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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 *GABA*ergic inhibitory activity [1]
- Synaptic and extrasynaptic *GABA_A* receptors are ubiquitous in the brain [2]
- GABA*ergic 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 *GABA*ergic modulation** [5] on such self-emerging synchronous activity

Neuron Model

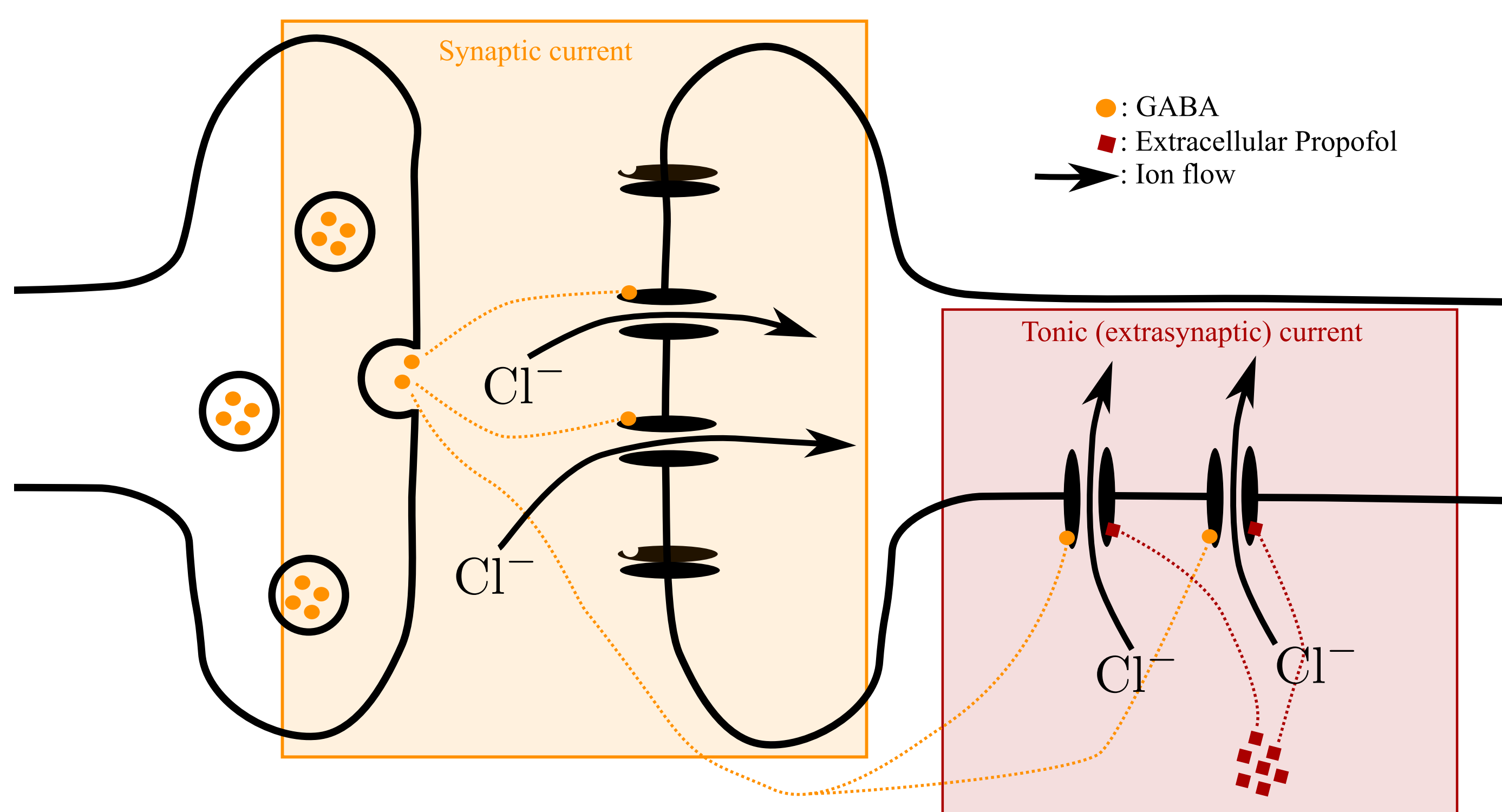
- Neuron Model:

$$C_m \cdot \frac{dV}{dt} = -I_L - I_K - I_{Na} - I_{Syn} - I_{SynTonic} + I_{Stim}$$

- Hodgkin-Huxley Currents and Stimulation:

$$I_{Leak} = f(V_m) \quad I_K = f(V_m, n^4) \quad I_{Na} = f(V_m, m^3, h) \quad I_{Stim} = 0.4 nA$$

Synapses and Propofol



Schematic of *GABA* (orange) binding on synaptic and extrasynaptic receptors causing Cl^- ion 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 (Phasic) Current:

$$I_{Syn} = -g_i \cdot (V_m - E_i) \quad \frac{dg_i}{dt} = -\frac{g_i}{\tau_i} \quad g_i \leftarrow g_i + w_{ii}$$

- Inhibitory Extrasynaptic (Tonic) Current [5]:

$$I_{SynTonic} = -g_t \cdot (V_m - E_i) \quad g_t \propto [C_{12}H_{18}O]_o \quad (\text{propofol})$$

- Network Topology:

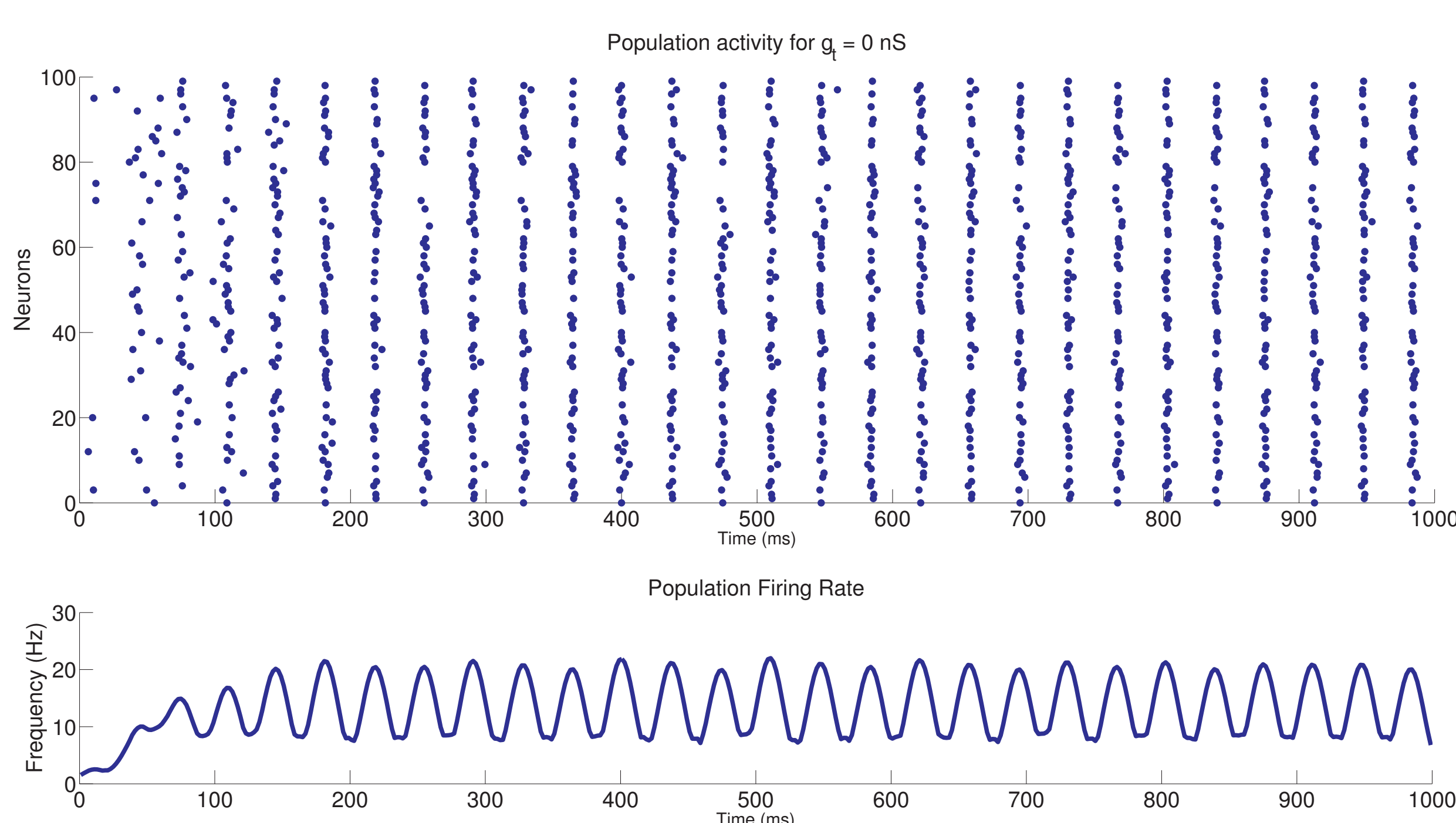
$$N = 100 \quad (\text{neurons}) \quad \rho = 0.6 \quad (\text{connection probability})$$

- Network Synchronisation Measure [3]:

$$\kappa_{i,j}(\tau) = \frac{\sum_{l=1}^L X_i(l)Y_j(l)}{\sqrt{\sum_{l=1}^L X_i(l) \sum_{l=1}^L Y_j(l)}} \quad \kappa(\tau) = \frac{\sum_{i=1}^N \sum_{j=1}^N \kappa_{i,j}(\tau)}{N^2} \quad 0 \leq \kappa(\tau) \leq 1$$

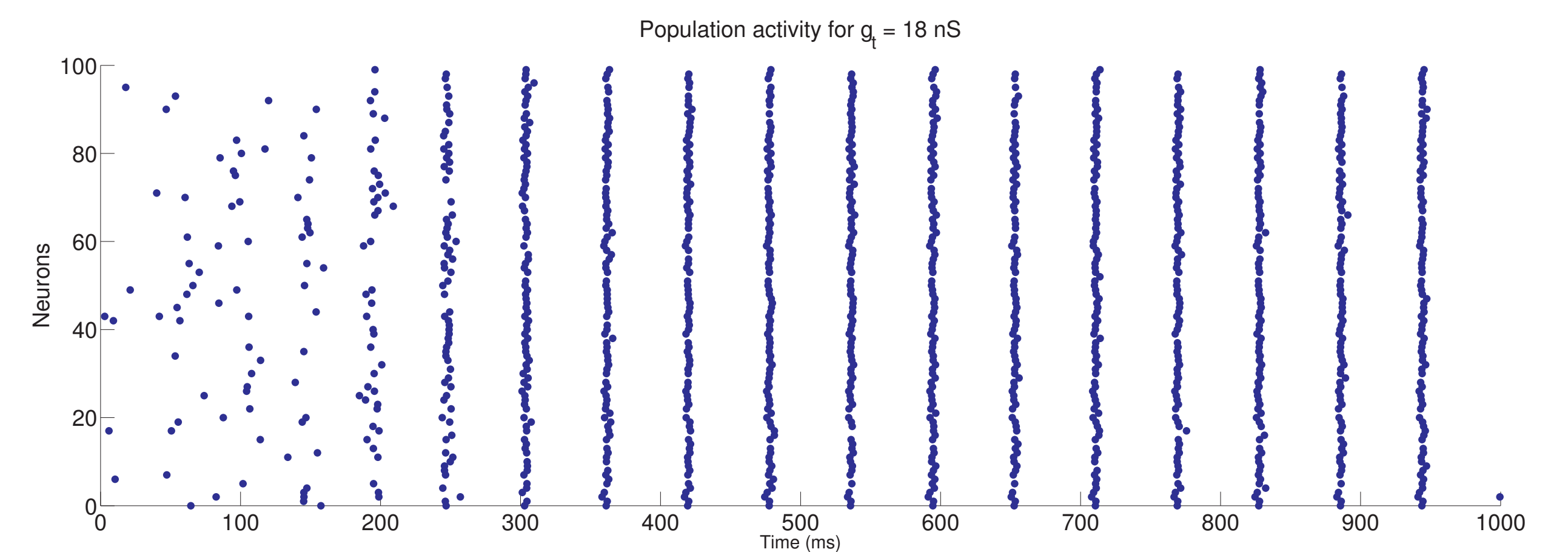
$$X_i(l), Y_j(l) \in \{0, 1\} \quad l = 0, 1, 2, \dots, L \quad L = \frac{t_{sim}}{\tau} \quad \tau = 10 ms$$

Results – γ -band Synchronisation

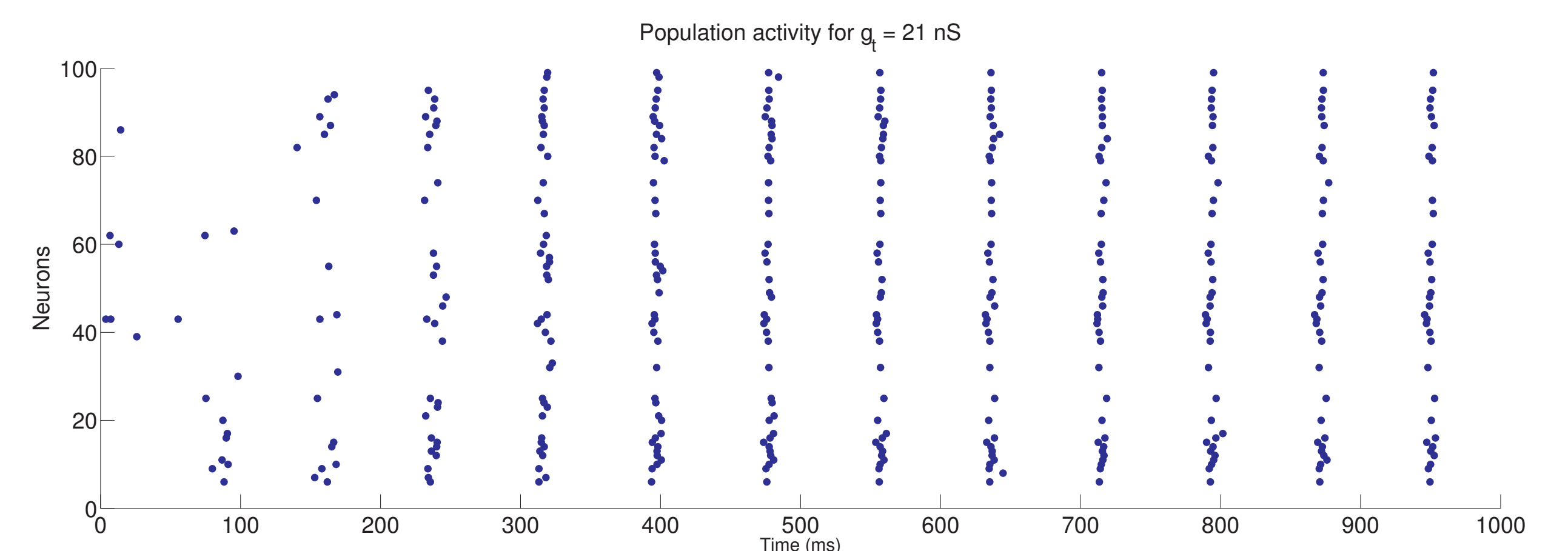


Networks of Hippocampal interneurons display synchronous activity with a value of $\kappa(\tau) = 0.4$, in the γ -band at an oscillatory frequency of $f_{osc} \simeq 25 Hz$, when subject to a constant stimulation, in the absence of propofol.

Results – Increasing Anaesthetic Dosage

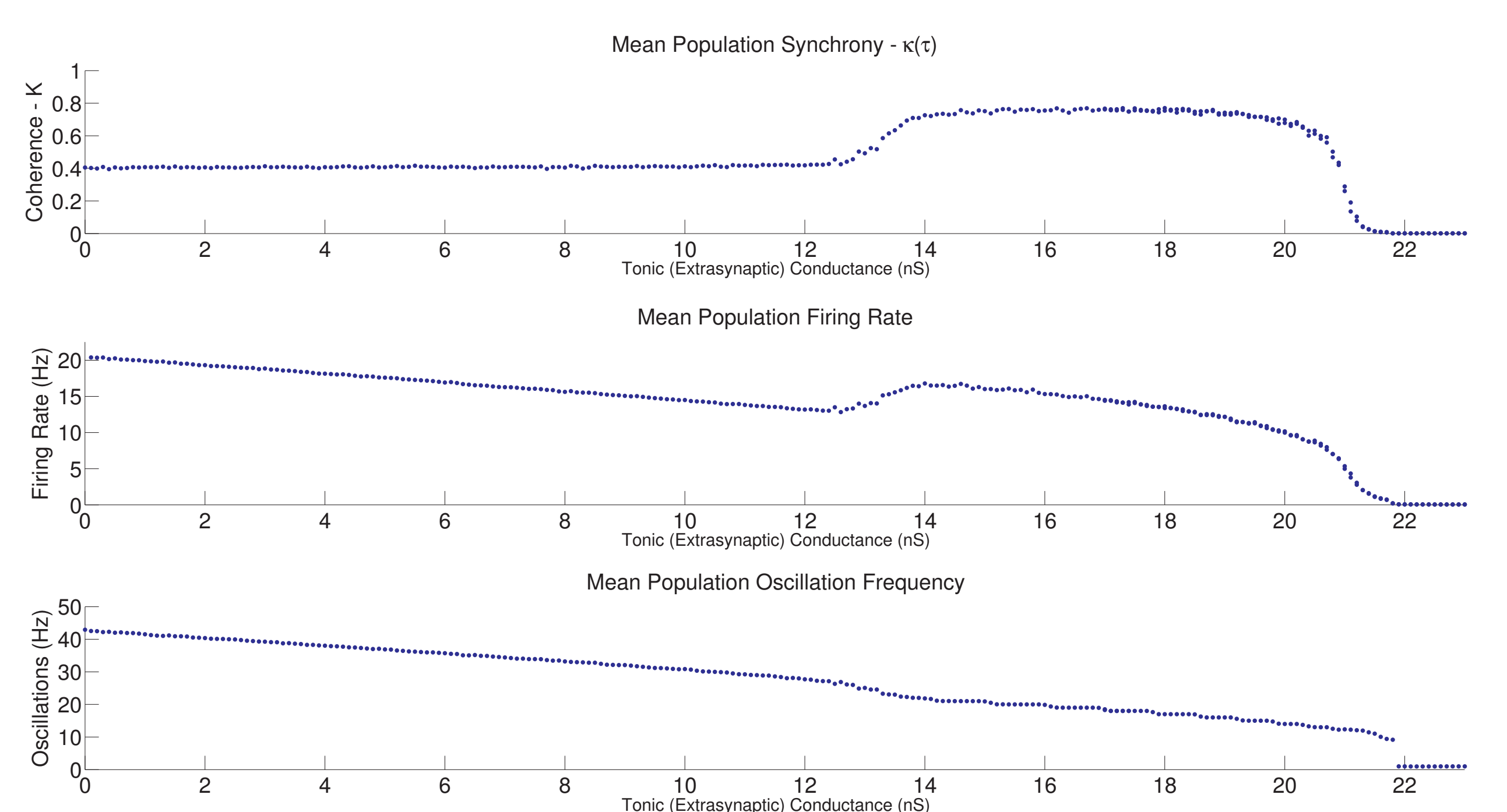


Increasing the dosage of propofol to $g_t = 18 nS$ causes stronger synchrony amongst the neurons in the network $\kappa(\tau) = 0.8$, while slowing down the oscillatory activity to a frequency of $f_{osc} \simeq 15 Hz$.



Increasing the dosage of propofol to $g_t \geq 21 nS$ weakens the synchrony amongst the neurons in the network $\kappa(\tau) = 0.2$, and slows down the oscillatory activity to a frequency of $f_{osc} \simeq 10 Hz$.

Results – Propofol Synchrony and Oscillations



Increasing the propofol dosage – by acting on the tonic conductance g_t – causes the overall activity of the network to decrease, until a critical value of $g_t = 14 nS$ at which both the network synchronisation and firing rate increase. When the concentration value reaches a value of $g_t \geq 21 nS$ the activity, synchronous or otherwise, fades out.

Conclusion

- Anaesthetics target both synaptic and extrasynaptic *GABA_A* receptors
- Increasing the dosage of anaesthetic agents can strengthen synchronous activity** in networks of hippocampal neurons
- Paradoxical excitation behaviours might be mediated by the effects of anaesthetics on extrasynaptic *GABA_A* receptors

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