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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. Think of a hoop that rolls down an incline plane and just keeps on going, something you probably first learned about in a high school physics class. At the end of the day, you write equations for the linear (v) and angular (ω) 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 one can ask "What is the function of the cart?" This line of questioning is never ending.

In neuroscience, the function of the nervous system is to compute something. In general, and somewhat like modern approached to robotics, there is a control layer and a cognitive layer. A control layer is close to the sensory input and motor output, like the preBötzinger circuit that controls breathing. Interestingly, this circuit was discovered by Jack Feldman, a physicist turned neuroscientist that chose the name Bötzinger after a bottle of northern German wine. The preBötzinger circuit is a group of a thousand neurons that sits at the base of the brain, i.e., near the ventral edge of the medulla (Figure 1). The computations involves an oscillator to set a rhythmic output and feedback from blood oxygen and body movement to modulate the rate of breathing. This is what a lot of circuits do - they control a motor output.

At the other extreme, is the cognitive function of a brain, This is the deep and so far dark secret of the brain which sets the course of future behaviors and, frankly, uses a calculus that we all would like to understand. For now, we will leave this to the psychologists. But we can us a tool like bold oxygen level dependent (BOLD) functional magnetic resonant imaging (fMRI), invented by Seji Ogawa, to see where the brain activity is likely to be localized during different tasks (Figure 2). This is both crude and exciting at the same time, as we don't know what leads to abstract thought and problem Figure 1: Axons from the preBötzinger 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.



solving, just that much of the brain appears to be involved in every task.

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 to large networks. Neurons send out processes that gather inputs from a few to ten thousand inputs; these are called dendrites and normally extend over a spatial distance of 100 μ m to 1 mm in mammals (Figure 3). In special cases like that of somatosensory cells, the distance that they have to communicate, such as from the tip of the toes to the spinal cord, is so long that they actively propagate their signal. Neurons integrate their many inputs from their dendrites within or near their soma. 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 reconstruction of a secondary sensory cell, whose body, or soma, is in the trigeminal nucleus but whose axons sprout broadly to multiple targets (Figure 4).



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

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-Perez, Demers, Kleinfeld and Deschenes, 2022.



1.1 Neurons signal with pulses

Neurons signal with spikes, so called action potentials, as first shown by Kenneth Cole in 1939. These signals look like derivatives in time of a rising edge (Figure 5). 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. Suffice it to say that neurons are quiet until the input exceed a threshold level, and then they spike with a spike rate that is monotonic with the input current. (Figure 6). Internal dynamics within the neuron can change the shape of the rate-input curve (Figure 7).



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

Figure 6: Estimation of the firing rate of a neuron and the complete input-output curve. Source unknown.



Neurons not only produce pulses as outputs, but they prefer to respond to derivatives as well as inputs. The most effective input to a neuron is a drop in current followed by a larger increase (Figure 8), something described only 70 years after the first action potentials were observed.

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 (Figure 9). They do this in a circuitous path, with the pulses in voltage causing an ion, 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

Figure 7: Calculated spike rate for a motoneuron in the facial nucleus in response to different input currents and adaptation currents. Golomb, Moore, Fassihi, Takatoh, Prevosto, Wang and Kleinfeld, 2022



cells that transiently open and allow ions to rush through. Thus a voltage on the presynaptic side of the synapse is converted to a current on the postsynaptic side. The signaling is solely one-way, from pre-synaptic to post-synaptic neurons. This is much like the functional operation of a field effect transistor (Figure 10) although the physics is completely different. We will not discuss this further for now - the key issue is that this complicated process ensures that signaling is unidirectional.

1.3 Threshold units with two rates can be used to build circuits

For some of 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 for the neuronal output (Figure 11), so that the output is now "spiking" or "quiescent", much like the "0" and "1" 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.

The simplest neuronal circuit has two neurons with output patterns labeled $\vec{\mathbf{S}}$, i.e.,

$$\vec{\mathbf{S}} = \left(\begin{array}{c} \text{output of neuron 1} \\ \text{output of neuron 2} \end{array}\right)$$



Figure 8: The optimal input to driving a Hodgkin Huxley neuron to spike. Aguera y Arcas, Fairhall and Bialek 2003

If we consider the neurons as threshold elements, there are four possible output patterns, i.e.,

$$\vec{\mathbf{S}} = \begin{pmatrix} +1 \\ +1 \end{pmatrix}$$
 or $\begin{pmatrix} -1 \\ +1 \end{pmatrix}$ or $\begin{pmatrix} -1 \\ -1 \end{pmatrix}$ or $\begin{pmatrix} +1 \\ -1 \end{pmatrix}$

1.4 Physical and biological flip-flops

It was known since the 1930's that bistable devices formed from threshold elements, like a digital flip-flop (Figure 12), 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

$$\vec{\zeta}_{1} = \begin{pmatrix} +1 \\ -1 \end{pmatrix}$$
 and $\vec{\zeta}_{2} \begin{pmatrix} -1 \\ +1 \end{pmatrix}$





Figure 11: Model of a neuronal input-output in terms of a threshold function. Source unknown.



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 12: The Set-Reset flip flop, with further gates to turn it into a toggle or D flip flop. Black circles denote inhibition. Source unknown.



1.4.1 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:

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

where N is the number of neurons. 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 θ_i .

$$S_{i} \leftarrow -1 \text{ if } \sum_{j=1; j \neq i}^{N} W_{ij}S_{j} + I_{i}^{\text{ext}} < \theta_{i}$$

$$S_{i} \leftarrow +1 \text{ if } \sum_{j=1; j \neq i}^{N} W_{ij}S_{j} + I_{i}^{\text{ext}} > \theta_{i}$$

$$(1.2)$$

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 (Figure 13); this already suggests the extension of the feedback viewpoint to loops with very many cells.





1.4.2 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

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, μ_i , as,

$$\mu_{i} = \sum_{j=1; j \neq i}^{N} W_{ij} S_{j} + I_{i}^{ext}$$
(1.3)

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

$$\theta = \langle \mu_i \rangle$$

$$= \sum_{\substack{j \neq i \\ j \neq i}}^{N} W_{ij} \langle S_j \rangle + \langle I_i^{ext} \rangle$$

$$= \langle I_i^{ext} \rangle$$
(1.4)

where we assumed equal activity for all neurons, so $\langle S \rangle = 0.5 * (-1+1) = 0$. Thus, for our choice of representation $S_i \pm 1$ and no eternal input, the optimal threshold is $\theta = 0$.

1.4.3 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 (Figure 14). Let check out the issues. First, we see that the neurons fire nearly as threshold units, albeit each cell has its own value of the threshold, θ . We also see that the neurons make inhibitory connections so that $\operatorname{sign}[W_{12}] = \operatorname{sign}[W_{21}]$ = -1. Then

$$\mu_1 - \theta_1 = -|W_{12}|S_2 - I_{O1}^{ext} - \theta_1$$

$$\mu_2 - \theta_2 = -|W_{21}|S_1 - I_{O2}^{ext} - \theta_2$$
(1.5)

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" (Figure 15). The network is now stable in the new state. A key issue in considering only cells as "on" or "off", is that the synaptic integrations must be slow enough to average other individual spikes; this holds for the more general case of considering rates. In the case of the neuronal flip-flop as the spike rates are one to a few Hertz while in integration time is about 10 seconds. Figure 14: A two-neuron circuit with reciprocal inhibition in vitro, and the F-I curves and synaptic response curves of the two cells. From Kleinfeld, Raccuia-Behling and Chiel 1990.



Figure 15: A two-neuron circuit in vitro with reciprocal synapses that shows bistability. From Kleinfeld, Raccuia-Behling and Chiel 1990.



The in vitro circuit 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 θ (Figure 16). The data also illustrate that the magnitude of 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.

1.4.4 Bistable circuits are a common motif

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 Tritonia (Figure 17) and Clione (Figure 18). Although the output oscillates with a slow period, the output is bistable within a period.

Similar circuits also drive whisking in the rodent (Figure 19).

Figure 16: Analysis of the stability diagram of a two-neuron circuit in vitro. From Kleinfeld, Raccuia-Behling and Chiel 1990.



While the whisking circuit is comprised of many neurons, the cells cluster into one of two groups and, using the method of averaging that we will learn later in the course, can be reduced to a circuit of two "effective" neurons. Bistable circuits show up in an abstract form in "high level" circuits that lead to "perceptual switching" in mammalian vision and cognition (Figure 20)..

Figure 17: Escape swimming and the circuit and neuronal drive for escape swimming in Tritonia. Mixed sources including experiments of Willows and Getting.



Figure 18: The circuit believed to drive escape swimming in Clione. Mixed sources that include Saterlee.
Buccal ganglion
C. limacina C. antarctica



Figure 18)

Figure 19: Whisking in the rodent is driven by both breathing, in a feedforward manner, and by an independent whisking oscillator. A detailed model of the oscillator with hundreds of neurons is reducible to one with reciprocal inhibition between two neurons for an autonomous whisking oscillator. Golomb, Moore, Fassihi, Takatoh, Prevosto, Wang and Kleinfeld, 2022.



 $Figure \ 20: \ {\rm Classic \ examples \ of \ perceptual \ rivalry}$



