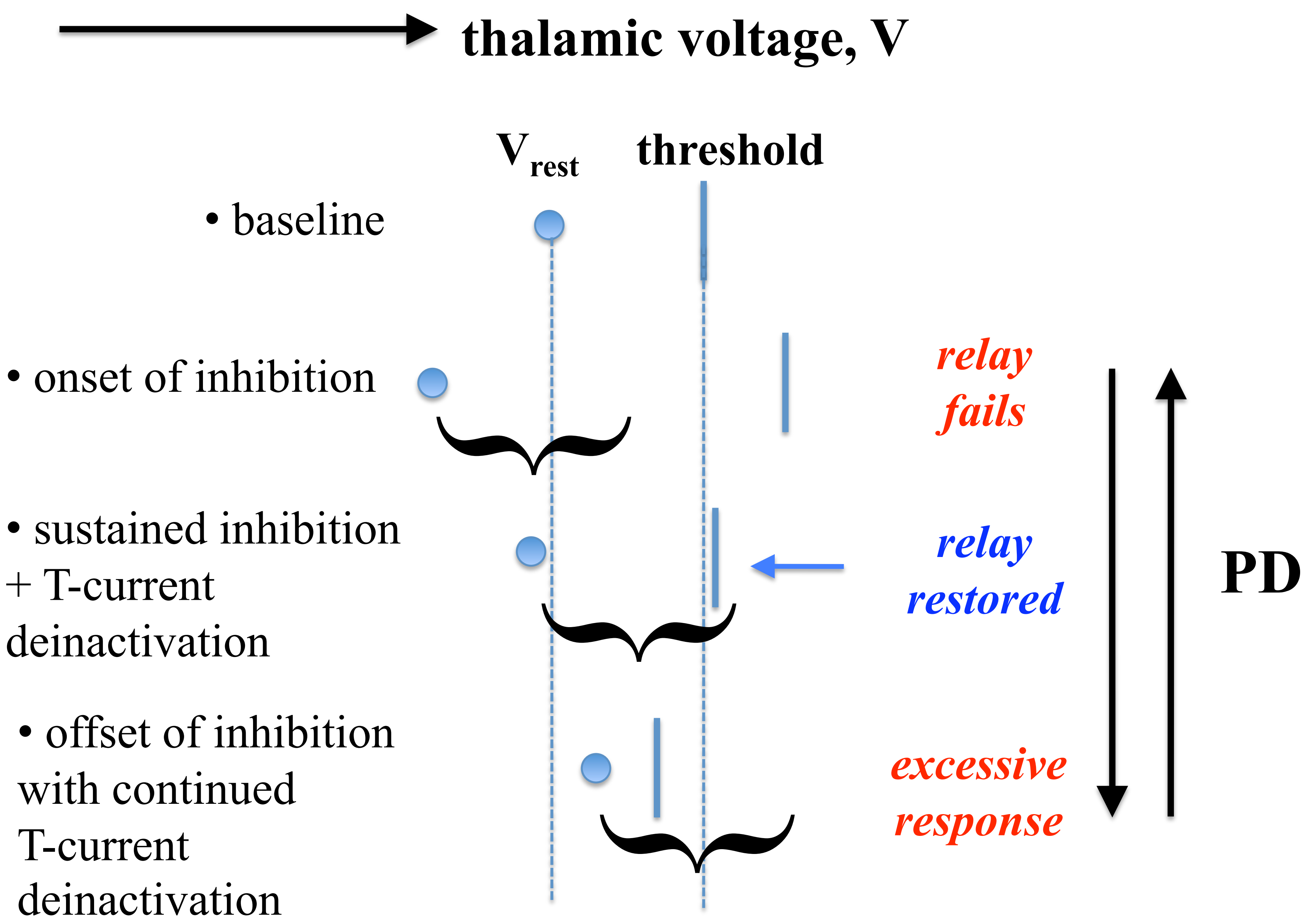


no channel, even w/ input on

no fixed point, even w/ input off



Rubin et al., *EJN*, 2012



Rubin et al., *EJN*, 2012

How do parkinsonian activity patterns lead to parkinsonian motor signs?

commission (2)

cortex

GPi

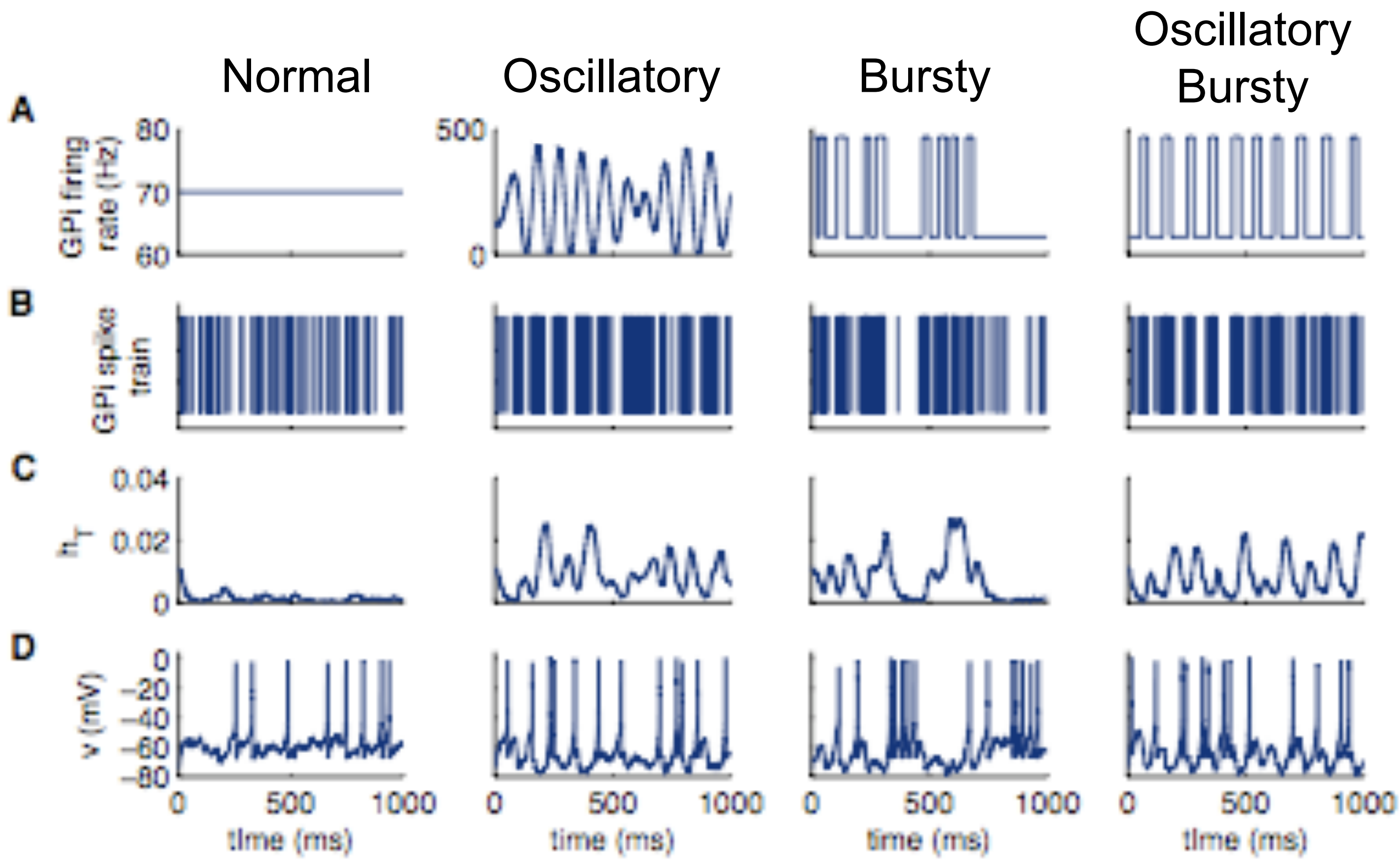
motor (VLa) thalamus

PD

cortex

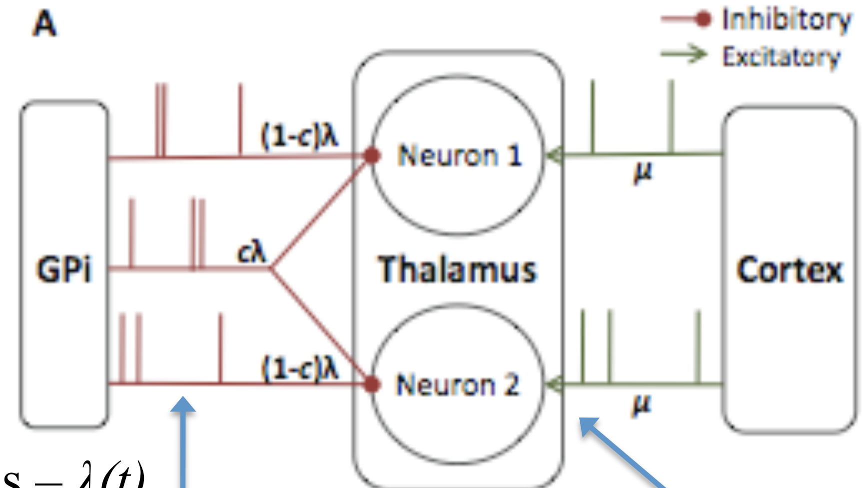
pallido-thalamic correlation transfer: preliminary computational study

simulated GPi outputs

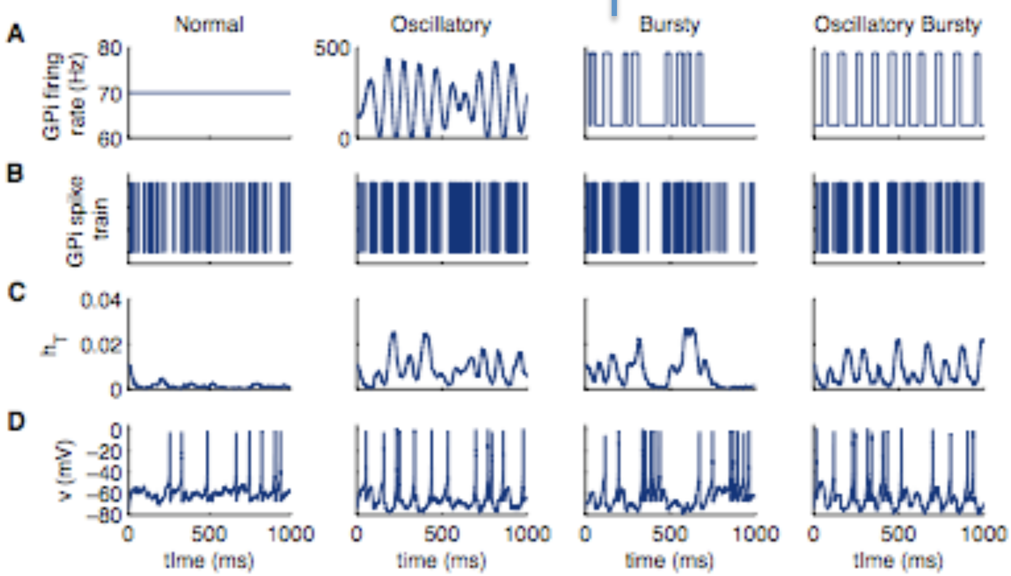


Reitsma, Doiron & Rubin, *Frontiers Comp. Neurosci.,* 2011

pallido-thalamic correlation transfer: preliminary computational study



GPi patterns – *λ(t)*
inhomogeneous



conductance-based,
integrate-and-fire-or-burst,
or point process models

correlation measures

spike count correlation:

$$\rho(T) := \frac{\mathrm{cov}(n_1(T), n_2(T))}{\sqrt{\mathrm{var}(n_1(T))\mathrm{var}(n_2(T))}},$$

correlation susceptibility:

$$\rho_{\mathrm{out}}(T) = S(T)\rho_{\mathrm{in}}(T) - k.$$

notes:

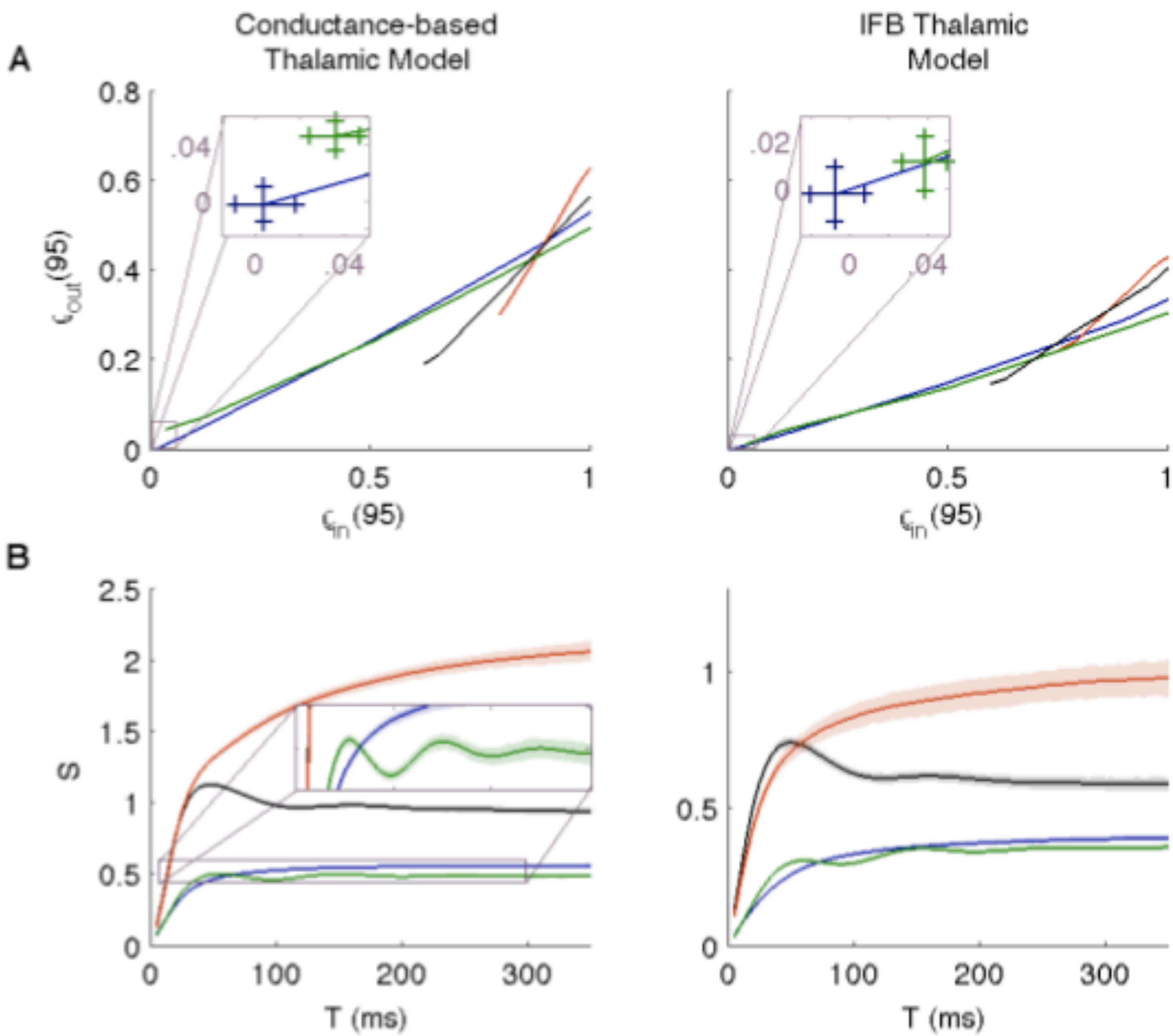
1) T is window size

2) $\rho_{\mathrm{in}}(T)$ depends on GPi spike correlation, c, as well as modulation of GPi rate, $\lambda(t)$

cf. de la Rocha*, Doiron* et al., *Nature,* 2007

result: input-output correlation & correlation susceptibility

$$(\rho_{\text{out}}(T) = S(T)\rho_{\text{in}}(T) - k)$$



blue: normal GPi

green: oscillatory GPi

red: bursty GPi

black: oscillatory bursty GPi

A. bursty cases give steeper curves – higher susceptibility!

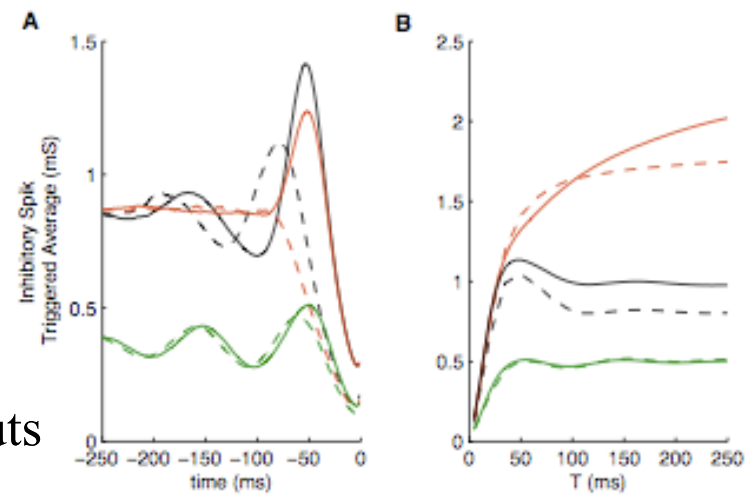
B. oscillatory cases give oscillatory T-dependence of susceptibility

some details…

with T-current (solid) vs. without (dashed)

(A) bursty case:

susceptibility results do not depend on T-current

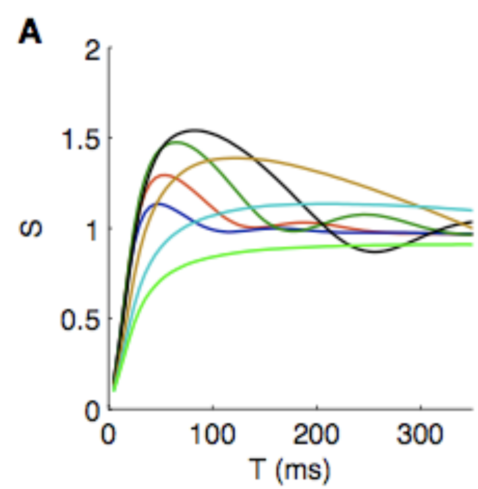


spike-triggered average inputs

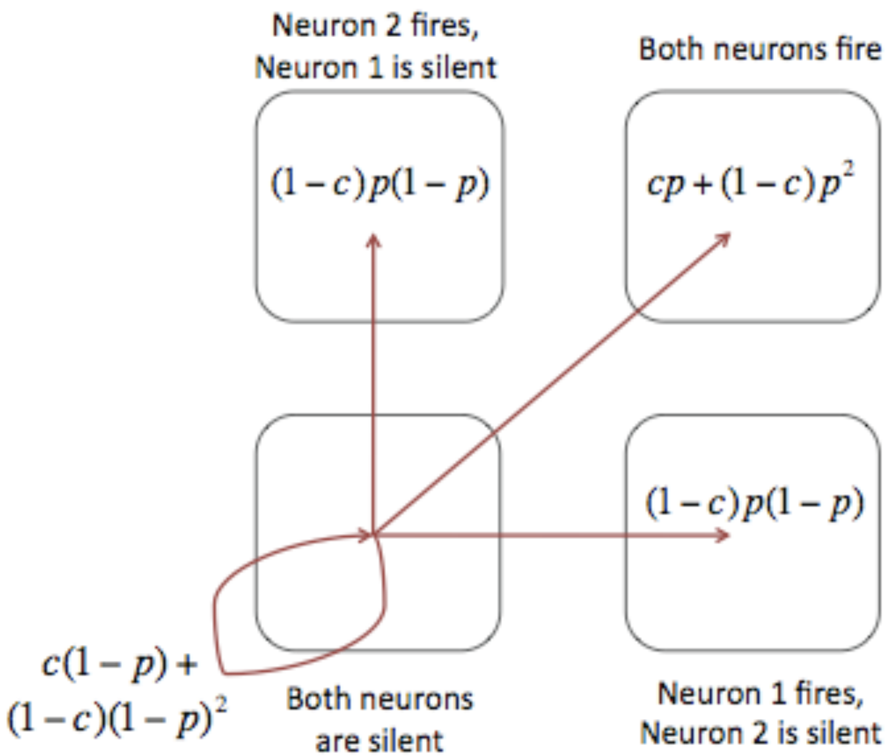
susceptibility

(B) oscillatory case: frequency from GPi, amplitude non-monotonic

ex/ conductance-based model



oscillation effects captured by point-process model



- firing probability in interval (t,t+dt):

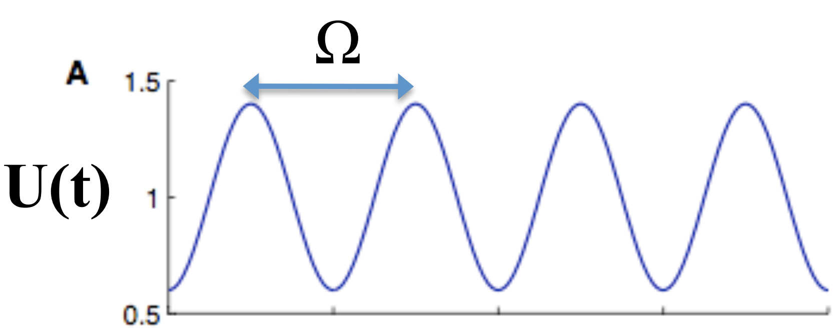
$$p(t) = \alpha(t)dt.$$

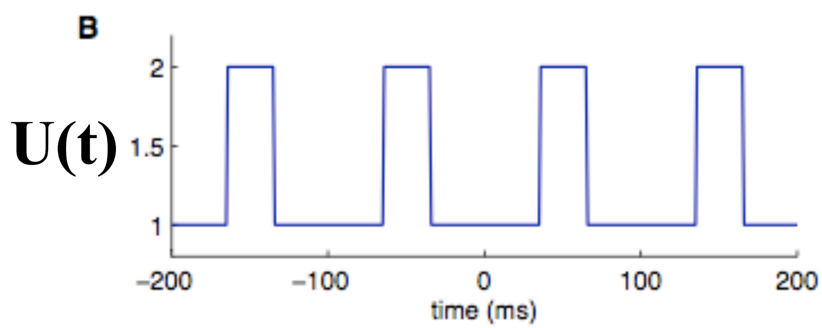
- assume Arrhenius escape rate:

$$\alpha(t) = \beta \exp\left[-\frac{U(t)}{D}\right]$$

$$= \alpha_0 + \sum_{n=1}^{\infty} \alpha_n \cos(2\pi n \Omega t)$$

- rhythmically modulate barrier height *U(t):*



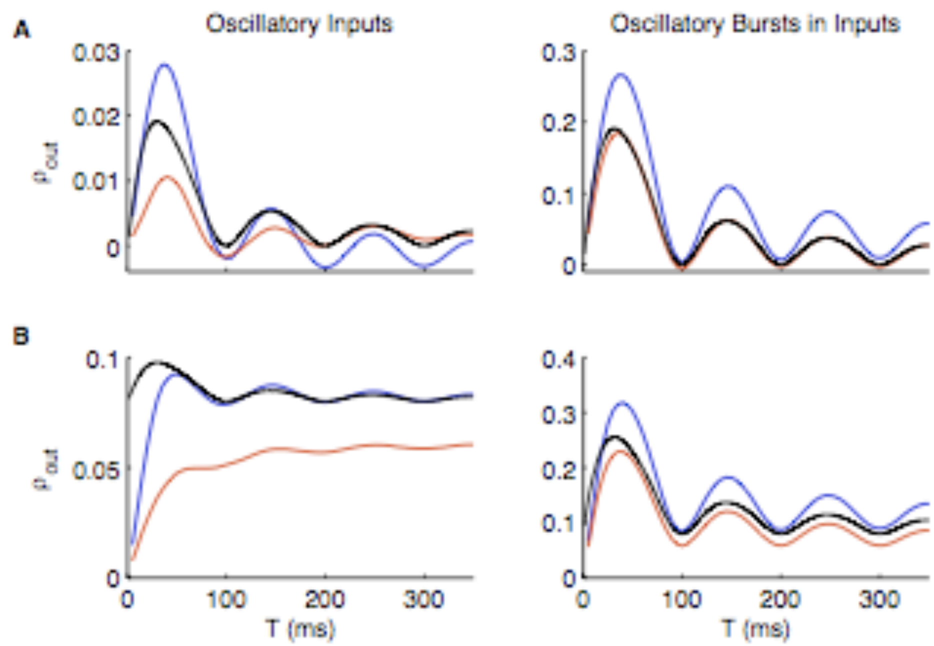


cf. Wiesenfeld et al., *PRL,* 1994

***result**: to leading order in dt,*

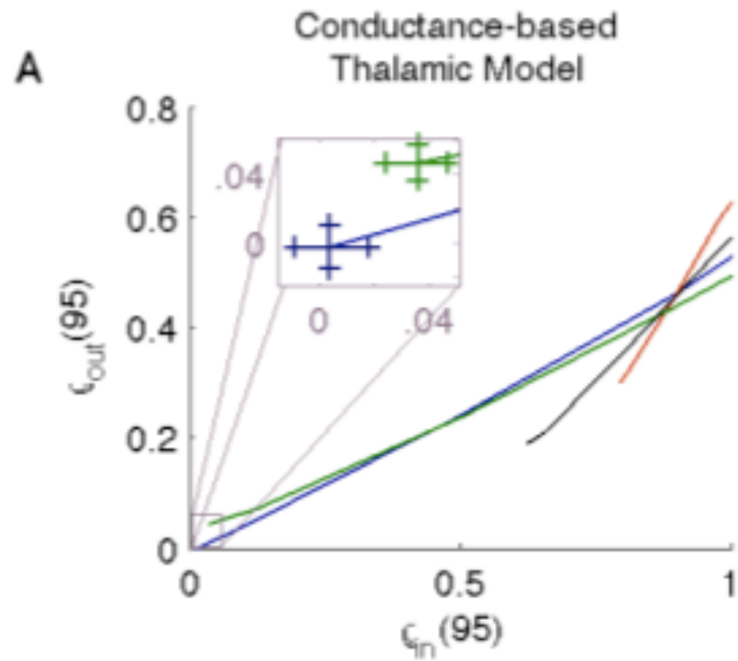
$$\rho(T) = \frac{c\alpha_0 T + \sum_{n=1}^{\infty} \left(\frac{\alpha_n}{2\pi n\Omega}\right)^2 [1 - \cos(2\pi n\Omega T)]}{\alpha_0 T + \sum_{n=1}^{\infty} \left(\frac{\alpha_n}{2\pi n\Omega}\right)^2 [1 - \cos(2\pi n\Omega T)]}$$

- *frequency of oscillations inherited from well modulation, U(t)*
- *oscillations damp out as T goes to infinity*
- *oscillations robust to changes in input rates*



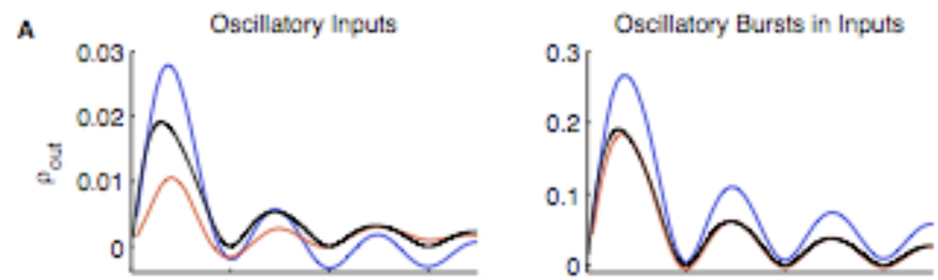
black: point process; blue: conductance-based; red: IFB

commission (2) – summary



GPi loss of functional segregation/ increased correlation + enhanced oscillations/burstiness yield increased thalamic:

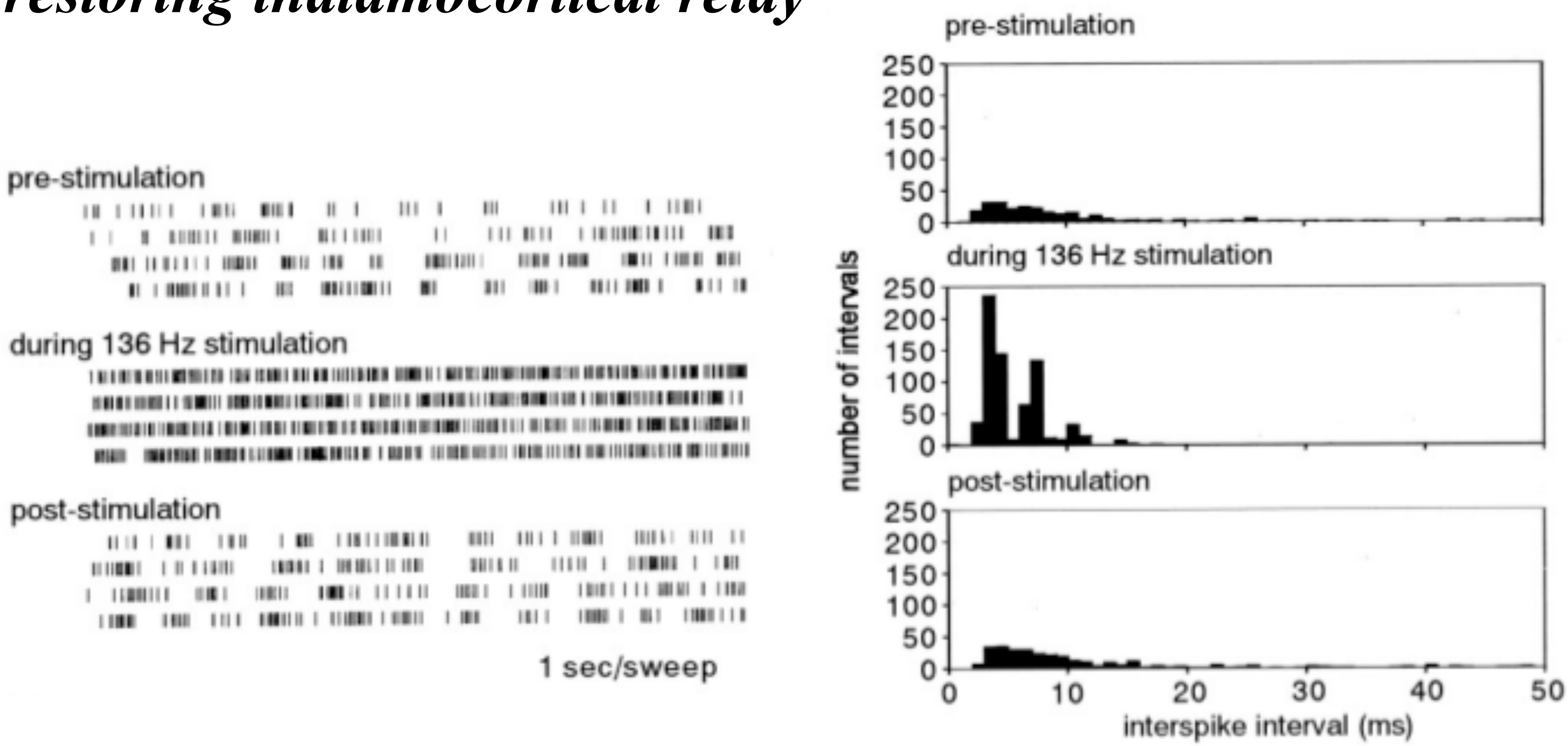
- *correlation*
- *sensitivity to changes in correlation*
- *correlation and sensitivity to correlation on certain timescales (set by frequency of GPi output oscillations)*



pathological implications? *future work…*

How do effects of DBS on parkinsonian activity patterns help to improve parkinsonian motor signs?

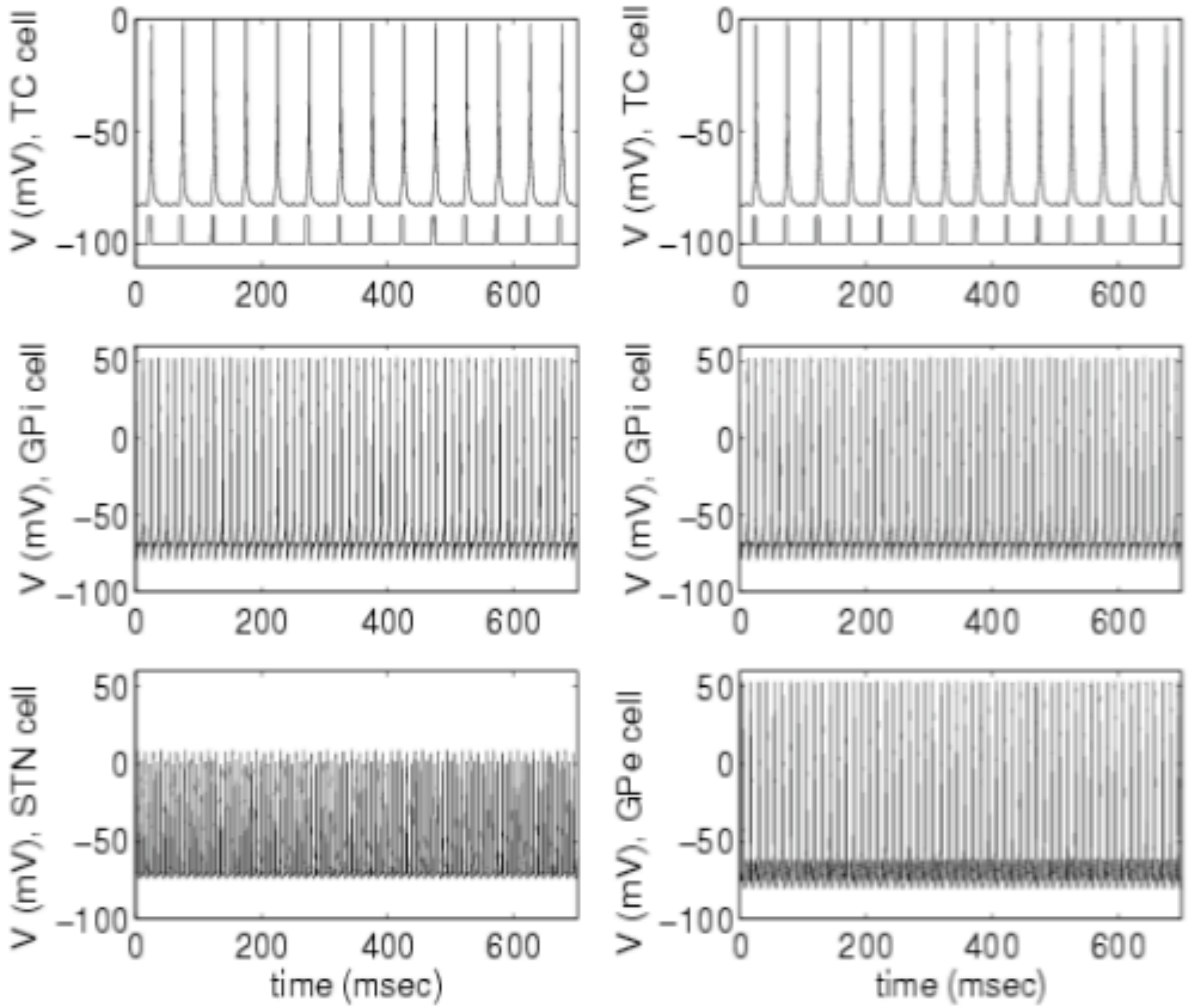
STN-DBS may work by regularizing GPi firing and restoring thalamocortical relay



Hashimoto et al., 2003; Hahn et al., 2008: MPTP primate GPi data:

GPi firing rates go up with STN-DBS but bursting is suppressed

DBS simulation (extreme example)



Rubin & Terman, *J. Comp. Neurosci.*, 2004

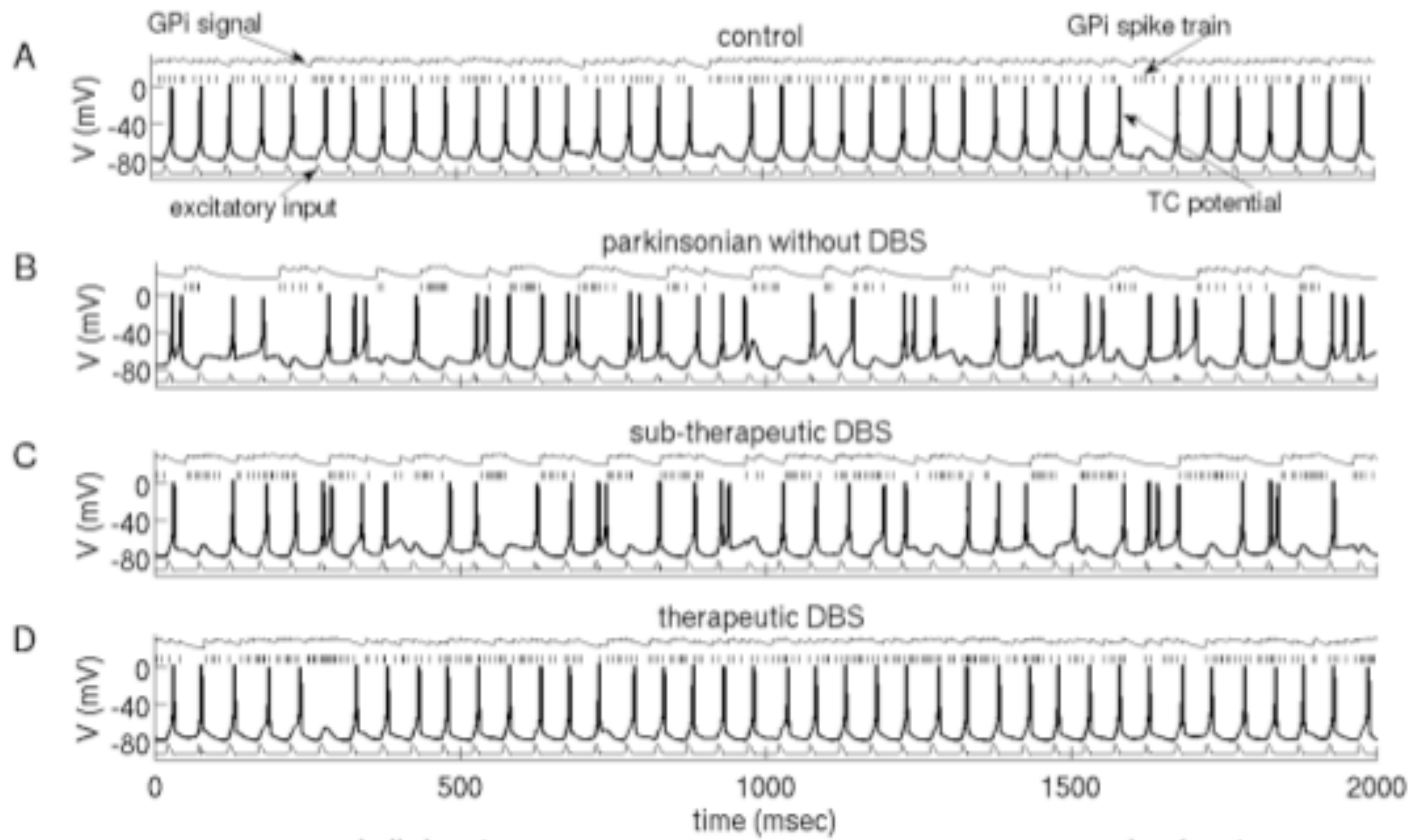
switch to data-driven computational model

- use GPi spike trains recorded from normal/parkinsonian/ sub-therapeutic DBS/therapeutic DBS primates (Hashimoto et al.) to generate inhibitory inputs
- use elevated spike time (EST) as measure of input structure (*irregular* < *bursty* < *tonic*)
- feed inhibitory inputs to conductance-based TC cell model
- consider TC cell relay of simulated excitatory inputs (periodic or Poisson)
- quantify relay performance with

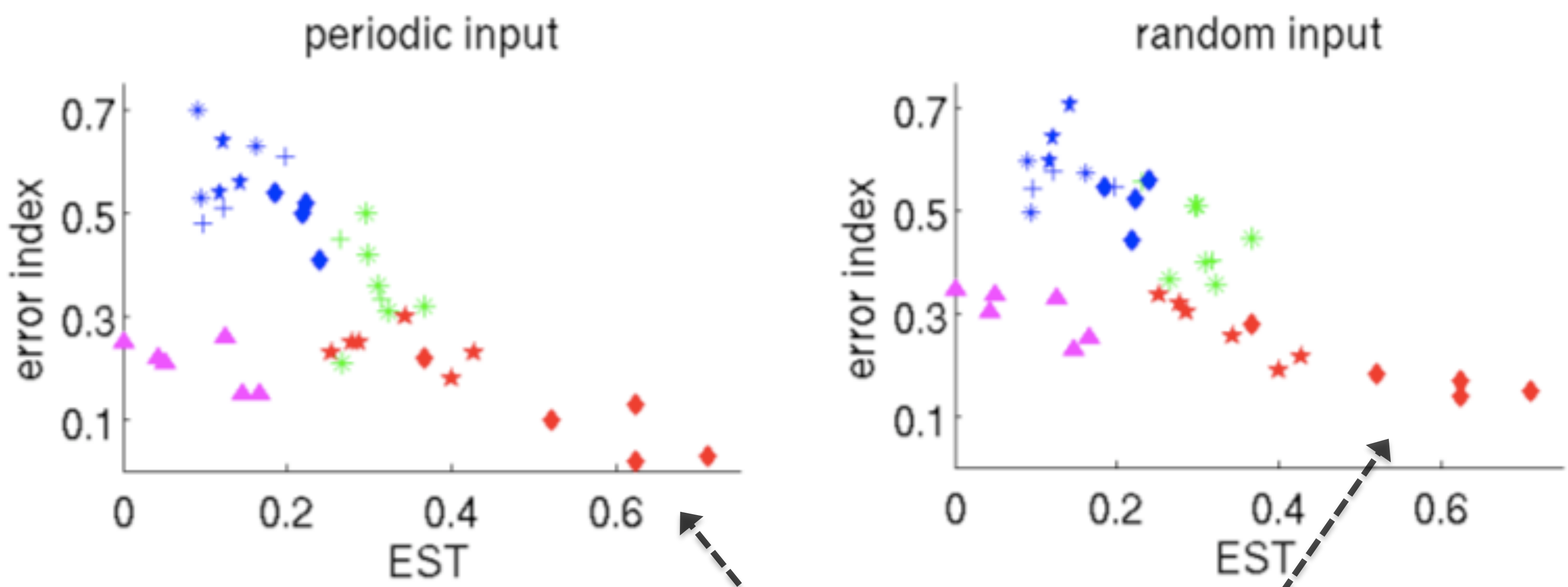
error index = (misses+bursts)/(excitatory inputs)

Guo*, Rubin* et al., *J. Neurophysiol.*, 2008

simulations driven by Hashimoto MPTP primate GPi data: *example*



Guo*, Rubin* et al., 2008: simulations driven by Hashimoto MPTP primate GPi data: *summary*

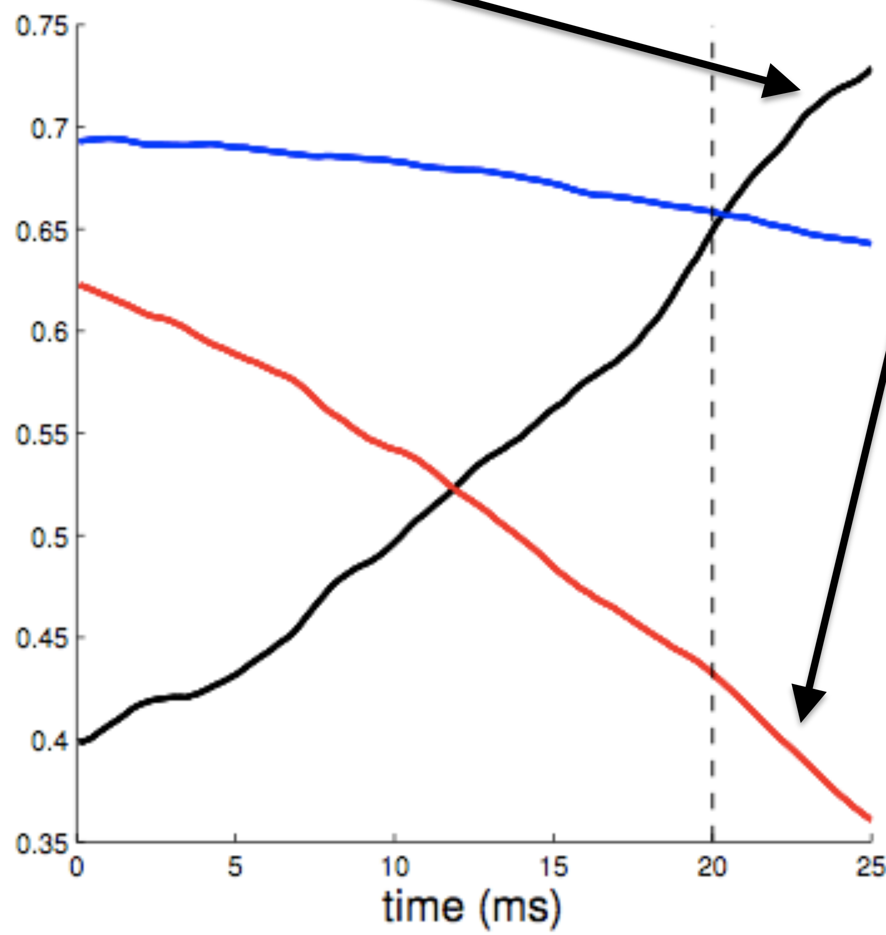


key point: therapeutic DBS (not sub-therapeutic!) restores TC relay!

TC-response-triggered averages (all cases): consistent with misses = inhibition onsets, bad (bursts) = inhibition offsets

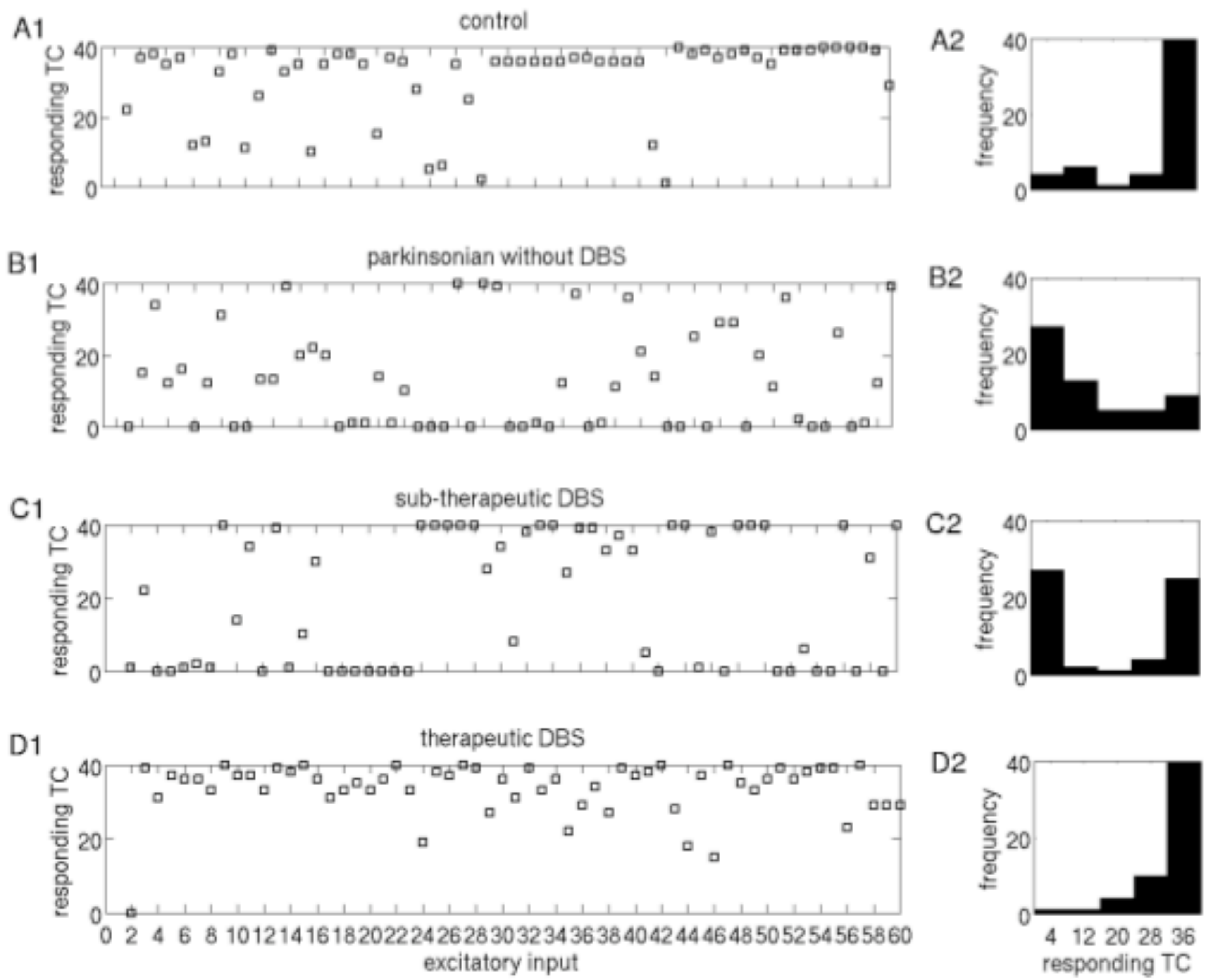
- average over 25 msec of GPi activity:
  - 20 msec preceding each TC response,
  - 5 msec following each response

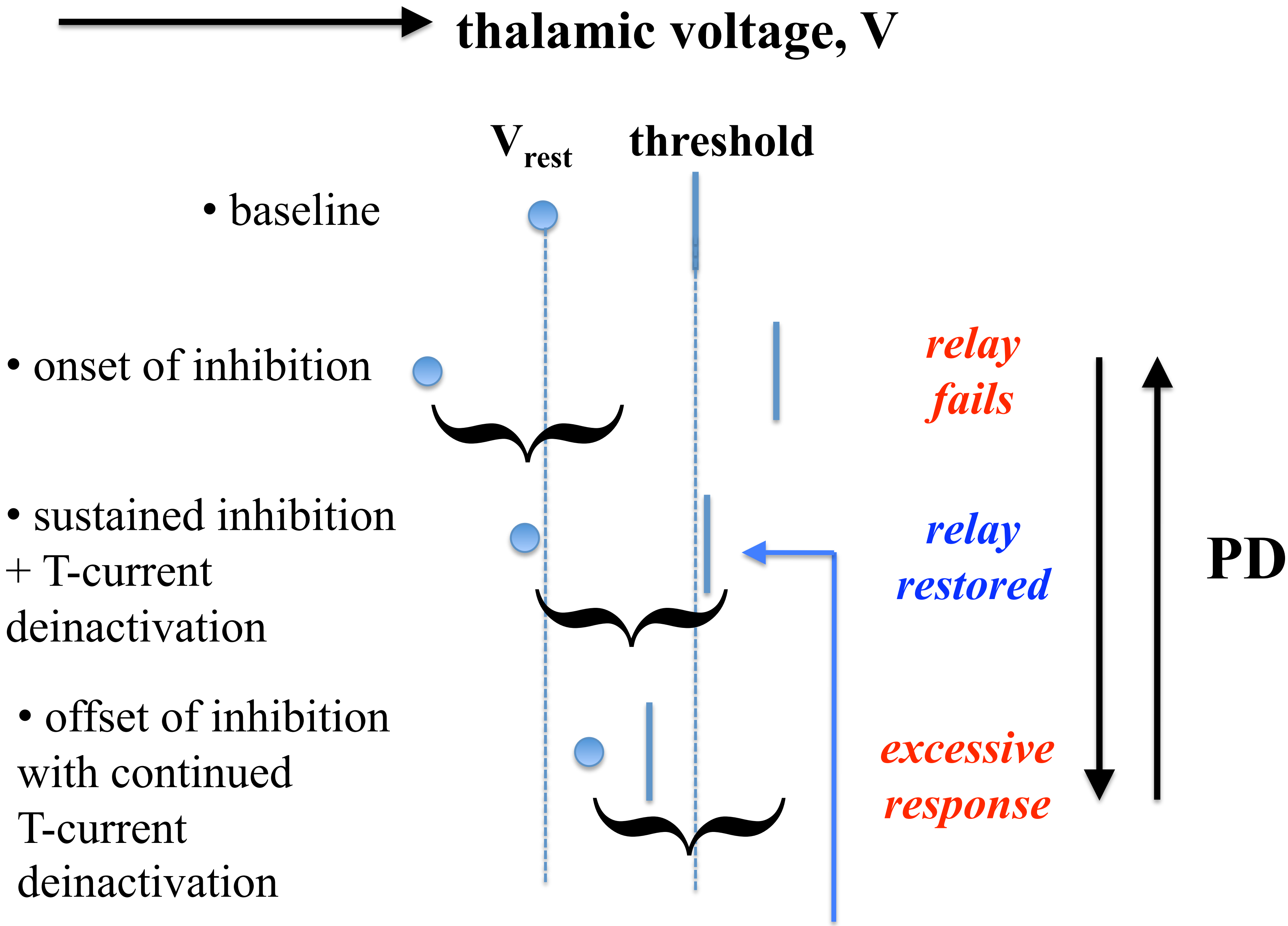
- cluster by 3 TC response types:
  - miss
  - bad
  - successful



Apply GPi data to heterogeneous TC population:

TC miss at the same time in PD/subDBS, not in tDBS!



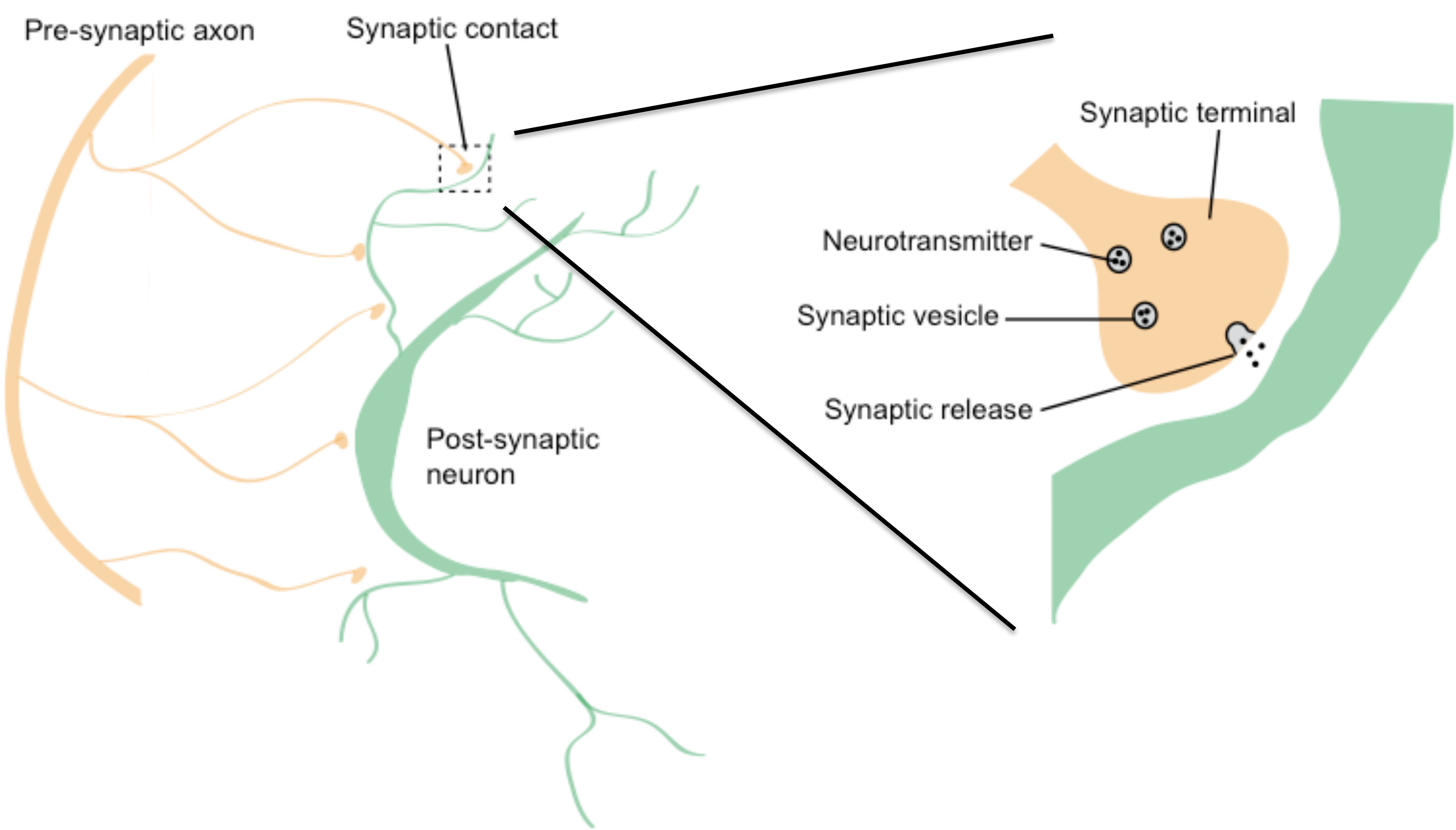


idea: *DBS pins thalamic cells here!*

How do effects of DBS on parkinsonian activity patterns help to improve parkinsonian motor signs?

STN-DBS may work by decoupling STN and GPi firing

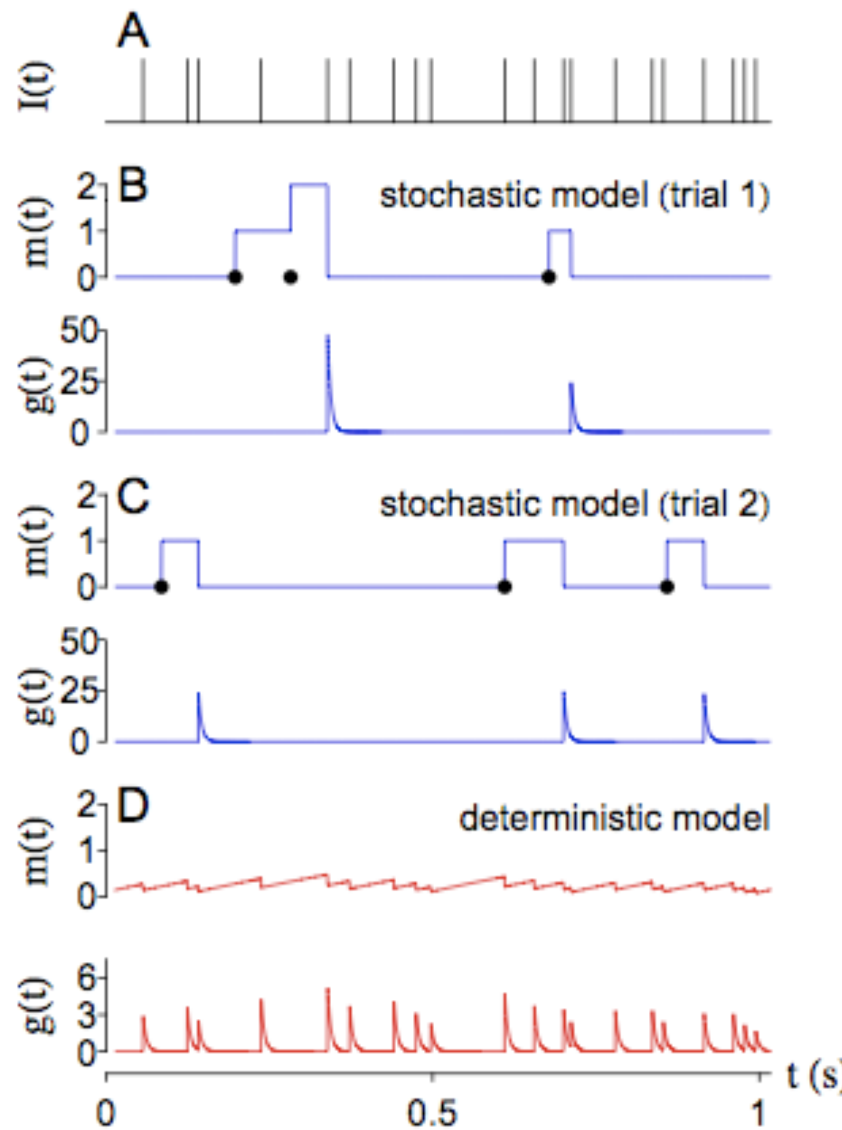
aside: synaptic dynamics



stochastic vesicle dynamics

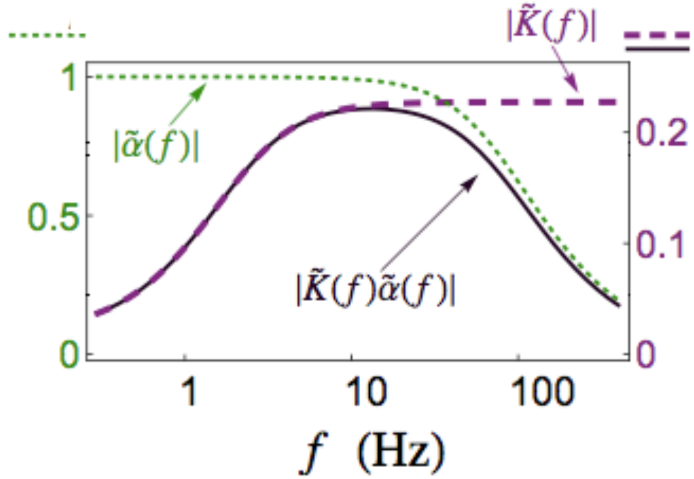
- let U = probability of vesicle release, given an input spike and available vesicle
- assume vesicle recovery is Poisson with rate $1/\tau_u$
- let m(t) = number of available vesicles
- let g(t) = synaptic conductance

Rosenbaum et al., *PLoS Comp. Biol.*, 2012



implications – (1) deterministic & stochastic

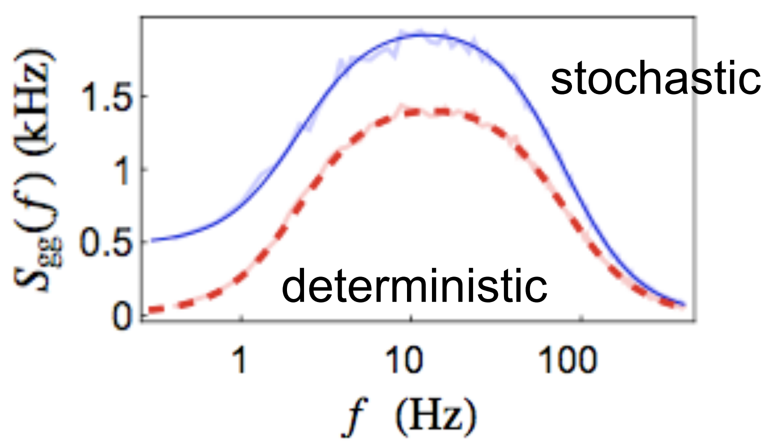
(a) band-pass synaptic filter yields peaked cross-spectrum of input/conductance



$$R_{Ig}(\tau) = \mathrm{cov}(I(t), g(t+\tau))$$

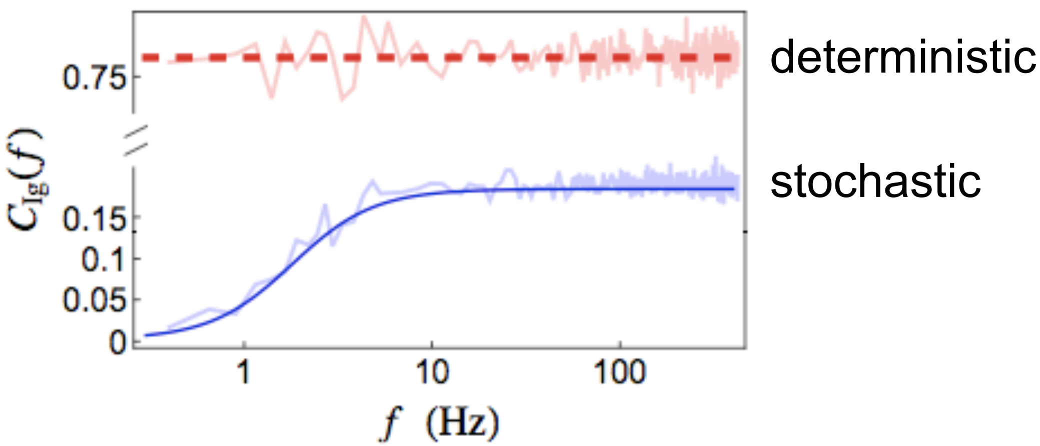
$$\begin{aligned} S_{Ig}(f) &= \int_{-\infty}^{\infty} R_{Ig}(\tau) e^{-2\pi I f \tau} d\tau \\ &= \widetilde{\alpha}(f)\widetilde{K}(f)\nu \end{aligned}$$

(b) at population level, power spectrum of total conductance is peaked



implications – (2) stochastic

for high rate inputs, uptake contributes relatively more to transmission ➞ decorrelate inputs and outputs, lower coherence



link back to STN-DBS*

***R. Rosenbaum poster, this workshop**

SUMMARY

- commission 1: low frequency rhythms in GPi can compromise TC relay (cf. sleep spindles)
- STN-DBS that entrains GPi can restore TC relay

- commission 2: bursts/oscillations in GPi affect (inhibitory!) correlation transfer to thalamus

- STN-DBS may have additional effects based on synaptic vesicle dynamics*

*Robert Rosenbaum, poster session