Intrinsic sources and functional impacts of asymmetry at electrical synapses

<https://doi.org/10.1523/ENEURO.0469-21.2022>

Cite as: eNeuro 2022; 10.1523/ENEURO.0469-21.2022

Received: 3 November 2021

Revised: 14 January 2022

Accepted: 2 February 2022

This Early Release article has been peer-reviewed and accepted, but has not been through the composition and copyediting processes. The final version may differ slightly in style or formatting and will contain links to any extended data.

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1 **Manuscript Title:** Intrinsic sources and functional impacts of asymmetry at electrical synapses

2 **Abbreviated Title:** On asymmetry at electrical synapses

3 **Authors:** Austin J. Mendoza¹ and Julie S. Haas^{1,*}

4 **Affiliation:** ¹ Department of Biological Sciences, Lehigh University, Bethlehem, Pennsylvania,
5 USA

6 * Corresponding author

7 **Author Contributions:** AJM and JSH Designed Research; AJM Performed Research; AJM
8 Analyzed data; AJM and JSH Wrote the paper.

9 **Correspondence should be addressed to:** julie.haas@lehigh.edu

10 **Figures:** 8

11 **Tables:** 0

12 **Multimedia:** 0

13 **Abstract:** 227 words

14 **Significance statement:** 66 words

15 **Introduction:** 1150 words

16 **Discussion:** 985 words

17 **Acknowledgements:** We would like to thank Mitchell Vaughn, Meghan Bauer, and Zachary
18 Laswick for input on drafts of this manuscript.

19 **Conflict of Interest:** Authors report no conflict of interest.

20 **Funding** was provided by the NSF (IOS 1557474)

21 **ABSTRACT**

22   Electrical synapses couple inhibitory neurons across the brain, underlying a variety of
23 functions that are modifiable by activity. Despite recent advances, many functions and
24 contributions of electrical synapses within neural circuitry remain underappreciated. Among
25 these are the sources and impacts of electrical synapse asymmetry. Using multi-compartmental
26 models of neurons coupled through dendritic electrical synapses, we investigated intrinsic
27 factors that contribute to effective synaptic asymmetry and that result in modulation of spike
28 timing and synchrony between coupled cells. We show that electrical synapse location along a
29 dendrite, input resistance, internal dendritic resistance, or directional conduction of the electrical
30 synapse itself each alter asymmetry as measured by coupling between cell somas. Conversely,
31 we note that asymmetrical gap junction conductance can be masked by each of these
32 properties. Furthermore, we show that asymmetry modulates spiking timing and latency of
33 coupled cells by up to tens of milliseconds, depending on direction of conduction or dendritic
34 location of the electrical synapse. Coordination of rhythmic activity between two cells also
35 depends on asymmetry. These simulations illustrate that causes of asymmetry are diverse, may
36 not be apparent in somatic measurements of electrical coupling, influence dendritic processing,
37 and produce a variety of outcomes on spiking and synchrony of coupled cells. Our findings
38 highlight aspects of electrical synapses that should always be included in experimental
39 demonstrations of coupling, and when assembling simulated networks containing electrical
40 synapses.

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45 **SIGNIFICANCE STATEMENT**

46 Asymmetry, or unequal transmission of current between two coupled neurons, is a
47 property of electrical synapses often noted but seldom explored. Here we show that multiple
48 intrinsic factors can either produce, or mask, asymmetry. Spike timing and rhythmic synchrony
49 are both affected by asymmetric connections between neurons. These results highlight
50 important consequences of asymmetry that are likely to be recapitulated within coupled
51 networks throughout the brain.

52 **INTRODUCTION**

53 Electrical synapses represent a major form of communication between neurons across
54 neuronal tissue, with many impacts that have not been extensively explored. Asymmetry of
55 transmission, is a frequently noted aspect of electrical synapses: it is the property of unequal
56 transmission of electrical signals between two neurons, and ranges in effect from minor to
57 complete. Electrical synapses have been well-studied in invertebrates, where evidence of
58 asymmetry comes from species including crayfish (Furshpan and Potter, 1959), drosophila giant
59 fibers (Phelan et al., 2008), lobster stomatogastric ganglion (Johnson et al., 1993), and the *C.*
60 *elegans* escape circuit (Liu et al., 2017; Shui et al., 2020). In invertebrate systems asymmetry
61 varies widely, with some synapses displaying full rectification. In contrast, asymmetry at
62 synapses between mammalian neurons is often more modest. Demonstrations of electrical
63 synapse asymmetry are numerous throughout the mammalian brain, including retina (Veruki
64 and Hartveit, 2002), cortex (Galarreta and Hestrin, 2002), inferior olive (Devor and Yarom,
65 2002), dorsal cochlear nucleus (Apostolides and Trussell, 2013), mesencephalic trigeminal
66 nucleus (Curti et al., 2012), cerebellar Golgi cells (Szoboszlay et al., 2016) and molecular layer
67 interneurons (Alcami and Marty, 2013; Mann-Metzer and Yarom, 1999), and the thalamic
68 reticular nucleus (TRN) (Haas et al., 2011; Sevetson and Haas, 2015; Zolnik and Connors,
69 2016). Recent results show that asymmetry can be modified during the activity that results in

70 electrical synapse plasticity (Fricker et al., 2021; Haas et al., 2011), indicating that it is a
71 dynamic property that is under activity-dependent regulation.

72 Asymmetry of electrical transmission can in principle result from a wide variety of
73 influences. It has been well established in non-mammalian systems that directional differences
74 in conductance between two coupled cells can result from heteromeric channels or heterotypic
75 gap junction plaques that coupled membranes (Bukauskas et al., 1995; Rash et al., 2013), or
76 from differences in hemichannel protein scaffolding (Marsh et al., 2017). Hemichannel
77 differences resulting in asymmetry have been demonstrated in HeLa cells expressing connexin
78 isoforms (Bukauskas et al., 1995) and at the mixed synapse onto Mauthner cells in goldfish
79 (Rash et al., 2013). Connexin-sourced asymmetry was thought to be unlikely for neuronal
80 mammal synapses, as connexin36 does not oligomerize or dock with other connexins (Li et al.,
81 2004; Teubner et al., 2013), and in expression systems appears to form perfectly symmetric
82 synapses (Srinivas et al., 1999). However, residual coupling has been noted between TRN
83 neurons in connexin36 knockout mice, and that coupling was more asymmetrical (Zolnik and
84 Connors, 2016), indicating a possible physiological source of synaptic asymmetry in mammalian
85 neuronal systems. Large gradients of Mg^{2+} concentration produce asymmetric signaling for
86 neuronal synapses (Palacios-Prado et al., 2013), and gating properties of connexin channels
87 produce asymmetry in computational models (Snipas et al., 2017). Cable properties of coupled
88 dendrites affect voltage transmission (Nadim and Golowasch, 2006), indicating that differences
89 in dendritic diameter may produce asymmetric coupling. Intrinsic differences between coupled
90 neurons, such as differences in input resistance (Bennett 1966; Fortier, 2010; Mann-Metzer and
91 Yarom, 1999; Veruki and Hartveit, 2002) or leak conductances (Alcami and Marty, 2013), have
92 long been mentioned as a straightforward reason that one might observe asymmetry in coupling
93 coefficients. For TRN synapses, asymmetry remains even after computing estimates of
94 conductance that should in principle minimize contributions of input resistance (Haas et al.,

2011; Sevetson and Haas, 2015). And while many reports of electrical synapses across the mammalian brain include asymmetry in their measurements, some reports do not note it, or only note that in their observations, synapses were symmetrical as expected. In all, asymmetry and its sources remain underappreciated at mammalian electrical synapses.

Beyond observations, the functional consequences of electrical synapse asymmetry on neural activity are not robustly understood. Electrical synapses have been widely shown to contribute towards synchrony of rhythmic activity in neuronal networks in both experiments (Bennett and Zukin, 2004; Blatow et al., 2003; Christie et al., 2005; Draguhn et al., 1998; Galarreta and Hestrin, 1999; Gibson et al., 1999; Hormuzdi et al., 2001; Landisman et al., 2002; Long, 2004; Long et al., 2005; Mann-Metzer and Yarom, 1999; Marder, 1998; Tamás et al., 2000; Vervaeke et al., 2010) and in computational models (Chow and Kopell, 2000; Destexhe et al., 1996; Kepler et al., 1990; Kopell and Ermentrout, 2004; Lewis and Rinzel, 2003; Manor et al., 1997; Nomura et al., 2004; O'Connor et al., 2012; Pernelle et al., 2018; Pfeuty et al., 2005; Saraga and Skinner, 2004; Sherman and Rinzel, 1992; Skinner et al., 1999; Traub et al., 2005; Whittington and Traub, 2003), and oscillations are more robust when asymmetrical electrical synapses are included (Gutierrez and Marder, 2013). Rectification at the LP-PY mixed synapse is a key component of coordinating the pyloric circuit of the spiny lobster (Mamiya et al., 2003). In non-rhythmic settings, strong asymmetry can produce nearly unidirectional communication that serves to reliably excite one coupled cell, as is the case with the club endings onto Mauthner cells in goldfish (Rash et al., 2013), and dorsal cochlear nucleus (Apostolides and Trussell, 2013). Electrical synapses modulate individual spike times in coupled neighbors in TRN by up to tens of milliseconds (Haas, 2015; Sevetson and Haas, 2015), and asymmetric coupling can add to that modulation, even reversing firing order between two coupled cells that receive closely-timed inputs (Sevetson and Haas, 2015). In a model thalamocortical circuit, coupling between feedback inhibitory neurons enhances discrimination of inputs sent to cortex

120 by relay cells (Pham and Haas, 2018). In a canonical model circuit with feedforward inhibition,
121 electrical synapses enhance subthreshold integration in principal cells (Pham and Haas, 2019).
122 In a toadfish vocal circuit, electrical coupling between feedforward inhibitory neurons enhances
123 synchrony and temporal precision (Chagnaud et al., 2021) and a similar effect occurs for
124 cerebellar basket cells (Alcami, 2018; Hoehne et al., 2020). These are some of the functions
125 that could be altered by asymmetry. While a few models have included electrical synapses in
126 morphologically extended cells (Amsalem et al., 2016; Nadim and Golowasch, 2006; Saraga
127 and Skinner, 2004), the sources or functions of asymmetrical synapses have not yet been
128 explored in that context.

129 Here we used compartmental models of coupled TRN neurons to investigate and
130 compare how a variety of fundamental neuronal properties could each contribute to electrical
131 synapse asymmetry, including synapse location, strength, direction of conductance, dendritic
132 geometry, and input resistance. We show that, as predicted, a variety of these factors can
133 produce effective differences in coupling coefficients as observed between somas. We then
134 demonstrate that conversely, these same properties can mask asymmetric conductance of
135 electrical synapses, resulting in apparently equal coupling as measured between somas.
136 Together, these results underline that asymmetric transmission and impacts are likely to occur
137 more widely than previously considered. Finally, we show that asymmetry regulates spike timing
138 and, unexpectedly, the form of rhythmic coordination in coupled neurons. We conclude that
139 electrical synapses between dendrites can exert locally powerful influence that is not readily
140 apparent at the soma, highlighting the necessity of including electrical synapses in
141 morphologically detailed models, circuits or connectomes.

142 MATERIALS AND METHODS

143 Modelling

144 Models were built upon those previously reported in (Destexhe et al., 1996; Haas and
 145 Landisman, 2012; Pham and Haas, 2019, 2018; Traub et al., 2005). We use Hodgkin-Huxley
 146 formalism (Eq. 1) solved by a second order Runge-Kutta ODE solver in MATLAB version
 147 R2020b (Mathworks), simulations were run on an ASUS desktop PC with Intel i7-10700K CPU
 148 running Windows 10.

$$\begin{aligned}
 C_m \frac{dV_i}{dt} = & G_{leak} \cdot (E_{leak} - V_i) + \sum_{\substack{ion \\ channels}} G_{ion}(t) \cdot (E_{ion} - V_i) \\
 & + \sum_{\substack{j \neq i \\ chemical \\ synapses}} G_{syn}(t, t_j^{events}) \cdot (E_{syn} - V_i) + \sum_{\substack{j \neq i \\ electrical \\ synapses}} G_{elec\ ji} \cdot (V_j - V_i) \\
 & + \sum_{\substack{external \\ inputs}} G_{syn}(t, t_{external}^{events}) \cdot (E_{syn} - V_i) + \sum_{\substack{j \neq i \\ coupled \\ compartments}} G_{internal\ ji} \cdot (V_j - V_i)
 \end{aligned}$$

149 (1)

150 The single compartment TRN cell model included the following ionic currents and maximal
 151 conductances: fast transient Na^+ (Na_T) 60.5 mS/cm², K^+ delayed rectifier (K_d) 60 mS/cm², K^+
 152 transient A (K_t) 5 mS/cm², slowly inactivating K^+ (K_2) 0.5 mS/cm², slow anomalous rectifier (AR)
 153 0.025 mS/cm², and low threshold transient Ca^{2+} (Ca_T) 0.75 mS/cm². Reversal potentials were 50
 154 mV for sodium, -100 mV for potassium, 125 mV for calcium, -40 mV for AR and -75 mV for leak.
 155 Capacitance was 1 $\mu\text{F}/\text{cm}^2$ with leak of 0.1 mS/cm². Three-compartment models were
 156 constructed consisting of one soma and two dendritic compartments, approximating the middle
 157 and distal regions of the dendrite. Compartments were connected by a static conductance
 158 $G_{internal}$ of 0.35 mS/cm² between distal and middle dendrites, and 0.4 mS/cm² between middle
 159 dendrite and soma. Membrane capacitance was 1.2 $\mu\text{F}/\text{cm}^2$. Maximal conductance for the
 160 compartmental model were: Na_T 60.5 mS/cm², K_d 90 mS/cm², K_t 5 mS/cm², K_2 0.5 mS/cm², AR
 161 0.005 mS/cm², and Ca_T 0.5 mS/cm². Leak conductance was set at 0.1 mS/cm² for soma

compartments, and 0.035 mS/cm^2 for dendrites, except when altering input resistance where leak conductance was scaled by 0.75 to 1.45 times, corresponding to $\pm 25\%$ change in input resistance. Dendritic compartments had lower Ca_T conductance of 0.15 mS/cm^2 . We removed the sodium current from dendrites, as TRN dendrites do not spike in recordings (Connelly et al., 2017). Electrical synapses were modeled as a static conductance G_{elec} (referred to as G_c in Results) applied to the voltage difference between the coupled compartments of the TRN cells. Asymmetry was implemented by varying G_{elec} for each cell. Excitatory synapses were AMPAergic with reversal potential of 0 mV with rise and fall time kinetics of 5 ms and 35 ms respectively.

Analysis

Coupling coefficients were measured by injecting hyperpolarizing current into the soma of one cell (A) and measuring the resulting current deflection in the soma of the other cell (B) compared to baseline ($cc_{AB} = \Delta V_B / \Delta V_A$), matching experimental methodology. We used 500 ms long square current injection and measured coupling in both directions between the cell pairs. The steady-state voltage during hyperpolarization was taken as the average voltage during the last 200 ms of stimulation. Coupling coefficient ratio was calculated as cc_{12}/cc_{21} .

To analyze latency modulation produced by electrical synapses we applied burst like EPSCs to distal dendrites of the model TRN cells and measured the time between onset of the first EPSC to the first action potential. Bursts consisted of 13 EPSCs of $1 \mu\text{A}$ amplitude with 5 ms ISI, $0.5 \mu\text{A}$ depolarizing current was applied to raise excitability of the cell model. Latency modulation was expressed as the difference in the change of latency between the two cells, compared to the latency of an uncoupled model cell. Synchrony was examined using single cell models driven to spike tonically, with one cell driven slightly higher, $I_1 = 0.575$, $I_2 = 0.6 \mu\text{A/cm}^2$. Cross-correlations were taken for a 500 ms time window during stable tonic firing, spike trains were filtered with a 5 ms hanning window. Time lag values from the peak of the cross

187 correlations were taken to calculate phase difference between the two spike trains (Phase
188 difference = $t_{\text{max lag}}/\text{ISI} \times 360$). To examine the effect of asymmetry, coupling was constant in the
189 cell 2 to 1 direction and scaled coupling in the 1 to 2 direction to obtain ratios between 0.3 to 3
190 times, the range observed from paired recordings at TRN.

191 Code Availability

192 The code/software described in the paper is freely available online at
193 <https://github.com/jhaaslab/Asymmetry>. The code is available as Extended Data.

194 RESULTS

195 To address the impact of neuronal excitability and morphology on electrical synapse
196 communication, we built a three-compartment TRN cell Hodgkin-Huxley model, including a T-
197 type calcium conductance in addition to leak, sodium, and potassium conductances, based on
198 those previously used (Destexhe et al., 1996; Pham and Haas, 2019, 2018; Traub et al., 2005).
199 To validate the model's dendritic responses, we used coupling between compartments that
200 generated reasonable amplitudes of backpropagated signals (Figure 1A), sublinear dendritic
201 responses to AMPAergic current injections (Figure 1B) that matched dendritic recordings from
202 TRN cells (Connelly et al., 2017) and firing responses from our own recordings (Haas et al.
203 2011; Sevetson and Haas, 2015). We then added an electrical synapse between matched
204 compartments of two identical TRN model cells and measured the coupling coefficients resulting
205 from hyperpolarizing current applied to and measured at the somas (Fig. 1C₁). We chose
206 coupling conductance values to match coupling coefficients observed in recordings, cc between
207 0 and 0.3 (Haas et al., 2011). For these matched-compartment connections, electrical
208 synapses produced higher coupling coefficients when synapses were closer to the soma, as the
209 current between electrodes has a more direct path (Figure 1D). A single-compartmental model
210 used for comparison (Fig. 1C-D, black) resulted in stronger coupling coefficients, as removing
211 dendrites reduced leaks from the circuit. Similarly, when current is applied and coupling

212 measurements are taken between distal dendrites (Figure 1C₂), coupling is stronger at
213 dendritically located synapses but decreases as the synapse location approaches the soma
214 (Figure 1D₂). This is a simple result of cable properties, but highlights the notion that electrical
215 synapses can produce strong and effective coupling between dendritic compartments (Fig. 1E)
216 that is not apparent from somatic measurements.

217   Next, we varied the location of electrical synapses between the dendritic compartments
218 of each cell, and again measured coupling between somas of cell 1 and cell 2. In all cases, the
219 coupling for mixed-location synapses was intermediate to the values obtained for connections
220 between matched compartments (Figure 2A-C). Interestingly, coupling values for pairs of
221 compartment connections that one might initially expect to produce the same coupling, such as
222 soma-middle (S-M) and middle-soma (M-S) (Fig. 2A, orange dots), do not produce identical
223 coupling coefficients. The source of asymmetry in this case is the differences in dendritic leaks
224 that siphon soma-applied current from the gap junction pathway. Specifically, for S-M
225 connections, the dendritic load for soma-applied current comprises resistance from both M and
226 D compartments and is larger than the remaining dendritic leak from a single D compartment
227 when current is applied to the opposite soma. These differences lead to differences in the
228 currents crossing the gap junction when current is separately applied to each soma, and thus
229 the coupling coefficients are asymmetric as measured between somas. Comparing Fig. 2A-C,
230 we note that this effect is strongest for connections closer to the soma, where the differences in
231 dendrites distal to the electrical synapse are largest.

232

233

Figure 1. Compartmental TRN model and characterization of coupling responses for gap junctions at varied dendritic locations. A) Schematic of compartmental TRN model and representative traces from each compartment in response to square depolarizing current injection at the soma compartment. Scale bars 10 mV, 25 ms. B) Postsynaptic response to an AMPAergic input delivered to distal dendrite. EPSP amplitudes were sublinear above 2 μ A, due to lack of active conductances in dendrites. C₁) Schematic for electrically coupled models. Voltage traces in both cells result from a hyperpolarizing current injection into the soma of cell 1 (left traces) and transfer to cell 2 (right traces). Scale bars 5 mV, 100 ms. C₂) Coupling coefficients (cc) measured between somatic compartments as in (C₁) for GJs located between the somas (yellow), middle compartments (red), and distal dendrites (blue). An identical single-compartment model is shown for comparison (black). D₁) Schematic and voltage traces for coupling measured between dendrites after dendritic current injection. D₂) Coupling coefficients (cc) measured between dendritic compartments as in (D₁) for GJs located between the somas (yellow), middle compartments (red), and distal dendrites (blue). E) EPSP amplitudes for each compartment for distally applied EPSC to cell 1 (left traces, scale bars 2mV, 25 ms), transmitted to cell 2 across a distal electrical synapse (right traces, scale bars 1 mV, 12.5 ms).

235 strength (Figure 2D). As expected, connections between the same compartments (eg M-M)
236 were perfectly symmetrical for all values of electrical synapse conductance. In contrast,
237 mismatched synapses are marked by decreasing or increasing cc ratios, with the mirror cases
238 producing similar degrees of effective asymmetry in opposite directions (eg M-D and D-M). We
239 also noted that asymmetry was greater for more-mismatched synapse pairs (eg S-D and M-D,
240 or the blocks in Fig. 2D), as the distal-soma connections produce cc ratios furthest from 1.
241 Further, asymmetry was greatest for synapses connected to the soma, while middle-distal
242 synapses showed a lesser degree of effective asymmetry. These simulations demonstrate that
243 effective asymmetry between somatic integrators can arise from difference in synapse location,
244 when perfectly symmetrical electrical synapses encounter asymmetrical spatial differences
245 between identical somas and dendrites, and thereby dictate effective asymmetry.

Figure 2. Electrical synapse location and strength contribute to coupling coefficient and asymmetry measured at the soma. A) Coupling coefficients measured from cell 1 to cell 2 for all sets of somatic and middle-compartment electrical synapses. Soma-soma synapses are in yellow, middle-middle synapses are in red, and both types of soma-middle synapses are orange with opposite coupling (middle-soma) indicated by darker shaded datapoints. B) as in (A) for somatic and distal synapse locations. C) as in (A) for middle and distal synapse locations; note overall decrease in coupling for more-distant synapses. D) Coupling coefficient ratio (cc_{12}/cc_{21}) for each synapse location and strength. Locations are grouped by effect; the top box shows GJs between matched compartments that are symmetric, as expected. In the middle box, the GJ was closer to the soma of cell 2, and thus cc_{21} was larger. In the bottom box, the GJ was closer to the soma of cell 1, and thus cc_{12} was larger. Asymmetry increased with difference between location of the GJ, and with proximity to the soma.

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248 Effective asymmetry can also arise from differences in basic excitability, e.g., membrane
249 input resistance R_{in} . To demonstrate this widely expected phenomenon, we altered R_{in} by
250 changing leak conductance in cell 2 of the model (Fig. 3A), and measuring coupling coefficient
251 cc in both directions. When gap junctions (GJs) coupled two somas of differing R_{in} , cc was
252 determined only by R_{in} of cell 2 (Fig. 3B, yellow); cc_{12} varied, while cc_{21} stayed constant. As GJs
253 were more distant from the soma, voltage divisions allowed both cc_{12} and cc_{21} to change, though
254 changes in cc_{12} were always larger. Differences in GJ location also contributed to asymmetry
255 here, again splitting the differences between the extremes, similarly to the effect shown in Fig.
256 2.

257 The combined effects of input resistance and location are summarized in Fig. 3E, which
258 shows simulations for three values of average electrical synapse strength G_C for all synapse
259 locations and input resistance mismatches. For matched-compartment locations (top boxes),
260 asymmetry was determined only by differences in R_{in} . For GJs that coupled cells with differing
261 R_{in} and synapses at mismatched locations, synapse location appeared to be a weaker effect
262 than input resistance mismatch: the cell with the GJ closer to its soma always yielded a smaller
263 coupling (e.g. middle box: synapses are closer to soma 2, and produced asymmetry < 1). As in
264 Fig. 2, asymmetry was strongest for synapses coupling the most spatially separate
265 compartments. These simulations showed us that increasing G_C amplified the asymmetry
266 produced by differences in R_{in} . Synapses that were mostly below one in cc ratio further
267 decreased in cc ratio (Fig. 3E, middle rows), while locations with cc ratio above one increased
268 with the strength of the synapse (Fig. 3E, bottom rows). Synapses between similar
269 compartments (top rows) showed minimal changes with increasing strength of the synapse.
270

Figure 3. Dependence of asymmetry on synapse location and input resistance differences. A) Schematics depicting differences in input resistance, and varied synapse locations. B) Coupling versus difference in input resistance for GJs ($G_C = 0.15$ mS/cm²) between middle-middle, middle-soma and soma-soma compartments. Difference in input resistance are expressed as cell 2 relative to cell 1. C) As in (B) for GJs between distal and soma compartments. D) As in (B) for GJs between distal and middle compartments. E) Asymmetry plotted against input resistance differences, grouped by electrical synapse strength (G_C), which increases across panels: 0.1, 0.15 and 0.2 mS/cm².

272 To further examine how heterogeneity between two coupled cells could contribute to
 273 effective asymmetry, we altered the internal coupling conductance between compartments of
 274 the cell. For all synapse locations, differences in dendritic coupling altered resulting cc ratios
 275 (Figure 4), but by amounts smaller than synapse mismatch or input resistance difference.
 276 Increasing dendritic conductance favors transmission into that cell and thus lowers cc ratio
 277 when cell 2 has more-conductive dendrites. Similarly, cc ratio increases when cell 1 is higher in
 278 dendritic conductance. This result is consistent for the connections between same cellular
 279 compartments, which are symmetric when morphology is the same, and the mismatched
 280 locations which are asymmetric in the same case. Though morphology may not produce
 281 substantial asymmetry alone, in conjunction with synapse location the intrinsic differences
 282 between two cells will fine-tune the overall coupling and asymmetry measured between them.

Figure 4. Differences in dendritic morphology fine-tune coupling coefficients and asymmetry. A) Internal conductances between the three subcellular compartments were altered in cell 2, as shown in schematics. Changes in middle-soma conductance is plotted on the x-axis, and change in distal-middle conductance is plotted on the y-axis. B) Heat maps of cc ratio for all synapse locations. In all cases, decreasing internal conductance increased cc ratio, while increasing internal conductance in decreased cc ratio. G_c was 0.15 mS/cm² for all synapses in these simulations.

283 The previous sets of simulations used a symmetrical synapse to show that several
 284 aspects of cellular properties and synapse locations can yield effective asymmetry, as expected.
 285 Next, we asked whether an electrical synapse that was itself asymmetrical could produce the
 286 same effective asymmetries. We varied the conductance G_c of the electrical synapse between
 287 somatic compartments, and again examined the effect of input resistance changes on effective
 288 asymmetry. Our results demonstrate that similar values of effective asymmetry could arise from
 289 either G_c ratio or input resistance difference (Figure 5). For each set of input resistances
 290 (column in Fig. 5), synaptic asymmetry could produce a range of effective asymmetry. These
 291 simulations illustrate the potential for cc values recorded from the soma to appear similarly
 292 asymmetric, whether asymmetry is produced from differential intrinsic properties or synapses

Figure 5. Asymmetry due to altering directional conductance produces similar response in coupling coefficients compared to synapse location asymmetry.

Directional conductance changes between the cells produces a similar degree of asymmetry in cc ratio, with input resistance difference between the two cells predictably shifts the cc ratio values. G_c ratio (G_{c12}/G_{c21}) from altering conductance from cell 1 to cell 2 was varied while the opposite direction was held constant ($G_{c21} = 0.15 \text{ mS/cm}^2$). Input resistance was altered in cell 2 relative to cell 1. Neuron schematics depict direction with larger conductance as a thicker resistor symbol, while size of the cell indicates change in input resistance.

293 themselves.

294 Together, the previous results show that asymmetry in coupling as measured between
295 somas can arise from a number of factors. We demonstrate this masking in Figure 6: the same
296 amount of asymmetry in coupling as measured at the soma can arise from independent
297 sources. We identified simulations that resulted in 20% coupling difference, as this is the most
298 common cc ratio observed in paired recordings at TRN (Haas et al., 2011). Higher transmission
299 to cell 2 by the same proportion (cc ratio ~ 1.2) can be produced by asymmetric gap junction
300 with G_c ratio of 1.8 and R_{in} change of -20% (Figure 6B), or M-D synapse location and +25% R_{in}
301 change (Figure 6D), or S-M synapse with higher dendritic conductance in cell 1 (Figure 6F).
302 Alternatively, higher transmission to cell 1 (cc ratio ~ 0.8) can be produced by asymmetric gap
303 junction with G_c ratio of 0.67 and +6% R_{in} change (Figure 6C), or M-S synapse and -12% R_{in}
304 change (Figure 6E), or D-S synapse with higher dendritic conductance in cell 2 (Figure 6G).
305 Thus, asymmetry measured at the soma is not informative as to its source, and more
306 pertinently, fails to provide insight into processing in coupled dendrites.

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Figure 6. Varied scenarios can produce identical asymmetry as measured at the soma. A) Approximate isoclines (black lines) show parameters that produce the same degree of asymmetry (cc ratio of 1 ± 0.2). Representative traces (B-G) were taken from data along these isoclines (white stars) for cases of directionally asymmetrical conducting gap junctions, differing synapse locations, or differing dendritic geometries. B) G_C ratio 1.8, R_{in} change -20%. Scale bars 5 mV, 200 ms. C) G_C ratio 0.667, R_{in} change +6%. D) M-D GJ: R_{in} change +25%. E) M-S GJ, R_{in} change -12%. F) S-M GJ, G_{MS} change -13.3%, G_{DM} change -20%. G) D-S GJ, G_{MS} change +20%, G_{DM} change +20%.

316 synapses have been previously shown to modulate latency of action potentials in coupled pairs
317 (Alcami, 2018; Haas, 2015; Sevetson and Haas, 2015). We measured latency to burst-like input
318 patterns of AMPAergic synaptic currents delivered to distal dendrites of both cells of a coupled
319 pair, in order to mimic excitatory afferent activity received by cells of the thalamic reticular
320 nucleus (Gentet and Ulrich, 2003) from bursting thalamic relay cells (Figure 7A). We tested
321 each synapse location, and also varied the arrival (onset) times of the AMPAergic bursts
322 between the two cells. For synapses between the similar compartments (Figure 7C, D-D),
323 latency difference increases with G_C and difference in input time. Dissimilar locations alter the
324 latency modulation with a variety of effects, with synapses in varied locations shifting latency
325 modulation curves either up (D-M) or down (M-D), producing a variety of outcomes in cell firing
326 by as much as 20 ms. This trend is generalized in the asymmetrically conducting synapse,
327 where G_C ratio >1 produces higher latency modulation, and values <1 shift latency modulation
328 lower (Figure 7B).

329

Figure 7. Asymmetry controls the latency modulation produced by electrical synapses. A) Each TRN cell received AMPAergic burst-like inputs (13 events with 1 μ A amplitude, 5 ms ISI) at varied onset times. Traces at right show responses of all compartments of a single cell to a burst input. Scale bars 10 mV, 25 ms. B) Differences in spiking latency between the two cells plotted against difference in onset of burst inputs ($t_{in2} - t_{in1}$) for the two TRN cells. Asymmetrical somatic gap junctions increased gap junction-mediated latency differences for G_c ratios greater than 1, and decreased them for G_c ratio is lower than 1. C) Changes in latency for varied electrical synapse locations, strengths and input time differences. D) Example bursts taken from C (red circles) for an uncoupled pair (1), a pair with a high conductance D-M synapse (2), and high-conductance M-D synapse (3). Asymmetrical location of an electrical synapse determines bursting order, and results in positive or negative latency change. Scale bar 20 mV, 25 ms, traces offset for clarity.

331 To examine the possible consequences of asymmetry on spike synchrony, a well noted
332 function of electrical synapses, we used single-compartment models used previously (Haas and
333 Landisman, 2012; Pham and Haas, 2018) to analyze correlations of tonic spike trains (Figure
334 8A-B) elicited by steady current injection, with one cell (here, cell 2) driven slightly faster.
335 Synchrony was demonstrated by peaks in steady-state cross correlation of the spike trains (Fig.
336 8C, D). As electrical synapse strength increased, spike rates of the two neurons converged for
337 coupling strength larger than 0.004 mS/cm^2 , and increased together with synapse strength due
338 to the increase in excitability contributed by the gap junction (Figure 8E). As expected from
339 theoretical models of coupled oscillators (Lewis and Rinzel, 2003; Saraga and Skinner, 2004)
340 our simulations revealed synchronous firing that transitioned from stable in-phase ($\sim 0^\circ$ lag) to
341 out-of-phase ($\sim 180^\circ$ lag) forms (Fig. 8E) for a symmetrical gap junction. We next observed that
342 asymmetry of the gap junction interacted with strength and altered the form of synchrony
343 (Figure 8F). For weak coupling, asymmetry that increased from 0.3 to 3, altering the identity of
344 the favored cell, brought spike times closer together and produced a transition from out-of-
345 phase to in-phase synchrony. The impact of asymmetry strengthened as synapse strength
346 increased (across panels in Fig. 8F). Asymmetry that favored transmission arising from the
347 slower cell (G_C ratio > 1) brought firing closer to in-phase, while asymmetry that favored the
348 faster cell (G_C ratio < 1) led to out-of-phase solutions (Figure 8G, H). These results together
349 show that asymmetry, regardless of its subcellular source, controls synchronous rhythmic
350 activity between coupled neurons.

Figure 8. Asymmetry determines the phase of synchrony. A) Traces of two coupled TRN cells driven to spike tonically; cell 2 received a slightly larger current pulse. $I_1 = 0.575$, $I_2 = 0.6$ μ A/cm²; scale bars 25 mV, 50 ms. B) Zoom of tonic spikes from (A) showing synchronous firing for low coupling strength ($G_c = 0.005$ mS/cm²) and out-of-phase synchrony for higher coupling strength ($G_c = 0.025$ mS/cm²). Scale bars 40 mV, 5 ms. C) Cross correlation of tonic spikes for varied values of symmetric gap junction strength. D) Histogram of cross correlations for a symmetric synapse. E) Interspike intervals for tonic spikes and phase difference (purple) of synchronous spike trains, dotted line indicates the emergence of synchrony from cross correlations in (D). F) Cross correlations for asymmetric synapses. Asymmetry values > 1 represent better transmission from cell 1 to cell 2. Initial strength of the gap junction, G_{c21} , increases across panels. G) Traces from weakly coupled cells in (F) for three different asymmetry conditions. Scale bars 40 mV, 5 ms. H) Phase difference for asymmetric gap junctions from (F), for weak (blue, $G_{c21} = 0.005$), medium (yellow, $G_{c21} = 0.0125$), and strong (red, $G_{c21} = 0.025$) initial synapse strengths.

352 **DISCUSSION**

353 Asymmetry of transmission at electrical synapses has been widely noted but its specific
354 sources rarely explored in depth, perhaps due to the experimental difficulties of identifying and
355 localizing specific GJs *in vitro* or *in vivo*. Nonetheless, because asymmetry is pervasive and can
356 result in extreme cases in which spikes in one cell more or less faithfully drives spiking in the
357 coupled neighbor (Apostolides and Trussell, 2013; Rash et al., 2013), we sought to understand
358 how basic neuronal properties could influence effective coupling, and thereby the function of
359 coupled networks. Here we have shown that asymmetry can arise from a variety of intrinsic
360 differences in neuronal properties as well as differences in subcellular localization of the gap
361 junction between somas. We expect additional heterogeneities, such as in the ionic currents
362 expressed in each cell, will similarly affect coupling measurements and thus effective
363 asymmetry, as similar activity patterns can be produced by a variety of models in pyloric circuit
364 (Prinz et al. 2004). In practice, asymmetry is a combined product of all of these factors together.
365 We also found that asymmetrical and/or strong synapses between dendritic compartments can
366 be masked from somatic detection by the same intrinsic properties. Our measurements here
367 focused on soma-to-soma transmission, as ultimately, asymmetry between somas is the last
368 stop before spike generation in the axon initial segment, and because electrical synapse
369 strength is traditionally measured between somas. Indeed, our results also highlight that
370 regardless of its source, asymmetry substantially impacts spike times and synchrony between
371 coupled cells (Gutierrez and Marder, 2013; Sevetson and Haas, 2015).

372 Precise locations of electrical synapses along dendrites have proven difficult to
373 exhaustively determine, but a handful of studies point towards asymmetrical localization. In
374 coupled interneurons of cortex layer IV, synapses are located all along the dendrites, and
375 measurements from 204 cells showed strong asymmetry in localization, with 90% synapses
376 within 50 - 75 μm of one soma, but up to 250 μm away from the coupled soma (Fukuda, 2017).

377 Asymmetrical localization also appears to be a feature of coupling between cerebellar Golgi
378 cells (Szoboszlay et al., 2016). The strongly asymmetrical synapses of the DCN also appear to
379 couple mismatched distances from fusiform and stellate somas (Apostolides and Trussell,
380 2013). Other studies indicate that dendritic location of GJs is diverse across brain areas, and
381 thus asymmetry could vary widely. In brainstem MesV cells, GJs appear to be located at or very
382 close to the soma (Curti et al., 2012). In contrast, in inferior olive (Devor and Yarom, 2002; Hoge
383 et al., 2011) cells are coupled at quite distal dendrites, such that somatic measurements of
384 coupling themselves are small. Average intersomatic distances between coupled cells in TRN
385 are ~100 μm (Lee et al., 2014), implying that GJs are dendro-dendritic, and have a great deal of
386 potential to create asymmetric localization of GJs between cells.

387 Dendritic integration is likely to be influenced by the presence of gap junctions along
388 dendrites (Vervaeke et al., 2012), as they have been shown to act as a shunt of current arising
389 from nearby chemical synapses (Lang et al., 1996; Llinas et al., 1974), and in *C. elegans*
390 coupled motor neurons, electrical synapses spread excitation during contraction and inhibit cell
391 pairs between cycles through a shunting effect (Choi et al., 2021). Asymmetry has also been
392 shown to amplify EPSPs in mixed synapses (Liu et al., 2017). Additionally, dendritic morphology
393 determines transmission across gap junctions (Nadim and Golowasch, 2006), as well as firing
394 patterns of extended morphological models (Mainen and Sejnowski, 1996), and as our results
395 demonstrate, substantial coupling influences on dendritic processing may not be appreciably
396 indicated by somatic measurements.

397 Effective asymmetry results in differentially directed signal and information flow through
398 a network that includes realistic electrical coupling. Our results here raise interesting questions
399 whether cells within a network regulate any of the factors that result in asymmetry in order to
400 produce precise direction of information flow within their network. Increasing electrical synapse
401 strength through trafficking of connexin proteins, a process which is controlled by cAMP

402 expression (Palumbos et al., 2021), may determine location or possibly effectively relocate a
403 synapse slightly closer to or distal from the soma. Distances of dendritically located electrical
404 synapses between cerebellar Golgi cells do not correlate with coupling strength measured
405 between somas (Szoboszlay et al., 2016), indicating a possible compensation for distance by
406 strength upregulation for those cells. Further, our previous work demonstrating activity-
407 dependent plasticity showed that asymmetry changes systematically with unidirectional activity
408 or ion flow across the gap junction (Fricker et al., 2021; Haas et al., 2011). Those results imply
409 that asymmetry is a modifiable element of electrical synapse plasticity. Our results here also
410 point out that cellular changes, such as activity-induced changes in dendritic resistance or
411 mutation-induced localization of GJs, could result in the changes in asymmetry measured, in
412 addition to the possibility of changing the conductance itself.

413   Asymmetry, as it influences spike times in coupled cells, has downstream effects on the
414 synaptic targets of the coupled cells. Symmetrical electrical synapses between model TRN cells
415 act to merge spike times of thalamocortical cells in response to inputs of similar strength or
416 timing, or can separate spikes from dissimilar inputs (Pham and Haas, 2018). We hypothesize
417 that TRN neurons with asymmetric gap junctions will inhibit thalamocortical relay cells
418 unequally, shifting the balance between merging or distinguishing signals as they are relayed to
419 cortex. Including asymmetry as a factor in TRN networks will be important to understanding how
420 TRN cells orchestrate the attentional spotlight at sensory thalamic nuclei. In canonical
421 feedforward circuits, coupling between inhibitory interneurons impacts integration in principal
422 cells (Pham and Haas, 2019). Recent investigations further show the influence of electrical
423 synapses on temporally precise inhibition in feedforward circuits (Chagnaud et al., 2021;
424 Hoehne et al., 2020). Asymmetry, as it can be applied to electrical synapses in these general
425 motifs may impact the many gap junction coupled feedforward and feedback circuits that embed
426 electrical synapses across the brain.

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