

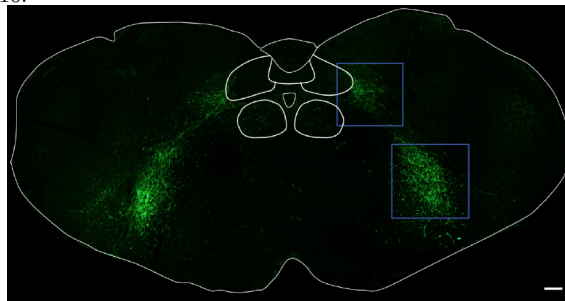
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# 1 Introduction to neuronal networks: A tale of two cells

Our focus is on the dynamics and function of neuronal circuits. Dynamics is a common term in physics and describes how the state variable of a system evolves over time. Such as a hoop that rolls down an incline plane and just keeps on going, something you probably first learned about as a teenager. At the end of the day you write equations for the linear ( $v$ ) and angular ( $\omega$ ) velocity and, if the hoop rolls without slipping, then  $v \propto \omega$  and life is particularly simple. One NEVER asks "What is the function of the hoop?". But biologists always ask about function. Here the loop may be part of a cart and the function of the hoop is to allow the cart to roll. Add a motor and the function of the loop is to transport the cart. Then what is the function of the cart? This is never ending.

In neuroscience, the function of the nervous system is to compute something. It could be homeostatic, like the circuit that controls to breathing, which was discovered by Jack Feldman and named the preBotzinger complex after a bottle of wine. The preBotzinger complex is a group of a few thousand neurons that sits at the base of the brain, i.e., near the ventral edge of the medulla. The computations involves an oscillator to set a rhythmic output and feedback from blood oxygen and body movement of modulate the rate of breathing. This is what a lot of circuits do - they control a motor output.

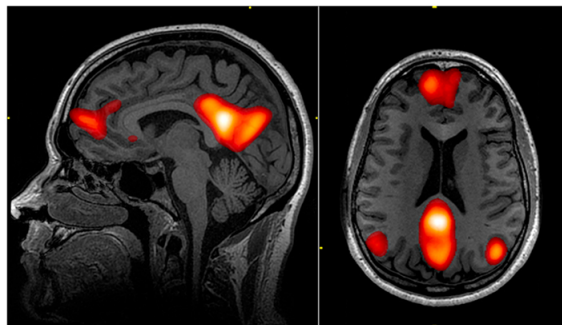
Figure 1: Axons from the preBotzinger complex that project to the parahypoglossal nucleus and the nucleus of the solitary tract regions (top) and ventral respiratory group complex (bottom). From Tan, Pagliardini, Yang, Janczewski and Feldman 2010.



At the other extreme, the function of a brain areas could be cognitive, which is something we all would like to understand as this is the deep and so far dark secret of the brain. All we know, using the BOLD fMRI technique of Seiji Ogawa, is that we can see where the brain activity is likely to be localized during different talks,

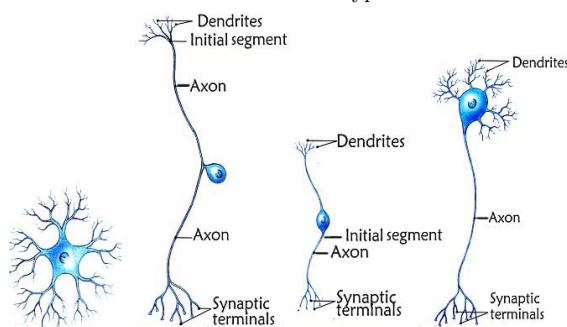
but we don't know that much more. We don't know what leads to abstract thought and problem solving.

Figure 2: BOLD fMRI image of the human brain highlights increased metabolism during different mental activity. From Fox and Raichle 2007



Let's start with some elementary circuits, composed of simple neurons, and work our way forward. Neurons send out processes that gather inputs from a few to ten thousand inputs; these are called dendrites and may extend over a spatial distance of  $100\text{ }\mu\text{m}$  to  $1\text{ mm}$  in mammals. In some cases the distance that they have to communicate, such as from the tips of the fingers, is so long that they actively propagate their signal. Neurons also integrate their inputs and, if the sum of all inputs exceeds a threshold, they produce an output spike (more on this later) that propagates down a long process, or processes, called axons. These can be up to meters in length. While cartoons of neurons draw them as rather stout, real neurons can span the entire brain with a labyrinth of axons, as seen in a recent HHMI MouseLight image of a secondary sensory cell, whose body, or soma, is in the trigeminal nucleus but whose axons sprout broadly to multiple targets.

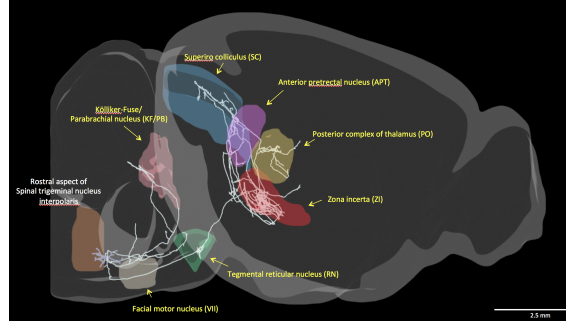
Figure 3: The classic cartoon of different types of neurons. Source unknown.



## 1.1 Neurons signal with pulses

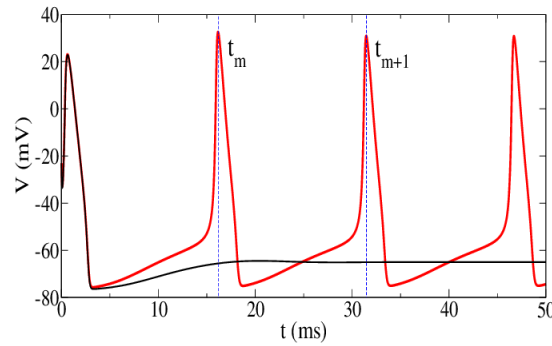
Neurons signal with spikes, so called action potentials, as first showed by Kenneth Cole in 1939. These signals look like derivatives in time of a rising edge. Actually,

Figure 4: A neuron from the spinal trigeminal nucleus interpolaris and its targets. This spiking output of this cell codes the valence of a stimulus. Elbaz, Callado-Prez, Demers, Kleinfeld and Deschne, in press.



neurons not only produces pulses as outputs but they prefer to respond to derivatives as well as inputs. The best input is a drop in current followed by an increase, something described 70 years after the first action potentials.

Figure 5: Calculated Hodgkin Huxley neuronal action potential in response to a pulse (black) and in response to a constant input (red). Source unknown.



## 1.2 Communication is unidirectional

Neurons signal through structures called synapses, which convert the voltage of an action potential in the presynaptic neuron into a current depolarizing or hyperpolarizing current in the postsynaptic neuron. They do this in a circuitous path, with the pulses in voltage causing an ion,  $\text{Ca}^{2+}$ , to flow into the presynaptic terminal, which causes vesicles with transmitter molecules to fuse with the membrane and release their molecules across a narrow cleft. These molecules bind to protein channels in the postsynaptic cells that transiently open and allow ions to rush through. We will not discuss this further for now - the key issue is that this complicated process ensures that signaling is solely one-way, from pre-synaptic to post-synaptic neurons. In this regard it acts like an electronic diode.

Figure 6: The optimal input to driving a Hodgkin Huxley neuron to spike. Aguera y Arcas, Fairhall and Bialek 2003

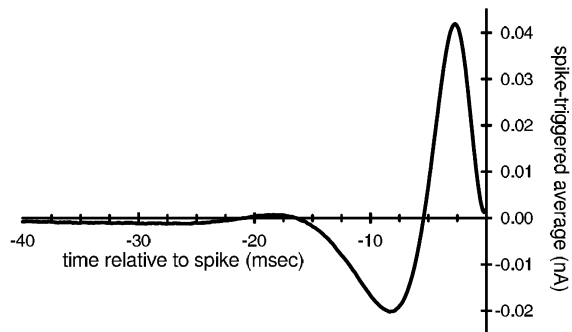
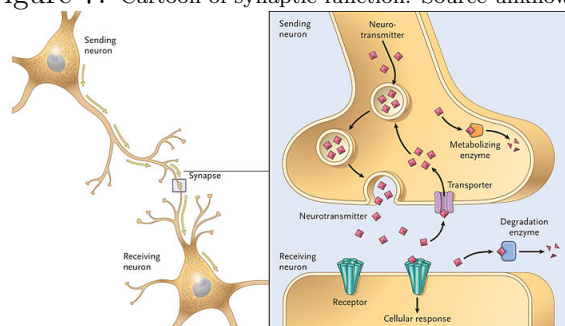


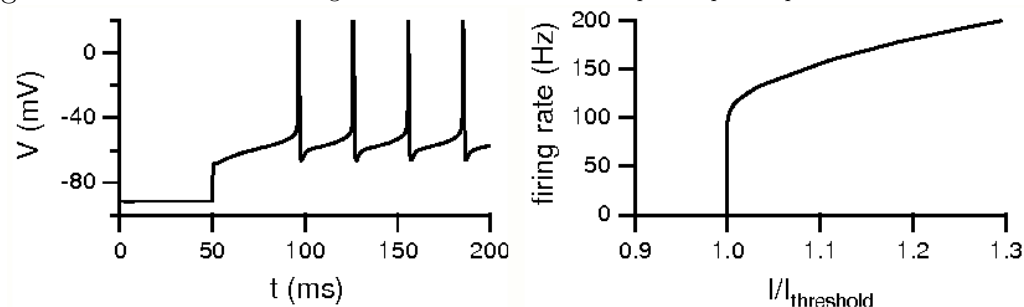
Figure 7: Cartoon of synaptic function. Source unknown.



### 1.3 Continuous activity is described by the firing rate

We will get back to the details of neuronal spiking later when we discuss (and then model) the ionic basis of the action potential famously described by Alan Hodgkin and Andrew Huxley. For now, we want to think in terms of average activity and not pulses and turn to a continuous variable, which is the rate of spiking. Then we can look at a curve of the spiking rate versus input current, which is a sort of input-output or gain curve.

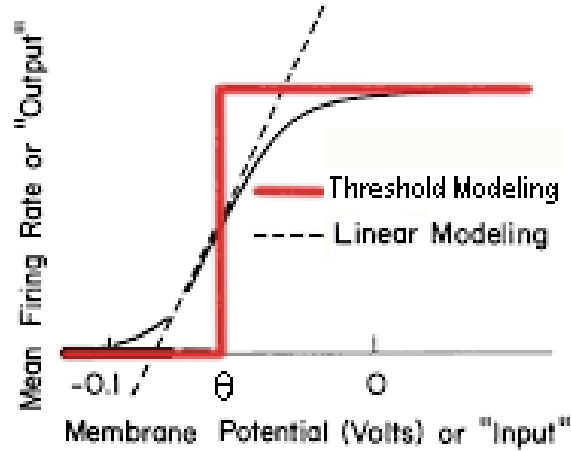
Figure 8: Estimation of the firing rate of a neuron and the complete input-output curve. Source unknown.



For the simplest neurons, input-output curve has a sharp jump followed by a

weak slope. We will brutalize this curve and think in terms of digital quantities, so that the output is now digital, much like the signals in digital logic. These threshold units can be used to build circuits. In fact, despite the complicated dynamics of biological neurons and the myriad of models to capture these properties, we can get pretty far toward understanding neuronal computation with just threshold units.

Figure 9: Model of a neuronal input-output in terms of a threshold function. Source unknown.



## 1.4 Threshold units with two rates can be used to build circuits

These threshold units can be used to build a neuronal circuit. And the simplest neuronal circuit has two neurons with four possible output patterns, in the sense of threshold units, labeled  $\vec{S}$ , i.e.,

$$\vec{S} = \begin{pmatrix} \text{output of neuron 1} \\ \text{output of neuron 2} \end{pmatrix} = \begin{pmatrix} +1 \\ +1 \end{pmatrix} \text{ or } \begin{pmatrix} -1 \\ +1 \end{pmatrix} \text{ or } \begin{pmatrix} -1 \\ -1 \end{pmatrix} \text{ or } \begin{pmatrix} +1 \\ -1 \end{pmatrix}$$

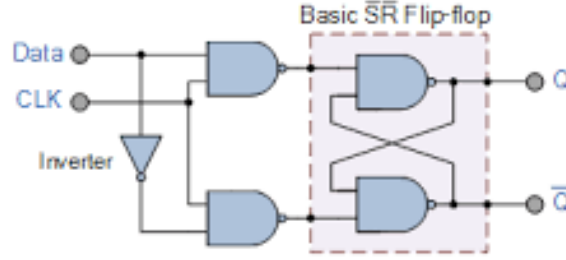
## 1.5 Physical and biological flip-flops

It was known since the 1930's that bistable devices formed from threshold elements, like a digital flip-flop, could be built using feedback to hold electronic summing junctions in a particular state after their inputs had decayed away. Let's see how to use two neurons to build a circuit that restricts the output to only two states, called stable states, denoted

$$\vec{\zeta}_1 = \begin{pmatrix} +1 \\ -1 \end{pmatrix} \text{ and } \vec{\zeta}_2 = \begin{pmatrix} -1 \\ +1 \end{pmatrix}$$

We are motivated by electronics, where inhibitory feedback between two gates is used to make a circuit with a bistable output that is called a flip-flop.

Figure 10: The Set-Reset flip flop, with further gates to turn it into a toggle or D flip flop. Source unknown.



### 1.5.1 Threshold units can be used to build model circuits

Let us now translate this into a neuronal circuit. The input of each neuron comes from two sources, external inputs denoted  $I_i^{ext}$  and inputs from other neurons through connections, i.e., synapses, with analog-valued synaptic weight  $W_{ij}$ . The total input to neuron  $i$  is]

$$\text{input to neuron } i = \sum_{j=1; j \neq i}^N W_{ij} S_j + I_i^{ext} \quad (1.1)$$

Each neuron samples its input at random times. It changes the value of its output or leaves it fixed according to a threshold rule with thresholds  $\theta_i$ ;

$$S_i \leftarrow -1 \text{ if } \sum_{j=1; j \neq i}^N W_{ij} S_j + I_i^{ext} < \theta_i \quad (1.2)$$

$$S_i \leftarrow +1 \text{ if } \sum_{j=1; j \neq i}^N W_{ij} S_j + I_i^{ext} > \theta_i \quad (1.3)$$

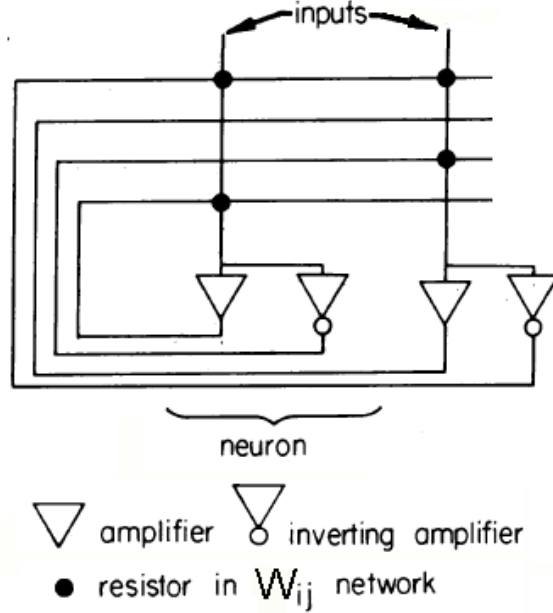
Thus if we take the case of two neurons, with  $W_{12} = W_{21} = -1$  and for simplicity  $I_1^{ext} = I_2^{ext} = 0$  and a threshold near zero, then we see that  $\vec{\zeta}_1$  and  $\vec{\zeta}_2$  are stable outputs. This circuit can be drawn in "Neural Network" style as nested feedback loops, which already suggests the extension of this viewpoint to loops with very many cells.

### 1.5.2 Setting the threshold

We want a cell to respond to its inputs, which means that the  $\sum_j^N W_{ij} S_j$  terms must drive the neuron back and forth across the threshold. In a sense, the inputs, their synaptic weights, and the value of the threshold are interconnected. To see this, we first denote the input to the cell,  $\mu_i$ , as,

$$\mu_i = \sum_{j=1; j \neq i}^N W_{ij} S_j + I_i^{ext} \quad (1.4)$$

Figure 11: A two-neurons feedback circuit drawn in "Neural Network" style. Hertz, Krogh and Palmer 1991, following Hopfield 1982.



The best guess for the best value of  $\theta$  is found from the average mid-point of the input to the cell. We thus average the input over time, denoted  $\langle \dots \rangle$ . Then

$$\begin{aligned} \theta &= \langle \mu_i \rangle \\ &= \sum_{j \neq i}^N W_{ij} \langle S_j \rangle + \langle I_i^{ext} \rangle \\ &= \langle I_i^{ext} \rangle \end{aligned} \tag{1.5}$$

where we used  $\langle S \rangle = 0.5 * (-1 + 1) = 0$ . Thus, for the choice of representation  $S_i \pm 1$  and no external input, the optimal threshold is  $\theta = 0$ .

### 1.5.3 Neuronal dynamics as a drop in "Energy"

Another way to look at the dynamics of the circuit is in terms of a quadratic form, or energy function. We want the energy to do down on each transition, following Aleksandr Lyapunov's second theorem. This is a critical issue pointed out by John Hopfield. Any symmetric network, i.e., where  $W$  is a symmetric matrix with zero diagonal elements, i.e.,  $W_{ij} = W_{ji}$  and  $W_{ii} = 0$ , will produce a downhill flow in energy. We take the energy as the sum of pair-wise interactions among neurons and the interaction with the external input and threshold. Thus

$$E = -\frac{1}{2} \sum_{i=1}^N \sum_{j \neq i}^N S_i W_{ij} S_j - \sum_{i=1}^N I_i^{ext} S_i + \sum_{i=1}^N \theta_i S_i. \tag{1.6}$$

The factor of  $1/2$  occurs because the summation over all  $i$  and  $j$  counts each interaction twice. This is shown by the topographic representation of hills and valleys in

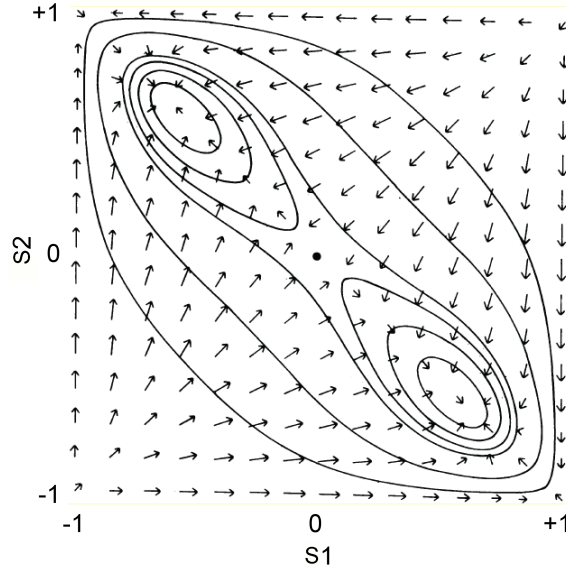
the energy diagram below.

The change in E due to changing the state of neuron is found from  $\Delta E/\Delta S_i$ , or

$$\begin{aligned}\Delta E &= - \left( \sum_{j \neq i}^N W_{ij} S_j - I_i^{ext} + \theta_i^{ext} \right) \Delta S_i \\ &= - (\mu_i - \theta_i) \Delta S_i.\end{aligned}\tag{1.7}$$

If  $S_i$  stays the same, the energy is unchanged. If  $S_i$  changes, which means  $S_i^{\text{final}} = S_i^{\text{initial}}$ , then both  $(\mu_i - \theta_i)$  and  $\Delta S_i$  are both positive or both negative and  $\Delta E < 0$ .

Figure 12: The Energy of a two-neuron inhibitory feedback circuit has two minima. For clarity in this illustration, a sigmoidal rather than a threshold input/output relation was used; thus the neuronal outputs in the stable states are less than the saturation levels of  $\pm 1$ . From Hertz, Krogh and Palmer 1991, following Hopfield 1984.



#### 1.5.4 Neurons that act as threshold units can be used to build real circuits

We saw that biological neurons have input-output relations that appear as threshold phenomena. Can we use these to make model networks, in the dish, that illustrate this basic functions. This was accomplished back in ca 1990 using neurons dissected from the invertebrate *Aplysia*. Let check out the issues. First, we see that the neurons fire nearly as threshold units, albeit each cell has it's own value of the threshold,  $\theta$ . We also see that the neurons make inhibitory connections.

When combined together, we see that the circuit functions as a flip flop with reciprocal inhibitory connections. a pulse into the "off" cell will drive it "on" and inhibit the neighboring cell, driving it "off". The network is now stable in the new state. A key issue in considering only rate is that the synaptic integrations must be slow enough to average other individual spikes. This is the case, as the rates are one to a few Hertz while in integration time is about 10 seconds.



Figure 13: A two-neuron circuit in vitro, and the F-I curves and synaptic response curves of the two cells. From Kleinfeld, Raccaia-Behling and Chiel 1990.

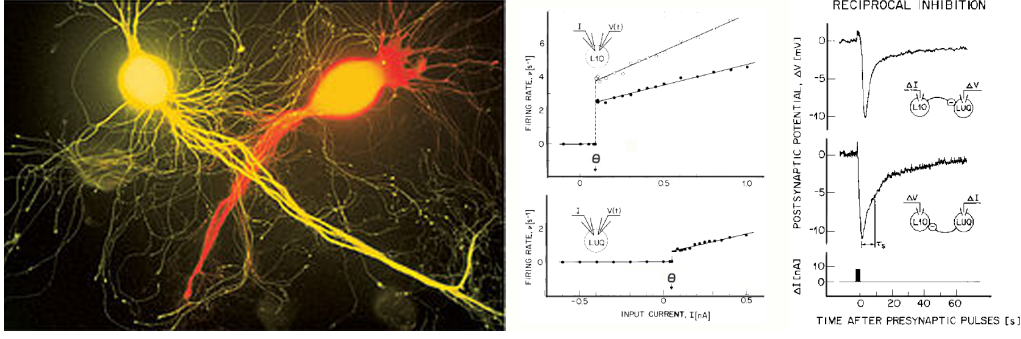
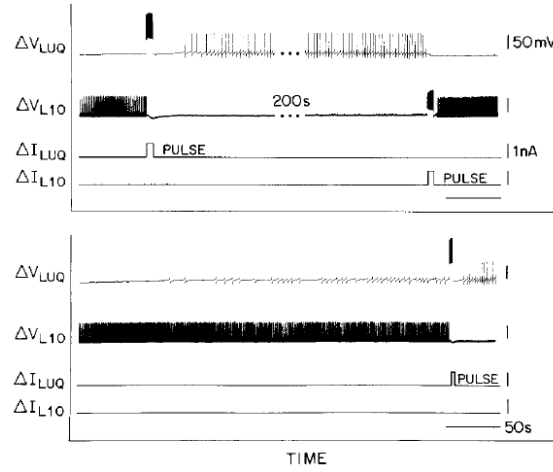


Figure 14: A two-neuron circuit in vitro with reciprocal synapses that shows bistability. From Kleinfeld, Raccaia-Behling and Chiel 1990.



The in vitro circuit also allowed us to explore how the output can be pinned by large inputs, i.e., the effect of  $I^{ext}$  terms relative to the threshold  $\theta$ . The data illustrate the main point that the synaptic input  $W_{1,2}S_2$  must be large enough to change the sign of  $I_1^{ext} - \theta_1$ , and vice versa.

Bistable circuits show up in many places in vivo. They occur at a "low level" as part of oscillators that drive swimming in the nudibranchs *Clione*, i.e., the work of Richard Satterlee, and *Tritonia*, i.e., the work of the late Peter Getting, among others. They show up in an abstract form in "high level" circuits that lead to "perceptual switching" in mammalian vision and cognition.

Figure 15: Analysis of the stability diagram of a two-neuron circuit in vitro. From Kleinfeld, Raccuia-Behling and Chiel 1990.

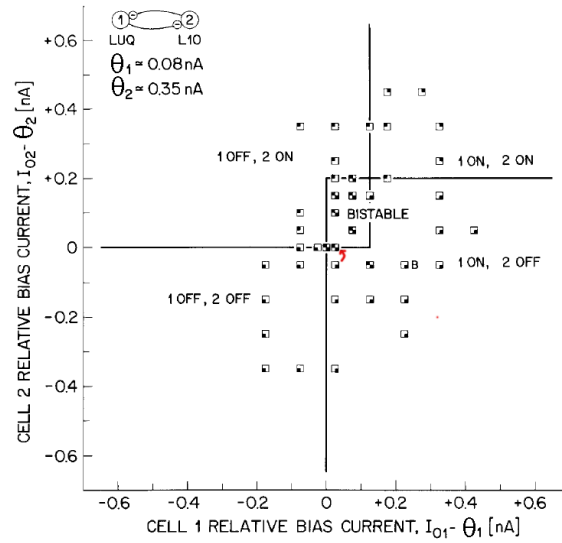


Figure 16: The circuit believed to drive escape swimming in Clione. Mixed sources.

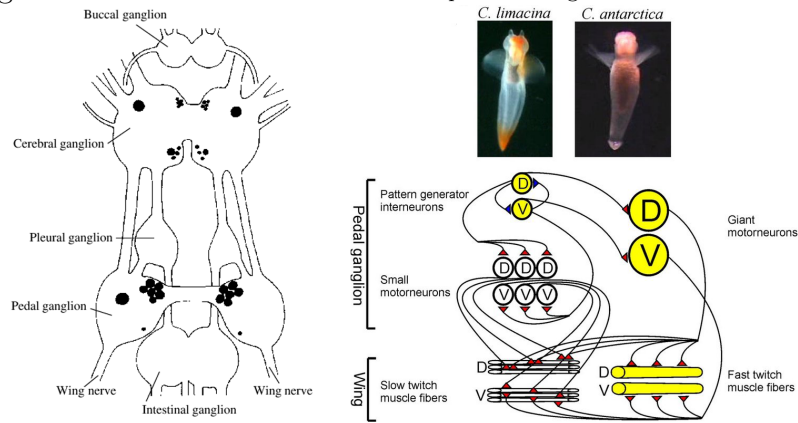


Figure 17: Escape swimming and the circuit and neuronal drive for escape swimming in Tritonia. Mixed sources.

