The Effects of Gabapentin on Epileptic Seizures: A Computational Model

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Introduction

- **Epilepsy** is a neurological disorder that causes repetitive episodes of sensory disturbance, often manifested as epileptic seizures, which occur due to electrical misfires in the brain.
- Current therapeutics have been shown to be harmful for long term use:
  - Sedatives, used to stop epileptic seizures tend to cause breathing difficulties in patients.
  - Some anticonvulsant, sedative drugs can cause seizures in patients with pre-existing epilepsy.
- Administering **gabapentin**, an alternative anticonvulsant and nerve pain medication, has shown to be a more effective method of treatment for epileptic seizures.

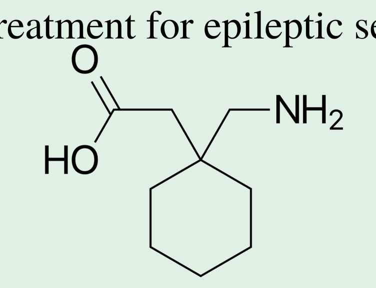


Fig. 1 Molecular structure of gabapentin.

- Gabapentin is a drug that interacts with cortical neurons at auxiliary subunits of voltage gated calcium channels, which control synaptic transmission in excitable neurons, in order to modulate certain types of Ca2+ current.
- Mechanism of action of gabapentin:
  - Increases GABA responses at non-synaptic sites in neuronal tissues
  - Reduces the release of mono-amine neurotransmitters by binding to NMDA receptors on the postsynaptic terminal
- The goal of our study was **to determine the conditions under which Gabapentin has the greatest potential to suppress epileptic seizures** through its interactions with voltage-gated calcium ion channels.

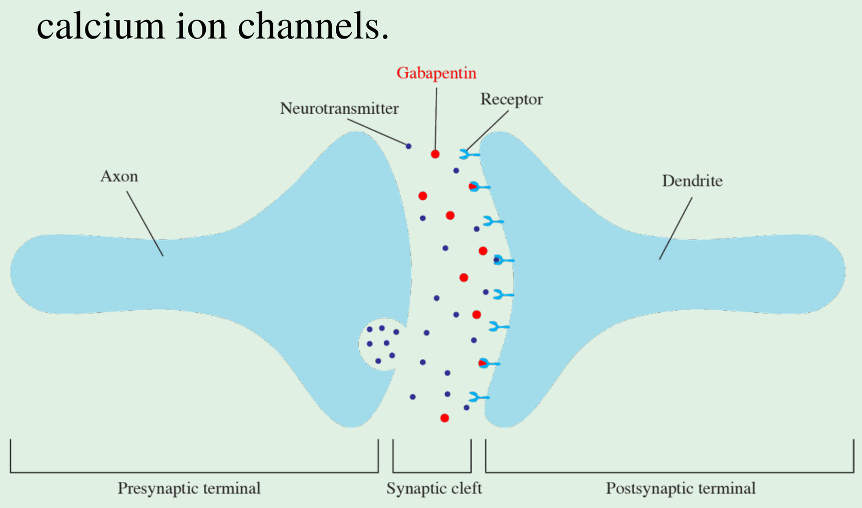


Fig. 2 Gabapentin binds to receptors to reduce neurotransmitter release.

Methods

- Adapted a Python NEURON model[2] that simulates seizures in the CA3 region of the hippocampus:
  - Simulates **CA3 neurons** consisting of:
    - Pyramidal cells
    - Basket cells
    - Oriens-lacunosum moleculare (OLM) cells
  - Rendered epileptic when dendritic inhibition to pyramidal cells is impaired due to the dysfunction of OLM interneurons.
  - After standardizing the baseline activity (theta-modulated gamma oscillations), systematic changes are made in the connectivitions between the neurons in order to compensate for the impairment of dendritic inhibition.
  - Utilizes GABA, AMPA, and NMDA receptors and both the HCN1 and HCN2 genes.
  - This model analyzes the **activity patterns, oscillations, and brain rhythms when the network becomes epileptic.**
  - After running, simulations will generate 3 graphs:
    - Raster plot
    - Local field potential (LFP) graph
    - Power Spectrum Density
- Implementing Gabapentin:
  - **Voltage gated calcium channels** are added to the soma and dendrites of excitatory pyramidal cells.

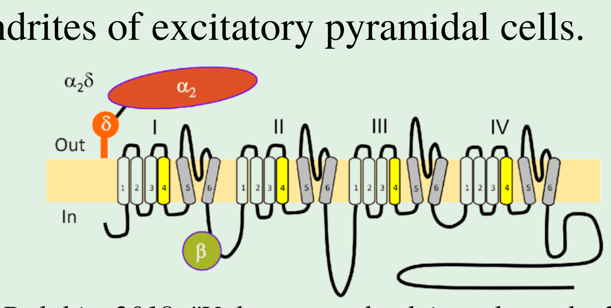
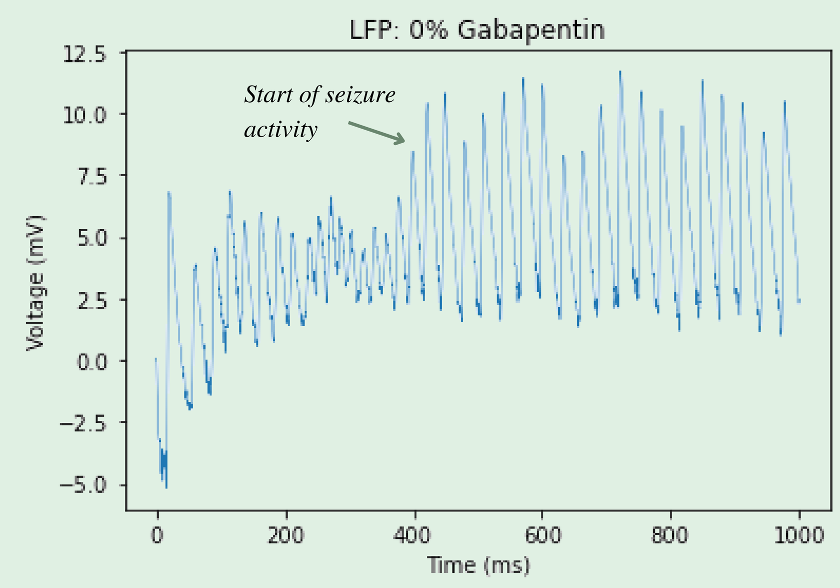


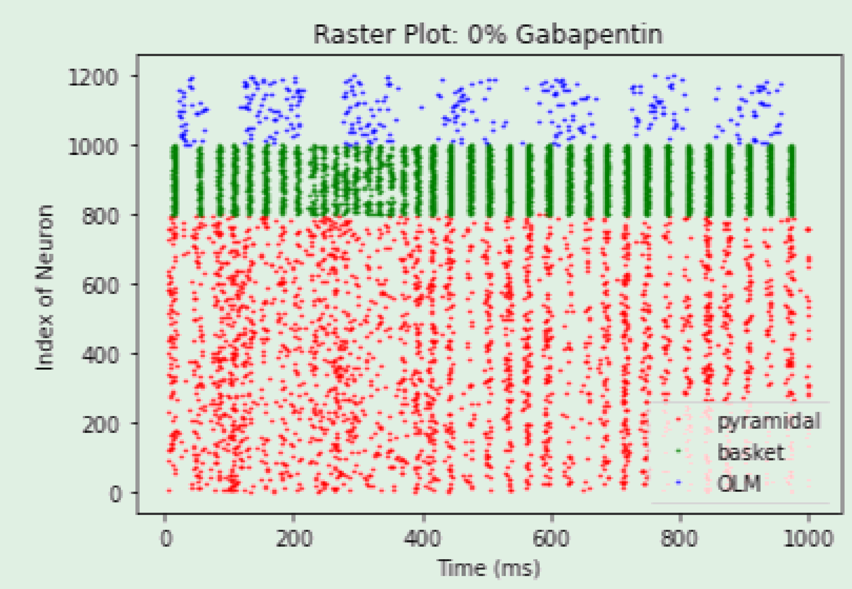
Fig. 3 Voltage gated calcium channels through which gabapentin acts

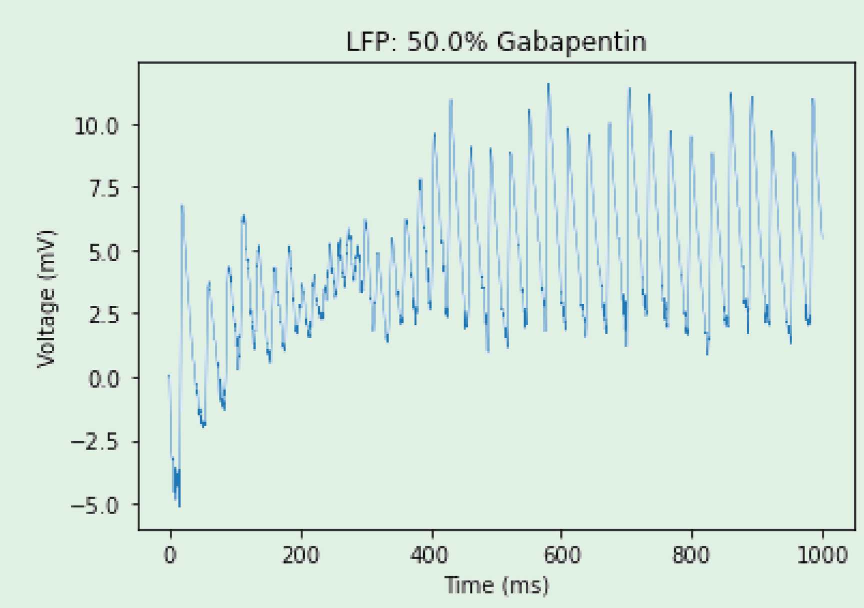
(Dolphin, 2018, "Voltage-gated calcium channel α2δ subunits")

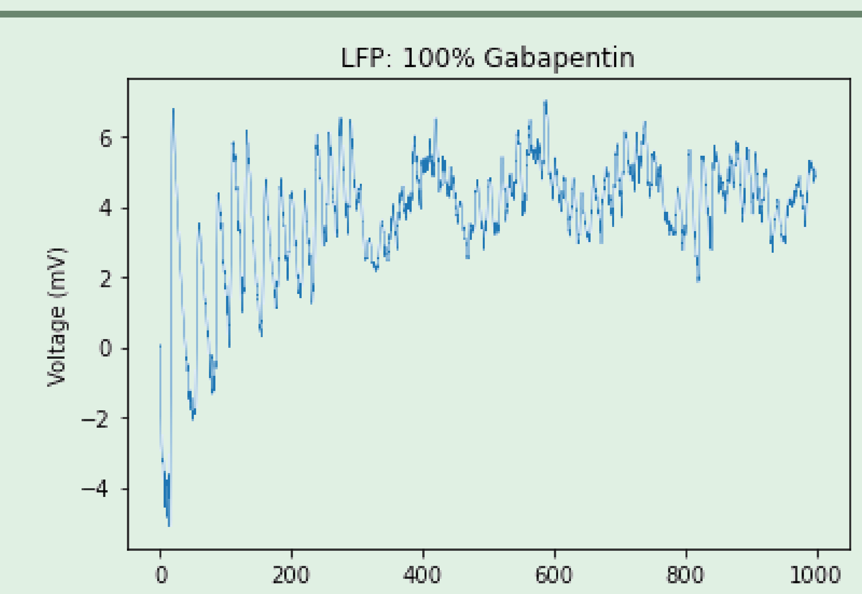
  - A gabapentin variable is created to assign various dosages of gabapentin on a scale from 0 to 1.
  - When the gabapentin dose is increased, the calcium channel conductance is reduced in the soma and dendrites of pyramidal cells.
  - 3 simulations were run at 3 gabapentin dose levels:
    - No dose, medial dose, and maximum dose
  - Data is graphed using matplotlib

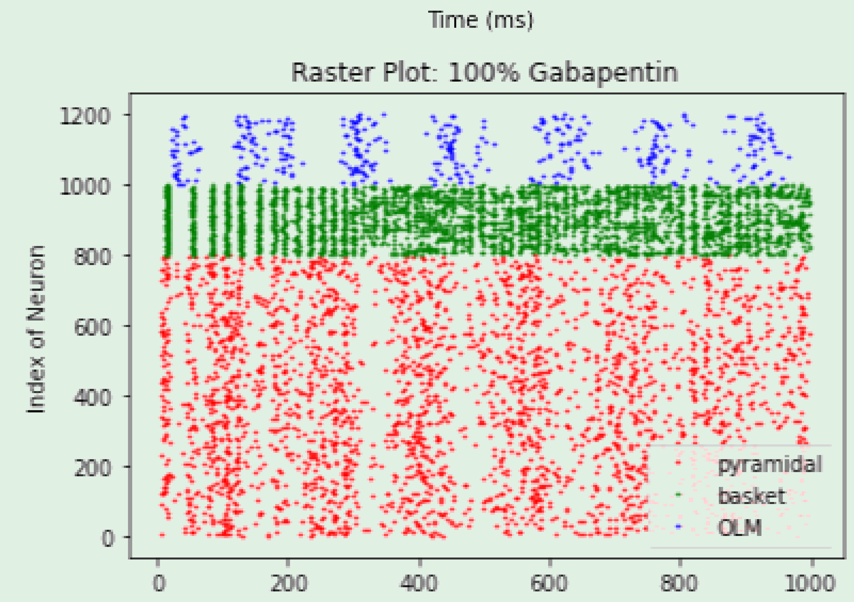
Results

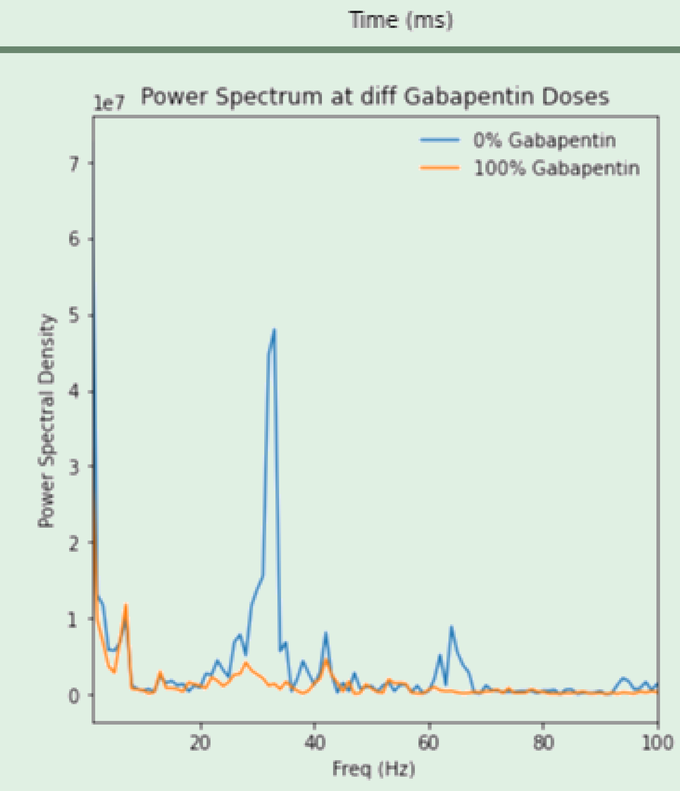












Conclusion

- Each simulation displays three graphs:
  - Local Field Potential
    - Graphs electrical activity in the brain in the CA3 region of the hippocampus
    - Plot shows voltage (mV) vs. time (ms)
    - Chaotic spiking activity is characteristic of seizure behavior
  - Raster Plot
    - Displays the spiking activity of the group of neurons over time
    - Seizure activity is characterized by frequent and irregular spiking
    - Regular spiking represents healthy baseline brain activity
  - Power Spectrum Density
    - Uses Fast Fourier Transforms to display dominant frequencies in firing activity
    - 0% gabapentin displays beta oscillations with high density at 32 Hz and gamma oscillations at 63 Hz.
    - 100% gabapentin dose reduces beta and gamma oscillations
- Based on our analysis, a maximum dosage of gabapentin was optimal in suppressing the seizure.
  - However, a small dosage had a minimal effect on the seizures.
- Our results support the current hypothesis that gabapentin is a viable anticonvulsant to treat epileptic seizures as long as it is supplied in appropriate doses.
- Our model has the potential to assist future studies of epileptic seizures by finding dosages of gabapentin that will result in the greatest decrease of uncontrollable epileptic brain activity.
- Future clinical trials are necessary to determine the adequate dosage and legitimacy of the drug in epilepsy patients.

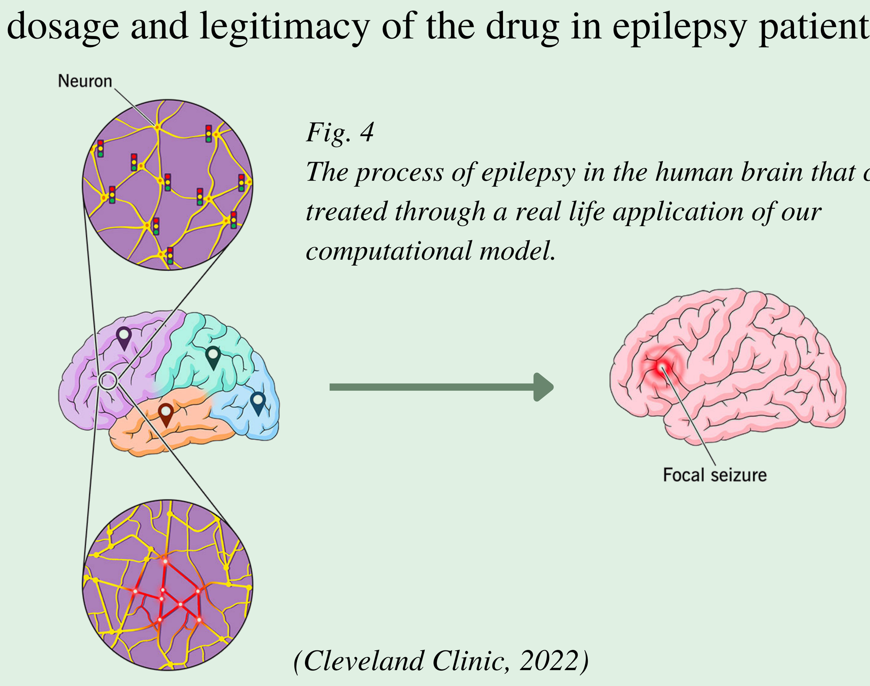


Fig. 4 The process of epilepsy in the human brain that can be treated through a real life application of our computational model.

(Cleveland Clinic, 2022)

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