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Investigating the effects of propofol-induced tonic inhibition on rhythmic neural activity in a hippocampal interneuron network

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Motivation

- Propofol-induced sedation is achieved by positively modulating GABAergic inhibitory activity [1]
- Synaptic and extrasynaptic GABA4 receptors are ubiquitous in the brain [2]
- GABAergic hippocampal interneurons have been shown capable of generating and maintaining γ-band (20–80 Hz) rhythmic neural activity [3]
- γ-band oscillations are thought to underlie long-term memory consolidation [4]
- We study the effect of the propofol-induced extrasynaptic GABAergic modulation [5] on such self-emerging synchronous activity

Neuron Model

- Neuron Model:
  \[ C_m \frac{dV}{dt} = -I_L - I_K - I_NA - I_{Ap} = I_{Prop} + I_{Syn} \]
- Hodgkin-Huxley Currents and Stimulation:
  \[ I_{Lax} = f(V_L) \quad I_K = f(V_K, m^4) \quad I_NA = f(V_NA, h) \quad I_{Prop} = 0.4 nA \]

Synapses and Propofol

Schematic of GABA (orange) binding on synaptic and extrasynaptic receptors causing CI\(^-\) ions influx in the postsynaptic neuron. Extrasynaptic GABA receptors mediate tonic inhibition, and are potentiated by extracellular propofol (red). Propofol also binds on synaptic GABA receptors (not modelled in the present work, thus not shown).

- Inhibitory Postsynaptic (Phase) Current:
  \[ I_{Syn} = -g_y(V_e - E) \]
- Inhibitory Extrasynaptic (Tonic) Current [6]:
  \[ I_{Prop} = -g_y(V_e - E) \quad g_y = C_yg_y \quad (propofol) \]
- Network Topology:
  \[ N = 100 \quad \rho = 0.6 \quad (connection probability) \]
- Network Synchronisation Measure [5]:
  \[ \kappa^2(r) = \sum_{i=1}^{N} \sum_{j=1}^{N} X_i(t) Y_i(t) \quad \kappa^2(r) = \frac{1}{N} \sum_{i=1}^{N} X_i(t) \quad 0 \leq \kappa^2(r) \leq 1 \]
  \[ L = \frac{t_{max}}{\tau} \quad \tau = 10 \text{ ms} \]

Results – Increasing Anaesthetic Dosage

Increasing the dosage of propofol to \( g \geq 21 \text{ nS} \) causes stronger synchrony amongst the neurons in the network \( \kappa^2(t) = 0.2 \), while slowing down the oscillatory activity to a frequency of \( f_{osc} \approx 10 \text{ Hz} \).

Results – Propofol Synchrony and Oscillations

Increasing the propofol dosage to \( g \geq 21 \text{ nS} \) reduces the synchrony amongst the neurons in the network \( \kappa^2(t) = 0.2 \), and slows down the oscillatory activity to a frequency of \( f_{osc} \approx 10 \text{ Hz} \).

Conclusion

- Anesthetics target both synaptic and extrasynaptic GABA4 receptors
- Increasing the dosage of anaesthetic agents can strengthen synchronous activity in networks of hippocampal neurons
- Parasynaptic excitation behaviours might be mediated by the effects of anesthetics on extrasynaptic GABA4 receptors

References