Latte for Leeches:

The Double-Coupleccino Model

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Introduction:

The experimental work of this project, alongside other previous findings, show that caffeine may influence the gap junctions of electrically coupled cells. Modifications to the coupling strength of such cells may also lead to variations in the features of the electrophysiological response - such as hyperpolarization amplitude, spike count, spike latency, inter-spike interval (ISI). To gauge the effects of this, a Hodgkin-Huxley (HH) type model was built to simulate coupled Retzius cells.

Methods:

A previous one-cell, two-compartment model was used to build to a three-compartment model, which mathematically represents the soma (compartment 1), gap junction (GJ - compartment 2), and spike initiation zone (SIZ - compartment 3) (figure 1). The soma contains leak and hyperpolarization activated current regulated by gL and gH, while the spike initiation zone, which is responsible for generating action potentials, has sodium alongside slow and fast potassium activation/inactivation currents, regulated by gA, gK, gKA respectively. These two identical cells were then combined at the gap junction compartment, and with current (Iinj) being applied to the soma compartment of the 'presynaptic' cell.

$$\mathbf{I_{GCoup} = g_{GCoup} \times (V2_{Pre} - V2_{Post})} \text{ – Current between 2 cell compartment regulated by the gGCoup parameter}$$

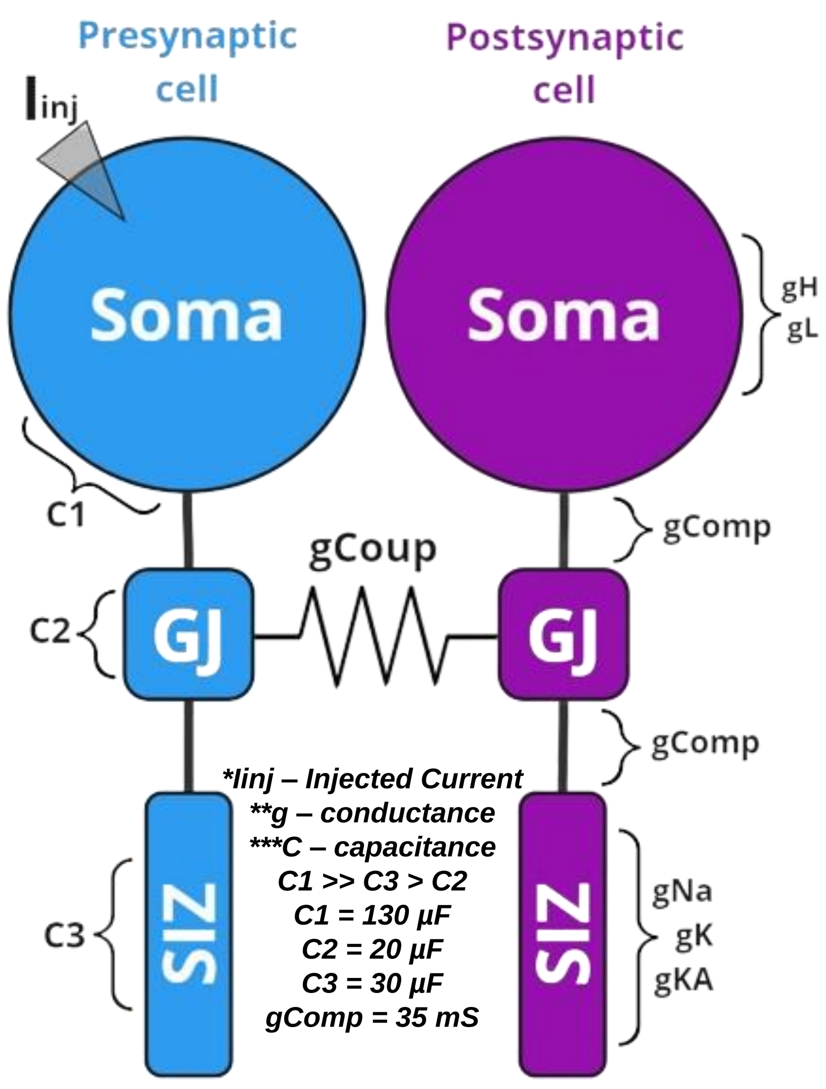
$$\frac{dV2_{Pre}}{dt} = \frac{(IC2_{Pre} - IC3_{Pre} - I_{GCoup})}{C2_{Pre}} \rightarrow \text{Update Vm for each time point} \rightarrow V2_{pre(j+1)} = V2_{pre(j)} + \frac{dV2_{Pre}}{dt} \times dt$$

$$\frac{dV2_{Post}}{dt} = \frac{(IC2_{Post} - IC3_{Post} + I_{GCoup})}{C2_{Post}} \rightarrow \text{Update Vm for each time point} \rightarrow V2_{post(j+1)} = V2_{post(j)} + \frac{dV2_{Post}}{dt} \times dt$$

Hyperpolarization amplitude, spike count, and latency were fitted to the average range of the experimental datasets of large leech Retzius cells. Passive features were fitted to a 1 s long, -1 nA current based on experimental measurements, while active features were fitted to 1 s long, +1.5 nA current, as it initiated analyzable spike properties.

Figure 1. Graphical representation of HH model for Retzius cells

Injected current goes into the presynaptic soma compartment and then flows to the SIZ of presynaptic cell. This compartment initiates spikes based on the simulation of three parameters (Na activation, K activation, and KA inactivation). Initiated spikes appear in the soma of the presynaptic cell and pass through the GJs. If enough current flows to the SIZ of the postsynaptic cell and exceeds the threshold, it leads to the initiation of a spike in the postsynaptic cell, appearing in the soma.



Result 1: Parameter Combinations

The simulation aimed to faithfully reproduce key electrophysiological features observed in large leech Retzius cells by strategically adjusting ion channel conductances, capacitances, and activation parameters. Critical combinations included gK (58 mS) for precise spike repolarization, gA (162 mS) essential for spike frequency adaptation, and gN (645 mS) ensuring robust action potential initiation.

Additionally, gL (10 mS) maintained resting membrane potential stability, while gH (1 mS) contributed to membrane potential dynamics during hyperpolarization. Capacitance parameters, such as c1 (130 µF) influencing soma dynamics, and c2 (20 µF) supporting effective electrical coupling via gap junctions, were crucial. The SIZ capacitance, c3 (30 µF), produced higher spikes at lower values.

Activation times (Tau) like TauH (20) for Hyperpolarization channel kinetics and TauN (50 ms) for sodium channel inactivation were pivotal in shaping spike properties. These parameters collectively optimized through simulation, closely mirrored experimental data, capturing membrane potential dynamics, spike features (count, latency, ISI), and responses to current injections accurately.

Certain combinations of activation time parameters can lead to other electrophysiological phenomena, such as chattering and double spikes, which are also noticed in experimental caffeine trials.

Further parameter calibration could be done over a longer time, or, for example, by an evolutionary classification algorithm.

Parameter type	Values
Channel Conductance	gK = 58 mS gA = 162 mS gN = 645 mS gL = 10 mS gH = 1 mS
Reversal Potentials	EL = -50 mV EH = -20 mV EN = +45 mV EK = -55 mV
Time Scale in/activation functions	TauH = 20 TauN = 50 TauB = 30 TauZ = 100
Compartment Conductance	gComp = 35 gGCoup = (5.0:21.5)

Table 1. Coupled Retzius cell Model Parameters

Result 2: Comparison to Real Responses

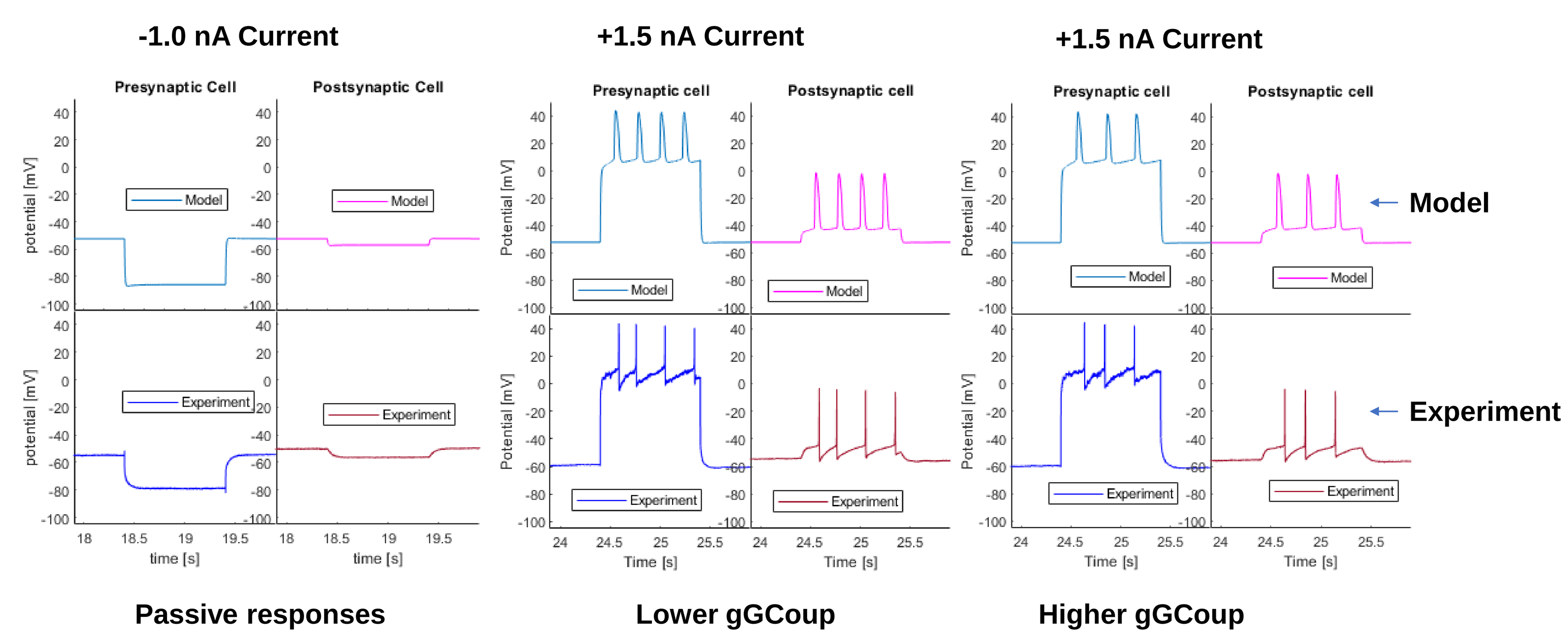


Figure 2. Model and Experimental Cell Responses to Injected Current: Model capabilities of passive and active response generation compared to biological responses. The first plot shows similar amplitude of hyperpolarization (33-35mV) and resting membrane potential (-50 to -55mV) to experimental examples. Second and third plots show active response properties to 1.5 nA stimulus; at lower and higher gGCoup values respectively, showing that higher gGCoup causes lower spike counts.

Result 3: Impact of Coupling Strength

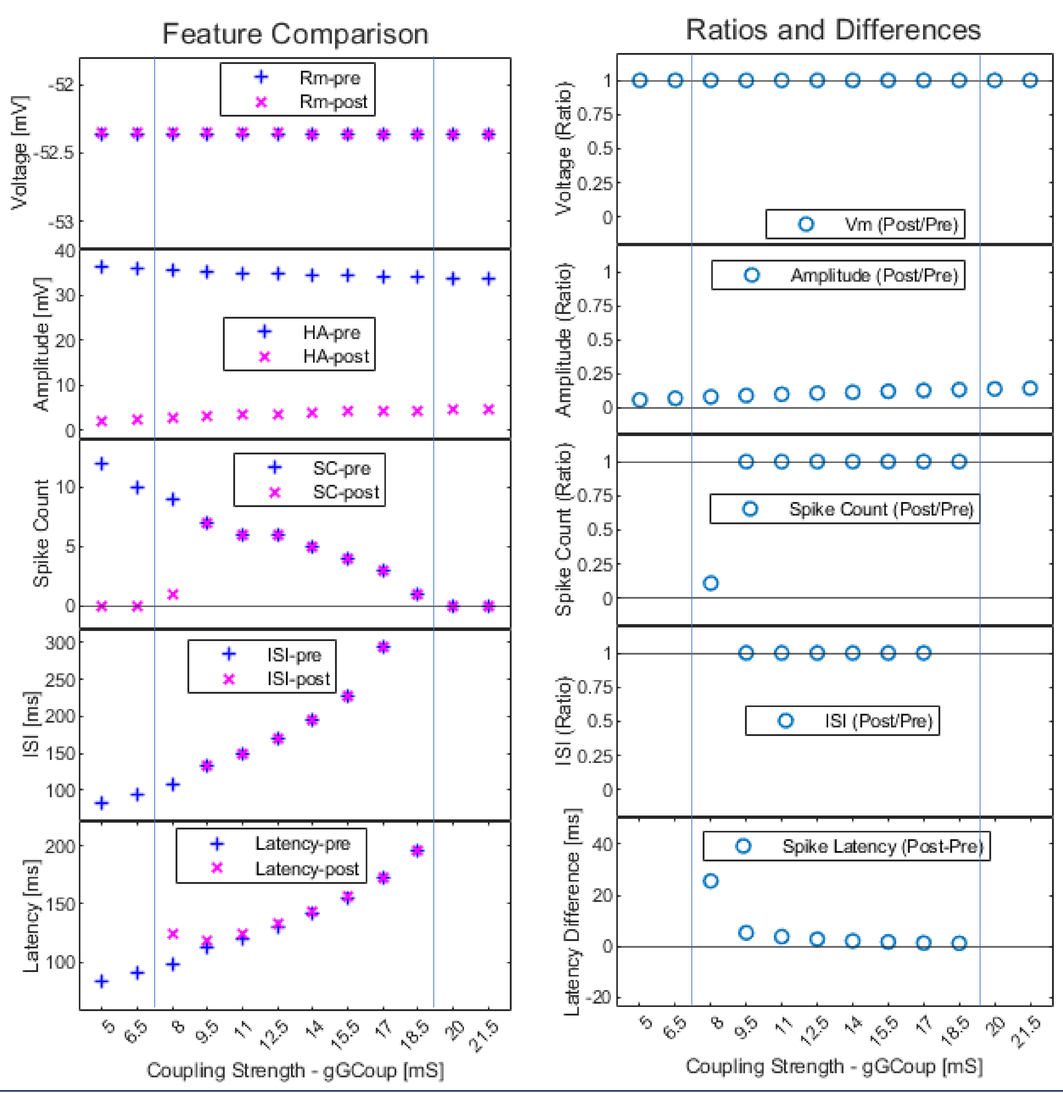


Figure 3. Figure shows how changes in gap junction conductance (gGCoup) affect various neural features.

The left plot depicts pre- (blue) and post- (magenta) values of these features as a function of coupling strength. The right plot focuses on the ratio or difference changes between pre- and post-values for each feature induced by gGCoup.

Increasing gGCoup leads to no change in resting membrane potential; a slight decrease in hyperpolarization amplitude of presynaptic cell and increase in postsynaptic cell (therefore increase in ratio); lower spike counts; an increase in ISI values, (ratio does not change); and higher spike latency (with the difference decreasing). Model breaks down at <= 6.5 mS and at >= 20.

Values for spike count and latency pre- and post -synaptic differ at 8 mS, then gradually equal out with increasing coupling strength.

Conclusion

1. Model does not represent fully expected action potential shapes, but shows similar response features, therefore it can help to understand which parameters are altered in pharmacological experiments. Further optimization of activation/inactivation parameters may produce expected spike shapes.
2. From observing the ratios of around 1 in all parameters produced by the model at specific gGCoup values, it can be said that caffeine has an effect not only on coupling strength, but also on the kinetics of each cell.
3. Optimizing further compartments in future could prove to produce a more robust representation of electrically coupled cells.

References

1. Prescott, S.A. (2014). Excitability: Types I, II, and III. In: Jaeger, D., Jung, R. (eds)
2. https://link.springer.com/referenceworkentry/10.1007/978-1-4614-7320-6_151-1