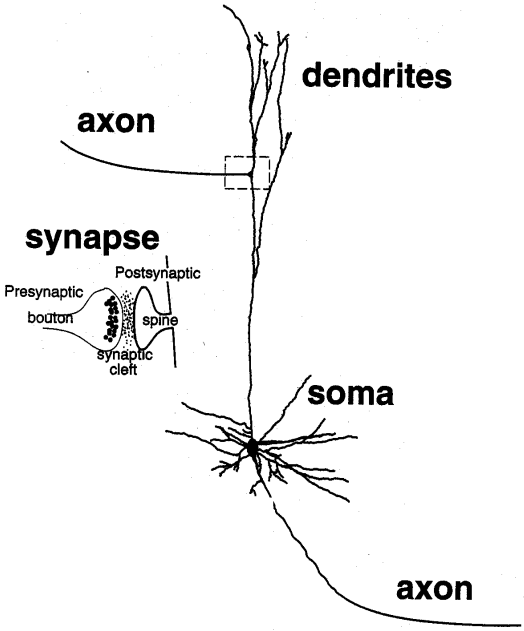
11 From Soap to Volts

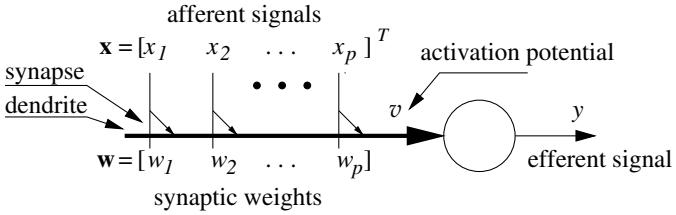
(based on chapter 11, W.W. Lytton, *From Computer to Brain*)

Recall a microscopic view of typical neuron of the mammalian cortex (a pyramidal cell):



- Note the cell body or soma, dendrites, synapses and the axon.
- According to Calaj's "neuron-doctrine" information carrying signals come into the dendrites through synapses, travel to the cell body, and activate the axon. Axonal signals are then supplied to synapses of other neurons.

This hypothesis has been encapsulated in the model of an artificial neuron



Transmitters (information-carrying chemicals) are released presynaptically, floats across the synaptic cleft, and activate receptors postsynaptically.

Concept-based theories

- Models of the nervous system based on the concept of artificial neurons and their networks are useful because they help to understand some of the complicated phenomena related to learning and perception.
- Too much reliance of such models can lead to "heart-break of premature definition"
- Current theories of neural information processing are still inadequate and need either lots of upgrades of a total paradigm shift.

Data-based theories

- Data-based theories are build around the experimental body of knowledge regarding the nervous system
- At the bottom of such theories is the fact that neurons are cells.
- Working of a cell, that is, its dynamics is described by the movement of chemicals and associated ions, that is electric carriers (or charges).
- Movements of electric charges creates an electric current which flows under the influence of related voltages.
- Therefore, a data-based model of a neuronal cell is formulated in terms of electrical quantities.

Cell Bio-Chemistry

- A cell (a neuron is a cell) is a complex piece of machinery. Do search on “cell membrane” and enjoy the richness of presentations
- Before a neuron can do any signaling and thinking it must take care of itself through complicated mechanisms for
  - energy metabolism,
  - protection against toxins, and
  - intracellular and intercellular communication

  as other cells in the body, e.g. kidney, liver or bone cells.
- Chemicals passed around the cell to obtain energy during metabolism are reused in neuronal information processing
- Three of the basic food groups for cells:
  - glucose,
  - adenosine triphosphate (ATP)
  - acetyl-coenzyme A (acetyl-CoA),

  are either used directly, or have close congeners that are used for information processing.

Cell Bio-Chemistry (cont’)

- The major **neurotransmitters**:
  - glutamate
  - GABA (gamma-aminobutric acid)

  are spin-offs from the tricarboxylic acid cycle (Krebs cycle), the main sugar digestion route.

  (Edwin G. Krebs was awarded (with E. Fisher) 1992 Nobel prize for psychology or medicine for demonstrating basic biochemical mechanisms)
- Similarly, acetylcholine (ACh) is related to acetyl-coenzyme A (acetyl-CoA), which is the main product of the Krebs cycle.
- Glucose is processed in order to produce adenosine triphosphate (ATP), the main energy storage medium. ATP is also a neurotransmitter.
- Various ATP by-products
  - adenosine diphosphate (ADP),
  - adenosine monophosphate (AMP),
  - cyclic adenosine monophosphate (CAMP)

  are also used in neuronal signaling.
- Are you thinking about food or is your food thinking about you?

Cell Bio-Chemistry (cont')

- This sharing of resources is not confined to information processing. The same compounds or their close relatives are also amino acids, the construction materials of the cell and the body.
- Both glutamate and GABA are close relatives of amino acids.
- Glycine, another neurotransmitter, is an amino acid. Glycine is the major constituent of collagen, making it the building block for skin and bones.
- Similarly, the nucleotides of DNA, the blueprint of the cell whose code is used to construct proteins, is also shared with neurotransmission and metabolism
- Cell maintenance also requires additional intracellular communication between and among various organelles (subcellular organs), as well as extracellular communication with various supporting cells.
- This type of communication cannot always be cleanly separated from classic neurotransmission.
- During development neurotransmitters and second messengers are being used to grow neurons and coordinate their wiring and relations with various supporting cells.
- While a child is using his transmitters to grow a brain, he also has to think using the same transmitters.

Cell Bio-Chemistry (cont')

- Because of this close enmeshment of functions, it may never be possible to cleanly separate fancy neural information processing from the boring information processing of housekeeping chores.
- Even the electrical charge at the cell membrane, the key attribute that permits action potential signaling between cells, has generic cell maintenance tasks as well.
- Similar electrical potentials are present in all body cells and in yeast and bacteria as well.
- Information transmission (and related encoding and decoding) has to be done in every organ.
- Bone cells communicate in order to adapt to changes in stress patterns when you learn to rollerblade.
- The liver and endocrine systems all have complex non-neural communication protocols in place.
- The immune system has a remarkable interplay of cell types that chat with one another and with other cells in the body, all of which have to continually remind white blood cells that they belong there and should not be eaten.

What is the neuron state?

- We have used a single number y to represent the state of the neuron output.
- An implicit assumption of the scalar model is that we are dealing with the functional equivalent of a point neuron — a neuron that has no geometry or spatial extent.
- Real neurons have a complex three-dimensional structure. Some of them are big enough to be seen with the naked eye.
- Signals come in at dendrites that may extend as much as a millimeter from the central soma (cell body).
- Signals then go out through axon terminals that may be more than a meter away from the cell body (e.g., the axon that goes to your big toe).
- However, from a signal-processing standpoint, what is important is not the physical size of a neuron but its electrical size — how far across the cell can a signal spread.
- Given the many different morphologies and different electrical properties of dendritic trees, some will turn out to be electrically large and others electrically compact, concording with the role they have to play.
- Axons, on the other hand, are all effectively compact; the action potential ensures that a signal that starts at one end will get to the other.

What is the neuron state? (cont')

- In addition to being three-dimensional in shape, neurons are also multi-dimensional in terms of the many different kinds of signals that are used.
- Many types of electrical signals and a variety of chemicals participate in neural signaling.
- These include the neurotransmitters that transmit information across synapses as well as a variety of second (and third, and fourth) messengers that transmit the signal further on inside the neuron.
- Many of these chemical signals are likely to be important in information processing.
- Thus, rather than think of neural state as a scalar, it might make more sense to consider a vector of voltages and chemical concentrations to describe the cell.
- Although the chemical and electrical complexity of neurons makes it clear that there is no single scalar state, it may be that multiple states occur in series as a temporal chain.
- In this case, each state determines the next, and any of the states could be used to represent the information processing state.
- Serial states are assumed in rate-coding theory: presynaptic firing rate determines synaptic potential determines soma potential determines soma firing rate determines axon firing rate.
- We can treat these different states as if they were the states of independent units and work out the signal transduction (weights) between them.

What is the neuron state? (cont')

- In the next two chapters, we do this analysis; working out how synaptic inputs determine summed membrane potential and how summed membrane potential determines spike rate.
- On the other hand, if multiple states are operating in parallel, then the neuron is more like a computer central processing unit (CPU) than like a single transistor.
- In that case, analysis of single-neuron information processing be- comes far more difficult.
- Many neurons have a single major output pathway, the axon.
- Even if such cells are processing multiple information streams in parallel, all of the information has to come through the axon.
- We can then take this axon output to be neuron state.

  However, this output state would just be the answer to whatever computational problem the neuron was calculating.

  We would have missed all the information processing.

What is the neuron state? (cont')

- Still more complex are neurons that have multiple inputs and multiple outputs.
- Thalamic cells are a prominent example of this in mammalian brains.
- The thalamic cell is likely not only multiprocessing but also multiplexing.
- Multiple signals come into the thalamic cell, multiple signals are spit out.
- Some of these inputs combine, others remain separate.
- As long as they are separate, the states can be understood separately.
- When the inputs combine into a single measurable state, this is multiplexing.
- The causes and results of such a signal can be hard to disentangle.
- If single neuron processing turns out to be this complex, then techniques for analyzing activity in the single neuron will be similar to the techniques that we currently use to analyze a neural network.

A synapse

- In artificial neural networks, scalars were also used to define the synaptic weights.
- The use of a scalar weight simplified learning theory, since learning was expressed as an increase or decrease in this single number. As you might guess, the scalar-weight concept will also need some revision.

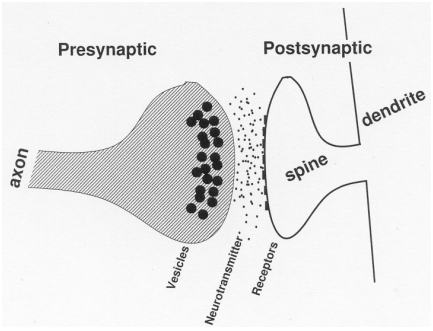


Fig. 11.2: Basic synapse design: presynaptic vesicles (big dots) release neurotransmitters (little dots) into the synaptic cleft. They float across the cleft to activate postsynaptic receptors (fat lines).

- An electrical signal, an action potential, invades the presynaptic axon terminal.
- This causes vesicles to release neurotransmitter into the synaptic cleft between the neurons.
- The neurotransmitter molecules float across and bind to receptors on the postsynaptic neuron.
- These receptors are linked to channels that open up and create an electrical signal, a postsynaptic potential, on the membrane of a spine or dendrite of the postsynaptic neuron.

A synapse

- Although there are multiple processes in this description, the synapse can still be assigned a single weight as long as these processes are occurring in series.
- Just as with our description of neural state, we would then define a scalar value for each process in sequence and determine transduction between them.
- Again things gain in complexity if there, is multiplexing going on at the synapse.
- Just as there is a wide variety of neuron types, there are also many different types of synapses, differing in their complexity.
- There are various sources of synaptic complexity.
- Many synapses have more than one kind of receptor postsynaptically.
- Some synapses release more than one neurotransmitter.
- Some synapses are electrical rather than chemical connections.
- Some synapses are not strictly one-way but have retrograde transmission or are involved in perverse three-ways (thalamic synaptic triads).
- Some axons synapse onto postsynaptic spines, as shown in Fig. 11.2.
- The function of spines is a mystery; it seems likely that they don’t provide a straight conduit to the main dendrite.

A synapse

- Some researchers suspect that significant chemical information processing may be happening inside these spines.
- Many neurotransmitters don't just head straight across the synaptic cleft but instead spread far across neural tissue.
- This is called volume transmission.
- Some nonclassical neurotransmitters are gases.
- Gases can pass straight through neural tissue, expanding in a cloud from their release site.

Different modeling tools

- Another distinction between the first and second half of the book is the set of tools used.
- The tools of the top-down approach were primarily those of discrete mathematics.
- "Discrete" here refers to the use of distinct digital numeric values instead of continuous analog values.
- Discrete math is the math of computer science and digital electronics: binary numbers, Boolean algebra, digital logic.
- By contrast, in the following chapters we mostly will be dealing with continuous analog phenomenon.
- For continuous mathematics, calculus is the primary tool.
- We discuss electronics and explain the mathematical descriptions of capacitors, resistors, and batteries.
- As it happens, the math of electronics is identical to the math of dynamics, the study of movement.
- This is the original realm of calculus, beginning with Isaac and the proverbial falling apple.

Whoops

- The foregoing was meant to be an introduction to the realistic neural modeling that will be discussed in the rest of the book.
- However, I have to backpedal a bit here.
- I emphasized the importance of chemical signals.
- I will now proceed to ignore them.
- The details of chemical signaling are not well understood, and there hasn't been very much modeling done on this.
- Therefore, the emphasis in what follows will be on electrical modeling.
- I also spent some of the foregoing maligning scalar state and scalar weight theories.
- I take that back, too.

  These remain the standard theories because they are still the best theories.
- Therefore, rather than abandoning these theories, I will explore their implications.

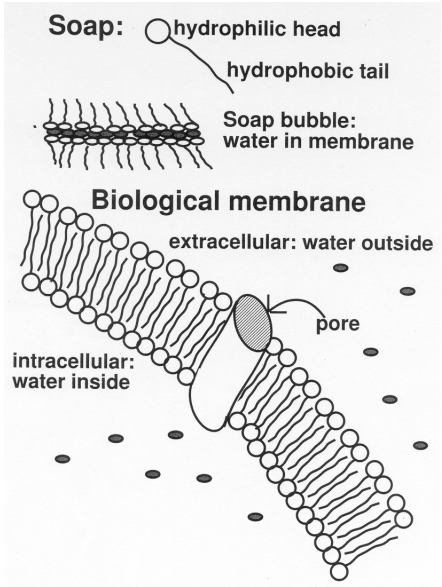
11.1 Why learn this

- In this chapter, I introduce the hardware of the brain.
- I develop some of the concepts of neural membrane modeling.
- I show how currents, capacitors, and resistors arise from the interactions of salt water with membranes.
- To demonstrate this, I have to address the relatively hard concept of capacitance, which must be handled with calculus.
- I explain some basic calculus algebraically by using numerical, rather than analytic, methods.
- Using numerical calculus as a simulation tool, I then explore a couple of fundamental concepts of neural signal processing: temporal summation and slow potential theory.
- Moving quickly from soap to volt to signal processing requires that I skip over some key concepts and issues that will be addressed in later chapters.
- As an alternative approach, I could have introduced all of the underlying material first and then moved on to discuss specific models and what they mean.
- I chose the get-there-quick approach for two reasons.
- First, delayed gratification is hard: the technical and algebraic details can get pretty dull.
- Applications and ideas brighten this chapter up a bit.
- Second, making the right simplifications is a major part of modeling.

- The use of a stripped-down model in this chapter demonstrates how ignoring some details can help focus attention on those details that are essential for the issue at hand.
- Specifically, I demonstrate why time constants are critical for understanding neural signal processing.
- In the following chapters, I fill in the details.
- In this chapter, the circuit only has one resistor and one capacitor.
- In the following chapters, I put in batteries and a few more resistors.
- In this chapter, I only use injected currents as signals.
- In the following chapters, I show how biological signals are largely conductance changes that cause current to flow secondarily.
- In this chapter, I have also tried to avoid stumbling over units, the volts, amperes, farads, siemens, hertz, and other famous guys immortalized as stuff.
- Units are unloved and under-appreciated (see Chap. 16, Section 16.2).
- Sizes, durations, and magnitudes offer insights about the limits, capacities, and capabilities of the hardware.
- Unfortunately, focusing on the units now will entangle us in a nest of confusing conversions. I have largely avoided this distraction.

11.2 Basic cell design

- Cell design is based on the separating of inside from outside by means of membranes.
- Most of the body is salt water. Water and salt can't pass through fat since oil and water don't mix.
- Soap is the compound that connects oil and water, thereby allowing showers to wash oily stuff off your skin.
- Soap works by having a fatty part that connects with the dirt and a hydrophilic (water loving) part.
- Fat is hydrophobic (water fearing).
- Soap thus provides a link that allows water to drag oil away.
- Soap bubbles form with the fatty part of soap pointing inside and outside, away from the water that stays on the interior of the bubble membrane.



- Cell membranes are called lipid bilayers. They are configured in the opposite way: the fatty part is in the interior of the membrane, and hydrophilic heads point both in toward the cytoplasm and out toward extracellular space.

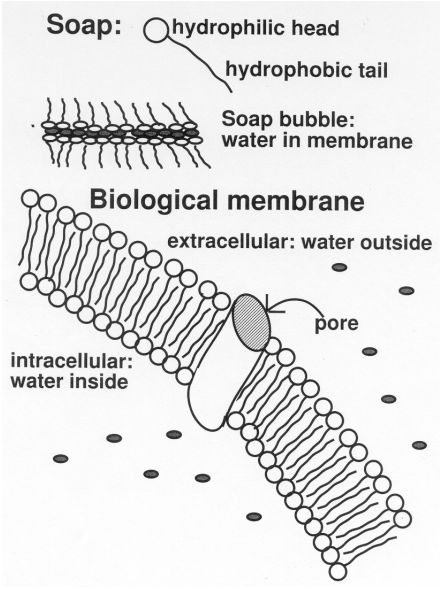
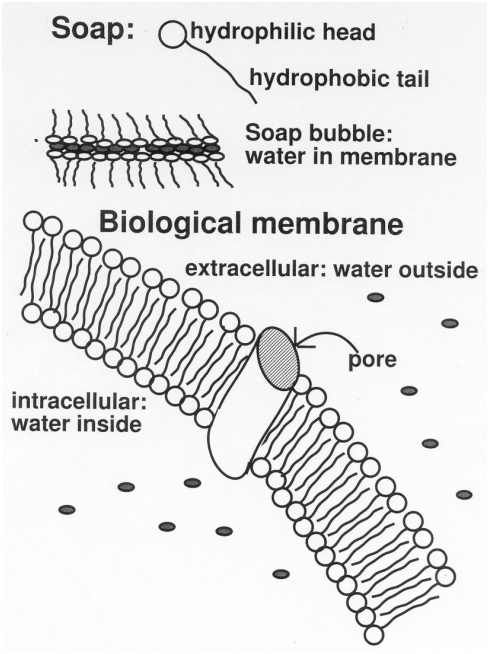


Fig. 11.3: Soap bubbles have fatty tails pointing in and out and water (shaded) interior. Biological membranes keep the fatty tails interior with hydrophilic heads sticking in and out. Proteins orient themselves using both hydrophilic and hydrophobic amino acids. They can form pores that allow ions to move between intracellular and extracellular space.

- Just as soap bubbles form spontaneously on the surface of soapy water, lipid bilayers form spontaneously from a mixture of phospholipids (biological soap) and water.
- The inside of the cell and the interior of the membrane are not the same thing.
- The cell is filled with a volume of intracellular solution (cytoplasm) that the membrane separates from the extracellular solution outside of the cell.
- Although the membrane is only a thin layer at the surface of the cell, there is enough room in the interior of the membrane for chemicals to float around and react with one another.
- Only hydrophobic compounds can exist in the interior of the membrane.



- Ions and many proteins are hydrophilic.

  Ions are the charged versions of certain elements, such as sodium, potassium, chloride, and calcium.
- They are charged because they have either lost or gained an electron, which carries a negative charge.
- The little plus or minus signs tell you how many electrons were lost or gained: Na^{+}, K^{+}, Cl^{-}, Ca^{++}.
- Positive and negative ions stick together to make a salt; NaCl is table salt.
- Many proteins are charged as well.

  Charge makes a compound hydrophilic since the hydrogen of H_2O will stick comfortably to a negative charge and the oxygen will stick comfortably to a positive charge.
- Fat will stick only to uncharged molecules.
- Therefore, ions and charged proteins can move around freely in either extracellular or intracellular space but can’t pass through the fatty part of the membrane.

- Some proteins and various other compounds are hydrophobic and can float around the interior of the membrane but not move into the water on either side.
- There are also information-carrying compounds that are gases. These don't care whether they're in fat or water. They can pass through anything.
- The most well known of these is nitric oxide (NO), a former molecule-of-the-year winner and the functional basis of Viagra.
- Proteins are the active components of cells, involved in metabolism, cell reproduction, and practically every other function.
- Transporters and pores are transmembrane proteins (e.g., the pore in Fig. 11.3).
- Although ions cannot move directly across the fatty membrane, they can flow through these pores.
- Ions will move passively from a high concentration to low concentration, a process of diffusion down a concentration gradient.
- Other proteins can provide ion pumps or transporters that push ions up against a concentration gradient.
- Additionally, proteins provide transport and structure within both the extracellular and intracellular spaces.
- Although the extracellular and intracellular space are usually, thought of as being salt water, the large amount of protein gives it structure, making it more like jello than seawater.

11.3 Morphing soap and salt to batteries and resistors

- Descriptions like the above are both model and metaphor: the extracellular space is jello, the membrane is an inside-out soap bubble, the proteins form holes.
- By switching to another representation, another language, we can describe the same thing in different terms. A particular model/metaphor will be better than another for a particular purpose.
- In this case, translation of the model into the language of electronics (batteries, resistors, capacitors) will allow us to describe neural signaling much more easily than we would be able to do just chewing the salt and the fat.
- Morphing from a membrane and salt representation to an electrical engineering representation obscures the biology somewhat.
- Any representation offers trade-offs and compromises. The advantage of the electrical representation is that we can now use the many mathematical tools developed for electrical circuit analysis.

- Ions moving through water carry charge.
- The movement of charge is electrical current.
- Current can flow through the cytoplasm and extracellular fluid freely.
- The pores in the membrane provide conduits (conductors) for current to go through the membrane as well.
- Protein pores of a particular type provide conductors through the membrane that are selective for a particular ion.
- These pores are parallel conductors providing parallel paths for current.
- A conductor is defined tendency to resist the flow of current.
- A resistor and a conductor are the same thing. It's just one of those pessimist-optimist things: half-empty or half-full; resisting or conducting.
- Resistance is expressed in ohms (Ω) and is represented by R. Conductance is measured in siemens (S) and is represented by g.
- Mathematically, conductance is the inverse of resistance, $g = \frac{1}{R}$

  Because of this, siemens, the unit for conductance, is also called R "rmo", which is ohm spelled backward (seriously).

- In the circuit diagram of Fig. 11.4, all of the pores of a single type are jumped together as a single big conductor (resistor).

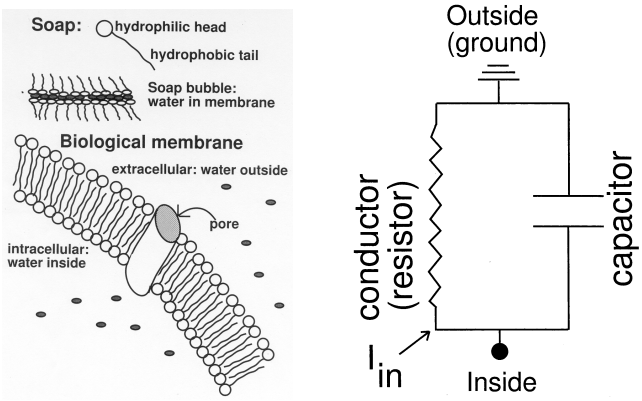


Fig. 11.4:
The membrane is represented as an RC (resistor-capacitor) circuit.
Current can be injected inside the cell (arrow) by using a hollow glass electrode.

- This ubiquitous conductance is known as the leak conductance (g_{leak} or R_{leak}).
- Later, when we add different types of pores to the circuit, we will have different conductors in parallel with this one.
- Made of fat, the membrane acts as an insulator.
- Current that does not flow through one of the pores will just sit next to the membrane.
- Charge acts at a distance to attract unlike charge or repel like charge.

- Charge that is sitting on one side of the membrane will cause equal but opposite charge to sit on the other side of the membrane.
- This phenomenon is known as capacitance.
- In electronics, a capacitor is built by placing an insulating material between two parallel metal plates that are attached to the wire leads of the capacitor.
- Since these plates do not touch, electricity cannot pass directly through the capacitor.
- However, electricity can flow indirectly as one plate induces electrical flow in the other plate.
- The two parallel lines in the standard symbol for the capacitor (Fig. 11.4) represent these two plates.
- In the biological situation, the two plates are just thin accumulations of ions in the water adjacent to either side of the membrane.
- Capacitance has this name because it is a measure of the capacity of the plates to hold charge.
- This capacity will have to do with the size of the plates, the distance separating them, and the nature of the material between them (its dielectric constant).
- A capacitor, or membrane, with high capacitance has the ability to hold a lot of charge with only a small voltage difference between the plates.
- Voltage times charge is a measure of energy.
- A high capacitance means that charge can be stored easily, i.e., without requiring as much energy.

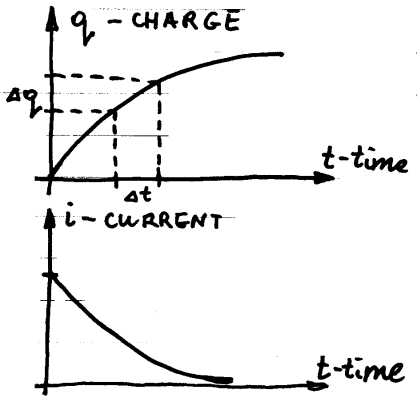
- As you put more voltage across a capacitor, it will hold more charge and more energy.
- A capacitor “expands” with voltage, as a balloon expands with pressure.
- Capacitance tells how much the capacitor can hold at a given voltage, just as a capacity measure for a balloon would tell how big the balloon would be at a given pressure.
- A resistor (R) and capacitor (C) placed next to each other (in parallel) is called an RC circuit (Fig. 11.4).
- In electrophysiology, we insert an electrode through the membrane and then inject current into the inside of the cell (arrow in Fig. 11.4). This current will pass out of the cell through the resistor or the capacitor (through the pores or via the capacitance).
- Once the current reaches the outside of the cell it will disperse to the rest of the body and the surrounding world.
- In the diagram this is represented by the ground symbol.
- The human body is big enough and the currents are small enough that the body can easily sink (conduct away) the current that cells produce.
- When we put a cell in a dish and inject current, we place a wire in the dish to conduct the current out to ground.
- This wire is attached to something metal that leads to the physical ground. This is the idea that Ben Franklin came up with for lightning - provide an electrode to lead current harmlessly to suburbia.

11.4 Converting the RC circuit into an equation

- Modeling the neuron as an electrical circuit involves predicting voltage changes based on current flow.
- One can also model an electrical circuit the other way around: given the voltages, predict the currents.
- In the case of neurons we typically are injecting currents, or thinking about the effects of extra pores that cause extra current to flow into the cells.

Charge and current

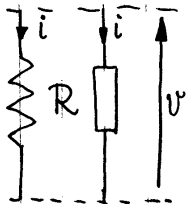
- Electric current is a rate of change of charge.
- Typical charges are: electrons, ions and charged proteins
- If the charge is compared to water flowing through a pipe, than the current will be compared to amount of water flowing through the pipe in a time unit.
- Mathematically, the current i is a time derivative of charge q.
- Imagine that the charge $q(t)$ varies with time as in the following plot:



$$i = \frac{dq}{dt} = \dot{q} \approx \frac{\Delta q}{\Delta t}$$

- Time derivative of the charge (current in this case) can be approximated as the ratio of the change of charge Δq over a small time interval Δt.
- Note that the rate of change of the charge is slowing down. Therefore the current, charge's derivative is being reduced.
- Derivative of a function is also called the gradient (slope) of the function.

Resistors

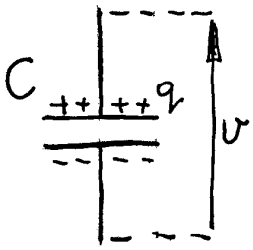


- Voltage across a resistor is proportional to the current flowing through the resistor.

$$v = R \cdot i$$

- Resistance (or its inverse, conductance) is a property of material through which the current flows.
- If we inject current into the resistor a voltage across the resistor appears.
- If we apply voltage then the current flows.

Capacitors

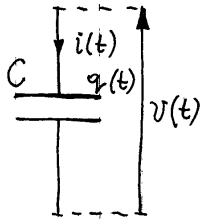


- Charge on a capacitor is proportional to the voltage applied to the capacitor.

$$q = C \cdot v$$

- Conversely, voltage across the capacitor is proportional to the amount of charge stored on the capacitor
- Capacitance is a property of the geometry of the charge storing plates, the membrane, in our case.

Current through a capacitor

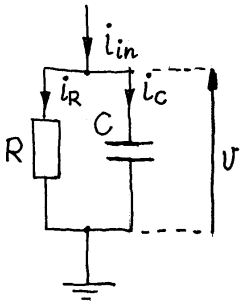


- If the charge stored in the capacitor varies, then the current (derivative of charge) flows and can be calculated as

$$q = C \cdot v \;\; ; \quad i = \frac{dq}{dt} = C\frac{dv}{dt}$$

- Current flowing through the capacitor is proportional to the gradient (time derivative) of the voltage on the capacitor

Analysis of the RC circuit



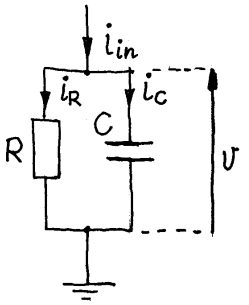
- Kirchhoff's law on conservation of charge says that the sum of currents incoming into an electric node and outgoing from the node is equal.

  Hence

$$i_{in} = i_R + i_C$$

  It means that the injected current, i_{in} flows into the resistor i_R and capacitor i_C

Analysis of the RC circuit (cont')



- Substituting expressions related currents and voltages in resistors and capacitors, we can write the following equation:

$$i_{in} = \frac{1}{R}v + C\frac{dv}{dt}$$

- For a given injected current, the unknown quantity is a time varying voltage across the membrane $v = v(t)$. Therefore the equation, after multiplication by R is usually re-written in the form with swapped left and right-hand sides:

$$RC\frac{dv}{dt} + v = R\,i_{in}$$

Let us denote

$$\tau_m = R \cdot C \;\; — \;\; \text{a time constant of the membrane, and} \quad V_{in} = R \cdot i_{in}$$

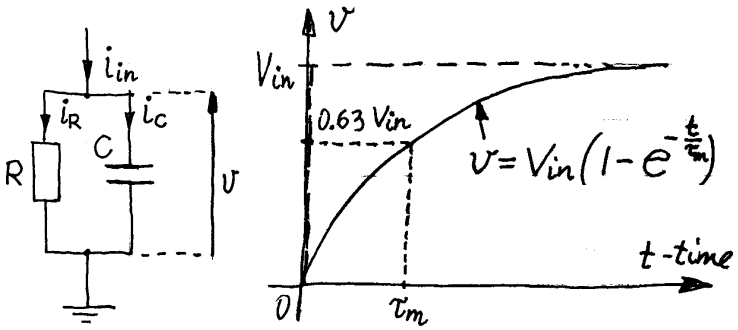
The equation for the voltage across the membrane can now be written as:

$$\tau_m\frac{dv}{dt} + v = V_{in}$$

It is a first order, linear differential equation for $v(t)$ that can be easily analytically solved if you know the trick. Let us guess that the solution for a constant i_{in} is:

$v(t) = V_{in}(1 - e^{-\frac{t}{\tau_m}})$ we can verify this solution substituting it back into the equation and confirming that LHS = RHS.

Analysis of the RC circuit (cont')

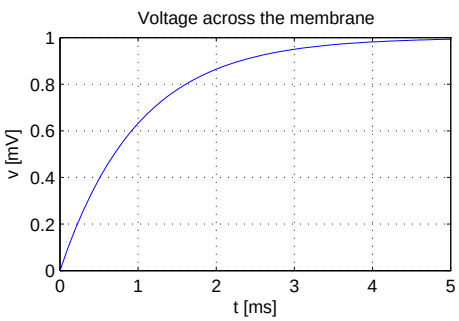


- If a constant current is injected, the voltage across the membrane (RC circuit) grows exponentially, until it saturates at the value $V_{in} = R\,i_{in}$

($e \approx 2.7183$ is the base of the natural logarithm)

- If analytical solution is known (which is hardly ever the case) it is simple to use your favourite MATLAB to get the plot of the voltage.

```
g = 1 ;       % mS/cm^2
% R = 1/g ;   % kOhm x cm^2
C = 1 ;       % uF/cm^2
taum = C/g ; % ms
Iin = 1 ;     % uA/cm^2
Vin = Iin/g; % mV
t = 0:0.1:5; % time in ms
v = Vin*(1-exp(-t/taum));
plot(t, v), grid on
```



Note the typical values of parameters:

- conductance : $g = 1$ mS/cm^2
- capacitance : $C = 1\mu$F/cm^2
- time constant : $\tau_m = \frac{C}{g} = 1$ ms
- injected current : $i_{in} = 1\mu$A/cm^2
- max voltage : $V_{in} = \frac{i_{in}}{g} = 1$ mv

If analytical solution cannot be found, differential equations can be solved recursively using approximation of derivatives.

$$\tau_m \frac{dv}{dt} + v = V_{in} \quad \text{use:} \quad \frac{dv}{dt} \approx \frac{\Delta v}{\Delta t} = \frac{v(t+\Delta t) - v(t)}{\Delta t}$$

Substitution yields:

$$\frac{\tau_m}{\Delta t}(v(t+\Delta t) - v(t)) + v(t) = V_{in}$$

Dividing by $\frac{\tau_m}{\Delta t}$ and grouping the like terms we obtain

$$v(t+\Delta t) = \left(1 - \frac{\Delta t}{\tau_m}\right) v(t) + \frac{\Delta t}{\tau_m} V_{in}$$

This can be written in the following simple form:

$$v(k+1) = r \cdot v(k) + (1-r) \cdot V_{in} \quad \text{where} \quad r = 1 - \frac{\Delta t}{\tau_m} \quad \text{and} \quad t = k \cdot \Delta t$$

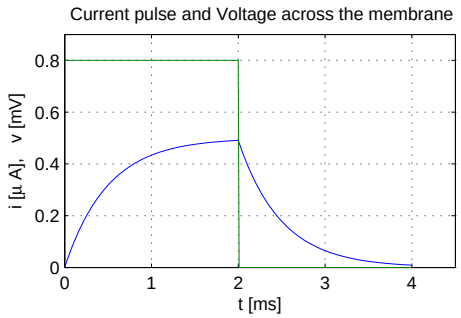
This equation is a simple geometric progression with the ratio r and can be easily solved recursively with a simple program, starting with zero initial value.

```
v(1) = 0;
for k = 1:K
  v(k+1) = r*v(k)+(1-r)*Vin;
end
```

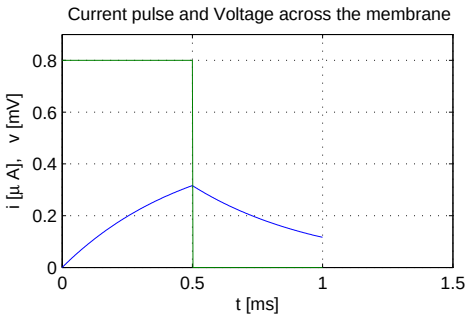

Injection of a current pulse into neuron through neuron's membrane

- Instead having a constant current injected through the membrane, let us consider a current pulse of duration t_p ms.
- It is still possible to get an analytical expression for the resulting membrane voltage, but it is easier to do computer simulation and plot the the signals.
- Results depends on the relative ration of the current pulse duration t_p and the membrane's time constant τ_m

$t_p = 4 * \tau_m$



$t_p = \tau_m$




```
v = zeros(1,2*K+1);
% during the pulse
for k = 1:K
  v(k+1)=r*Vm+(1-r)*v(k);
end
% after the pulse
for k = (1:K)+K
  v(k+1)=(1-r)*v(k);
end
```

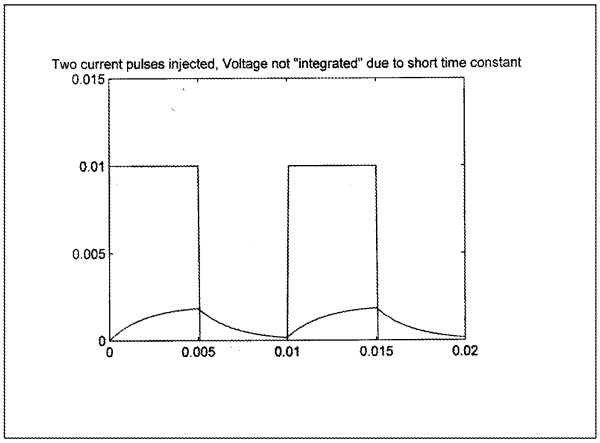
If the pulse duration is short comparing with the membrane time constant,

- the voltage across the membrane does not reach its maximum value during the pulse, and
- does not go back to zero in the period equal to the current pulse duration.

Injection of two current pulses into neuron through neuron's membrane

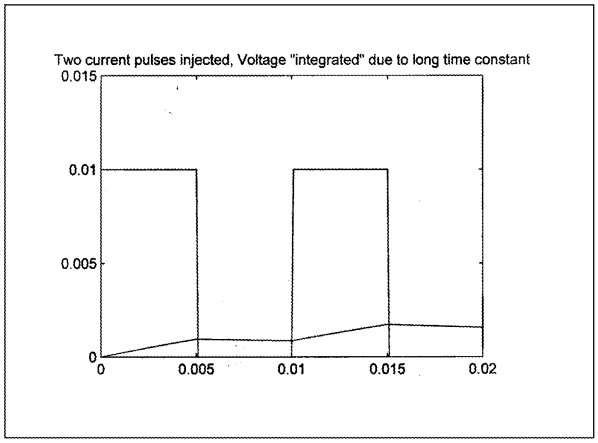
- Current pulses code information. This information is integrated in the neuron.
- Integration depends on the relative value of the membrane time constant τ_m
- In the example, pulses are $t_p = 5$ ms duration and repeated every 10 ms.

Short membrane time constant $\tau_m = 2$ms.



The membrane voltage is NOT integrated.

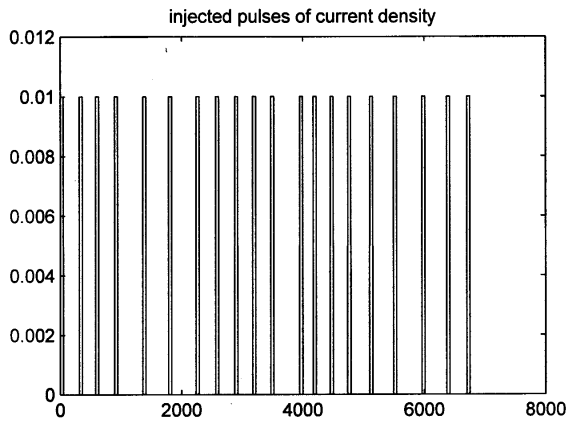
Long membrane time constant $\tau_m = 20$ms.

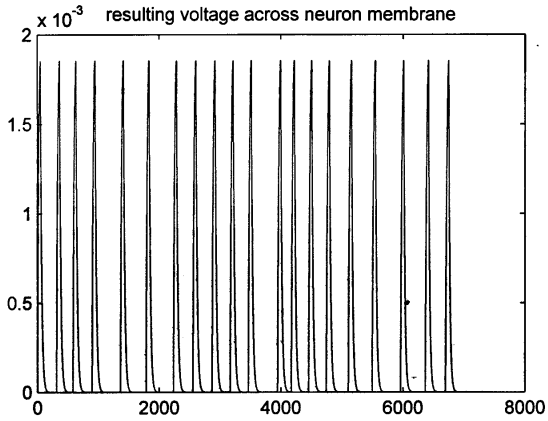


The membrane voltage is integrated (summed up).

Injection of many current pulses into neuron through neuron's membrane

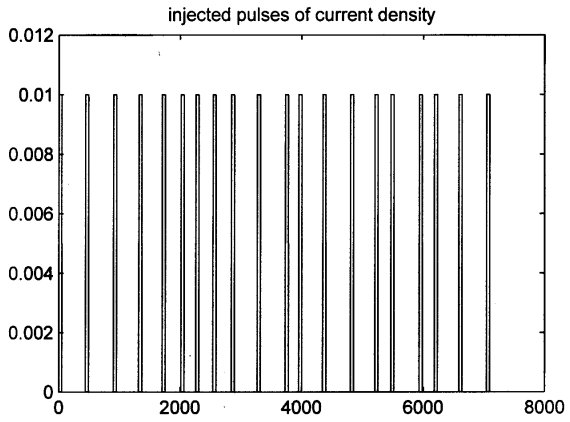
- The membrane time constant τ_m is short comparing with the pulse duration (a "fast membrane").
- 20 current pulses are injected
- The time intervals between pulses vary a little.
- Nothing interesting happens. The voltage resembles the current pulses in this case. The membrane is too quick to respond.

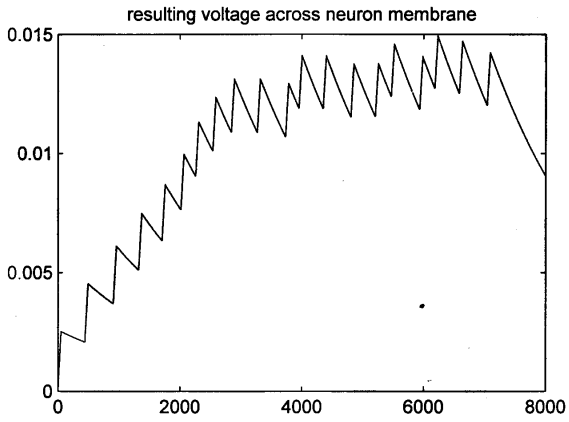




Injection of many current pulses into neuron through neuron's membrane

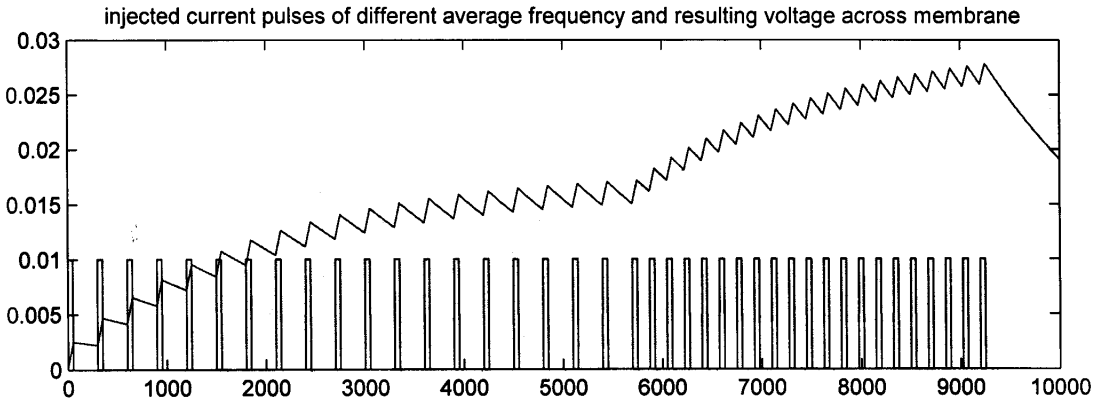
- The membrane time constant τ_m is long comparing with the pulse duration (a "slow membrane").
- Again 20 current pulses are injected with the time intervals between pulses varing a little.
- Here the membrane reacts slower to the pulses — the voltages caused by each current pulse are "stretched out" in time and therefore add up.
- This is **temporal integration**.





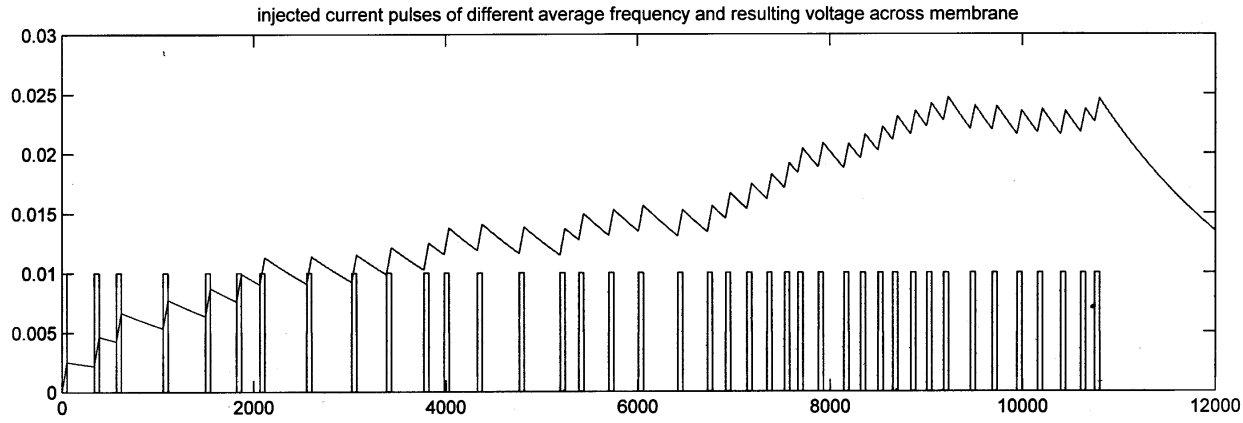
Injection of many current pulses into neuron through neuron's membrane

- The membrane acts as the frequency detector.
- The pulses have been generated to have a low frequency initially and a high frequency towards the end of the pulse train
- You can clearly see when the frequency changes, but the resulting voltage does not quite settle down within the time for the high frequency pulses.



Injection of many current pulses into neuron through neuron's membrane

- The pulses have been generated to have a low frequency initially and a high frequency towards the end of the pulse train
- There is, in addition, also some randomness in the times between the pulses (does the voltage settle down to its "right" value?)



Effect of conductance change the membrane voltage

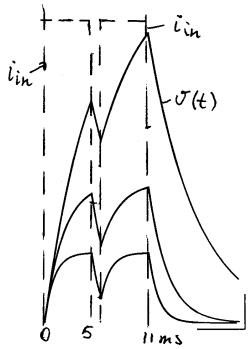


Fig. 11.9:
Reduction in conductance increases Vm and temporal summation.
Second current injection starts at $t = 6$ ms; $g = 1, 0.5, 0.2$ mS/cm.
Scale bar: 5 ms, 0.5 mV.

Remember that:

$$\tau_m = \frac{C}{g} \; ; \quad \text{and} \quad V_m x = \frac{I_{in}}{g}$$

- By decreasing g, we simultaneously increase the time constant and maximal response.
- Lower conductance (higher resistance) gives a bigger, slower response.
- For Fig. 11.9, I decreased g from 1 mS/cm^2 (lower trace) to values of 0.5 and 0.2 mS/cm^2 (upper trace).
- The second signal starts at $t = 6$ ms.
- The lower trace shows no temporal summation.
- By decreasing g, we prolong the time constant so that the membrane is not fully charged by the end of the first signal.
- Now when the second signal kicks in, there is room to grow and temporal summation occurs.
- The increased temporal summation is a direct consequence of the increase in τ_m.

11.7 Slow potential theory

- In Chap. 7 we discussed rate (or frequency) coding hypothesis that the neural state can be measured at the axon as frequency of spiking.
- Rate coding uses the firing frequency of a presynaptic neuron as that neuron's output state.
- According to the basic artificial neural network model, this output state (the afferent signal) x_i will be multiplied by a weight w_i and added to the other $w_i \cdot x_i$ products to produce the total postsynaptic activity $\mathbf{v} = \mathbf{w} \cdot \mathbf{x}$ that goes to a squashing function σ.
- To look at the artificial neural network model in the context of neural membrane theory, we need to find membrane-model parameters that correspond to the weight in the artificial neural network model.
- This weighting process will transduce presynaptic firing frequency to a postsynaptic value corresponding to the $\mathbf{w} \cdot \mathbf{x}$ product.
- The obvious postsynaptic value for this purpose is membrane voltage.

  The voltage due to one input can add to voltages due to other inputs to give the total-summed-input needed for the squashing function.
- As we see in the next chapter, membrane voltage can also be transduced into firing rate (postsynaptic neuron state) through the dynamics of the Hodgkin-Huxley equation.

- To determine a firing frequency, one has to wait until at least two spikes have arrived.
- If we measure the time between two spikes and invert the interval between them, this gives us the instantaneous frequency.
- For example, if two spikes occur 2 ms apart, then the instantaneous frequency is 1/(0.002 s) = 500 Hz (hertz, the unit of frequency, is equal to events per second).
- In the context of rate-coding theory, instantaneous frequency is not a very useful measure because instantaneous frequency values tend to jump around a lot.
- Biological spike trains look noisy. Noise interferes with frequency estimation and makes it necessary to smooth out the noise by signal averaging. Is this spiking irregularity really noise? What looks like noise may actually be some kind of uninterpreted signal that is being used by neurons in their calculations.
- Rate-coding theory postulates that the apparent noise really is noise.
- Noise means that instantaneous frequencies vary and do not consistently reflect the underlying average frequency.
- Frequency can only be reliably assessed after the arrival of several spikes. Spikes are counted over a period of time to determine average rate.
- This counting and adding up of spikes is signal integration.

- Slow potential theory describes how signal integration is performed as spikes trigger postsynaptic potentials (PSPs), which add up to produce a voltage that estimates the average presynaptic frequency.
- These PSPs are the slow potentials. They have to be relatively slow, long in duration, in order to give a reliable estimate.
- Temporal summation occurs as more spikes come in during the time while previous PSPs are still active.
- From listening to the radio, you know that amplitude modulation (AM) and frequency modulation (FM) are two methods of transmitting information using an oscillatory signal.
- Since biological spikes do not vary meaningfully in height (Chap. 3), the system is not using AM.
- Rate coding theory assumes that the system is using FM.
- To describe an FM signal, we need to discuss two different frequencies: the carrier frequency of the spikes and the frequency at which the rate changes.

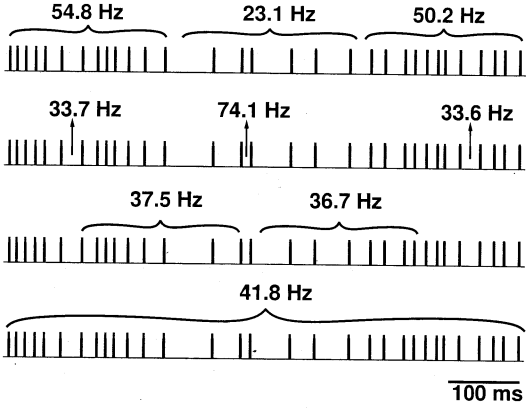


Fig. 11.11:
Different frequency estimates from a noisy FM spike train. Top trace: estimates are fairly accurate reflections of the underlying $50 \rightarrow 25 \rightarrow 50$ frequencies.
Second trace: Measurements of instantaneous frequency can be highly inaccurate.
Third trace: Averaging with correct duration but wrong phase (timing of start of average) also gives bad estimates.
Fourth trace: averaging for too long a duration misses the modulation entirely.

- It is a noisy spike train with carrier frequency varying between 25 and 50 Hz.
- This frequency is modulated at a rate of 4 Hz, meaning that we have a shift in frequency every quarter second (250 ms – the length of the brackets at the top of Fig. 11.11).
- Clearly, the frequency of modulation must be considerably lower than the carrier frequencies.
- In Fig. 11.11, rates for a single artificial noisy frequency modulated spike train are estimated correctly, and then incorrectly in several ways.
- Biologically, it is not possible to be confident of whether a particular signal estimation is correct or incorrect.

From square to realistic current pulses or PostSynaptic Potentials (PSP)

- We used square waves (pulses) as models of artificial current injections.
- Real biological signals are more curvy.
- One of a more realistic models of a postsynaptic potential (PSP) is described by the alpha function.

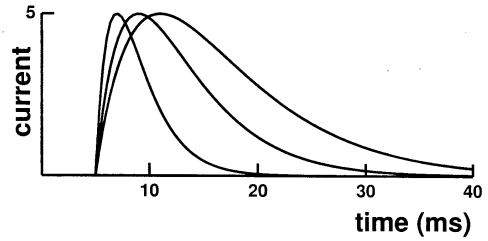


Fig. 11.12: Alpha functions with onset at 5 ms and amplitude of 5 μA/cm^2. Three curves with $\tau_\alpha = 2, 4, 6$ ms.
Note that τ_α equals the time from onset to peak. τ_α also determines decay time.
This is used as a model of a postsynaptic potential (PSP).

We start with the following function:

$$y = t \cdot e^{-\frac{t}{\tau_\alpha}}$$

Note that y attains maximum for time: $t = \tau_\alpha$. The maximum is equal to $y_m = \tau_\alpha \cdot e^{-1}$. Dividing y by y_m we get the alpha function with the maximum equal to one. Renaming y to current I_{in} we get

$$I_{in} = I_m \cdot \frac{t}{\tau_\alpha} \cdot e^{1-\frac{t}{\tau_\alpha}}$$

The alpha function rises quickly for τ_α time and then falls slowly over about $5\tau_\alpha$ (a little slower than exponentially).

- Note that we now have a couple of time constants to discuss:

  the alpha function time constant τ_α and

  the membrane time constant τ_m
- The time constant of the slow potential must be chosen so that the PSPs are long enough to average a reasonable number of spikes.
- Choice of too short a τ_α, will not allow integration to occur — the PSP will end after only one or two impulses so that only instantaneous frequency can be measured.
- An overly long τ_α, will not allow enough PSP decay during the arrival of many spikes, and will therefore average across the frequency modulation.

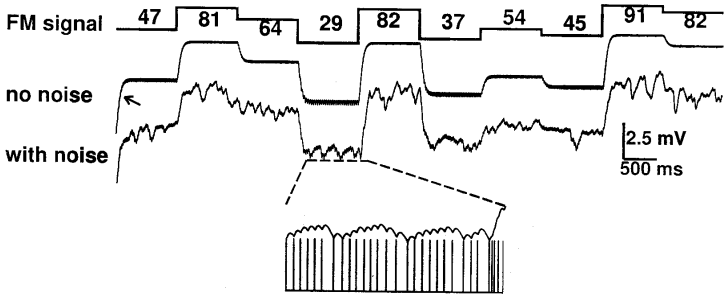
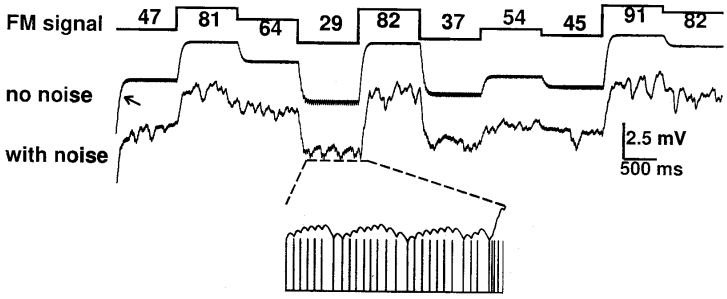
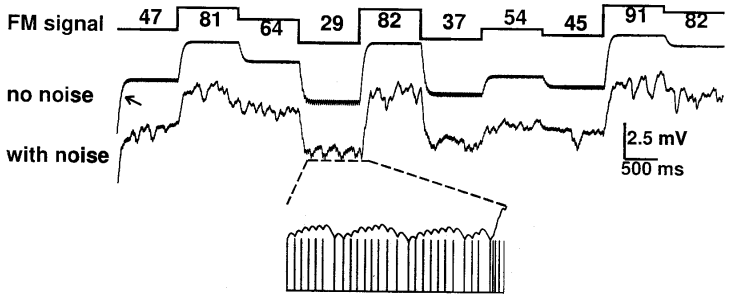


Fig. 11.13: Slow PSP response to FM square wave (carrier frequencies shown in Hz). PSP parameters: $\tau_\alpha = 30$ms; $\tau_m = 1$ms

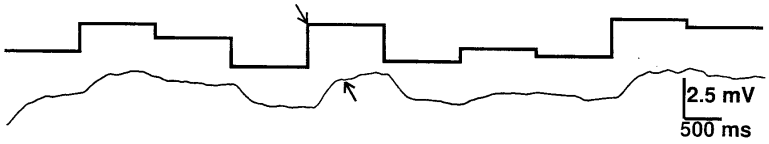
- An FM signal with spike-train frequencies varied randomly between 20 and 100 Hz.
- The frequency changed every second (1 Hz modulation frequency) for 10 seconds.
- The carrier frequencies are shown graphically in the top trace with the values given in Hertz.
- I didn't show all the spikes since at this scale they would just scrunch together into an indistinguishable blob.
- However, at the bottom of the figure I expanded an 800-ms period to show the spikes and membrane response together.
- With carrier frequency between 20 and 100 Hz, the interspike intervals (ISIs) ranged from 50 to 10 ms (period is inverse of frequency: ISI = $\frac{1}{f}$).
- A good choice of τ_α, would be somewhere in this range; I used 30 ms.
- Membrane time constant, τ_m is 1 ms, which allows the membrane to follow the PSP without substantial lag and without adding any additional delay.



- Fig. 11.13 shows membrane potential in response to two spike trains with the same underlying frequencies but without and with noise.
- There is an initial charging period (arrow) when the membrane rises from resting membrane potential by about 3 mV.
- Then the potential plateaus in response to the constant-frequency input.
- When the input frequency shifts upward from 47 to 81 Hz there is another charging period as the membrane rises another 2 mV and plateaus.
- The correspondence between shifts in frequency and shifts in membrane voltage can be easily appreciated.
- The scaling is arbitrary: the change in millivolts as a number is not the same as the change in frequency as a number.
- However, the relationship is linear: a doubling of input frequency leads to a doubling of potential.



- During the plateau there is a low-amplitude oscillation from the waveforms of the constituent alpha functions.
- In the absence of noise, membrane potential closely reflects frequency modulation, even reflecting small frequency shifts such as the shift at right from 91 to 82 Hz.
- Once noise is added to the FM signal (Fig. 11.13, with noise), frequency estimation suffers.
- It is no longer possible to reliably identify frequency shifts of under 10 Hz.
- Even the shift from 81 to 64 Hz is hard to see.
- The expanded trace below shows the alpha function responses to individual spikes up to the shift from 29 to 82 Hz.



- Fig. 11.14: Slower PSP response to noisy FM signal of Fig. 11.13. $\tau_\alpha = 100$ms.

- With τ_α increased to 100 ms, averaging occurs over a greater number of spikes and most of the noise is filtered out.
- As well as averaging over a greater period, the longer τ_α also produces longer charging delays.
- This means, a longer wait for the voltage to stabilize on an estimate of the incoming signal (arrows).
- With a charging delay of nearly half a second and frequency modulation of 1 Hz (period of 1 second), the frequency estimate barely registers as a plateau before the frequency shifts again.

11.8 Summary and thoughts

- My recurring theme is that hardware determines software.
- In this chapter, I started with salt, water, and soap, the basic ingredients of the brain.
- Out of these, the body builds capacitors and resistors.
- In the next chapter we'll see that it builds batteries as well.
- The physical limitations of these building blocks makes neurons very slow compared to transistors.
- In particular, the relatively large capacitance translates into slow signaling.
- Rather than be dismayed by this slowness, I presented models that use it to advantage.
- The slowness allows the membrane to hold onto a signal, permitting temporal summation.
- The amount of summation has to do with the length of the membrane time constant.
- Slow potential theory is a model that makes slowness a feature, using long time constants to do signal averaging that blurs out noise.
- This chapter showed how the parameters of the membrane and of the signal itself determine the influence a signal has on the neuron.
- These interactions explained signal transduction from presynaptic spike rate to postsynaptic membrane potential.

- They also explained the signal summation required to arrive at a total-summed-input.
- The next step of an artificial neural network update rule is signal transduction from total-summed-input to output state, in this case from membrane potential to spike rate.
- In the next chapter, we explore how the size of the membrane potential will determine the likelihood and frequency of neuron firing.
- Although rate coding and slow potential theory are about the best we can do right now, I find them unsatisfying.
- As mentioned above, they are too slow.
- Also as I'm sitting and thinking, it bugs me to think that most of my substantial metabolic effort is just producing noise.
- Worse yet, I have to wait around just so I can ignore most of what my brain is doing.
- Anyway, I'm always complaining about other people using intuition to understand the brain, and here I am doing it.