Exploring the emergence of abnormal oscillations in the basal ganglia during Parkinson’s Disease

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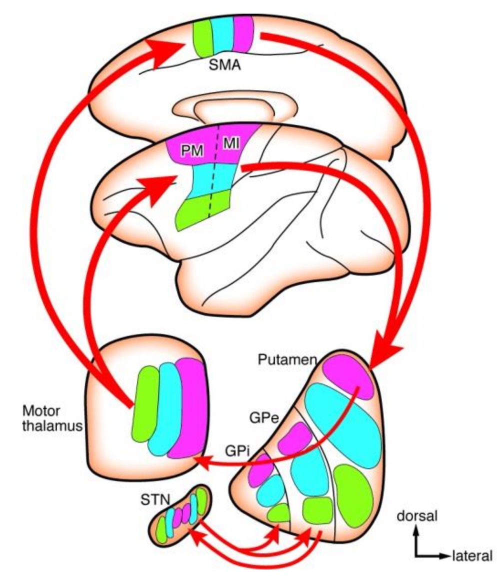
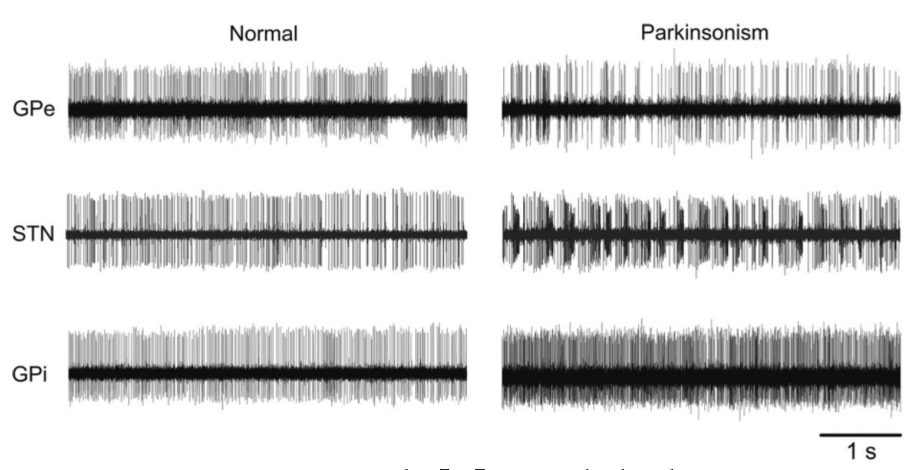
Introduction

Muscle rigidity associated with **Parkinson's disease (PD)** is thought to be correlated with the loss of dopamine and the emergence of beta oscillations in the basal ganglia. As dopamine-producing neurons die off, synaptic connection strengths change leading to increased inhibition on the thalamus.

The Motor Circuit is a four-step process in the brain [1] (right).

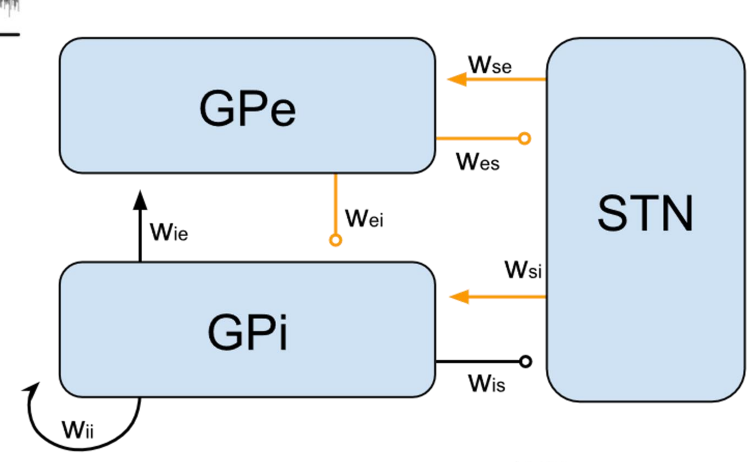
1. You decide to move
2. The cortex sends a signal to the basal ganglia
3. The basal ganglia decides how much to inhibit the thalamus
4. The thalamus relays a signal to the cortex

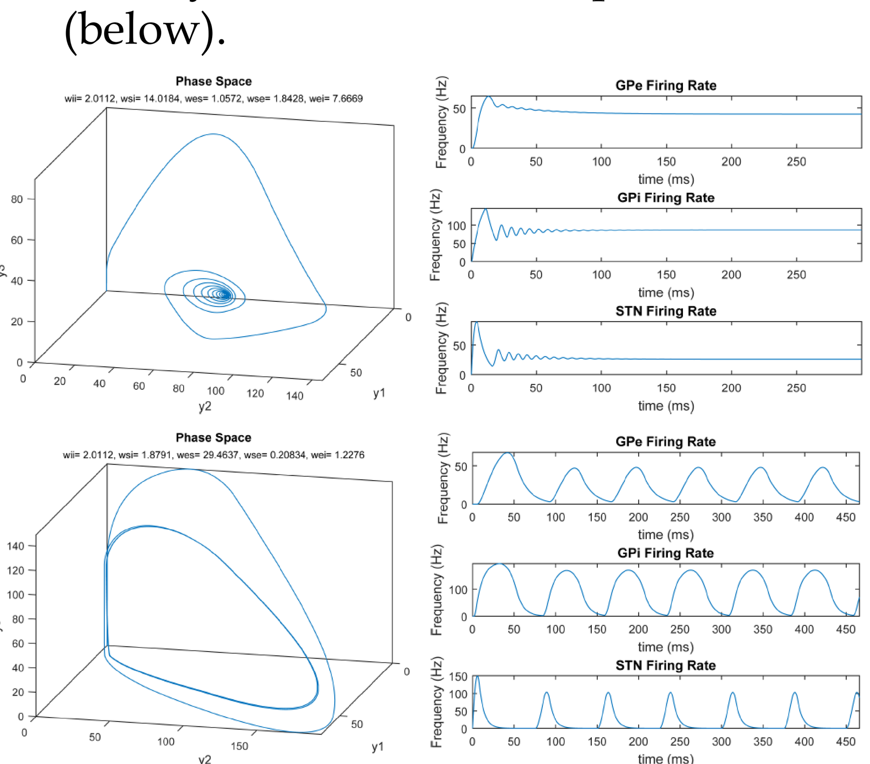


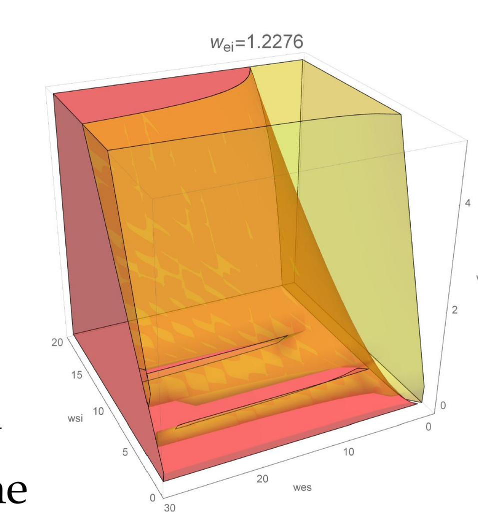


As PD progresses, firing rates shift from a uniform firing frequency to oscillating in the beta-band (13-25 Hz) frequency [2] (*left*).

Our previous work [3] modeled a simplified motor circuit (*right*) with **three relays** (black) and was able to match both healthy and Parkinsonian primate data (below).







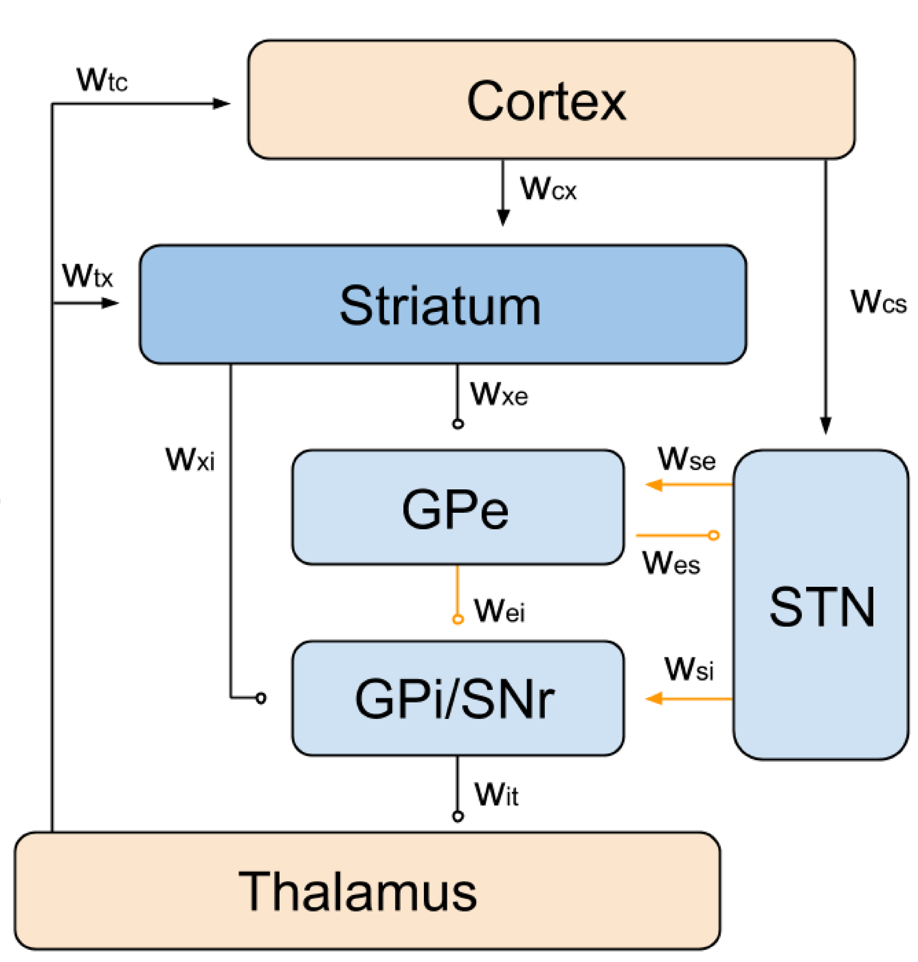
This model structure allows us to examine the network dynamics. The stability regions of the four orange weights is shown above.

Extended Model

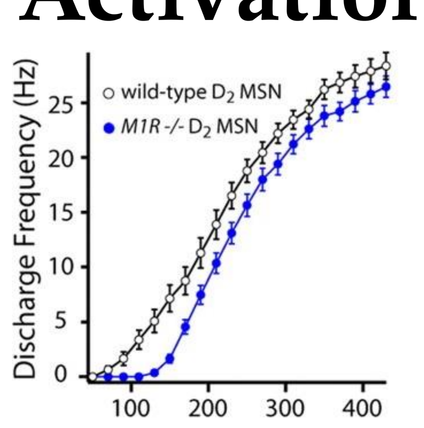
Modeling the basal ganglia with its connecting cortical and thalamic regions forms a closed loop (right) with six distinct populations of neurons.

$$\tau_1 y_1' = -y_1 + F(w_{se}y_3 - w_{xe}y_4 + \beta_1)$$
$$\tau_2 y_2' = -y_2 + F(-w_{ei}y_1 + w_{si}y_3 - w_{xi}y_4 + \beta_2)$$
$$\tau_3 y_3' = -y_3 + F(-w_{es}y_1 + w_{xs}y_4 + \beta_3)$$
$$\tau_4 y_4' = -y_4 + F(w_{cx}y_5 + w_{tx}y_6 + \beta_4)$$
$$\tau_5 y_5' = -y_5 + F(w_{tc}y_6 + \beta_5)$$
$$\tau_6 y_6' = -y_6 + F(-w_{it}y_2 + \beta_6)$$

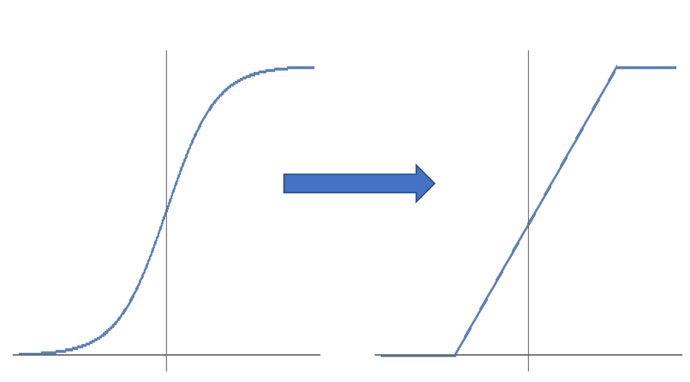
With $\tau_k, w_{ij}, F, \beta_\ell$ being time membrane constants, synaptic weights, activation function, and resting firing rate, respectively.



Activation Function

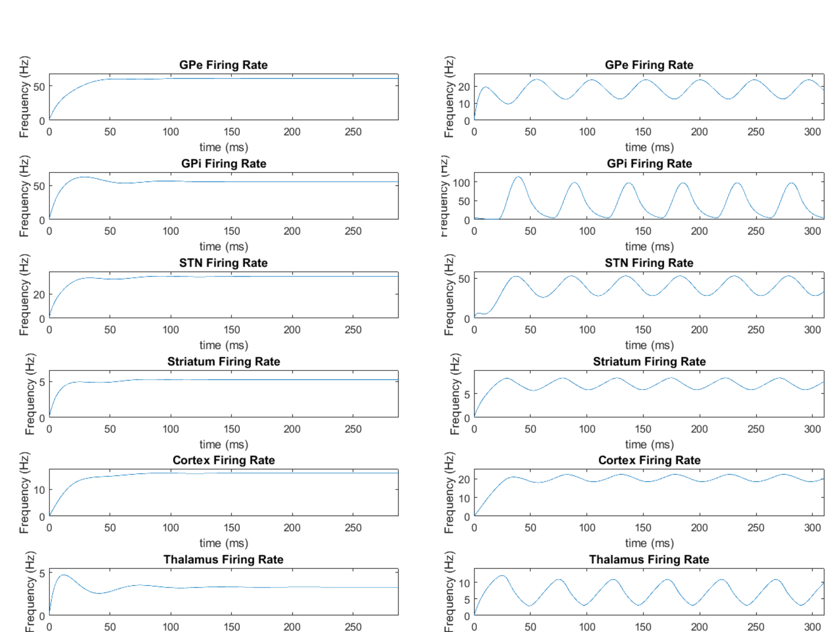


Most neurons discharge in a sigmoidal-like fashion (*left* [4]), however we approximate it to a piecewise linear (*right*).



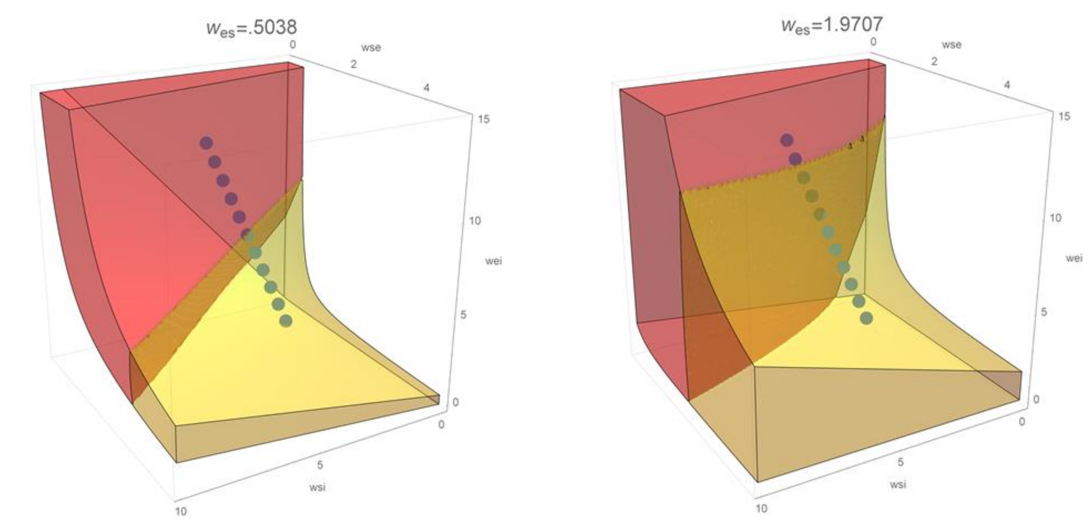
Matching

Using firing rate data from healthy nonhuman primates, parkinsonian nonhuman primates, and systems that have had some connections chemically “blocked”, we were able to find both **stable healthy** and **oscillating parkinsonian solutions** validating our system.



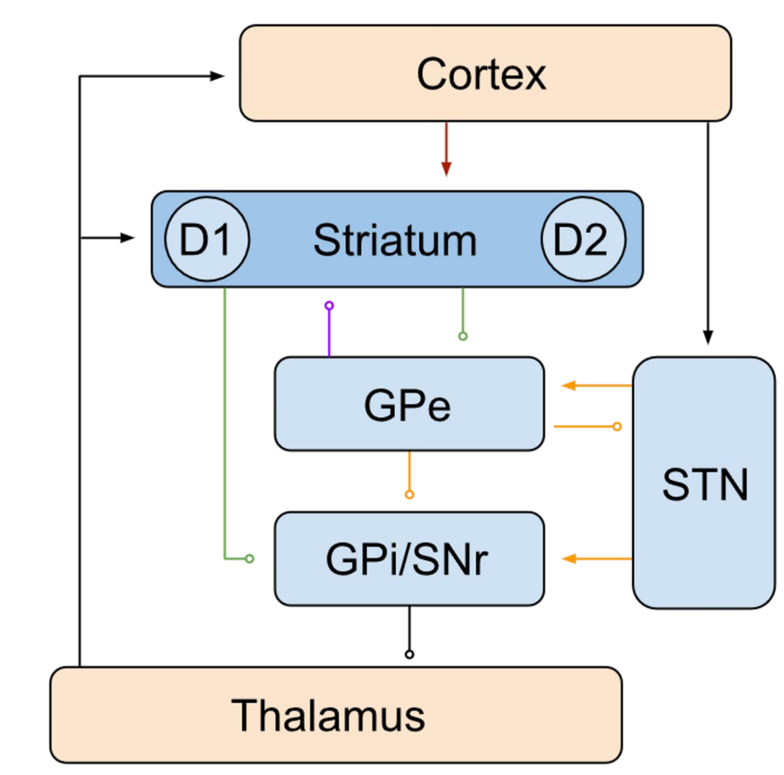
Stability

By varying the orange weights, we can obtain a 4-D region of stability (*yellow*) that corresponds to a healthy brain and a region of instability (*red*) that corresponds to the oscillations commonly seen in PD.



Arkypallidal Model

To make the model more realistic, we separate the striatum into its corresponding direct and indirect components and the **arkypallidal (pallidostriatal)** connections (*right*).



We then investigate the **only** region in which our stable fixed point can exist, leaving us the linear system:

$$\tau y' = Ay + \beta = \begin{pmatrix} -1 & 0 & w_{31} & -w_{41} & 0 & 0 & 0 \\ -w_{12} & -1 & w_{32} & 0 & -w_{52} & 0 & 0 \\ -w_{13} & 0 & -1 & 0 & 0 & w_{63} & 0 \\ -w_{14} & 0 & 0 & -1 & 0 & w_{64} & w_{74} \\ -w_{15} & 0 & 0 & 0 & -1 & w_{65} & w_{75} \\ 0 & 0 & 0 & 0 & 0 & -1 & w_{76} \\ 0 & -w_{27} & 0 & 0 & 0 & 0 & -1 \end{pmatrix} y + \beta$$

Stability Conditions

$$\boldsymbol{a_7\lambda^7 + a_6\lambda^6 + a_5\lambda^5 + a_4\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0}$$

1. $a_0 = |A| < 0$

2. $a_5 a_6 - a_4 a_7 > 0$

3. $a_6(a_4 a_5 - a_3 a_6$

4. $a_6(a_4 a_5 - a_3 a_6 + a_2 a_7) - \left(-a_4 a_5 a_6 + a_4^2 a_7 + a_6 (a_3 a_6 - a_2 a_7)\right)\left(a_3^2 a_6^2 + a_2^2 a_7^2 + a_2 a_5 (a_5 a_6 - a_4 a_7)\right.$

5. $a_6\left(a_5\left(-a_2 a_3 a_4 + a_2^2 a_5 + a_4 (a_1 a_4 - a_0)\right) + \left(a_3 (-a_1 a_4 + a_0 a_5) + a_2(a_3^2 - 2 a_1 a_5)\right) a_6 + a_1^2 a_6^2\right) + \left(a_4 \left(a_2 a_3 a_4 - a_2^2 a_5 + a_4 (-a_1 a_4 + a_0 a_5)\right) + a_2 (-2 a_2 a_3 + 3 a_1 a_4 + a_0 a_5) a_6 - 2 a_0 a_1 a_6^2\right) a_7 + (a_2^3 - 2 a_0 a_2 a_4 + a_0^2 a_6) a_7^2 < 0$

6. $a_6(a_5(a_1^2 a_4^2 + a_1(-a_2 a_3 a_4 + (a_2^2 - 2a_0 a_4)a_5) + a_0(a_3^2 a_4 - a_2 a_3 a_5 + a_0 a_5^2)) - \left(a_0 a_3^3 - a_1 a_3(a_2 a_3 + 3a_0 a_5) + a_1^2(a_3 a_4 + 2a_2 a_5)\right) a_6 + a_1^3 a_6^2) - \left(a_1^2(a_4^3 - 3a_2 a_4 a_6 + 3a_0 a_6^2) + a_0\left(a_0 a_4 a_5^2 + a_3 a_5(-a_2 a_4 + 3a_0 a_6) + a_3^2(a_4^2 - 2a_2 a_6)\right)\right)$

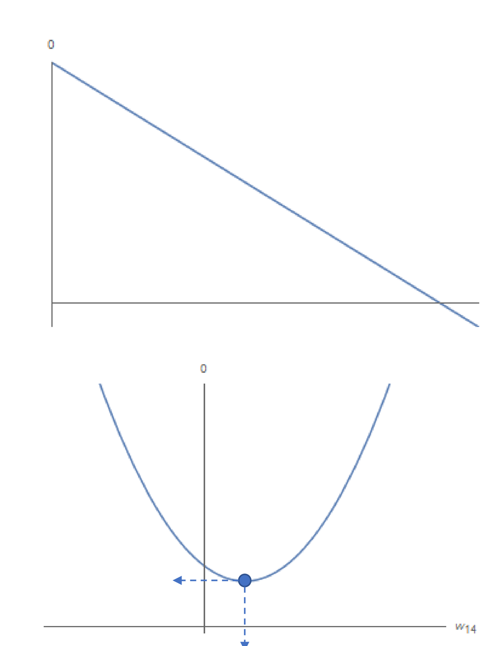
Above are the 5 stability conditions for the system and the condition on the determinant:

$$|\tau^{-1}A| = \prod_{i=7} \lambda_i = \prod_{i=7} \frac{\sigma_i}{\tau_i} < \prod_{i=7} \sigma_i = |A| < 0.$$

In our Parkinsonian condition, we must break one of the conditions (2)-(5) to create our stable oscillations. Since (1) cannot be broken, we must flip the sign of an even number of eigenvalues during the break, forcing our system to have what is almost certainty a **Hopf bifurcation**.

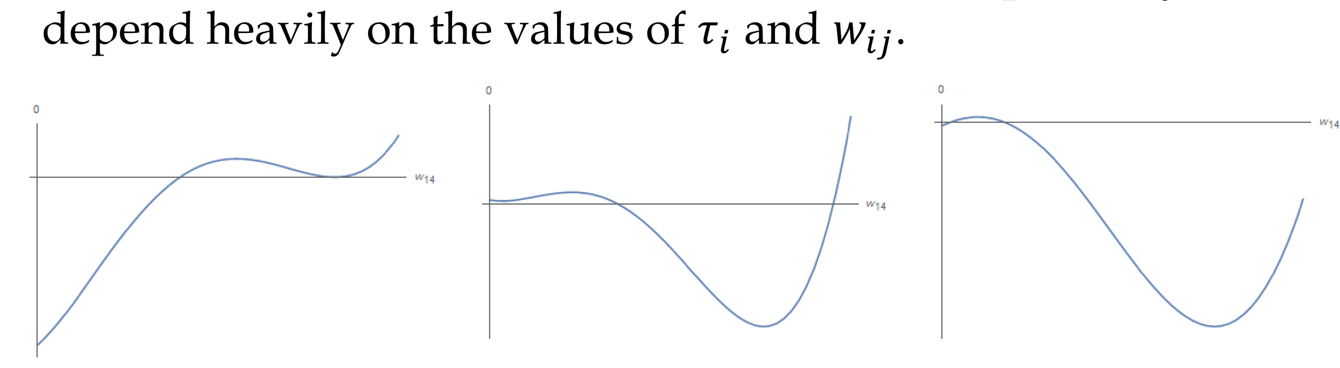
Arkypallidal Perturbation

If inputs to the striatum are not specialized per D1/D2, we can examine how $w_{14} = w_{15}$ can lead to oscillations. Using (1) we can bound $0 < w_{14} \leq w_{14}^*$. (2) is **linear** in w_{14} with negative slope and positive y-intercept (*upper right*), leading to a possible bifurcation.



Assuming (2) holds, we can examine (3) which is **degree 2**. Though we are concave up, we cannot determine if we break the condition (*right*).

Condition (3) – (5) are of **degrees 5, 4, and 5**, respectively and will depend heavily on the values of τ_i and w_{ij}.



The figures to the right show examples of conditions (3)-(5) (*left to right*) with random weights changing sign as w_{14} varies from $0 < w_{14} \leq w_{14}^*$.

Conclusions & Future Directions

- We created a firing rate Parkinsonian model that has been validated using primate data.
- This model was able to show both **stable healthy firing** as well as **oscillating parkinsonian solutions.**
- Using our *Arkypallidal Model*, we were able to determine that arkypallidal neurons **can** drive the system towards abnormal oscillations.

- ➢ Continue to examine the higher dimensional stability conditions
- ➢ Exploring how the D1/D2 connections and the GPe/STN loop can cause oscillations
- ➢ Matching to data generated in our lab, using similar experimental techniques, same species, and same Parkinsonian model

Acknowledgements

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References

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[2] A. Galvan and T. Wichmann, *GABAergic circuits in the basal ganglia and movement disorders*, in Prog. Brain Res., vol. 160, Elsevier Science, 2007.
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[3] Caiola et al., *Model and Analysis For The Onset And Progression of Parkinson's Disease in A Simplified Basal Ganglia.* Inter. J. Neural Systems, 2019.