Correlation and Synchrony: A Computational model study of LC of crab

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INTRODUCTION

• The crustacean cardiac ganglion (CG) coordinates the rhythmic contractions of a single heart muscle for the crab. For *Cancer Borealis*, the ganglion consist of 9 cells, 5 large motor cells (LCs) and 4 small endogenous pacemaker cells (SCs). Despite having variable underlying conductances, recent studies have shown that even isolated LCs burst in synchrony (Ransdell et al., 2012, 2013).

• Our main objective is to understand how cells with different intrinsic make up maintain synchronous output.

• TEA experiments, which may mimic neuromodulation in vivo, show a drastic change in synchrony in responses for isolated LCs. **Why is this so? Also, what might help establish synchrony in network output?** We developed a computational model of single cell and regional 2- and 3-cell networks to study the potential role of co-regulation of (A) intrinsic, and (B) electrical synaptic conductances in re-establishing synchrony in LC and network output.

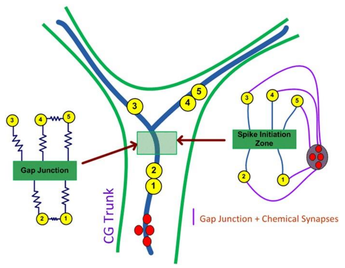

Fig. 1 Cardiac ganglion with 5 LCs and 4 SCs.

METHODS

• All currents in an LC were modeled using Hodgkin-Huxley equations.

• A total of 8 active channels were modeled to match the responses of LCs to different voltage clamp protocols.

$$C\frac{dV}{dt} = -I_A - I_{Kd2} - I_{Nap} - I_{CaPQ} - I_{CaL} - I_{SKKCa} - I_{CAN} - I_{BKKCa} - I_{Leak} + I_{inj}$$

• Using these currents, a nominal LC model was developed and its conductances were tuned to match biological data.

• The model successfully matched passive properties, total outward current traces, and neuromodulation effects (TEA).

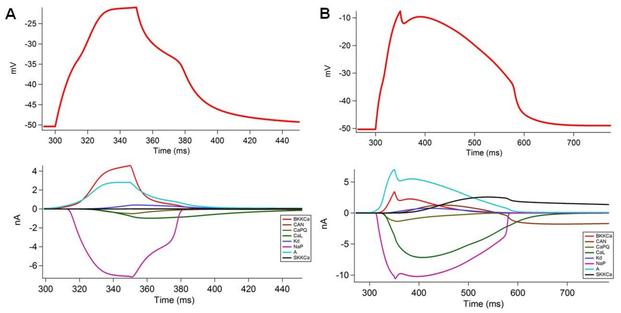

Figure 2. Single cell model of LC with ligatured soma. (A) Current injection response s of nominal LC model to 50ms 6nA injection. (B) Response s of nominal LC to 50ms 6nA injection, post TEA. Response in Panel B top shows a 'Driver Potential' (DP).

Can conductances co-regulate to maintain cellular output?

Using the nominal model, a 8-D parameter space was created using a 5-fold range of conductance values for all active currents. Random points from this space were then screened as follows, to check if they could represent 'viable' parameter sets for the model.

Rejection Sampling Technique:

• For each parameter set selected, G_{leak} was varied from 7e-5 S/cm^2 to 30e-5 S/cm^2 in steps of 1e-5 S/cm^2 and input resistance was calculated. If the input resistance was within the acceptable range (2.63-7.43 MΩ), the responses to square pulse injections (50ms 6nA) for the Pre-TEA, Post-TEA and Post TTX cases were saved. The response to a synaptic drive (see figure 3) when clamped at -40mV was also saved for each case.

• The parameter set was deemed 'acceptable' if it satisfied the following conditions:

(a) The duration of the Pre-TEA response to current injection should be less than 120ms. Also the peak should not be higher than -22mV.

(b) The duration of the Post-TEA response should be between 255-667 ms and its peak should be greater than -15mV.

(c) For the Post TTX response, the peak should decrease at-least 15 mV from its Post TEA response, and the duration should reduce to less than 120ms.

(d) Synaptic Drive response should have an r^2 value of at least 0.8 or higher when compared to an 'ideal' biological Synaptic Drive response (from the Schulz Lab).

RESULTS

A. Single Cell: Co-regulation of conductances

Finding – Ratio of CAN to SKKCa currents control DP termination post-TEA in a model LC

• Using the sampling technique we found that out of the 20,000 different combinations we tried, most of the cells which passed the selection criteria did not have a proper termination of Driver Potential (Fig. 2 Panel B top).

• We found the reason for this mismatch to be magnitude of currents I_{CAN} and I_{SKKCa} . We had to have them be in a certain proportion for a DP elicited post-TEA to terminate properly.

• Trial and error runs varying the ratio of I_{CAN} and I_{SKKCa} suggested a ratio of 1:0.83 for proper termination of the DP. Larger ratios cause V_{rest} to be higher due to the moderate reversal potential (-30mV) of CAN current. A higher fraction of I_{SKKCa}(reversal potential -80mV) caused the high AHP after termination of DP and reduced the duration of DP.

• We updated the selection criteria using this finding, which remains to be biologically verified.

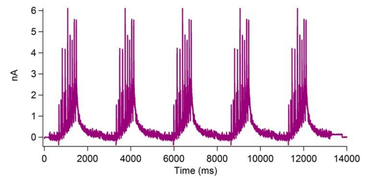

Figure 3. Current injection protocol 'Synaptic Drive' used to inject in cells was obtained by measuring voltage from an intact network cell and calculating current needed to reproduce it in an isolated cell.

Finding – Correlations exist among some current pairs that preserve synchrony

• Using the updated selection criteria we found 180 parameter sets that passed. Of these 180 potential model sets, we selected only the ones that had Synaptic Drive response r^2 value > 0.9 compared to the 'ideal' biological Synaptic Drive response. This resulted in 49 potential parameter sets.

• Using these parameter sets we computed correlations among different pairs of currents. We used *linear polynomial fit* to compute r between two currents. Higher r values imply strong correlation between the conductances whereas lower values imply weaker correlation.

	Leak	A	BKKCa	Kd1	Kd2	CaL	CAN	SKKCa	CaPQ	Nap
Leak	1									
A	-0.8141	1								
BKKCa	0.1501	-0.1943	1							
Kd1	-0.1889	0.3849	-0.3142	1						
Kd2	0.0646	-0.0408	0.0396	-0.0578	1					
CaL	-0.0819	0.3698	0.2572	0.3777	-0.0579	1				
CAN	-0.0178	0.2484	0.3006	0.0689	0.2419	0.5413	1			
SKKCa	-0.0179	0.2485	0.3008	0.06962	0.2423	0.5413	0.9999	1		
CaPQ	0.0347	0.199	-0.2385	-0.0585	-0.3634	-0.1093	-0.2048	-0.2055	1	
Nap	0.0999	0.0025	0.026	0.017	0.2575	-0.5671	-0.0231	-0.0228	0.062	1

Table 1. Correlation Coefficient values (r) between different currents. Currents with High Correlation are shown in **Red,** Moderate Correlation in **Brown** and model put correlation in **Purple**.

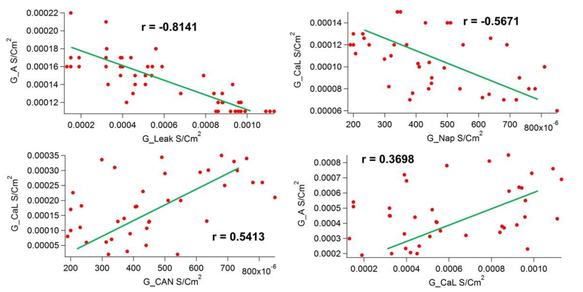

Figure 4. Some of the correlations from Table 1 with their conductance and coupling coefficient (r) values.

Further screening using biologically observed correlation between A and HTK currents

• We have observed that A and HTK (High Threshold Potassium) currents show a negative correlation of r^2 = -0.65 (Ransdell et al., 2012). So, we added this to our criteria for screening potential parameter sets. We converted biological IA-IHTK current data into factor data by dividing IA and IHTK by its average.

• G_A and G_{BKKCa} values of passed parameters were similarly divided by its average to gets its factor data.

• The biological data was fit using a linear polynomial from 95% to 70% confidence intervals, in steps of 10%.

• The model points which were inside the 70% confidence interval were selected as viable parameters. Using this parameter sets, the observed correlations (table 1) were maintained, and a high correlation matching biology was obtained between A-BKKCa (r^2 = -0.834) .

B. Network Model - Compensation

SCI and DCI studies with 2-cell network

• To study the effects of electrical synapses, we used two tests; Both these test were done pre- and post- TEA application:

1) SCI (Single current injection) – For this test we injected the synaptic drive in one cell and recorded its voltage and then we injected it in other and recorded that cell voltage. The two voltages were then correlated to check for synchrony.

2) DCI (Dual current injection) – For this test the current was injected into both cells simultaneously and their voltages recorded. As before, the two voltages were correlated to check for synchrony.

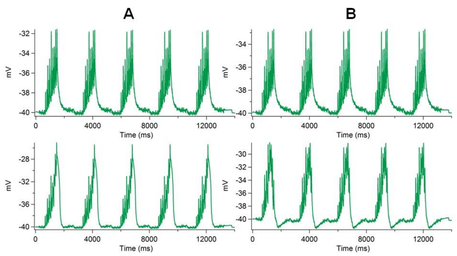

Figure 5. Response of 2 connected cells to DCI protocol (A) Pre-TEA and (B) Post-TEA.

• We did this with 3 pairs of cells selected from 6 randomly chosen ones, using three different electrical synapse values:: No coupling, Low coupling (Normal / 5) and Normal coupling observed between LC4-LC5, LC3-LC4 and LC3-LC5.

• The tests reveal that pre-TEA results do not depend on coupling conductance values since we found no significant change in synchrony (r^2 > 0.96 for all cases). For post-TEA tests, increase in electrical synapse strength typically increased synchrony; however, reduction in synchrony was observed in a few cases. This suggest that electrical synapse conductance could be used by a cell to re-establish synchrony that may be lost due to neuromodulation.

RESULTS

BKKCa magnitude v/s Coupling strength studies using 2 cell network

• We wanted to see how cells with similar and different BKKCa conductance magnitudes effect synchrony. For this we created three pairs of cells, cells with similar BKKCa conductance values (both high BKKCa and both low BKKCa) and cells with very different BKKCa values.

• We connected them in varying coupling strengths (0.01 µS – 0.5 µS) and checked for synchrony.

• We found that if two cells had very different BKKCa currents, higher values of electrical synapse strengths were needed to maintain synchrony, compared to two cells both of which had low BKKCa conductances.

• For the case where both cells have high BKKCa conductances, moderate electrical synaptic strengths resulted in a small decrease in synchrony. Analysis is on-going to determine why this happens.

DCI studies with 3-cell network

• For this case, three cells were connected using biologically observed coupling conductances (LC3-LC4-LC5). We then varied one coupling conductances at a time from 0.01 µS – 0.5 µS with the others unchanged, and then tested Pre-TEA and Post-TEA cases with DCI stimulation.

• The results were similar to those of the 2-cell model, with the only difference being that synchrony was high (r^2 > 0.8) even after TEA application for the LC3-LC5 case. The reason for this might be due to the high coupling among other pair of cells.

DISCUSSION and FUTURE WORK

A. The model predicts potential correlations among LC currents that might maintain synchrony in output for isolated cells (Table 1, Figure 4).

- Interestingly a negative correlation was found between Nap and CaL conductances . This could suggest that neuromodulation effects on Nap (e.g,, TTX type) can be countered by CaL.

- Another finding is the A-Leak correlation. Since A is active at low voltages, our model suggests that it works with leak conductance to regulate input resistance and threshold for the cell. This could be testing in biology – do cells with input resistance in the low range have high A.currents and vice versa?

•B. Electrical synapses may co-regulate with intrinsic conducatnaces to maintain synchrony (with biologically realistic inputs) in network output in the face of neuromodulation.

- For the TEA cases (where isolated cells showed differences), when LCs were embedded in 2 and 3-cell networks, cells with varying BKKCa conductances were found to maintain synchrony with strong electrical synaptic coupling.

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