A Model of Electrostimulation Based on the Membrane Capacitance as Electromechanical Transducer for Pore Gating

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**Background:** Electrostimulation has gained enormous importance in modern medicine, for example, in implantable pacemakers and defibrillators, pain stimulators, and cochlear implants. Most electrostimulation macromodels use the electrical current as the primary parameter to describe the conventional strength-duration relationship of the output of a generator. These models normally assume that the stimulation pulse charges up the passive cell membrane capacitance, and then the increased (less-negative) transmembrane potential activates voltage-gated sodium channels. However, this model has mechanistic and accuracy limitations.

**Novel concept:** Our model assumes that the membrane capacitance is an electromechanical transducer and that the membrane is compressed by the endogenous electric field. The pressure is quadratically correlated with the transmembrane voltage. If the pressure is reduced by an exogenous field, the compression is released and, thus, opening the pores for Na\(^+\) influx initiates excitation.

**Results:** The exogenous electric field must always be equal to or greater than the rheobase field strength (rheobase condition). This concept yields a final result that the voltage-pulse-content produced by the exogenous field between the two ends of a cell is a linear function of the pulse duration at threshold level. Thus, the model yields mathematical formulations that can describe and explain the characteristic features of electrostimulation.

**Conclusions:** Our model of electrostimulation can describe and explain electrostimulation at cellular level. The model's predictions are consistent with published experimental studies. Practical applications in cardiology are discussed in the light of this model of electrostimulation. (PACE 2015; 38:831–845)

**electrostimulation, membrane capacitance, electromechanical transducer, rheobase, chronaxie, strength-duration relationship, rheobase condition, pore gating**

**Introduction**

Electrostimulation has gained enormous importance in modern medicine. Implantable pacemakers and defibrillators, pain stimulators, and cochlear implants are obvious. Though electrostimulation has been studied for centuries, the theoretical background is still not completely understood.

Most electrostimulation macromodels use the electrical current as the primary parameter to describe the conventional strength-duration relationship. These models normally assume that the stimulation pulse charges up the passive cell membrane capacitance and then the increased (less-negative) transmembrane voltage activates voltage-gated sodium channels.

Early in his career author Werner Irnich had the surprising finding that the threshold current was reduced considerably when the surface areas of pacemaker electrodes were reduced from 90 mm\(^2\) to 30 mm\(^2\). Existing current-based theory could not explain why the threshold was reduced when the diminished surface area increases the impedance to current flow. This experience led to four hypotheses:

1. The current is a threshold parameter that is dependent on several characteristics such as electrode area and conductivity.
2. The strength-duration relationship describes only the output characteristics of the stimulation generator. It does not express what happens at the cellular level.
3. The strength-duration relationship offers no indication of how pulse shapes other than rectangular should be treated.
The strength-duration relationship advises to stimulate with the lowest energy at “chronaxie,” but gives no other indication of how the stimulation system can be optimized.

The electric fields within the cell membrane are difficult to explain with the existing theory\(^1\): the excitable membrane is said to be around 8-nm thick and to have a resting voltage across the membrane of about 80 mV. Consequently, the electric field within the membrane should be approximately 10 MV/m. It is impressive that such high field strengths are maintained across the membrane insulation without destruction when some rubbers, porcelain, wax, and oils are broken down with similar fields. On the other hand, one can stimulate the heart with 100 V/m fields.\(^1\) How is it possible to influence 10 MV/m within the membrane with only 100 V/m (a difference of five orders of magnitude)?

The physics of electrostimulation can be described by a field theory and developed with the assumption that the electric field produced by electrodes is responsible for the stimulation effect.\(^2\) This can explain the phenomena associated with electrostimulation including cardiac pacing and defibrillation\(^1–5\) but the model also appears valid for other excitable cells.

**Ion Concentration Profile Normal to Excitable Cell Membranes**

We begin with the basic facts that the resting potential of an excitable membrane is characterized by a potential difference (voltage) between the extracellular space—as the “0” (zero) potential reference—and the intracellular space that equals \(-70\) mV to \(-100\) mV. This voltage is primarily determined by the diffusion of potassium (K\(^+\)) through the semipermeable membrane from inside with a concentration of 150 mmol to the outside with its concentration of 4.5 mmol (averaged over five textbooks). In the resting state, there is equilibrium between the diffusional force and the electric force built up by separation of the charges that tends to oppose the outward flow of K\(^+\).

There is an important mechanistic issue that is glossed over: Where are the diffused K\(^+\) ions localized in the extracellular space? Are they penetrating the extracellular space with a decreasing density, or are they all exclusively attached to the surface of the membrane like an ideal metal-film capacitor? Is there only a surface charge density built up by separation of the charges that tends to oppose the outward flow of K\(^+\)?

Potential difference is equal to transmembrane voltage, as was assumed above for calculation of the field strength within the membrane, or whether there is also a voltage drop along space charges in the extracellular and the intracellular space, reducing the transmembrane voltage compared to the bulk voltage. Figure 1, adopted from Hille\(^6\) describes the potential course of the concentration alternatives. Curve A assumes a space charge density with a voltage drop that reduces the true transmembrane voltage to only 9 mV. Curve B is valid if all diffused K\(^+\) ions are attached to the membrane surface. Defining the “effective” membrane thickness as the physical thickness divided by the membrane dielectric constant, Buysman and Koide\(^7\) calculated that, if the effective membrane thickness is <1 nm, the charge, voltage, and K\(^+\) concentration differ considerably from bulk measurements.

Hille\(^6\) used the definition of a parallel-plate capacitor to calculate the thickness of the insulating lipid bilayer of an excitable membrane:

\[
C = \frac{\varepsilon_r \varepsilon_0 A}{d}, \tag{1}
\]

where C is capacitance, \(\varepsilon_r\) is relative permittivity, \(\varepsilon_0\) is permittivity of free space, \(A\) is area of the plates, and \(d\) is thickness of the insulating layer.

By dividing Eq. (1) by the area \(A\), we obtain the capacitance per area, or the specific capacitance, \(C'\):
A MODEL OF ELECTROSTIMULATION

\[ C' = C_0 = \frac{\varepsilon_0}{\varepsilon_r} \]  

Equation (2) can be rewritten as a tailored quantity equation to determine the thickness, \( d \):

\[ \frac{d}{nm} = 0.885\varepsilon_r/(C'_{\mu F/cm^2}). \]  

where the thickness, \( d \) (in nanometer), is 0.885 times the relative permittivity, \( \varepsilon_r \), divided by the specific capacitance, in microfarad per square centimeter.

Inserting a specific capacitance, \( C' \), of 0.8 \( \mu F/cm^2 \) for a pure hydrophobic lipid bilayer structure, the thickness, \( d \), is calculated to be only 2.3 nm. Since the capacitance of an excitable membrane is nearly 1.0 \( \mu F/cm^2 \), there must be a portion of the membrane that consists of hydrophilic pores with a relative permittivity of \( H_2O \approx 70 \). If this portion is assumed to be 3% of the membrane surface area (this number will be justified later), the total capacitance is the sum of the capacitances of the pores and of the bilayer structures:

\[ 1 \mu F/cm^2 = 0.03C'_{\text{pores}} + 0.97 \times 0.8 \mu F/cm^2. \]  

(4a)

From Eq. (4a), a specific capacitance for pores filled with electrolyte with a relative permittivity of 70 can be deduced:

\[ C'_{\text{pores}} = \frac{1 \mu F/cm^2 - 0.97 \times 0.8 \mu F/cm^2}{0.03} = 7.5 \mu F/cm^2. \]  

(4b)

Inserting this value into Eq. (3) yields the thickness of the pores within the membrane, \( d_{\text{pores}} \), as approximately

\[ d_{\text{pores}} = (0.885 \times 70 / 7.5) \text{ nm} = 8.3 \text{ nm}. \]  

(5)

The thickness of 8.3 nm (slightly greater than the average membrane thickness of 7 nm) is in agreement with current assumptions in physiology texts. If the portion of hydrophilic pores would be assumed with 4%, the thickness would already increase to 10.7 nm. Though the thickness follows from a heuristic assumption, the result in Eq. (5) suggests that (near the pores) the Buysman and Koide calculation of the effective membrane thickness is always <1 nm. In the vicinity of the pores, there should be clouds of ions, predominantly K⁺, thereby creating a voltage drop between bulk and membrane, as described in Figure 1 by curve A.

Electrical Fields Acting on Membrane Permeability

The excitable membrane is charged to a transmembrane voltage that produces an electric field between the surface charges (negative inside, positive outside). This field causes the charges to attract each other. Assuming an averaged thickness, \( d \), of the membrane of 8 nm and a transmembrane voltage, \( U_{\text{mem}} \), of about 10 mV, the endogenous electric field, \( E \), is:

\[ E = \frac{U_{\text{mem}}}{d} = \frac{10 \text{ mV}}{8 \text{ nm}} = 1.25 \text{ MV/m} \]  

(6a)

directed from outside to inside. A specific capacitance of 7.5 \( \mu F/cm^2 \) (equal to 75 \( \text{mF/m}^2 \)) is assumed for pores (see Eq. (4b)), the charge density, \( Q' \), on the surface of the pore is, then

\[ Q' = C'U_{\text{mem}} = 75 \text{ mF/m}^2 \times 10 \text{ mV} = 750 \mu C/m^2. \]  

(6b)

The pressure, \( F' \), exerted by the electric field, \( E \), on the surface charge, \( Q' \), is given by the Coulomb force:

\[ F' = Q' \times E = (C'U_{\text{mem}}) \times \frac{U_{\text{mem}}}{d}. \]  

(7a)

\[ F' = \frac{C'U_{\text{mem}}^2}{d} = 750 \mu C/m^2 \times 1.25 \text{ MV/m}^2 = 938 \text{ (Ws/m)/m}^2. \]  

(7b)

Since 1 Ws = 1 Nm, it follows that

\[ F' = 938 \text{ N/m}^2 = 938 \text{ Pa}. \]  

(7c)

Note that 938 Pa corresponds to 7.1 mm Hg. According to Eq. (7b), the pressure \( F' \) depends quadratically on the membrane voltage, \( U_{\text{mem}} \). Diminishing this voltage to 71% means a pressure reduction to more than half its original value as \( d \) in Eq. (7b) will also increase. On the other hand, if the membrane voltage is not 10 mV, as assumed above, but 14 mV, the pressure is doubled to 14 mm Hg.

Any pressure applied to a material or a compound of materials results in some compression. Thus, the membrane capacitance can be regarded as electromechanical transducer that transforms a voltage into a pressure.

The current understanding of cardiac myocyte activation is based on the voltage gating of the sodium channels. The voltage-sensitive portion of the sodium channel has been studied in...
exquisite detail. An extensive review published by W.A. Catterall reveals the complexity of the structure and the difficulties of its exploration. However, this body of knowledge does not appear to recognize the considerable mechanical Coulomb forces on the channels nor consider the primary or complementary role that these might play.

A sodium channel is a specific protein embedded in the plasma membrane. The principal subunits of the voltage-gated sodium channel are polypeptide chains. They form homologous transmembrane domains that consist of six helical transmembrane segments (S1–S6) of which S4 is said to form a voltage-sensitive segment. It carries positively charged residues on the surface of a cylinder that should be attracted by the negative charges of the inner part of the cell in the resting position. In our opinion, it is not firmly established that the S4-segment is a structure that is affected by the exogenous electrical field. There are at least two reasons for scepticism:

1. Hysteresis: First, the S4-segment moves outward from its resting position along a spiral path, initiating a conformational change that opens the pore. Why should it change position if the transmembrane voltage is only reduced to 70% of the resting value (e.g., −90 mV to −68 mV)? If 100% of the transmembrane potential is able to attract the segment, 70% should be sufficient to hold it in position.

2. Uniqueness: It was found that neutralization of the key positively charged residues in S4 markedly reduces the voltage-dependence of gating but does not remove it. Hence, it is not clear that direct voltage-gating of S4 controls the sodium channel.

Our calculations suggest that the mechanical effects of the Coulomb electrostatic forces play a significant role in gating the sodium channel. Specifically:

1. The pressure as expressed with Eq. (7b) compresses the membrane and deforms the pore structure embedded in it. We do not hypothesize which domain or which segment of the pore structure is influenced by the pressure decrease that opens the pores. However, we note that the “sliding helix” or the “helical screw” models of gating make the idea of pressure gating plausible as they can be regarded as springs. If a segment is pressure sensitive, it is simultaneously voltage sensitive as both parameters are firmly linked together by Eq. (7b).

2. If the transmembrane voltage is reduced to approximately 70% of its original value (corresponding to a field of 0.88 MV/m), the compression pressure is diminished to less than 470 Pa (or 3.6 mm Hg), resulting in stretching of the membrane and alignment of the cross-sections of the deformed part of the pores, thereby opening the Na⁺ pores, so that hydrated sodium ions can enter the intracellular space.

Electrostimulation can, thus, be explained by an exogenous pressure that reduces the intramembranous pressure to <50% of its resting value by an exogenous electric field. This model of the membrane capacitance as electromechanical transducer is capable of explaining why a certain minimal field is required for the pores to be opened so that Na⁺ ions can pass. It also explains the closing of the pores by the efflux of K⁺ ions in phase 3 of the action potential, where the endogenous field again surpasses the threshold value of 0.88 MV/m.

The pressure acting on the membrane has to fulfill two conditions to establish stretching and alignment:

1. A certain amount of time is required for the pressure to stretch the membrane and for the Na⁺ ions to have the opportunity to enter the pores due to inertia of moving material. This pressure-time-product is known as “mechanical impulse” in physics and is given by integrating the force with respect to time.

2. The pressure must be higher than a minimal pressure, $F_{\text{min}}$, that keeps the pores closed for Na⁺ ions.

The mechanical impulse, $I$, as a function of pulse duration, $PD$, must be applied to the intracellular and extracellular charge layers just at the membrane surface. The exogenous Coulomb’s force, $F_{\text{ex}}$, must be greater than $F_{\text{min}}$ to contribute to the impulse needed to open the pores, or:

$$F_{\text{ex}} \geq F_{\text{min}}. \tag{8}$$

By integration over pulse duration, $PD$, we get:

$$I(PD) = \int_0^{PD} F_{\text{ex}} \, dt \geq \int_0^{PD} F_{\text{min}} \, dt = F_{\text{min}} \cdot PD + IC \tag{9}$$

[Correction added on 20 March 2015, after first online publication: Equation (9) contained formatting errors and has been corrected.] where $I(PD)$ is the mechanical impulse as a function of pulse duration $PD$, $F_{\text{ex}}$ is the exogenous force acting on the ions on both sides of the membrane, $F_{\text{min}}$ is a constant that characterizes the minimal force that must be surpassed to open the pores, and IC is the constant of integration.
IC, the constant of integration, has an important function; it determines where the straight line formed by $F'_{\text{min}} \times PD$ intersects with the ordinate in the I-PD-plane. IC must be $>0$, as it is physically not imaginable that a zero-impulse is effective if PD approaches zero. IC can, therefore, also be designated $I'_{\text{min}}$.

We formulated these ideas already earlier in a slightly different way.\textsuperscript{3,5}

Substituting the specific exogenous force, $F'_{\text{ex}}$, exerted by an exogenous electric field and inserting Eq. (7a) in (9), we get:

$$\int_{0}^{PD} E_{\text{ex}} dt \geq E_{\text{min}}PD + \frac{I'_{\text{min}}}{Q'}$$  \hspace{1cm} (10a)

with the additional condition that:

$$E_{\text{ex}} \geq E_{\text{min}}.$$  \hspace{1cm} (10b)

Dividing both sides of Eq. (10a) by PD, we get:

$$\frac{1}{PD} \int_{0}^{PD} E_{\text{ex}} dt \geq \frac{1}{PD} \left[ \frac{I'_{\text{min}}}{Q'} + E_{\text{min}}PD \right]$$

$$= E_{\text{min}} \left[ 1 + \frac{I'_{\text{min}}}{Q'E_{\text{min}}PD} \right]$$

$$= E_{\text{min}} \left[ 1 + \frac{I'_{\text{min}}}{F'_{\text{min}}PD} \right]$$  \hspace{1cm} (11)

[Correction added on 20 March 2015, after first online publication: Equation (11) contained formatting errors and has been corrected.]

Introducing the terms “rheobase” and “chronaxie” that are usually used in electrostimulation, Eq. (11) appears in the well-known form\textsuperscript{1,3}:

$$\frac{1}{PD} \int_{0}^{PD} E_{\text{ex}} dt \geq E_{\text{rheo}} \left[ 1 + \frac{t_{\text{chron}}}{PD} \right]$$  \hspace{1cm} (12a)

with the additional “rheobase condition”\textsuperscript{1,10}:

$$E_{\text{ex}} \geq E_{\text{rheo}}.$$  \hspace{1cm} (12b)

where $E_{\text{rheo}}$ is the rheobase field strength identical to the minimum field strength, $E_{\text{min}}$, that must be surpassed to open the pores, $t_{\text{chron}} = I'_{\text{min}}/F'_{\text{min}}$ is the chronaxie, a time parameter that depends on the minimum specific impulse divided by the minimum specific force required to open the pores, which is, thus, determined by the specimen to be investigated.

Equations (12a) and (12b) are interpreted as follows:

The mean value of the exogenous electric field,

$$E = \frac{1}{PD} \int_{0}^{PD} E_{\text{ex}} dt$$

applied to an excitable membrane during pulse duration, PD, must be equal to or larger than a minimum field strength, termed the “rheobase field strength,” multiplied by a hyperbolic expression of PD to reach or surpass the stimulation threshold. The exogenous electric field, $E_{\text{ex}}$, must always be equal to or greater than $E_{\text{rheo}}$.

Analogously to Eq. (12a), Eq. (9) can be rewritten as:

$$\int_{0}^{PD} E_{\text{ex}} dt \geq E_{\text{rheo}} t_{\text{chron}} \left( 1 + \frac{PD}{t_{\text{chron}}} \right)$$  \hspace{1cm} (13a)

with the “rheobase condition”:

$$E_{\text{ex}} \geq E_{\text{rheo}}.$$  \hspace{1cm} (13b)

Equations (13a) and (13b) are interpreted as follows:

The time integral over the exogenous electric field during pulse duration, PD, $\int_{0}^{PD} E_{\text{ex}} dt$, applied to an excitable membrane, must be equal to or larger than a linear function of PD to reach or surpass the stimulation threshold. This exogenous electric field, $E_{\text{ex}}$, must always be equal to or greater than $E_{\text{rheo}}$.

It is assumed that the pulse duration, PD, of the exogenous field is 5 ms or less, which is much shorter than the relaxation time of the $K^+$ ions so that the space charge density remains essentially undisturbed (short term or “faradic” stimulation). This assumption includes that there is only “make stimulation” and no “break stimulation.” The latter is possible if the duration of exogenous fields is extended to about 1 second, thereby altering the space charge density (long-term or “galvanic” stimulation).

Physics of Electrostimulation

Consider an excitable myocardial cell within a fiber of other equally shaped cells. They are assumed to be cylindrical with a length, $L$, of 100 μm and a diameter, $D$, of 20 μm. A homogeneous exogenous field, $E_{\text{ex}}$, is applied parallel to the cell axis (longitudinal field) as shown in Figure 2 from left to right. The exogenous field, $E_{\text{ex}}$, produces a homogenous potential field in the extracellular space. The potentials on the ends of the cell are $P_1$.
and $P_2$, respectively, with the potential difference being:

$$P_1 - P_2 = LE_{ex}. \quad (14)$$

The membrane—with its high specific resistance—insulates the intracellular from the extracellular space. The intracellular space is capacitively charged by electrical pulses with rise times of $<1 \mu s$ within microseconds\(^1\) to the mean value $P_{in}$:

$$P_{in} = \frac{P_1 + P_2}{2}. \quad (15)$$

The potential drop across the membrane at the cell ends, $U_1$ or $U_2$, is calculated as:

$$U_1 = P_1 - P_{in} = P_1 - \frac{P_1 + P_2}{2} = \frac{P_1 - P_2}{2} \quad (16)$$

and:

$$U_2 = P_2 - P_{in} = P_2 - \frac{P_1 + P_2}{2} = \frac{P_2 - P_1}{2} = -\frac{P_1 - P_2}{2}. \quad (17)$$

With the assumption that $P_1 > P_2$, the potential difference across the membrane with thickness $d = 7.5 \text{ nm}$ on the right side of the cell in Figure 2, expressed as field values, is:

$$U_2 = -\frac{P_1 - P_2}{2} = -\frac{LE_{ex}}{2} = -\frac{dE_{m2}}{2}. \quad (18)$$

where $E_{m2}$ is the electric field within the membrane on the right side pointing outward from the cell, thereby reducing the endogenous field (hydropolarization).

Equation (18) explains the difference in magnitude between the extracellular field, $E_{ex}$, and the field across the membrane, $E_m$:

$$\frac{E_m}{E_{ex}} = L \frac{E_{m2}}{2d} = 6.7 \times 10^3. \quad (19)$$

With the assumption that $d = 8 \text{ nm}$ for myocardial cells, the exogenous field is transformed to a much larger membrane field, which answers the question posed in the introduction: How is it possible to influence the 10 MV/m field of the membrane with only 100 V/m? The 100 V/m exogenous fields are transformed to a membrane field of 0.67 MV/m, that is, 58% of the field that we assumed to be realistic in the section “Electrical Fields Acting on Membrane Permeability.” If the polarity of the electric field $E_{ex}$ is changed, hypopolarization takes place on the left side of the cell in Figure 2 with an equal threshold.

If the exogenous electric field is not homogenous but decreases with the distance, $r$, from the electrode center, the influence on the membrane electric field, $E_{m1/2}$, can still be estimated. Assuming that an electrode is positioned on the lower right side of Figure 2, the potential $P_1$ is increased compared to $P_2$, thereby increasing the intracellular potential. The transmembrane field on the right side, $E_{m2}$, is increased, whereas that on the left side, $E_{m1}$, is decreased. The consequences are that: (1) the threshold is lowered and (2) stimulation is now polarity-dependent. Thalen

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**Figure 2.** Cell with length of $100 \mu m$ and diameter of $20 \mu m$ within a homogeneous electric field parallel to the cell axis (longitudinal field) and with potentials generated along and across the membrane of 7.5-nm thickness; the cathodic electrode is on the right side outside the figure.
and coworkers found that diastolic cathodic thresholds were below anodic thresholds by a factor of 2.6.\textsuperscript{12}

We have assumed above that the electric field is parallel to the cell axis. If this is not the case we must calculate the projection of the field component parallel to the cell axis (see Fig. 3):

\[ E_{\text{parallel}} = E_{\text{ex, longitudinal}} \cos \alpha, \]  

where \( \alpha \) is the angle between the cell axis and the field orientation.

If the stimulating field is perpendicular to the axis, the projection is zero. Nevertheless, stimulation is possible. Consider the potential difference across the cell diameter. Calculations with the aid of conformal mapping indicate that the difference in potential across the diameter, \( D \), of a circular cell with a field perpendicular to the cell axis (transversal field) is distorted due to the cylindrical and circular cross-section insulator within a conductive medium.\textsuperscript{4} The fact that a medium within a field distorts the original field is expressed by a “coefficient of distortion,” \( \delta \), that is defined according to formula: \( \delta = \frac{E_{\text{dist}}}{E_{\text{undist}}} \) (distorted vs. undistorted field). For a long cylindrical conductor the field strength \( E_{\text{dist}} \) is increased to \( 2 \times \) (twice) its undistorted value \( E_{\text{undist}} \) direct on the surface (\( \delta_{\text{cylinder}} = 2 \)). The transmembrane electric field in this case of a transversal field is analogous to Eq. (18):

\[ P_2 - P_1 + P_2 \frac{1}{2} = -\frac{P_1 - P_2}{2} = 2DE_{\text{ex}} \]  

and

\[ \frac{E_m}{E_{\text{ex}}} = \frac{D}{d} = 2670. \]  

From Eqs. (19) and (22), if \( E_m \) is equal in both cases, we can derive the following ratio:

\[ \frac{E_{\text{ex, transversal}}}{E_{\text{ex, longitudinal}}} = \frac{d}{D} \div \frac{2d}{L} = \frac{L}{2D} = 2.5 \]  

or the transversal field must be 2.5 times larger than the longitudinal field to reach the threshold with the dimensions of the myocardial cell as assumed above.

If the field is not exactly perpendicular, the projection of the transversal field on the perpendicular axis must be calculated (Fig. 3):

\[ E_{\text{perpendicular}} = E_{\text{ex, transversal}} \sin \alpha, \]  

where \( \alpha \) is the angle between the cell axis and the field orientation.

If the field direction is arbitrary with respect to angle \( \alpha \), the relative threshold is a function of angle \( \alpha \) and varies between 1 and 2.7 (see Fig. 4) for the assumed myocardial cell geometry. The angle \( \alpha_x \), where the intensity of the stimulation of the longitudinal field crosses that of the transversal field, is, with a coefficient of distortion \( \delta = 2 \), assumed:

\[ \frac{L}{2D} \sin \alpha_x = \frac{1}{\cos \alpha_x} \]  

or

\[ \alpha_x = \tan^{-1} \left( \frac{L}{2D} \right). \]

For the ratio \( (L/2D) = 2.5 \) (for a cell with a circular cross-section), it follows that

\[ \alpha_x = 68.2^\circ. \]

If the cross-section of the cell is other than circular, the coefficient of distortion, \( \delta \), must be determined, which may be cumbersome. The general expression for the crossing angle \( \alpha_x \) is, then:

\[ \alpha_x = \tan^{-1} \left( \frac{L}{2D} \right). \]  

What thresholds are to be expected if the direction of the field with respect to the cell structures to be captured is random with equal chance for every angle? This may be important for far-field stimulation such as tachycardia cardioversion, defibrillation, and medium voltage therapy.\textsuperscript{13} Assume a cell situated symmetrically within a sphere with the cell’s axis corresponding to the vertical Z-axis of the sphere. To calculate the probability of discrete positions on the surface of the sphere, we introduce horizontal circles (perpendicular to the vertical cell axis) on the surface with a distance of 3.1° to each other and calculate how many points could be distributed on
Figure 4. The threshold as a function of the angle $\alpha$ of the electric field with respect to the cell axis orientation (myocardial cell assumed).

Figure 5. Expected thresholds if the orientation between the electric field and the cell axis is chaotic with equal chance for every angle $\alpha$. The chance that the lowest threshold is reached is very low. The curve is called “success rate” as a function of energy or voltage in literature and is said to be sigmoidal. Our theoretical consideration yields, however, that the curve is by no means sigmoidal.

the circles with different radii in $3.1^\circ$ steps. The step of $3.1^\circ$ was chosen because the 22nd circle amounts to the value of just $68.2^\circ$, calculated with Eq. (25), and the 29th circle reached nearly $90^\circ$ ($29 \times 3.1^\circ = 89.9^\circ$), where the number of points is maximal. As the threshold for all points on a horizontal circle is equal, the voltage distribution is easily derived and Figure 5 shows the result. Such a curve might play an important role in the cardioversion of ventricular tachycardia as it expresses that in an anatomically random system (i.e., with an unknown location of the exact excitable gap) with the dimensions described in Figure 2 the relative threshold may vary over a range of $1.0–2.7$ with a median value of $1.96$ for $59^\circ$. The probability of the lowest threshold, $1$, is very low. Such a probability curve may play a role in the “probability of success” curves seen in the defibrillation literature due to the unpredictability of the wave fronts. The results are normally fitted to a presumed sigmoidal dose-response curve by a logistic regression analysis. Our theoretical consideration yields, however, that the curve is by no means sigmoidal and our results are consistent with the curve fitting analysis of Gliner et al.\textsuperscript{14}
Deduction of the “Fundamental Equations of Electrostimulation”

The results of section “Electrical Fields Acting on Membrane Permeability,” expressed with Eqs. (13a) and (13b), can be listed with those of section “Physics of Electrostimulation,” expressed with Eqs. (20), (24), and (26):

\[
\int_0^{PD} E_{\text{ex}} t \geq E_{\text{rheo} t_{\text{chron}}}, \quad (13a)
\]

\[
E_{\text{ex}} \geq E_{\text{rheo}}, \quad (13b)
\]

\[
E_{\text{parallel}} = E_{\text{ex}, \text{longitudinal}} \cos \alpha, \quad (20)
\]

\[
E_{\text{perpendicular}} = E_{\text{ex}, \text{transversal}} \sin \alpha, \quad (24)
\]

\[
\alpha_x = \tan^{-1} \left( \frac{L}{3D} \right), \quad (26)
\]

and considering the potential calculations in the section “Physics of Electrostimulation,” a combination of all findings can be formulated by introducing the operation of a scalar product of two vectors. The voltage, \(U_{\text{long}}\), along a cell at its surface is determined by the line integral:

\[
U_{\text{long}} = \int_0^L E_{\text{ex}} (r, t) ds, \quad (27)
\]

where \(E_{\text{ex}}\) and \(ds\) are vectors and \(E_{\text{ex}}(r, t)\) is a function of the distance \(r\) from the center of the field-producing electrode and of the duration \(t\), \(ds\) is an infinitesimal line element on the surface of the cell and parallel to the cell axis.

The time dependency of the electric field, as expressed on the right side of Eq. (13a), is formulated by analogy:

\[
\int_0^{PD} U_{\text{long}} dt = \int_0^{PD} \int_0^L E_{\text{ex}} (r, t) ds dt 
\geq U_{\text{rheo} t_{\text{chron}}} \left( 1 + \frac{PD}{t_{\text{chron}}} \right). \quad (28a)
\]

The additional “rheobase condition” according to Eq. (13b) is now expressed as the voltage over the cell length and with longitudinal field, \(U_{\text{long}}\):

\[
U_{\text{long}} \geq U_{\text{rheo}}. \quad (28b)
\]

We define the time integral \(\int_0^{PD} U_{\text{long}} dt\) on the left side of Eq. (28a) as the “voltage-pulse-content” (VPC). VPC and the rheobase condition are depicted in Figure 6. With this definition Eq. (28a) can be rewritten as:

\[
VPC = \int_0^{PD} L \int_0^L E_{\text{ex}} (r, t) ds dt 
\geq U_{\text{rheo} t_{\text{chron}}} \left( 1 + \frac{PD}{t_{\text{chron}}} \right). \quad (28a)
\]

The voltage-pulse-content, VPC, produced by the exogenous longitudinal electric field just at the surface of the cell between the two ends at threshold level is a linear function of the pulse duration, PD, related to the chronaxie \(t_{\text{chron}}\). Georges Weiss first described this form of a linear threshold function in 1901 with his charge-based model.

If both sides of Eq. (28a) are divided by PD, the result appears as the well-known hyperbola introduced by Lapicque in 1909:

\[
\frac{VPC}{PD} = \frac{U_{L}}{PD} = \frac{1}{PD} \int_0^{PD} \int_0^L E_{\text{ex}} (r, t) ds dt 
\geq U_{\text{rheo}} \left( 1 + \frac{t_{\text{chron}}}{PD} \right). \quad (29)
\]

where \(\frac{VPC}{PD} = \frac{1}{PD} \int_0^{PD} U_{\text{long}} dt\) is the mean value of the voltage, \(U_{L}\), during pulse duration PD.

Equations (27) through (29) characterize the threshold for longitudinal fields. If the angle \(\alpha\) is too large, the transversal field dominates stimulation of the cell at angle \(\alpha_x\). Recall that for a cell with circular cross-section, the line integral over the exogenous transversal field perpendicular to the cell in Eq. (21), yields the voltage \(U_{\text{trans}} = 2DE_{\text{ex}}\). If the field is not perpendicular to the cell axis but there is an angle \(\alpha\) between them, the voltage across the diameter is:

\[
U_{\text{trans}} = 2DE_{\text{ex}} \sin \alpha \quad (30)
\]

with a coefficient of distortion \(\delta = 2\) for a cell with a circular cross-section in a transversal electric field. If the profile is other than circular, the coefficient of distortion, \(\delta\), must be determined. The general expression of voltage \(U_{\text{trans}}\) for an arbitrary cell profile with coefficient of distortion, \(\delta\), is then:

\[
U_{\text{trans}} = \delta DE_{\text{ex}} \sin \alpha \quad (31)
\]
yielding the threshold equation:

$$VPC = \int_0^{PD} U_{\text{trans}} \, dt = \int_0^{PD} \delta E_{\text{ex}} \sin \alpha \, dt$$
\[
\geq U_{\text{rheo}} t_{\text{chron}} \left( 1 + \frac{PD}{t_{\text{chron}}} \right).
\] (32)

The angle \(\alpha_{x}\) where stimulation of the longitudinal field is taken over by the transversal field can be calculated with Eq. (26).

Both Eqs. (24) and (32) can be combined as a set of Eqs. (FE1) to (FE4) that constitute the stimulation model with four “fundamental equations of electrostimulation”:

$$VPC = \int_0^{PD} U_{\text{long}} \, dt = \int_0^{PD} E_{\text{ex}} (r, t) \, ds \, dt$$
\[
\geq U_{\text{rheo}} t_{\text{chron}} \left( 1 + \frac{PD}{t_{\text{chron}}} \right) \quad \text{(FE1)}
\] for \(\alpha \leq \alpha_{x}\).

$$VPC = \int_0^{PD} U_{\text{trans}} \, dt = \int_0^{PD} \delta E_{\text{ex}} \sin \alpha \, dt$$
\[
\geq U_{\text{rheo}} t_{\text{chron}} \left( 1 + \frac{PD}{t_{\text{chron}}} \right) \quad \text{(FE2)}
\] for \(\alpha \geq \alpha_{x}\).

$$\alpha_{x} = \tan^{-1} \left( \frac{L}{2D} \right).$$ \hspace{1cm} (FE3)

Additionally, the rheobase condition expressed as the cell voltage for longitudinal and transversal fields applies:

$$U_{\text{long}} \geq U_{\text{rheo, long}} \quad \text{and} \quad U_{\text{trans}} \geq U_{\text{rheo, trans}}. \quad \text{(FE4)}$$

where \(VPC\) is the voltage-pulse-content, \(U_{\text{long}}\) is the voltage between cell ends in a longitudinal field, \(U_{\text{trans}}\) is the voltage across the diameter in a transversal field, \(PD\) is the pulse duration, \(L\) is the cell length, \(E_{\text{ex}}\) is the exogenous electric field, \(ds\) is a line element at the surface of the cell and parallel to the cell axis, \(r\) is the distance to electrode center, \(D\) is the cell diameter, \(\delta\) is the coefficient of distortion in transversal electric fields, \(\alpha\) is the angle between cell axis and electric field, \(\alpha_{x}\) is the angle where stimulation intensity of the longitudinal field is equal to that of the transversal field, \(U_{\text{rheo}}\) is the rheobase voltage between cell ends, and \(t_{\text{chron}}\) is the chronaxie.

**Discussion**

We present a simple model based on the membrane capacitance as electromechanical transducer and assuming that an exogenous electric field is capable of relieving the compressing force on the membrane caused by diffusion of \(\text{K}^{+}\) ions through the semipermeable membrane from inside to outside. We note that Rattay has also presented a
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Figure 7. Effective pulse duration of a sinusoidal pulse with voltages ≥ rheobase. The mean value is equally effective as a rectangular pulse of the same pulse duration. This was proven experimentally (with permission).

We believe that this theory can be extended to nonrectangular waveforms. The fundamental equation (FE4) demands that the “effective pulse duration” ends where the rheobase is reached. This condition (FE4) is suited to determine the “effective pulse duration” of a nonrectangular pulse shape. The procedure is explained with Figure 7 for a haversine pulse. It is assumed that the rheobase is known either by measuring the stimulation threshold with rectangular pulses or by calculation. Then, all parts of the haversine pulse below rheobase do not contribute to the stimulation effect. This reduces the pulse duration to its “effective pulse duration” depending on how steep the ascending and descending flanks are. The averaging procedure for calculating the value of the amplitude according to Eq. (29) must be based on the effective pulse duration. The result, then, is equal to the threshold of a rectangular pulse of equal duration. Taking simply the period of the haversine would reduce the averaged amplitude thereby suggesting that sinusoidal pulses are more efficient than rectangular pulses. The occasionally reported results of ascending-ramp waveforms being more efficient than rectangular or exponential pulses may equally be explained by the use of a nonphysiologic pulse-duration definition instead of the above described “effective pulse duration.” Thus, the rheobase condition (FE4) is suited to unmask alleged superiority of certain pulse shapes as they are sometimes asserted in literature. Indeed, Wongsarnpigoon et al. recently showed that the rectangular waveform is the most energy-efficient stimulation waveform when compared to other waveforms including the ascending ramp. The model even explains the reported advantages seen between ascending and descending ramp waveforms in defibrillation thresholds. The ascending as well the descending pulse possesses a portion with amplitudes below rheobase that do not contribute to the defibrillation effect but may be proarrhythmic. If it is before the defibrillating pulse, this effect is extinguished by the effective defibrillation pulse, if it is behind, it may refibrillate as was shown for excessively long exponential pulses.

The superiority of biphasic over monophasic waveforms cannot be explained by the fundamental equations. Whereas biphasic pulses will increase thresholds in electrostimulation, they are decreased in defibrillation. However, the second phase appears to have the function of a repair pulse that avoids refibrillation by reducing overstimulation in the near-field region of the electrode and by removing residual charge in uncaptured cells. Support for these fundamental equations is found in experimental results:

1. Stimulation with time-varying magnetic pulses with different waveforms (rectangular and sinusoidal), which occurs just at perception threshold during magnetic resonance imaging procedures, form a straight line for both waveforms with a high correlation coefficient of $r = 0.995$, if the rheobase condition is applied to the sinusoidal fields.

2. The exponentially decaying first phases of biphasic defibrillation pulses truncated at or above the rheobase form a linear threshold curve with a high correlation coefficient of $r = 0.987$ as predicted by theory. Figure 8 demonstrates these results obtained from defibrillation threshold (DFT) measurements in 10 swine.

3. Defibrillation pulses whose trailing edge voltages fall below rheobase need higher energies than shorter optimally truncated pulses.

4. Note that the traditional RC membrane charging only approximates the hyperbolic strength-duration curve and the linear charge versus duration line. A corollary of this fact
is that linear charge versus duration relationship suggested by Weiss—and found in numerous studies—cannot be precisely explained by the membrane charging model.

Assuming the correctness of the theory, the “fundamental equations of electrostimulation” (Eqs. (FE1) to (FE4)) can be used to describe and to explain certain characteristic properties of electrostimulation including defibrillation:

1. The voltage-pulse-content, VPC, is a linear function of the pulse duration, PD. This linear relationship was already discovered and formulated in terms of charge for a specific stimulation arrangement by George Weiss in 1901. In analogy to “voltage-pulse-content,” one can also introduce the “current-pulse-content” that is identical to “charge.” Such a handy term as “charge” does not exist for the term “voltage-pulse-content.”

2. If Eqs. (FE1) or FE2 are divided by the pulse duration, PD, the result is a hyperbola, as already deduced with Eq. (29), with the important finding that it is the mean value of the voltage, $\bar{U}$, during the pulse duration, PD, that is responsible for stimulation. The shape of the pulse is, thus, irrelevant as long as the cell voltage $U_{\text{long}}$ or $U_{\text{trans}}$ is above rheobase.

3. The characteristic parameters of Eqs. (FE1) or (FE2) are introduced by the terms “rheobase” and “chronaxie” introduced by Lapicque more than 100 years ago. The fundamental equations are, thus, consistent with well-established results.

4. The threshold behavior is formulated for a cell at the cell surface. The link between the cell and the field-producing generator is the exogenous electric field, $E_{\text{ex}}$, that must be determined for each test design. Large planar electrodes in the experimental set-up can generate homogenous fields. But quasi-homogeneity can also be assumed if the cells to be stimulated are far away from the electrode. For instance, if the myocardial cells are 5 cm apart from the defibrillating electrodes and the cell is 100 μm in length, the relative electric fields between the proximal and distal ends of the cell is of the order of $(1–50 \text{ mm}/50.1 \text{ mm})^2 = 0.996$, that is, both ends possess virtually equal field strengths. In these cases the stimulation threshold should be independent of the polarity of the field and hence the DFT should be independent. This may explain why polarity has such a minor effect (15–18%) on the DFT compared to small-electrode contact pacing (up to 1,000%). We found no polarity effect on the DFT in animals when the anode and cathode were of the same material. Some of the human DFT polarity effects may be partially explained by dissimilar electrode metals (platinum iridium against titanium) and with differing impedances.

5. Nonhomogeneous fields must be estimated using the distance from the electrode. For instance, knowing the radius of a ball-shaped electrode and the distance of the excitible tissue from the surface of the electrode, the field and, consequently, the voltage of the generator can be determined. In this case, the stimulation threshold is polarity dependent and lower for a cathode next to the cell, a well-established result in the pacemaker application.

6. The scalar product of the exogenous field, $E_{\text{ex}}$, with the line element, ds, guarantees that the
orientation of the field with respect to the cell axis is taken into account. For defibrillation, the field generator (defibrillator) leads are spatially fixed but the critical myocardial cells, to be influenced by the far-field, change randomly in time and in localization (circus movement), with consequent threshold variations as indicated by Figure 5. For myocardial cells, the relative DFT varies between 1 and 2.7 with a median value (50% chance) of about 2. In contrast to defibrillation, stimulation of the heart with electrodes pressed against the myocardial wall will always find cells with longitudinal orientation and, thus, will have the lowest possible threshold.

7. The rheobase condition in Eq. (FE4) is an important part of our novel model, especially for nonrectangular pulses. The question of where the voltage amplitude crosses the rheobase can be transformed into the question of what pulse duration is reached at rheobase if the chronaxie is known. For large-area electrodes, myocardial stimulation chronaxie can be assumed to be around 2 ms. With decreasing electrode area, however, the chronaxie decreases.

8. The rheobase condition has an important influence on exponentially decreasing defibrillation pulses. They must be truncated if the trailing edge reaches rheobase. This was first reported by Schuder et al. We found an increase of 43.3% of the stored energy at threshold level if the pulse duration was 70% longer as compared to an optimal one. This implies that increasing the pulse duration (to deliver more energy) actually interferes with efficient defibrillation. Optimal pulse durations can be calculated in dependency of the time constant of the pulse. A table of optimal pulse durations under the assumption of a chronaxie of 2 ms can be found in the above-mentioned paper. Some studies have reported larger chronaxie values, but they considered the rheobase as a lower limit for the average current and not for the instantaneous current (or field).

9. The rheobase field for myocardial cells is of the order of 60 V/m. This finding is a strong argument against the hypothesis that the voltage across the actual membrane is assumed to be 75 mV in curve B in Figure 1. If the myocardial cell length of 100 μm is assumed, the rheobase voltage, $V_{rheo,long}$ in Eq. (FE1) is approximately 60 V/m × 100 μm = 6 mV. Together with a chronaxie of 2 ms, the voltage-pulse-content, VPC, in Eq. (FE1) can be approximated for longitudinal, homogenous fields by:

$$VPC = 6 \text{ mV} \times 2 \text{ ms} \times (1 + \text{PD}/2 \text{ ms}) 12 \mu \text{Vs} \times (1 + \text{PD}/2 \text{ ms}).$$  (33)

The rheobase-chronaxie product is the smallest possible value for VPC with very short PDs. As pulse durations of stimulating pulses are, or should be, close to chronaxie, VPC in Eq. (33) would yield a value of 24 μVs. In the context of cardiac pacing, the VPC of a pacemaker is between 250 μVs and 750 μVs; that is, the VPC of the output of a pacemaker is 10 to 30 times higher than the VPC at cellular level.

10. The timing parameters of the cell voltage—namely pulse duration (PD), chronaxie ($t_{chron}$), and rate—must be identical to those of the field-producing generator. If the electro-tissue interface of the stimulating system is ohmic (nonpolarizable electrodes), one can generally assume that the voltage of a stimulating generator is proportional to the cell voltage in Eqs. (FE1) and (FE2). Thus, the VPC of the generator’s output must obey a rule that is principally identical to that for the cell voltage in Eqs. (FE1) and (FE2): the strength-duration relationship of VPC is a linear function of PD related to chronaxie. According to Eq. (29), the threshold voltage expressed as mean voltage, $U$, during pulse duration is a hyperbola of the form of Eq. (4):

$$U_{threshold} = U_{rheo} \left(1 + \frac{t_{chronaxie}}{PD}\right).$$  (34)

11. Nowadays, implantable defibrillators are implicitly designed (or at least marketed) according to Nernst’s 100-year-old misconception that energy is responsible for stimulation. Today, physicians only ask for generators with high stored energy (40 J or even 47 J), while typically ignoring other parameters. It is generally not appreciated that the size of the output capacitance and the pulse duration play an important role in defibrillation efficiency. We have previously reported that the stored energy at threshold level is lowest if the time constant $RC$ of the system (lead resistance, $R$, times capacitance, $C$) is $0.8 \times t_{chronaxie}$. Increasing the capacitance to gain higher stored energy is counterproductive as the efficiency of the defibrillator is thereby decreasing. An optimal capacitance of a defibrillator with respect to energy efficiency would be about 40 μF, with 40 Ω load assumed. Obviously, there are limits due to practical electronic component voltage ratings that lead to some compromise here. Truncating the “tail” of a capacitive discharge monophasic shock has been long known to decrease the threshold.27 This is often explained—without evidence—that the tail tends to refibrillate. Our model explains the benefit of truncation as reflecting the need for the rheobase condition to be observed.
Limitations

Certain abstractions or simplifications are assumed in our derivation of the fundamental equations to find solutions with relatively simple mathematics. Some of them are only applicable to electrostimulation:

1. The shape of the cell is a cylinder with a circular cross-section and planar perpendicular ends.
2. The membrane thickness is assumed to be constant, though it is pressure- and thereby voltage-dependent.
3. The pores are assumed to be perpendicular to the cell membrane.
4. The membrane possesses a very high resistivity so that only capacitive coupling takes place with pulses possessing rise-times smaller than 1 μs. This has also the consequence that the inner volume of a cell is an equipotential volume.
5. The neighboring cells are assumed to be without reciprocal interaction.
6. The electric field applied longitudinally is assumed to be homogenous in the extracellular space because of its resistivity and its consistent charge carrier concentration.

All of these assumptions suggest that the modelling can only imperfectly address the most simplistic aspects of electrostimulation. Inaccuracies due to these simplifications and abstractions may have a quantitative influence but do not negate the qualitative principle of a stimulation threshold formulation at cellular level.

Conclusions

A model of electrostimulation was developed, yielding mathematical formulations of fundamental equations that can describe and explain the characteristic features of electrostimulation at a cellular level. Although it was derived mainly for stimulation and defibrillation of myocardial cells, it can also be applied to stimulation of other excitable tissue if the corresponding dimensions and shapes of the cells are considered. Correct stimulation or defibrillation thresholds are only obtained if the voltage-pulse-content, VPC, or the mean voltage, U, during the pulse is measured or calculated and if the voltage of the pulse does not fall below the rheobase at any time. The strength-duration curves are, then, either linear or hyperbolic if and only if these conditions are observed. The resulting linear function of the voltage-pulse-content, VPC, is simpler than the exponential solution with a membrane time constant and better explains the existing data.

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