CHAPTER 1.1

PASSIVE MODELS OF EXCITABLE CELLS

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Excitable cells show a strongly nonlinear relationship between the transmembrane potential and the membrane current. In particular, after the membrane potential reaches threshold, the membrane potential follows a stereotyped wave shape called the action potential. Nevertheless, up to about 80% of the threshold level, the membrane potential and current can be described accurately using linear, or passive, models. In this chapter, we focus on the description of biological tissue as a target for electrical stimulation based on the passive properties of excitable cells. We first look at the relevant structure of the excitable cell with regard to electrical activation: the cell membrane, and the presence of ion channels. Then the resting potential is described and, finally, linear models for the response of excitable cells to intracellular and extracellular electrical stimuli are given for various kinds of cells.

1. Introduction

Although the term neuroprosthesis might very well comprise several modes of action, current practice in neuroprosthetic devices leaves a wide area of possibilities untouched. Typically, neuroprosthetic devices restore or support parts of the neuromuscular or neurosensory systems by stimulating muscle or neural tissue electrically. A chemical / pharmacological mode of action, or even a mechanical one, may open up a whole new area within neural prostheses but is beyond the state of the art of the field. Electric current can activate nerve and muscle cells to set off a stereotyped sequence of events mainly taking place at the cell membrane. Cells that exhibit the property of being activated are said to be *excitable*, whereas the process of initiating the cell's electrochemical activity is called *excitation*. The cell's activity can be recorded as a change of potential difference across the cell membrane, a process that actually travels over the cell membrane to other parts of the cell or to other cells. At rest, when the cell is inactive, the *transmembrane_potential* of an excitable cell is between -50 and -100 mV, depending on the type of cell. The cell membrane is thus normally *polarized*, where the inside is negative relative to the outside. During excitation the inside first becomes less

negative and even slightly positive, after which the resting state is gradually restored. The duration of the whole process, the *depolarization* and *repolarization*, also called the *action potential*, strongly depends on the type of cell. In a typical nerve cell this duration is about 0.5–1 ms, whereas in cardiac muscle cells it may be more than 400 ms, and in smooth muscle the action potential may last even longer[3].

Electric current can be induced in the body through electrodes or by the application of a varying magnetic field. Some examples are pacing and defibrillation of the heart, spinal cord stimulation for pain management, stimulation of nerves and muscles for restoration of functional movement or perception, stimulation of the auditory nerve or its receptors for cochlear prostheses, and electrical stimulation of peripheral nerves for diagnostic purposes to assess parts of the neuromuscular system. The characteristics of the activation depend on 1) the current sources (e.g., the electrical stimulator: amplitude, waveform, repetition rate), 2) the conducting biological tissue between and around the electrodes and the target cells, and 3) the properties of the target cells.

In turn, the electrical or electrochemical activity of muscle and nerve can be measured extracellularly and be used in neuroprosthetic devices as well as in many diagnostic methods in daily clinical practice (electrocardiogram, electromyogram, electroencephalogram, electro-oculogram, electroretinagram, electroneurogram, electronystagmogram, evoked potentials, etc). In neural prosthesis, recorded signals from muscle and nerve will mainly be utilized to control prosthetic devices or to replace sensory perception. The characteristics of the recorded signals depend on 1) the current sources, being at the membranes of the nerve and muscle cells, 2) the conducting biological tissue between and around the active cells and the recording sites, and 3) the way the signals are recorded.

Excitable tissue can thus serve as a target tissue for electrical stimulation or as a current source for recording purposes. In both cases, the tissue is part of a conducting medium. Whether physiologically evoked currents or artificially impressed currents are studied, they all obey the same laws of physics, which can be derived from Maxwell's equations. Because most of the energy of biological signals is always in a frequency band below 10 kHz, it is in general safe to assume that the tissue is purely resistive. However, cell membranes in particular have very low conductivities and, therefore, on a microscopic scale the time-varying term of the current cannot be neglected. Usually, this is taken into account by assigning leaking capacitors to the membranes as soon as a microscopic scale is considered. But on a macroscopic scale the time varying terms in Maxwell's equations can be neglected. Even though in electrical stimulation often square pulses are used and those pulses certainly have higher frequency components than 10 kHz, the energy in those higher frequencies is relatively low, and the response of excitable tissue to those high frequencies is negligible. Therefore, for all practical cases, the low frequency -quasi static- approach can be used in electrical stimulation as well as in recording situations.

For our considerations the relevant Maxwell equation is Ampère's law, which relates the magnetic field strength to the total current density, **J**, in each point in space. When we take the divergence of Ampère's law it reduces to

$$\nabla \cdot \mathbf{J} = 0 \tag{1}$$

which is the mathematical formulation of the property of resistive materials that the current generated in a certain volume (source current) is equal to the total current flowing out of the volume through the surface enclosing that volume (conduction current). In other words: it is Kirchhoff's current law for volume conductors.

For us the interesting case is the one where **J** is the sum of a conduction current, $\mathbf{J}_c$, and a source current (free current, or impressed current) $\mathbf{J}_s$:

$$\mathbf{J} = \mathbf{J}_C + \mathbf{J}_S \tag{2}$$

Here, the source current is the current generated at the membranes of cells or the current through a stimulation electrode. According to Ohm's law the conduction current or ohmic current can be written as:

$$\mathbf{J}_C = \sigma \mathbf{E} \tag{3}$$

where **E** is the electric field strength, given in Volt/meter, and σ is the conductivity of the conducting medium, in Siemens/meter, or 1/(Ohm.meter). Instead of working with the electric field it is easier to work with the electric potential, especially because potential differences (voltages) are easy to measure. The electric potential φ is defined as $\mathbf{E} = -\nabla\varphi$, where $\nabla\varphi$ is the gradient of the potential field. Combining this with Eqs. (1—3) gives the potential as a function of the source current:

$$\nabla \cdot \sigma \nabla \varphi = \nabla \cdot \mathbf{J}_S \tag{4}$$

which is a form of Poisson's equation. This equation directly relates the electric potential to the current density of the source and to the conductivity of the tissue. All conduction problems in bioelectricity are contained in this equation, although appropriate boundary conditions are needed to define a unique solution. Above all, Eq. (4) makes clear that to understand the electrical part of neuroprosthetics we must understand the properties of the tissue as a conductor and we must understand either the tissue or the electric stimulator as a current source. In the latter case, the response of the nerve cells or muscle cells to an extracellular field φ has to be understood.

The step from stimulation to movement, or from stimulation to perception is a wholly different area, involving several mechanical, chemical, physiological and psychological processes.

Moreover, the interface between the neuroprosthesis and the living organism is a complicated one, not only in terms of biocompatibility, but the conversion from electronic conduction of electric current (as in the electronic part of the prosthesis) to ionic conduction (in the body or organic parts of the prosthesis) or vice versa, is by no means simple (see chapter 2.2).

2. Properties of Various Excitable Cells

2.1. Excitable cells

The excitation of a cell is the result of a stimulus, either physiological or artificial, or it is the result of a cyclic process inside the cell itself. The latter occurs in cardiac or intestinal pacemaker cells or in certain nerve cells that are rhythmically active even if isolated. All excitable cells exhibit some commonalities that makes it possible to describe the process of excitation in a general way, but at the same time the number of differences is enormous, leading to a wealth of different cells all with their individual characteristics.

One of the most important commonalities is that all excitable cells have selective ion channels in their cell membrane that makes it possible for certain ions to cross the membrane easily whereas for other ions the membrane is an effective barrier. This property of ion selective permeability of the membrane is the basis of the resting potential. However, the membrane permeabilities are not constant. On the contrary, the selective ion channels can open and close, making it respectively possible and impossible for a certain ion species to cross the membrane. This property, together with the resting potential, forms the basis of the action potential. The ion channels thus play a crucial role in the excitation process.

2.2. Membrane

The cell membrane of excitable cells has the same basic structure as other cells in the body. Primarily, it consists of a double lipid layer with a total thickness of 5–8 nm. The lipids are phosphoglycerides consisting of heads of phosphoric acids and long glycerid tails (fatty acids). The heads are hydrophilic, whereas the hydrocarbon chains, forming the tails of the glycerids, have a low solubility in water and thus are hydrophobic. The solubility properties form the basis for the double layer structure of the membrane where the phosphoric acids are in contact with the extracellular fluid on one side and with the intracellular fluid on the other side of the membrane. The hydrocarbon tails of these two layers are pointing towards each other.

The membrane is covered on both sides by loosely bound proteins (peripheral proteins), which are water soluble. Non-soluble, so-called integral proteins are embedded in the lipid bilayer and form lipid protein complexes. Some of these proteins cross the membrane completely (transmembrane proteins), being in contact with both the extracellular and intracellular fluids. They are the main transport carriers for ions, but also for water-soluble substrates such as glucose.

At body temperature the lipid bilayer is in a fluid state, like oil, which makes it possible for the proteins to rotate and to move around in a 2D fashion, but not to topple over easily. In principle, the proteins that do not extend through the membrane but are exposed to either the extracellular or the intracellular fluids can move through the membrane from one side to the other (flip-flop), but this mode of transport is very energy inefficient.

Some of the proteins in the cell membrane of excitable cells are passively or actively involved in the maintenance of excitability as well as the excitation process itself. They can be divided into ion transporters and ion channels.

2.3. Ion channels

Voltage-controlled and ion-selective variability of the membrane permeability is the key to the action potential. To account for experimentally observed membrane behavior, Hodgkin and Huxley postulated ion channels to be the active components needed to create action potentials and they gave a statistical description of their opening and closing behavior, based on voltage clamp experiments. But until the development of patch-clamp techniques with which the quantile behavior of single channels was established, the real evidence for the existence of channels was meager. The physical structure of the channels is still an important research topic, although much has been exposed in recent years.

An ion channel is basically a protein consisting of chained helical domains, each of them crossing the membrane. A well studied bacterial K^+ channel consists of four subunits, each consisting of two membrane spanning helices. For other types of K^+ channels each subunit spans the membrane four, six, or seven times. The four subunits together form a water filled pore in the membrane, narrow enough to dehydrate a K^+ ion (strip it from its water mantle) and just wide enough to let the naked ion go through. Larger ions cannot pass the bottle neck, whereas smaller ions, such as Na^+ are too small to be effectively dehydrated by the channel, whereas they are too big in their hydrated state. The ion channel is thus selective for K^+ ions. In the same way, other types of channels can be selective for Na^+ ions, for Cl^- ions, for Ca^{++} ions, etc.[3,8]

An important property of some ion channels is that they can be open or closed. Many types of channels can bind signaling molecules (ligands) to open or close, other channels, especially in receptors, are activated by heat or by mechanical deformation. Another mode of action is electrical: a voltage across the membrane, which gives rise to the so-called voltage-gated ion channels. Although the molecular structure of the voltage-gating

part of the channels is far from clear yet, it is known that some of the membrane spanning (helical) domains contain amino acids that are electrically charged. A changing voltage across the membrane then rotates the helix, thereby deforming the protein and thus allowing the channel to open or to close.

The molecular structure of ion channels thus allows for the membrane permeability to be selective for specific ions and to be voltage controlled.

2.4. Ion transporters

Ion transporters are divided into pumps and exchangers, but in all cases the duty of the transporter is to move specific ions against their electrochemical gradients in order to maintain a non-equilibrium steady state, such as the resting membrane potential. The required energy is obtained either from the hydrolysis of ATP (adenosine tri-phosphate), as in the case of the important Na-K pump, or from the electrochemical gradients of ions or molecules that are co-transported, as is the case for the Na-Ca exchanger, where the energy released by the downhill transportation of Na^+ is used to transport Ca^{++} against the electrochemical gradient.

The Na-K pump is the best known transporter, but its mode of action is still hypothetical. It is an integral protein, which spans the membrane eleven times. Its function is to move Na^+ ions from inside to outside the cell, and to take K^+ ions in the opposite direction, thus maintaining the concentration gradients across the membrane. In each cycle three Na^+ ions are transported for only two K^+ ions. This means that the pump generates a (small) net current and therefore this kind of transporter is called *electrogenic*. Intracellularly, K^+ is released, whereas Na^+ is bound to a part of the protein. Intracellular phosphorylation of the protein, involving the hydrolysis of ATP, somehow (by deformation of the protein) moves the Na^+ ions through the protein, to be released extracellularly, after which extracellar K^+ is bound in order to be transported into the cell, mediated by intracellular dephosphorylation of the protein.

It is estimated that in the brain approximately 30% of the energy consumption is used to fuel the Na-K pump.

3. Action Potential

When measuring with micro electrodes between the inside and the outside of an excitable cell, i.e., across the cell membrane, a potential difference is observed. When the cell is inactive, or at rest, this potential difference is in the order of -50 to -100 mV, depending on the type of cell. The minus sign in this so-called resting potential appears because the intracellular potential is negative relative to the extracellular potential and convention prescribes that the transmembrane potential be defined as the intracellular potential minus the extracellular potential: $V_m = V_i - V_e$.

Now, when the cell is activated an action potential develops across the cell membrane. Figure 1 shows action potentials for three types of cells: nerve, skeletal muscle and cardiac muscle. Starting at the resting potential the transmembrane potential quickly rises to a slightly positive value after which the polarization of the membrane is restored: relatively quickly in the nerve fiber, where the whole process lasts less than a millisecond, about 1.5 ms in the skeletal muscle fiber, and 200–400 ms in the cardiac fiber. During the action potential and some time after the action potential the cell is not excitable by additional stimuli (absolute refractory period) and less excitable for a further short duration (relative refractory period), up to 2 ms for the nerve cell. The muscle cell in Fig. 1 shows a very slow final return to baseline and stays slightly depolarized for quite a long period (after-depolarization). Instead of after-depolarization, also after-hyperpolarization may occur, in particular in nerve cells.

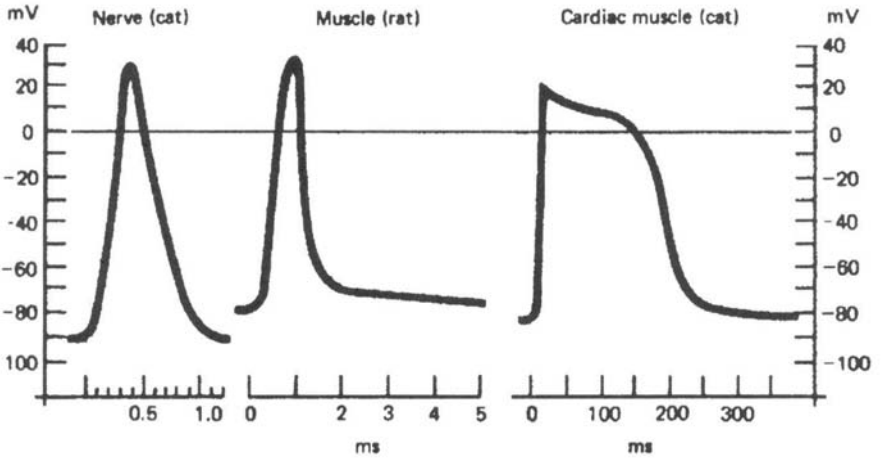

Fig. 1. Transmembrane action potentials of nerve, skeletal muscle, and cardiac muscle. Note the widely varying time scale. (From [10])

4. Resting Potential

The resting potential of an excitable cell is dependent on several factors, the most important of which are: 1) the presence of intracellular charged proteins that cannot pass the cell membrane, 2) the presence of (constant) concentrations of various ion species, 3) the ion selective permeability of the cell membrane, 4) the existence of an active ion pump. These factors will be analysed in the following.

For the purpose of describing the transmembrane resting potential, an excitable cell can roughly be described as a compartment containing charged molecules and ions immersed in water. The extracellular space can similarly be described as a compartment

with ions in water. Starting with this point of view we need to consider two driving fields that act on the ions in the compartments:

1. The concentration gradient (giving rise to *diffusion*), and
2. The electric field (giving rise to *migration*).

Both these driving fields give rise to fluxes of charge carriers and thus to electric currents. During rest, the net current has to be zero. It will turn out that this view is insufficient and that a third mechanism has to be included:

3. Active (using energy) transport of ions through the membrane.

First we will consider the effects of diffusion and migration on a single ion species k.

4.1. Diffusion

Fick's first law gives the relationship between the flux of an ion species k and its concentration gradient as follows:

$$\mathbf{j}_{diff,k} = -D_k \nabla C_k \tag{5}$$

where $\mathbf{j}_{diff,k}$ is the number of ions that pass a unit area per unit time (mole/m^{2}s), C_k is the concentration (mole/m^3) for ion species k, and D_k is Fick's constant (m^2/s) for this ion species in this solvent. This law describes that the movement or flux of ions from a high concentration to a low concentration is proportional to the concentration gradient with a proportionality constant D_k. Fick's constant depends on the size of the ion, including its mantle of water molecules, and the viscosity of the solvent (in this case water). The minus sign arises because the gradient is defined as pointing in the direction from a low value to a high value, whereas the actual flux is "downhill".

4.2. Migration

The flux of ions driven by an electric field is proportional to the electric field, the mobility of the ions, and the concentration of the ions:

$$\mathbf{j}_{migr,k} = -\mu_k \frac{z_k}{|z_k|} C_k \nabla \Phi \tag{6}$$

where $\mathbf{j}_{migr,k}$ is the flux, or the number of ions that pass a unit area per unit time (mole/m^{2}s), μ_k is the mobility (m^2/Vs), which is defined as the velocity achieved under a unit electric field, and $z_k$is the valence of the ion (the ratio $z_k/|z_k|$ is but the sign of the charge of the ion: $z_k/|z_k|=1$ for a cation and $z_k/|z_k|=-1$ for an anion). $\mathbf{E} = -\nabla\Phi$ is the electric

field (V/m), where Φ is the electric potential in Volts. Equation (6) implies that positive ions move from a higher potential to a lower potential (hence the minus sign) and negative ions move from a lower to a higher potential. The mobility depends on the viscosity of the solvent, on the size of the ion and its valence. It is therefore not surprising that Fick's constant and the mobility of an ion species are proportional to each other. The exact relationship was given by Einstein (1905) as:

$$D_k = \frac{RT}{|z_k|F}\mu_k \tag{7}$$

where R is the gas constant (8.3143 J/moleK), F is Faraday's constant (9.64867×10^4 C/mole), and T is the temperature in Kelvin (RT/F=26.7 mV at normal human body temperature (37 °C)).

4.3. Nernst-Planck equation

With Einstein's relation we can arrive at a form of Nernst-Planck equation by writing for the total flux for ion species k: $\mathbf{j}_k = \mathbf{j}_{diff,k} + \mathbf{j}_{migr,k}$, or

$$\mathbf{j}_k = -D_k\left(\nabla C_k + \frac{Fz_kC_k}{RT}\nabla\Phi\right) \tag{8}$$

From ion flux it is a small step to current density. With Fz_k being the charge carried per mole of ions with valence z_k, the current density is $\mathbf{J}_k=\mathbf{j}_kFz_k$.

When considering a thin membrane (5–8 nm), where thin means thin as compared with the membrane's lateral extent, the gradients within the membrane are safely assumed to have non-vanishing components in the transverse direction only (normal to the membrane). Using x for this transverse dimension, the gradients reduce to simple derivatives $\nabla C_k \rightarrow dC_k/dx$ and $\nabla\Phi \rightarrow d\Phi/dx$. The Nernst-Planck equation for the membrane can then be rewritten after some rearrangement as:

$$\frac{dC_k}{dx}(x) + z_k\frac{F}{RT}\frac{d\Phi}{dx}(x)C_k(x) = -\frac{1}{D_k}j_k(x), \quad \text{for } k=1,\ldots,N \tag{9}$$

where now $j_k(x)$ is the flux of ions species k in the x-direction as a function of x inside the membrane, and N is the number of ion species to be considered. Equations (9) are N ordinary differential equations, one for each of the ion species, coupled by the common potential function $\Phi(x)$.

Before giving the solution of this set of equations it is instructive to look at a special case where the membrane is permeable to a single ion species only.

4.4. Nernst equation

During rest the membrane has a relatively high permeability for potassium (K^+) ions as compared with other ions. Now consider a cell separated by the cell membrane from the extracellular space. In the two compartments the substance KA is dissolved, but in the intracellular space the concentration is higher than in the extracellular space. The membrane is permeable for cation K^+ but not for the large anion A^-, which could be a large protein. Note that for this initial condition both compartments are electrically neutral.

Since the membrane is permeable for K^+ and we assume that, initially, there is no potential difference between the compartments, there will be a net movement (by diffusion) of K^+ from the intracellular space to the extracellular space, resulting in an increasing potential difference across the membrane, such that the extracellular space becomes positive with respect to the intracellular space. This in turn results in a migration flux, from the extracellular space to the intracellular space. After some time the resulting migration of K^+ ions (from outside to inside) will balance the diffusion flux (from inside to outside). Under this equilibrium condition there is no further net ion flux: $j_{K^+}(x) = 0$, which means that the right hand side in Eq. (9) vanishes. With $C_k = [K^+]$ and $z_k = z_K$ Eq. (9) thus reduces to:

$$\frac{d\Phi}{dx} = -\frac{RT}{z_K F}\frac{1}{[K^+]}\frac{d[K^+]}{dx} \tag{10}$$

Integrating Eq. (10) across the membrane yields:

$$E_K = \Phi_i - \Phi_e = \frac{RT}{z_K F}\ln\frac{[K^+]_e}{[K^+]_i} \tag{11}$$

where $[K^+]_e$ is the extracellular K^+ concentration and $[K^+]_i$ the intracellular K^+ concentration. z_K is the valence for potassium, which is z_K=1.Because the extracellular concentration is lower than the intracellular concentration, E_K is negative.

Equation (11) is known as the Nernst equation and E_K is the Nernst potential. The Nernst equation has to be derived under equilibrium conditions during which the net flux or current of ions is zero[7].

4.5. Donnan equilibrium

Now suppose that we do not only have large anions and potassium, but also sodium ions Na^+ and chloride ions Cl^- in the solutions, and suppose that all ions are in equilibrium, i.e., that for each ion species the diffusion current cancels the migration current through the membrane. According to the Nernst equation for potassium, sodium and chloride, this means:

$$E_K = \frac{RT}{F} \ln\left(\frac{[K^+]_e}{[K^+]_i}\right)$$
$$E_{Na} = \frac{RT}{F} \ln\left(\frac{[Na^+]_e}{[Na^+]_i}\right)$$
$$E_{Cl} = \frac{RT}{F} \ln\left(\frac{[Cl^-]_i}{[Cl^-]_e}\right) \tag{12}$$

Because there can be only one potential difference across the membrane these three Nernst potentials must be equal: $E_K=E_{Na}=E_{Cl}$, leading to

$$\frac{[K^+]_e}{[K^+]_i} = \frac{[Na^+]_e}{[Na^+]_i} = \frac{[Cl^-]_i}{[Cl^-]_e} \tag{13}$$

This condition, arising when all permeable ions are in equilibrium, is known as the Donnan equilibrium (see, e.g., [5]).

4.6. Sodium-potassium pump

In the cat motoneuron the ratios of the extracellular and the intracellular concentrations for potassium, sodium and chloride were found to be approximately 0.037, 10, and 14, respectively. This is far from the Donnan equilibrium. In general, in excitable cells the Donnan equilibrium does not exist, i.e. the ions are not in equilibrium, not even during the resting condition of the cell.

The reason for this lack of equilibrium is that an active mechanism is disturbing the situation. The sodium-potassium pump (K-Na pump) pumps potassium into the cell and sodium out of the cell at a ratio of 2:3. Other pumps have also been identified, the most

important one, after the Na-K pump, being a Na-Ca pump in, for example, cardiac muscle.

4.7. Goldman's equation

Under the non-equilibrium condition the $j_k(x)$ in Eq. (9) are not zero, and the set of equations is not solvable unless certain assumptions are adopted. In general, the potential function Φ is implicitly given by Poisson's Equation (4) and depends directly on the charge distributions inside the membrane. A crude assumption, which implies that there are no fixed charges in the membrane (which is definitely wrong) and that the influence of external surface charges is negligible (which may not be true either), is that the electric field E_x=-dΦ/dx is constant across the membrane (Goldman's assumption). In this case the term dΦ/dx in Eq. (9) can be written as

$$\frac{d\Phi}{dx} = \frac{V_m}{h} \tag{14}$$

where V_m is the transmembrane potential and h is the membrane thickness.

With this assumption and "a little algebra" the membrane potential can be solved as

$$V_m = -\frac{RT}{F} \ln \frac{P_K[K^+]_e + P_{Na}[Na^+]_e + P_{Cl}[Cl^+]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^+]_e} \tag{15}$$

where P_K, P_{Na}, and P_{Cl} are the permeabilities for the potassium, sodium and chloride ions. An additional assumption used to derive Eq. (15) is that, where the individual ion fluxes were not zero, during the resting state we may assume that the total flux of all ions vanishes:

$$j_K + j_{Na} + j_{Cl} = 0 \tag{16}$$

Equation (15) is Goldman's equation, also called the Goldman-Hodgkin-Katz equation[2].

Despite the crudeness of the constant field assumption, Goldman's equation turns out to be a very good approximation of the resting potential given the various concentrations of the ions involved.

Because during rest the permeability for potassium is much greater than for sodium and chloride, the resting membrane potential is close to the Nernst potential for potassium.

During the development of an action potential net current is flowing into (depolarization) and out of (repolarization) the cell. This means that the Goldman

equation is not valid during the action potential, except at those points where the net current is (close to) zero. This occurs at the peak of the action potential and, for example, for cardiac muscle fibers, at the plateau phase of the action potential. At the peak of the action potential the permeability of sodium is very high compared with the other permeabilities, which means that at the peak the membrane potential tends towards the Nernst potential for sodium.

5. Subthreshold Phenomena

Subthreshold phenomena may be interesting in themselves, but the active behavior of a nerve or a muscle fiber is, seen from a functional point of view, the most important part of the physiological description of nerve and muscle. However, in the context of bioelectricity, and up to about 80% of the threshold, the neural membrane can be adequately described as a passive RC network. This implies that, even when studying electrical stimulation, where the goal is to activate neurons, study of the passive behavior can give a good insight in the behavior of the neurons and the effect of several stimulus parameters. Roughly speaking, the passive behavior of the cell explains 80% of the phenomena during electrical activation.

5.1. I-t curve (based on passive model of membrane patch)

The simplest model of a cell is a spherical passive membrane. If a stimulation electrode, carrying a current, I_s, with duration T, would be placed in the center of such a cell, together with a reference electrode far away from the cell, then the membrane voltage due to the current would be spherically symmetrical. Therefore, this whole cell membrane can be represented by a lumped R_mC_m network (Fig. 2).

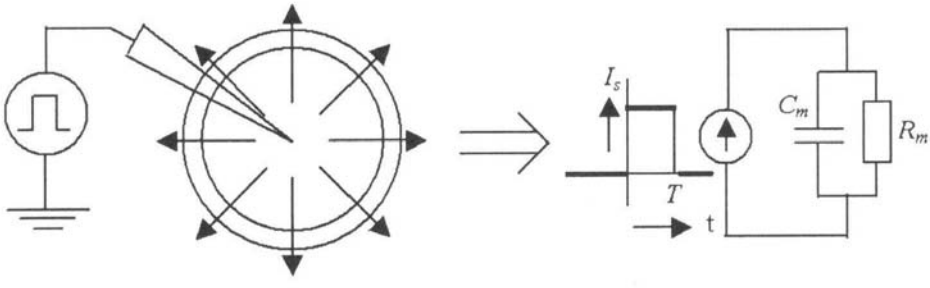

Fig. 2. Left: schematic view of a stimulation electrode in the center of a spherical cell; the arrows indicate the current flow through the cell membrane. Right: RC network as an electric circuit model of the cell.

The total current, I_s, through the membrane is then divided into a capacitive (displacement) current and a current through the membrane resistor (ionic):

$$I_s = I_c + I_i = C_m \frac{dV_m}{dt} + \frac{V_m}{R_m} \tag{17}$$

The membrane potential $V_m = V_m(t)$ can then be solved for the duration of the pulse ($0 \le t \le T$) as:

$$V_m(t) = I_s R_m \left(1 - e^{-t/\tau_m}\right), 0 \le t \le T \tag{18}$$

where τ_m is the membrane time constant: $\tau_m = R_m C_m$. This function is monotonically increasing with t. Thus, for a pulse with length T, the maximum voltage will be reached at the end of the pulse, $t=T$.

If we assume that the threshold for excitation is simply a constant voltage V_{th}, then the lowest current needed to reach V_{th} will be obtained when the duration of the current pulse is infinitely long.

The minimum current to reach threshold with the infinitely long pulse is called the *rheobase*, I_{rh}.

$$\lim_{t \to \infty} V_m(t) = V_{th} = \lim_{t \to \infty} \left(I_{rh} R_m \left(1 - e^{-t/\tau_m}\right)\right) = I_{rh} R_m \tag{19}$$

which gives

$$I_{rh} = \frac{V_{th}}{R_m} \tag{20}$$

Then, for pulse durations $T<\infty$ the threshold V_{th} will be reached at the end of the pulse ($t=T$) when the stimulus current is:

$$I_{s,th} = \frac{I_{rh}}{1 - e^{-T/\tau_m}} \tag{21}$$

The graph of the threshold current $I_{s,th}$ as a function of the pulse duration, T, is called the *strength-duration curve*, or in short, *I-t curve* (Fig. 3).

A useful parameter is the *chronaxy* of the cell. Chronaxy, T_{chr}, is defined as the minimum pulse duration needed to reach threshold if the current is twice the rheobase: $I_{s,th} = 2I_{rh}$. From Eq. (21) it follows directly that

$$T_{chr} = \tau_m \ln 2 \approx 0.69\tau_m \tag{22}$$

It is important to note that for a given membrane thickness and membrane material, R_m depends only on the size of the spherical cell: $R_m = c/r^2$, where c is a constant and r is the radius of the cell. According to Eq. (20) the rheobase will then increase with the square of the radius of the cell.

The chronaxy, however, depends on both R_m and C_m. And because $C_m = k.r^2$, with k a constant, we see that the membrane time constant, τ_m, is independent of the size of the cell. With Eq. (22) this means that the chronaxy is independent of the size of the cell. Chronaxy can, therefore, be used to characterize the membrane independent of the size of the cell. We will see later that this is true only for a spherical cell, but not for the general case of stimulation of nervous tissue (even though generally it is true that chronaxy is much less dependent on parameters such as cell size and electrode-tissue distance than rheobase).

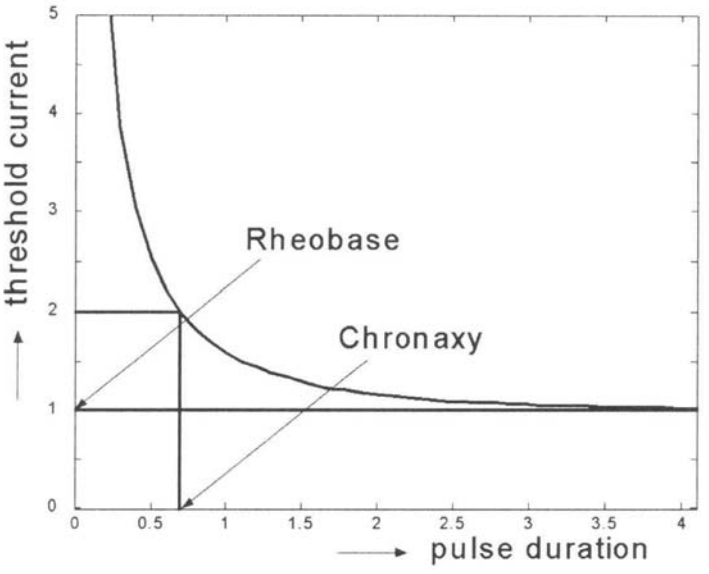

Fig. 3. Strength duration curve for the spherical cell of Fig. 2. Rheobase is defined as the minimum threshold for infinite pulse duration; chronaxy is the minimum pulse duration needed to excite the cell with a current that is twice the rheobase. The I_s-axis is normalized to the rheobase, and the membrane time constant τ_m=1.

The derivation above was made with an electrode in the center of the cell. Because the intracellular fluid has a much higher conductivity than the cell membrane, it is almost irrelevant what the exact location of the electrode inside the cell is. Even if the current

source is not an electrode but a synaptic transmission, which can be modeled as a small current injected through the membrane into the cell, the considerations as given above still hold: larger cells have a lower input impedance, which means that the cell needs higher currents (i.e., more synaptic inputs) than smaller cells to be excited.

Note however that a model is just a model. In reality larger cells tend to have higher membrane time constants and smaller cells have lower values for the membrane time constant, which indicates that the constants c and k are not really constant or that the non-spherical shape of the cell plays a role as well.

For practical stimulation purposes, not only current is of interest, but also the charge injection is important. The threshold charge, associated with the threshold current $I_{s,th}$ is given by

$$Q_{th} = T\, I_{s,th} \tag{23}$$

From Eqs. (21) and (23) it follows that

$$Q_{th}(T) = \frac{T \cdot I_{rh}}{1 - e^{-T/\tau_m}} \tag{24}$$

This function has a minimum for T=0: $Q_{th}(T=0)=I_{rh}/\tau_m$ which means that short pulses give the best conditions in terms of total injected charge (relatively low charge for short pulses with high currents as compared with the injected charge for longer pulses with lower currents).

The spherical cell as described above serves as a paradigm for other situations. Especially, the nomenclature rheobase, chronaxy, and I-t curve are derived from it.

5.2. Passive axon model (unmyelinated axon)

Whereas the resistance and capacitance of the membrane of a perfectly spherical passive cell in the case of current injection in the center of the cell can be lumped into a single RC network, current injection in an axon demands a more elaborate description of the membrane.

A very popular, highly stylized model of an axon is the description of the membrane as a cable network. Let us first consider the unmyelinated axon. The axon membrane is considered to be a perfect, long cylinder and the electric current and membrane potential are assumed to be perfectly cylindrically symmetrical, as for example, in the case of a point current injection at the axis of the cylinder (Fig. 4) or a long wire electrode at the axis of the axon.

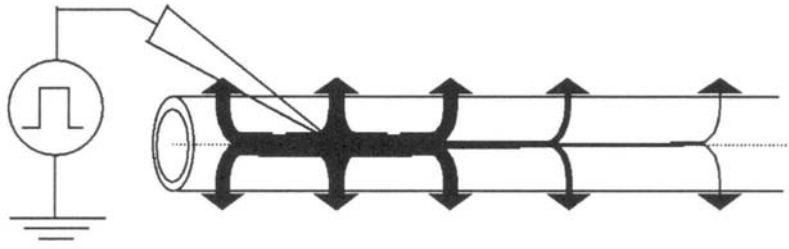

Fig. 4. Current injection in a cylindrical cell. The line thickness of the current flow schematically indicates the current density.

In this case the membrane can be collapsed into a one dimensional cable structure consisting of resistances and capacitances: a resistance times unit length, r_m (Ωm), and a capacitance per unit length, c_m (F/m). The core of the cylinder (the intracellular space) is modeled as a resistive one dimensional medium with a resistance per unit length (r_i, in Ω/m) as is the extracellular space (r_e, in Ω/m) (Fig. 5).

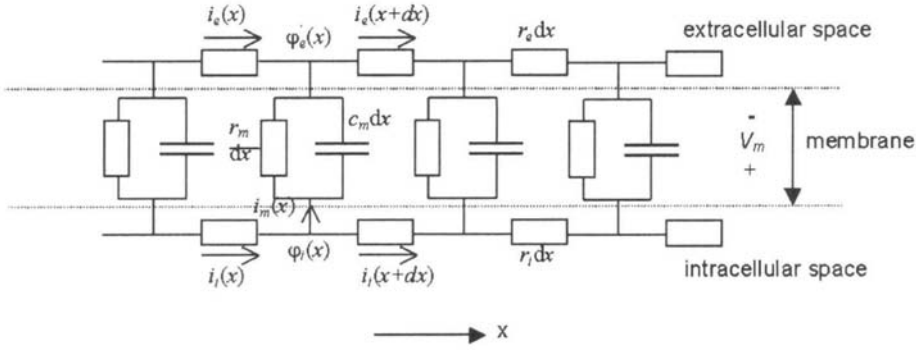

Fig. 5. RC cable model of the cylindrical cell.

The differential equation describing the membrane potential in this cable model is obtained as follows.

$$V_m(x,t) = \varphi_i(x,t) - \varphi_e(x,t) \tag{25}$$

$$\frac{\partial \varphi_i}{\partial x} = -r_i i_i \tag{26}$$

$$\frac{\partial \varphi_e}{\partial x} = -r_e i_e \tag{27}$$

$$i_m = -\frac{\partial i_i}{\partial x} = \frac{\partial i_e}{\partial x} = \frac{V_m}{r_m} + c_m \frac{\partial V_m}{\partial t} \tag{28}$$

Differentiating Eq. (25) twice with respect to x, and using Eqs. (26) and (27) and subsequently Eq. (28) yields

$$\frac{\partial^2 V_m}{\partial x^2} = \frac{\partial^2}{\partial x^2}(\varphi_i - \varphi_e) = \frac{\partial}{\partial x}(r_e i_e - r_i i_i) = \frac{r_e + r_i}{r_m} V_m + (r_e + r_i) c_m \frac{\partial V_m}{\partial t} \tag{29}$$

or

$$-\lambda^2 \frac{\partial^2 V_m}{\partial x^2} + \tau_m \frac{\partial V_m}{\partial t} + V_m = 0 \tag{30}$$

where $\lambda^2 = \dfrac{r_m}{r_e + r_i}$ is the square of the so-called length constant and $\tau_m = r_m c_m$ is the time constant of the membrane. The interpretation of the length constant can be highlighted by considering a steady state situation, in which the membrane potential does not change as a function of time. In that case the second term in Eq. (30) vanishes, leaving a simple second order ordinary differential equation. With boundary condition $V_m(0)=V_0$ and a vanishing potential at infinity, the solution then is

$$V_m(x) = V_0 \cdot e^{-|x|/\lambda} \tag{31}$$

In other words: the length constant is the distance from the site x=0 of a (steady state) disturbance in the membrane potential to the position where the influence of the disturbance is reduced to $e^{-1} = 0.37$ ($x=\pm\lambda$).

For an interpretation of the time constant a similar exercise can be made. Assume the membrane potential is independent of x. Then Eq. (30) reduces to

$$\tau_m \frac{\partial V_m}{\partial t} + V_m = 0 \tag{32}$$

which is of the same form as Eq. (17). Without sources, but with the initial condition $Vm(0)=V_0$, we have

$$V_m(t) = V_0\, e^{-t/\tau_m} \tag{33}$$

The time constant thus gives an indication of how quickly the membrane potential changes after a disturbance.

These two cases, the membrane potential either being independent of time or independent of the spatial coordinate, have relatively simple solutions. If we do not assume these simplifications, then the solution of Eq. (30) becomes quite complicated indeed. Suppose we have a sudden intracellular current injection in x=0 at t=0 with a current I_0: $I_s(x,t)=I_0\delta(x,t)$. In this case the solution of Eq. (30) can be obtained as

$$V_{m,I_s=\delta}(x,t) = r_m I_0 \sqrt{\frac{\tau_m/t}{4\pi\lambda^2}} \exp\left(-\frac{\tau_m}{t}\left(\left(\frac{t}{\tau_m}\right)^2 + \left(\frac{x}{2\lambda}\right)^2\right)\right) \tag{34}$$

which shows a rather complicated interaction between t and x.

Because Eq. (34) is the impulse response of the membrane, the membrane potential for an infinitely long fiber, due to a current injection with a different current waveform, $I_s=I_s(x,t)$, in time, t, and a distribution in space, x, can be obtained by a convolution of V_m as given in Eq. (34) with the current $I_s(x,t)$ with respect to both x and t:

$$V_m(x,t) = \int_{\xi=-\infty}^{\infty} \int_{\tau=0}^{\infty} I_s(\xi,\tau)\, V_{m,I_s=\delta}(x-\xi, t-\tau)\, d\tau d\xi \tag{35}$$

A detailed analysis of Eq. (34) or even more complex situations (Eq. (35)) is beyond the scope of this text, but can be found in [1].

The time constant, $\tau_m = r_m c_m$, is independent of axon diameter since r_m is reciprocal with diameter and c_m is proportional with diameter. The length constant, $\lambda^2=r_m/(r_i+r_e)$, depends on axon diameter because r_i is reciprocal with diameter squared, whereas r_e is negligible under normal circumstances, where the extracellular space is much larger than the intracellular space. Therefore, λ^2 is linear with fiber diameter: larger fibers have greater length constants. In other words a change in membrane potential in a thick fiber is spread over a longer distance than in a thin fiber. This is the key to understanding why thick unmyelinated fibers have a higher conduction velocity than thin unmyelinated fibers.

Typical length constants are in the order of 0.1–1 mm. Typical time constants are in the order of 1 ms.

5.3. *Myelinated axon*

The simplest way to model the (passive) myelinated axon is to consider each node of Ranvier as a discrete RC network, the axonal cylinder between adjacent nodes as a single resistor, and the extracellular space between adjacent nodes as a single resistor as well. Labelling the membrane potentials for node of Ranvier number n as $V_{m,n}(t)$, the membrane potential can be written as:

$$-\lambda^2\left(V_{m,n-1}-2V_{m,n}+V_{m,n+1}\right)+\tau_m\frac{\partial V_{m,n}}{\partial t}+V_{m,n}=0 \qquad (36)$$

similar to Eq. (30), but with a second order difference term with respect to the discrete space coordinate n, instead of the second order derivative with respect to the continuous space coordinate x.

$\tau_m=R_mC_m$, and $\lambda^2=R_m/(R_i+R_e)$, where R_m (Ω) is the nodal membrane resistance (inversely proportional to the axon diameter), C_m (F) is the nodal membrane capacitance (proportional to axon diameter, R_i is the intra-axonal resistance between adjacent nodes (inversely proportional to axon diameter), and R_e, the extracellular resistance is negligible because it represents a much larger space than R_i. The proportionalities mentioned are valid only under the assumptions that the length of the node of Ranvier (1–2 μm) is independent of fiber diameter, and that the distance between adjacent nodes of Ranvier (internodal distance) is proportional to fiber diameter (proportionality constant approximately 100). In that case it turns out that both τ_m and λ are independent of fiber diameter, which implies that Eq. (36), and thus the membrane potential, is independent of fiber diameter. However, experiments show that the conduction velocity is close to linear with fiber diameter and that excitation thresholds for electrical stimulation also have a strong dependence on fiber diameter. The key is that the distance between nodes n and $n+1$ is proportional to fiber diameter, which explains the linearity of conduction velocity with fiber diameter when assuming that the conduction velocity is constant in terms of number of nodes per second.

5.4. *Extracellular stimulation*

Within the framework of neuroprostheses we are particularly interested in the situation where the stimulating electrodes are not inside the cell, but at some distance outside the cell, and in the case of nerve stimulation we are often interested in axons rather than cell bodies. If the field is created by external electrodes at some distance from the cell, it is the larger cell, or the larger axon that has the lower threshold, opposite to the situation of intracellular current injection.

5.5. Spherical cells

Consider an extremely simplified spherical cell, with a membrane having a very high resistivity and a plasma having a very high conductivity. If such a cell is placed in a flat electric field E, for example, because of a stimulation electrode at some distance from the cell, then the cell membrane will become depolarized on one side of the cell and hyperpolarized at the other side, with membrane potential[1]:

$$V_m = -\frac{3}{2} E r \cos\theta \tag{37}$$

where r is the cell's radius and θ is the angle with the field axis as shown in Fig. 6.

The mathematics used to derive Eq. .(37) involves the Laplace equation in polar coordinates with suitable boundary conditions (Eq. (4) with vanishing right hand side) and is beyond the scope of this chapter. The importance of Eq. (37) is that it shows that the membrane potential is linear with the size of the cell. Or, equivalently, that the stimulus threshold is inversely proportional with the cell radius, which is the opposite of the result that we obtained for intracellular stimulation of a spherical cell. In summary:

Intracellular stimulation ⇒ stimulus threshold proportional to the square of the cell's radius.

Extracellular stimulation ⇒ stimulus threshold inversely proportional to the cell's radius.

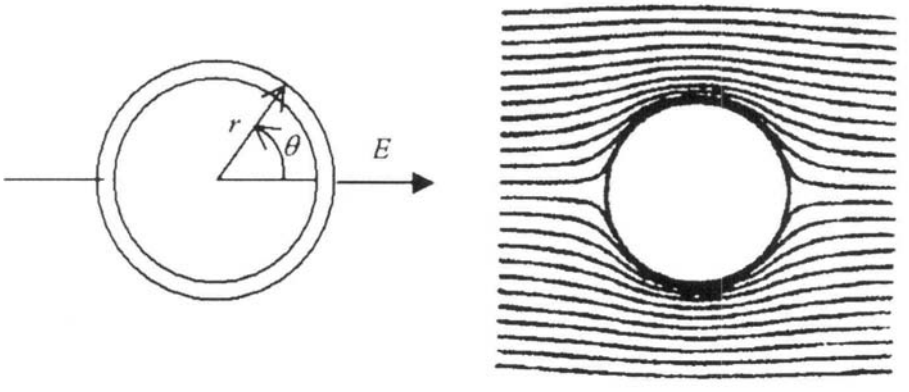

Fig. 6. Left: Spherical cell with the definition of the angle θ relative to the direction of the electric field E. Right: current flow around a spherical cell with very high membrane resistivity (from [1]).

5.6. *Nerve fibers*

For cylindrical cells, and for a homogeneous field perpendicular to the fiber, the same approach as for the spherical cell could be used, now based on Laplace's equation in cylindrical coordinates, resulting in[4]

$$V_m = -2Er\cos\theta \tag{38}$$

However, for a cylindrical cell the field along the cylinder can usually not be considered to be homogeneous, but a clear nonhomogeneous potential profile along the fiber will usually exist, together with a longitudinal component of the field. It turns out that the longitudinal component becomes the dominating factor in virtually all cases of interest, making Eq. (38) useless. A different approach has thus to be used.

Moreover, the models for the unmyelinated and myelinated nerve fibers as presented in earlier sections, are difficult to use for the case of electrical stimulation with an electrode at some distance from the fiber. But, for this situation a modification of the models was made by McNeal[6], who used the extracellular potential field V_e, due to electrical stimulation, as the driving source for the membrane potential (Fig. 7). Thus the external potential field at the nodes of Ranvier serve as ideal voltage sources in the cable model.

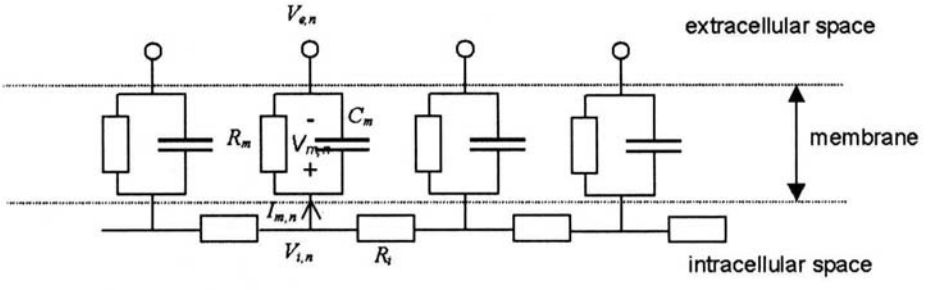

Fig. 7. McNeal's cable model of a myelinated fiber for extracellular stimulation[6].

For the passive model the governing equation for the membrane potential can be derived as follows.

$$V_{m,n} = V_{i,n} - V_{e,n} \tag{39}$$

where $V_{e,n}$ is the known, impressed, extracellular potenital at node n.

$$I_{m,n} = \frac{V_{i,n-1} - V_{i,n}}{R_i} - \frac{V_{i,n} - V_{i,n+1}}{R_i} = \frac{1}{R_i}\left(V_{i,n-1} - 2V_{i,n} + V_{i,n+1}\right) \tag{40}$$

$$I_{m,n} = \frac{1}{R_m} V_{m,n} + C_m \frac{dV_{m,n}}{dt} \tag{41}$$

Combining Eqs. (40) and (41) and subsequently substituting Eq. (39) finally gives:

$$-\lambda^2\left(V_{m,n-1} - 2V_{m,n} + V_{m,n+1}\right) + \tau_m \frac{\partial V_{m,n}}{\partial t} + V_{m,n} = -\lambda^2\left(V_{e,n-1} - 2V_{e,n} + V_{e,n+1}\right) \tag{42}$$

Note that the left hand side of Eq. (42) is identical to Eq. (38), whereas the right hand side now is the second order difference of the extracellular potentials at the nodes of Ranvier.

A similar derivation for the extracellular stimulation of unmyelinated fibers yields:

$$-\lambda^2 \frac{\partial^2 V_m}{\partial x^2} + \tau_m \frac{\partial V_m}{\partial t} + V_m = -\lambda^2 \frac{\partial^2 V_e}{\partial x^2} \tag{43}$$

which is similar to Eq. (30) but with the right hand side now being the second derivative of the extracellular potential along the fiber.

The right hand side in Eq. (43) was termed "activating function" by Rattay[9], and this activating function is very useful to see what initially happens to the membrane potential when a stimulus pulse is applied. Suppose that a fiber is stimulated with a rectangular stimulus pulse, and that initially the membrane potential $V_m(0)=0$. Then V_e will be constant for the duration of the stimulus pulse, and so will $\frac{\partial^2 V_m}{\partial x^2}$. Then Eq. (43) reduces to $\tau_m \left.\frac{\partial V_m}{\partial t}\right|_{t=0} = -\lambda^2 \frac{\partial^2 V_e}{\partial x^2}$ with a solution

$$V_m(t) \approx -\frac{\lambda^2}{\tau_m} \frac{\partial^2 V_e}{\partial x^2} \cdot t\,, \quad \text{for small values of } t \text{ (relative to } \tau_m). \tag{44}$$

Thus, a positive activating function will decrease the membrane potential (hyperpolarize the membrane) and a negative activating function will increase the membrane potential (depolarize the membrane). In other words: if activation of the fiber occurs, it will be there where the activating function is negative

For a long fiber in a large homogeneous medium and a monopolar point electrode in x=0 at some distance, h, from the fiber, the extracellular potential at the fiber is given by

$$V_e(x,t) = \frac{I_s(t)}{4\pi\sigma\sqrt{x^2+h^2}} \tag{45}$$

The second order derivative with respect to x then is

$$\frac{\partial^2 V_e(x,t)}{\partial x^2} = \frac{I_s(t)}{4\pi\sigma} \cdot \frac{2x^2 - h^2}{\left(x^2+h^2\right)^{5/2}} \tag{46}$$

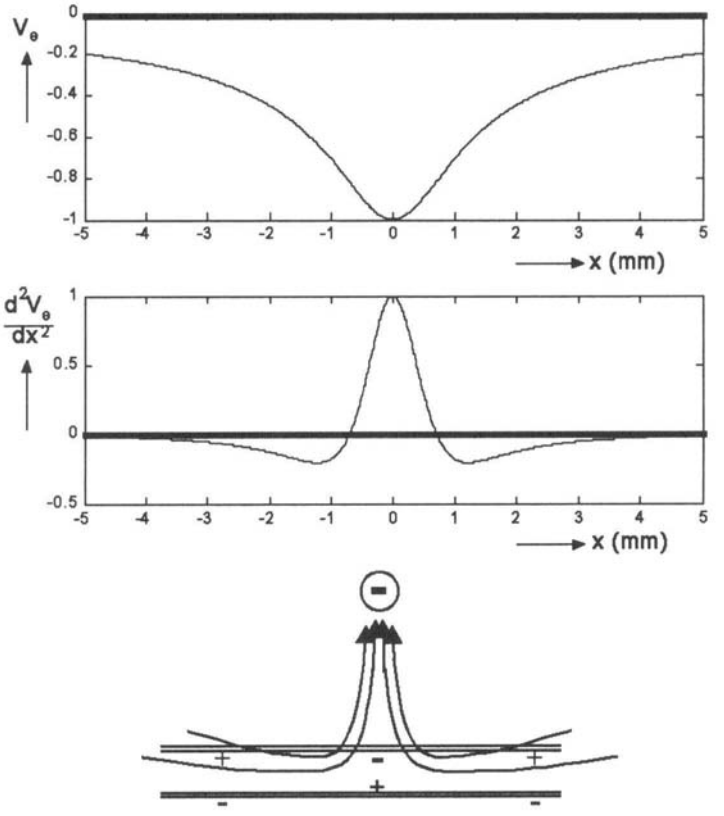

Fig. 8. Top: extracellular potential along the nerve fiber. Middle: 2nd order derivative of the extracellular potential. Bottom: schematic drawing of the current flow towards the negative electrode (cathode). The high density current leaves the fiber close to the cathode, strongly depolarizing the membrane, whereas the current is more diffuse where it enters the fiber.

Figure 8 shows the extracellular potential profile along the fiber and the activating function, apart from the constant $-\lambda^2$, for a monopolar cathode at 1 mm from the fiber (normalized to their peak values).

We see that the activating function (including $-\lambda^2$) is negative near the cathode (x=0) where the membrane depolarizes, corresponding to an outward current from the fiber towards the negative electrode. The relatively limited region of outward current is flanked by regions of more diffuse inward current, which is shown in the activating function as sidelobes with sidelobe amplitudes that are approximately 20% of the main lobe amplitude.

For an anodal electrode the signs of V_e and d^2V_e/dx^2 would be reversed, meaning that close to the electrode there would be a region of hyperpolarization and somewhat away from the electrode there would be regions of depolarization with a much lower amplitude. This is confirmed by experimental data that show that direct anodal stimulation requires higher currents than cathodal stimulation of nerves.

For longer pulses the transmembrane potential becomes a smeared version of the activating function, but even in the steady state case (infinitely long pulse) the activating function is a useful indicator for the transmembrane potential.

The analysis as described in this section can be extended to more complicated situations, such as nerve fibers with collateral branches and curving fibers. For examples see [11,12].

5.7. Rheobase and chronaxy for the case of external stimulation

Where for the round cell chronaxy was found to be related to the membrane time constant in a very straightforward way, Eq. (22), for the axon the matter is much more complicated (Table 1). One would not like to do an analysis similar to the one made for the spherical cell, on basis of, for example, Eqs. (34) and (35). Simulations show that for extracellular stimulation of the stylized axon as described above, chronaxy depends on, for example, electrode-fiber distance, in such a way that a point source close to the fiber gives the lowest value for the chronaxy, which monotonically increases by up to a factor two for increasing electrode-fiber distance.

Table 1. Chronaxy values for various tissues.

Tissue	Chronaxy (ms)
Skeletal muscle	0.1–1
Cardiac muscle	1–3
Smooth muscle	100
Myelinated nerve fiber	0.1–0.3

Of course, rheobase values are dependent on the size of the target cell, electrode-cell distance, electrode configuration, surrounding tissue, and cell orientation. The value of the rheobase can vary over several decades of magnitude for different situations. Chronaxy is much less variable, and, even though chronaxy is not completely independent of the stimulation conditions, it makes sense to give chronaxy values to classify various tissues.

Note the importance of chronaxy for the choice of pulse width for electrical stimulation: it doesn't make sense to try to stimulate smooth muscle with 100 μs pulses, whereas for myelinated nerve fibers this would be a perfectly sensible thing to do.

Other important electrical properties of nerve and muscle cells are shown in Table 2.

Table 2. Electrical properties of nerve and muscle cells.

membrane capacitance	0.05–0.2 F/m^2
membrane resistivity*	0.1–1 Ωm^2
intracellular resistivity*	0.5–2 Ωm

*: values for nerve are in the lower range, for muscle in the higher values

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