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Course 5: Semiconductors and Nanostructures

Neuro-Transistors

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Architecture of a neuron

Most neuron can be described by a model neuron which consists of four functional units. These are an input component (receptive), a trigger component, a long-range conducting component and an output component. These four components correspond to four physiological units. These are the dendrites, the cell body, the axon and the presynaptic terminals.
The centre of the cell (cell body or soma) has two kinds of extensions: the short, tree-like dendrites which are specialized to receive incoming information and one thin tubular structure called axon which carries outgoing signals to other neurons.
Neurons communicate by electrical signalling. These signals consist of brief, invariant and large electrical impulses called action potentials. Action potentials are all-or-none signals. That means that stimuli below a certain threshold produce no action potential, all signals above this threshold generate the same signal. Action potentials are propagated along an axon at a speed of up to $150\,{}^{m}\!/\!_{s}$ without decaying.
At rest no current flows through the cell membrane. The neuron becomes excited when a local change in membrane potential occurs. If this change is above the threshold the neuron "fires" action potentials. The number of APs is determined by the amplitude and duration of the input stimulus. So information transmitting is frequency-coded. Input stimuli can be received either from other neurons through the dendrites or by a direct physical or chemical stimulation, e.g. olfactory sensory neurons.

Membrane potential

The membrane of a neuron consists of a double layer of hydrophobic lipid molecules. Due to its chemical properties a separation of charges across the membrane is maintained. This gives rise to a difference in electrical potential across the membrane called membrane potential (V_m).

$$V_m = V_{in} - V_{out}$$

Typical values of the membrane potential at rest (resting membrane potential V_r) are from -60mV to -70mV.

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Ions in a cell are subject to two different forces:

(i) chemical force depending on the concentration gradient
(ii) electrical force depending on electrical potential difference across the membrane.

At some point equilibrium is reached where both forces compensate each other.
The equilibrium potential can be calculated from an equation derived by Walter Nernst.

$$V_K = \frac{k_B \cdot T}{z \cdot e} \cdot \ln\left(\frac{[K]_o}{[K]_i}\right) \qquad \text{Nernst Equation}$$

Here $[K]_o$ and $[K]_i$ are the concentration of K^+ outside and inside the cell, respectively.

This process is a passive process which means that it does not consume energy. Energy supply however is needed to set up the initial concentration gradient which is produced by ion pumps. These pumps are proteins in the cell membrane that couple ion transport with hydrolysis of ATP to ADP.

For several ion species the dependence of the membrane potential on ion permeability and concentration is given by the Goldman-Hodgkin-Katz (GHK) equation.

$$V_m = \frac{k_B \cdot T}{e} \cdot \ln\left(\frac{P_K \cdot [K^+]_o + P_{Na} \cdot [Na^+]_o + P_{Cl} \cdot [Cl^-]_i}{P_K \cdot [K^+]_i + P_{Na} \cdot [Na^+]_i + P_{Cl} \cdot [Cl^-]_o} \right) \qquad \text{GHK Equation}$$

Generation of an action potential

Actions potentials are generated in a special region o f the neuron called axon hillock which has a high density of voltage-gated ion channels. A depolarization of the membrane in this region leads to a change in the permeability of K^+ and Na^+. If the depolarization exceeds a certain threshold an action potential is generated.
This process can be explained by a rapid opening of Na^+-channels which leads to an inward current of Na^+. An inward current of cations leads to further depolarization of the membrane creating a positive feedback loop that drives the action potential to its maximum value. But the depolarization also closes the Na^+-channels again, a process called inactivation. The inactivation state of the Na^+-channels is different from the closed state. The Na^+-channels must first proceed to the closed state before they are able to open again.
Also at the time of inactivation a delayed opening of K^+-channels begins leading to outward potassium current. As a result the membrane potential returns to its resting value. After the generation of an action potential the cell is unable to create another one for a certain time span called refractory phase.
Polarization below the threshold voltage just causes electrotonic potentials which are proportional to the stimulating current pulse.
The timing and nature of the ionic currents related to an action potential are described by the Hodgkin-Huxley-Model of the squid giant axon which can explain most features of the generation and propagation of action potentials. This model is based on the time-dependent parameterization of the membrane conductance g_{Na} and g_K for sodium and potassium.

Recording electrical signals from neurons

Most measurement techniques make use of glass micropipettes filled with a concentrated salt solution. Wires inserted into the back are connected via an amplifier to an oscilloscope. Due to their small diameter (<1µm) these electrodes can be inserted into the cell without to much damage. While one pair of electrodes measures the voltage across the membrane another one can be used to insert current pulses.

- Voltage-Clamp-Technique.
  Holds the cell potential at a certain value. Used to analyse the mechanisms of ionic conductance.
- Patch-Clamp-Technique.
  Allows the measurement of currents through single ion channels.

Propagation of an action potential along an axon

The axon can be treated as a one-dimensional cable. It consists of an insulating coat and a conductive core. The coat is formed by the cell membrane which can be electrically

characterized by a capacitance, ionic conductance and ohmic leakage conductance. The core is formed by the intracellular fluid with high ohmic conductance.
Now if a depolarizing stimulus occurs at one point along the axon a large inward current develops due to the fast opening of Na^+-channels. This inward current passively flows along the conducting core depolarizing adjacent regions of the membrane thereby opening new Na^+-channels. This continuing cycle spreads until the action potential reaches the end of the axon. Spreading of the action potential in the direction of its origin is inhibited by the inactivation of Na^+-channels.
To increase the velocity of propagation the axonal membrane is electrically insulated reducing the ability of current to leak out. The insulating sheet on the axonal membrane is called myelin. This myelination can speed up the propagation velocity from 0.5-10 m/s up to 150 m/s. However the insulation of the membrane has to be interrupted to allow the current to flow in or out of the axon generating an action potential. The sites called nodes of Ranvier have a highly increased density of ion channels. The action potential propagating along a myelinated axon jumps from node to node.

Physics of neuron-silicon junctions

Generally spoken it is tried to achieve a link between brain and computer. Both systems work with electrical signalling but with very different hard- and software.
Today brain-computer interfacing with neuronal networks and digital devices fused to thinking computer-systems is still science-fiction. The issue is the investigation of the fundamental concepts of neuro-silicon coupling and the fabrication of ionoelectronic devices.

Principles of coupling

As we have seen before all neuronal activity leads to polarization of the cell membrane resulting in ionic and displacement currents through the membrane. These currents flowing into or out of the cell spread along the cleft between neuron and transistor. Current flow along the cleft gives rise to a potential called Transductive Extracellular Potential (TEP). Applying a voltage transient to the silicon chip causes a displacement current through the silicon oxide. As a result also giving rise to a TEP. Recognition of neuronal activity is achieved by probing the electrical field in the oxide with a field-effect-transistor. In the other direction stimulation of neuronal cells is mediated through an electrical field in the cell membrane affecting voltage-gated ion channels.
The Transductive Extracellular Potential mediates the coupling of neurons and silicon. It is determined by the currents flowing into and out of the junction. The voltages and currents are described by a one-dimensional electrical model called point-contact model.
The junction between neuron and chip forms a cable-like structure. The upper coat of this cable is represented by the cell membrane, the lower coat by the silicon dioxide surface of the chip and the core by the conductive cleft between them.

Point contact model

The conductive cleft is represented by an Ohmic conductance G_J, membrane and silicon dioxide by capacitances C_{JM} and C_S . In the attached membrane ion specific conductances

C^i_{JM} and reversal voltages V^i_0 are also taken into account. The reversal voltages originate in the concentration differences of ions between cell and environment.
The potentials are V_M in the cell, V_J in the junction, V_S in the substrate and V_E in the bath.
Now we can apply Kirchhoff's law to a point in the junction.

$$g_J \cdot (V_J - V_E) = c_S \cdot \left(\frac{dV_S}{dt} - \frac{dV_J}{dt} \right) + c_M \cdot \left(\frac{dV_M}{dt} - \frac{dV_J}{dt} \right) + \sum_i g^i_{JM} \cdot \left(V_M - V_J - V^i_0 \right)$$

For the point-contact model Kirchhoff's law applied to a point in the cell gives us:

$$A_{FM} \cdot \left[c_M \cdot \left(\frac{dV_M}{dt} - \frac{dV_E}{dt} \right) + \sum_i g^i_{FM} \cdot \left(V_M - V_E - V^i_0 \right) \right] = -A_{JM} \cdot \left[c_M \cdot \left(\frac{dV_M}{dt} - \frac{dV_J}{dt} \right) + \sum_i g^i_{JM} \cdot \left(V_M - V_J - V^i_0 \right) \right]$$

A_{FM} : Area of the free membrane.
A_{JM} : Area of the attached membrane.

Equations (1) and (2) together describe the coupled dynamics of the intracellular and extracellular potentials $V_M(t)$ and $V_J(t)$.
Efficient recoding and stimulation also requires high ionic conductances in the attached membrane and a high specific capacitance of the chip.

Transistor recording

Due to the environment a cell needs to live measurements of neuronal activity can't be performed with standard MOSFETs. To get biological compatibility the metal gate is replaced by an electrolyte forming an electrolyte oxide silicon field effect transistor (EOSFET). Like in a MOSFET the source drain current I_D is controlled by the voltage between gate and source V_{GS} which in our case is given by $V_{GS} = V_J - V_S$. The resulting current is changed into a voltage, amplified and can then be watched on an oscilloscope. The characteristic $I_D(V_{GS})$ is measured in a calibration experiment by variation of the bath potential without a cell.

If an action potential is elicited by current injection through a patch pipette two kinds of extracellular responses are observed according to whether A-type or B-type junction. The extracellular voltage transients are biphasic with a positive peak in the rising phase of the action potential when capacitive currents are dominating. The waveform hereby resembles the first derivative of the AP due to capacitive coupling (A-type). Or there is a monophasic response representing the AP itself which is due to dominating Ohmic currents (B-type). This can be seen from a small signal approximation of equation (1). It is assumed that the extracellular potential is small with $V_J << V_M - V^i_0$ and $dV_J << dV_M$, and the capacitive current to the chip is negligible. Equation (1) is then simplified to:

$$g_J \cdot V_J = \sum_i g^i_{JM} \cdot \left(V_M - V^i_0 \right) + c_M \cdot \frac{dV_M}{dt}$$

When the attached membrane contains no voltage-gated conductances we get:

$$g_J \cdot V_J = g_M \cdot V_M + c_M \cdot \frac{dV_M}{dt}$$

This relation clearly shows the two types of junctions.

A third type of junction (C-type) is observed when regions with high density of ion channels like the axon stump are attached to a transistor. If an action potential is elicited by current injection through a patch pipette the extracellular transient in the junction is dominated by a negative peak during the rising phase of the action potential and a weaker positive transient in the falling phase. This biphasic response is opposite to the signal of capacitive coupling.
The experiment is again evaluated with the point-contact model now taking voltage-dependent ionic conductances into account. The corresponding equations have to be treated by numerical simulation where the ionic conductances are described on the basis of the Hodgkin-Huxley model.
These results show that field-effect-transistors are able to probe the local flow of ionic currents in the attached membrane.

Capacitive stimulation of neuronal activity

A changing voltage $V_S(t)$ applied to a stimulation spot beneath a neuron leads to a capacitive current through the insulating oxide. As a result of the concomitant current along the cleft a extracellular potential develops as mentioned before. As a result voltage gated ion channels in the membrane may open and an action potential may arise.
The three junctions observed at transistor recording can also be seen when neurons are stimulated by a transistor.

Towards neuronal networks

After the recording of neuronal activity with a transistor one the one side and their stimulation on the other side has been achieved, the next steps are hybrid circuits with two neurons on a chip. The first circuit realizes a signal transmission from a neuron through a chip to another neuron. The principles of recording and stimulation are the same as mentioned above.

The pathway neuron-silicon-neuron shows that single action potentials from individual nerve cells can be reliably fed into a digital electronic processor, and that this processor can elicit a single action potential in an individual nerve cell.
The next experiment realizes the pathway chip-neuron-neuron-chip. This requires a precise placement of the cells on the transistors or stimulation spots and also a “wiring” by neurites that form synaptic connections.
When neurons are attached to defined sites on the chip the sprouting neurites exert strong forces on the cell bodies which results in a displacement of the cells. To overcome this problem the neurons are mechanically fixed by inserting them into cages made from polyimide.
The next goal is then the observation of small neuronal networks with defined geometry with two-way recording and stimulation contacts. To produce defined neuronal networks the growth of neurites has to be controlled and guided in some way. This can be achieved by either chemical guidance or topological guidance.
Patterns of extracellular matrix proteins are able to guide the outgrowth of neurons so that the grown cones are forced to collide and to form a synapse.
Topographical guidance uses the immobilization of grown neurites by microscopic groves fabricated from a polyester photoresist on the chip.
These small networks can be observed with highly integrated transistor arrays that allow a high spatial resolution.
A different approach in observing larger networks of neurons uses neuronal nets grown in the brain. 2-dimensional brain slices of a few cell layers are observed and stimulated with

transistor arrays. The interfacing of brain slices is in its infancy and two-way interfacing of groups of neurons in a tissue has to be studied in detail.

One of the main drawbacks of the silicon-based FETs is the electrochemical instability of the silicon-dioxide surface which results in a long-term drift of their electrical properties. Another one is their high noise level which makes it difficult to observe the small signals of neurons. One approach to overcome these problems is the application of alternative material systems for the realization of the FETs such as AlGaN/GaN heterostructure FETs. These materials are chemically stable under physiological conditions and non-toxic to living cells. The recording of extracellular action potentials with a AlGaN/GaN FET array demonstrated, due to low noise, a much higher signal resolution than currently used Si-based devices.