Neuronal Heterogeneity Underlies Electrical Synapse Asymmetry and Spike Time Variability in Coupled Neurons

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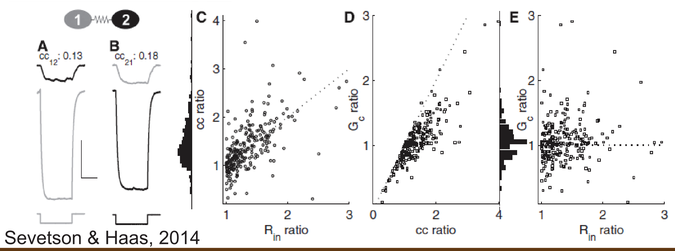
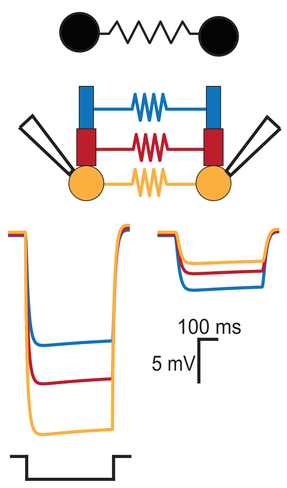
Introduction

Electrical synapses, composed of gap junctions of the Cx36 protein, allow direct communication between two neurons. Often, these connections are asymmetric and preferentially pass electrical currents to one cell compared to the other. Differences in conductance of the gap junction itself, or intrinsic cellular difference do not explain the full extent of asymmetry measured between neurons of the thalamic reticular nucleus (**C-E**). Asymmetry has been shown to switch firing order between two neurons (Sevetson & Haas, 2014). In this study, we use a multi-compartmental Hodgkin-Huxley model to further explore properties that may produce asymmetry seen in experimental measurments. We show many factors: synapse location, dendritic geometry, and input resistance can all produce similar asymmetric outcomes measured at the soma. We also show asymmetry, regardless of how it was produced, resulted in a change in latency to fire action potentials in our model.



Sevetson & Haas, 2014

Multi-Compartmental Model



We expanded our single-cell TRN model (black) to include dendritic compartments, and allow for varying electrical synapse location and dendritic morphology. Ion channel conductance, electrical and chemical synaptic inputs were modeled the same as our previous model (Pham & Haas, 2018), with the exception of no Na^+ conductance and lower Ca^{2+} at the dendrite compartments.

Analysis
Coupling coefficient (cc) was computed by injecting hyperpolarizing current into one cell soma and measuring the proportion of resulting voltage deflection at the other soma (i.e. $cc_{12} = dV_2/dV_1$). To measure asymmetry we take the ratio of coupling coefficients from both directions (cc ratio = cc12/cc21).

To measure latency we injected burst like AMPAergic EPSPs, to replicate the activity of thalamic neurons which activate these cells. We varied input time between the two cells from 0-20 ms

Conclusions and references

1. Effective electrical synapse asymmetry may arise from synapse location if coupling is only measured at the soma, as it is in experiments.

2. Intrinsic cell differences (input resistance, dendritic geometry) interact with this form of asymmetry similarly to conductional asymmetry.

3. Asymmetry influences latency to fire action potenetials between a two-cell pair regardless of how it arose, likely due to their influence on dendritic integration.

J. Sevetson, J. S. Haas, Asymmetry and modulation of spike timing in electrically coupled neurons. J. neurophys 113, 1743-1751 (2014)
T. Pham, J.S. Haas, Electrical synapses between inhibitory neurons shape the responses of principal neurons to transient inputs in the thalamus: a modeling study. Sci Rprts. 8:7763 (2018)
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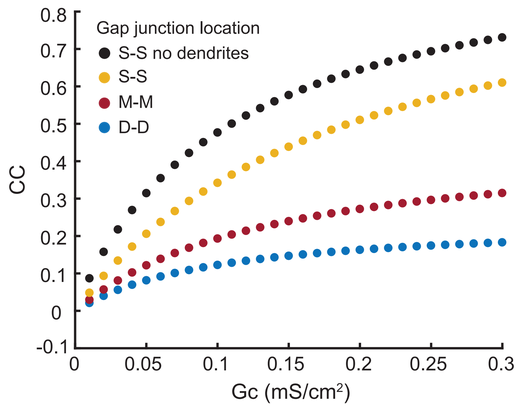
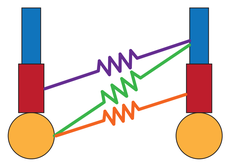
1. Coupling varies with dendritic distance

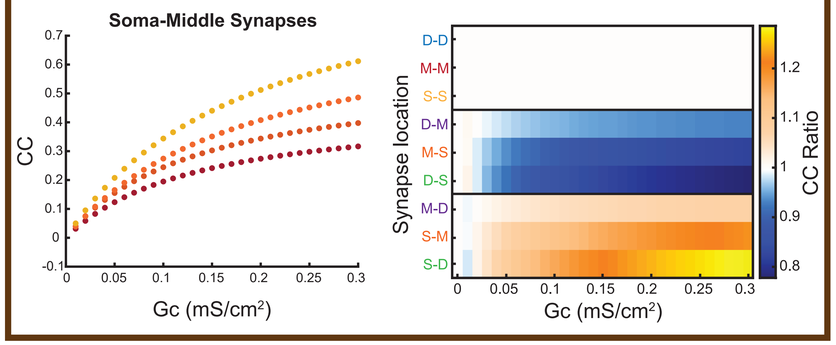
Coupling coefficients vary with electrical synapse location and strength (Gc, coupling conductance). The previous single-cell model (black) had considerably higher coupling values as the addition of dendrites increases the load of the cell network. Synapses further away from the soma results in lower coupling even for considerably high values of synapse strength.



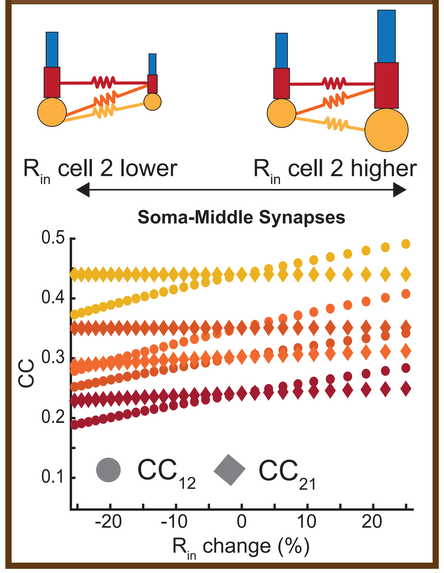
2. Asymmetry produced by coupling between different cell compartments



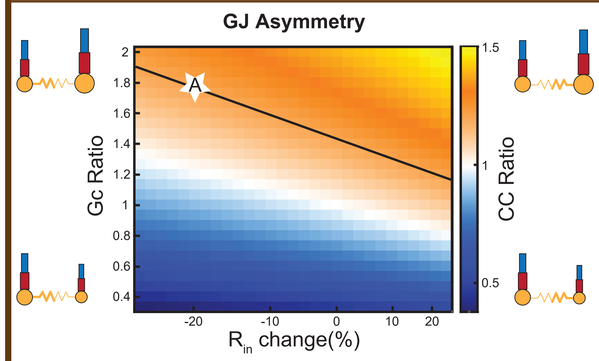
Coupling coefficients from symmetrical electrical synapses between different cellular compartments resulted in apparent asymmetry measured at the soma. Coupling between same compartments were always symmetric (eg. M-M). In contrast, mismatched synapses are marked by decreasing or increasing cc ratios, with the mirror cases producing the same degree of asymmetry in opposite directions (eg M-D and D-M). This effect increased with increasing mismatch (S-D) and with the strength of the electrical synapse, or Rin difference (**Panel 3**, on the left).

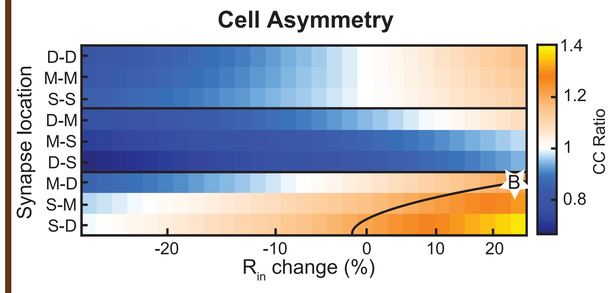


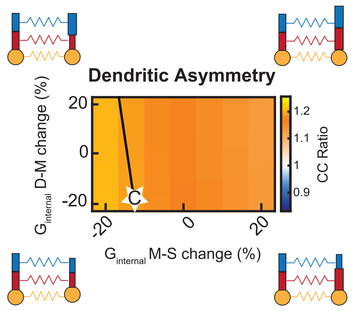
3. Input resistance differences amplify asymmetry



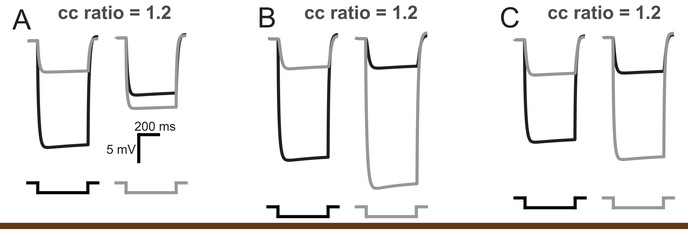
4. Synaptic or intrinsic factors can produce the same asymmetry at the soma







Isoclines show simulations that resulted in approximately the same asymmetry (cc Ratio = 1.2) for three senarios we characterized: (**A**) a conductionally asymmetric S-S gap junction with altered input resistance between the two cells, (**B**) a middle-distal gap junction with altered input resistance between the cells, and (**C**) a soma-middle gap junction with altered dendritic geometry. In all cases, measurment of cc ratio at the soma are the same. In experimental work, all of these factors may combine to produce exact degree of asymmetry, or mask true conductional asymmetry, though revealing all of these factors would not be feasable.



5. Latency to fire action potentials is modulated by asymmetry

Asymmetry shifts response times to synaptic input depending on direction of asymmetry. This is true for both conductionally asymmetric gap junctions, or for asymmetry due to synapse location.