Neurokinematic Modeling of complex swimming patterns of larval Zebrafish

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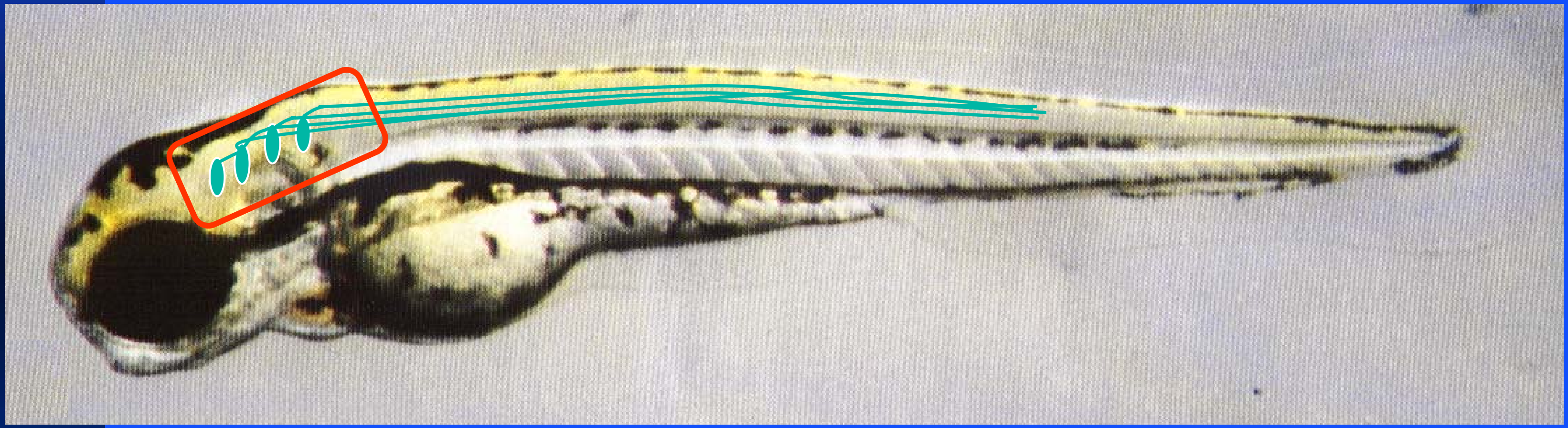
KTIP04, September 14th, 2004

with S. Hill, D. Knudsen, M. McElligott, D. O'Malley and Xiao-Ping Liu.

Wullimann, Rupp & Reichert
Neuroanatomy of the Zebrafish Brain
1996, Birkhauser Verlag, Basel

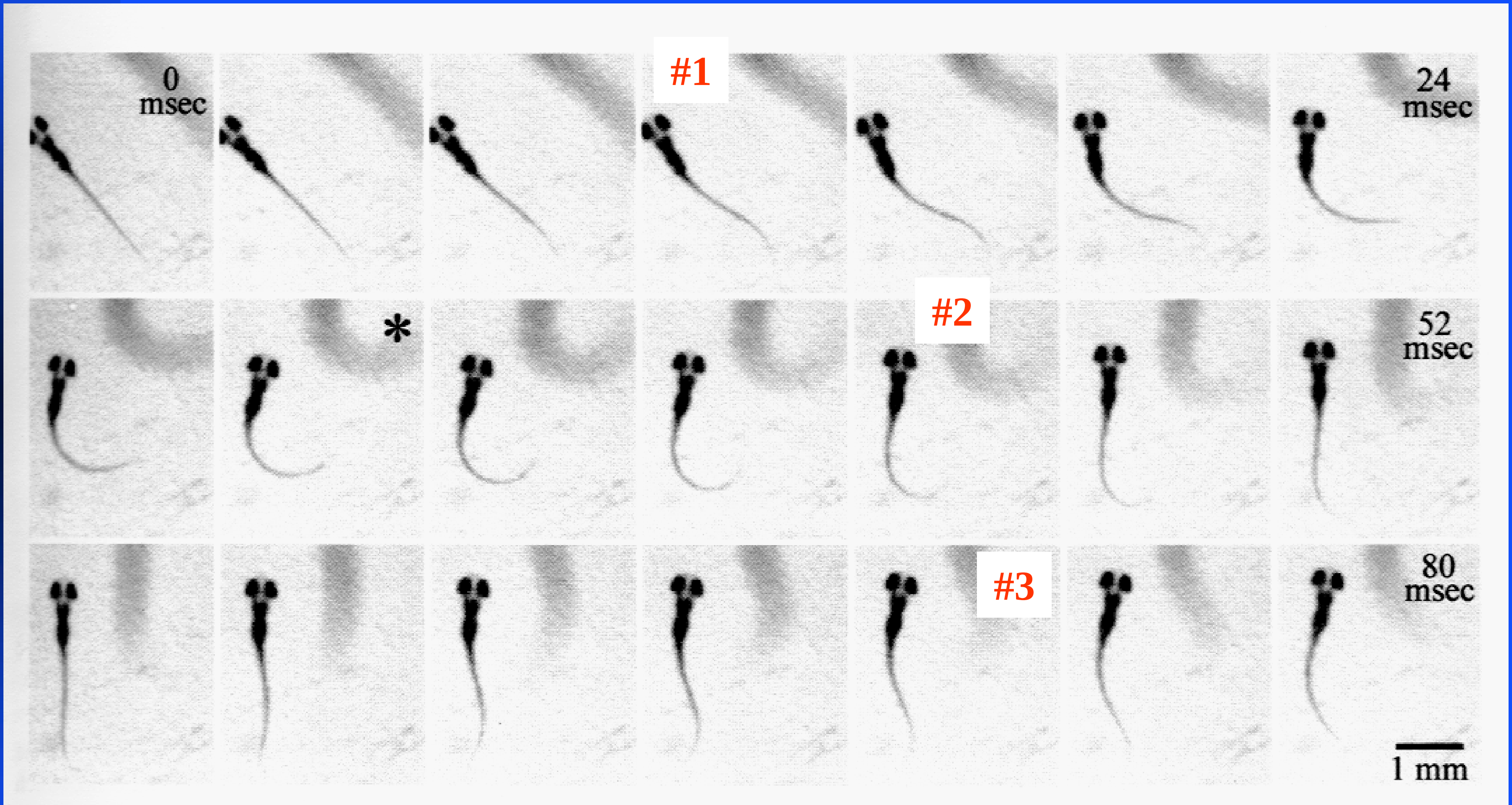
The Descending Motor Control (DMC) System of the Larval Zebrafish (5 days old)



300 neurons 40 distinct cell types

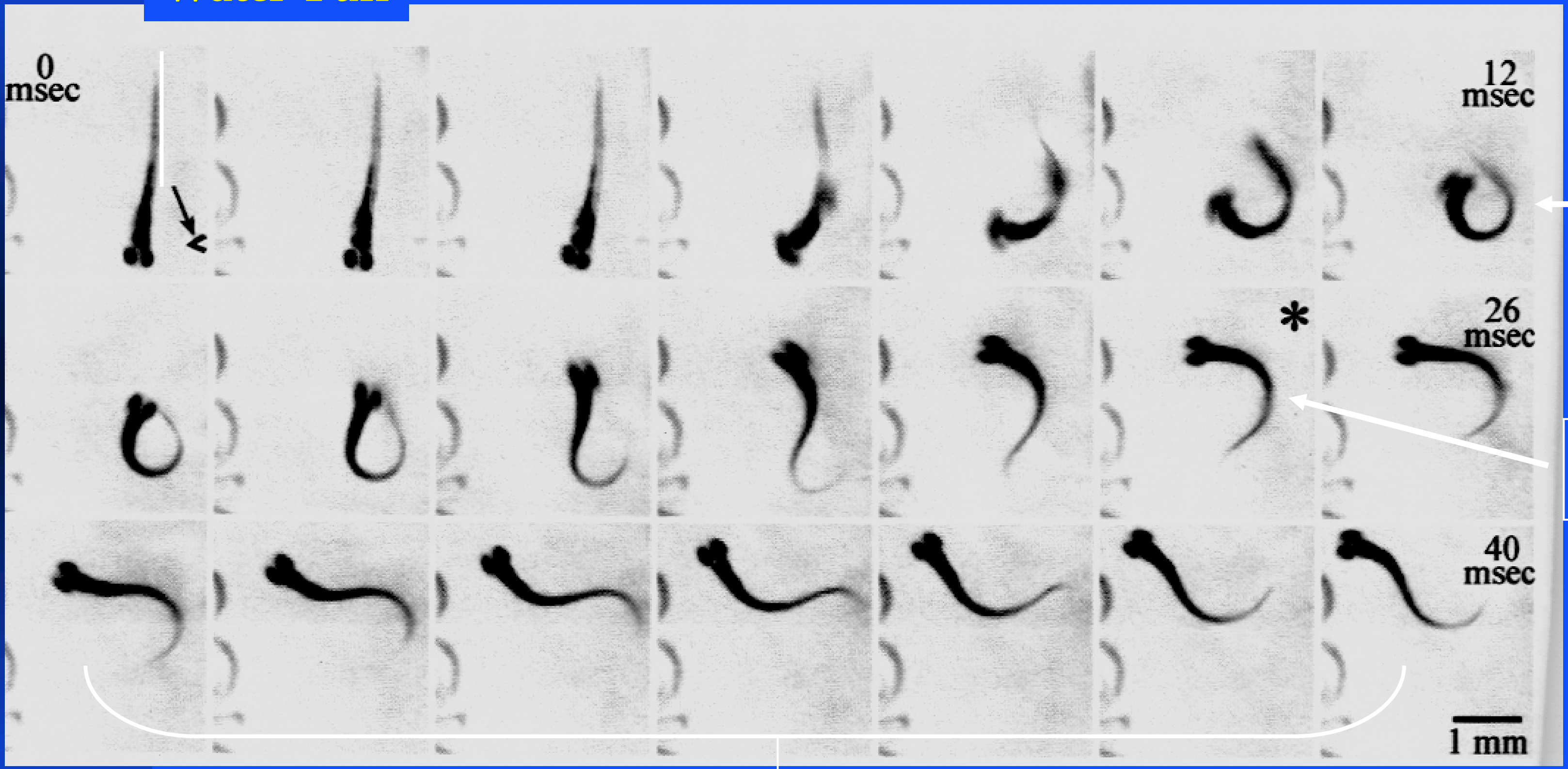
Neurons project varying distances into spinal-cord

Spontaneous Routine Turn



#'s – indicate frames that would be observed at video rate

Puff-Elicited Escape Behavior



Locomotive Repertoire of the Larval Zebrafish, 2000

Turning Behaviors:

Escape Turns

Routine Turns

Swimming Behaviors:

Burst Swims

Slow Swims

Budick & O'Malley, 2000
J. Exp. Biol., **203**:2565-2579.

Locomotive Repertoire of the Larval Zebrafish, 2003

Turning Behaviors:

- Escape Turns
- Counter-Turns
- Large-Delayed Turns
- Routine Turns
- J-Turns

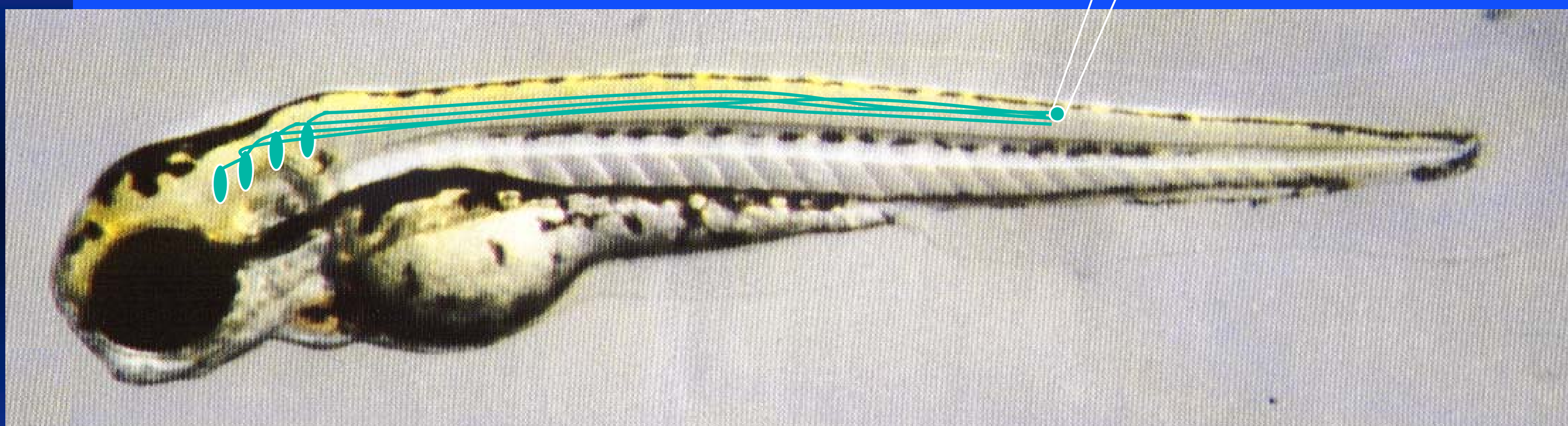
Swimming Behaviors:

- Burst Swims
- Slow Swims
- Sleeping Swims
- Tracking Swims
- Reverse Swims

Labeling of Neurons in the Descending Motor Control System

Microinjection Pipette
10,000 MW Dextran*

Retrograde Labeling of Descending Neurons

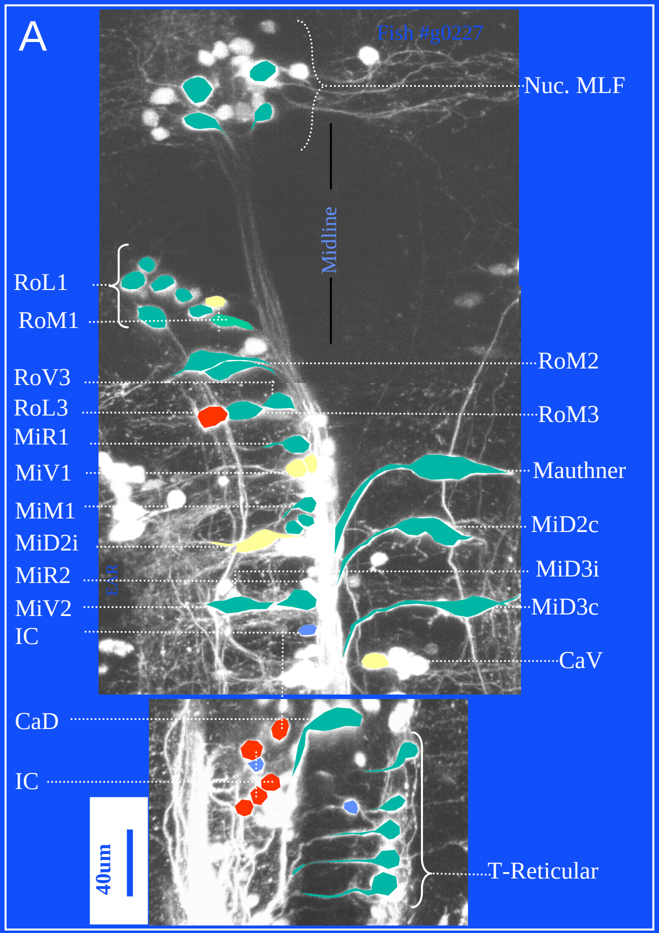


*Dextrans can be anatomical tracers or fluorescent calcium indicators

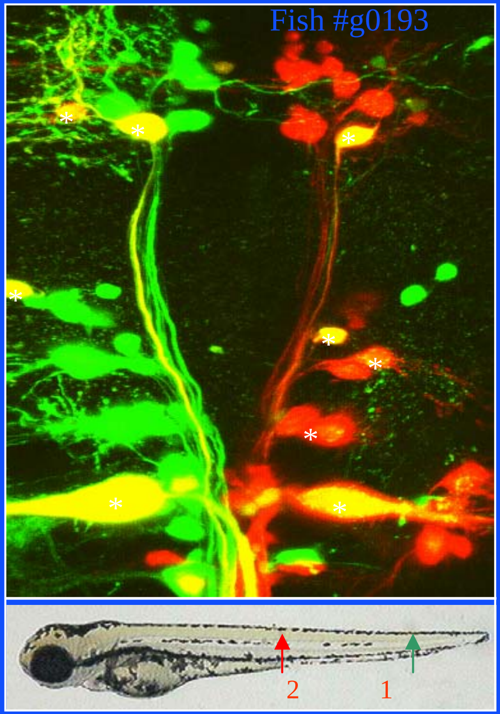
Experimental Results

Confocal imaging of neural activity and high-speed imaging of behavior are being used to investigate the neural control of larval locomotive behaviors: **swimming, escaping, prey-capture and navigation.**

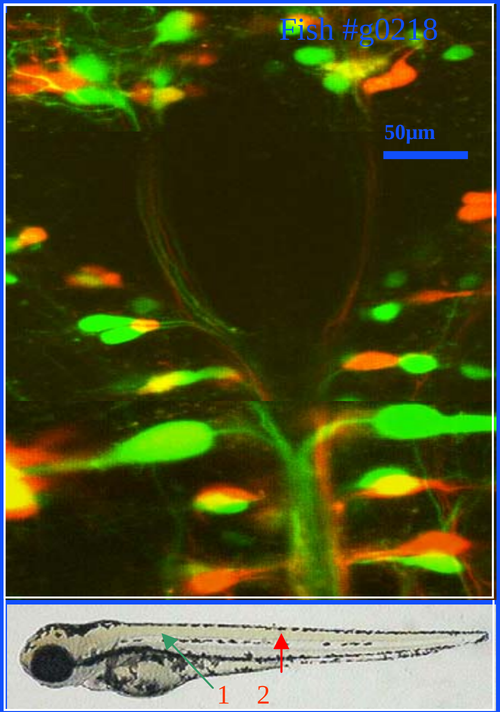
Image at right illustrates the wide-spread activation of many identified **brainstem neurons** during C-start escape behaviors (J. Neurophys. Jan 2002).



Rostral Injections Sever Axons



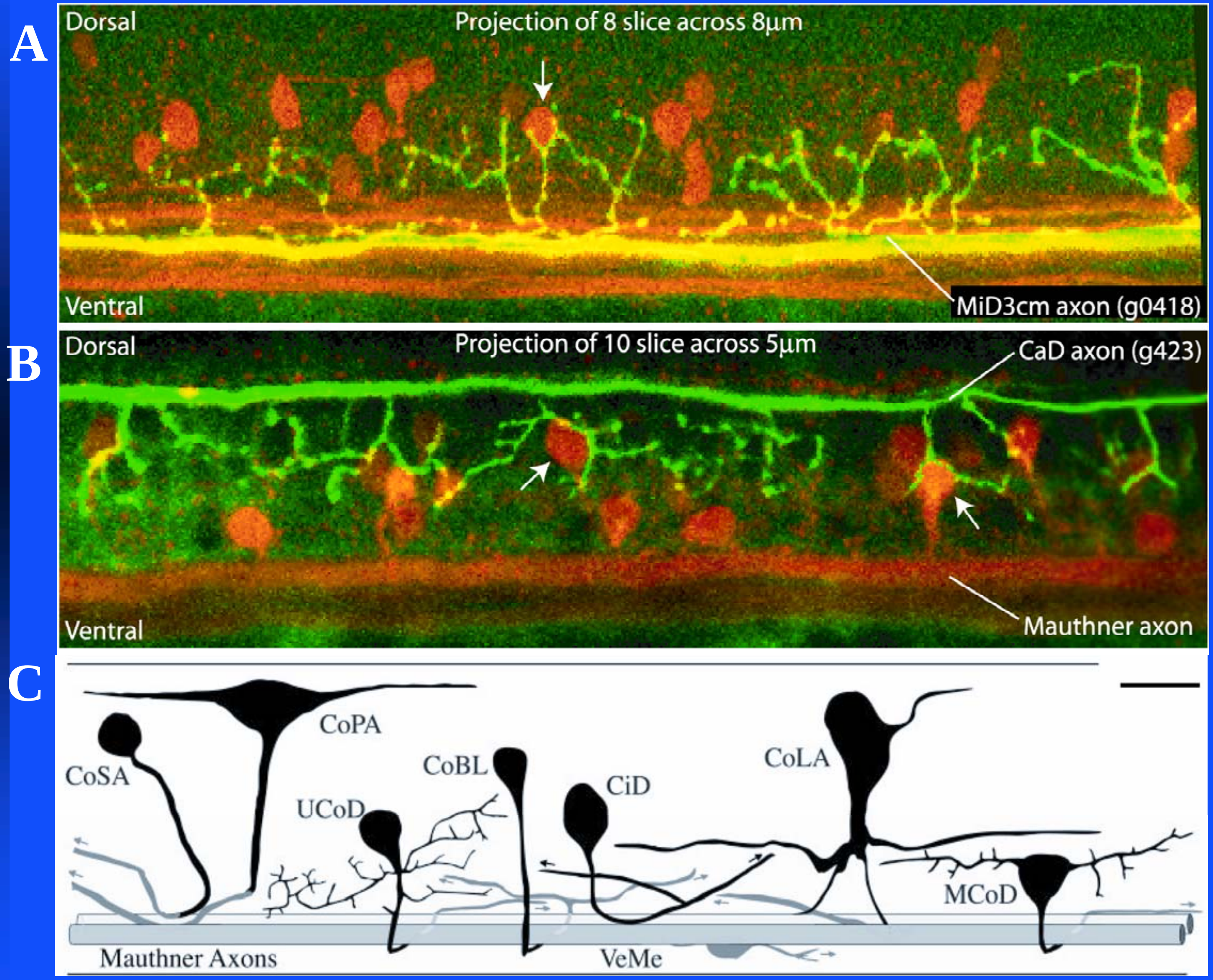
First injection caudal



First injection rostral

Gahtan and O'Malley, 2001
J. Neurosci. Meth., 108:97-110

Possible Synaptic Contacts onto Identified Spinal Neurons



C. is from Ritter et al., 2001, *J. Neurosci*.

Objective

Model the DMCS and spinal cord of the Larval Zebrafish: Understand spinal motor control

Input Data for Computational Model:

- **Behavioral**
- **Physiological**
  - **Neural Activity**
  - **Perturbation**
- **Neuroanatomical**

Models of Descending Motor Control in lower vertebrate animals

1. Neural Control of the Escape Behavior

2. Left-Right Alternation during Rhythmic Locomotion (swimming in Xenopus tadpoles)

3. Intersegmental Coordination in Lamprey

Fine Axial Motor Control
in relation to
Existing Models of the Neural Control of Aquatic Locomotion

Current Models of Swimming:

1. Based on: Xenopus, Lamprey
2. Cellular-level Networks: explain right-left alternation
3. Longitudinal Networks: explain intersegmental coordination

New Control-System Requirements:
(based on larval prey capture)

1. Bend-to-bend control of iTBF
2. Bend-to-bend control of bend location
3. Bend-to-bend control of bend amplitude
4. Asymmetric control of bending
5. Dynamic vs. "canned" programming (??)

Other Constraints on a Realistic Model of the DMCS:

1. Spinal Axon Collaterals/Branching
2. Widespread, multi-modal activation of descending neurons
3. Resistance of DMCS to perturbation by ablation of numbers of descending neurons

Williams et al. Model
Intersegmental Coupling in Lamprey

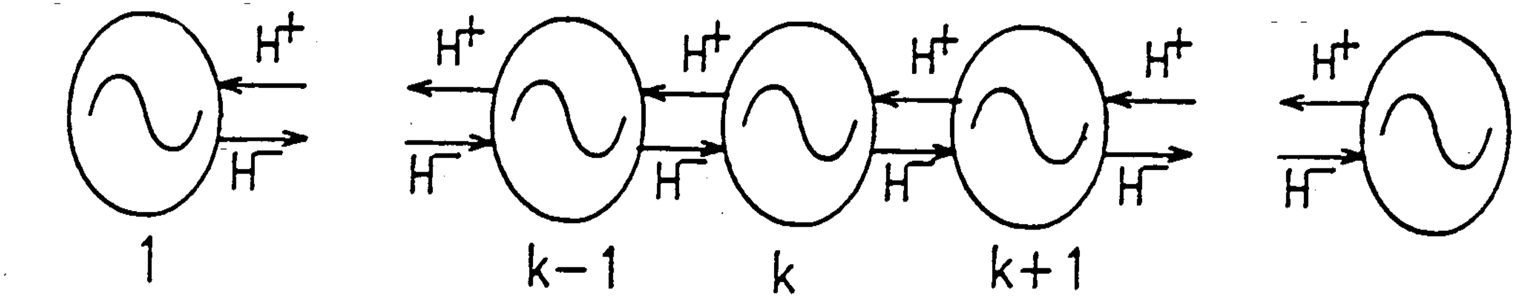
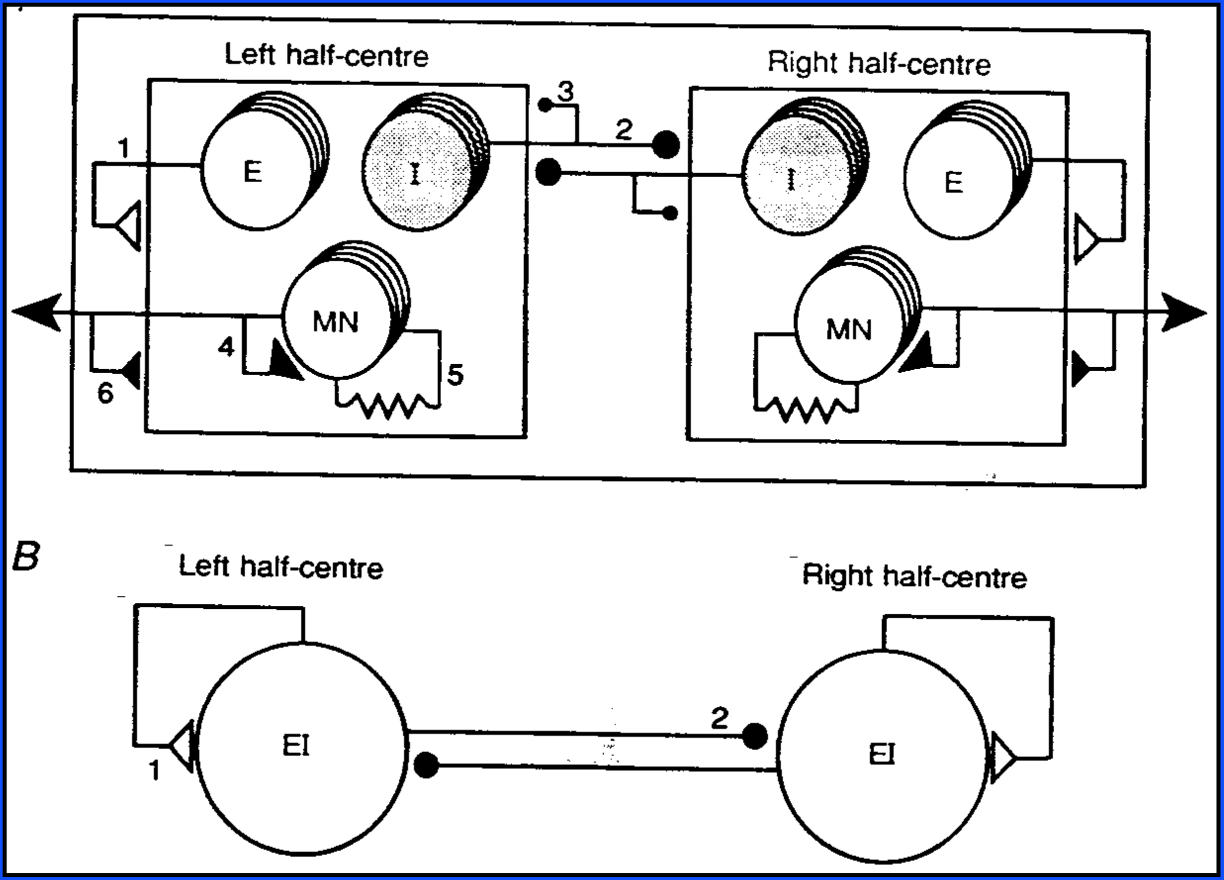


FIG. 1. Lamprey spinal cord represented as a chain of coupled nonlinear oscillators. Each oscillator sends signals to its rostral neighbor via ascending fibers and to its caudal neighbor via descending fibers. These signals are represented by the ascending and descending coupling functions $H^+(\phi)$ and $H^-(-\phi)$, respectively.

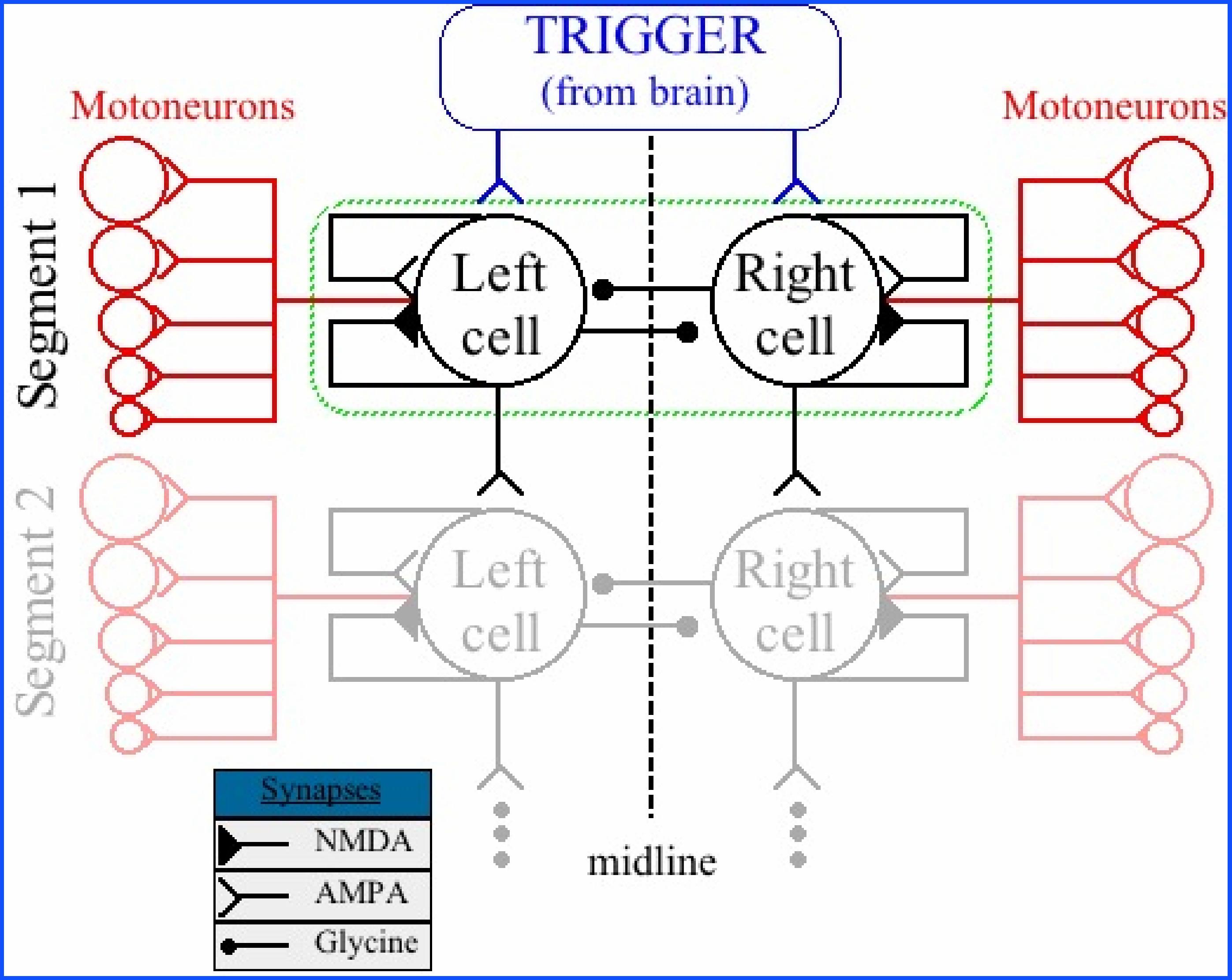
Williams, Sigvardt, Kopell, Ermentrout & Remler, 1990
J. Neurophysiol. 64:862-871

Dale Model
Left-Right Alternation in Xenopus Spinal Cord

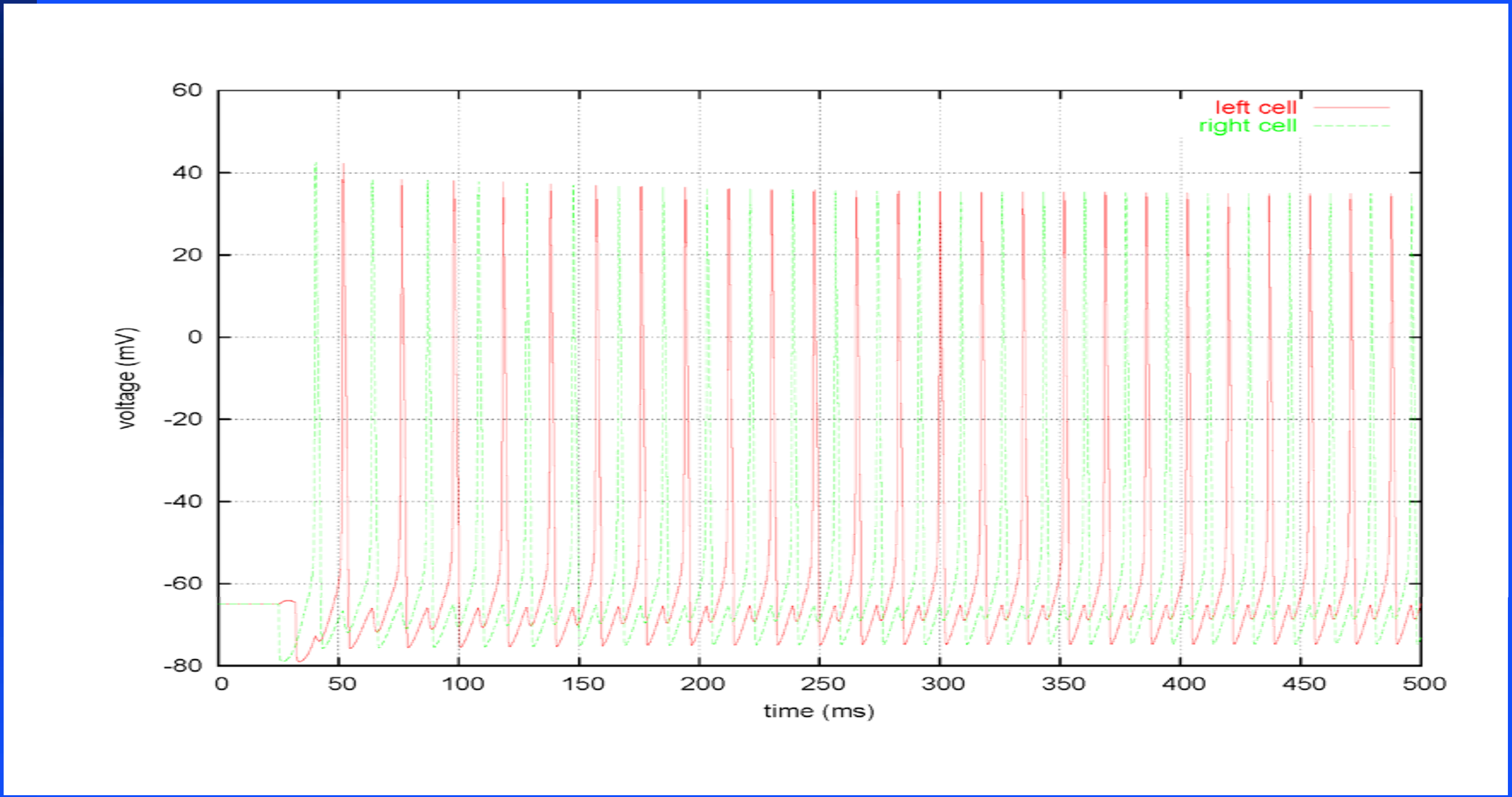


Dale, 1995, *J. Physiol*. **489**:489-510

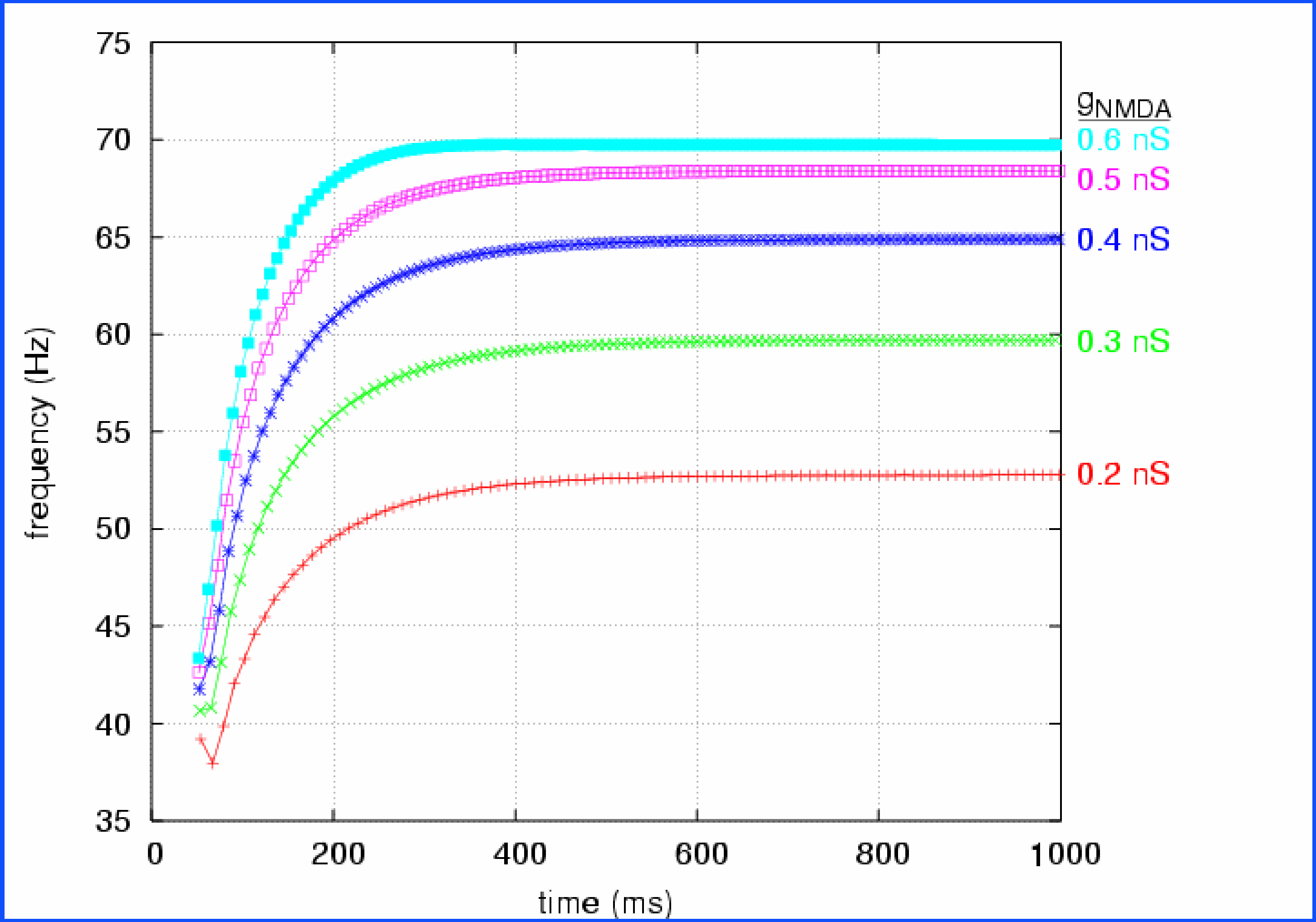
Neural Model 2-Cell Segmental Oscillator



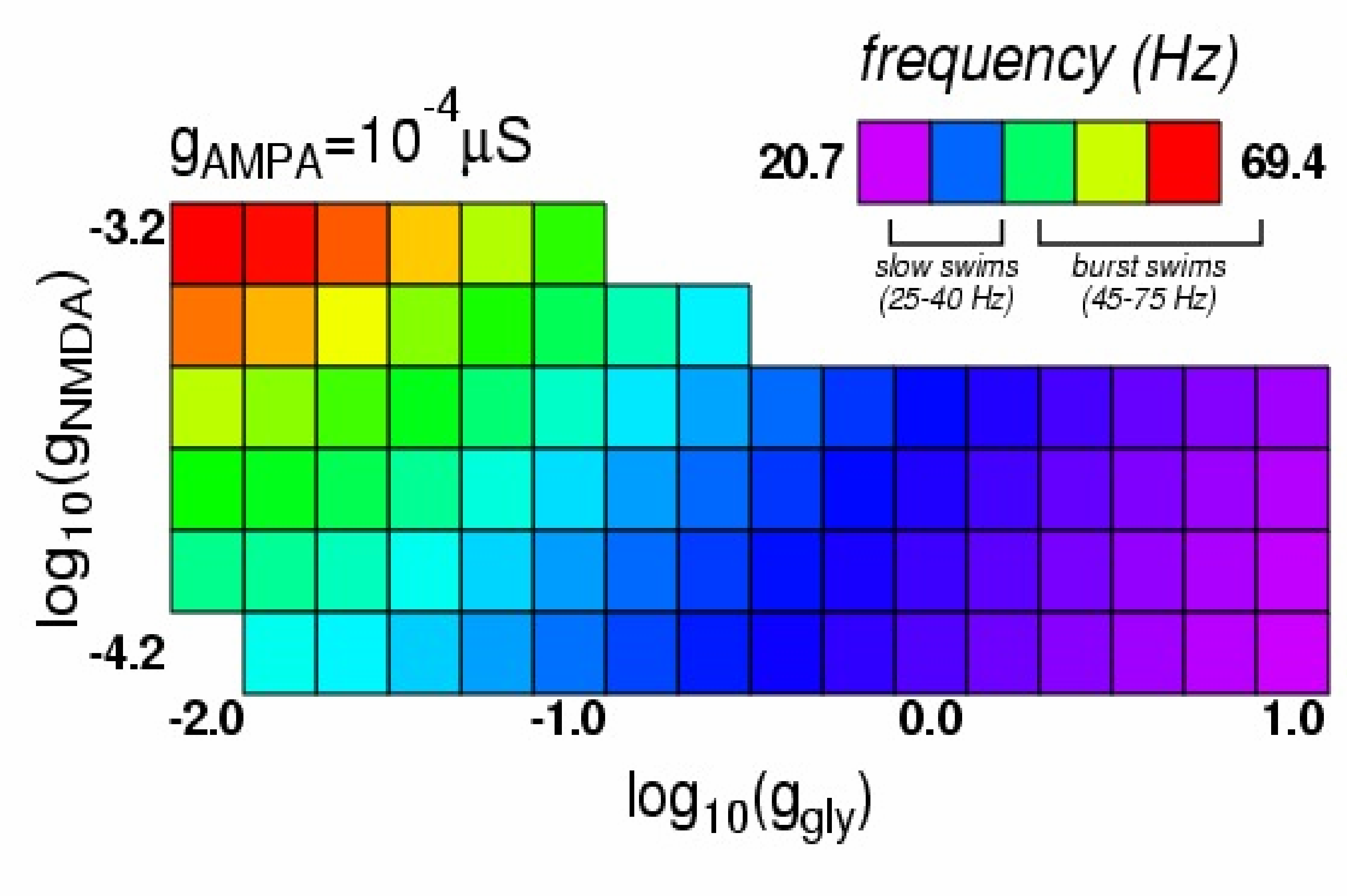
Activity triggered by a single pair of pulses (with a left/right delay) Initiates regular rhythm in single-segment model of oscillator



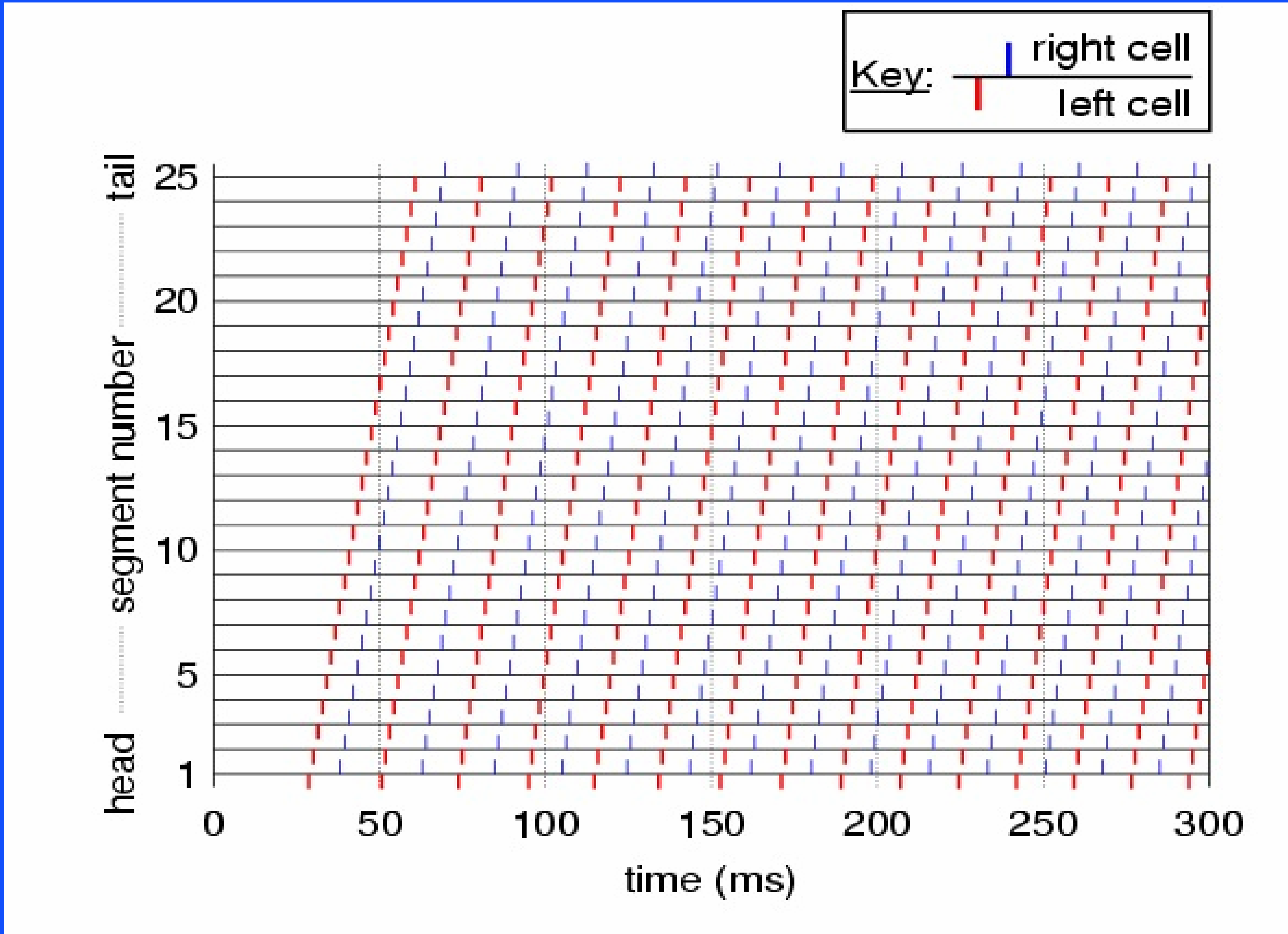
Frequency Accelerates over the Early Part of the Simulation



Oscillator Frequency Depends on the Balance of Excitatory and Inhibitory Inputs



Behavior of 25-Segment Model



Neurokinematic model

$$F_m(x,t) = \int_{\infty}^{t} F_s(x,t')[e^{(t-t')/\tau_2} - e^{(t-t')/\tau_1}]dt'$$

$\tau_2 = 8ms$ $\tau_1 = 6ms$

$F_s(x,t)$

$F_s(x,t)$

$\mathrm{F}_s(x,t) > 0$ **for a signal to the left**

$\mathrm{F}_s(x,t) < 0$ **for a signal to the right**

$R(x,t) = W(x)/F_m(x,t)$ **Radius of curvature for segment x**

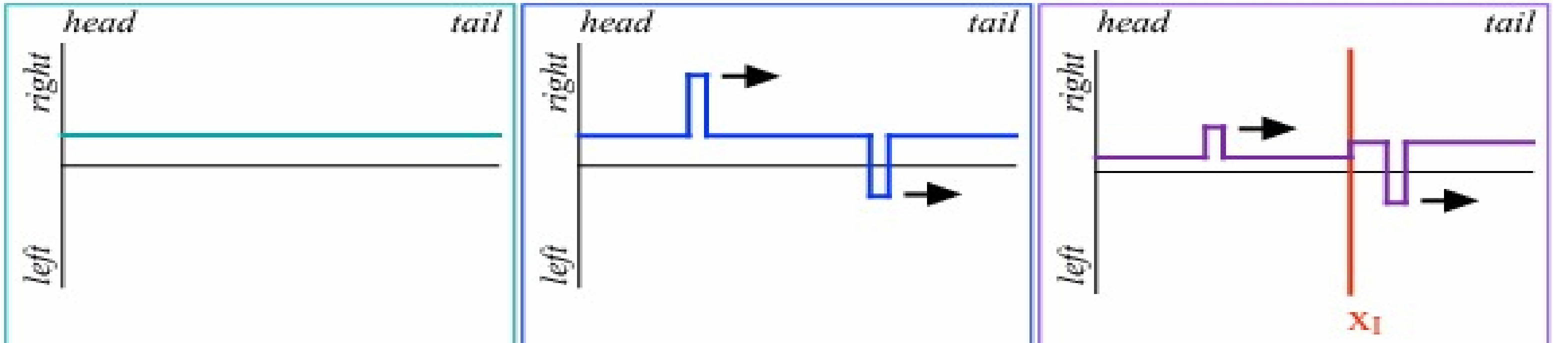
Artificial signal

$$F_s(x,t) = (F_{osc} + F_{bend})x \begin{cases} f_{inh}, x \le x_{inh} \\ 1, x > x_{inh} \end{cases}$$

$$F_{osc} = f_{osc} \begin{cases} 1 & x = & 2\pi\nu t (\operatorname{mod} \lambda) \\ -1 & x = & 2\pi\nu t + \lambda/2 (\operatorname{mod} \lambda) \\ 0 & & otherwise \end{cases}$$

*Artificial CNS signal

We construct an artificial signal using three steps.



A tonic signal causes the whole fish to bend to the left or right.

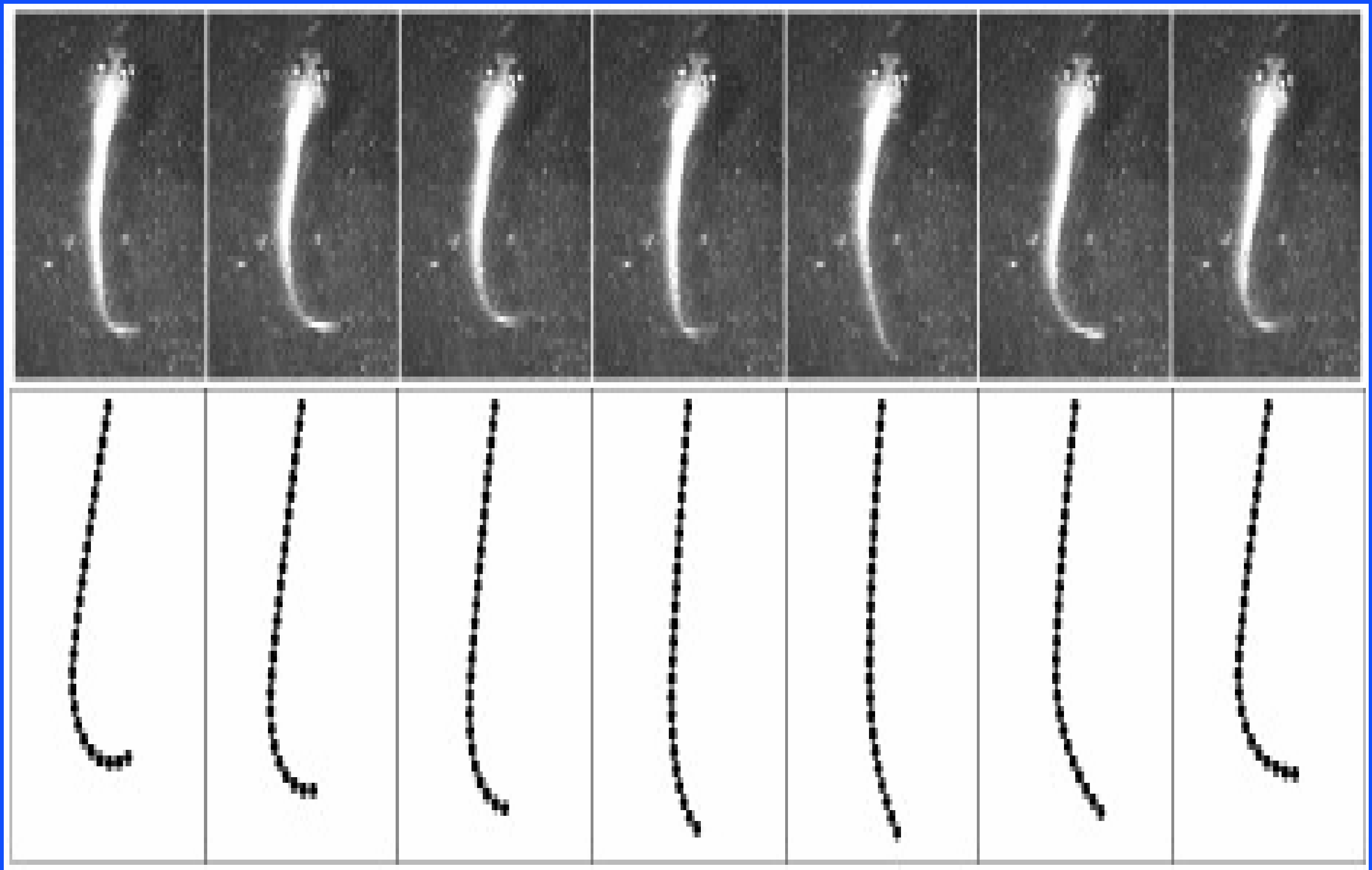
A series of alternating square pulses, propagating caudally, cause oscillation.

The signal is then passed through an inhibitory filter which reduces the signal to those segments rostral of some point x_I.

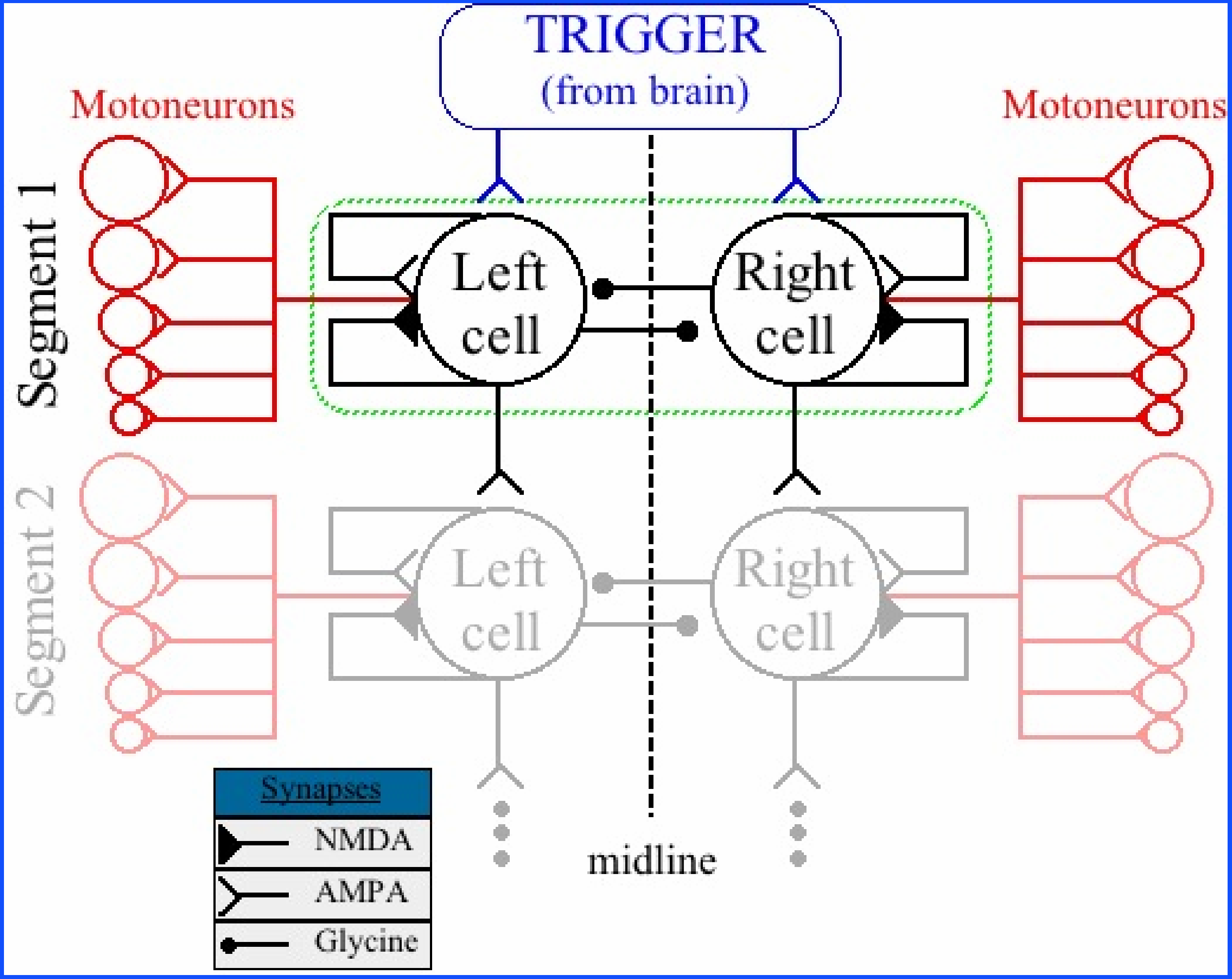
Mathematically, we write the signal as

$$F(x,t)=(F_{osc}(x,t) + F_{bend}) \times \begin{cases} f_{inh}, & x < x_{inh} \\ 1, & x \geq x_{inh} \end{cases}$$

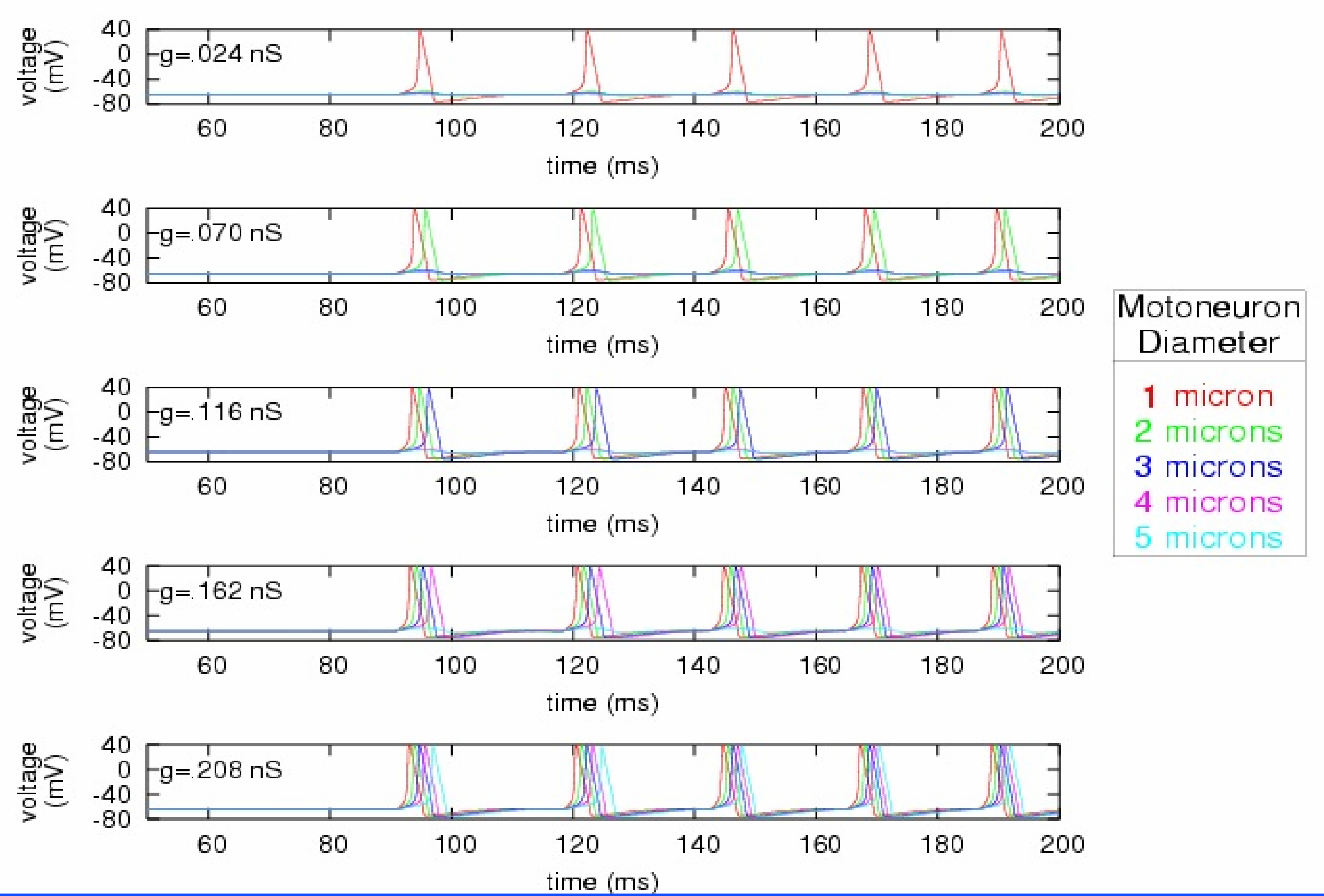
J-turn precapture swimm

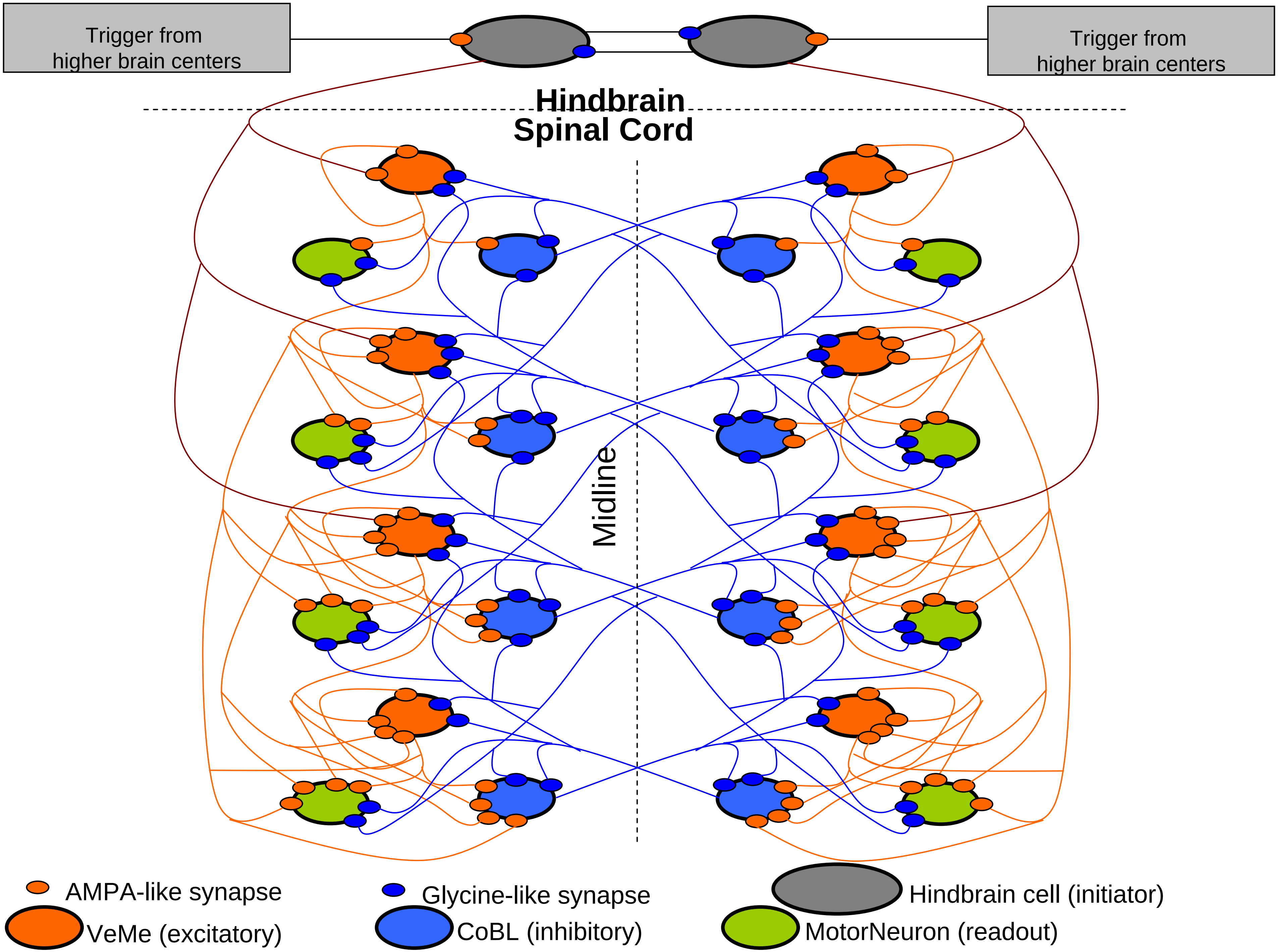


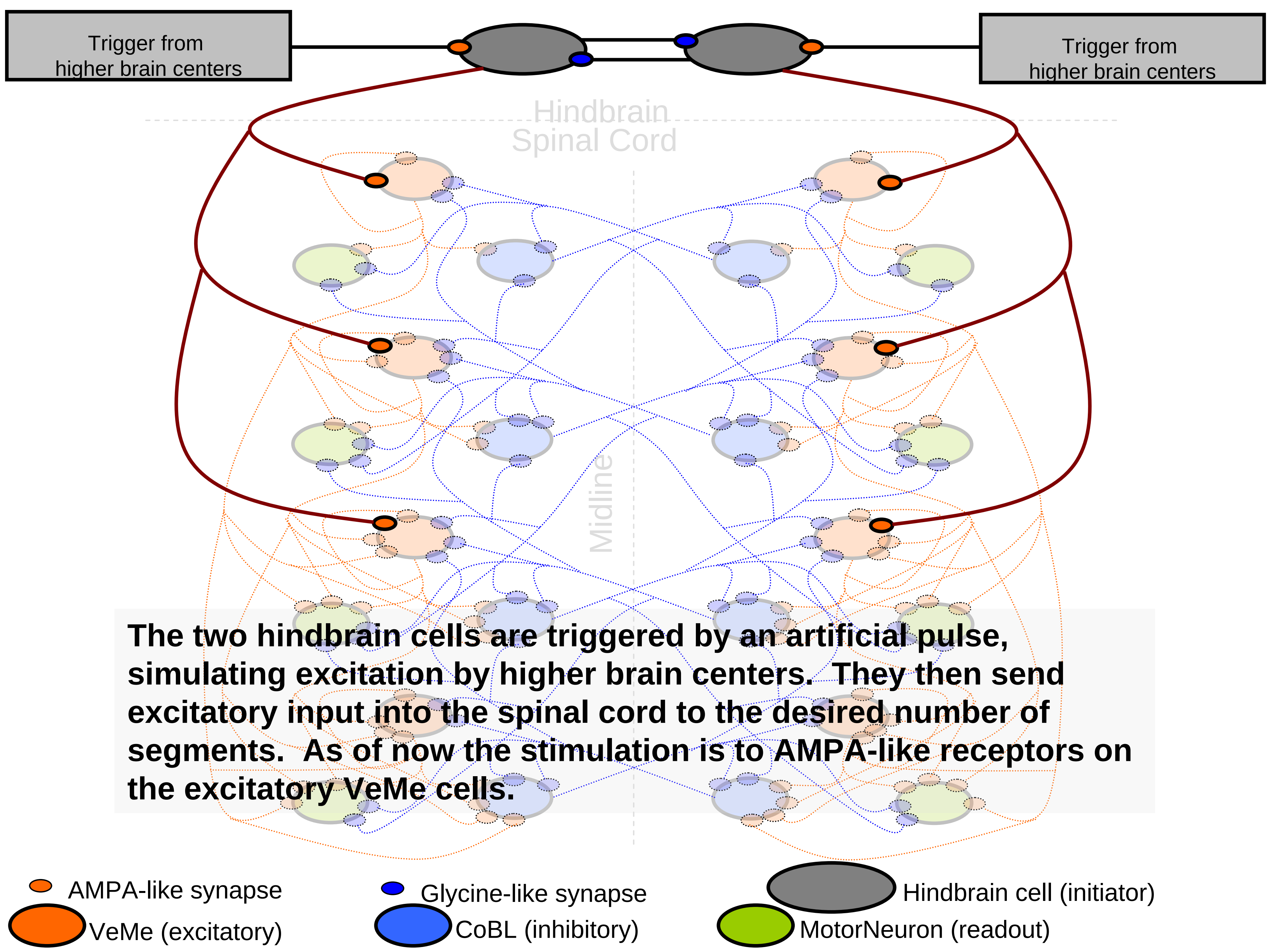
Neural Model 2-Cell Segmental Oscillator



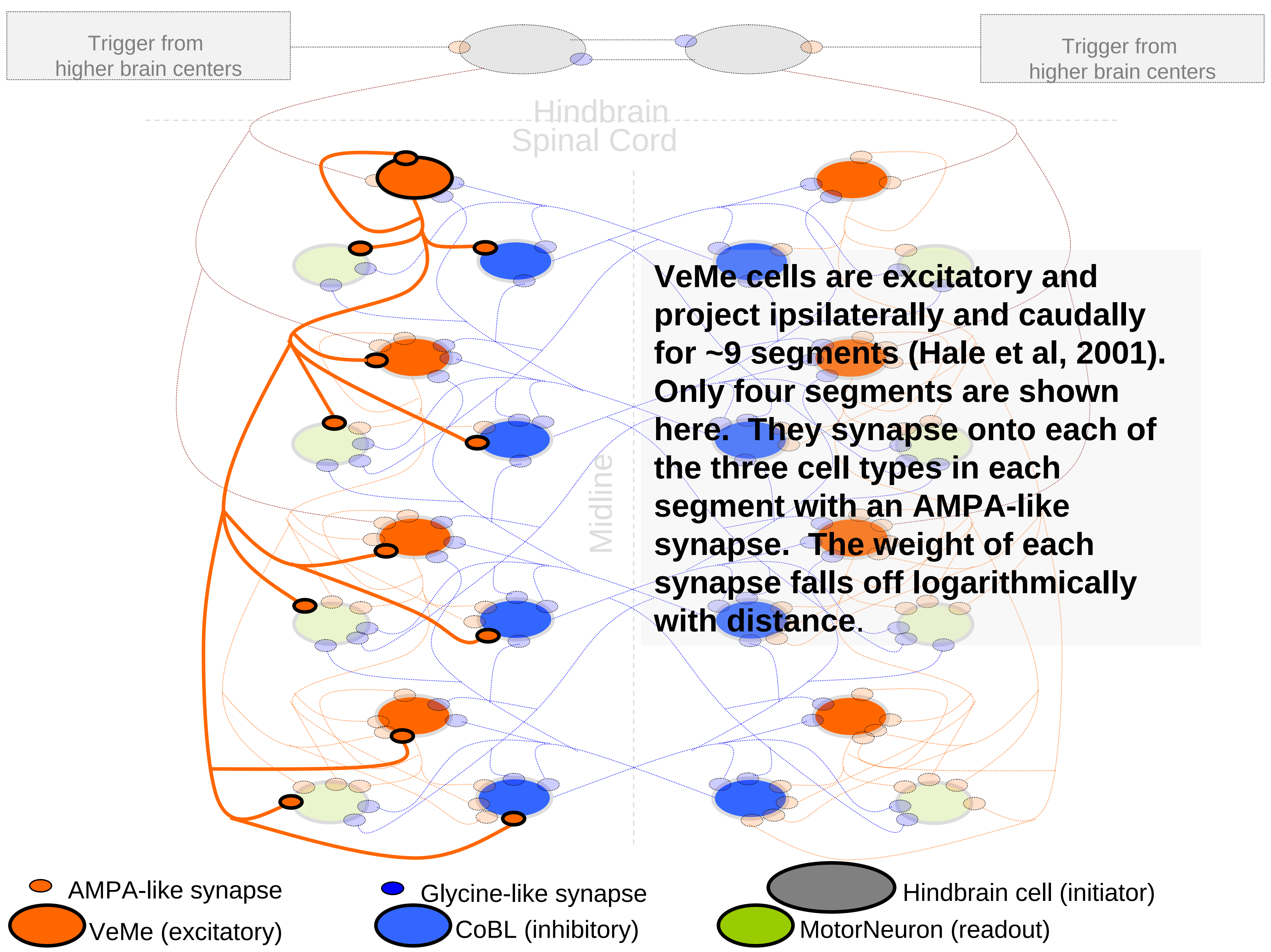
Modulation of Bend Amplitude



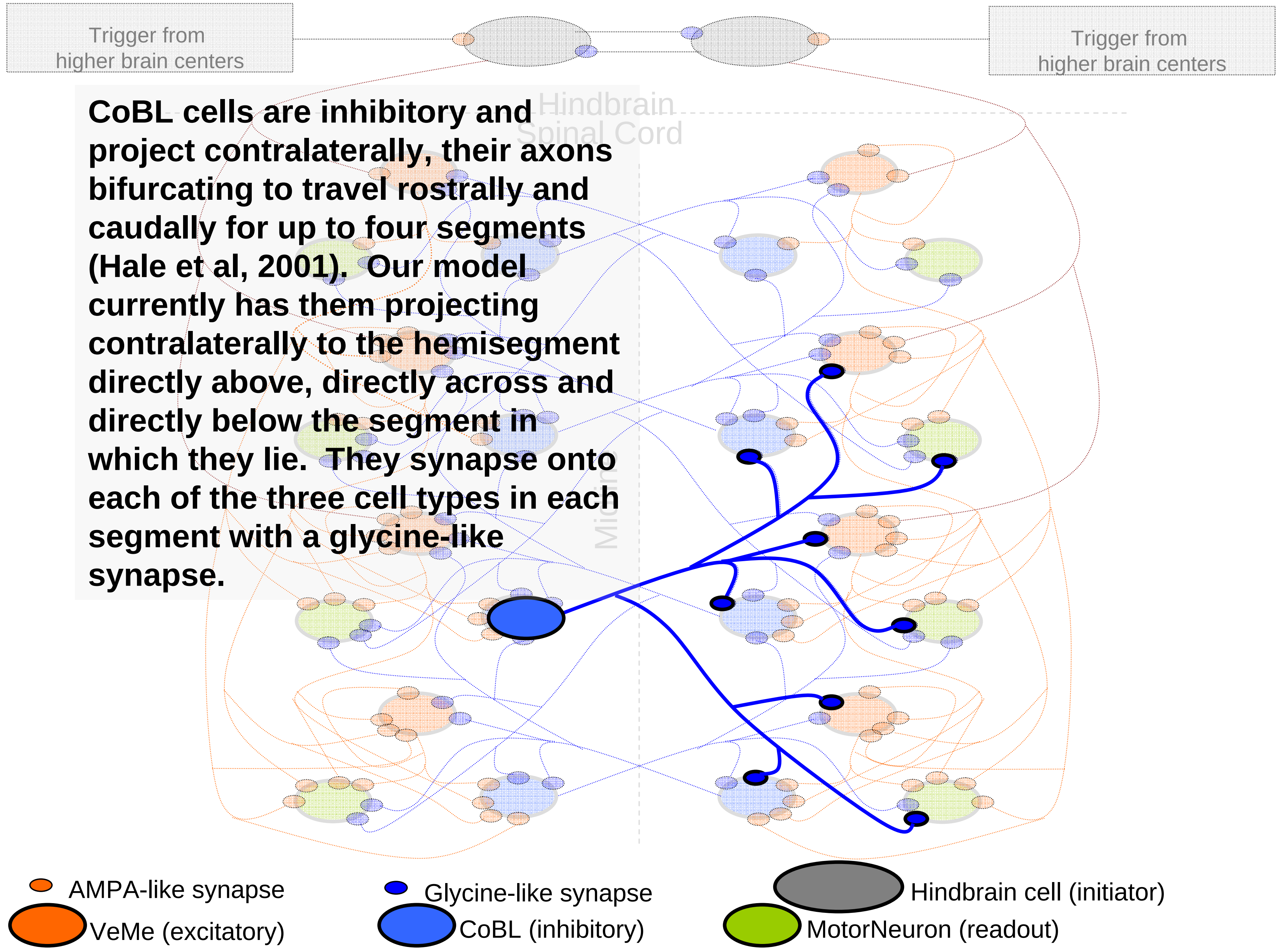

Trigger from higher brain centers
Trigger from higher brain centers
Hindbrain
Spinal Cord
Midline
AMPA-like synapse
Glycine-like synapse
Hindbrain cell (initiator)
VeMe (excitatory)
CoBL (inhibitory)
MotorNeuron (readout)

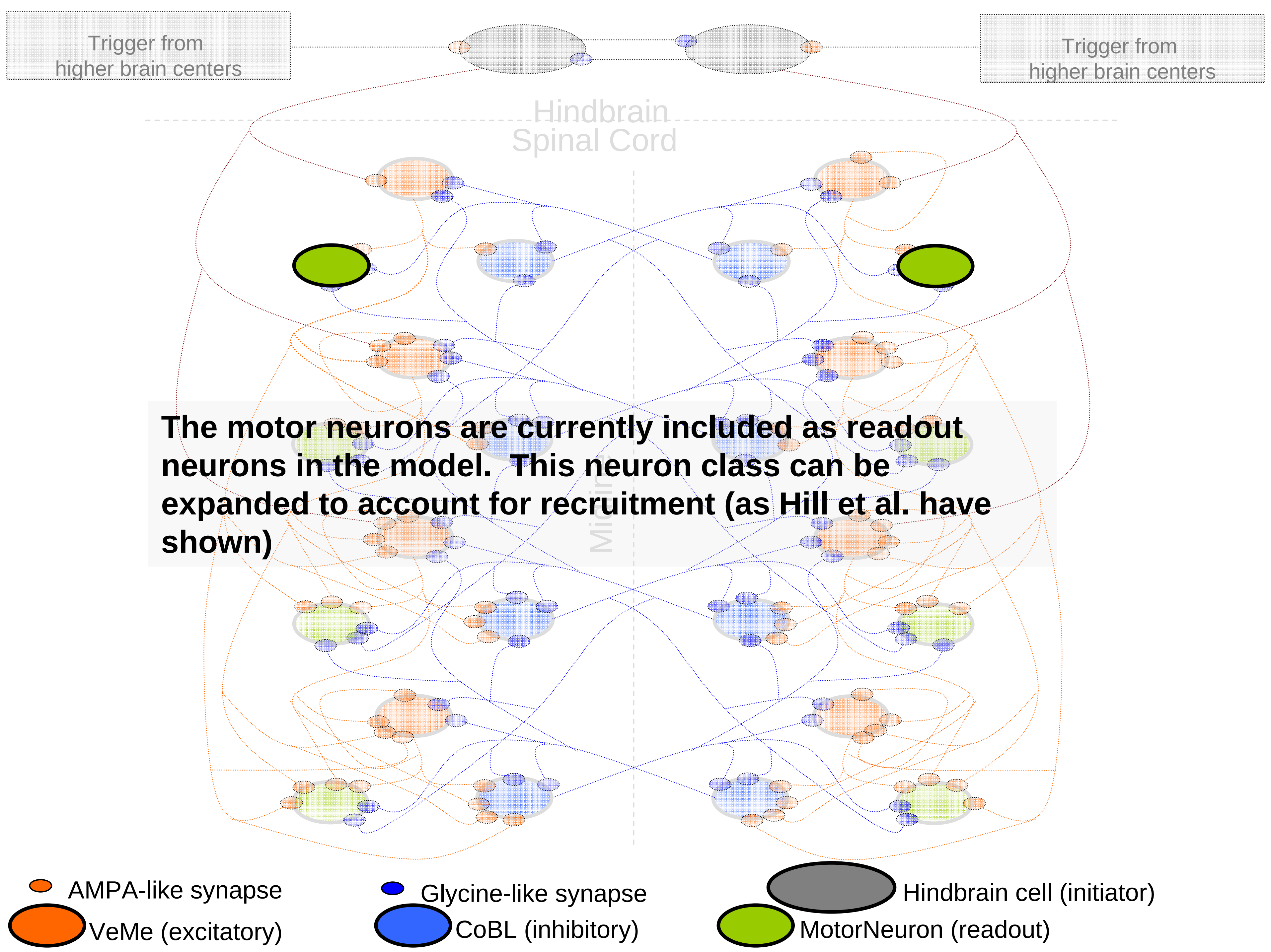


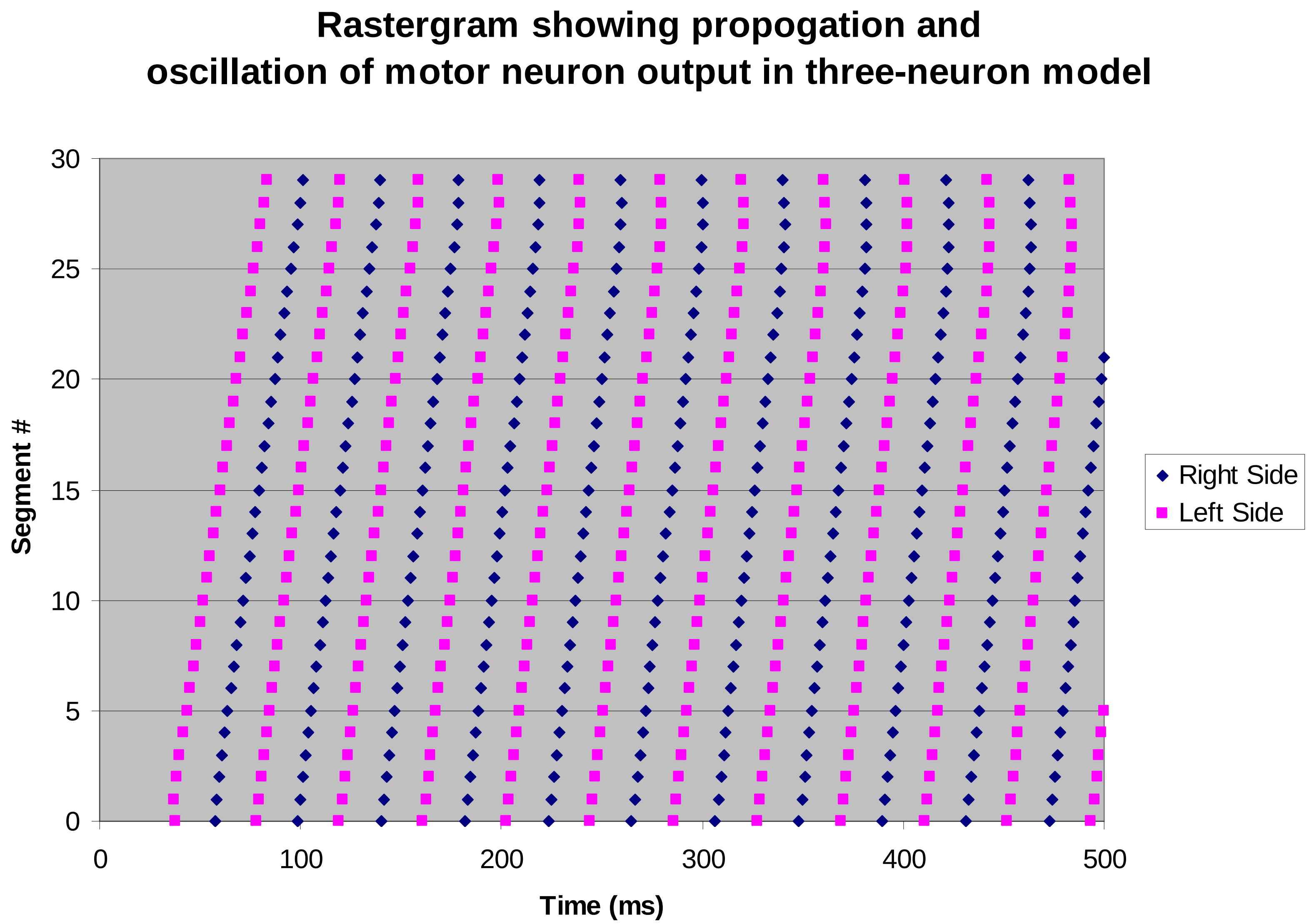
The two hindbrain cells are triggered by an artificial pulse, simulating excitation by higher brain centers. They then send excitatory input into the spinal cord to the desired number of segments. As of now the stimulation is to AMPA-like receptors on the excitatory VeMe cells.


Trigger from higher brain centers
Trigger from higher brain centers
Hindbrain
Spinal Cord
Midline
VeMe cells are excitatory and project ipsilaterally and caudally for ~9 segments (Hale et al, 2001). Only four segments are shown here. They synapse onto each of the three cell types in each segment with an AMPA-like synapse. The weight of each synapse falls off logarithmically with distance.
AMPA-like synapse
VeMe (excitatory)
Glycine-like synapse
CoBL (inhibitory)
Hindbrain cell (initiator)
MotorNeuron (readout)

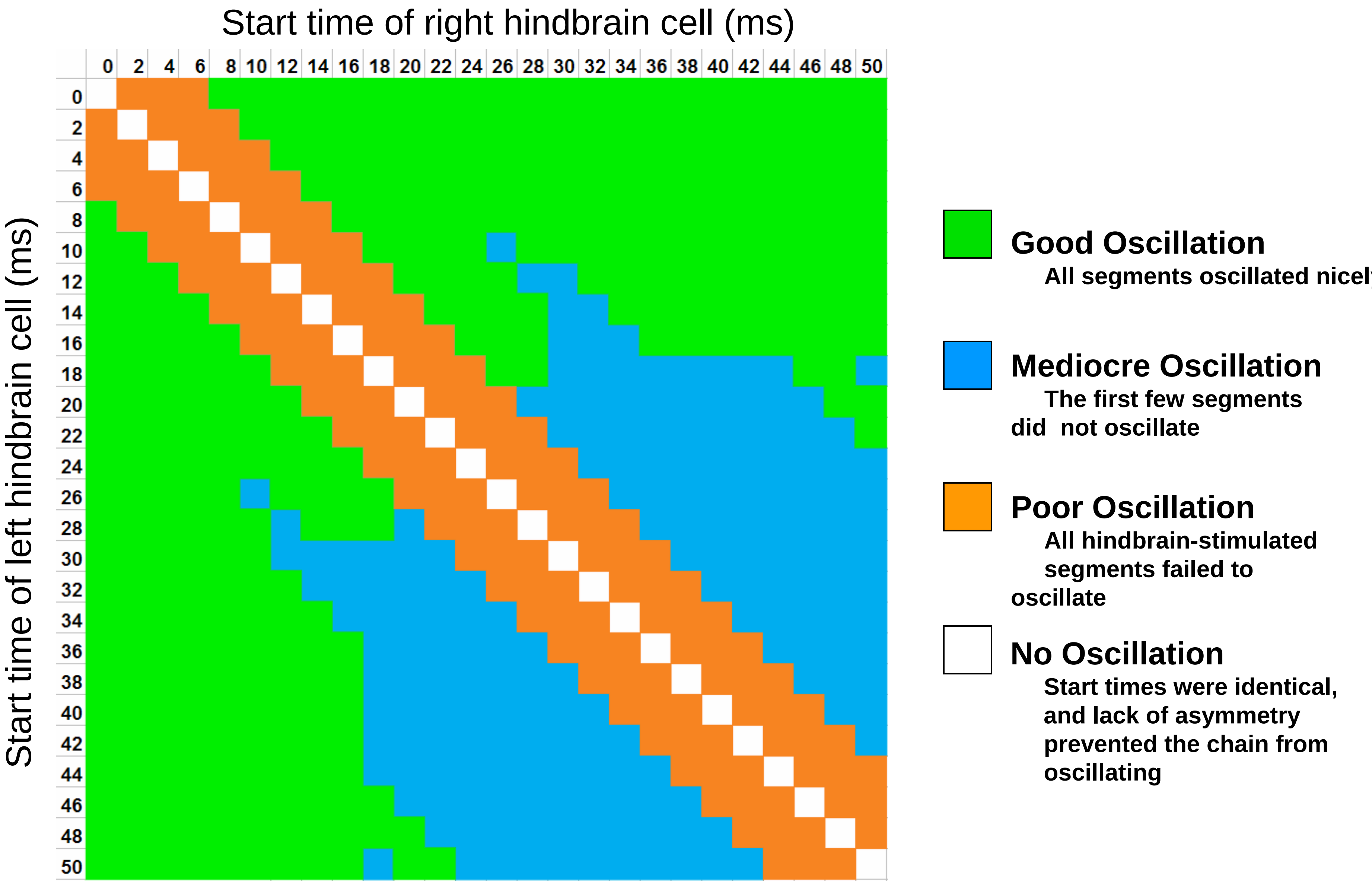
CoBL cells are inhibitory and project contralaterally, their axons bifurcating to travel rostrally and caudally for up to four segments (Hale et al, 2001). Our model currently has them projecting contralaterally to the hemisegment directly above, directly across and directly below the segment in which they lie. They synapse onto each of the three cell types in each segment with a glycine-like synapse.




Trigger from
higher brain centers
Trigger from
higher brain centers
Hindbrain
Spinal Cord
The motor neurons are currently included as readout neurons in the model. This neuron class can be expanded to account for recruitment (as Hill et al. have shown)
AMPA-like synapse
VeMe (excitatory)
Glycine-like synapse
CoBL (inhibitory)
Hindbrain cell (initiator)
MotorNeuron (readout)



Rastergram showing propogation and oscillation of motor neuron output in three-neuron model
Segment #
30
25
20
15
10
5
0
0
100
200
300
400
500
Time (ms)
Right Side
Left Side



Start time of right hindbrain cell (ms)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50
Start time of left hindbrain cell (ms)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50
Good Oscillation
All segments oscillated nicel
Mediocre Oscillation
The first few segments did not oscillate
Poor Oscillation
All hindbrain-stimulated segments failed to oscillate
No Oscillation
Start times were identical, and lack of asymmetry prevented the chain from oscillating

Conclusions

- Developed a model that describes different types of larva swimming patterns, using simulated descending motor control elements.
- Determined spinal mechanism involved in the control and right frequency of TBFs used in different swimming behaviors.
- We have added motor control neurons to the model
- Lesions in the spine change of behavior
- Different types of neurons 40/300 is that important?

S. Hill,
D. Knudsen,
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The End