Mathematical Foundations of Neuroscience - Lecture 2. Electrophysiology of neurons.

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Electricity

Electricity is a general term that encompasses a variety of phenomena resulting from the presence and flow of electric charge.

In particular the brains activity is based on electrochemical phenomena. To study the brain one has to study neurons. To study neurons one has to study electricity.

Differential equation

- An equation which involves the derivative of an unknown function of a single independent variable is called an ordinary differential equation. It is usually of the form

$$\begin{cases} \frac{df(t)}{dt} & = F(t, f(t)) \\ f(t_0) & = y_0 \end{cases}$$

  where F is some function and $f(t_0) = y_0$ is called the boundary condition.

- The task of solving a differential equation is to find a function f that satisfies both conditions. There are multiple theorems which relate the existence of solutions with conditions imposed on function F.

Differential equation

- A differential equation can also be expressed in an integral form:

$$f(t) = y_0 + \int_{t_o}^{t} F(\tau, f(\tau))d\tau$$

- It is easy to verify that any $f(t)$ satisfying above equation is a solution to a differential equation as in previous slide.
- One can build systems of ODE expressed in concise vector form. The only condition is that only derivatives with respect to a single variable are used.

Total derivative

- Recall that a derivative of a function $f : U \subset \mathbb{R}^n \to \mathbb{R}^m$ at some point p is a linear map $df_p : U \subset \mathbb{R}^n \to \mathbb{R}^m$ such that:

$$\lim_{x \to p} \frac{||f(x) - f(p) - df_p(x - p)||}{||x - p||} = 0$$

- In other words, the function can be approximated in point p via a linear map df_p.
- There is a weaker notion of partial derivative with respect to some variable $\frac{\partial f(x_1, x_2, \ldots, x_n)}{\partial x_k}$. In this case the function is assumed constant with respect to other parameters. A function may have all partial derivatives (with respect to all variables) but lack the total derivative!

Partial differential equations

- Equations which involve partial derivatives of an unknown function of many independent variables are called partial differential equations (PDE).
- Such equations are more general than ODE and harder to deal with, both mathematically and computationally
- Nevertheless PDE are a basic tool used do describe physical phenomena like fluid flow or spread of electric and magnetic fields. Fortunately we will not have to use partial differential equations to much...

Mathematical prerequisites

- A scalar field is a function $\phi : \mathbb{R}^n \to \mathbb{R}$
- A vector field is a function $V : S \subset \mathbb{R}^n \to \mathbb{R}^n$. That is a vector field attaches a vector to every point of space S. Vector fields are convenient for describing velocity of a fluid, strength and direction of electric force etc.
- Any scalar field induces a vector field called its gradient. The gradient at point $[x, y, z]$ of scalar field ϕ is defined as a vector of partial derivatives of ϕ, i.e $\left[\frac{\partial \phi}{\partial x}, \frac{\partial \phi}{\partial y}, \frac{\partial \phi}{\partial z}\right]$. Gradient vector field are very special, in general most vector fields can not be obtained as gradients of scalar fields.

Mathematical prerequisites

- Nabla, the differential operator

$$\nabla = \left[\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z}\right]$$

Use it like a vector. It has no meaning alone, it only works as a formal operator in equations.

- E.g. curl operator

$$\nabla \times F = \begin{vmatrix} i & j & k \\ \frac{\partial}{\partial x} & \frac{\partial}{\partial y} & \frac{\partial}{\partial z} \\ F_x & F_y & F_z \end{vmatrix} =$$

$$= \left(\frac{\partial F_z}{\partial y} - \frac{\partial F_y}{\partial z}\right)\mathbf{i} + \left(\frac{\partial F_x}{\partial z} - \frac{\partial F_z}{\partial x}\right)\mathbf{j} + \left(\frac{\partial F_y}{\partial x} - \frac{\partial F_x}{\partial y}\right)\mathbf{k} = 0$$

.

Mathematical prerequisites

- Vector field whose curl is zero $\nabla \times F = 0$ is called an irrotational vector field. It is easy to verify that any gradient field is irrotational:

$$\nabla \times \nabla \phi = \begin{vmatrix} i & j & k \\ \frac{\partial}{\partial x} & \frac{\partial}{\partial y} & \frac{\partial}{\partial z} \\ \frac{\partial \phi}{\partial x} & \frac{\partial \phi}{\partial y} & \frac{\partial \phi}{\partial z} \end{vmatrix} =$$

$$= \left(\frac{\partial^2 \phi}{\partial zy} - \frac{\partial^2 \phi}{\partial yz} \right) \mathbf{i} + \left(\frac{\partial^2 \phi}{\partial xz} - \frac{\partial^2 \phi}{\partial zx} \right) \mathbf{j} + \left(\frac{\partial^2 \phi}{\partial yx} - \frac{\partial^2 \phi}{\partial yx} \right) \mathbf{k} = 0$$

for $\phi \in C^2$.

Mathematical prerequisites

- Vector field is called conservative if its a gradient of some scalar field.
- A key property of a conservative vector field is that its integral along a path depends only on the endpoints of that path, not the particular route taken. That is for any rectifiable path P from A to B there is :

$$\int_P v dr = \phi(B) - \phi(A)$$

- Many physical vector fields like the gravitational field and static electric field are conservative.

Electric charge

- Electric charge is a fundamental conserved property of some subatomic particles like electrons and protons, which determines their electromagnetic interaction.
- Electric charge is measured in coulomb (C), equivalent to 6.25×10^{18} electron charges.
- The charge measures the "density" of electrically charged particles in some area.
- Most of electrical phenomena are related to movement of electrical charge.

Electric current

- Electric current is a rate of flow of electric charge
- Current is measured in ampereres (A). $1A = \frac{1C}{1s}$, that is the current of 1A transfers 1C of electric charge during 1s.
- Generally the current is a rate of change of charge:

$$I = \frac{dQ}{dt}$$

For steady (constant) flow we have

$$I = \frac{Q}{t}$$

Voltage

- If current is the rate of flow, Voltage can be thought as a force that pushes the current through the conductor
- Voltage is commonly used as a short name for difference in electrical potential (a hypothetically measurable physical dimension)
- Voltage is measured in volts (V). $1V = \frac{1W}{1A}$. That is the voltage is equal 1V when a current of one ampere dissipates one watt of power in the conductor.

Capacitance

- Capacitance is the ability of a body to hold an electrical charge
- Capacitance is measured in farads (F). $1F = \frac{1C}{1V}$. That is a capacitor has 1F capacitance if attached to voltage source of 1V stores 1C of charge (or that 1C of charge on capacitor plates induces 1V potential difference across the device).
- Capacitors can store energy, which is used to charge the capacitor. The energy could be then restored by a discharge.
- The voltage across a capacitor can be computed as follows:

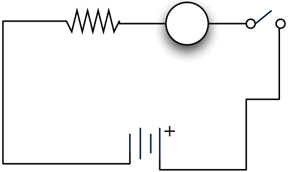
$$V(t) = \frac{Q(t)}{C} = \frac{1}{C}\int_{t_0}^{t} I(\tau)d\tau + V(t_0)$$

Resistance

- The electrical resistance of an object is a measure of its opposition to the passage of a steady electric current.
- Resistance is measured in ohms (Ω), equivalent to Js/C^2. That is a conductor has the resistance of 1Ω when a voltage of 1V induces a current of 1A.
- $$R = \frac{V}{I}$$

  that is resistance can be measured as the ratio of voltage to current.

Hydraulic analogy

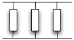


Electric potential ~ Water pressure
Voltage ~ pressure difference
Current ~ the quantity of flowing water over time

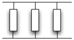
Figure: More on http://en.wikipedia.org/wiki/Hydraulic_analogy

Circuits

- Electrical elements can be joined into larger circuits, much like water pipes are joined into large water system.
- The two easiest ways of joining two or more elements are either parallel or series circuit. Different electrical elements behave differently in both configurations.

Connection	Series 	Parallel 
Resistance	$R_{\text{total}} = R_1 + R_2 + R_3 + \ldots$	$\frac{1}{R_{\text{total}}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \ldots$

Circuits

Connection	Series 	Parallel 
Voltage	$V_{\text{total}} = V_1 + V_2 + V_3 + \ldots$	$V_{\text{total}} = V_1 = V_2 = V_3 = \ldots$
Capacitance	$\frac{1}{C_{\text{total}}} = \frac{1}{C_1} + \frac{1}{C_2} + \frac{1}{C_3} + \ldots$	$C_{\text{total}} = C_1 + C_2 + C_3 + \ldots$

Neurons

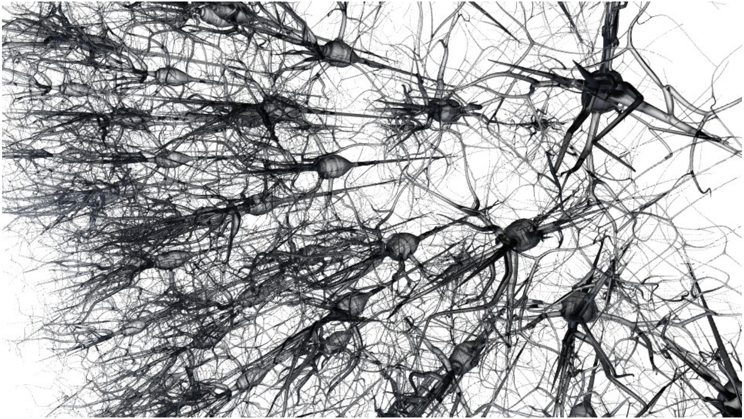


Figure: A rendered image of neurons.

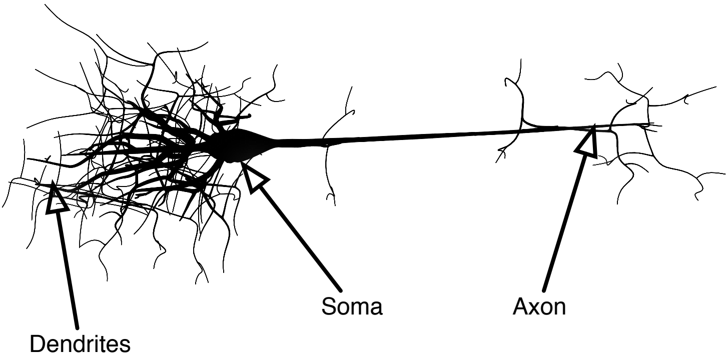


Figure: A schematic anatomy of a neuron.

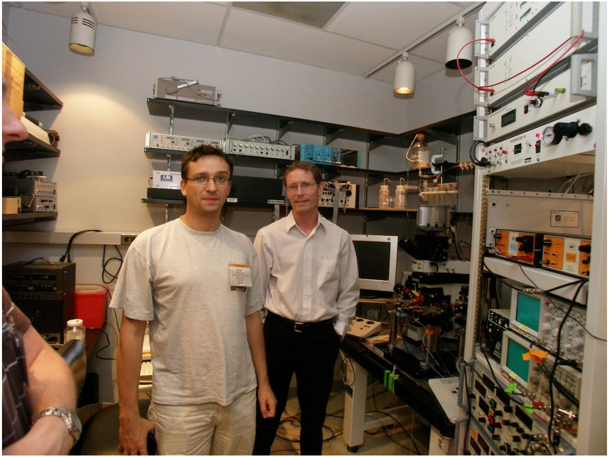


Figure: Equipement used to perform in vitro recordings.

Figure: Equipement used to perform in vitro recordings. The neuron is connected to a set of electrodes (colorful wires)

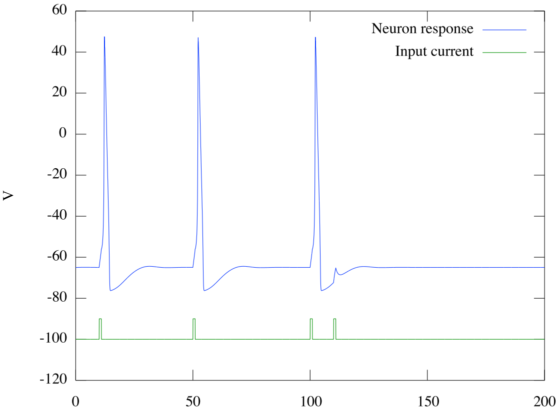


Figure: Transient changes to membrane polarization - the so called spikes are the essence of neural activity.

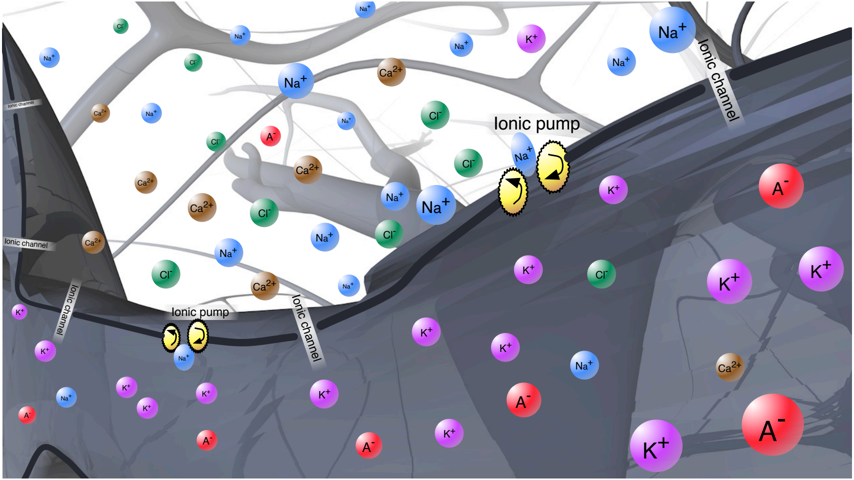


Figure: Neuronal membrane and ions

Ions

- The intracellular and extracellular medium is filled with ions dissolved in water
- Various concentrations of ions inside and outside the cell introduce electric potential across the membrane
- Most important are four ionic species: sodium (Na^+), potassium (K^+), calcium (Ca^{2+}) and chloride (Cl^-)
- The extracellular medium has high concentration of $Na^+$and Cl^-(much like salty water), and Ca^{2+}
- The intracellular medium has high concentration of $K^+$and large negatively charged molecules denoted $\mathbf{A}^-$.

Membrane

- The cellular membrane has certain large protein molecules forming channels through which ions (excluding $\mathbf{A}^-$) can freely flow.
- The flow of Na^+ and Ca^{2+} is small but the flow of K^+ and Cl^- is significant. However concentration asymmetry persist. Why is that?
- There are two main mechanisms which prevent extra and intra cellular media from agreeing their ionic solutions:
  - *Passive redistribution* - $\mathbf{A}^-$ molecules which are too big to fit inside the channel attract more K^+ and repel Cl^-
  - *Active transport* - ions are pumped via molecular ionic pumps. For example Na^+-K^+ pump pumps out three Na^+ ions for every two K^+ pumped in.

- There are two concurrent forces which drive the ionic movement:
  - Diffusion which tends to equalize concentrations on both sides of the membrane.
  - Electric force which tries to equalize electric charges on both sides of the membrane.
- Since not all elements can diffuse ($\mathbf{A}^-$) and active transport pumps ions, eventually an equilibrium is achieved. The differences of concentrations of various ions induce an electric potential across the membrane.

Concentrations

Ion	Inside	Outside
Na^+	5-15mM	145mM
K^+	140mM	5mM
Ca^{2+}	0.1μ M	2.5-5mM
Cl^-	4mM	110mM
$\mathbf{A}^-$	147mM	25mM

Table: Ionic concentrations in typical mammalian neuron.

The electric potential which results from different concentrations of a particular ion on the sides of the membrane can be computed from the Nerst equation:

$$E_{\text{ion}} = \frac{RT}{zF} \ln \frac{\text{Ion}_{\text{out}}}{\text{Ion}_{\text{in}}}$$

where Ion_{out} and Ion_{in} are ionic concentrations, R is the universal gas constant (8315 mJ/(KMol)), T is temperature in Kelvin scale, F is Faraday's constant (96480 coulombs/Mol), z is the valence of the ion (e.g $z = 1$ for $Na^{+}$and K^{+}, $z = 2$ fot Ca^{2+}). Assuming body temperature (310K) the equation can be simplified:

$$E_{\text{ion}} \approx 62 \log \frac{\text{Ion}_{\text{out}}}{\text{Ion}_{\text{in}}}$$

for $z = 1$

Equilibrium potentials

Ion	Potential
Na^+	E_{Na} =61-90mV
K^+	E_K =-90mV
Cl^-	E_{Cl} =-89mV
Ca^{2+}	E_{Ca} =136-146mV

With typical concentrations the equilibrium potentials for each ionic species are shown in table.

If V denotes total potential difference across the membrane, then net current corresponding to, say K^+ions is expressed by

$$I_K = g_K(V - E_K)$$

where g_K is the conductance of K^+across the membrane that is reciprocal of resistance of the membrane to conduct K^+ions. Conductance is expressed in Siemens unit $1S = \frac{1}{1\Omega}$

Currents across the membrane

- The membrane has some capacitance C (of order $1\mu F/cm^2$). Recall that the voltage across the capacitor is

$$V(t) = \frac{Q(t)}{C} = \frac{1}{C}\int_{t_0}^{t} I_c(\tau)d\tau + V(t_0)$$

Taking derivative of both sides and multiplying by C yields the derivative form

$$I_c(t) = \frac{dQ(t)}{dt} = C\frac{dV(t)}{dt}$$

- This yields membrane capacitive current

Currents across the membrane

- By Kirchfoff's law the total current flowing across the membrane is the sum of all electrochemical currents and the capacitive current.
- We then have:

$$I(t)_{\text{total}} = I_c(t) + I_{Na} + I_K + I_{Cl} + I_{Ca}$$

- By expressing the capacitive current in terms of voltage we get

$$I(t)_{\text{total}} = C\frac{dV(t)}{dt} + I_{Na} + I_K + I_{Cl} + I_{Ca}$$

$$C\frac{dV(t)}{dt} = I(t)_{\text{total}} - I_{Na} - I_K - I_{Cl} - I_{Ca}$$

Recap

- We know from elsewhere that in the steady state equilibrium the total current across the membrane is $I_{\text{total}} = 0$.
- We know the Nerst potentials of Ions, we only need to know the respective conductances to get the equation:

$$C\frac{dV(t)}{dt} = I(t)_{\text{total}} - I_{Na} - I_K - I_{Cl} - I_{Ca}$$

running and find out what is the steady state membrane voltage.

- Sadly this is where the neuronal story begins...