

Choosing a Direction: Neural Models of Decision Making

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**AFOSR Program Review:
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Choosing a Direction: Neural Models of Decision Making

Mailler (Univ of Tulsa), Manjarrez (OSU HSC)

Objective:

- Determine the roles and interrelationships of the neurons involved in managing speed and direction.
- Develop a biologically accurate computational model of this circuitry.
- Validate the model by demonstrating that it produces the various locomotion modalities using a realistic simulated environment.

Approach:

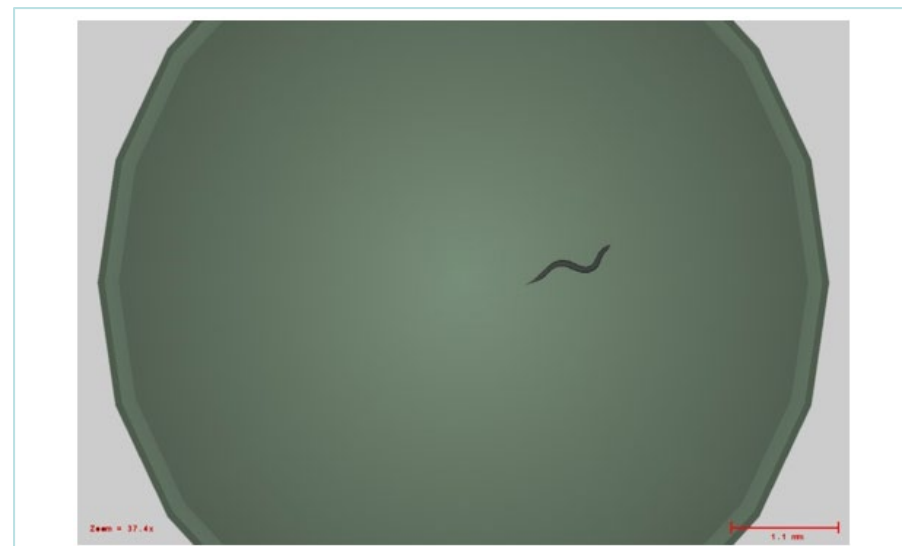
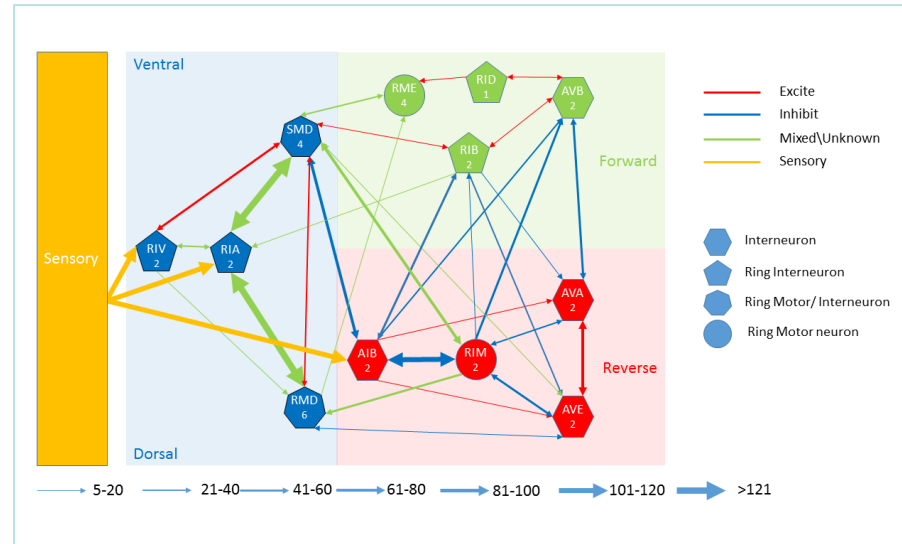
- Measure the behavior of the cells using optogenetics
- Develop bottom up models based on the SBIF neural model
- Test the model in simulation

DoD Benefits:

- Foundational knowledge used to develop autonomous decision making

Progress:

- Protocols and strains ready for data collection
- Model under construction



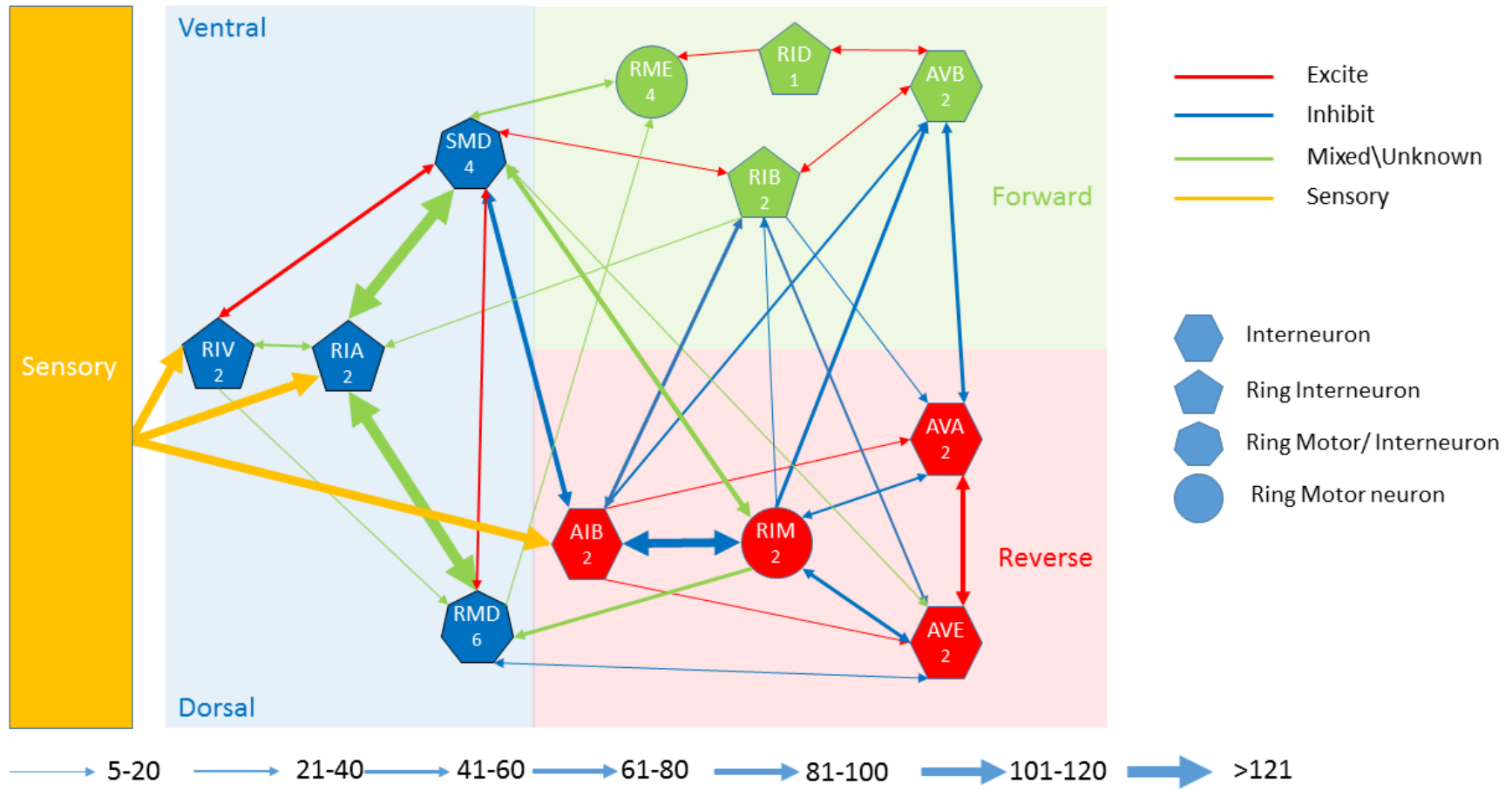
List of Project Goals

1. Perform experimentation to determine the neurons involved in decision making, their operations, and interrelationships.
2. Develop simulation models of *C. elegans* decision making circuitry for forward-reverse locomotion, speed control, and turning.
3. Improve upon our current software used for behavioral analysis to include optogenetic experimentation and analysis.
4. Integrate the three individual circuit models into a single model and connect it to our current locomotion circuitry model.

Progress Towards Goals (or New Goals)

- Goal 1: All base strains created. Several crosses need to be complete. Measurement will resume soon.
- Goal 2: Literature review nearly complete. Pared down simulator well underway with model of reverse circuit being completed.
- Goal 3: New software in place. Current analysis software will need to be adapted to new simulator.
- Goal 4: Complete model is implemented. Testing and correction is underway. Integration still pending.

What are we doing? Research



Goal 1: Measure activity

- Introduction of new confocal microscope has been very helpful

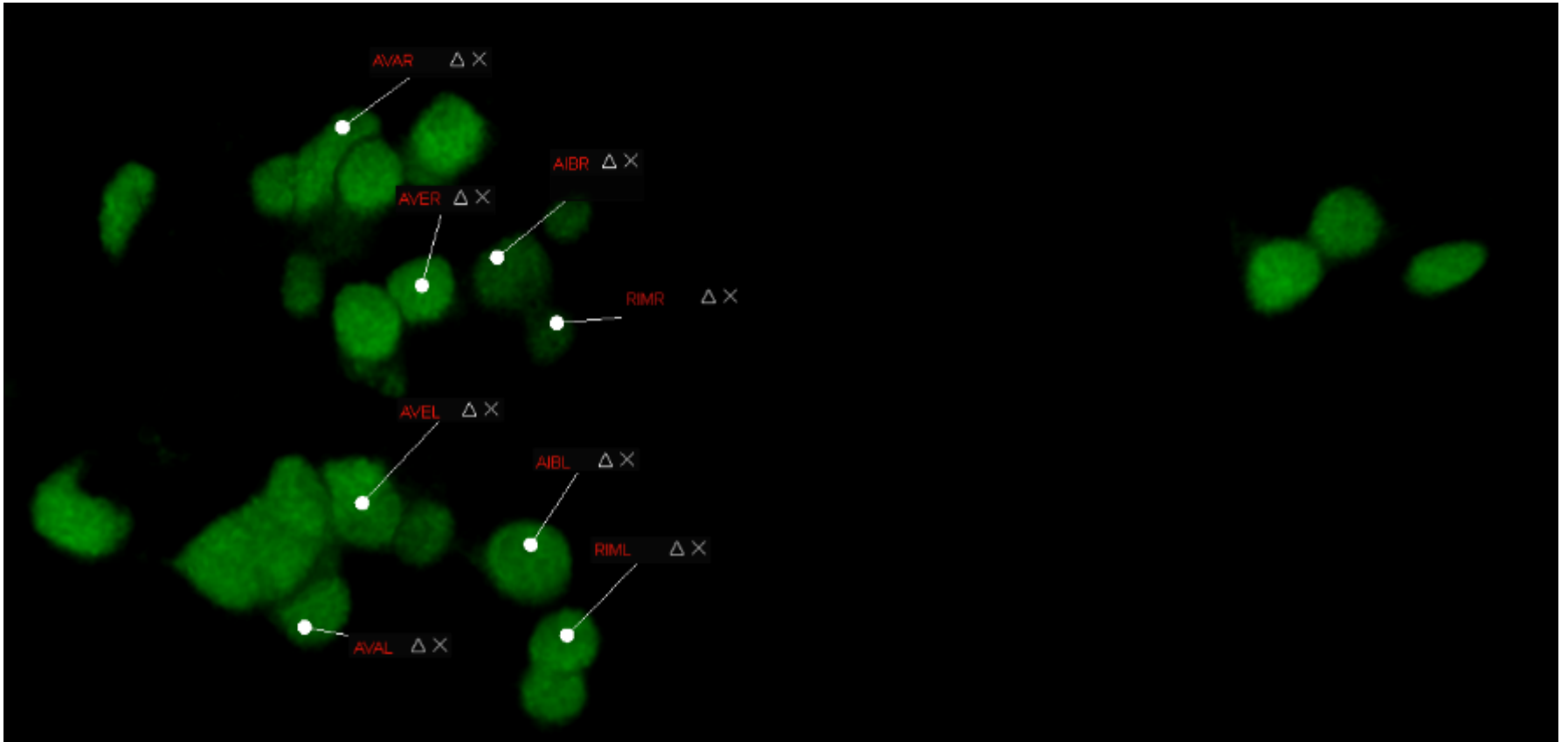
	Neuron	lim-4 + unc-47	dop-2 + zig-5	mgf-1 + ser-4	glt-1 + sra-11	odf-2(2b) + mgf-2	gpa-14 + flp-18	opt-3 + flp-1	dop-1 + glf-1	glt-3	zig-5 + odf-2	rig-5	lad-2 + unc-42	unc-4 + glf-4	flp-12	lad-2 + lim-4	Cells	Circuit
1	RME	x															4	Forward
2	RID		x														1	
3	RIB			x													2	
4	AVB				x												2	
5	AIB					x											2	Reverse
6	AVA						x										2	
7	AVE							x									2	
8	RIM								x								2	
9	RIA									x							2	Turning V-D
10	RIV										x						2	
11	RMD											x					6	
12	SAA												x				4	
13	SAB													x			3	
14	SMB														x		4	
15	SMD															x	4	

Before – 15 base strains

	Neuron	glt-1	glt-3	add-1	zig-5	Cells	Circuit
1	RME	x		x		4	Forward
2	RID				x	1	
3	RIB				x	2	
4	AVB			x		2	
5	AIB	x		x		2	Reverse
6	AVA	x		x		2	
7	AVE	x		x		2	
8	RIM	x		x		2	
9	RIA		x			2	Turning V-D
10	RIV				x	2	
11	RMD	x		x		6	
12	SAA					4	
13	SAB					3	
14	SMB					4	
15	SMD	x		x		4	

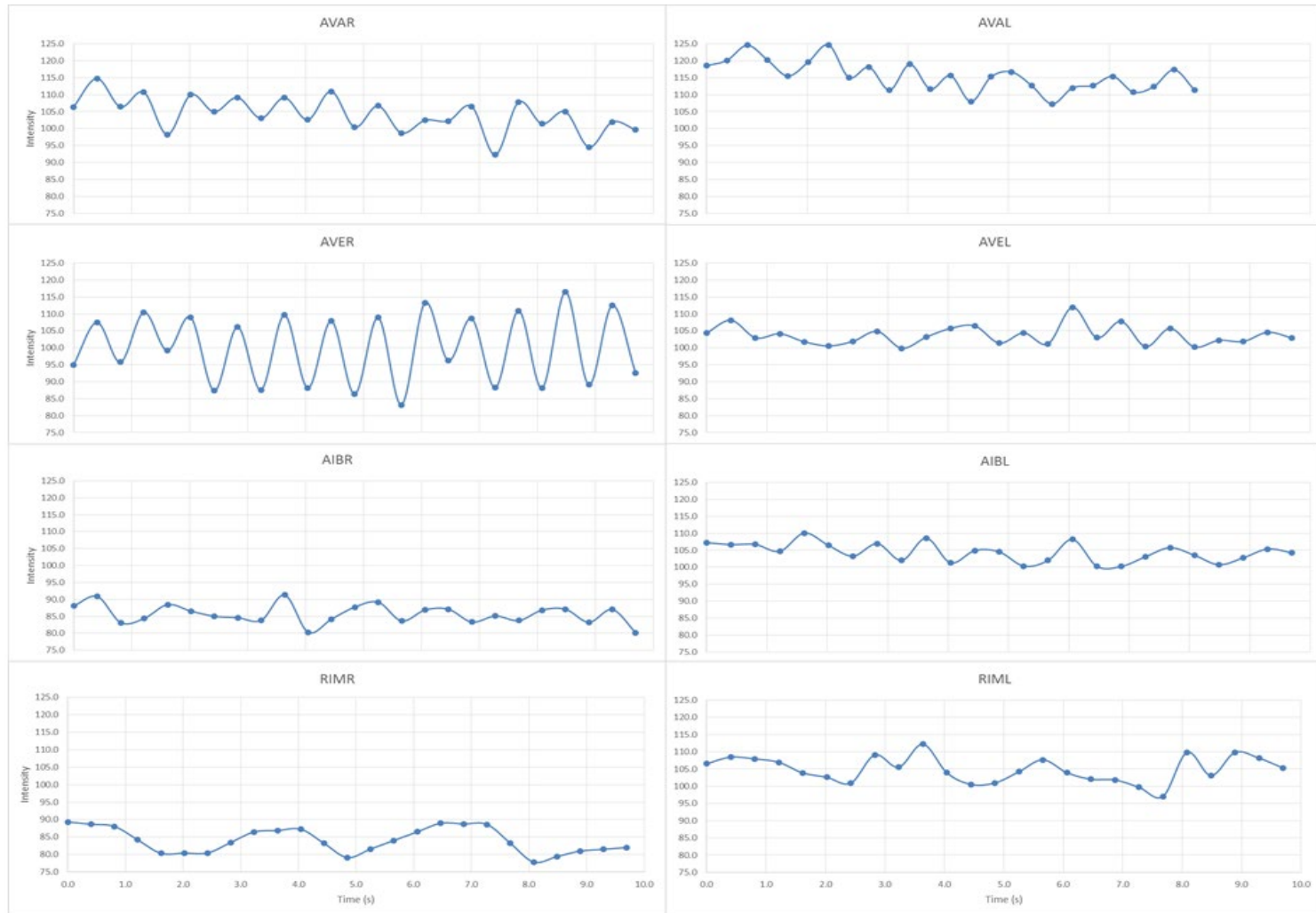
Now – 5 base strains

Reverse cells



glr-1::NLSGCamp5k

Signal traces



Correlation

	AVAL	AVAR	AVEL	AVER	AIBL	AIBR	RIML	RIMR
AVAL	1							
AVAR	0.421409	1						
AVEL	0.293522	0.535482	1					
AVER	-0.00863	0.571366	0.468055	1				
AIBL	0.476301	0.478561	0.239887	0.124734	1			
AIBR	0.12921	0.02255	-0.06876	-0.06617	0.169392	1		
RIML	0.045899	0.127774	0.089209	0.043411	0.12523	-0.00119	1	
RIMR	0.126125	-0.05012	0.008566	-0.05461	0.070121	0.017054	0.025504	1

Primary correlations are between

- AIBL and AVAL
- AIBL and AVAR
- AVAR and AVAL
- AVAR and AVEL
- AVAR and AVER
- AVEL and AVER

Goal 2: Develop models

- Focus on subcircuits
- Perform literature review
 - Neuron electrophysiological data
 - Neurotransmitter types
 - Channel expression
 - Incoming and outgoing synapses
 - Believed behavior

Example entry

RIM Neurons

Type: Graded [3,3.1]

Neurotransmitter: Glutamate + Tyramine [2, 22]

Receptors: acc-4 [wb], mgl-2 [wb], avr-14 [3]

Cell	Ext Chem Syn	Ext Elec Syn
RIML	146	11
RIMR	178	7

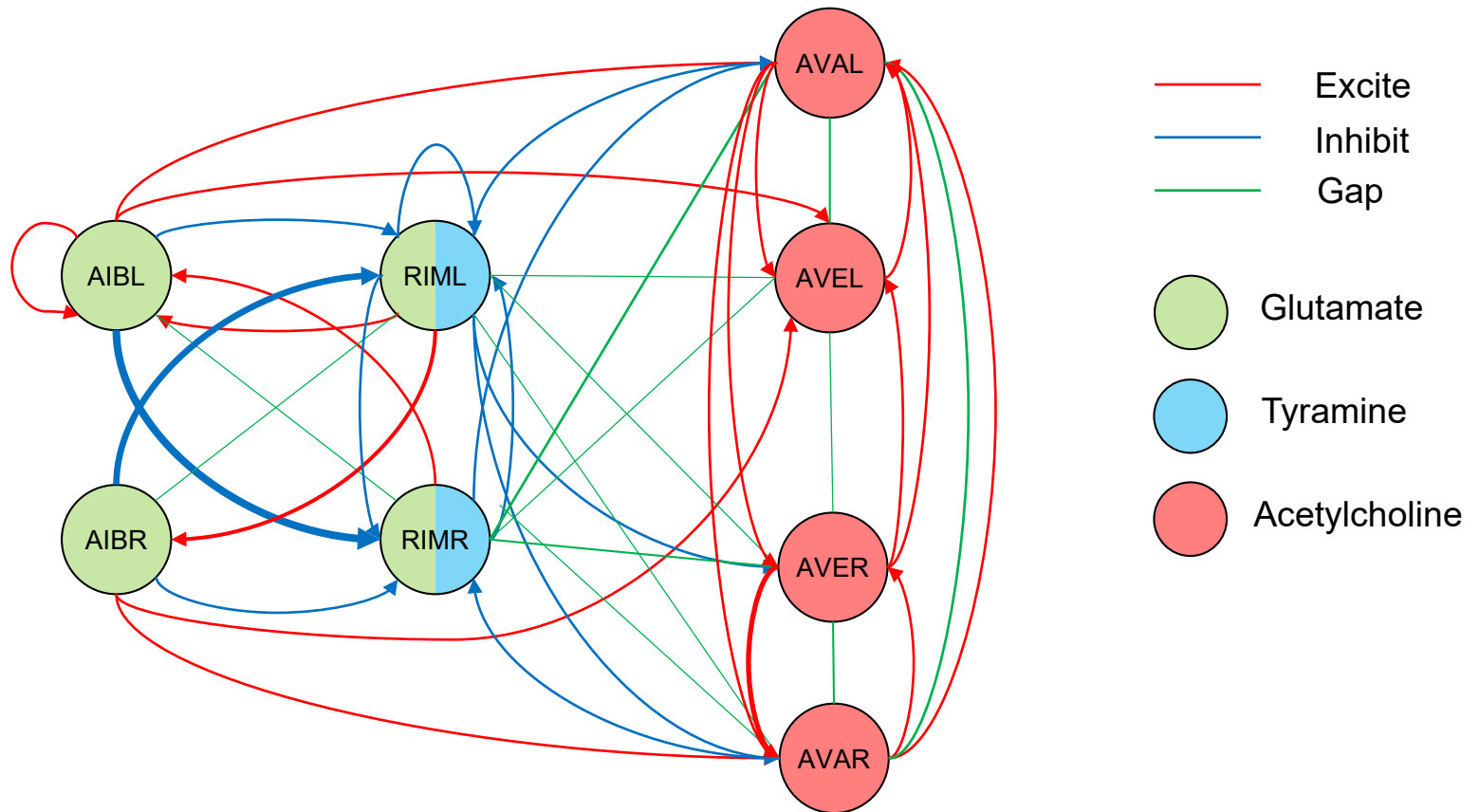
From	To	#	Chem/Elec	+/-/=	Source #
RIML	RIBL	9	Chem	-	21
RIML	AVBL	9	Chem	-	22
RIML	AVBR	11	Chem	-	22
RIML	AIBL	1	Chem	+	14
RIML	AIBR	22	Chem	+	14
RIML	AVAL	5	Chem	+	14
RIML	AVAR	2	Chem	+	14
RIML	AVER	5	Chem	-	
RIML	RIML	11	Chem	-	
RIML	RIMR	2	Chem	+	21

It's not what's said, it's what's heard

- Knowing neurotransmitter is insufficient to determine influence
 - The combination of transmitter type and receptor type
- Many types of receptors in *C. elegans*

Gene	Receptor	Ion selectivity
<i>glr-1 thru 8</i>	Glutamate	cation
<i>glc-1 thru 3</i>	Glutamate	Cl ⁻
<i>nmr-1 & mgl-2</i>	Glutamate	NMDA
<i>ggr-3</i>	GABA/Glycine	Cl ⁻
<i>acr-14 & 15</i>	Acetylcholine	cation
<i>acc-1 thru 4</i>	Acetylcholine	Cl ⁻
<i>lgc-55</i>	Tyramine	Cl ⁻

Reverse Circuitry



→ 1-10 → 11-20 → 21-30 → 31-40 → 41-50 → 51-60

Simulator

- Two neuron types
 - Bistable - On or off states triggered by external input
 - Graded – Output based on input
- Excitatory, Inhibitory, and Gap junction synapses
- Simulates every combination of inputs to AIBL and AIBR (0.0 – 1.0 step 0.1)
- Simulations run for 100 steps

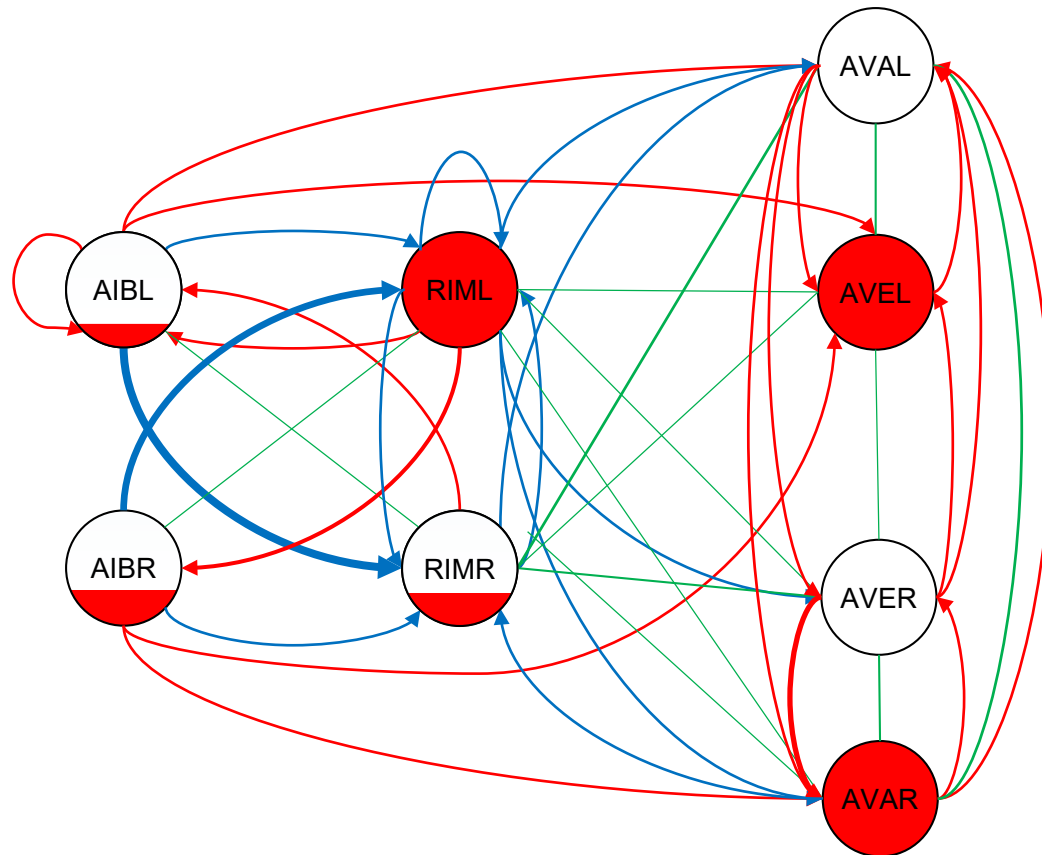
Results

- 118 out of 121 configurations are unstable
- 78 out of 118 the primary instability was in AVEL, AVER, AVAL, AVAR

	<i>extAIBL</i>	<i>extAIBR</i>	<i>valAIBL</i>	<i>valAIBR</i>	<i>valAVAL</i>	<i>valAVAR</i>	<i>valAVAL</i>	<i>valAVER</i>	<i>valRIML</i>	<i>valRIMR</i>	<i>e (0=unsta</i>
<i>extAIBL</i>	1										
<i>extAIBR</i>	0	1									
<i>valAIBL</i>	0.976569	0.011734	1								
<i>valAIBR</i>	0.050048	0.980554	0.061797	1							
<i>valAVAL</i>	0.194365	0.125766	0.220669	0.17329	1						
<i>valAVAR</i>	0.344016	0.312261	0.296668	0.33207	-0.40906	1					
<i>valAVAL</i>	0.142899	0.243458	0.10542	0.261155	-0.616	0.728571	1				
<i>valAVER</i>	-0.05249	-0.14171	-0.01375	-0.09385	0.712906	-0.64474	-0.93503	1			
<i>valRIML</i>	0.249092	0.27807	0.252616	0.460212	0.283868	0.216432	0.157686	0.202371	1		
<i>valRIMR</i>	0.854079	0.015149	0.731153	0.059508	0.207565	0.293712	0.103434	-0.02132	0.229094	1	
state (0=u	-0.2185	-0.2353	-0.22251	-0.39159	-0.24501	-0.1868	-0.1361	-0.17467	-0.85454	-0.1924	1

Conclusions: AVAs and AVEs form a CPG
RIML turns the CPG on and off

Typical Pattern



Where does this leave us?

- Given a neural circuit, it is difficult to determine its role and function
 - Complex neurons
 - Complex interdependencies
- Good news – we have a lot more to learn
- Bad news – hard to imagine we will figure out humans anytime soon

List of Publications, Awards, Honors, etc.

Attributed to the Grant

- Jacob R Manjarrez, Magera Shaw, and Roger Mailler. “Optogenetic analysis of Ca^{++} transients in *Caenorhabditis elegans* muscle cells during forward and reverse locomotion.” Journal of Neuroscience. 2020. Under Review.
- Jacob R Manjarrez and Roger Mailler. “Time and Stress Constraints of *Caenorhabditis elegans* Immobilization Methods.” Heliyon. Jul 2020.