Firing Patterns in the Subthalamopallidal Network

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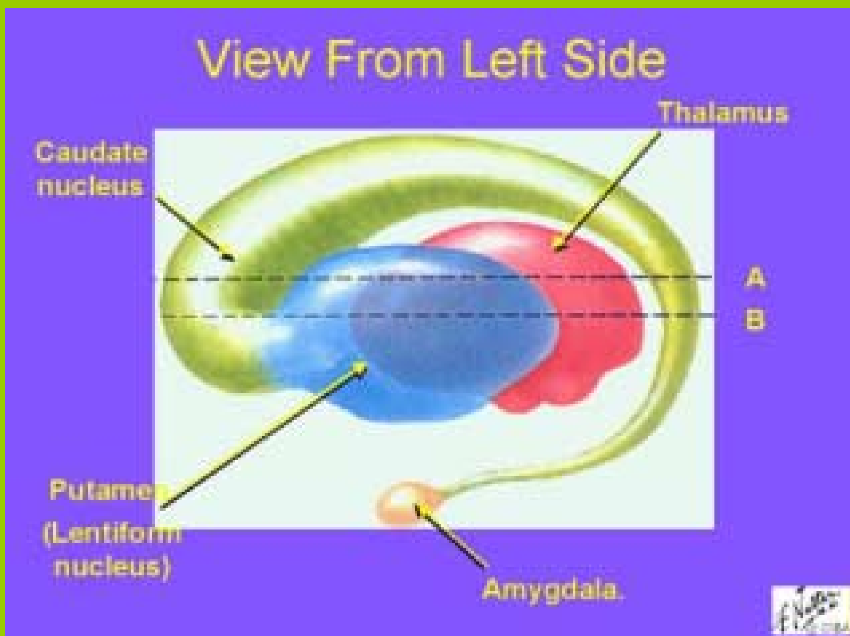
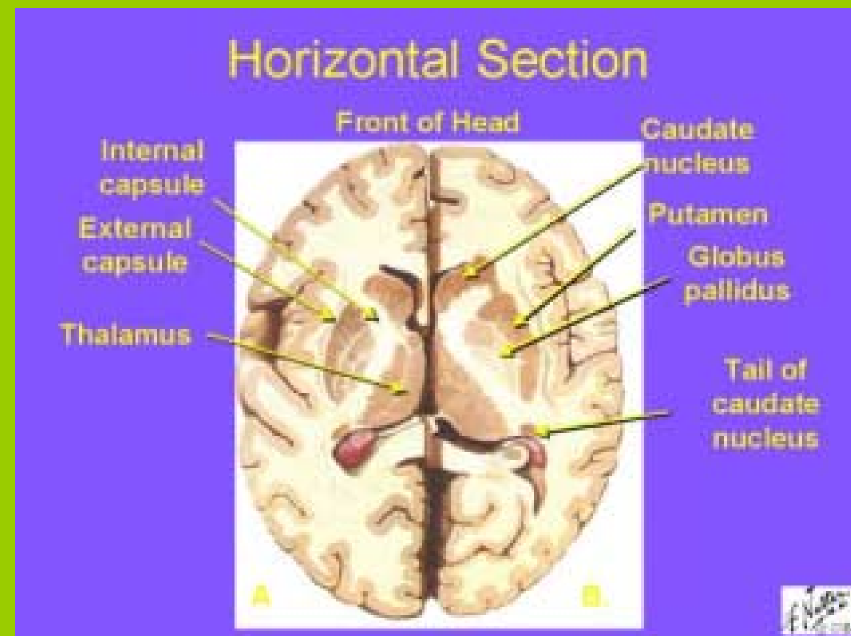
BASAL GANGLIA





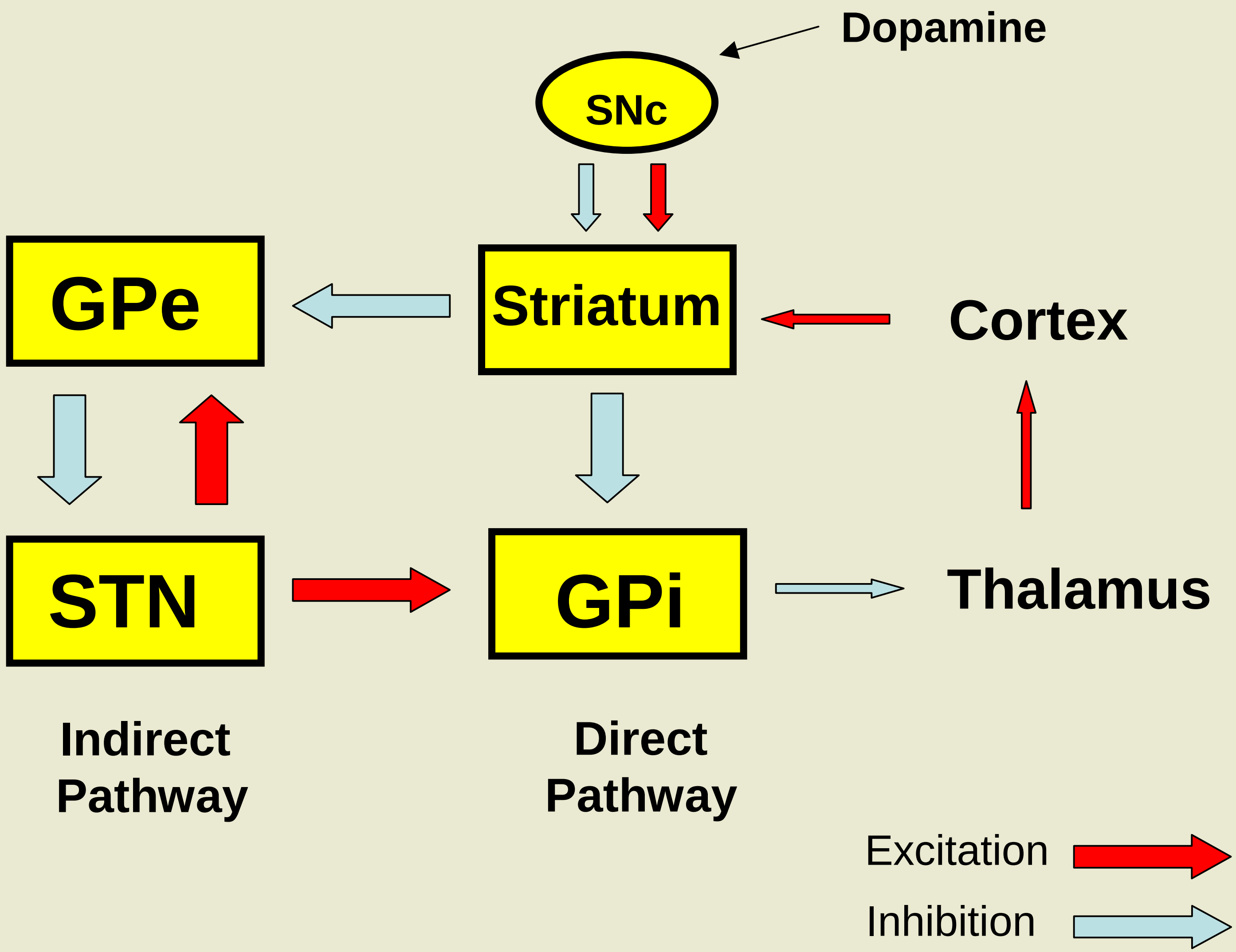
BASAL GANGLIA

- Involved in the Control of Movement
- Dysfunction Associated with Parkinson's and Huntington's Disease
- Site of Surgical Procedures
  -- Deep Brain Stimulation (DBS)

Motivation of Computational Study

- Previous Models for Neuronal Activity in BG are Static, Based on Mean Firing Rate.
- Recent Experiments have Shown that Pattern of Neuronal Activity may be Important.
- During PD, Neurons Display:
  - Increased Synchrony
  - Increased Bursting Activity
- Earlier Models do not Explain Tremor.
- Mechanism Underlying DBS Mysterious.

BASAL GANGLIA



Note: Other Pathways May Be Important

Parkinson's Disease

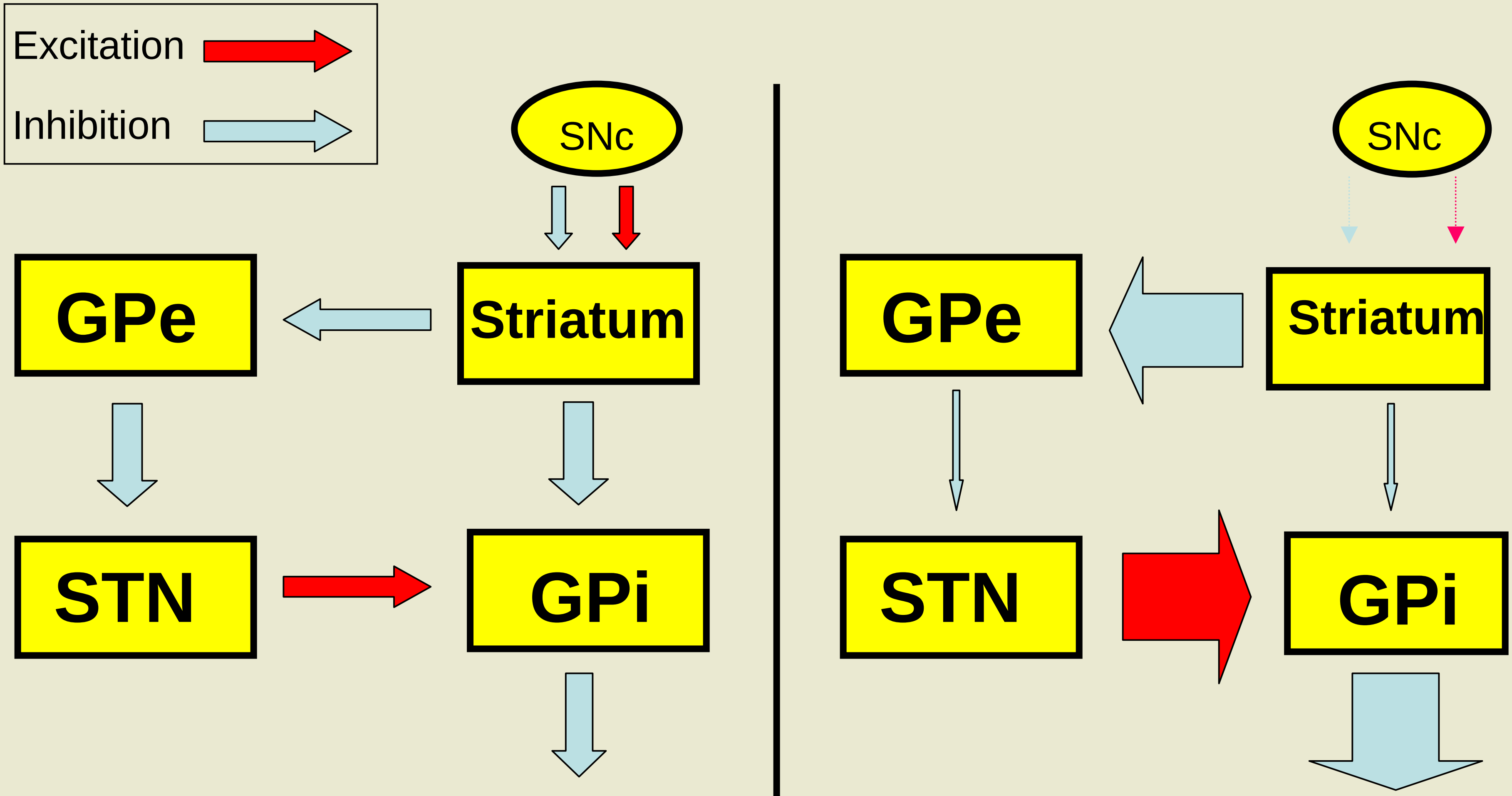
- *Movement Disorder*
  - Slowness of Movement
  - Inability to Initiate Movement
  - Rigidity
  - Tremor
- *Reduction of Dopamine*
- *Increased Activity in Output Nuclei*

Parkinson's Disease

- *Movement Disorder*
  - Slowness of Movement
  - Inability to Initiate Movement
  - Rigidity
  - Tremor
- *Reduction of Dopamine*
- *Increased Activity in Output Nuclei*

QUESTION: How Does the Loss of Dopamine Lead to Increased Activity in Output Nuclei?

Standard Theory (Albin / DeLong)



Normal

Parkinsonian

- ***Problems With The Standard Theory***
  - **Does Not Explain Tremor**
  - **Unclear if GPe Activity Decreases in Parkinsonian State**
  - **Lesions alleviate hyperkinetic disturbances**

- ***Problems With The Standard Theory***
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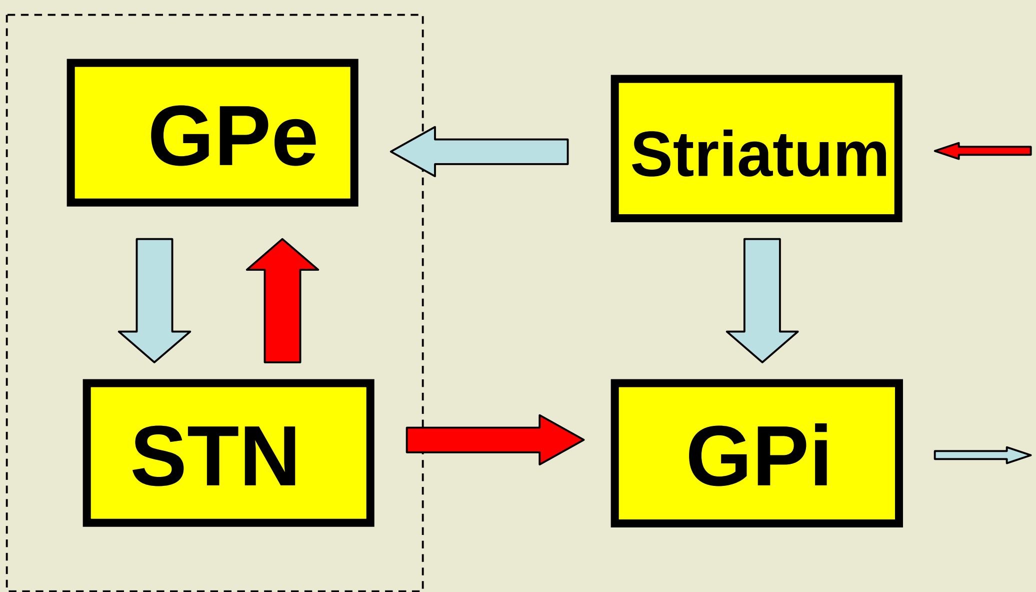
- ***Possible Explanations***
  - **Only Considers Mean Firing Rate**
  - **Role of Inhibition/Excitation More Complicated**
  - **Pattern of Activity May Be Important**
  - **Synchronization**

Experimental Results

- **Neurons Display Increased Synchrony During Parkinsonian State**
- **Isolated GPe/STN Network Can Generate Synchronous Rhythms** (Plenz,Kitae – slow rhythm)



MODELING STUDY

(T., Rubin, Yew, Wilson)

- Construct Model GPe/STN Network.
- Can Such a Network Generate Synchronous, Tremor-Like Rhythms?
- What Other Activity Patterns Arise?
- Reinterpret Role of Indirect Pathway.

MODEL STN NEURON

$$C_M \frac{dV}{dt} = -I_L - I_K - I_{Na} - I_T - I_{AHP} - I_{Ca}$$

$$I_L = g_L(V - V_L), \qquad I_K = g_K n^4 (V - V_K),$$

$$I_{Na} = g_{Na} m^3(V)(V - V_{Na}), \quad I_T = g_T a_\infty^3(V) b_\infty^2(r)(V - V_{Ca}),$$

$$I_{Ca} = g_{Ca} s_\infty^2(V)(V - V_{Ca}), \quad I_{AHP} = g_{AHP} \frac{[Ca]}{[Ca] + k}(V - V_K)$$

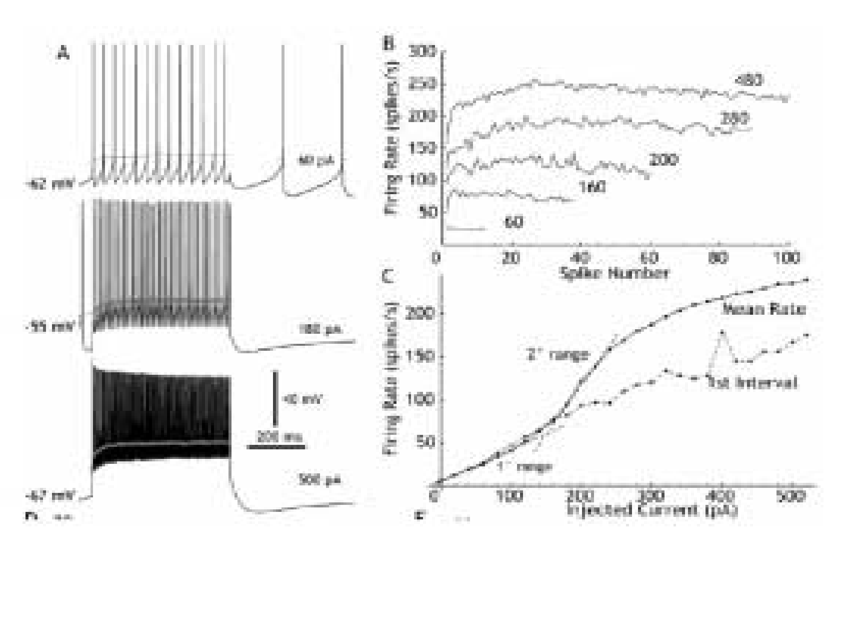
$$X' = \phi_X \left(\frac{X_\infty(V) - X}{\tau_X(V)} \right), \qquad X = n, h, r$$

$$[Ca]' = \epsilon(-I_{Ca} - I_T - k_{Ca}[Ca])$$

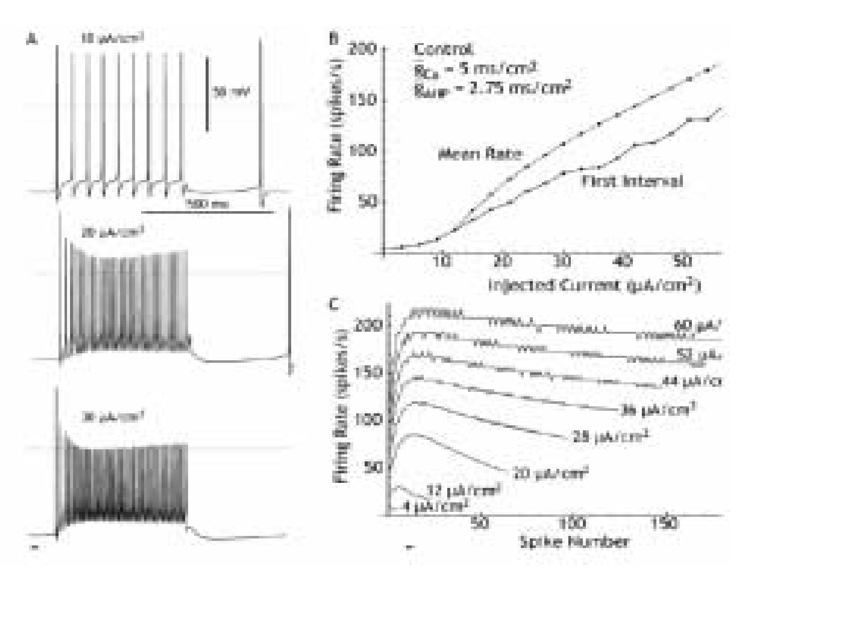
Based on Experiments
(Bevan and Wilson)

Firing Properties of STN Cells

Experiment

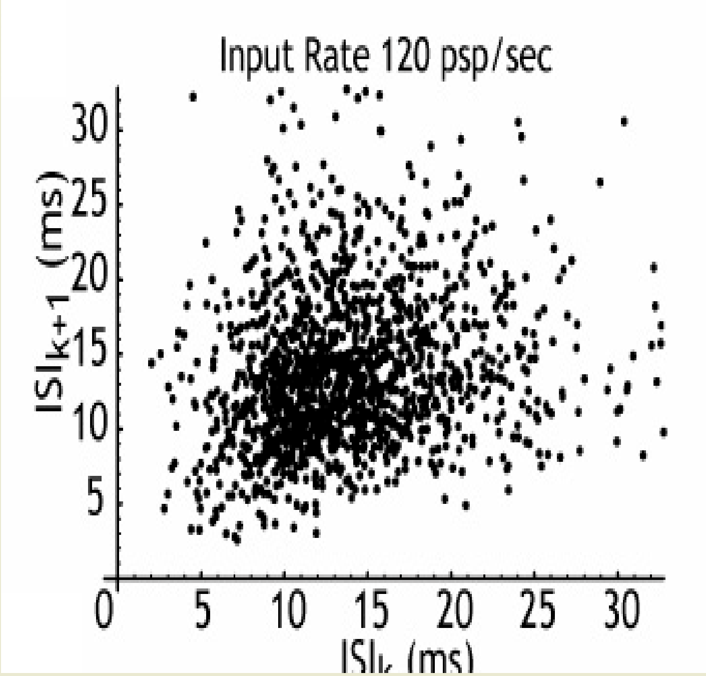


Model

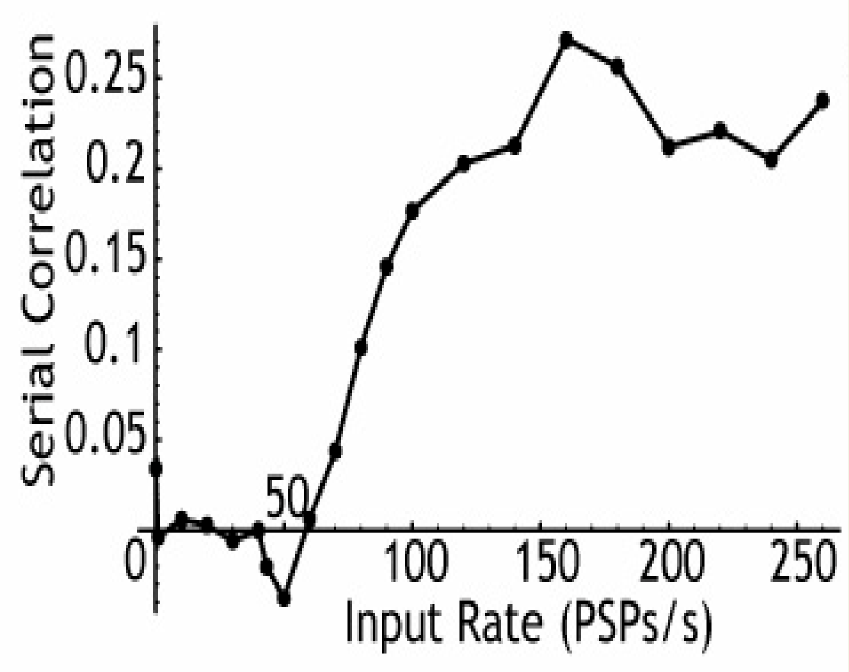


- **High Frequency Firing with Applied Current**
- **Secondary Range in F-I Curve**
- **Reverse Spike Frequency Adaptation**

Reverse Spike Frequency Adaptation Leads to Increased Correlation of Incoming Signal



First Return Map for ISIs



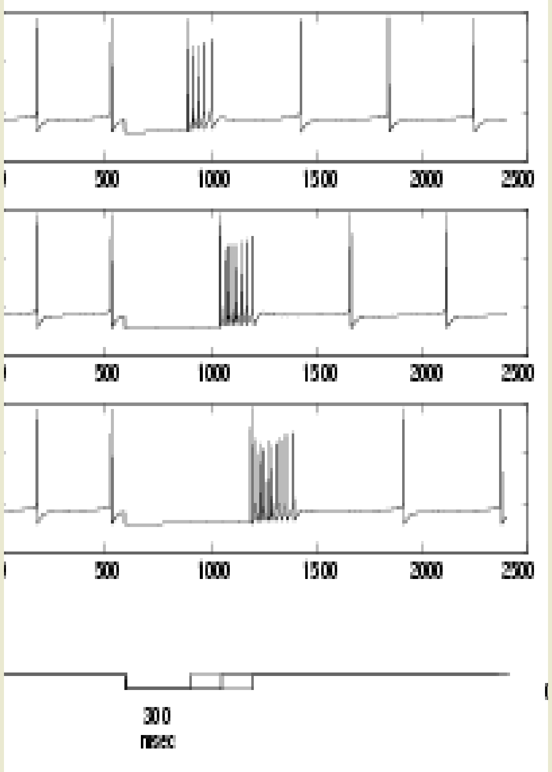
Serial Correlation

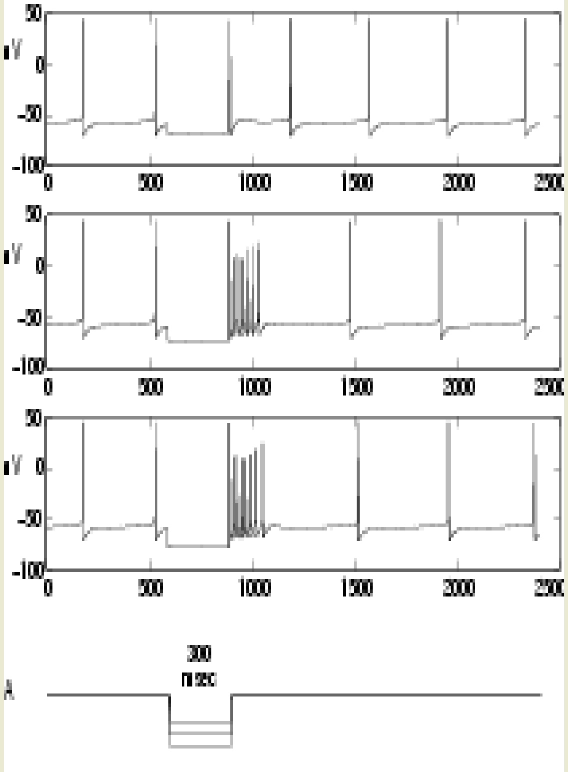
(Wilson, Weyrick, T. ,Hallworth, Bevan)

Firing Properties of STN/GPE Neurons

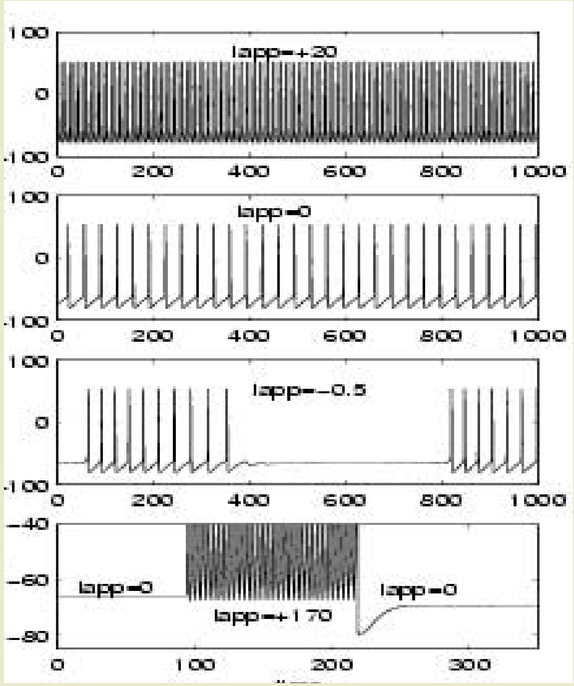
STN

GPE



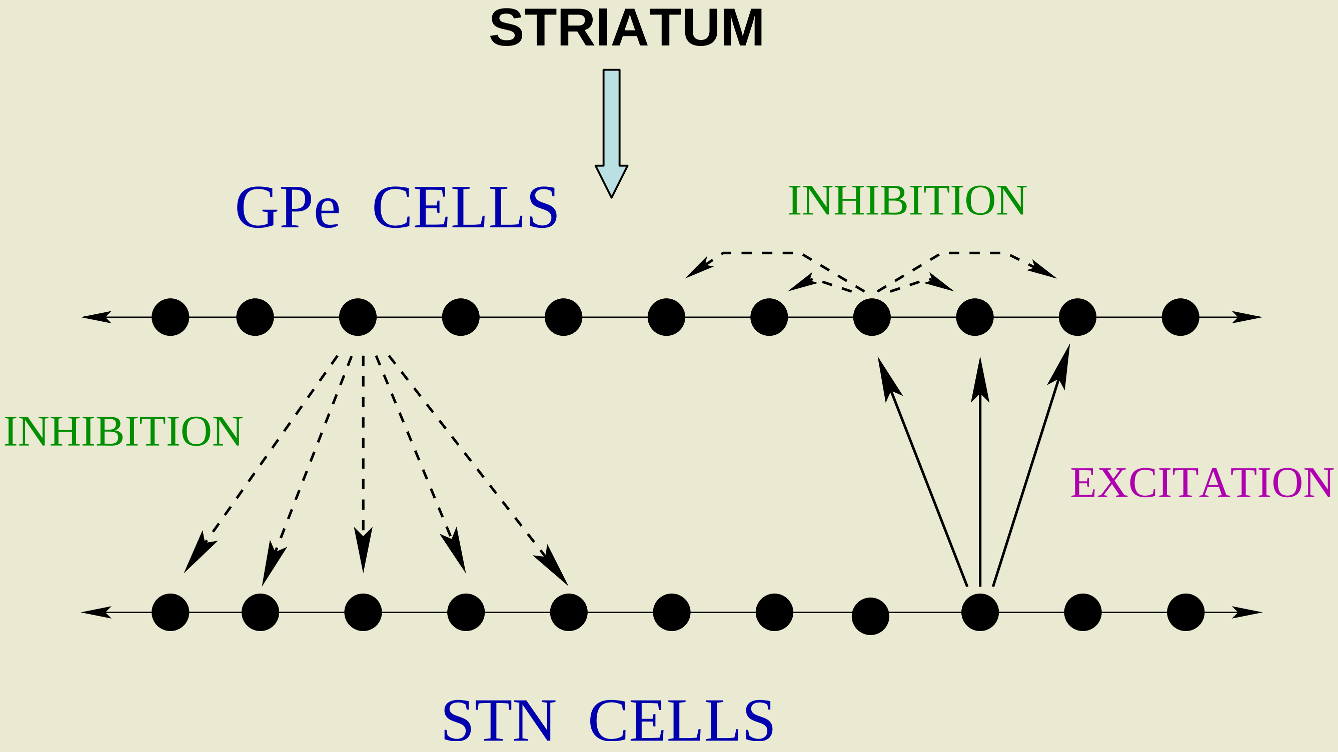


Post Inhibitory Rebound

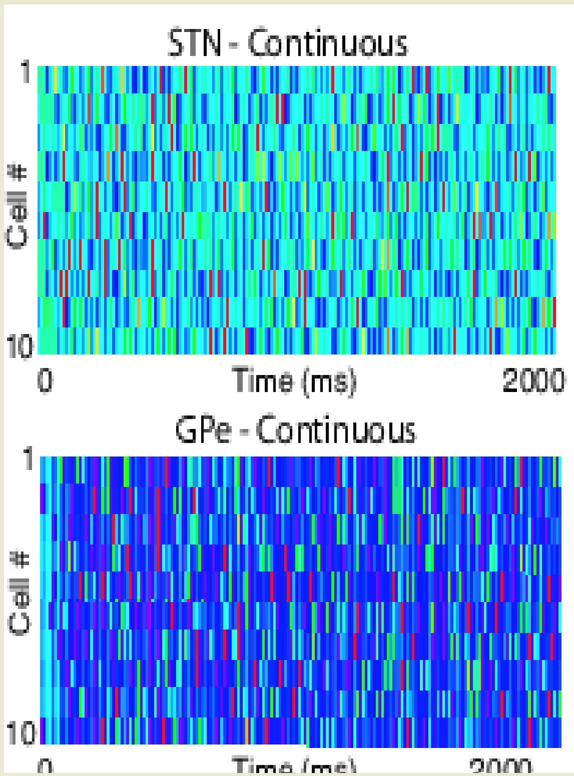


Firing Profiles

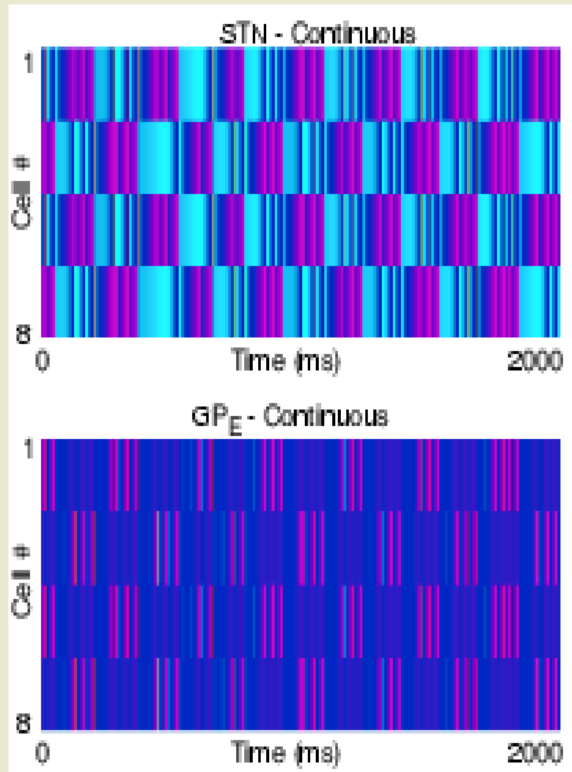
STN / GPe NETWORK



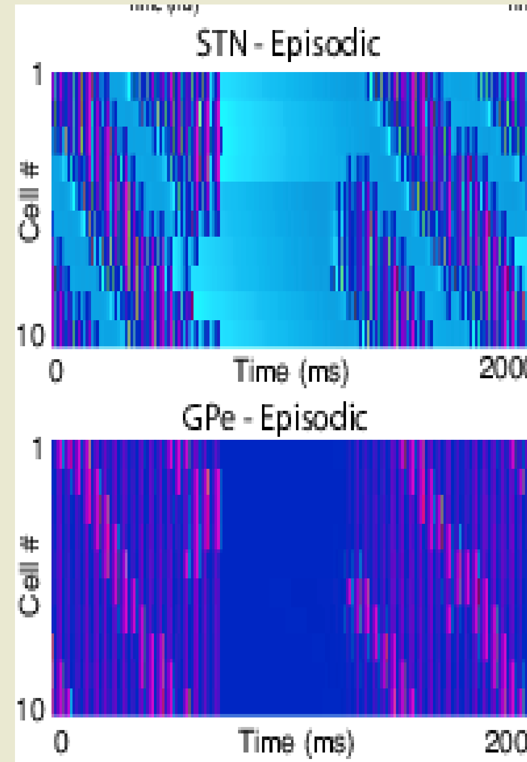
The Model Exhibits a Variety of Activity Patterns



Irregular
(Normal)

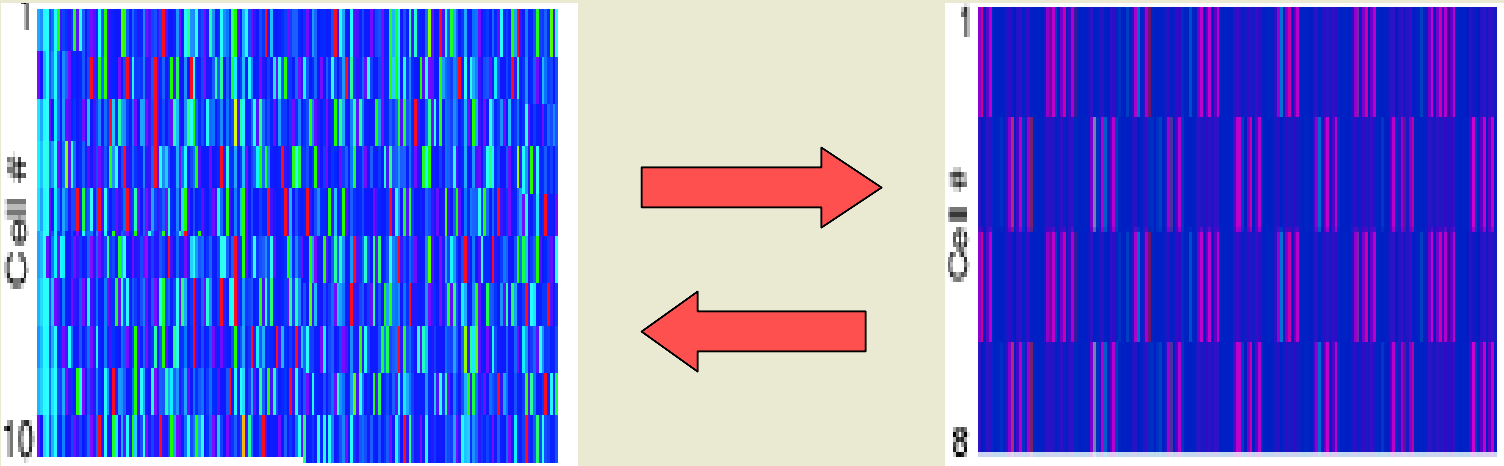


Synchronous
Clusters (Park)



Propagating
Waves

Transition between Irregular and Rhythmic Activity



Irregular (Normal)

Clustering (Parkinson)

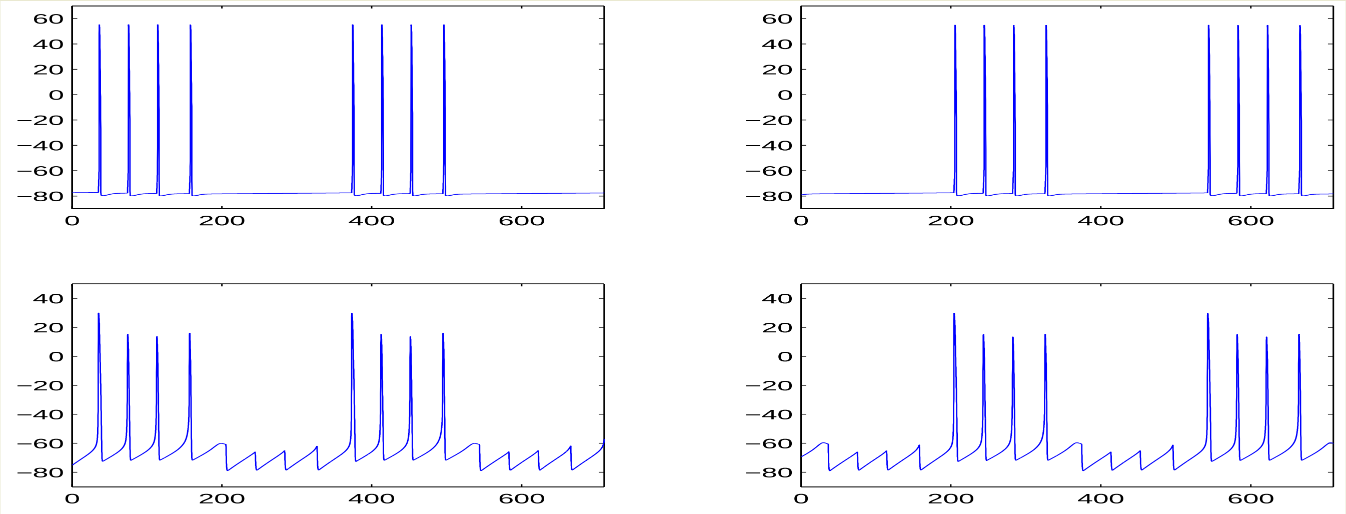
- **What Parameter Changes Can Account for this Transition ?**
- **Can This Transition Arise Due to Rebound Properties of STN Cells ?**

(Best,Park,Wilson,T.)

Clustering

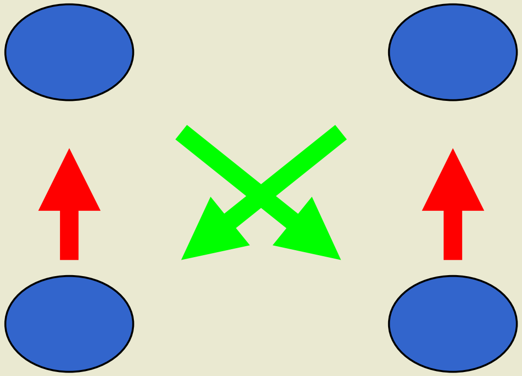
GPe

STN

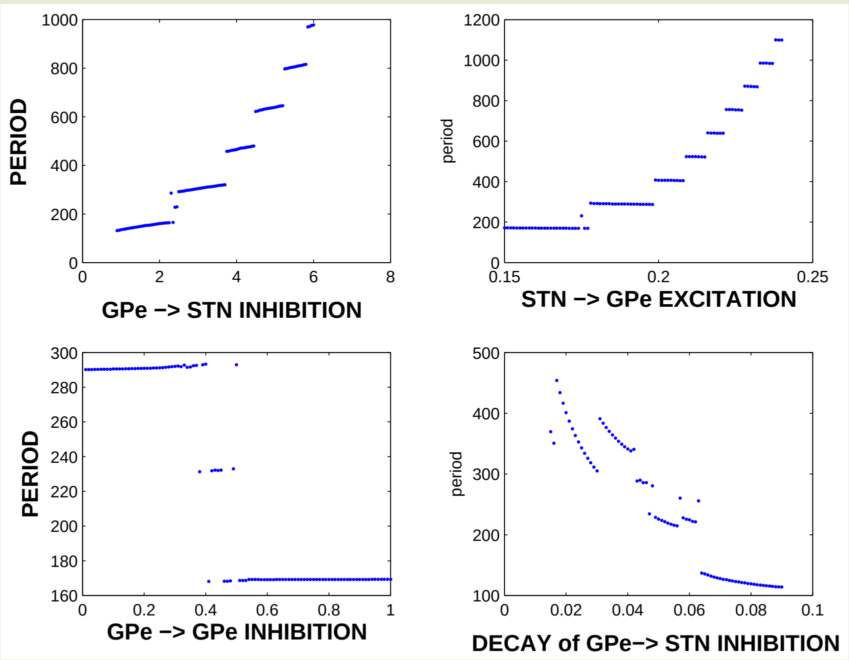


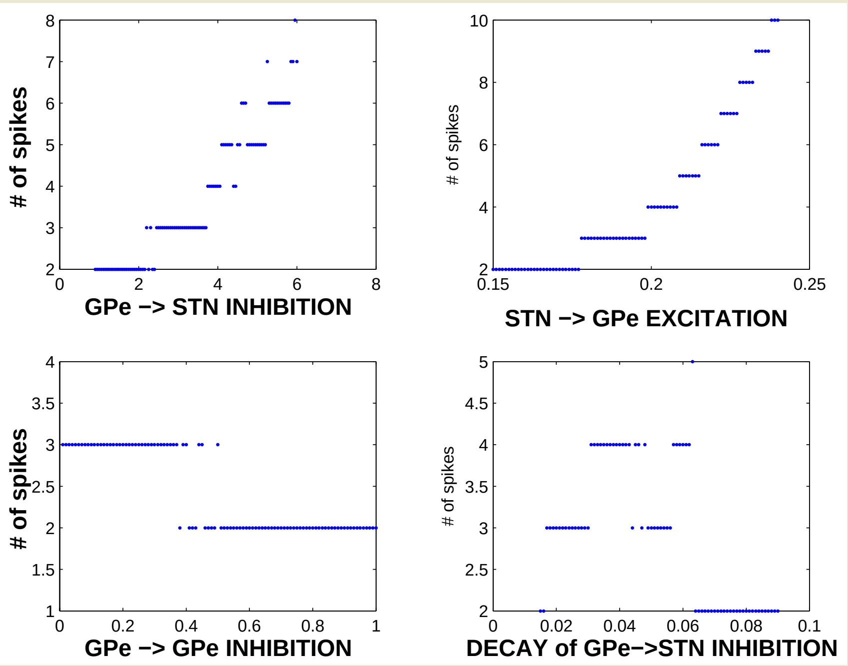
GPe Cell Fires due to Excitation from STN

STN Fires due to Post-Inhibitory Rebound



Dependence on Parameters

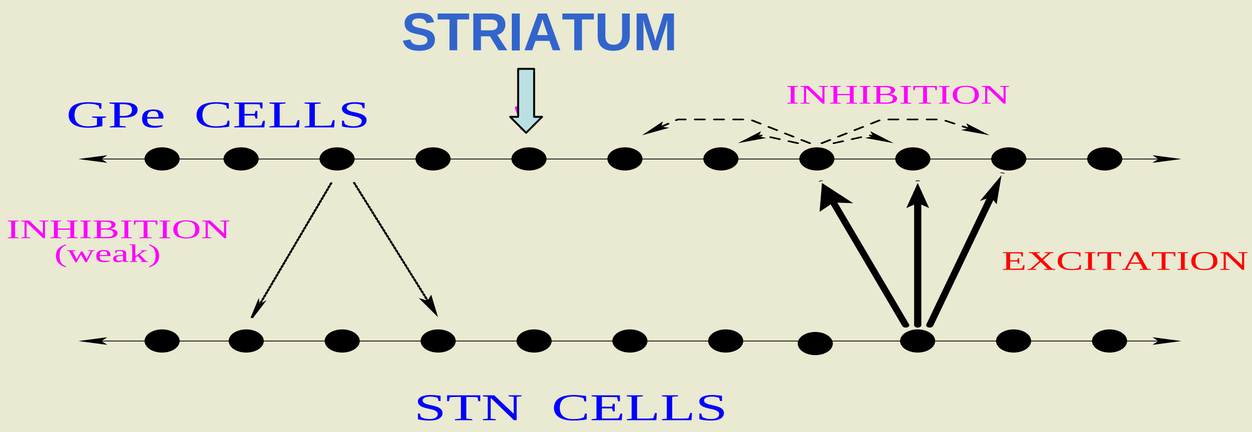


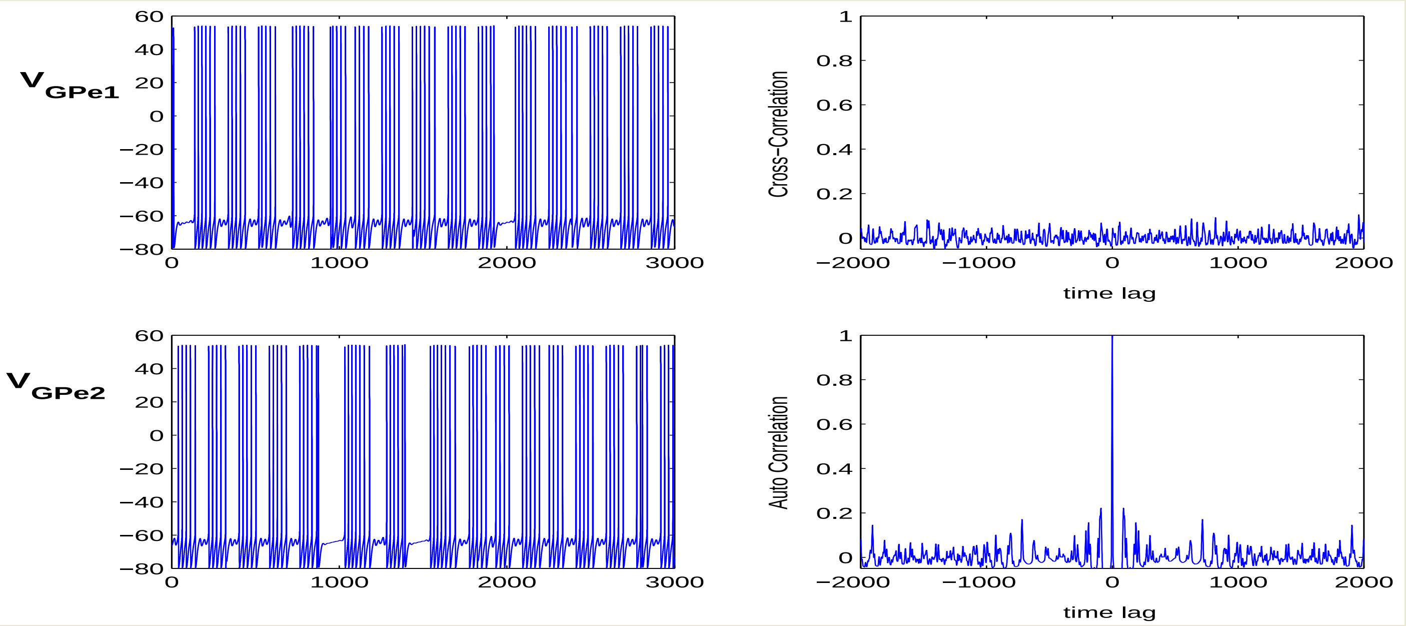


Period

 # Spikes / Cluster

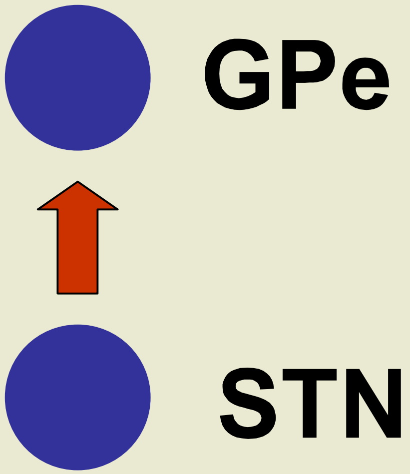
Irregular Firing Can Arise if Inhibition to STN Cells is Weak





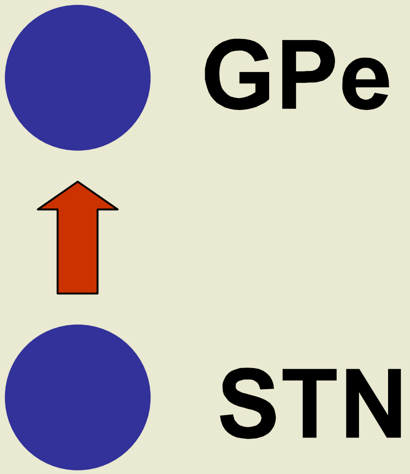
Analysis of Irregular Firing

Consider a Periodically Forced GPe Cell:



Analysis of Irregular Firing

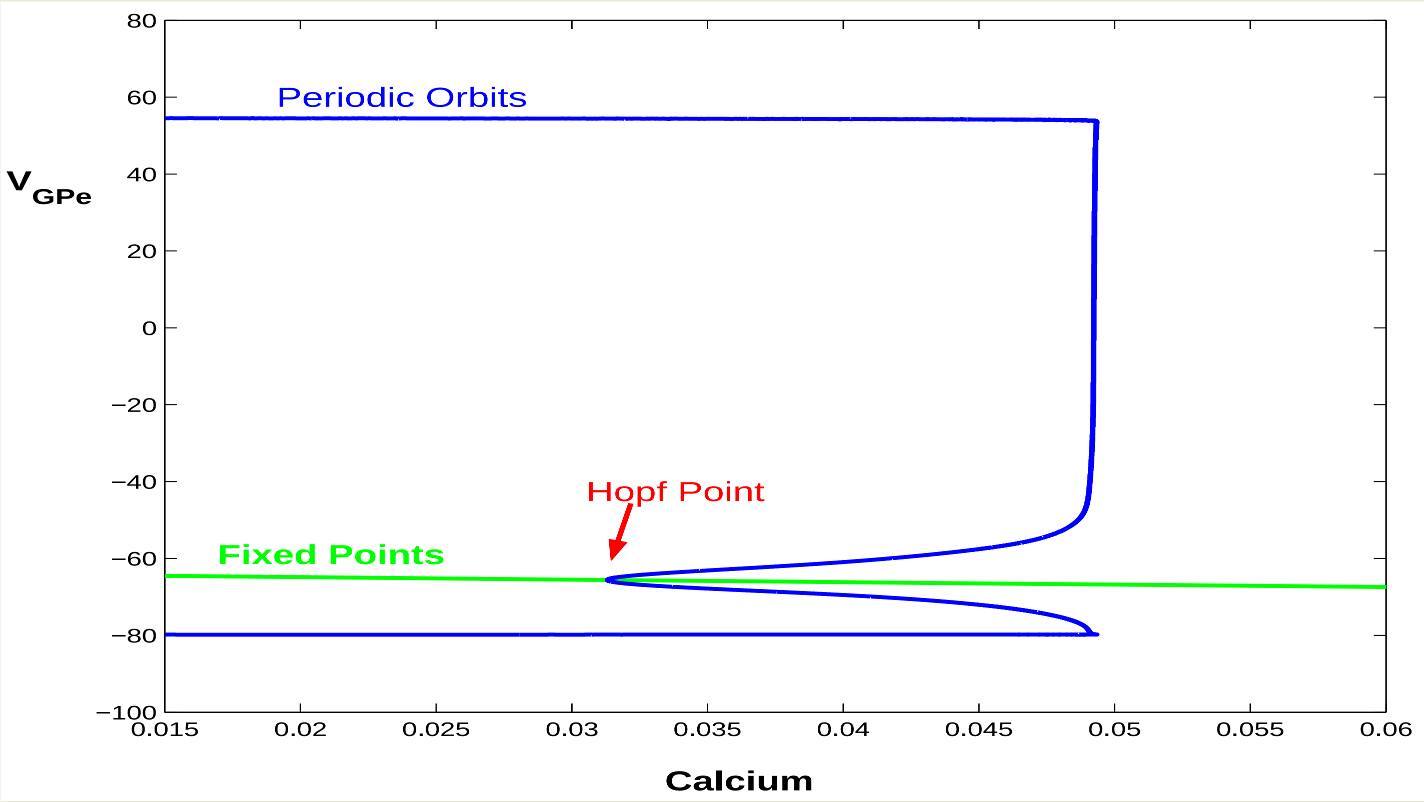
Consider a Periodically Forced GPe Cell:



OUTLINE of ANALYSIS

- Fast/Slow Analysis of GPe Cell
- Phase-Response Curve for GPe Cell
- Construct a 1-D Map

GPe Cells Are Elliptic Bursters



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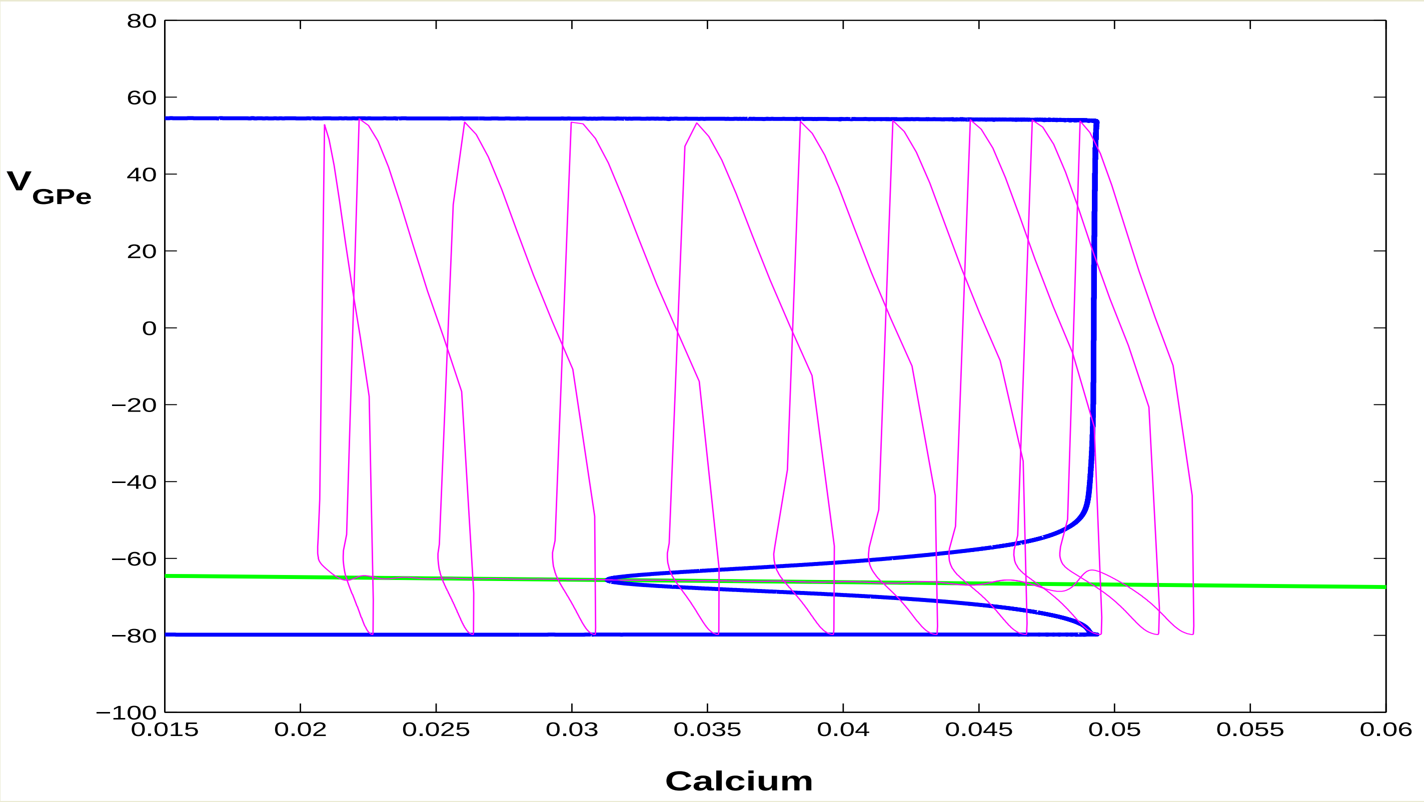

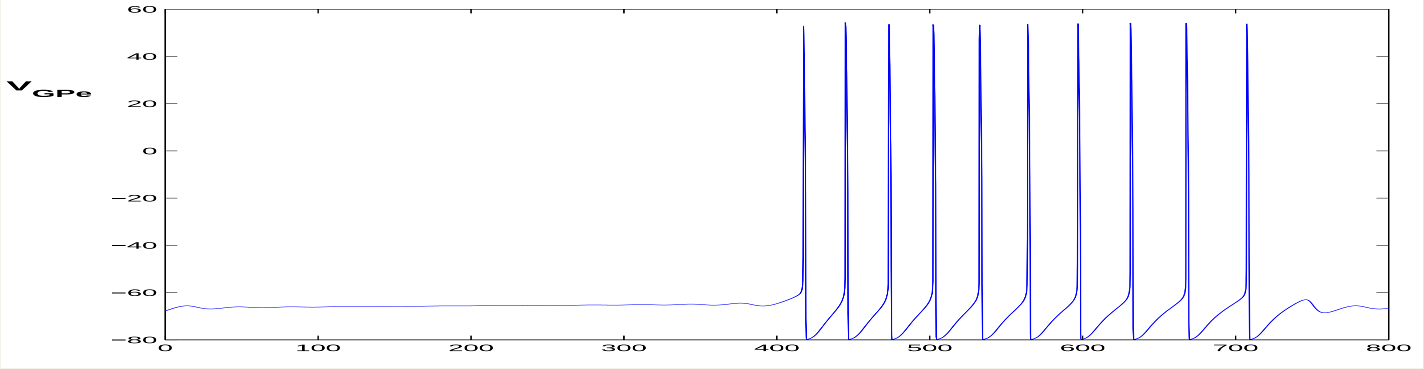

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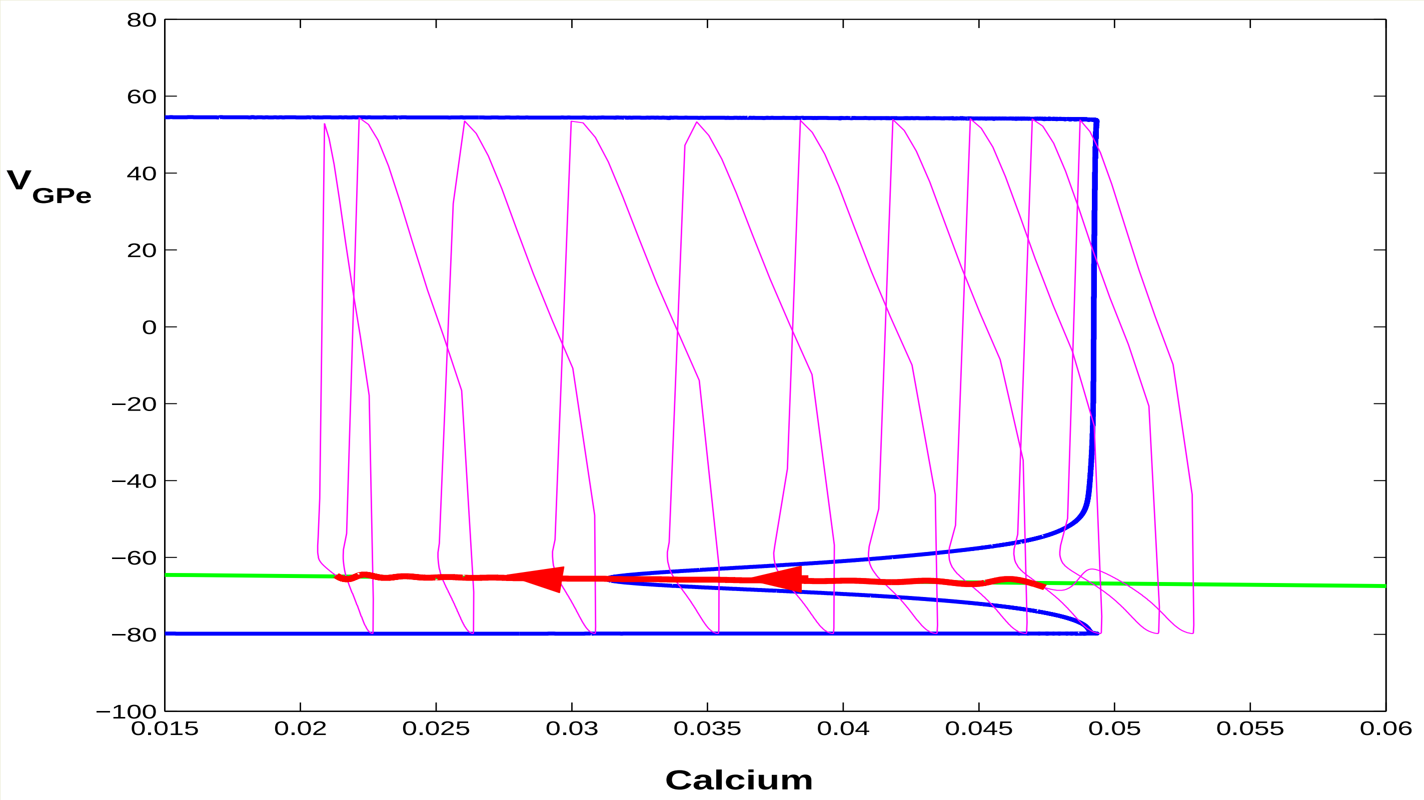

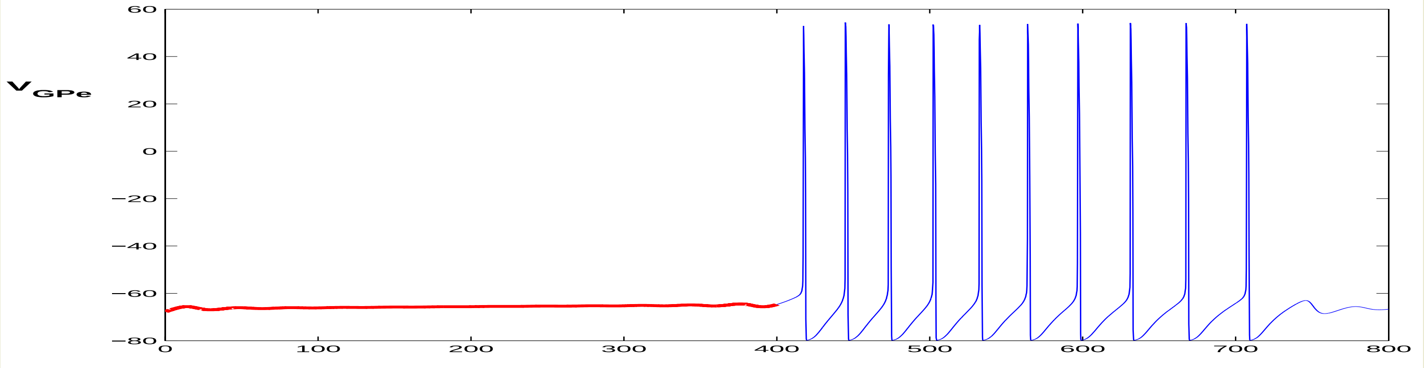

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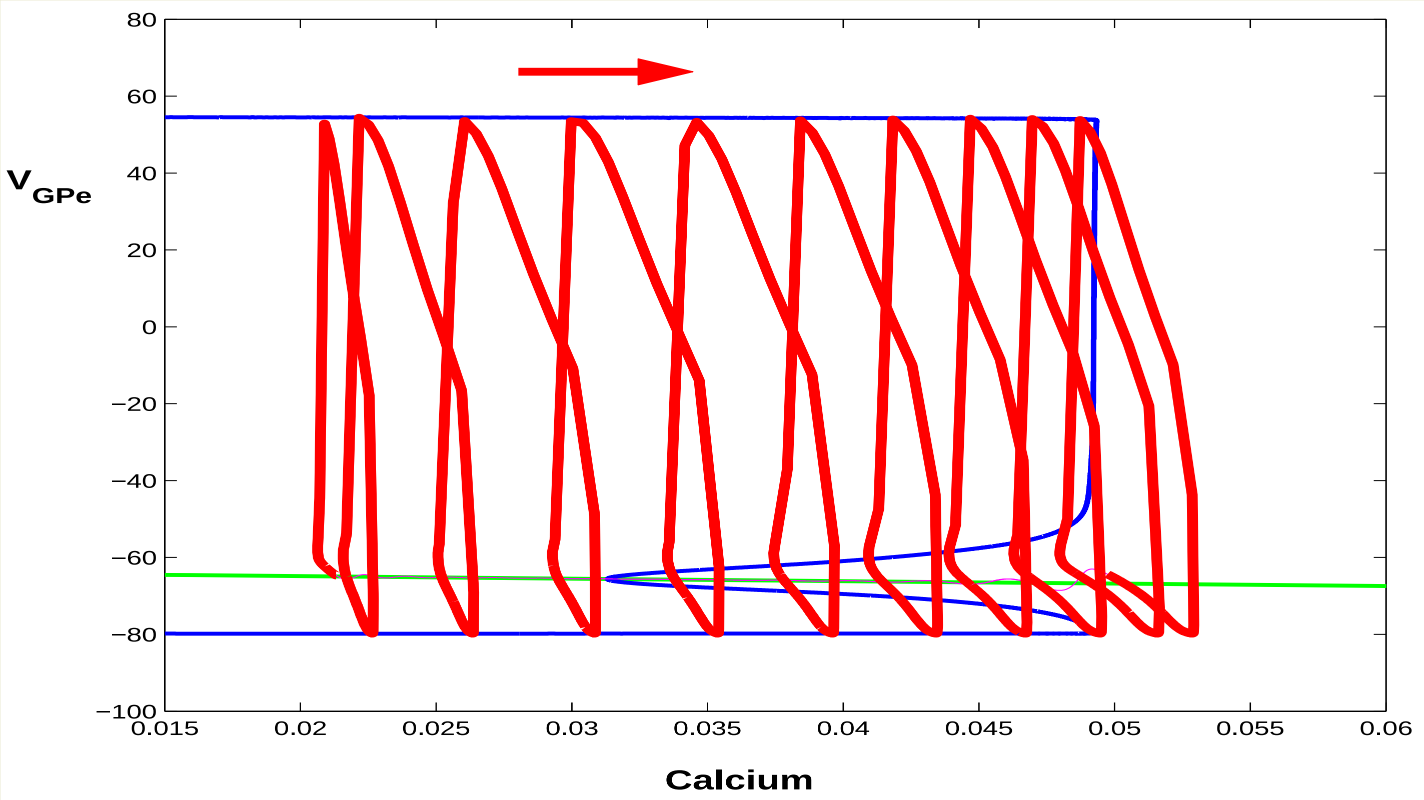
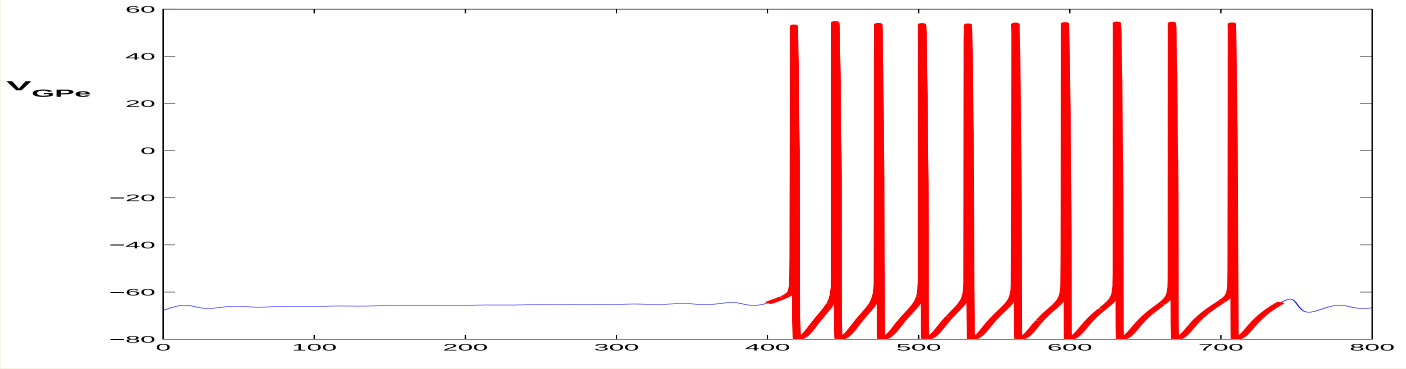




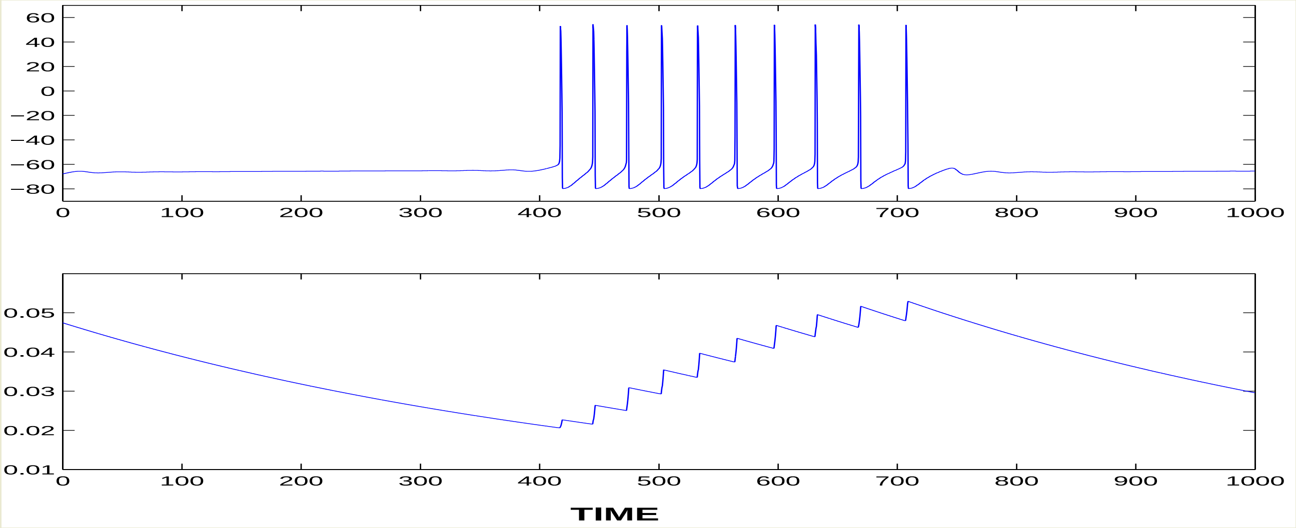
Dynamics Reduce to a Single Equation for the Slow Variable

Good Approximation:

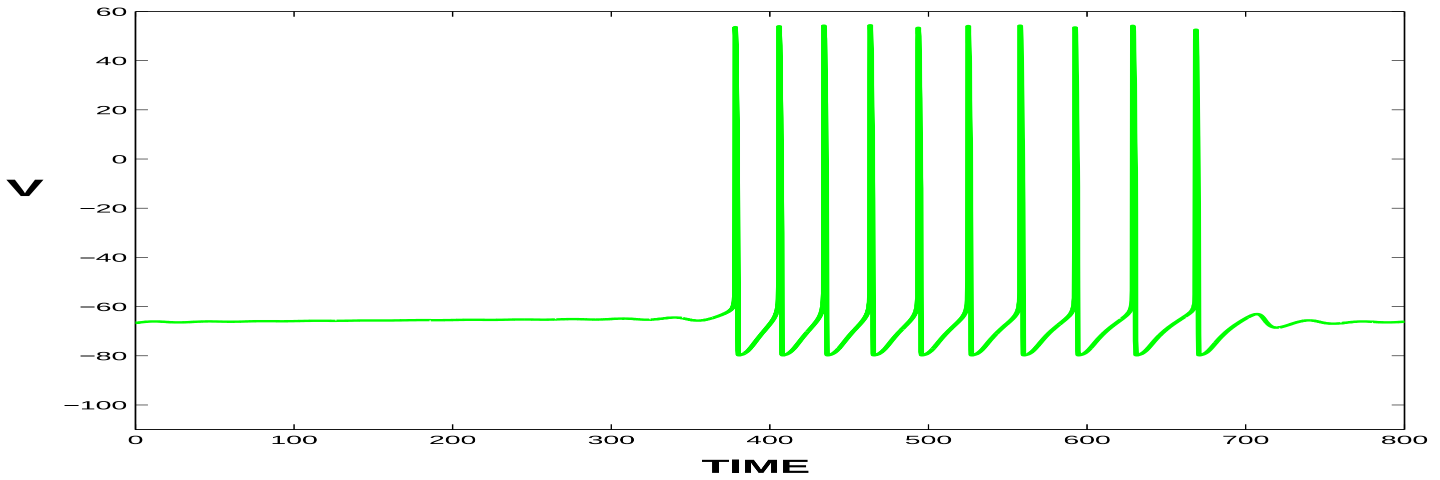
$$Ca' = \begin{cases} -\lambda_S & \text{cell silent} \\ \lambda_A & \text{cell active} \end{cases}$$

V_{GPe}

Ca



Phase-Response Curve for GPe Cell



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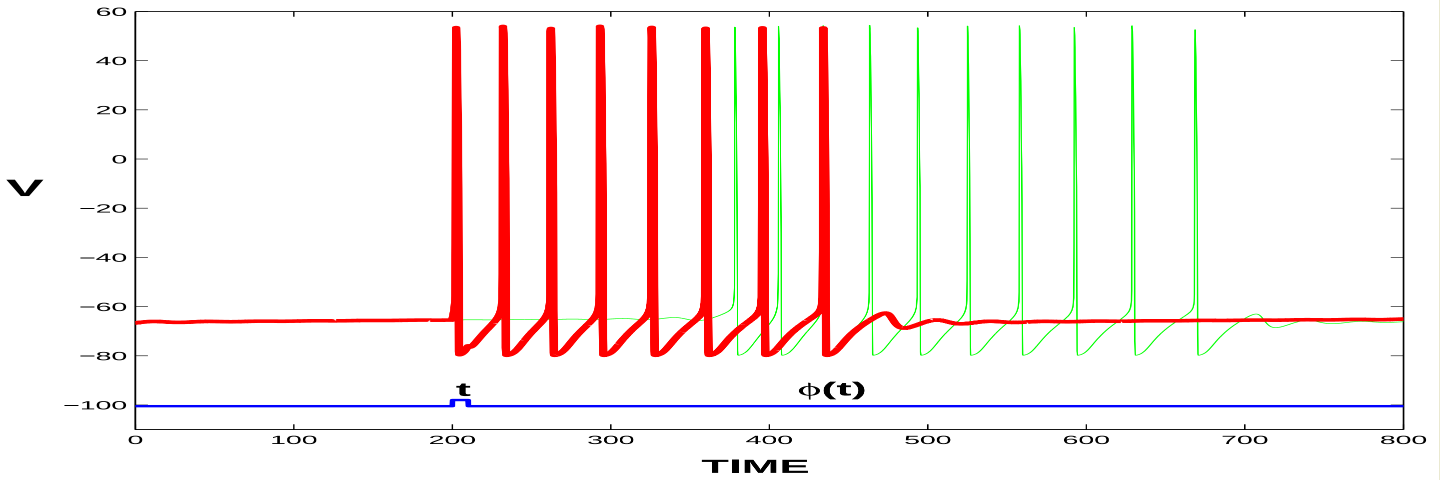
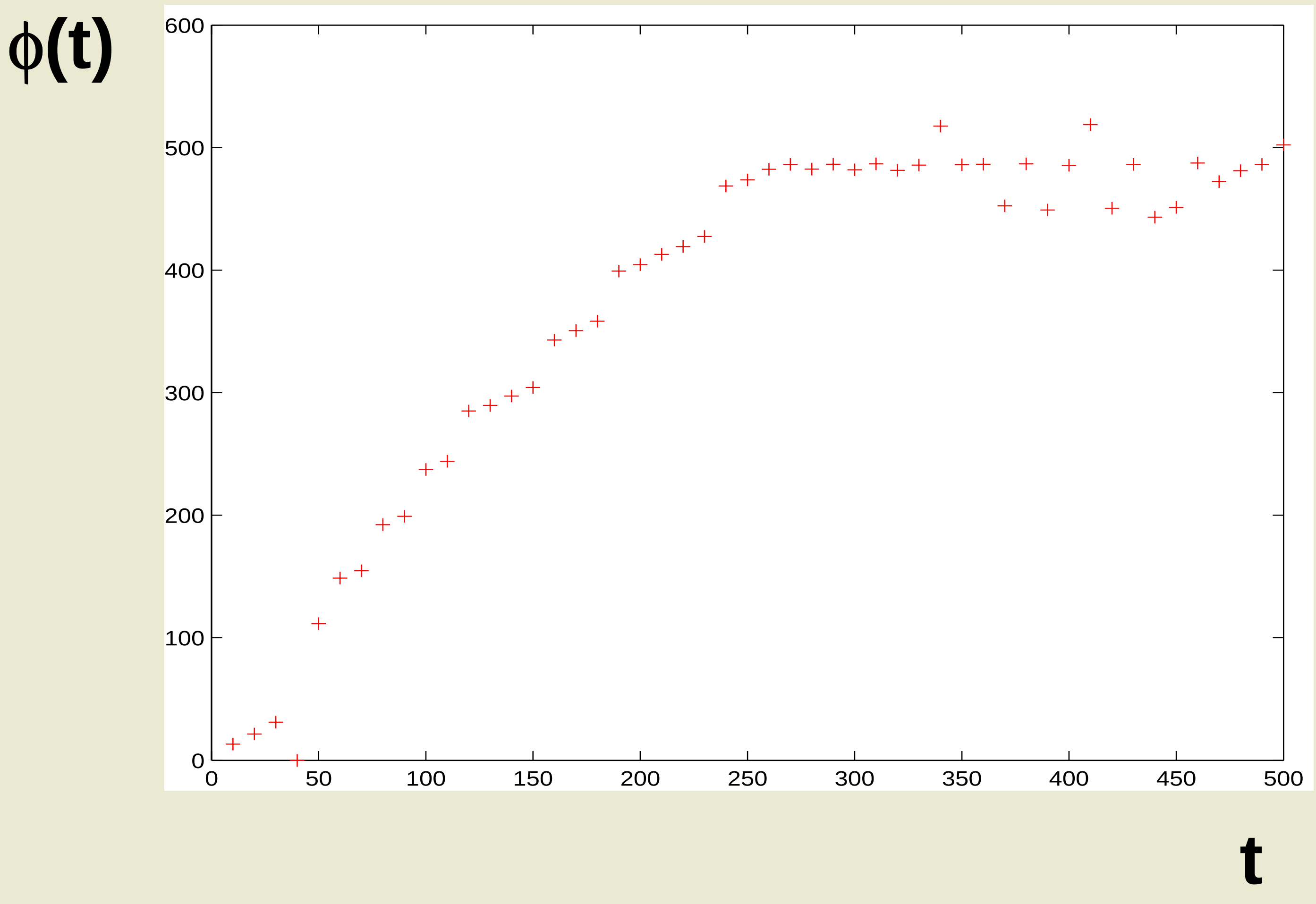


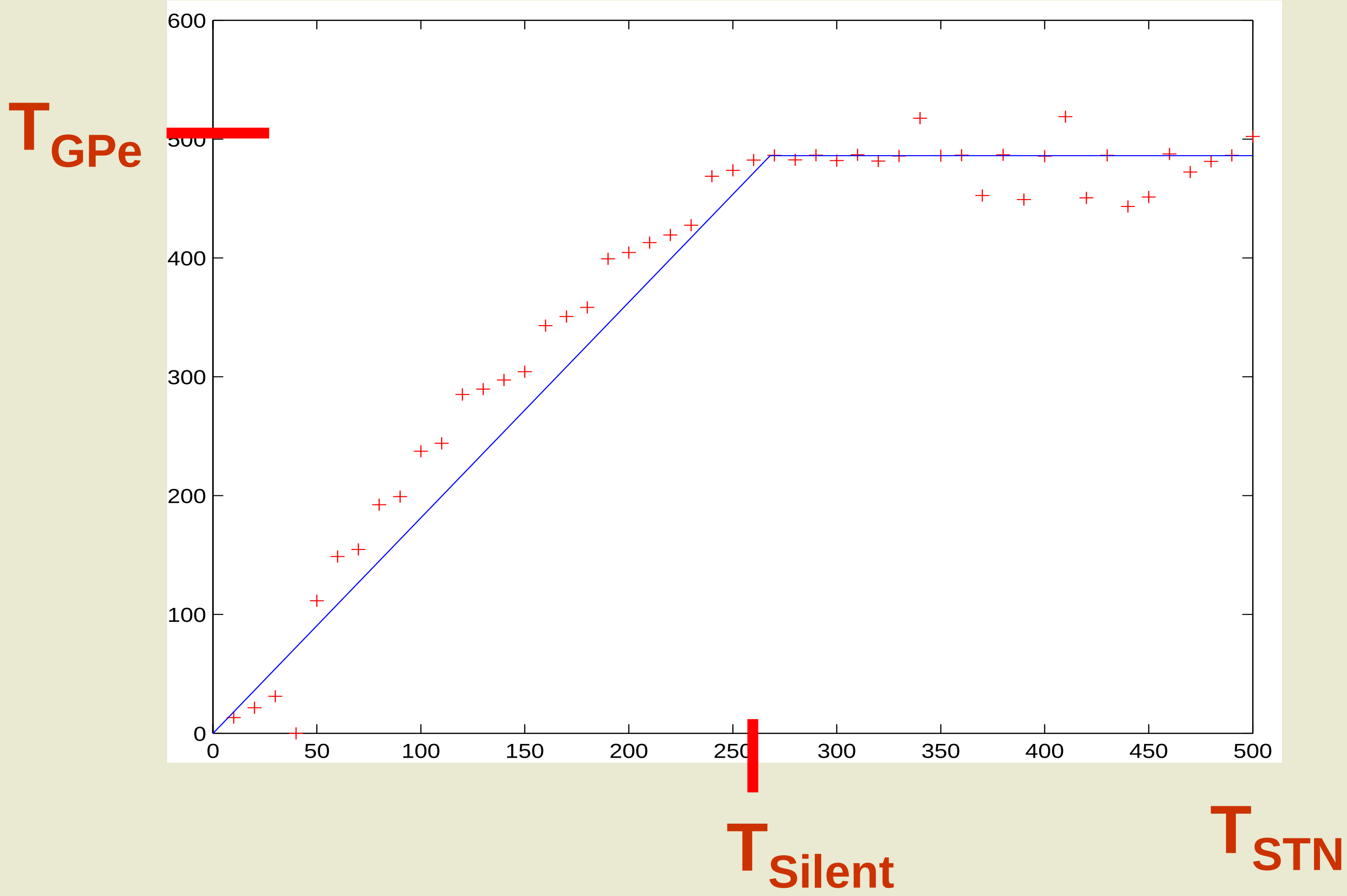
- Perturb GPe Cell at Time t
- $\phi(t)$ = time when GPe cell ends its next active phase

Choose t=0 when GPe cell ends an active phase

Phase Response Curve



Phase Response Curve



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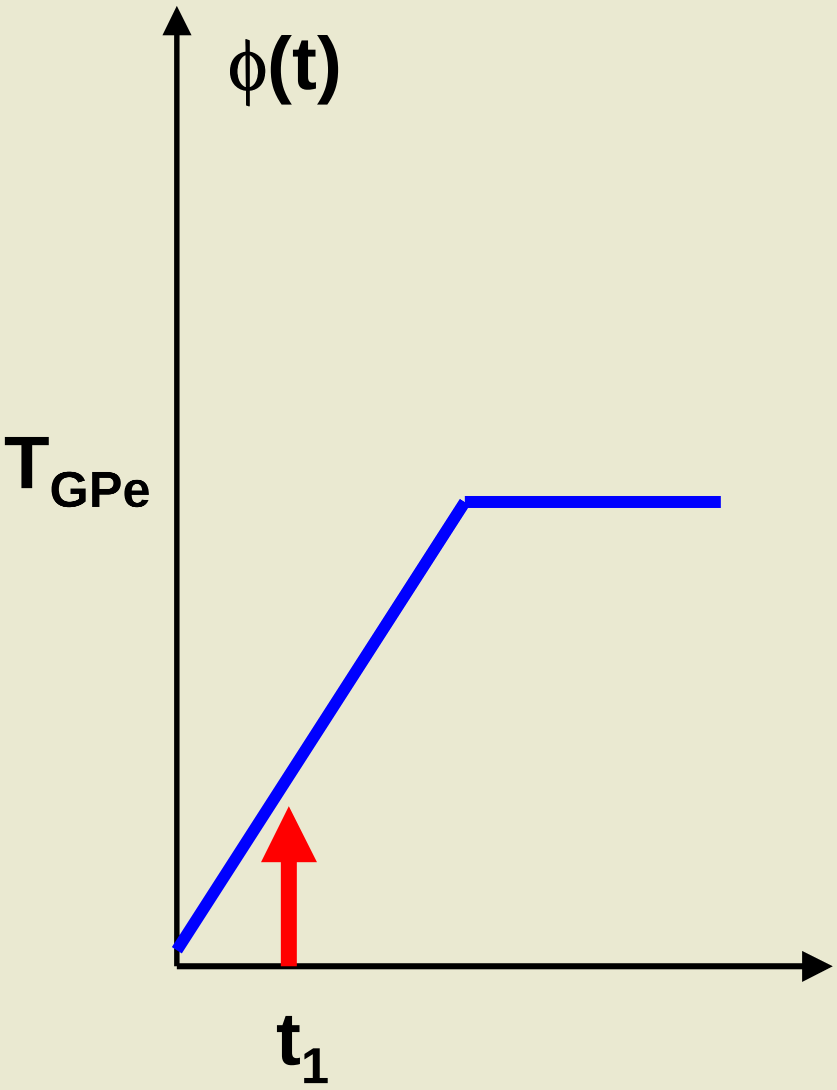
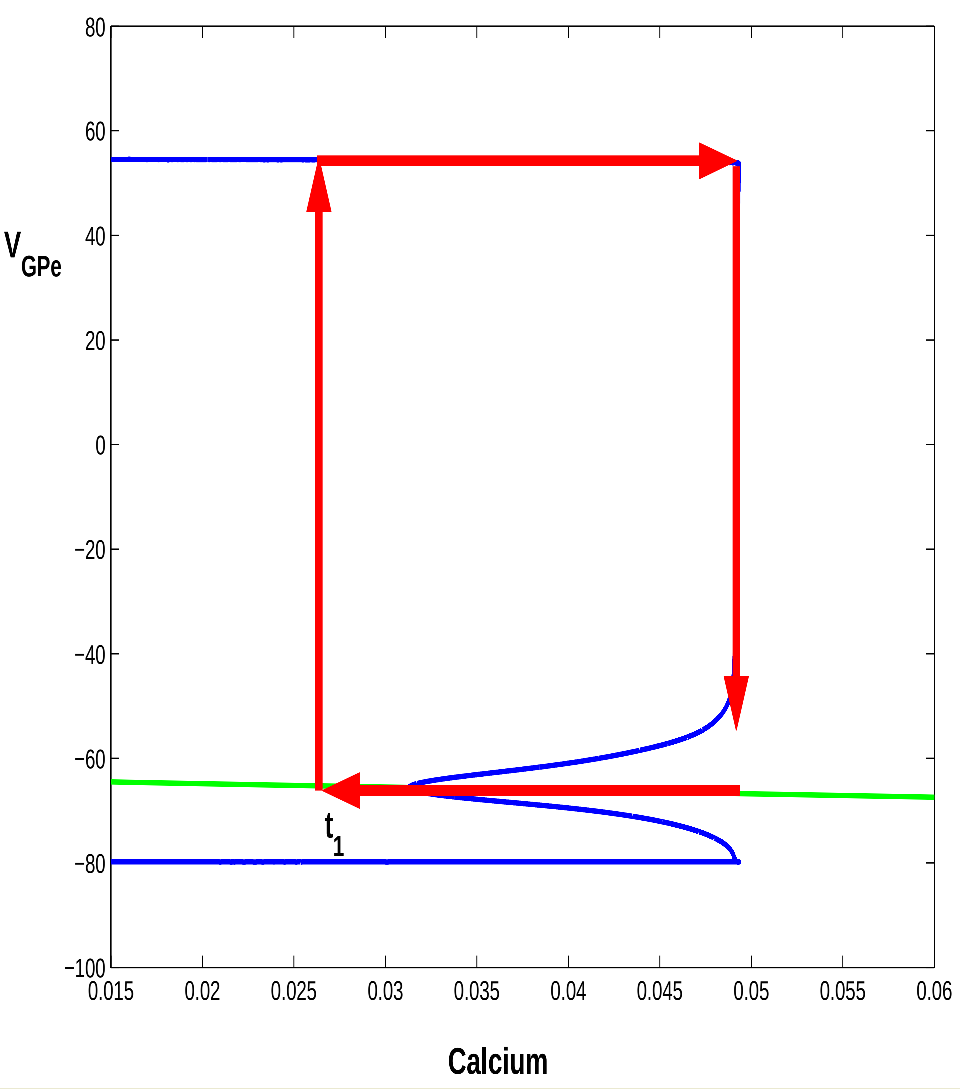
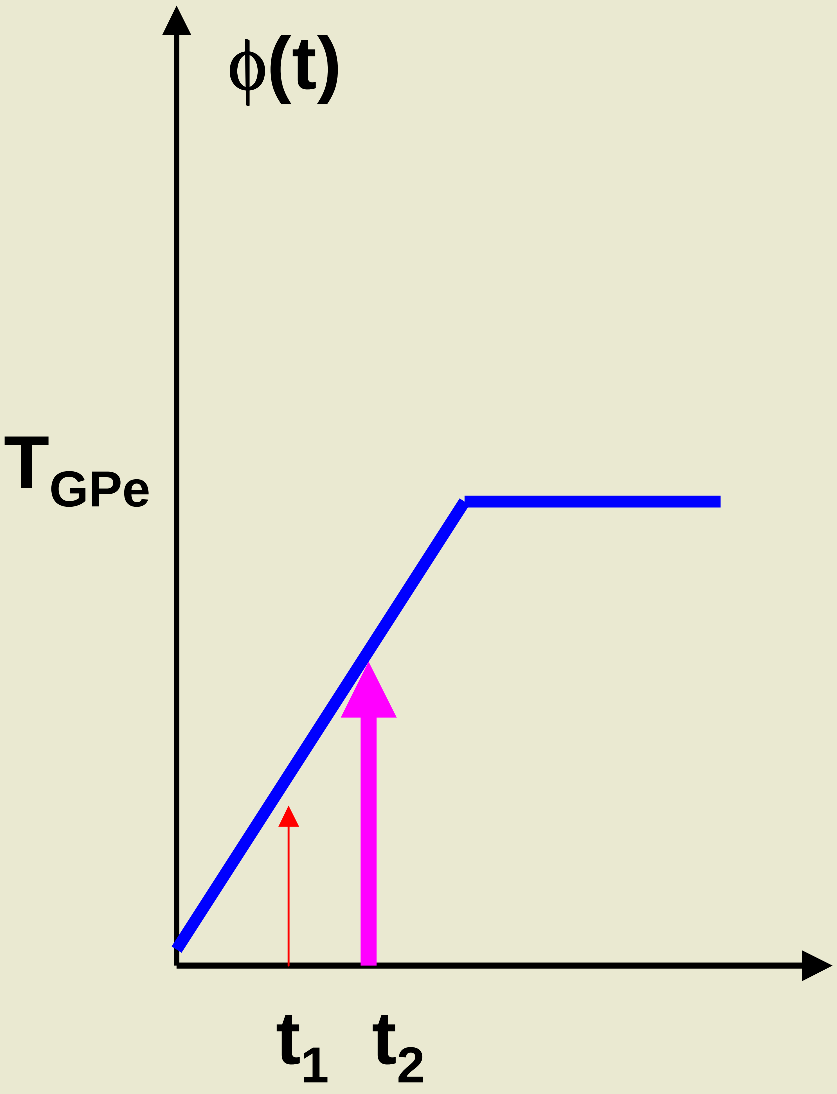
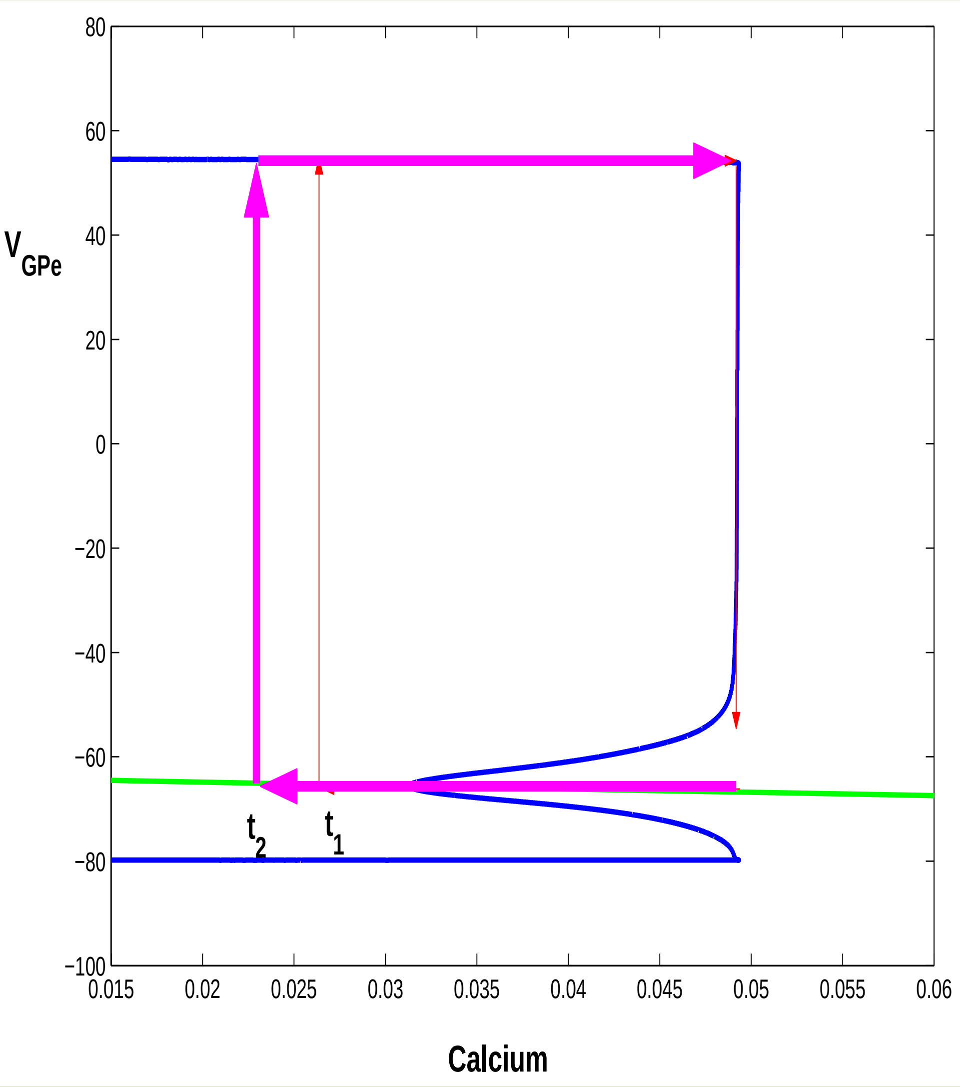


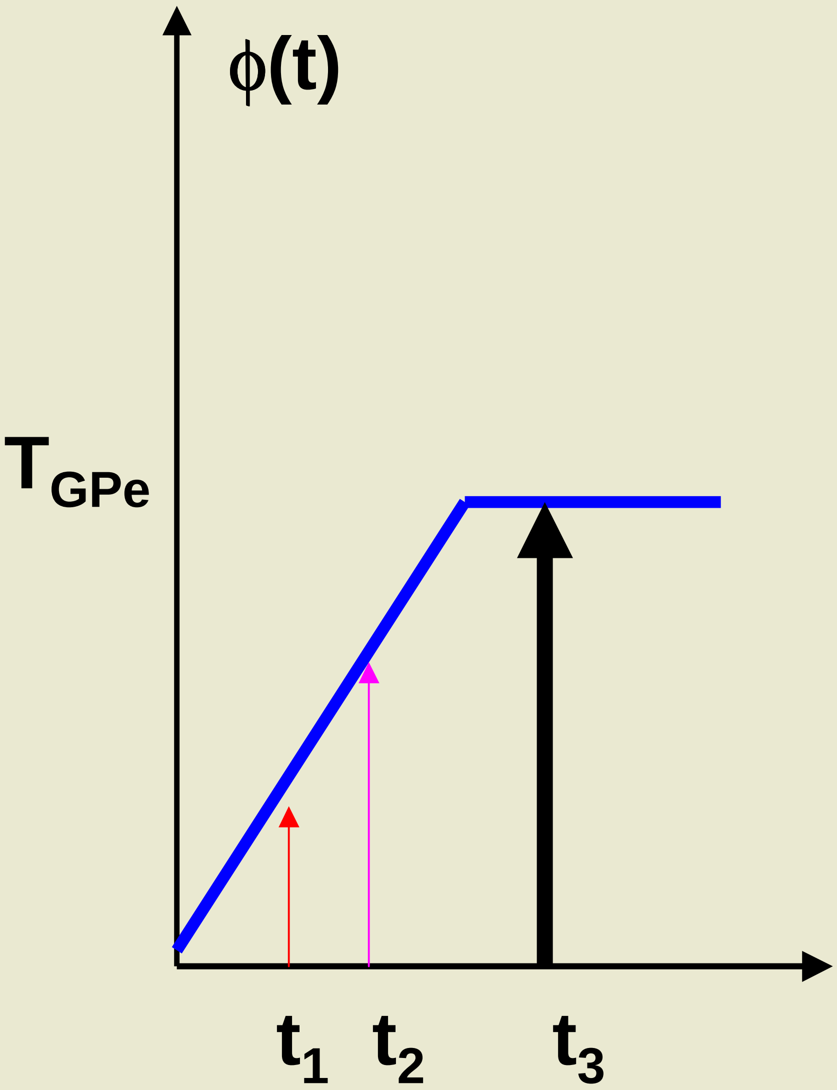


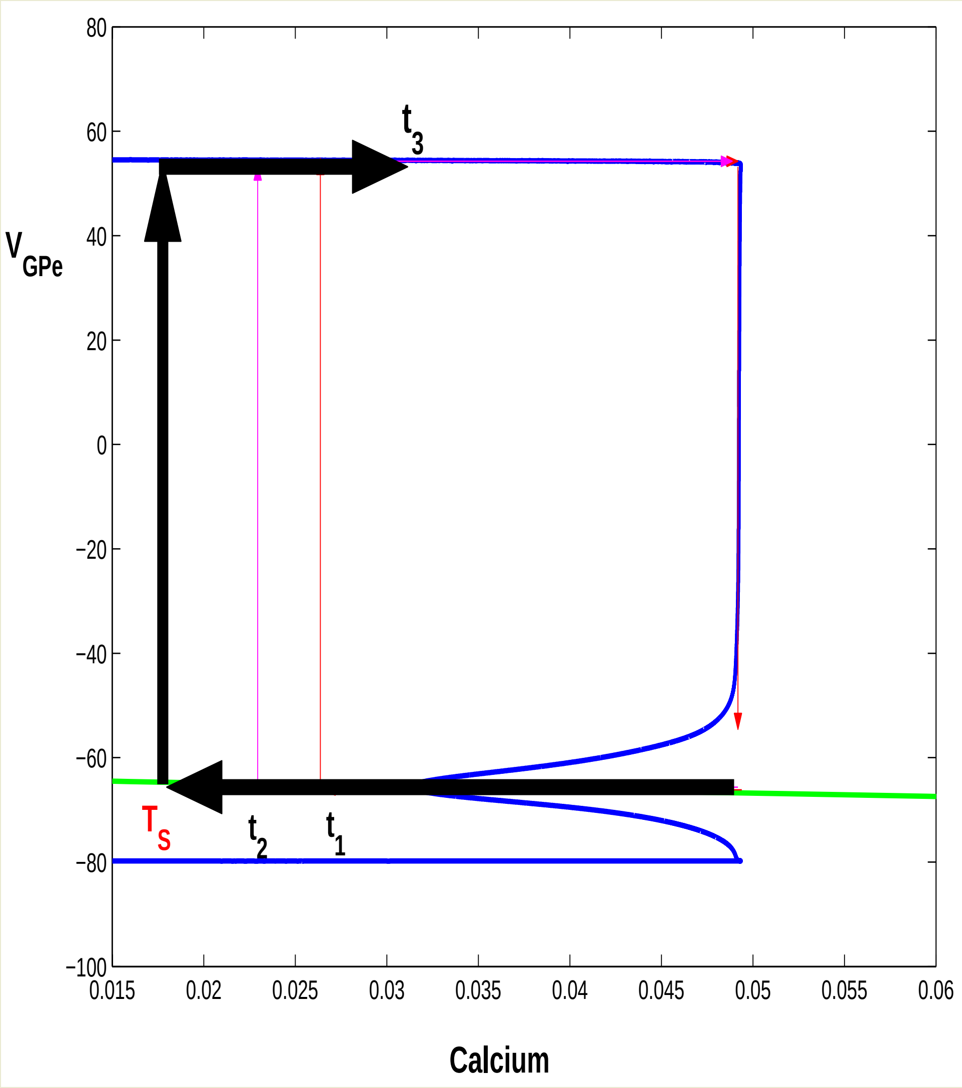
Phase Response Curve





Phase Response Curve





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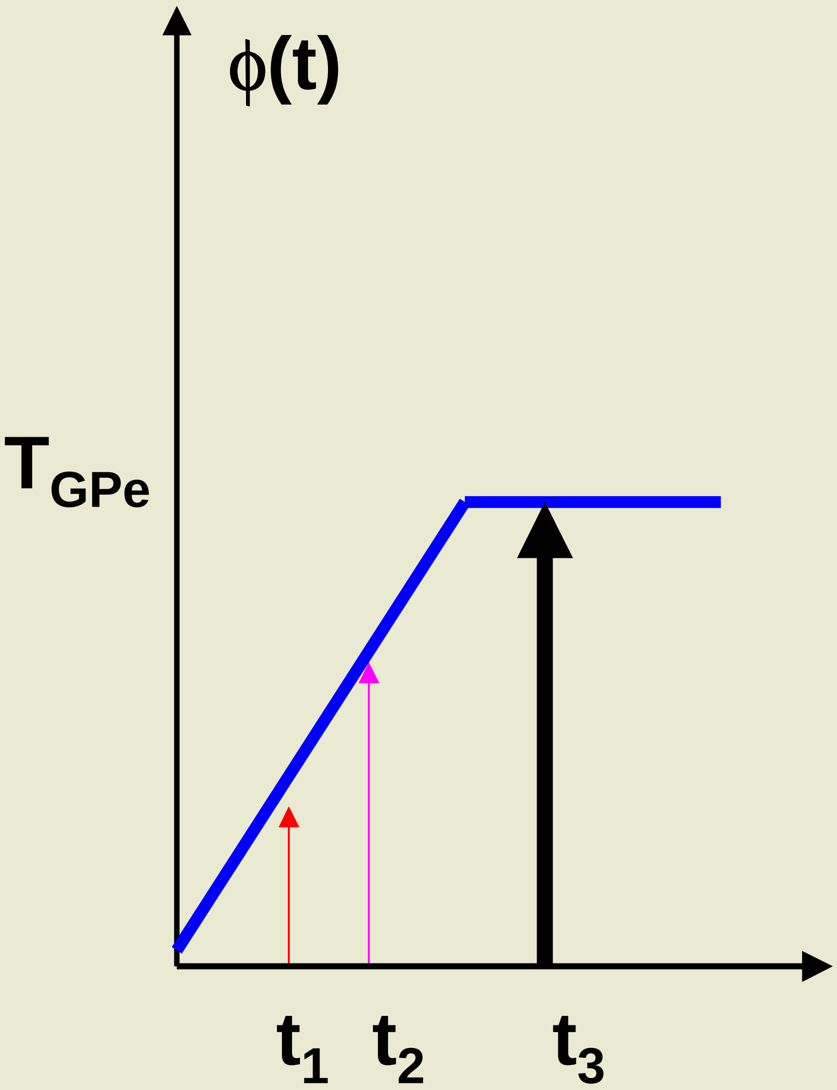
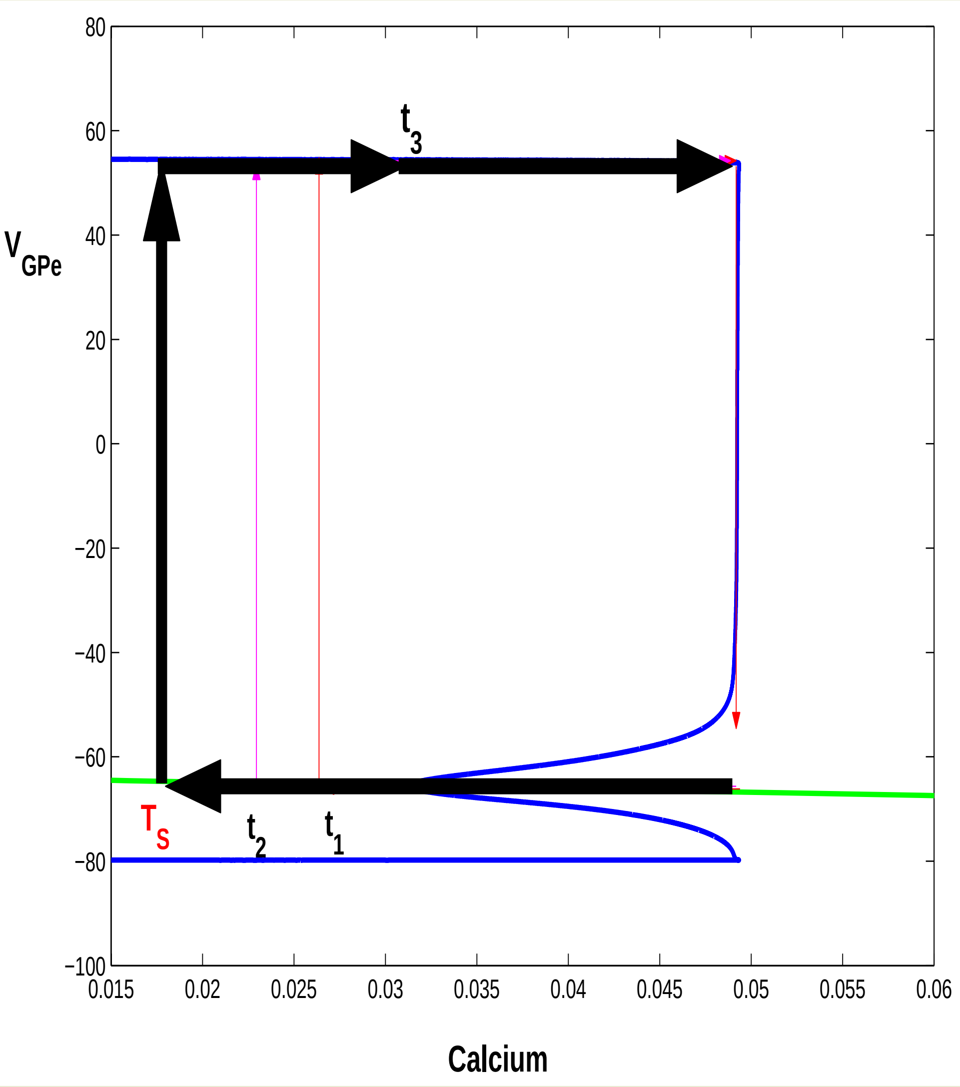
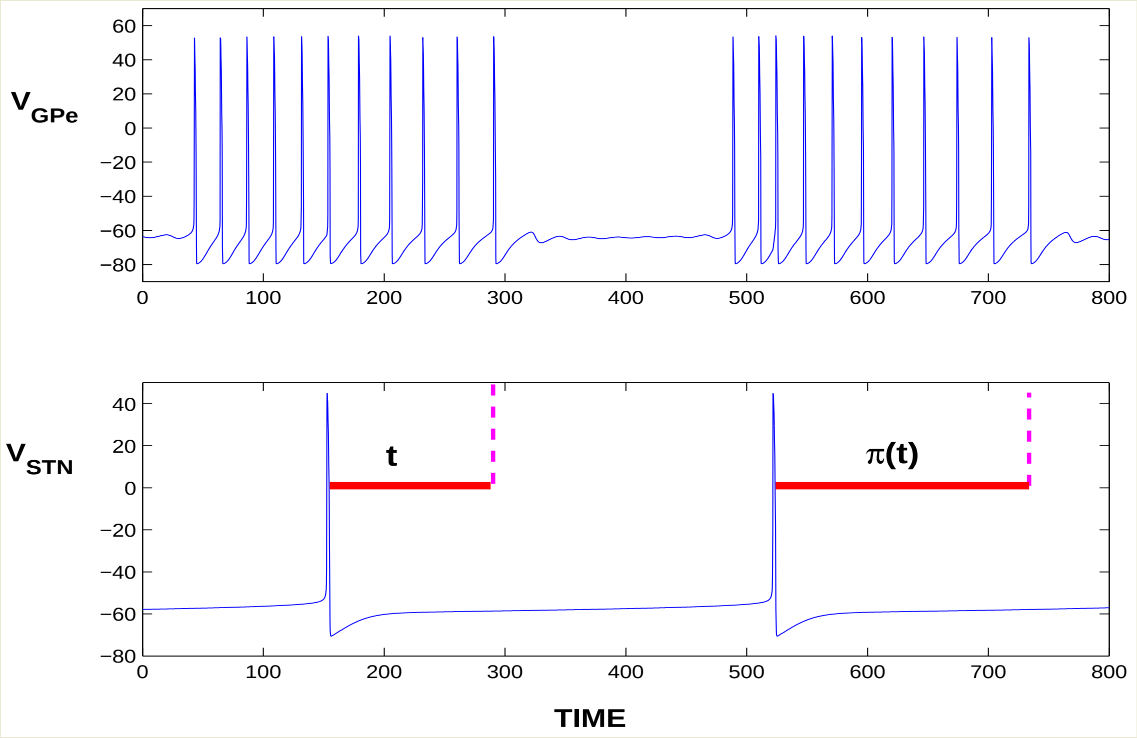
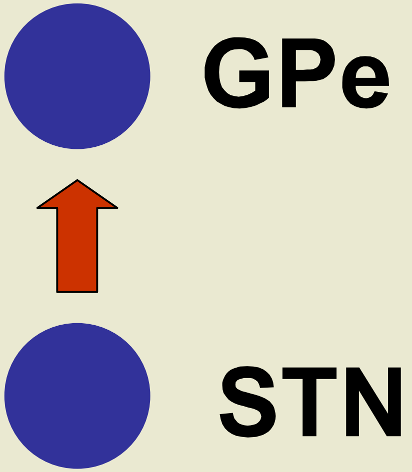




One Dimensional Map

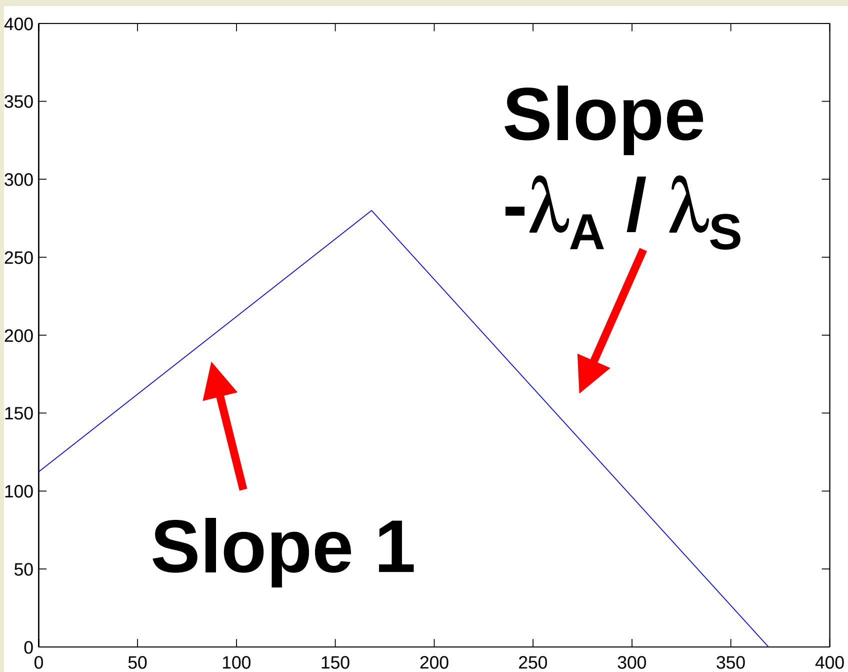




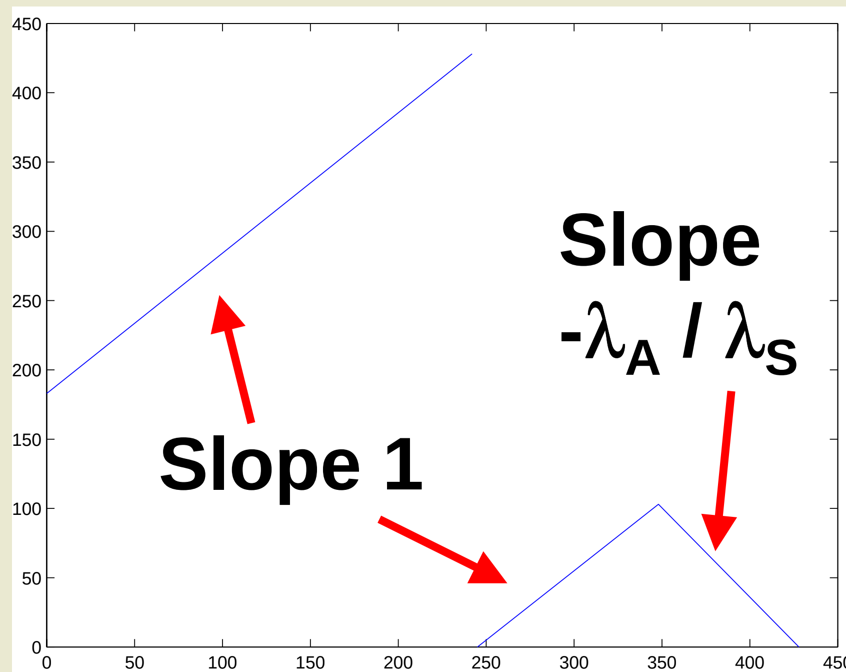
- t = time from STN firing to fall-down of GPe cell
- π(t) = time of next GPe fall-down since STN firing

Linear Approximation of Map

$T_{GPe} > T_{STN}$

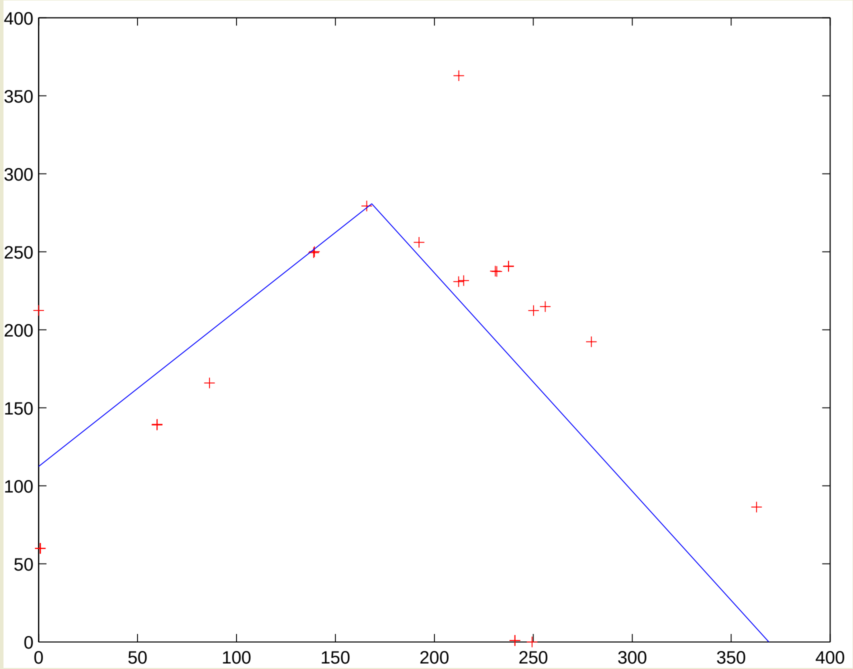


$T_{GPe} < T_{STN}$

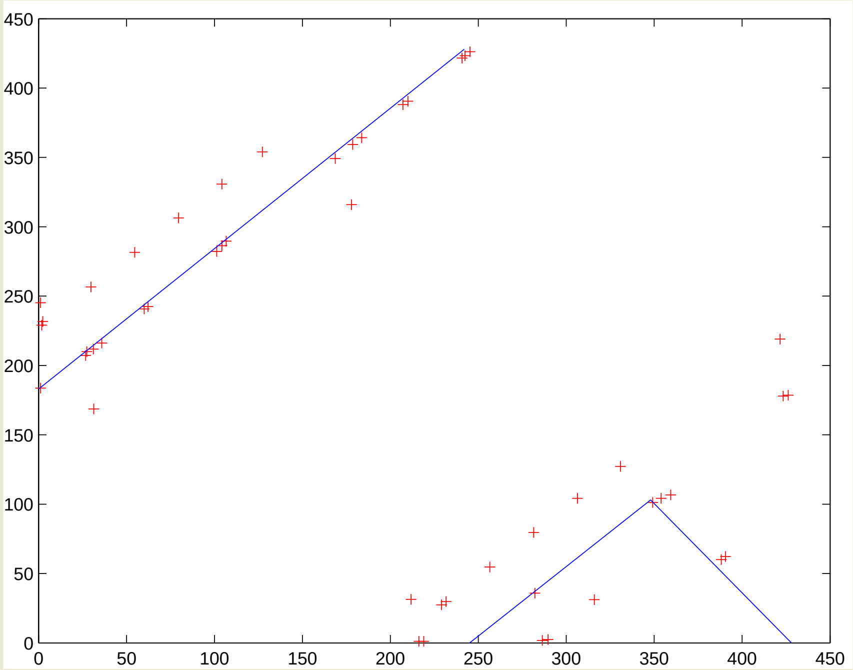


Numerically Computed Map

$T_{GPe} > T_{STN}$



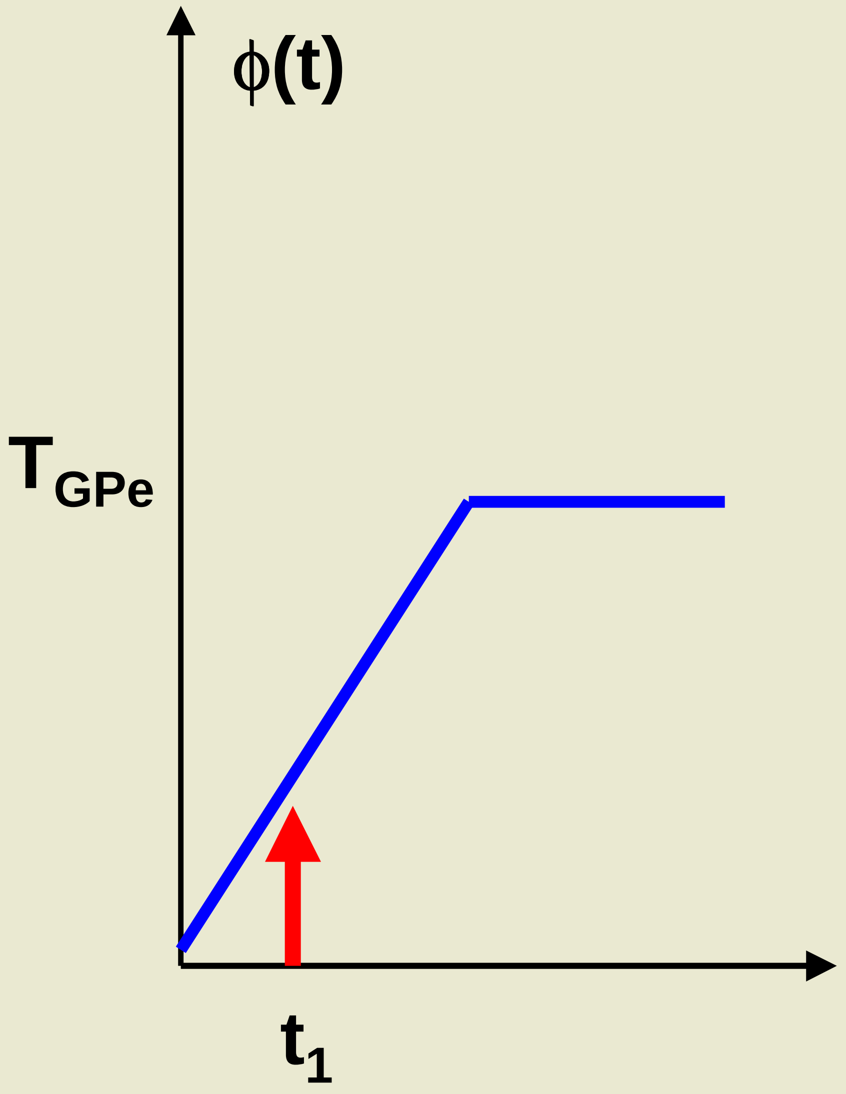
$T_{GPe} < T_{STN}$

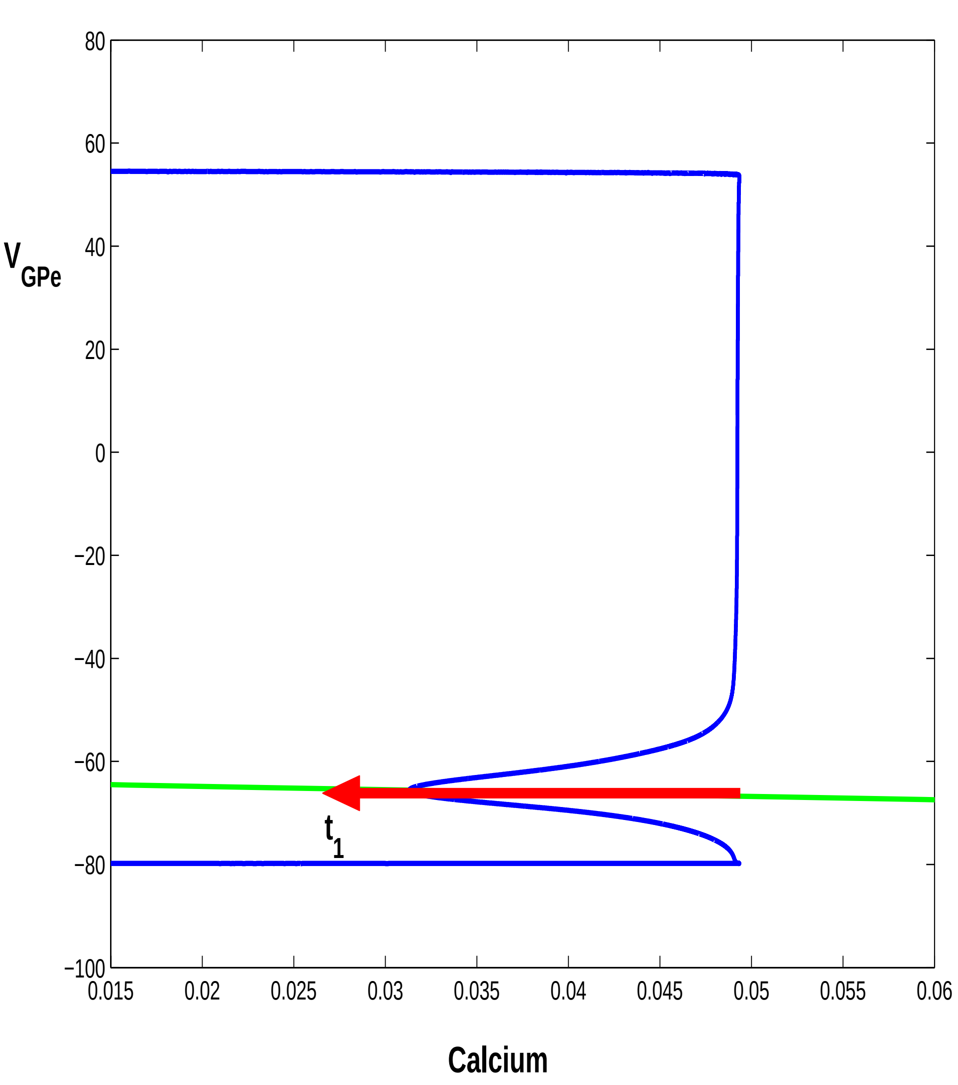


SUMMARY

- STN/GPe Network Exhibits Both Irregular and Synchronous Rhythmic Activity
- STN Cells show Reverse Spike Adaptation that May Increase Correlations
- Transition Between Irregular and Rhythmic Patterns May Arise from Changes in Rebound Properties of STN Cells
- Dynamics of Irregular and Clustered Rhythms can be analyzed using lower-dimensional maps

Phase Response Curve





Phase Response Curve