Performance Limitations of Thalamic Relay: Insights into Motor Signal Processing, Parkinson's Disease and Deep Brain Stimulation

INSTITUTE for COMPUTATIONAL MEDICINE

JOHNS HOPKINS UNIVERSITY

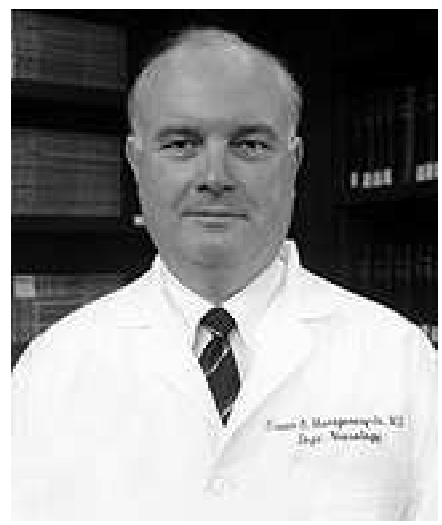
Whiting School of Engineering

Acknowledgements

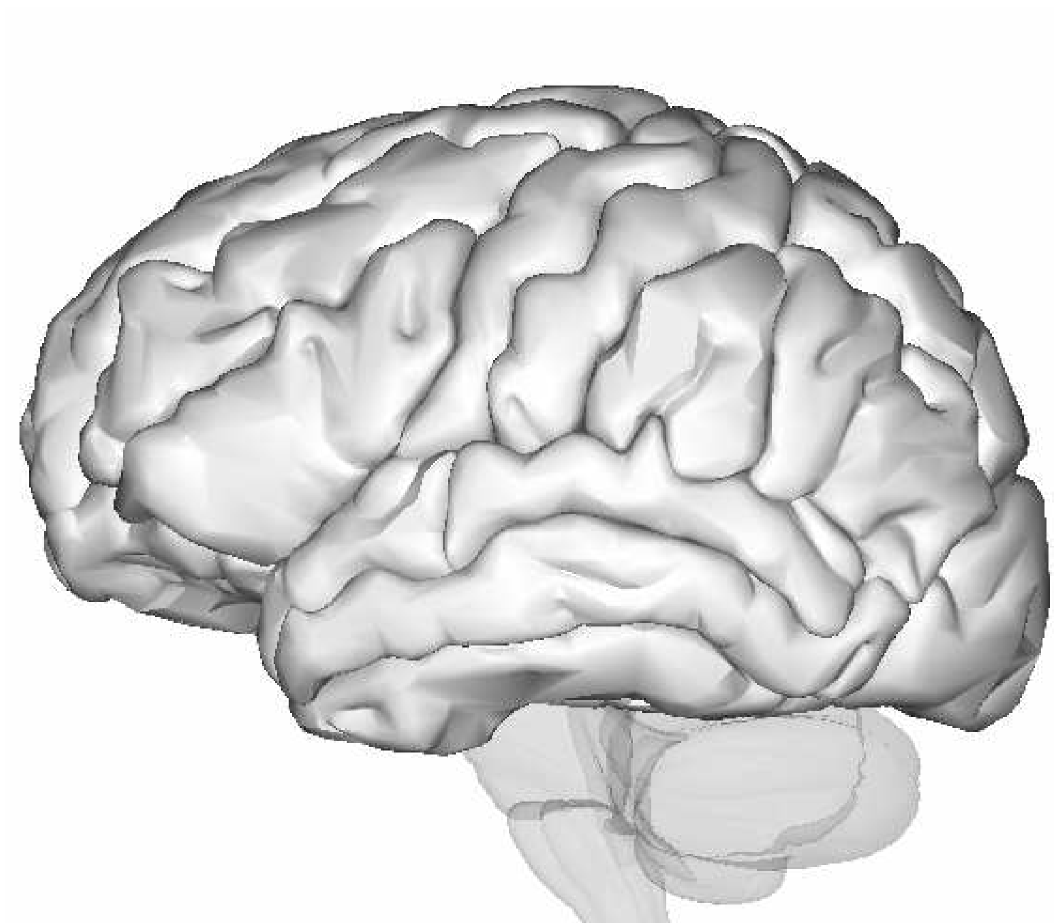
Rahul Agarwal

Shreya Saxena

John Gale & Erwin Montgomery

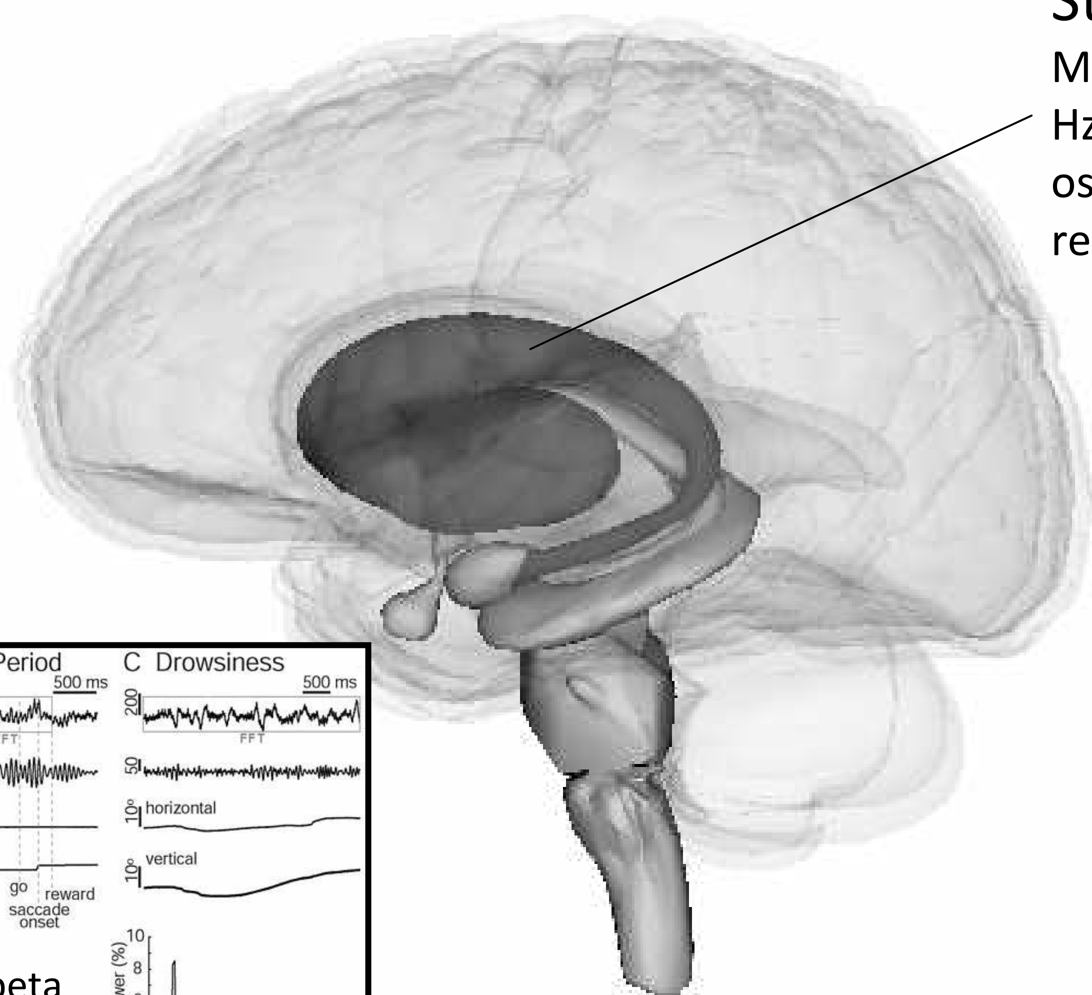


Communication Through Oscillations



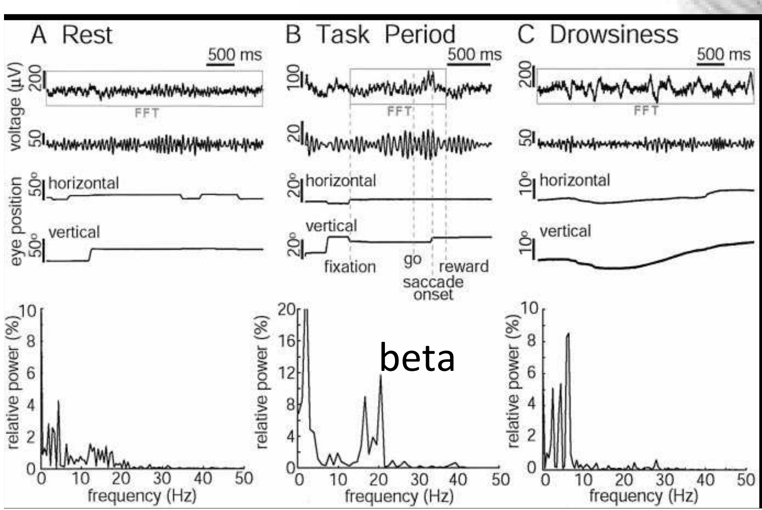
Oscillatory modulations in neural activity have been observed during task related events.

Communication Through Oscillations



Striatum

Modulation of 15-30 Hz (beta band) oscillations during task related activity

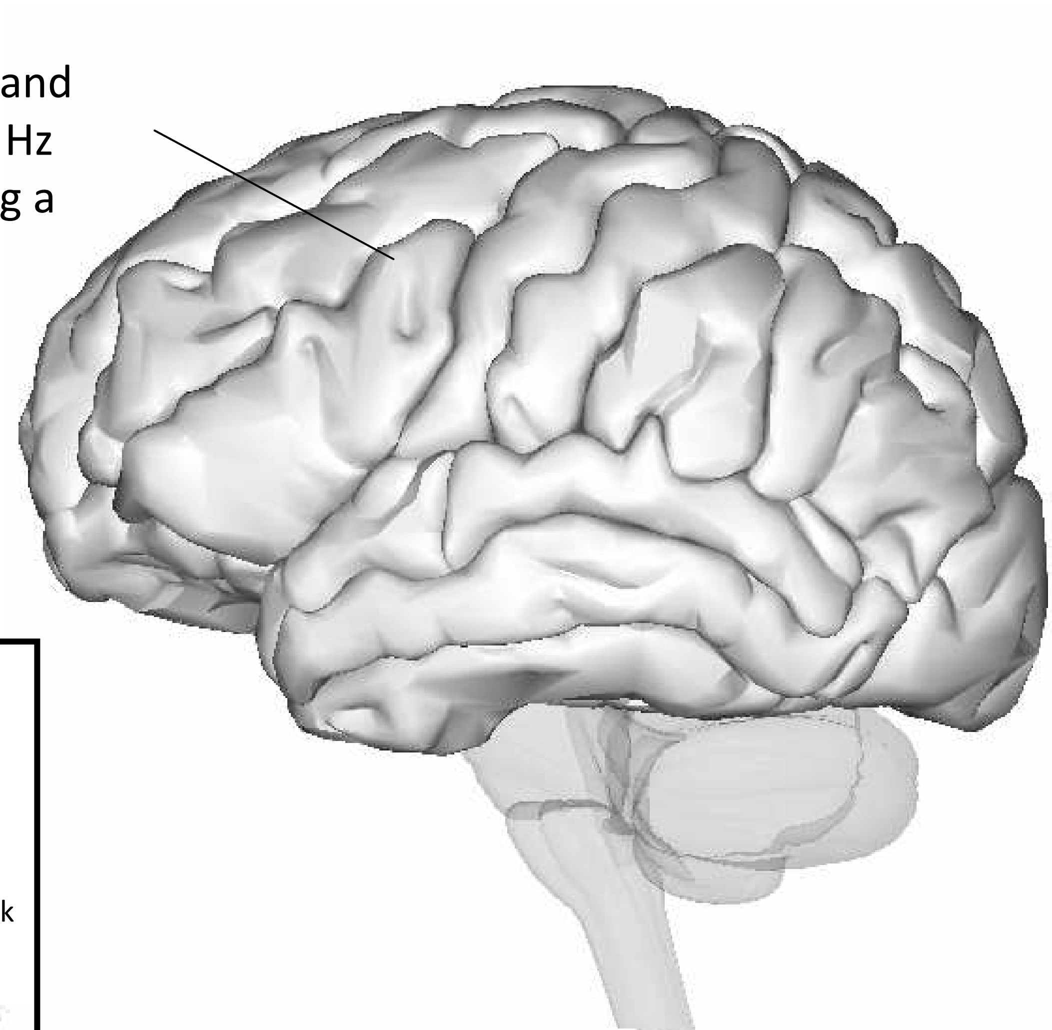


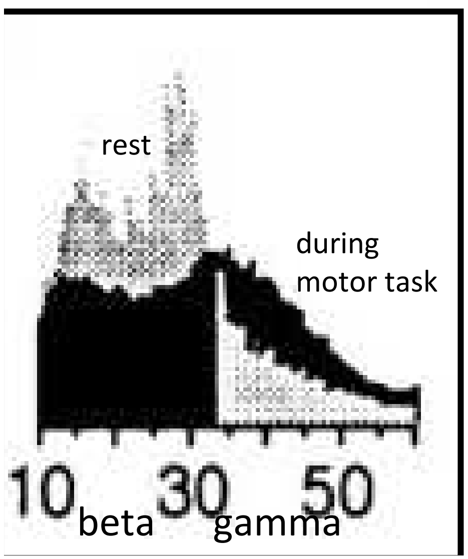
Courtemanche, “Synchronous, focally modulated β-band oscillations characterize local field potential activity in the striatum of awake behaving monkeys”, *J Neurosci*

Communication Through Oscillations

Motor Cortex

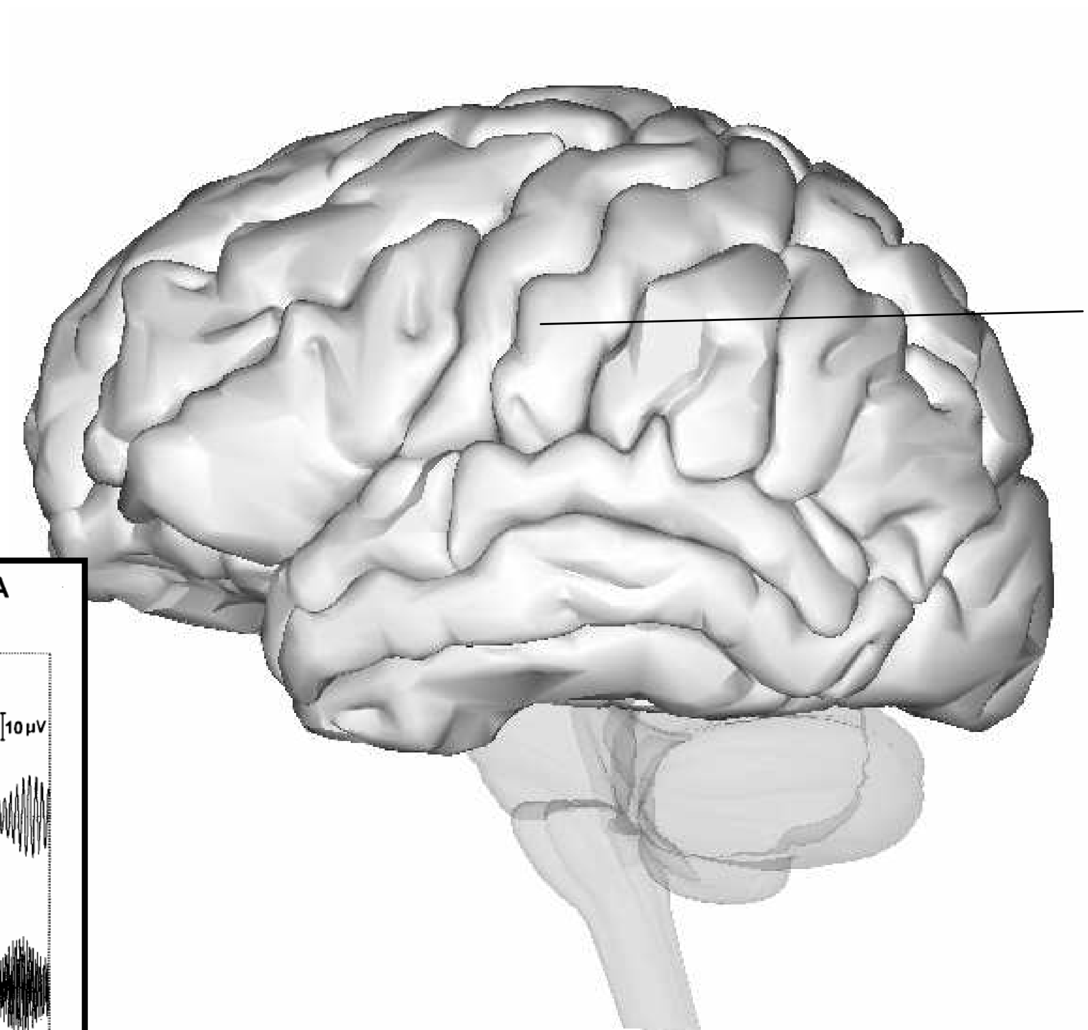
Suppression of beta and emergence of 30-80 Hz (gamma band) during a motor task





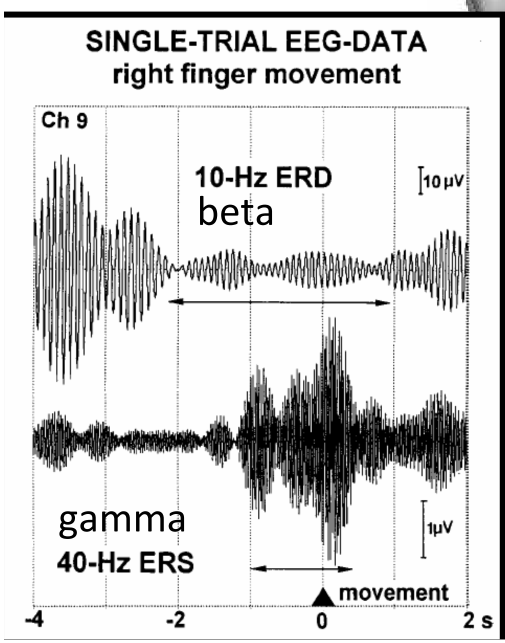
Donoghue, "Neural Discharge and Local Field Potential Oscillations in Primate Motor Cortex During Voluntary Movements", *J Neurophys* (1998)

Communication Through Oscillations



Sensorimotor Cortex

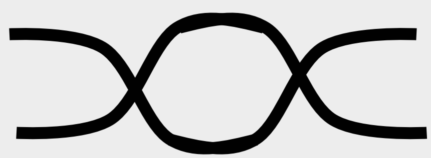
Simultaneous increase in gamma band and a suppression in beta band (cross-over) observed before movement

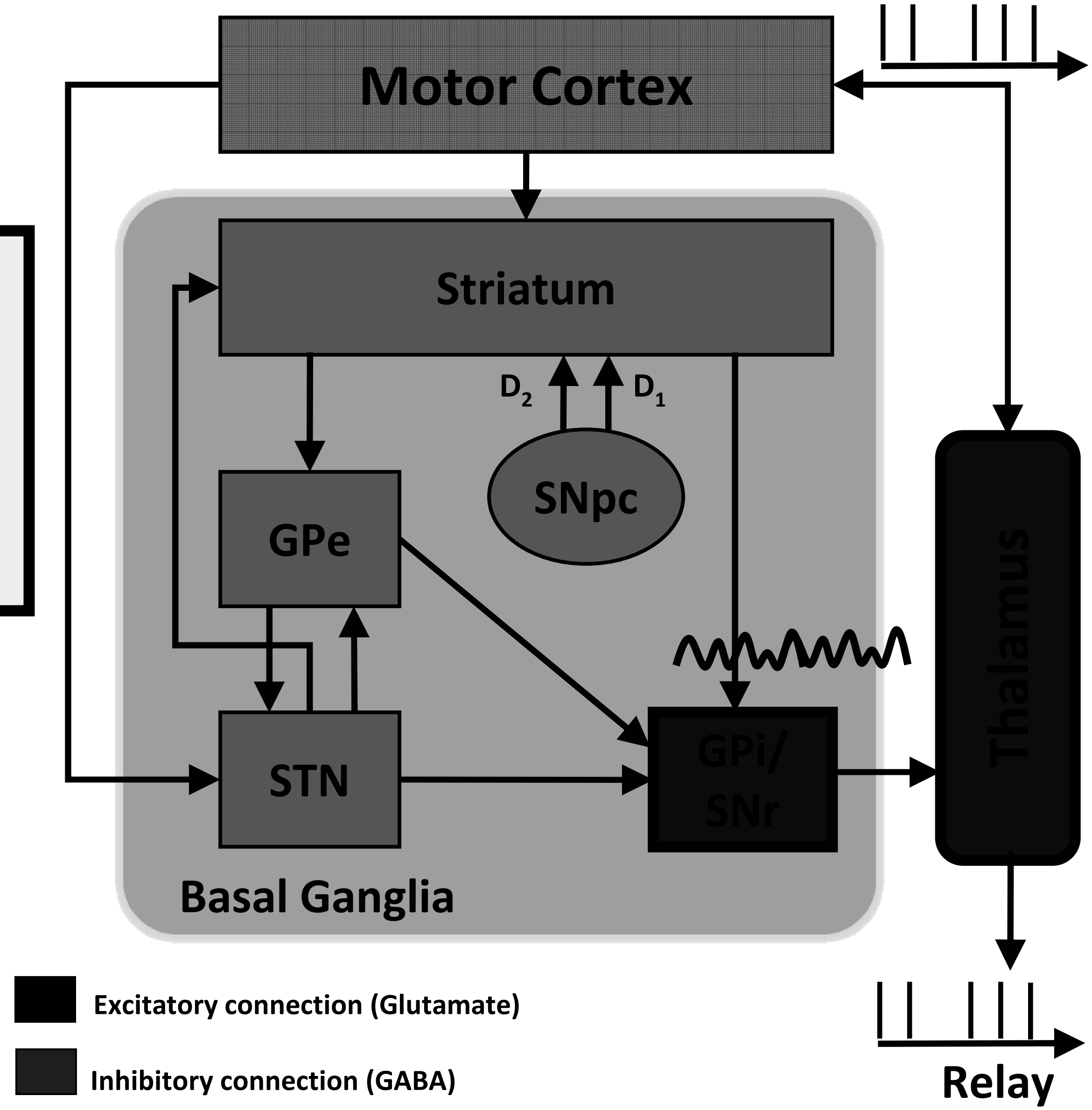


Pfurtscheller, “Simultaneous EEG 10Hz desynchronization and 40 Hz synchronization during finger movements”, NeuroReport (1992)

Oscillations in the Basal Ganglia

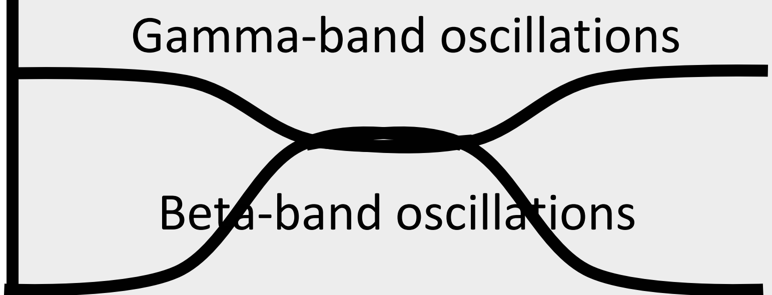
H1: When movement is planned there is a crossover effect in Gpi.

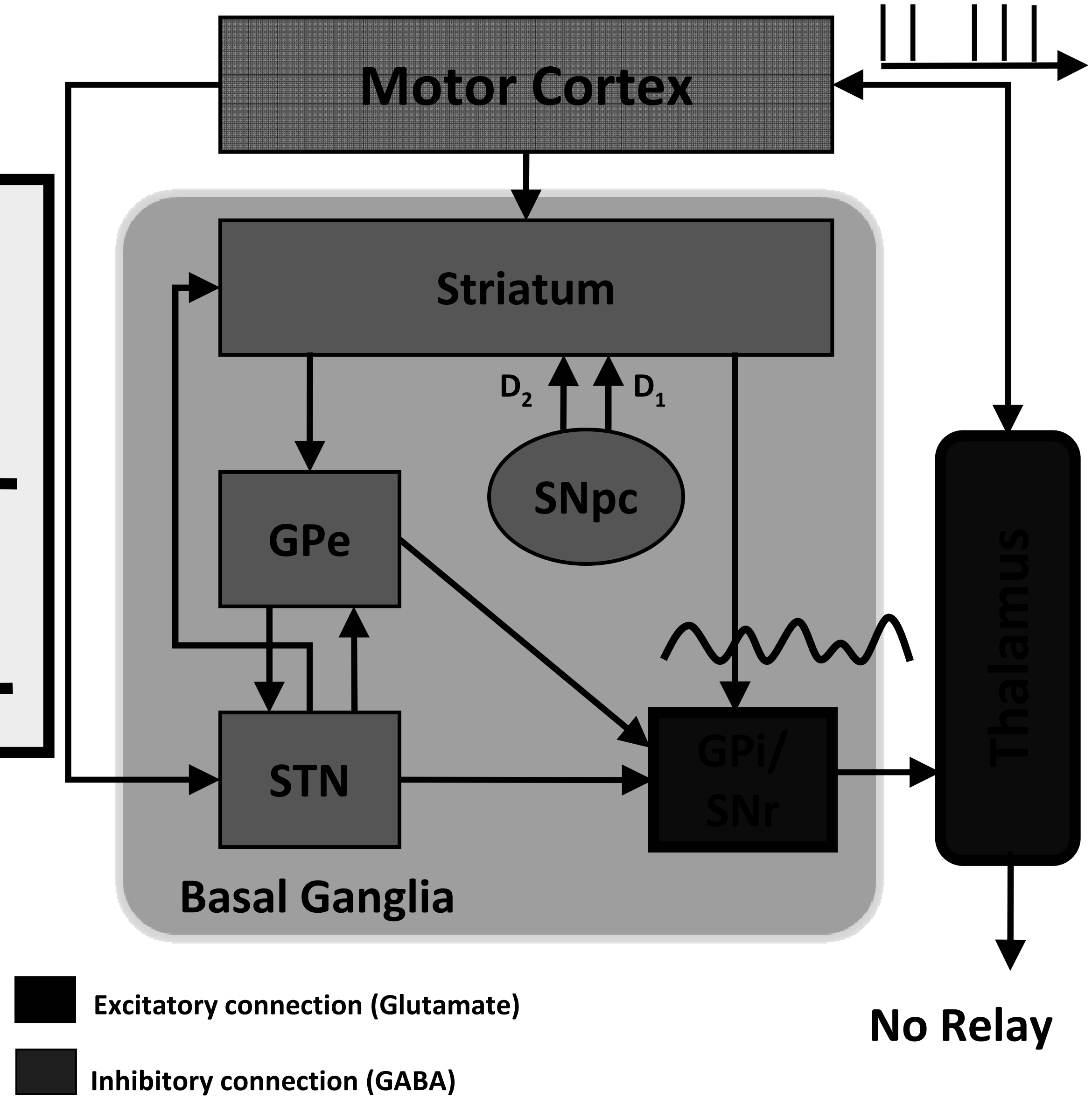




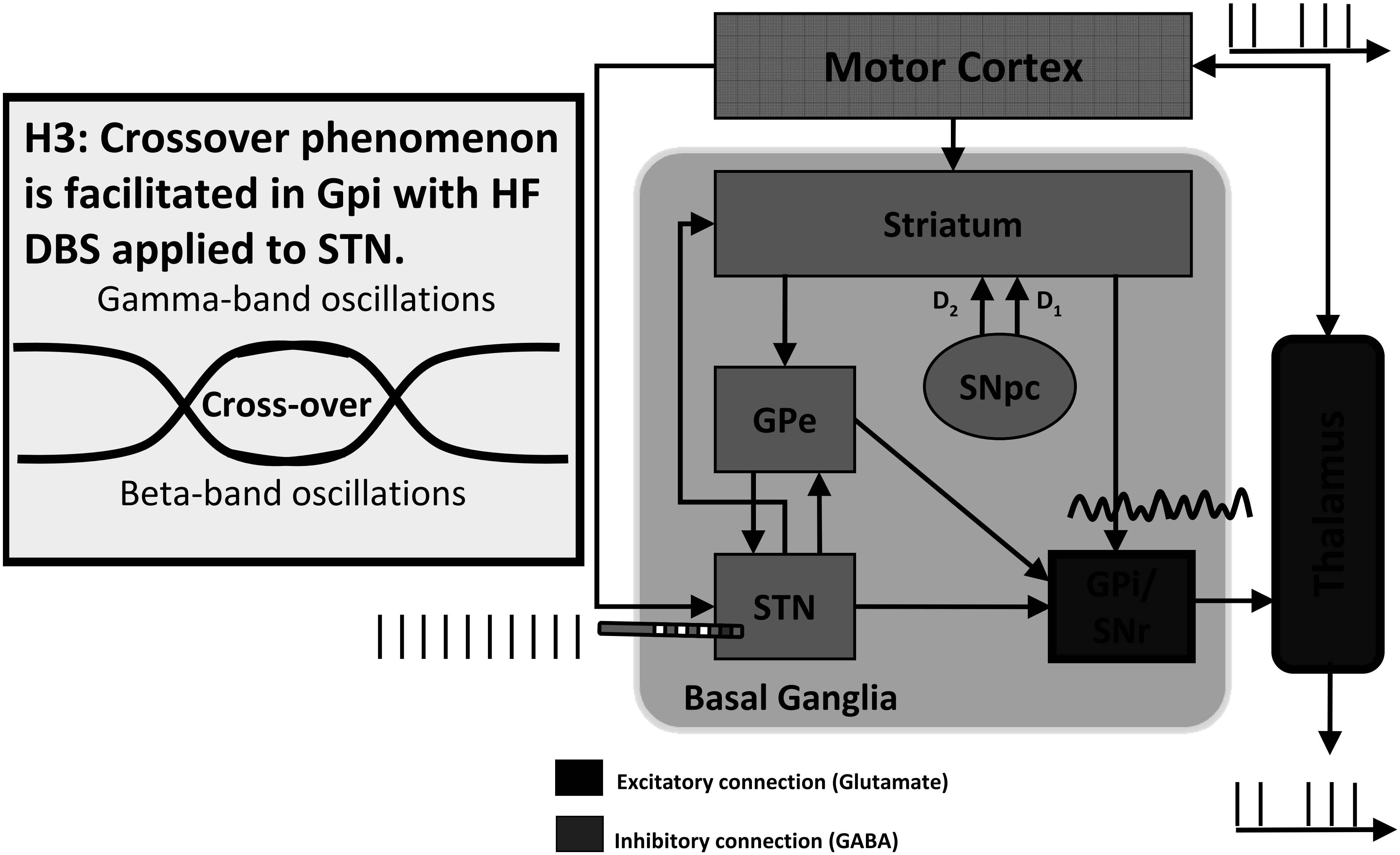
Oscillations in the Basal Ganglia in PD

H2: Crossover impaired in PD due to prominent beta oscillations in BG.



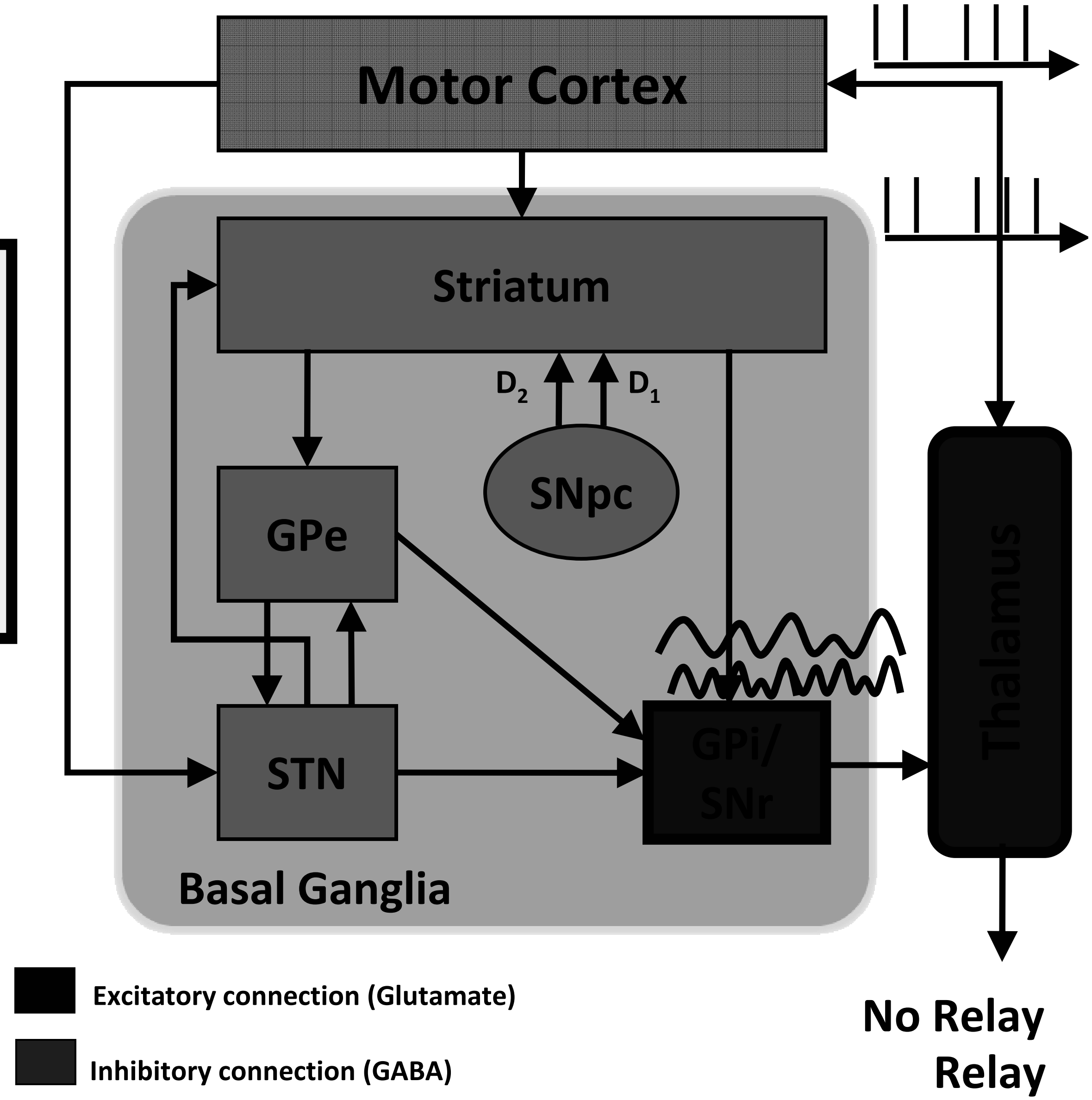


Oscillations in the Basal Ganglia w/HF STN DBS



Oscillations in Basal Ganglia and Thalamic Relay

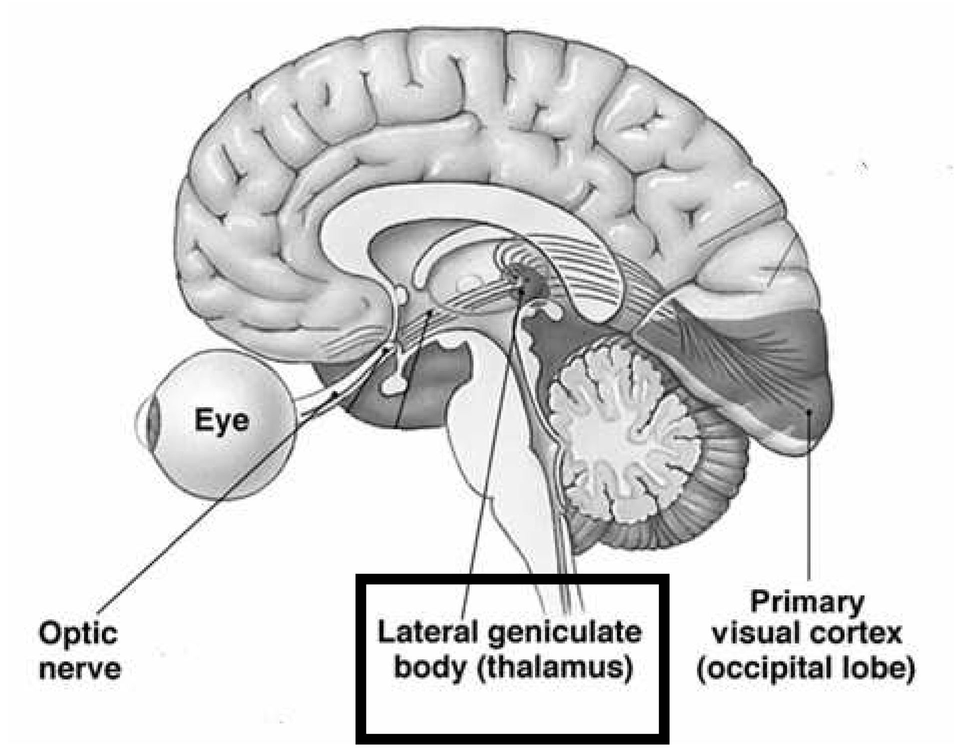
H4: Motor thalamus doesn't/does relay cortical signals when GPi activity has beta/gamma power.



H4: Motor thalamus doesn't/does relay cortical signals when GPi activity has beta/gamma power.

Relay Neurons

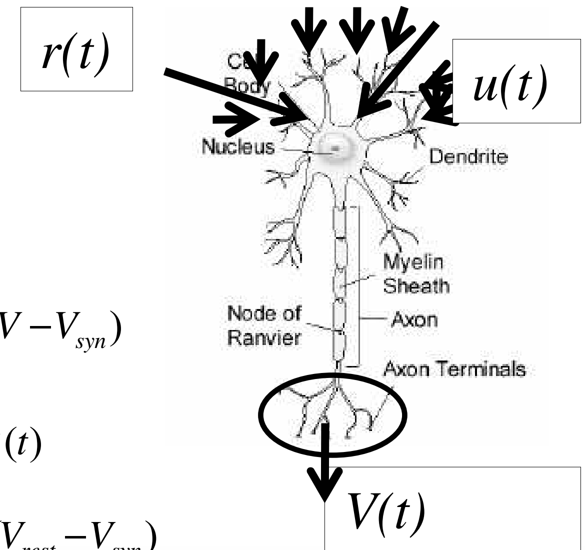
- Widely found in CNS:
  - thalamus
- Function is to strategically filter and relay information
- Open Questions:
  - when?
  - how?



http://www.colorado.edu/intphys/Class/IPHY3430-200/image/10-29.jpg

Inputs & Outputs of a Relay Neuron

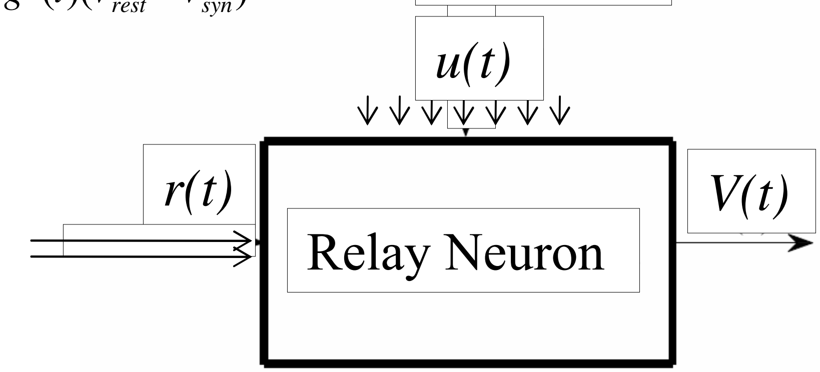
- Two input types
  - reference input $r(t)$
    - signal to be relayed
    - represents few neurons
    - on proximal dendrites
  - modulating input $u(t)$
    - modulates the relay of reference input
    - represents many neurons
    - on distal dendrites
- Output: $V(t)$



$$I_{syn} = \sum_i g_i (V - V_{syn})$$

$$u(t) = \sum_{i=1}^{N} g_i^m(t)$$

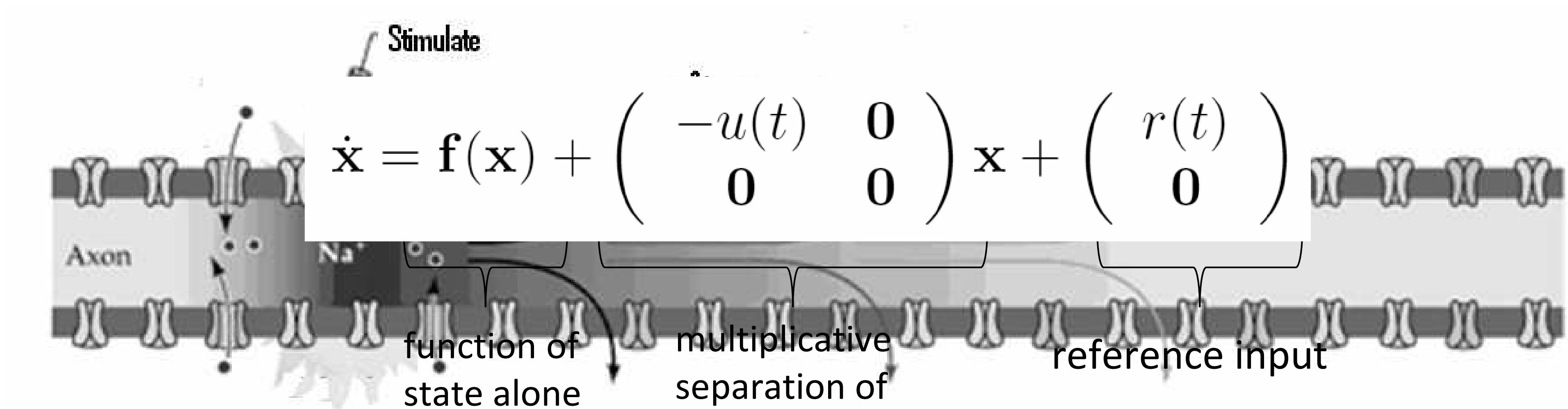
$$r(t) = g^r(t)(V_{rest} - V_{syn})$$



How and when does $u(t)$ affect relay of $r(t)$?

Sherman S. Murray and Guillery R. W. On the actions that one nerve can have on another: Distinguishing "drivers" from "modulators". PNAS, 95(12):7121{26, 1998. 92

Model of a Relay Neuron



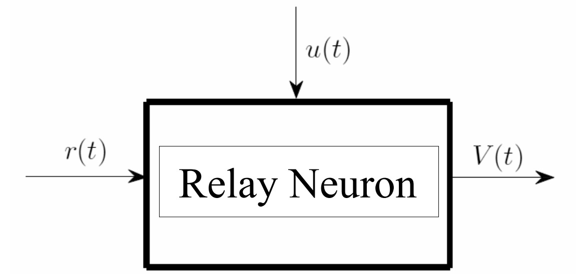
$$\dot{\mathbf{x}} = \underbrace{\mathbf{f}(\mathbf{x})}_{\text{function of state alone}} + \underbrace{\begin{pmatrix} -u(t) & \mathbf{0} \\ \mathbf{0} & \mathbf{0} \end{pmatrix}\mathbf{x}}_{\text{multiplicative separation of modulating input and state}} + \underbrace{\begin{pmatrix} r(t) \\ \mathbf{0} \end{pmatrix}}_{\text{reference input}}$$

$$\mathbf{x} = [V - V_{syn}, h_1, h_2, \cdots, h_{n-1}]^T$$

$$\mathbf{f}(\mathbf{x}) = \begin{pmatrix} -\frac{1}{C_m}(\sum_{i=1}^{l} \underbrace{\boxed{g_i \left(\prod_{j=k_{i-1}+1}^{k_i} x_j\right)(x_1 + V_{syn} - V_i)}}_{I_{ion}} + I_{ext}) \\ \alpha_1 \frac{(h_1^{\infty}(x_1+V_{syn})-x_2)}{(\tau_1(x_1+V_{syn}))} \\ \vdots \\ \alpha_{n-1} \frac{(h_{n-1}^{\infty}(x_1+V_{syn})-x_n)}{(\tau_{n-1}(x_1+V_{syn}))} \end{pmatrix}$$

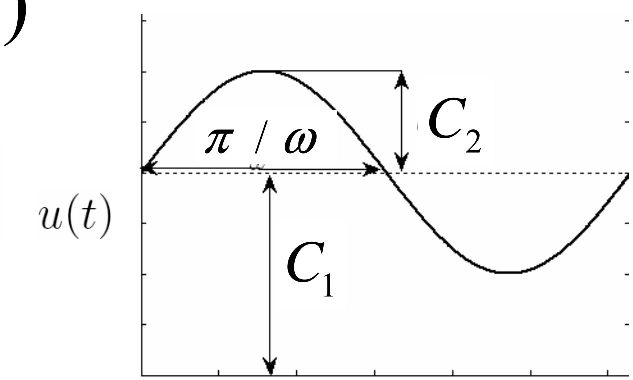
http://home.apu.edu/~jsimons/Bio101/action_potential.gif

Models of Inputs



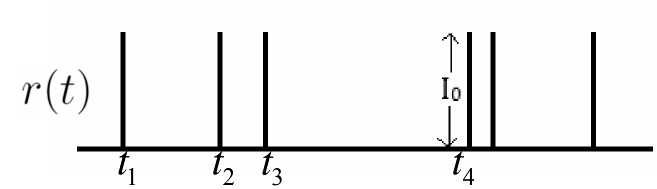
- $u(t)$: sinusoidal signals ~(c_1, c_2, ω)

$$U = \{u(t) \in \mathbb{R} \mid u(t) = c_1 + c_2 sin(\omega t)\}$$



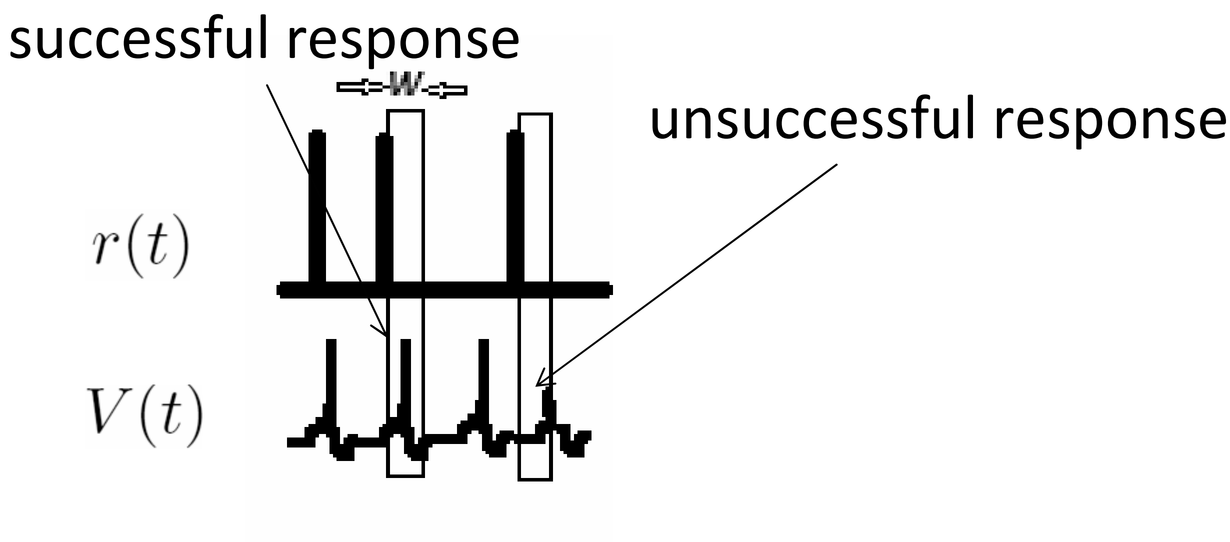
- $r(t)$: Poisson process ~(T, T_0, I_0)

$$S = \{r(t) \in \mathbb{R} \mid r(t) = I_0 \sum_{i=1}^{n} \delta(t - t_i)\}$$



Relay Reliability

Successful response occurs if $V(t)$ generates an action potential within W ms after a pulse in $r(t)$



Problem Statement

To find:

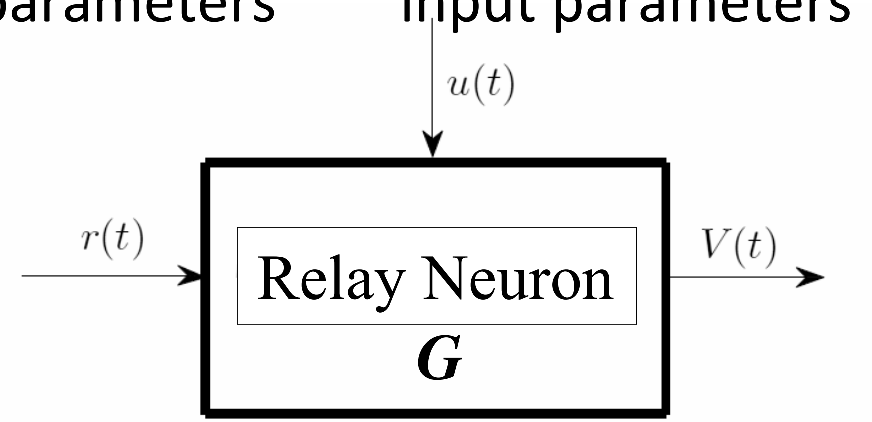
$$R = g(r(t), u(t), G)$$

$$= h(c_1, c_2, \omega, I_0, T_0, T, G)$$

Modulating input parameters

Reference input parameters

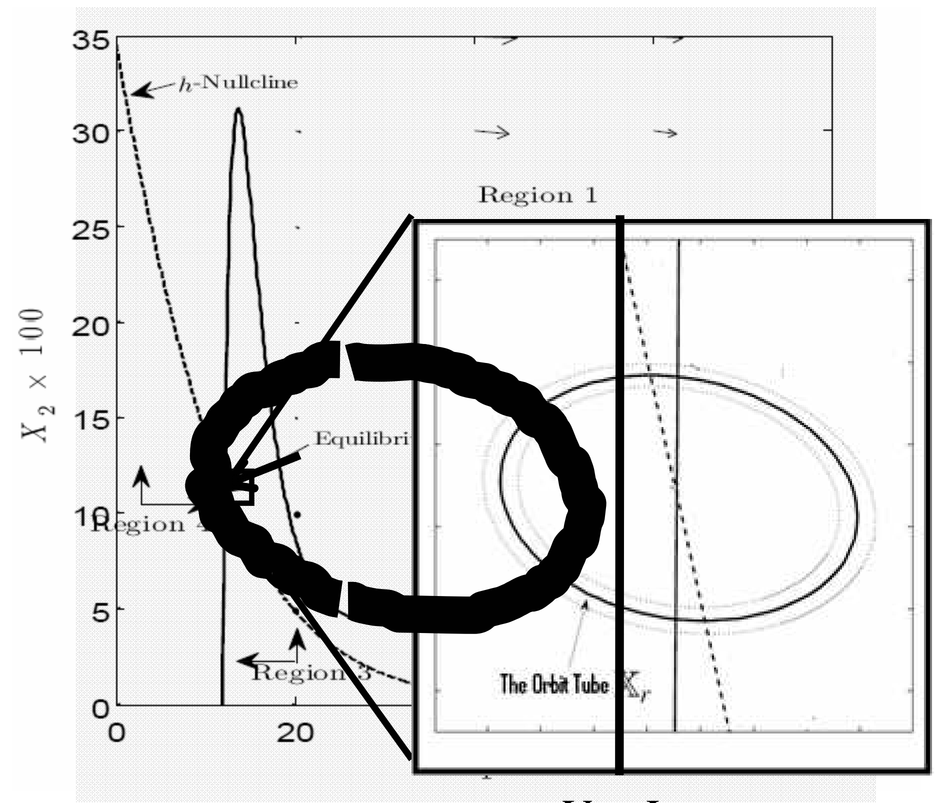
Neuron model parameters



Input Responses

$$u(t) = c_1, r(t) = 0$$

- Periodic $u(t)$, $r(t)=0$:
  - makes solution rotate in an orbit tube $\mathbb{X}_r$
- Cell dynamics: Only $X_1 > V_{th} - I_0$ generates an action potential with a pulse in $r(t)$
- $\mathbb{X}_{us} \subseteq \mathbb{X}_r$ does not generate action potential
- $\mathbb{X}_s \subseteq \mathbb{X}_r$ generates an action potential



$V_{th} - I_0$

Solution

$$\frac{P_{response}}{1+(1-\alpha)P_{response}} \geq R \geq \alpha \cdot P_{response}$$

Modulating
input parameters

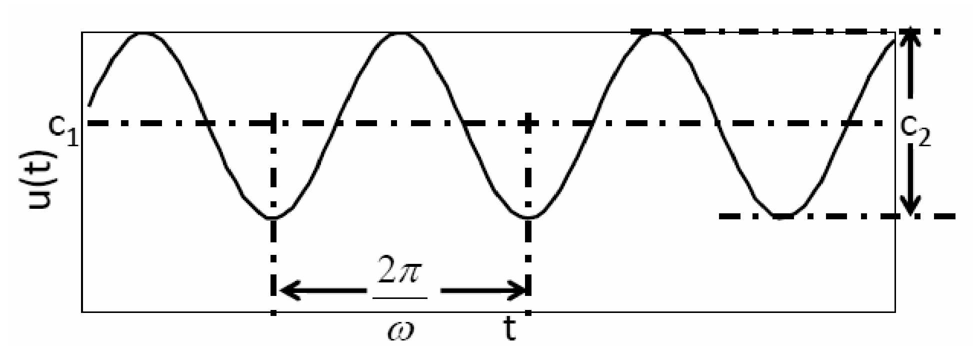
$$P_{response} = \frac{\pi + 2sin^{-1}\left(\frac{(I_0 - I_{th}(c_1))}{c_2 G(\omega)}\right)}{2\pi}$$

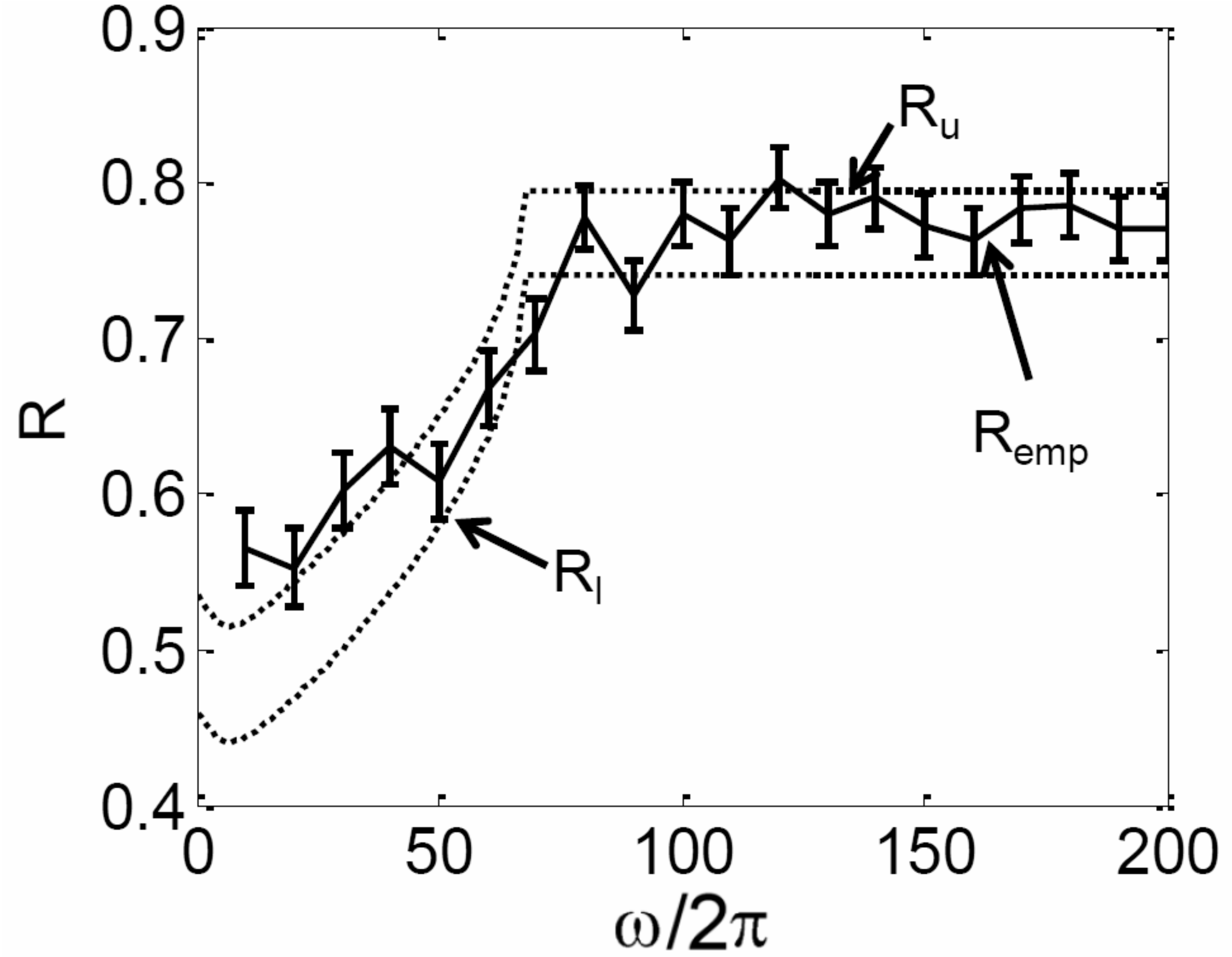
Reference
input parameters

Neuron model
parameters

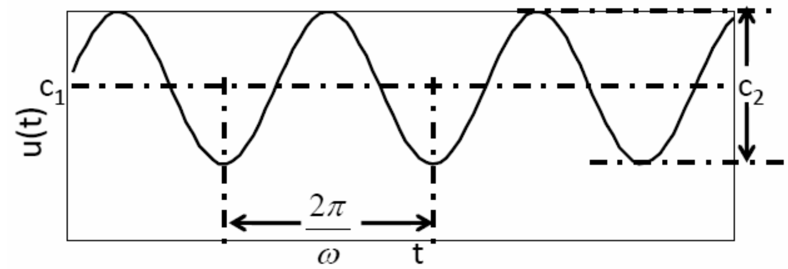
$$\alpha = \begin{cases} e^{\frac{-(T_R - T_0)}{T - T_0}} & T_R - T_0 \geq 0 \\ 1 & T_R - T_0 < 0 \end{cases}$$

R vs $\omega / 2\pi$

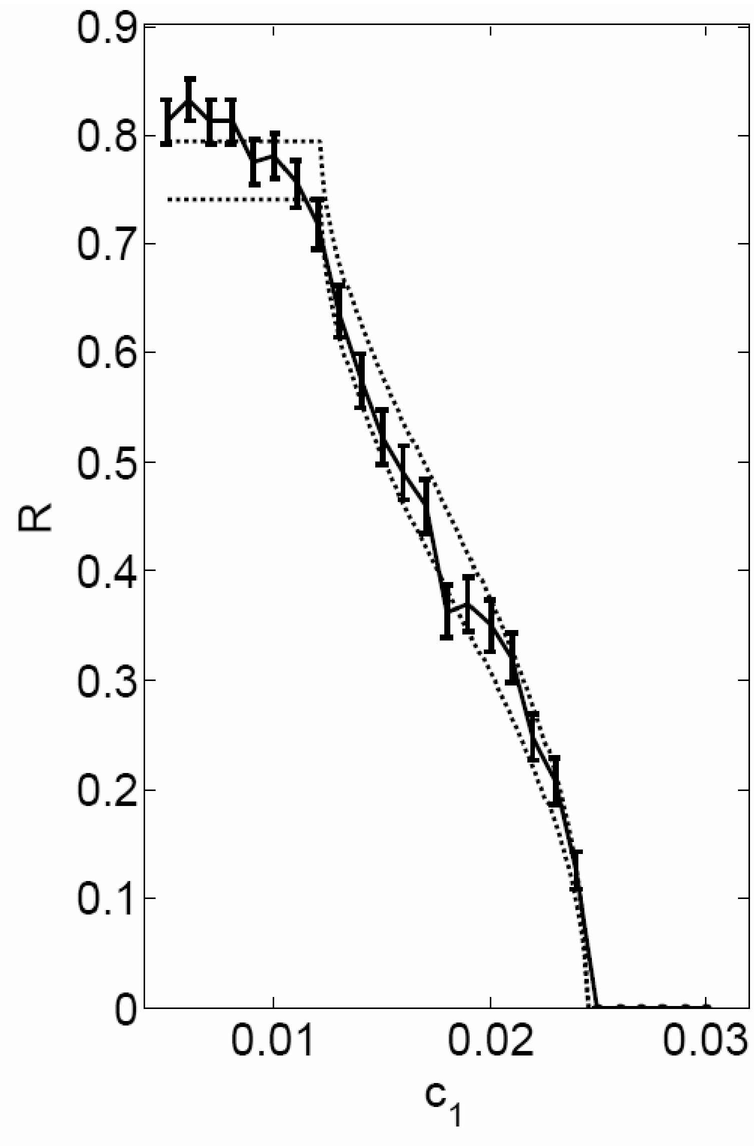




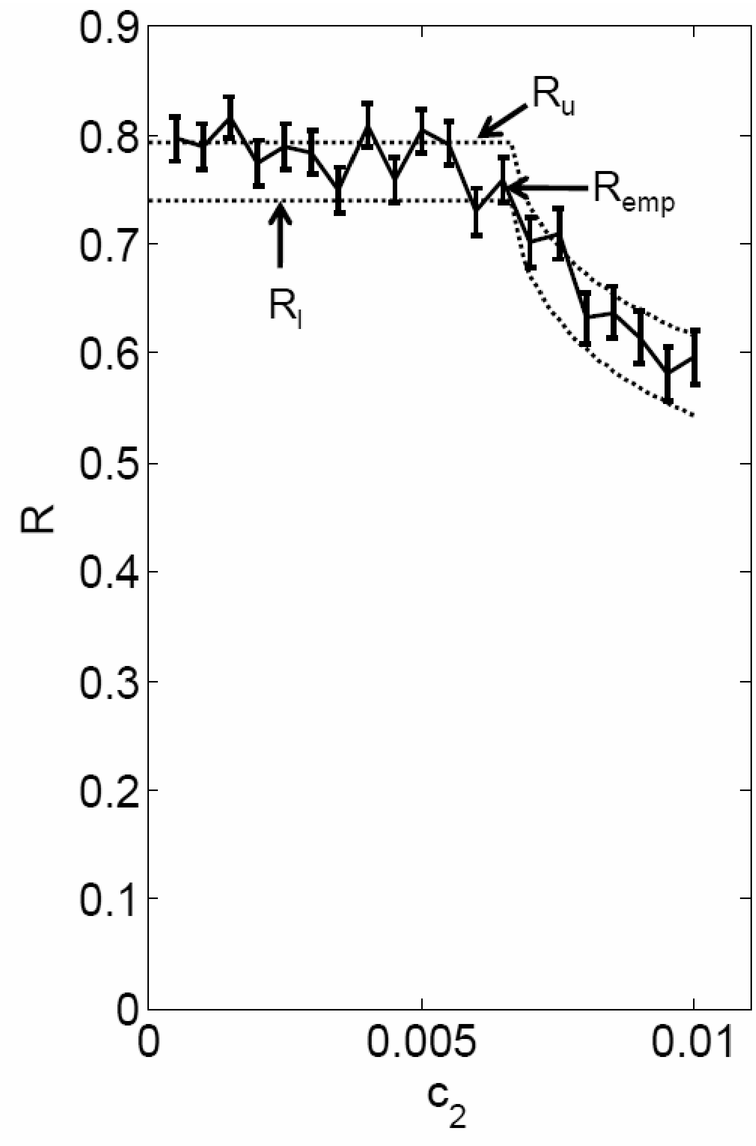
R vs c_1, c_2



u(t)
c_1
c_2
$\frac{2\pi}{\omega}$
t

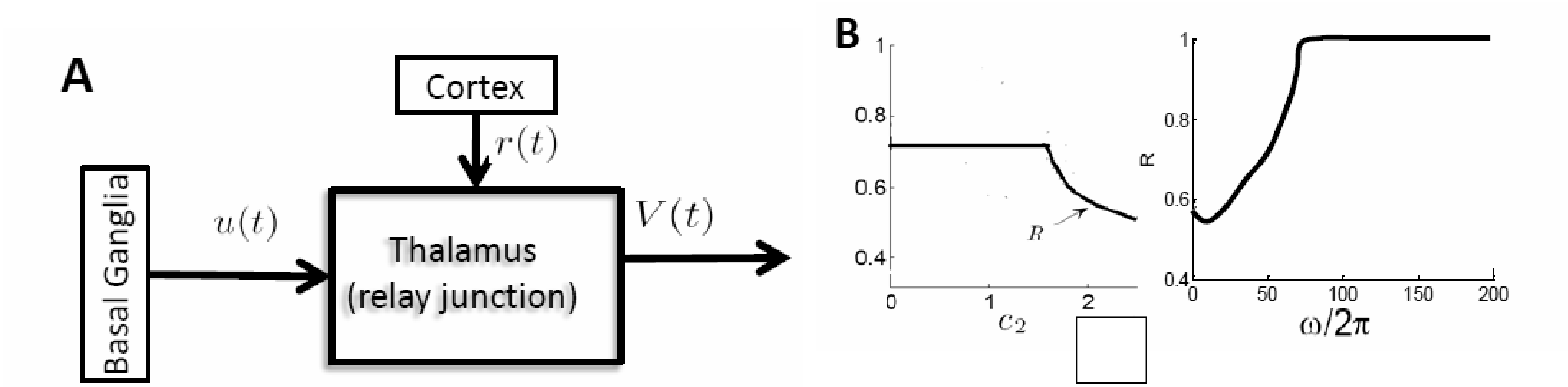


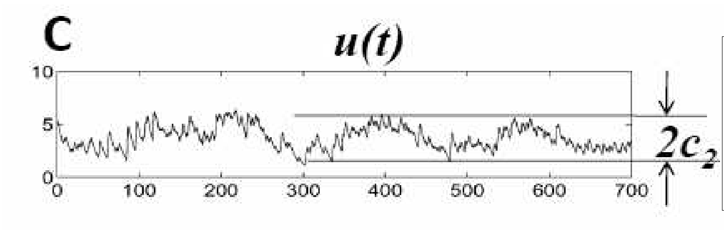
R
c_1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.01
0.02
0.03



R
c_2
R_u
R_{emp}
R_l
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.005
0.01

Application to Motor Signal Processing





Healthy: high relay reliability - low c_2

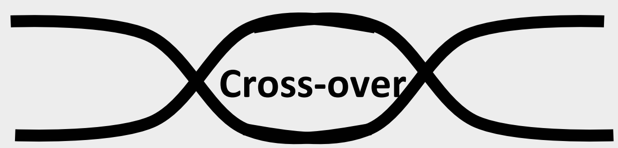
time (msec)

*Rubin & Terman 2004, J. Comp. Neuro 16 211-215

Summary

- Our analysis
  - Shows how relay reliability varies as a function of multiple parameters.
  - High frequency modulating inputs enable higher reliability
  - This is indicative that the gamma band oscillations observed in LGN LFPs & GPi activity are required to achieve higher relay reliability at thalamus.

H1: When movement is planned, there is crossover from beta to Gamma in Gpi;



Thalamic relay occurs.

Experimental Set Up

Single unit activity of GPi neurons from two healthy primates (n=27 and n=56) was recorded while they were performing a directed radial center-out reaching task.

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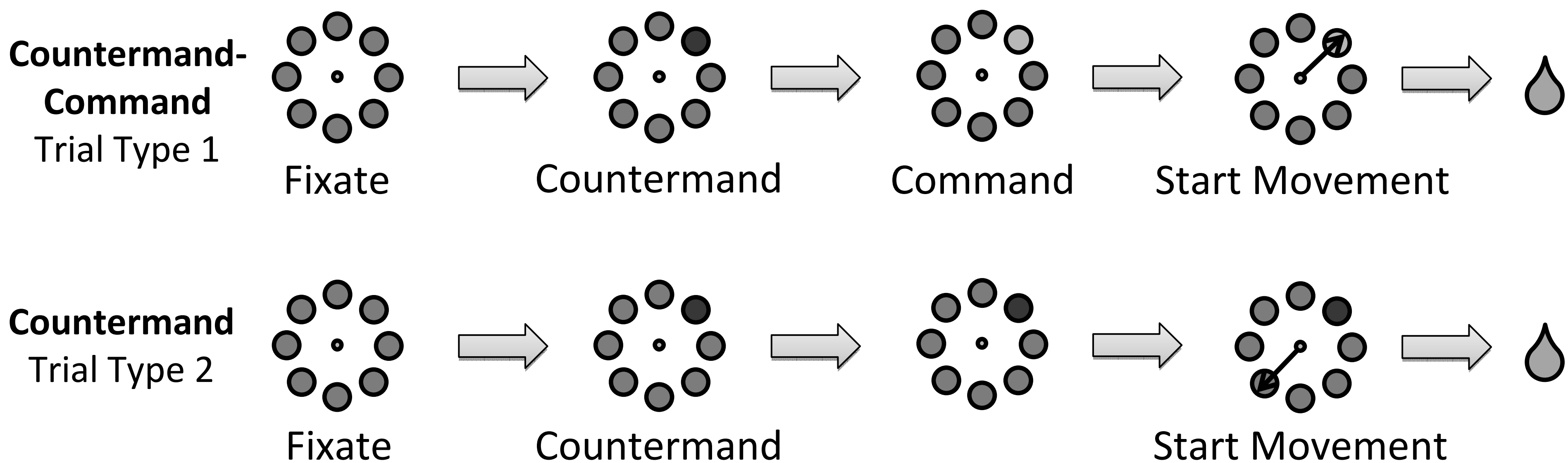
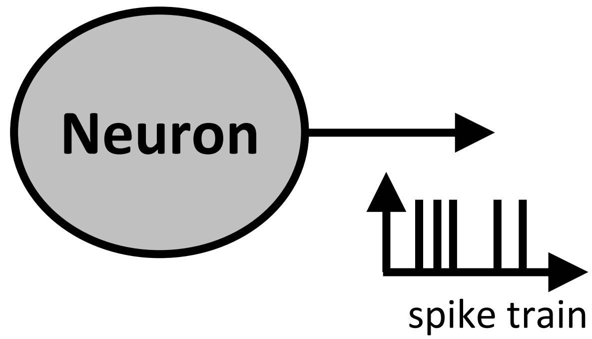
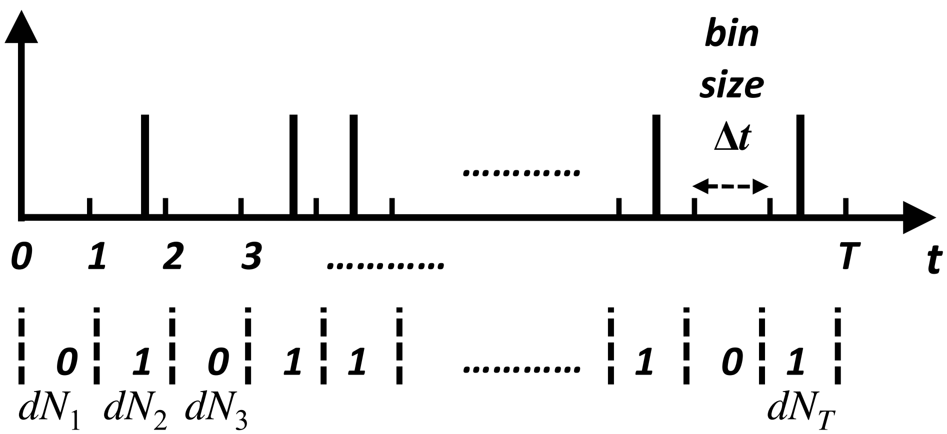


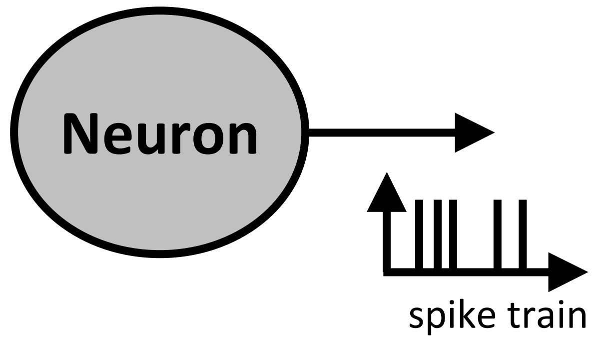
Point Process Analysis



spike train



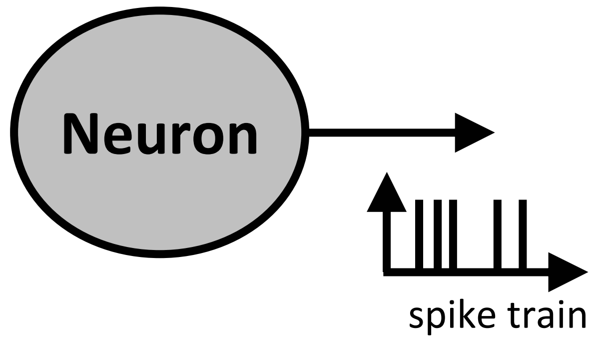
Point Process Analysis



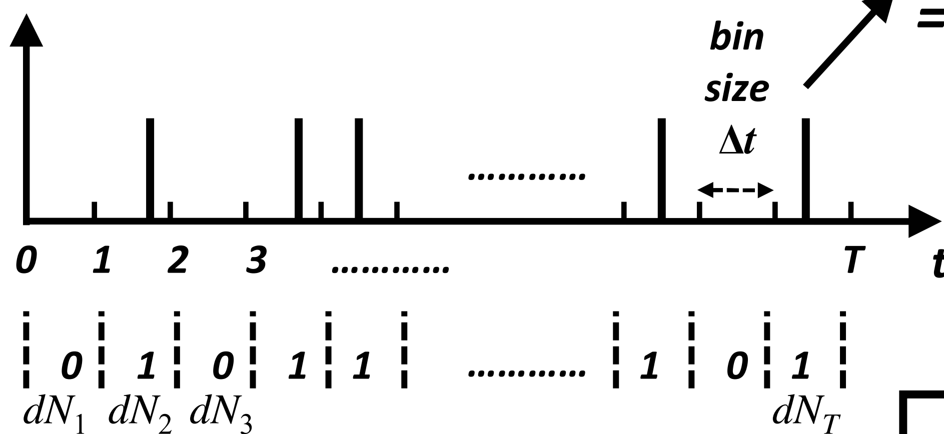
spike train

$$\lambda(t|H_t) = \lim_{\Delta t \to 0} \frac{Pr(\text{spike in } (t, t+\Delta t)|H_t)}{\Delta t}$$

Point Process Analysis



spike train

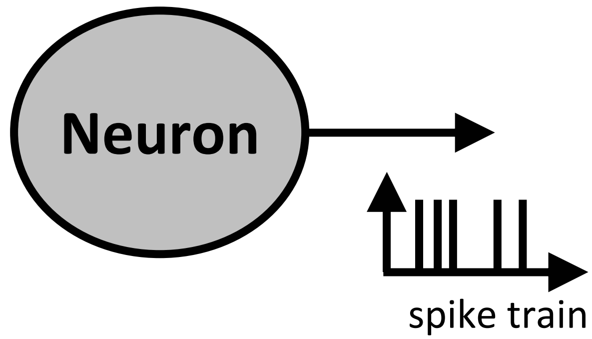


probability of a spike =

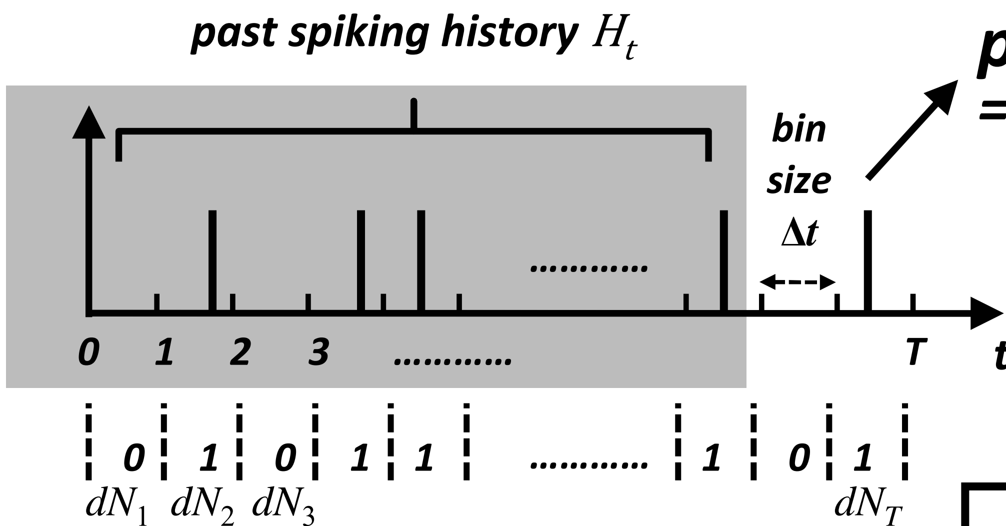
= $P(dN_t = 1 \mid H_t^O) \approx \lambda(t \mid H_t)\Delta t$

$$\lambda(t \mid H_t) = \lim_{\Delta t \to 0} \frac{P(N(t + \Delta t) - N(t) = 1 \mid H_t)}{\Delta t}$$

Point Process Analysis



spike train



probability of a spike =

= $P(dN_t = 1 | H_t^O) \approx \lambda(t|H_t)\Delta t$

$$\boxed{\lambda(t|H_t) = \lim_{\Delta t \to 0} \frac{P(N(t, t+\Delta t)|H_t)}{\Delta t}}$$

Point Process Analysis

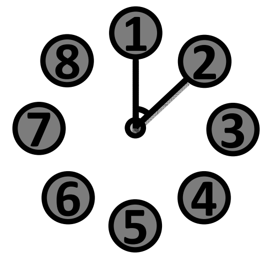
At key epochs, we express the CIF for each neuron using a multiplicative structure.

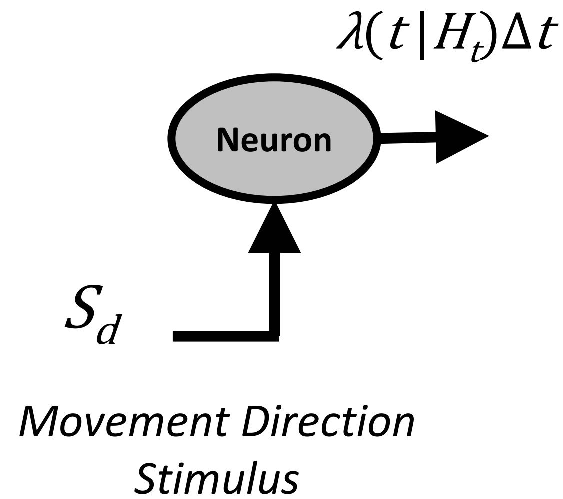
$$\lambda(t|H_t,\Theta) = \lambda^S(t|\Theta) \cdot \lambda^H(t|H_t,\Theta)$$

- $\lambda^S(t|\Theta)$ represents the effect of the *movement direction stimulus*
- $\lambda^H(t|H_t,\Theta)$ describes the effect of *spiking history*

Generalized Linear Model (GLM) of λ^S and λ^H

$$\log \lambda^S(t|\alpha, d) = \alpha_d$$





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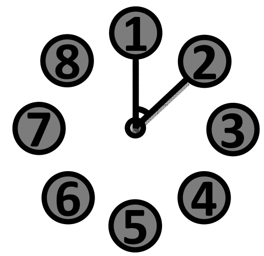
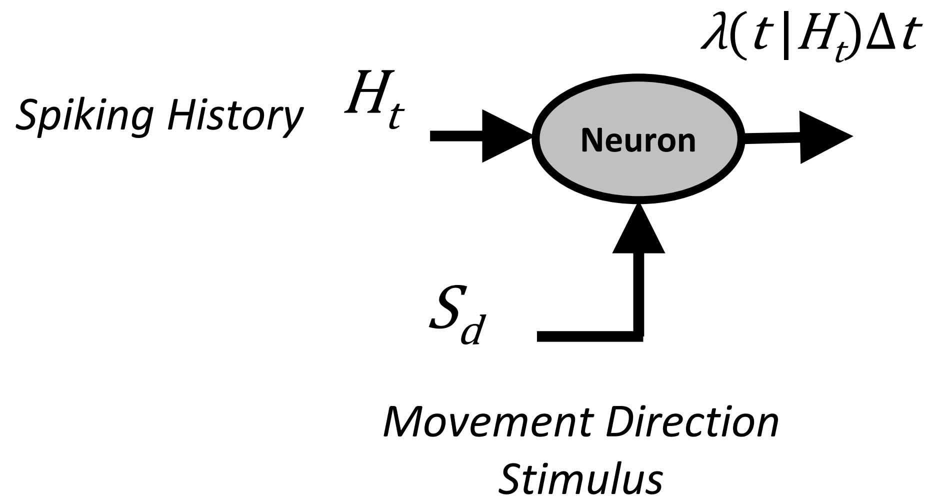




$$\log \lambda^{H}(t|\phi, \gamma, \beta)$$

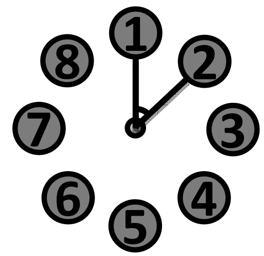
$$= \sum_{\square=0}^{9} \square_{\square} \square(\square - \square\, \square - (\square + 1))$$

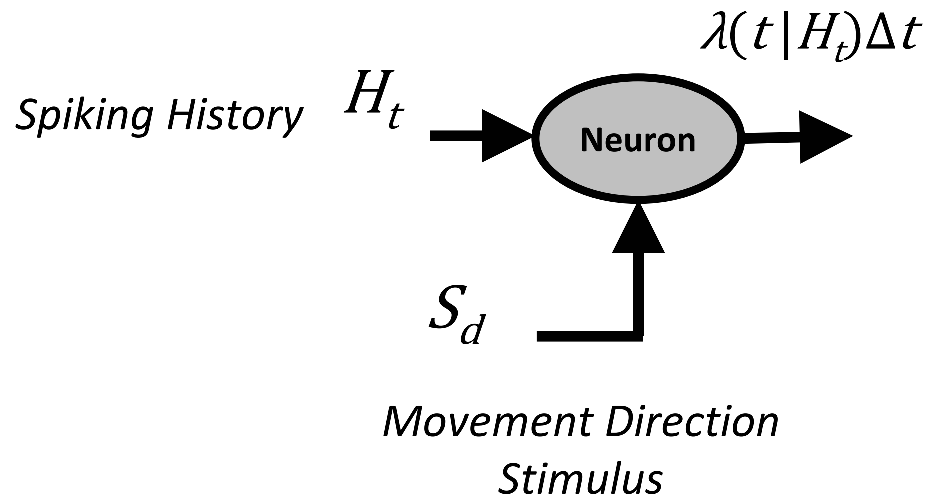
$$+ \sum_{\square=0}^{8} \square_{\square} \square(\square - (2\square + 12) : \square - (2\square + 14))$$

$$+ \sum_{\square=0}^{8} \square_{\square} \square(\square - (5\square + 30) : \square - (5\square + 35))$$

Generalized Linear Model (GLM) of λ^S and λ^H

$$\log \lambda^{S}(t|\alpha, d) = \alpha_{d}$$





$$\log \lambda^{H}(t|\phi, \gamma, \beta)$$

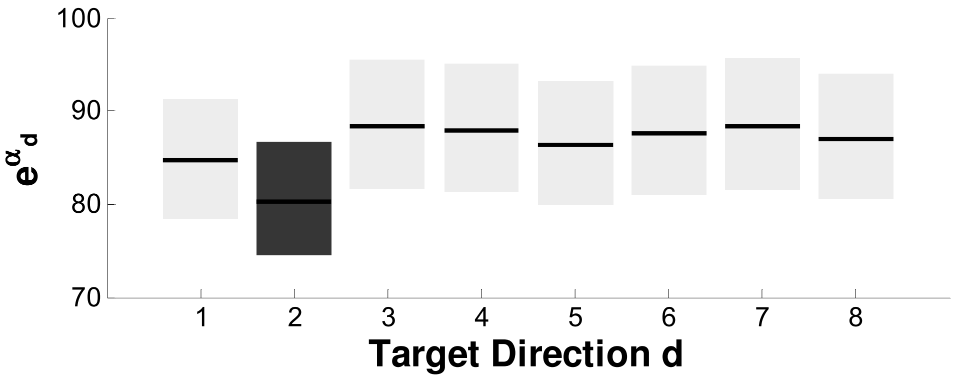
$$= \sum_{\square=0}^{9} \square_{\square} \square(\square - \square\, \square - (\square + 1))$$

$$+ \sum_{\square=0}^{8} \square_{\square} \square(\square - (2\square + 12) : \square - (2\square + 14))$$

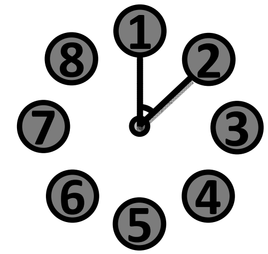
$$+ \sum_{\square=0}^{8} \square_{\square} \square(\square - (5\square + 30) : \square - (5\square + 35))$$

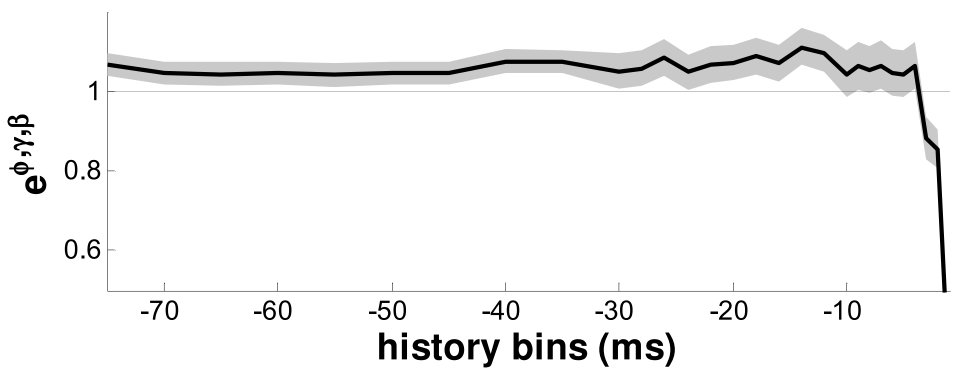
$$\Theta = \left[\{\square_{\square}\}_{\square=1}^{8}, \{\square_{\square}\}_{\square=0}^{9}, \{\square_{\square}\}_{\square=0}^{8}, \{\square_{\square}\}_{\square=0}^{8} \right]$$ *estimated via Maximum Likelihood*

Directional Tuning (DT)

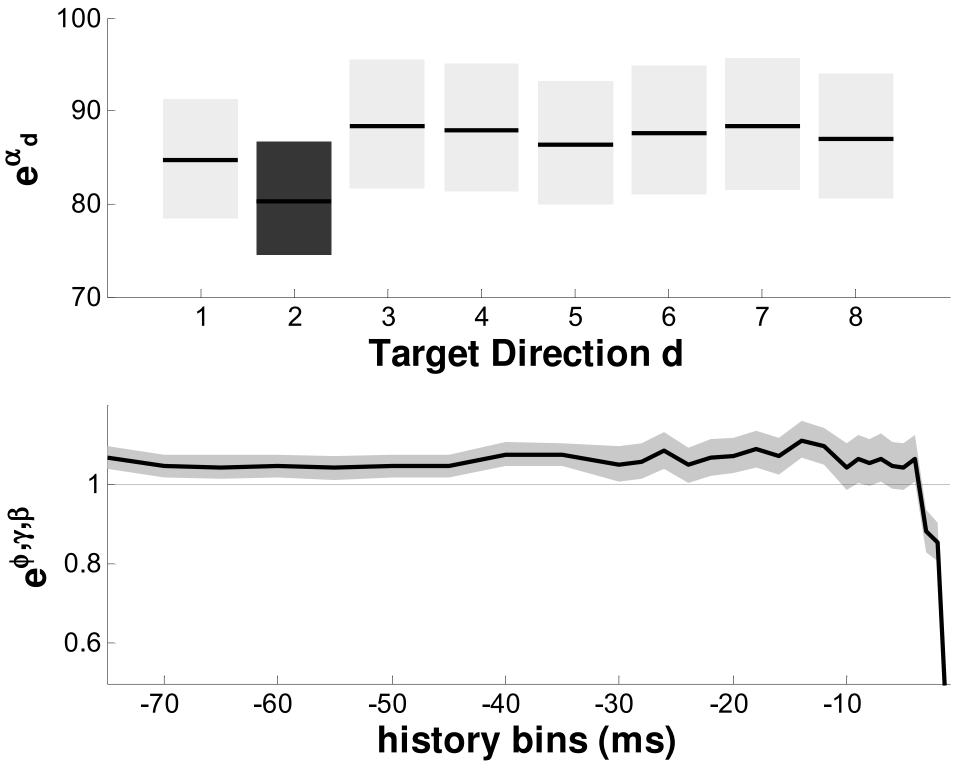


$$\log \lambda^S(t|\alpha, d) = \alpha_d$$

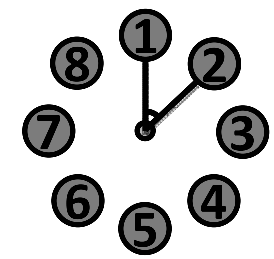




Directional Tuning (DT)

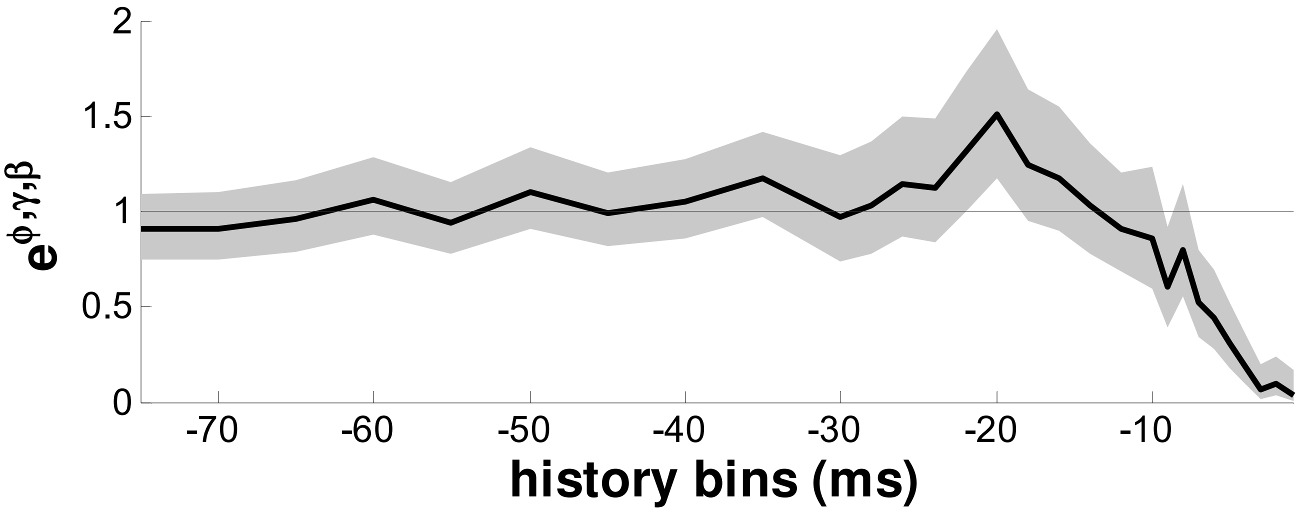


$$\log \lambda^S(t|\alpha, d) = \alpha_d$$

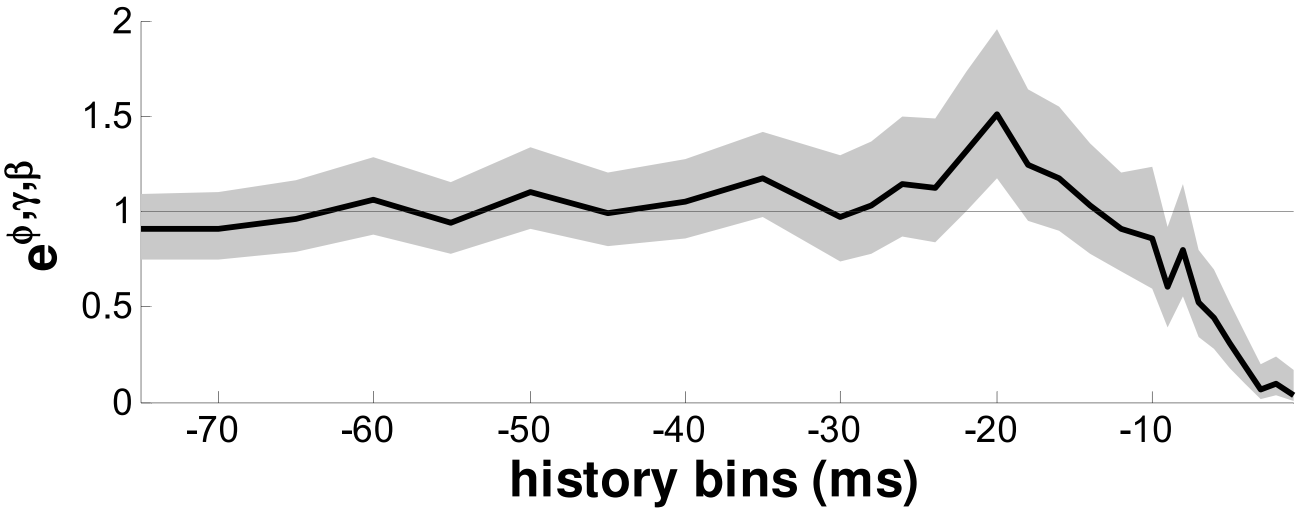


The neuron is DT if the history-independent firing in one direction was found to be significantly different from that in at least 4 other directions at a 95% confidence level.

Generalized Linear Model (GLM) of λ^H



Generalized Linear Model (GLM) of λ^H



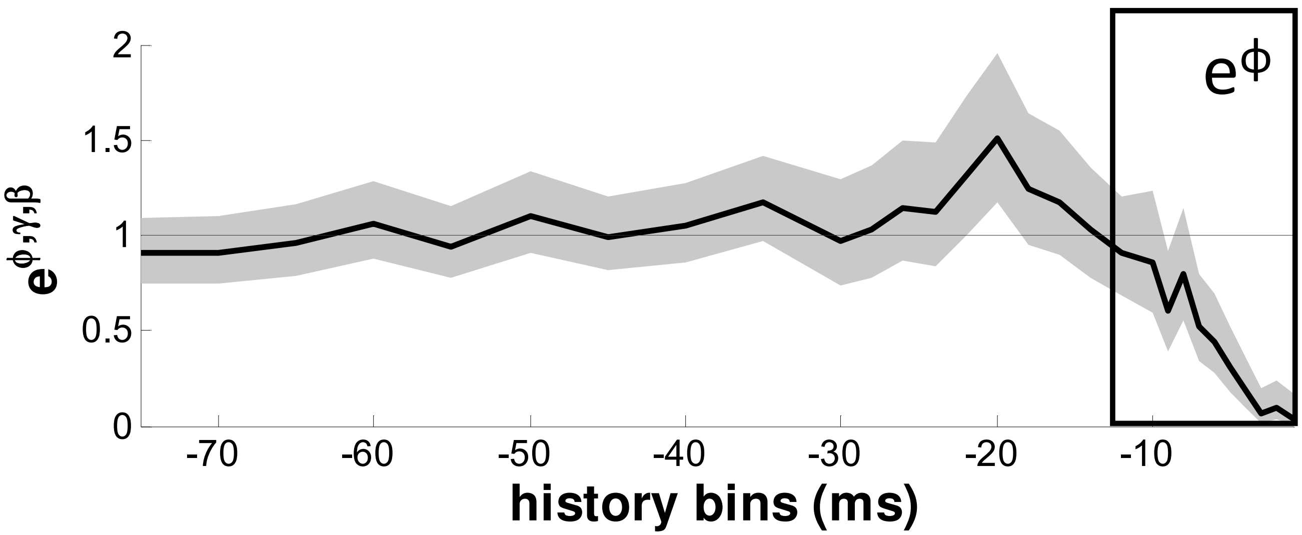
$$\log \lambda^{H}(t|\phi, \gamma, \beta)$$

$$= \sum_{\square=0}^{9} \square_{\square} \square(\square - \square\ \square - (\square + 1)$$

$$+ \sum_{\square=0}^{8} \square_{\square} \square(\square - (2\square + 12) : \square - (2\square + 14)$$

$$+ \sum_{\square=0}^{8} \square_{\square} \square(\square - (5\square + 30) : \square - (5\square + 35)$$

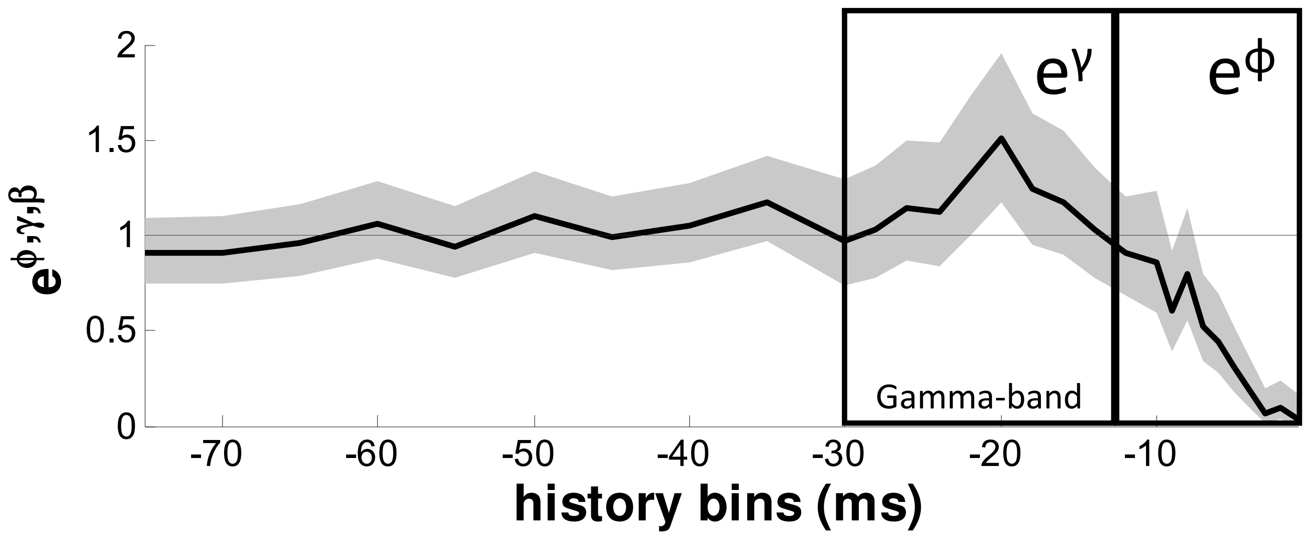
Generalized Linear Model (GLM) of λ^H



$$\log \lambda^{H}(t|\phi,\gamma,\beta)$$
$$= \boxed{\sum_{k=0}^{9} \phi_k n(t-k: t-(k+1))}$$
$$+ \sum_{k=0}^{8} \gamma_k n(t-(2k+12): t-(2k+14))$$
$$+ \sum_{k=0}^{8} \beta_k n(t-(5k+30): t-(5k+35))$$

It captures short-term (<=10 ms) recurrent patterns (e.g., intra-burst activity)

Generalized Linear Model (GLM) of λ^H



$$\log \lambda^{H}(t|\phi,\gamma,\beta)$$

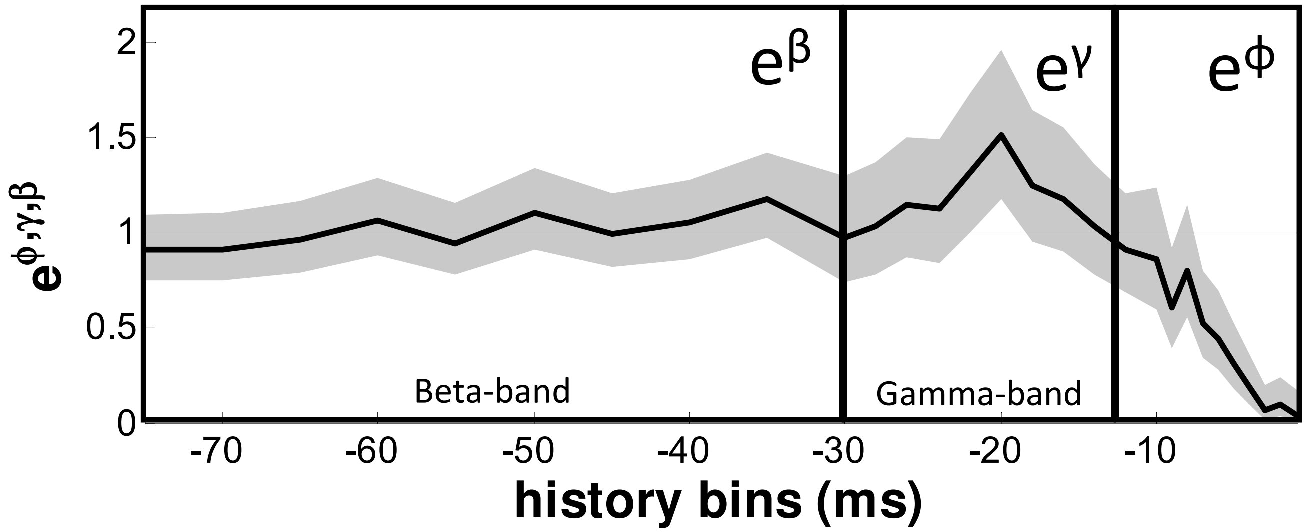
$$= \sum_{k=0}^{9} \phi_k n(t-k : t-(k+1))$$

$$+ \boxed{\sum_{k=0}^{8} \gamma_k n(t-(2k+12) : t-(2k+14))}$$

$$+ \sum_{k=0}^{8} \beta_k n(t-(5k+30) : t-(5k+35))$$

It captures recurrent patterns with period 12-30 ms (oscillations in gamma frequency band)

Generalized Linear Model (GLM) of λ^H



$$\log \lambda^{H}(t|\phi,\gamma,\beta)$$

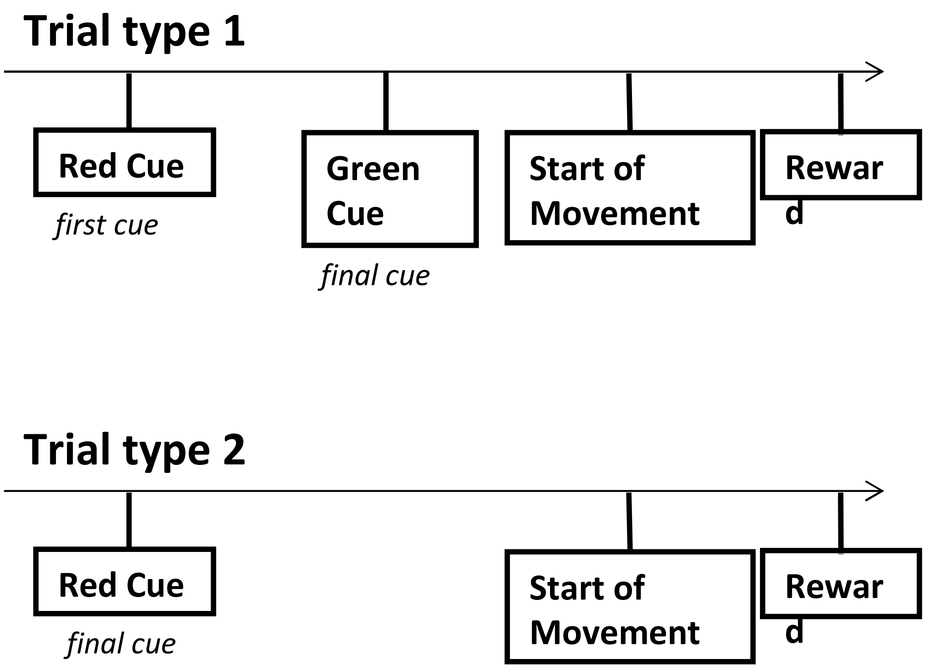
$$= \sum_{\square=0}^{9} \square_{\square}\square(\square - \square\ \square - (\square + 1)$$

$$+ \sum_{\square=0}^{8} \square_{\square}\square(\square - (2\square + 12) : \square - (2\square + 14)$$

$$+ \boxed{\sum_{\square=0}^{8} \square_{\square}\square(\square - (5\square + 30) : \square - (5\square + 35)}$$

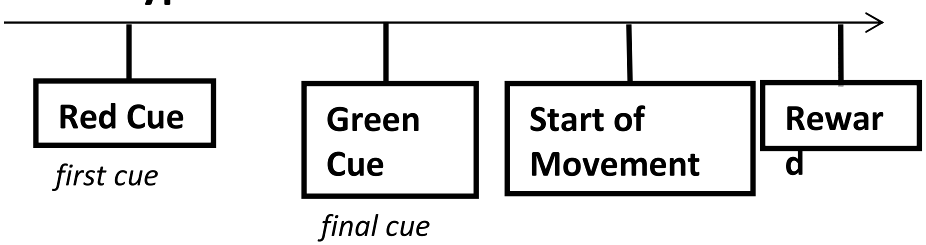
It captures recurrent patterns with period 30-75 ms (oscillations in $beta$ *frequency band)*

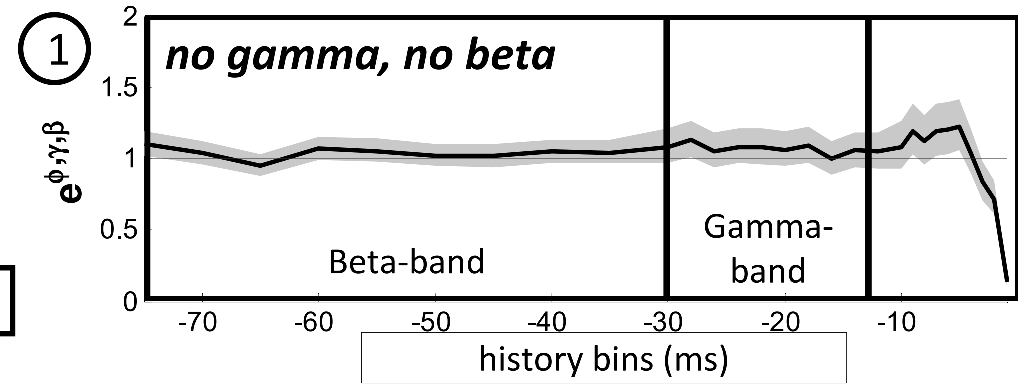
Determining Cross-Over Effect



Determining Cross-Over Effect

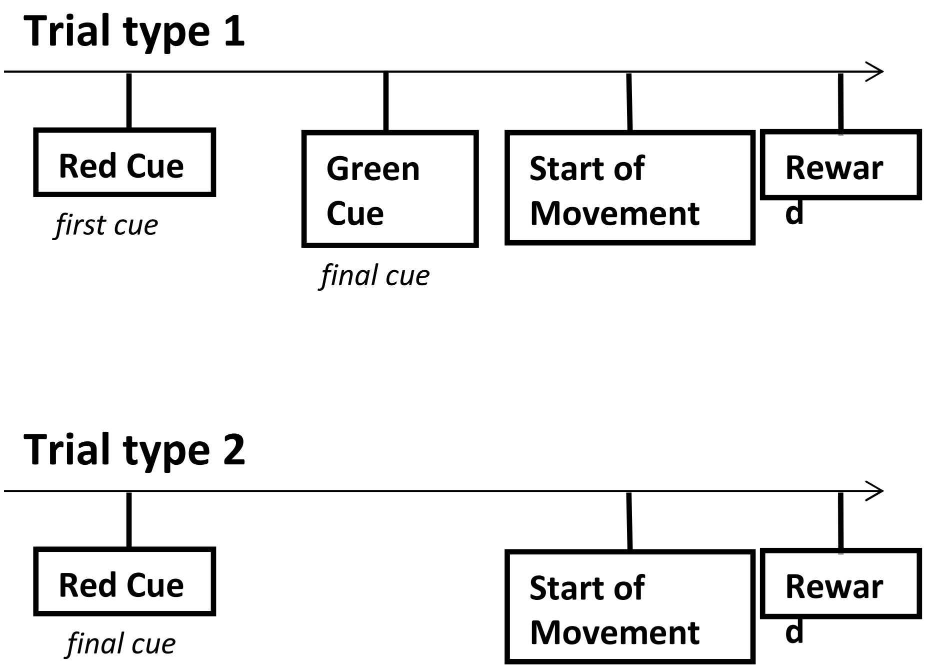
Trial type 1

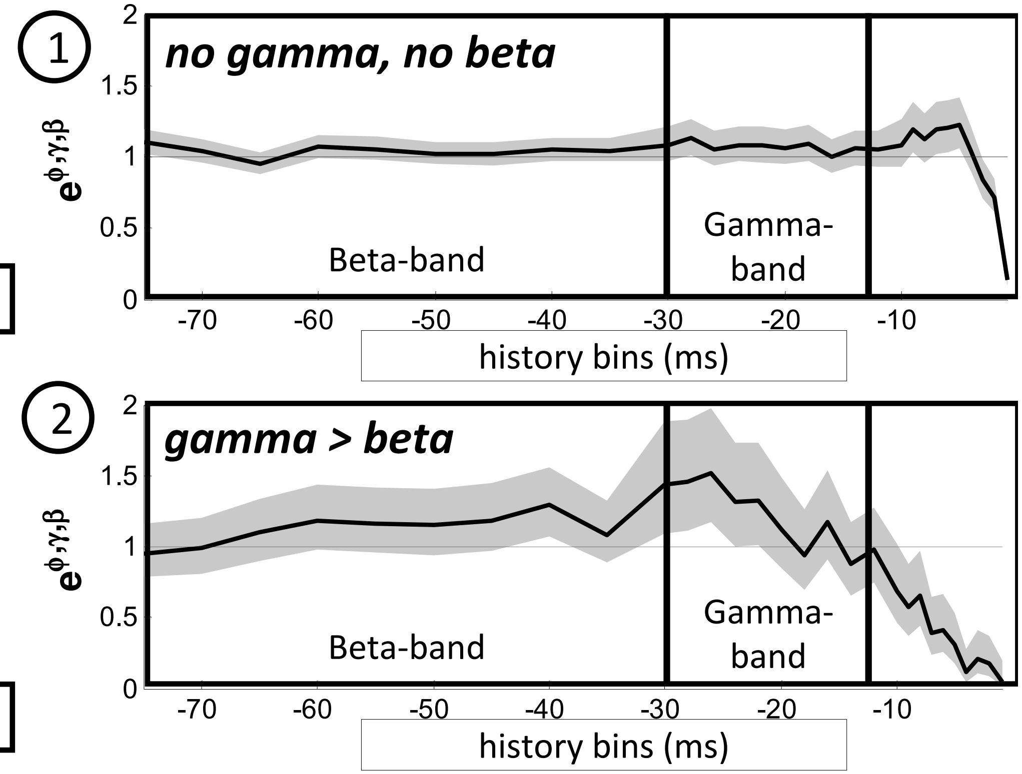




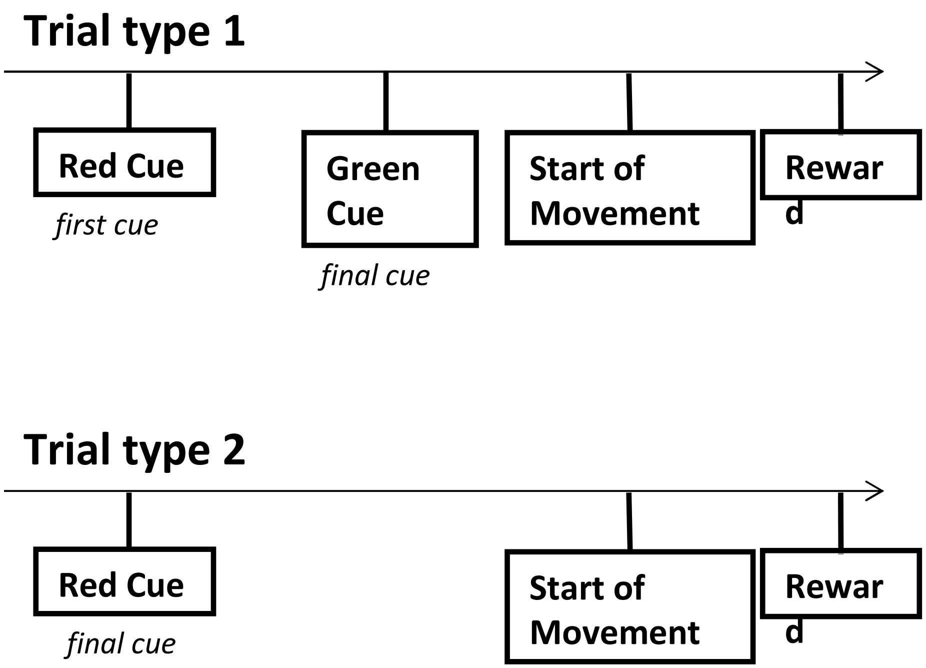
Trial type 2

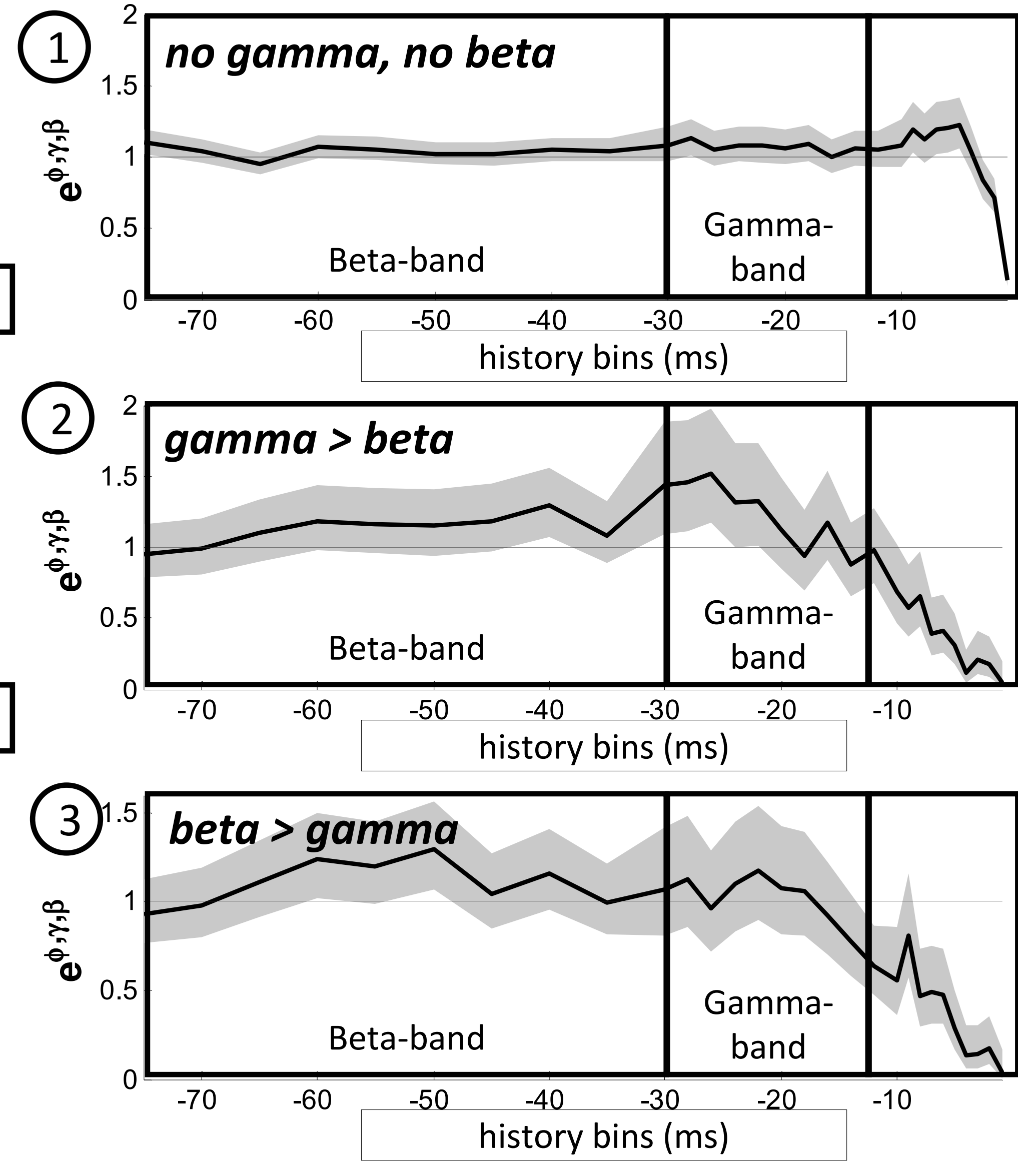
Determining Cross-Over Effect





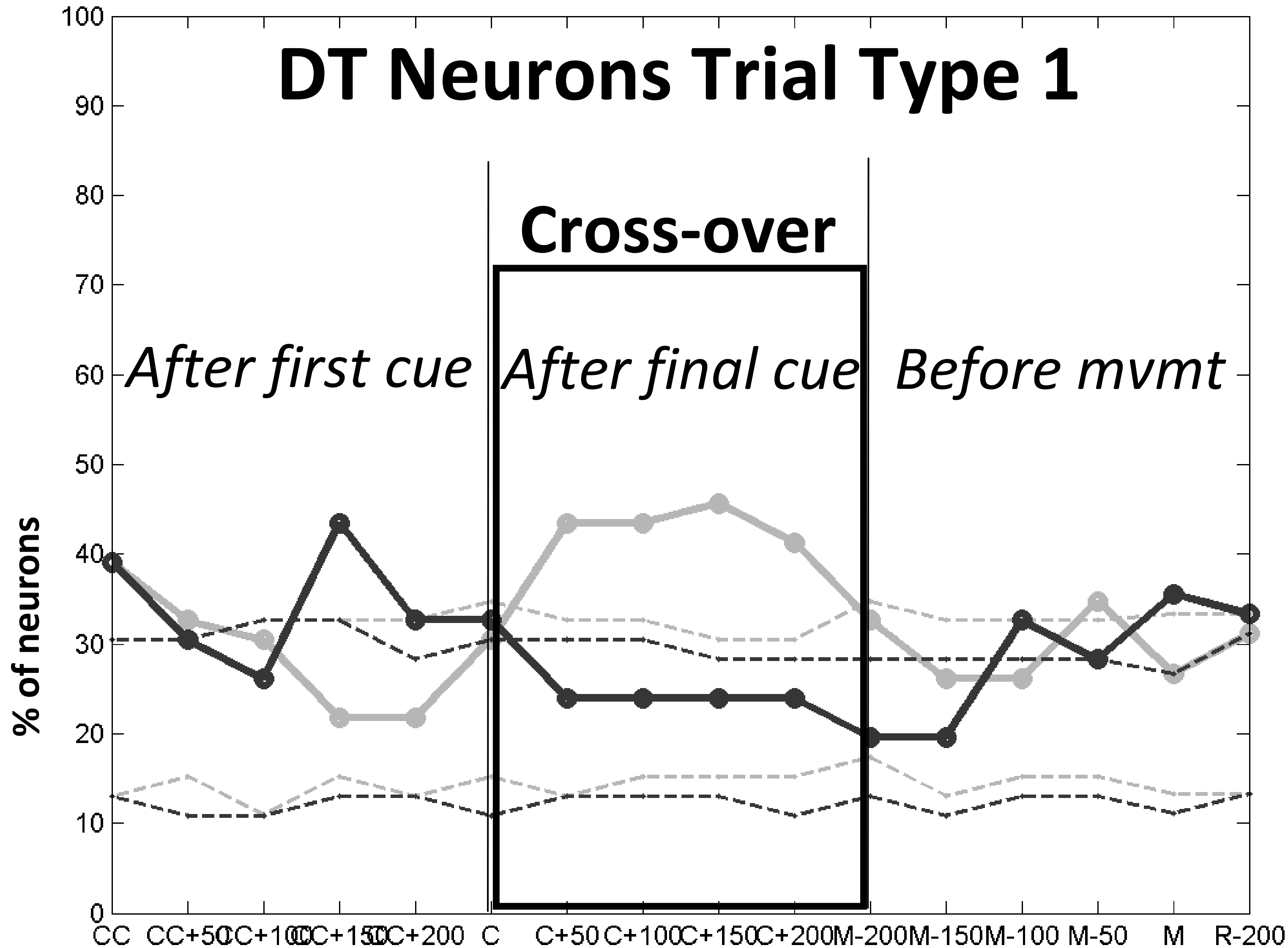
Determining Cross-Over Effect





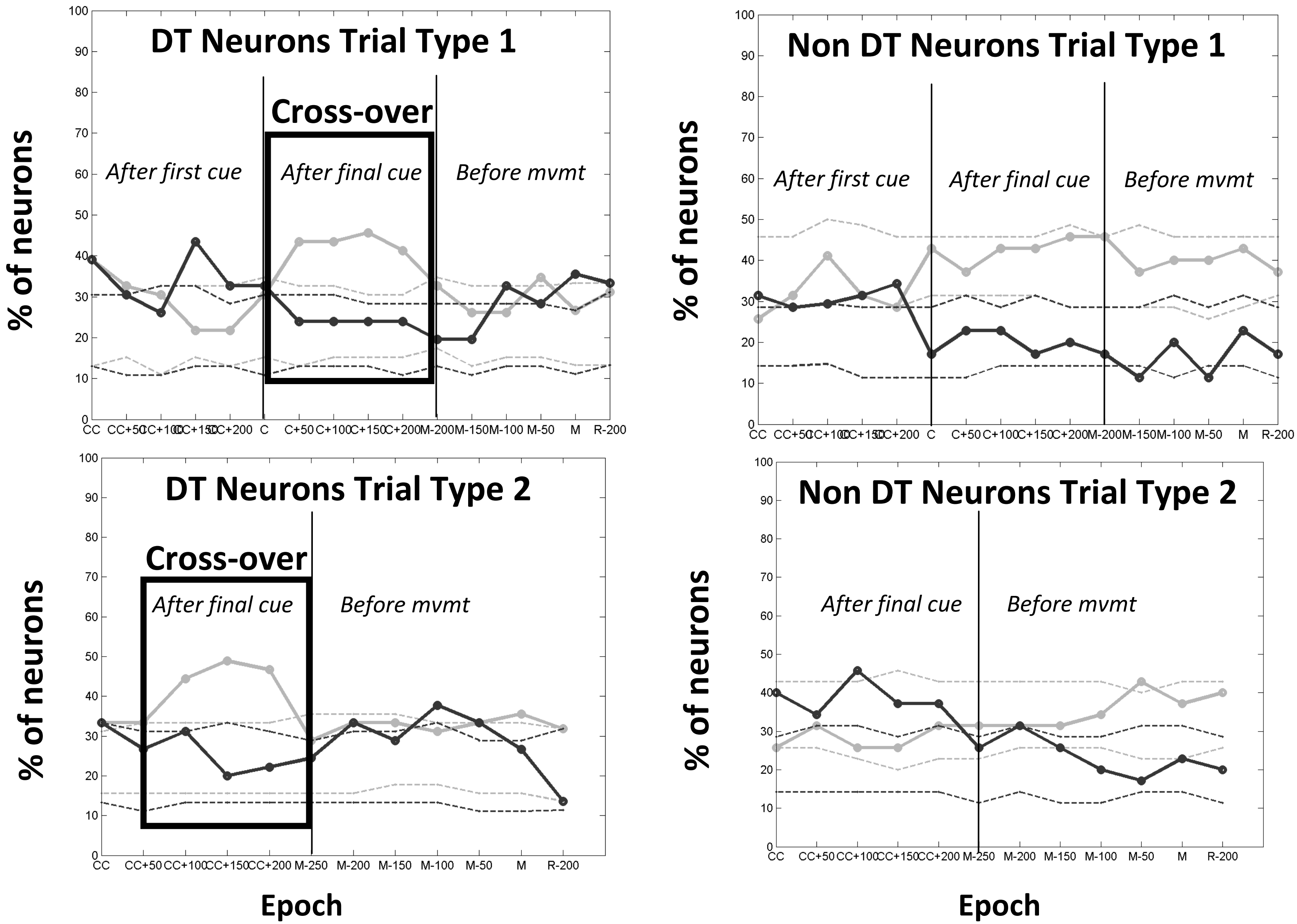
Results

gamma > beta
beta > gamma



Results

gamma > beta
beta > gamma

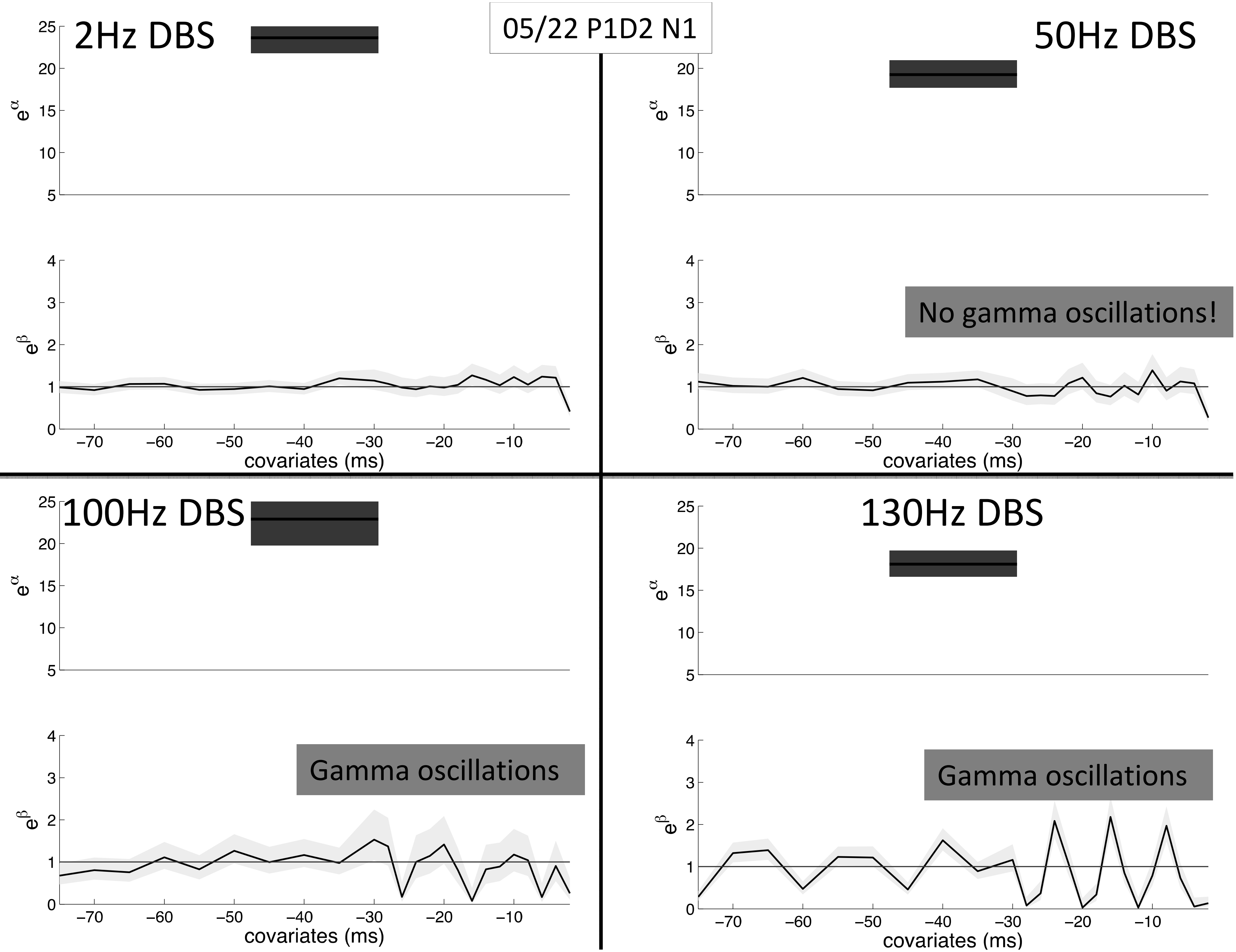


Summary

- A cross-over effect is seen only in the task specific, i.e. directionally tuned neurons during the planning of movement.

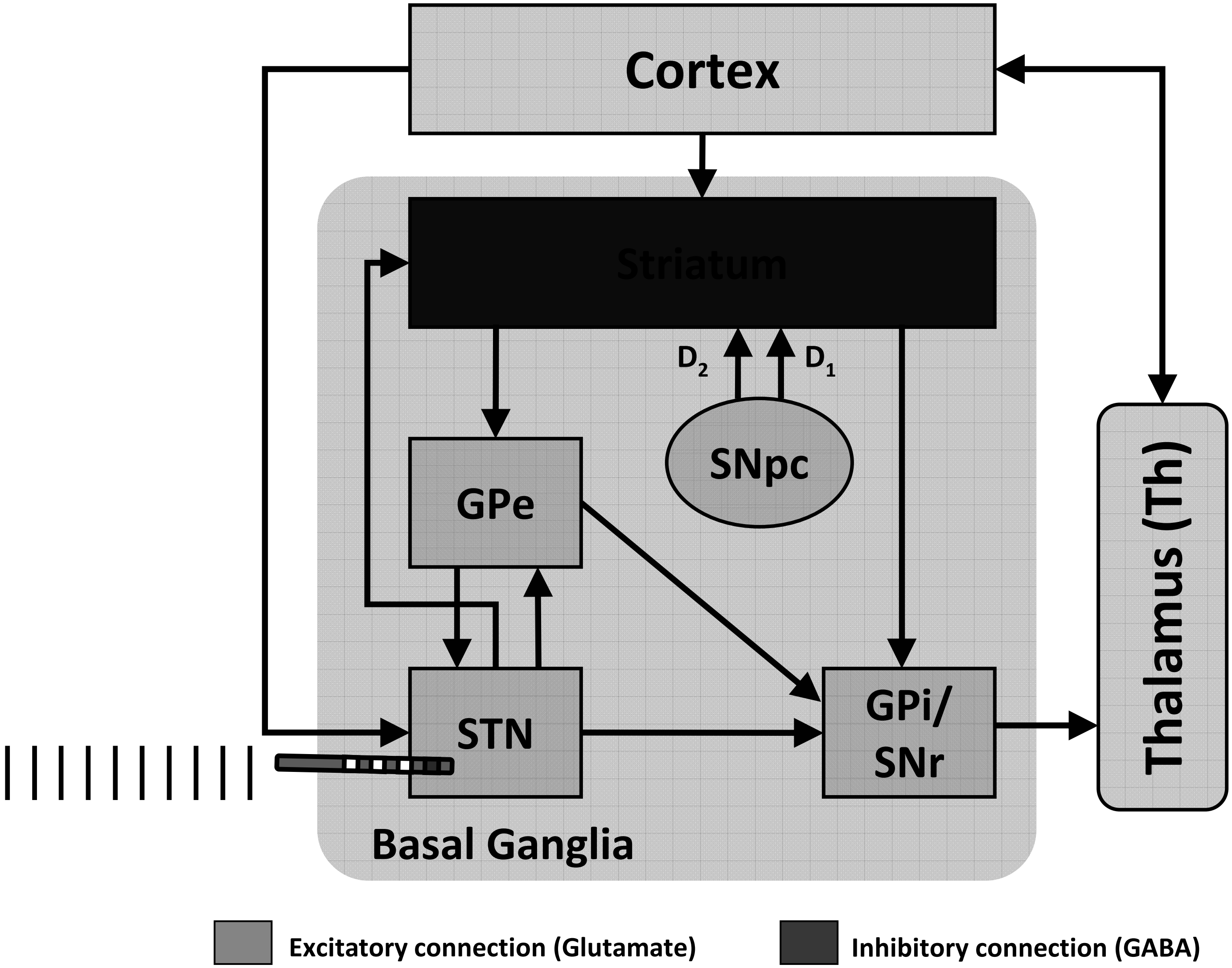
- This is an indication that a cross-over effect (suppression of beta and emergence of gamma oscillations) may be a mode of communication in GPi, encoding the planning of a movement.

H3: Crossover phenomenon is facilitated in GPi with HF DBS applied to STN.

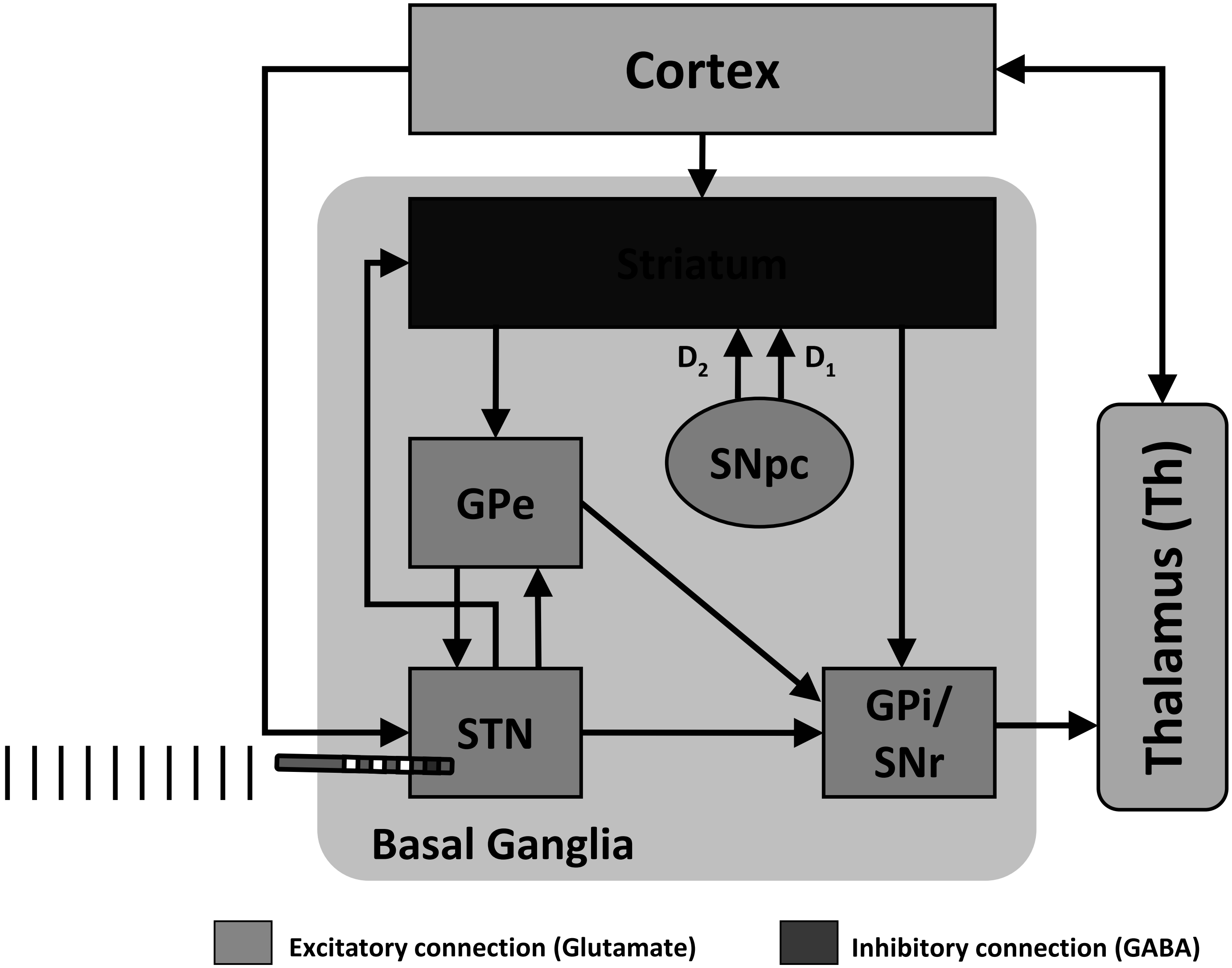

05/22 P1D2 N1
2Hz DBS
50Hz DBS
100Hz DBS
130Hz DBS
No gamma oscillations!
Gamma oscillations
Gamma oscillations
e^{α}
e^{β}
covariates (ms)

Appendix

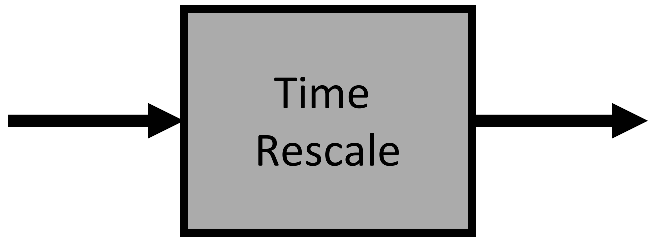
Striatum responses to STN DBS



Reinforcement Hypothesis

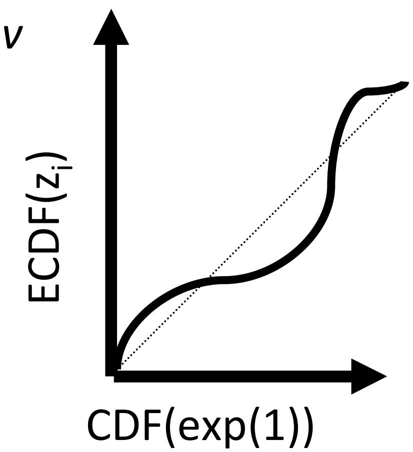


Methods: Model Evaluation



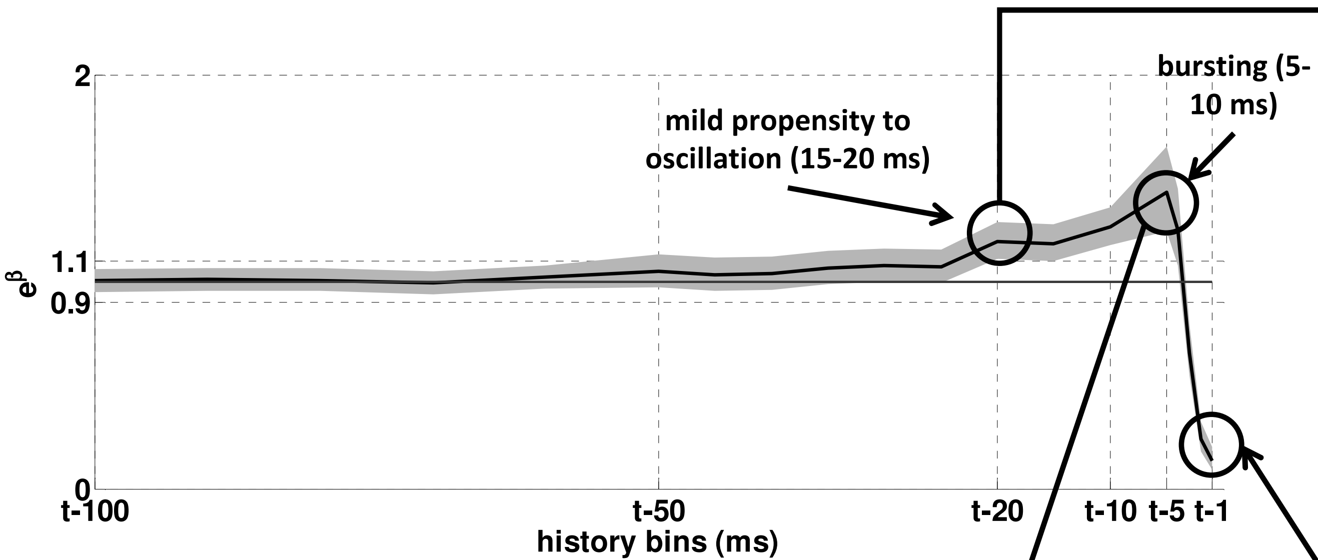
Time-Rescaling Theorem: z_i's are i.i.d. exponential rate 1

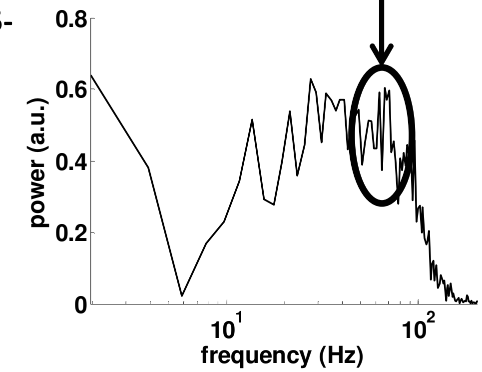
Kolmogorov-Smirnov (KS) Plot:



In our analysis, only neurons whose KS-plot after time rescaling was within the 95% confidence interval were included and inferences were conducted from their model parameters

Inferences from Model Parameters



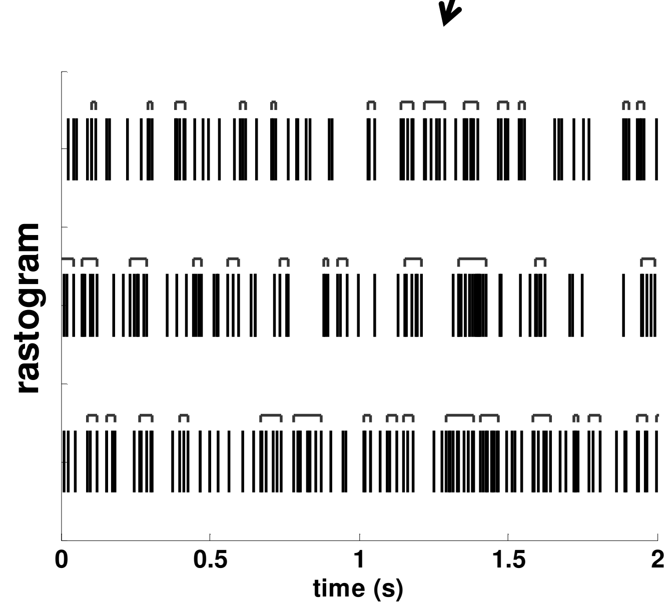


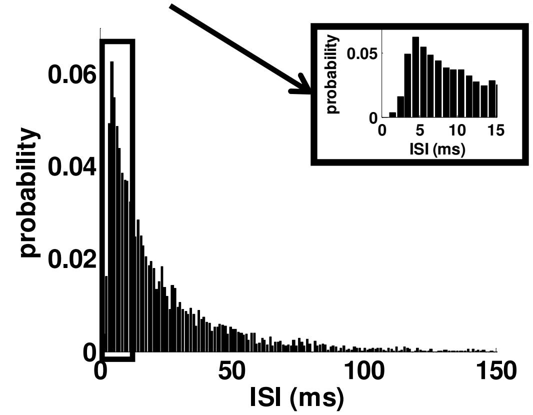
autocorrelation function (250 ms lag)
band-pass filtered (150 Hz)

Refractoriness: *a neuron shows refractoriness if UB(e^{β_i})<0.90 for at least 1 value of 1≤i ≤5. Depending on i, the refractory period is determined.*

Bursting: *a neuron shows bursting if LB(e^{β_i})>1.10 for at least 1 value of 3≤i ≤6 (i.e., 3-10 ms). Depending on i, the intra-burst average period is determined.*

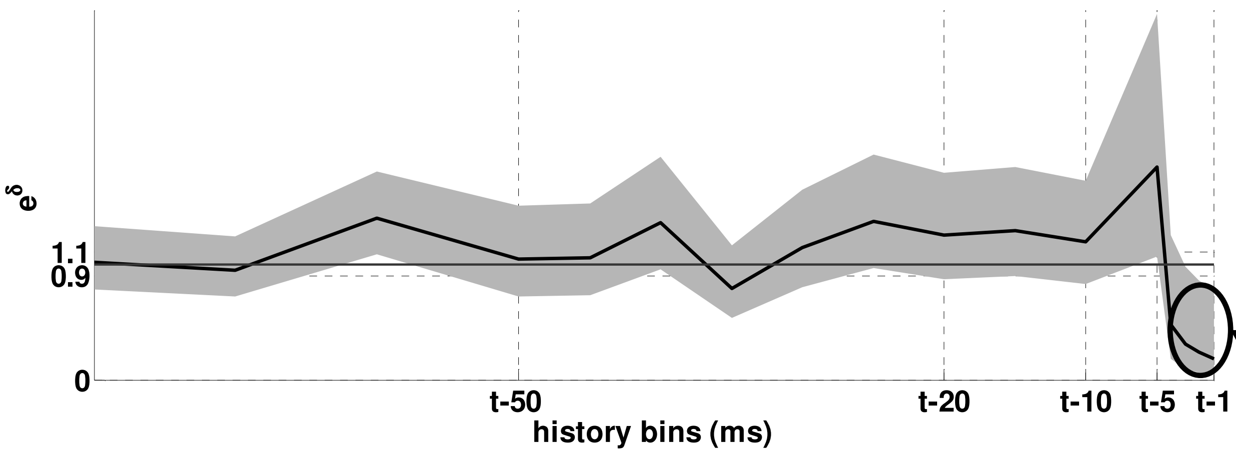
Oscillation: *a neuron shows an oscillation if LB(e^{β_i})>1.10 for at least 1 value of 7≤i ≤31 (i.e., 15-1000 ms). Depending on i, the oscillation period is determined.*

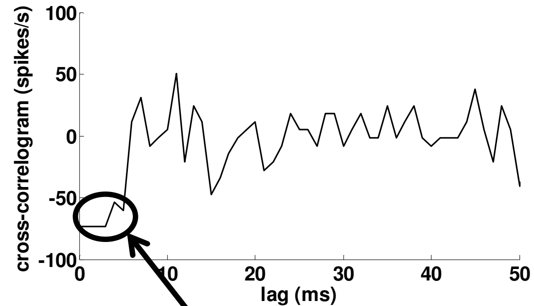




Bursts detected by applying the <u>Poisson Surprise Method</u> (Legendy & Salcman, J. Neurophysiol., 1985, 53:926). Intra-burst period is <u>7.95±0.004 ms</u> (mean±s.e.m.)

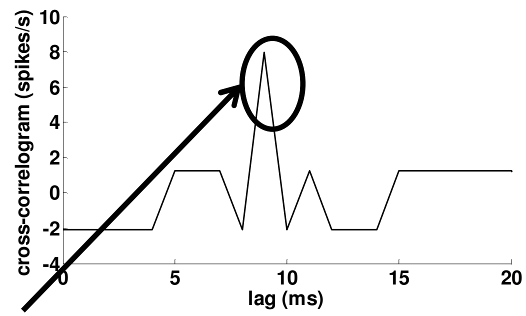
Inferences on Ensemble Effects

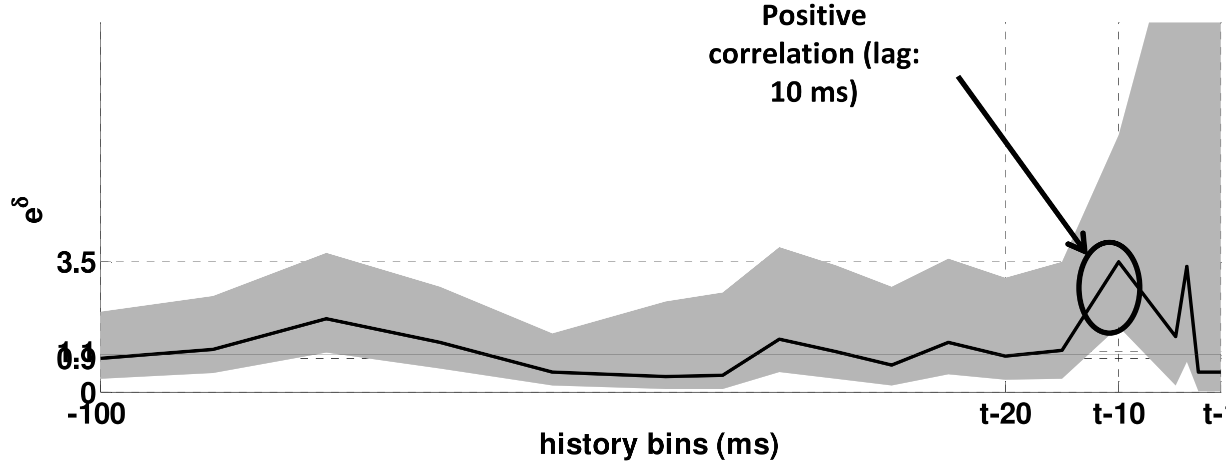




Inhibition: *a neuron n_1 is inhibited by another neuron n_2 in the same ensemble if UB($e^{\delta i,2}$)<0.90 for at least 1 value of 1≤i ≤5*

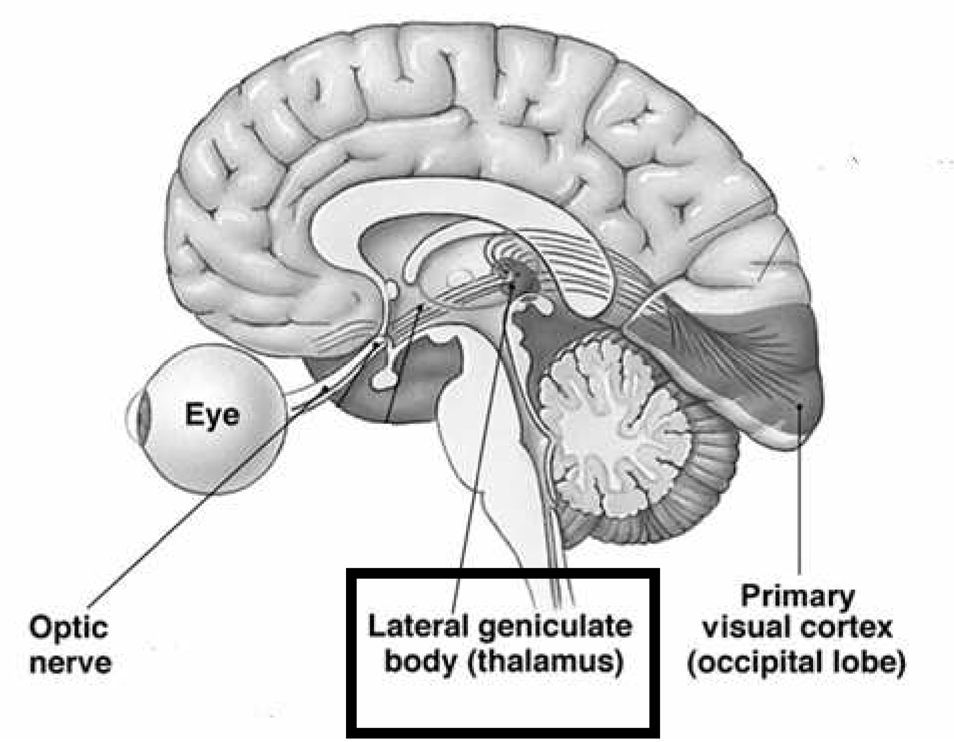
Positive correlation: *a neuron n_1 is correlated with another neuron n_2 in the same ensemble if LB($e^{\delta i,2}$)>1.10 for at least 1 value of 3≤i ≤31. Depending on i, the lag of the correlation is determined*





Application to Visual System

- LGN
  - Driver input from retina
  - Modulating Input from Layer 6 of cortex and brain stem
  - Function is to strategically relay information



- Modulating Input
  - Ensemble synaptic activity on a LGN neurons
  - **Major contributor to local field potentials (LFPs) recorded in LGN (Logothetis2002)**

http://www.colorado.edu/intphys/Class/IPHY3430-200/image/10-29.jpg

Cont…

- LFPs in LGN[1]
  - **Delta rhythms ->deep sleep**
  - **Alpha rhythms -> awake and naturally behaving cats**
  - **Gamma rhythms -> high attentional tasks**

Increased attention

Increased LFP frequency

Increased modulating input frequency

1 Hughes S W, Lorincz M, Cope D W, Blethyn K L, Kekesi K A, et al. (2004) Synchronized oscillations at α and θ frequencies in the lateral geniculate nucleus. Neuron, Vol 42, 253268, April 22, 2004, .