An Interactive Channel Model of the Basal Ganglia: Bifurcation Analysis Under Healthy and Parkinsonian Conditions

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Michael Meyers
Basal Ganglia

• Input: Cortex
• Output: Thalamus – motor and sensory gating

• Striatum
  • Caudate Nucleus
  • Putamen

• Globus Pallidus
  • Interna (GPi)
  • Externa (GPe)

• Subthalamic nucleus (STN)

• Substantia Nigra
  • Pars compacta (SNC)
  • Pars reticulata (SNr)
Parkinson’s Disease

• Symptoms: bradykinesia and rigidity
• Death of SNc neurons
• β-band synchrony increased in STN and GPi local field potential (LFP)
  • 8-30 Hz
  • Correlates with symptom severity
  • Product of local neural activity?
  • Causes symptoms of Parkinson’s?
  • This paper looks for the source
• GPe-STN coupling can mathematically produce β-band oscillations
  • Requires STN self-excitation
  • No experimental evidence of this
β-band Synchrony

• How to resolve need for STN self-excitation without gap junctions or local axon collaterals?
• Relatively isolated “channels” in basal ganglia
• STN excites GPe, which inhibits neighboring channel GPe, releasing neighboring STN from inhibition (rebound firing)
Model

\[ \tau_{\downarrow s} x_{\downarrow i} = -x_{\downarrow i} + Z_{\downarrow s} (w_{\downarrow ss} x_{\downarrow i} - w_{\downarrow gs} y_{\downarrow i} + I) \]
\[ \tau_{\downarrow g} y_{\downarrow i} = -y_{\downarrow i} + Z_{\downarrow g} (-w_{\downarrow gg} y_{\downarrow i} + w_{\downarrow sg} x_{\downarrow i} - \alpha w_{\downarrow gg} \sum_{j \in L_{\downarrow i}} y_{\downarrow j}) \], \ i = 1, 2, \ldots, N

\[ Z_{\downarrow j}(x) = \frac{1}{1 + \exp(-a_{\downarrow j}(x - \theta_{\downarrow j}))} - \frac{1}{1 + \exp(a_{\downarrow j} \theta_{\downarrow j})}, \ j \in \{s, g\} \]

Line connectivity

\[ L_{\downarrow i} = \{i - 1, i + 1\}, \ 1 < i < N \{i + 1\} \]

Circle Connectivity

\[ i = N \{i - 1, i + 1\}, \ i = N \{i + 1, N\} \]

\[ i = 1 \{i - 1, 1\}, \ i = N \]
## Model Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy</th>
<th>Parkinsonian</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>$w_{gg}$</td>
<td>6.6</td>
<td>12.3</td>
<td>-</td>
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<tr>
<td>$w_{gs}$</td>
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<td>10.7</td>
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<td>$w_{sg}$</td>
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</tr>
<tr>
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<td>6 ms</td>
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<tr>
<td>$\tau_g$</td>
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<td>-</td>
<td>14 ms</td>
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<td>-</td>
<td>4</td>
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<td>$\theta_s$</td>
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<tr>
<td>$\theta_g$</td>
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Analyses

• First in an isolated channel
  • Without STN self-excitation
  • With STN self-excitation and healthy parameters
  • With STN self-excitation and Parkinsonian parameters
    • Frequency analysis

• Coupled channels (no STN self-excitation)
  • Healthy
  • Parkinsonian
Isolated Channel w/o Self Excitation Analysis

\[ \tau_{ls} x_i = -x_i + Z_{ls} (w_{ss} x_i - w_{gs} y_i + I) \]
\[ \tau_{lg} y_i = -y_i + Z_{lg} (-w_{lg} g y_i + w_{sg} x_i - a w_{lg} \sum_{j \in L} y_j), \quad i=1,2,\ldots,N \]

- Set \( \alpha = 0 \)
- Set \( w_{ss} = 0 \)

\[ [-1/\tau_{ls} & -a_{ls} w_{gs} e^{a_{ls}} (\theta_{ls} - I + w_{gs} y_i) / \tau_{ls} (e^{a_{ls}} (\theta_{ls} + w_{gs} y_i - I) + 1)] \uparrow 2 \quad @a_{lg} w_{lg} e^{a_{lg}} (\theta_{lg} - I + w_{lg} y_i) / \tau_{lg} (e^{a_{lg}} (\theta_{lg} + w_{lg} y_i - I) + 1)] \uparrow 2 \]

Negative trace
Positive determinant
Isolated Channel w/o Self Excitation Analysis

\[
\begin{align*}
\tau_{ls} \, x_{li} & = -x_{li} + Z_{ls} (w_{ls} \, x_{li} - w_{gs} \, y_{li} + I) \\
\tau_{lg} \, y_{li} & = -y_{li} + Z_{lg} (-w_{lg} \, y_{li} + w_{sg} \, x_{li} - aw_{lg} \sum_{j \subseteq L \, \uparrow \, y_{lj}}), \quad i = 1, 2, \ldots, N
\end{align*}
\]

• Authors don’t exclude possibility of pairs of stable/unstable limit cycles
Healthy, Isolated Channel w/ Self Excitation

\[
\tau_L x_i = -x_i + Z_L (w_{ss} x_i - w_{gs} y_i + I)
\]

\[
\tau_G y_i = -y_i + Z_G (-w_{gg} y_i + w_{sg} x_i - \omega w_{gg} \sum_{j \in \mathcal{L}_i} y_j), \quad i = 1
\]

• \( w_{ss} \) is now a bifurcation parameter

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**Fig. 2:** Isolated channel phase space under healthy conditions. Behaviour of the isolated channel system under healthy conditions with \( \omega_{ss} = 3.4, I = 0 \). Left: The nullclines and fixed points of the system. Right: Fixed points, stable and unstable manifolds of the saddle point, and example trajectories.
Healthy, Isolated Channel w/ Self Excitation

Bifurcation diagram for healthy, isolated channel
Healthy, Isolated Channel w/ Self Excitation
Healthy, Isolated Channel w/ Self Excitation

1. $w_{ss} < 2.191$

Fix $l = 1$ and look at the five regions.
Healthy, Isolated Channel w/ Self Excitation

Fix $I = 1$ and look at the five regions

1. $w_{ss} < 2.191$
2. $2.191 < w_{ss} < 2.753$
Healthy, Isolated Channel w/ Self Excitation

Fix $I = 1$ and look at the five regions

1. $w_{ss} < 2.191$
2. $2.191 < w_{ss} < 2.753$
3. $2.753 < w_{ss} < 2.783$
Healthy, Isolated Channel w/ Self Excitation

Fix $l = 1$ and look at the five regions:

1. $w_{ss} < 2.191$
2. $2.191 < w_{ss} < 2.753$
3. $2.753 < w_{ss} < 2.783$
4. $2.783 < w_{ss} < 2.822$
Healthy, Isolated Channel w/ Self Excitation

Fix $l = 1$ and look at the five regions

1. $w_{ss} < 2.191$
2. $2.191 < w_{ss} < 2.753$
3. $2.753 < w_{ss} < 2.783$
4. $2.783 < w_{ss} < 2.822$
5. $2.822 < w_{ss}$
Healthy, Isolated Channel w/ Self Excitation

Fix $I = 1$ and look at the five regions:

1. $w_{ss} < 2.191$
2. $2.191 < w_{ss} < 2.753$
3. $2.753 < w_{ss} < 2.783$
4. $2.783 < w_{ss} < 2.822$
5. $2.822 < w_{ss}$

Still no stable oscillations
Parkinsonian Isolated Channel

Fig. 3 2D bifurcation diagram for isolated channel under Parkinsonian conditions. 2D bifurcation diagram showing the bifurcations that the isolated channel system undergoes under variation of $I$ and $w_2$ in the Parkinsonian case. A zoom of the area inside the small rectangle in the lower right-hand corner is shown in Fig. 4.

Fig. 4 2D bifurcation diagram for isolated channel under Parkinsonian conditions (zoom). Zoom of the part of the diagram inside the black rectangle in Fig. 3.

Fig. 5 Phase portraits of isolated channel system under Parkinsonian conditions. Example phase portraits showing the behaviour of the isolated channel system within each of the regions of parameter space.
Parkinsonian Isolated Channel

Bifurcations w/ changing $w_{ss}$ when $l=3.5$

SNIC at $l=3.5$ $w_{ss}=9.705$
Parkinsonian Isolated Channel
Stable Oscillations

Region D

Fig. 3 2D bifurcation diagram for isolated channel under Parkinsonian conditions. 2D bifurcation diagram showing the bifurcations that the isolated channel system undergoes under variation of \( I \) and \( w_X \) in the Parkinsonian case. A zoom of the area inside the small rectangle in the lower right-hand corner is shown in Fig. 4.

Region C

Fig. 4 2D bifurcation diagram for isolated channel under Parkinsonian conditions (zoom). Zoom of the part of the diagram inside the black rectangle in Fig. 3.
Parkinsonian Isolated Channel
Stable Oscillations – Frequency Analysis

• Simulate system at points on a mesh in parameter space
• FFT used to generate power spectrum
• Frequency and Amplitude of highest power oscillation visualised
Parkinsonian Isolated Channel
Stable Oscillations – Frequency Analysis
Coupled Channel Frequency Analysis

• Repeated same frequency analysis for 5 coupled channels in line topology
• Set $w_{ss} = 0$
  • in line with biological observations
• Replace with $\alpha$
• Took too long to reproduce

\[
\begin{align*}
\tau_s x_i &= -x_i + Z_s (w_{ss} x_i - w_{gs} y_i + I) \\
\tau_g y_i &= -y_i + Z_g (-w_{gg} y_i + w_{sg} x_i - \alpha w_{gg} \sum_{j \in L \setminus i} y_j), \quad i=1,2,...,N
\end{align*}
\]
Summary

- Healthy STN-GPe network cannot oscillate in isolated channel condition
  - I found oscillations in this condition, but they are unstable
- Parkinsonian STN-GPe network can oscillate with isolated channels
  - oscillations are stable and in the beta band
  - but this depends on self-stimulation by STN (which does not occur physiologically)
- Networked STN-GPe channels don’t require self-stimulation
  - oscillations still in beta band for healthy conditions
  - much larger oscillatory region in parkinsonian condition
  - much of parkinsonian oscillation is faster than beta band
- More connected networks of channels may slow down oscillations into the beta band
- In Parkinson’s, it is possible for beta band oscillations to originate from GPe-STN interaction