Mathematics behind Parkinsonian Tremors

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Table of contents

Preliminaries

The Discrete Model

The Convergence theorems

The Continuous Model

Results
Disclaimer

- The work here represents the author’s personal views and not that of his employer. Even though the work was done in his spare time, the author is thankful to his employer for providing an environment conducive to do research.
Parkinsonian Tremors

- Tremors are a classic symptom of Parkinson's.
- The mid-brain is most affected, in particular,
  - The STN and
  - The GPe
  are most involved.
- Tremors are characterized by increased activity in the STN.
- Origin of tremors can be at a cellular level or due to network effects.
The Mid-Brain

Not to scale!
Prior work

- Austin and Tsai in 1960s – mapped neuronal activity during tremors to a Van der Pol oscillator.
- Limit cycle implies oscillation.
- Break the circuit and tremors go away.
- Lots of mathematical work on Parkinsons tremors: Rubin, Best, Terman ... and on neuronal synchronization: Peskin, Newhall ... (apologies for the list being incomplete).
Our Contribution

▸ Build upon Austin and Tsai.
▸ Start with an arbitrary set of rules for neuronal interaction – a discrete Markov chain.
▸ Use convergence theorems to obtain a Itô diffusion (not always feasible! (cf. jumps)).
▸ Analyze the drift and diffusion PDEs to obtain conditions on existence of limit cycles; (cf. the Van der Pol oscillator in Austin and Tsai).
Proof Overview

- Markov Chain model
- Ito diffusion
- Non-vanishing vol.
- vanishing vol.
- Random wavelength
- Hopf bifurcation
- Saddle node bifurcation
Rules for neuronal excitation

- There are $n$ neurons in each of the STN, GPe and the motor cortex.
- Underlying connections modelled as Erdős-Rényi random graph.
- Each neuron can be excited or unexcited.
  - An excited neuron in the STN can excite an unexcited neuron in the GPe.
  - An excited neuron in the GPe can inhibit an excited neuron in the STN.
  - ....
Dovzhenok and Rubchinsky [2013]

[Mid−Brain circuit; from Dovzhenok and Rubchinsky]
The model as a graph
Scaling Limits

Standard Brownian Motion

OU Process
Scaling limit of discrete model

- The fraction of excited neurons in STN, GPe and MC at time $t$ be $x_t$, $y_t$ and $z_t$.
- Then the discrete model translates to (roughly),

\[
\begin{align*}
    dx_t &= \theta c_{GS} x_t y_t + c_{RS} (1 - x_t) z_t dt + \sigma_S dW_t^1 \quad (1) \\
    dy_t &= c_{SG} x_t (1 - y_t) - c_{RS} y_t z_t dt + \sigma_G dW_t^2 \quad (2) \\
    dz_t &= -c_{SR} x_t z_t + c_{RR} dt + \sigma_R dW_t^3. \quad (3)
\end{align*}
\]

- $\theta$ parametrizes rebound excitation, $c_{XY}$ parametrize delays, volatility $\sigma_S$ can go to zero (deterministic) or to $x_t(1 - x_t)$ depending on how one scales.
Deterministic case

- Drifts give a 3d dynamical system.
- Some easy to deduce results, based on simplifying assumptions.
- Assuming $\theta > 0$ one can show hopf bifurcation exists.
- No hopf bifurcation for $\theta < 0$.
- Recall hopf bifurcation implies limit cycle.
- (work in progress) computing the Lyapunov coefficient.
- (work in progress) Study chaotic property – no predicatibility in tremors.
Noisy case

- Define the wavelength as a random variable measuring the time from peak to trough.
- If variance is smaller than the mean it will look periodic.
- Variance is non-increasing in $\theta$.
- Can also show that the asymptotic measure for $(x_t, y_t, z_t)$ is far from uniform based on the zeroth order coefficient of the adjoint.