Simulating Hodgkin-Huxley-like Excitation using Comsol Multiphysics

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Abstract:
Most simulations concerning electrical activation of human muscles are based on the modeling approach of Hodgkin and Huxley. Calculating the response of a muscle or nerve fiber membrane to an applied electrical field, needs to consider two different potential distributions. On the one hand the "macroscopic", extracellular potential distribution in the tissue surrounding the fiber, and on the other hand the "microscopic", intracellular potential distribution inside the fiber. Knowledge of the potential distributions in both domains is necessary for calculating the development and the propagation of action potentials along the fiber. Consequently, the simulation is based on 2 coupled models: a simplified 1D line model of a muscle fiber and a 2D model of the surrounding thigh.

Keywords: Hodgkin-Huxley, Coupling, Comsol Multiphysics

1. Introduction

The most important mathematical models for simulating nerve or muscle fiber excitation are based on the theory of Hodgkin and Huxley [1]. Their theory on excitation and spike propagation in nerve fibers has inspired many other modelers, always trying to adopt the current research in neurosciences [2, 3]. Hodgkin and Huxley were awarded the Nobel Prize in physiology and medicine in 1963.

Functional Electrical Stimulation is a rehabilitation technique for e.g. paraplegic patients. With pulsed stimulating currents between two electrodes placed on the human thigh muscles are activated and thereby trained. Paralysis can be divided in two major groups. Spastic paralysis on the one hand and denervation on the other hand. In therapy denervation, where the nerves in the affected regions are lost, is the more difficult part. Due to lack of nerve tissue the muscle fibers can only be activated directly by applying very long impulses, with high amplitudes [4]. To get a better understanding for the distribution of the electrical field and the activation of target muscle fibers computer simulations were made [5-9]. Most of such simulations for functional electrical stimulation were based on compartment models, where first the electrical field and then as a result of the field, the neural or the muscle fiber response was calculated using a Hodgkin Huxley like model.

Knowledge of the potential distribution in both domains (extra- and intracellular) is necessary for calculating the development and the propagation of action potentials along the fiber. In the past it was difficult to simulate this task within one model because of the complexity of the problem and the major difference in the scales of both geometries.

Therefore the area of interest was divided in two domains, the surrounding tissue and the muscle fiber, and each domain was calculated on its own in dependency on each other. The two domains are connected by their boundary conditions. Such bidomain models have been mainly used for analyzing excitation effects and spike propagation in the human heart [10, 11].

This work should be a "proof" of concept, if it is possible to use Comsol Multiphysics for calculating Hodgkin-Huxley like excitation in the human thigh by creating a bidomain model defined on a (simplified) geometry of the thigh including muscle fibers and if the results are comparable to results of other simulations or "real-life" data.

2. Governing Equations

2.1 Physiological basics

Muscle and nerve fibers are surrounded by a semipermeable cellular membrane that allows an

exchange of certain ions between inside and outside of the cell. Nerve and muscle fiber cells usually have increased negative charge inside the fibers compared to the outside. This leads to a negative resting membrane potential. In human muscle cells this resting potential is around -80 to -90mV [12]. The potential difference between the inside and the outside of the fiber is one of the causes for the ability of evoking action potentials.

Action potentials are the main part of the transmission process in a nerve or muscle fiber. They are all-or-none impulses with an amplitude of about 100mV. Action potentials are generated in the membrane of nerve and muscle fibers and are initiated when the transmembrane voltage reaches a certain threshold. Once excited the action potential propagates along the fiber with constant velocity and constant amplitude. The main part is carried mainly by voltage gated ion channels in the membrane of the fiber. Whenever the fiber region is excited by a sufficient depolarization voltage, gates in sodium channels open. The influx leads to a further shift in the membrane potential. This depolarization is counteracted by activation of the voltage sensitive potassium channels and the inactivation of the sodium channels. Due to the efflux of potassium ions the membrane potential is drawn back to the resting membrane potential (Fig. 1).

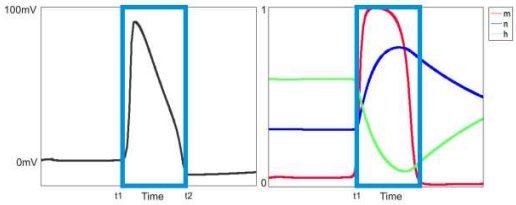

Fig. 1. Illustration of action potential (left) and the associated gating variables *m*, *n* and *h* (right). The gating variables m and h affect the flux of the sodium ions. The gating variable n is responsible for the opening of the potassium channels.

The currents involved in a locally active action potential are strong enough to excite neighboring regions of the membrane resulting in spike propagation along the axon.

2.2 Hodgkin Huxley Model

Hodgkin and Huxley conducted a series of experiments, examining the time and voltage dependence of the sodium and potassium conductances of the membrane of a giant squid axon [1]. The results of the experiments were fitted into a set of four differential equations: one nonlinear (Equ. 1) and three linear (Equ. 2).

$$C_m \frac{\partial V}{\partial t} = \frac{r}{2\rho}\frac{\partial^2 V}{\partial x^2} + g_{NA} m^3 h (V_{Na} - V) + g_K n^4 (V_K - V) + g_L (V_L - V)$$

C_m ... *capacitance of membrane*
r ... *radius of axon*
ρ ... *resistance of intracellular space*
g_{Na}, g_K, g_L, ... *conductance of Natrium, Potassium and Leakage*

Equ. 1: Hodgkin Huxley - PDE

$$\frac{dw}{dt} = \alpha_w (1 - w) - \beta_w w \quad (w \text{ is } m, n \text{ or } h)$$

$$\alpha_m = \frac{2.5 - 0.1V}{e^{2.5-0.1V} - 1} \quad \beta_m = 4e^{-\frac{V}{18}}$$

$$\alpha_n = \frac{1 - 0.1V}{10(e^{1-0.1V} - 1)} \quad \beta_n = 0.125e^{-\frac{V}{80}}$$

$$\alpha_h = 0.07e^{-\frac{V}{20}} \quad \beta_h = \frac{1}{e^{3-0.1V} + 1}$$

Equ. 2: ODEs for a local Hodgkin-Huxley model

Equ. 1 describes the behavior of the membrane potential in dependency on the voltage gated sodium and potassium channels. In equ. 2 the further differential equations for calculating the parameters m, n and h are described. These parameters represent the probabilities that the voltage-dependent sodium (m, h) and potassium channels (n) are open (Fig. 1).

The resting state conditions are defined by

$$V(0) = 0, m(0) = 0.05,$$
$$n(0) = 0.32, h(0) = 0.6$$

2.3 Potential distribution

The differential equation for calculating the time dependent potential distribution of the tissue surrounding the fiber is based on a simplification of the Maxwell's Equations by using the continuity and the constitutive relations (Equ. 3)

$$-\nabla(\sigma \nabla V_e) - \nabla\left(\varepsilon \nabla \frac{\partial V_e}{\partial t}\right) = 0$$

Equ. 3: PDE to calculate extracellular potential

In Comsol Multiphysics 3.4 the PDE in coefficient form was taken (Equ. 4)

$$e_a \frac{\partial^2 V}{\partial t^2} + d_a \frac{\partial V}{\partial t} + \nabla(-c\nabla V - \alpha V + \gamma) + aV + \beta \nabla V = f$$

Equ. 4: Comsol, PDE, Coefficient Form

For implementing Equ. 4 in Equ. 5 it is necessary to extend Equ. 5 with 1st-order time derivatives of V using the following terms [13]: The first component of the γ-Term has to be extended by Equ. 5.

$$\gamma = \begin{cases} -d_c * Vxt \\ -d_c * Vyt \end{cases}$$

Equ. 5: Addition of the γ-Term of Eq. 4. (*Vxt* stands for the derivation of *V* on time *t* and place *x*).

By using Equ. 4, Equ. 5 and Equ. 6 and by replacing the variables with appropriate expressions it is possible to represent Equ. 3 in Comsol Multiphysics.

In the model the intracellular potential (potential in the fiber) and the extracellular potential are connected by Equ. 6.

$$V = V_i - V_e - V_{Rest}$$

Equ. 6: V_i – intracellular potential (potential in fiber); V_e – extracellular potential (potential in surrounding tissue); V_{Rest} – transmembrane resting voltage of the fiber.

3. Methods

3.1 1D model of muscle fiber

For evaluating the simulation, comparing the results with "real-life" data and analyzing the effects of different stimulation or fiber parameters a 1D line model of a fiber is implemented using the HH equations (Equ. 1, 2). The implementation is done in the PDE mode (PDE, general form) with 4 dependent variables (V, m, n, h). The extracellular potential of the tissue surrounding the fiber is calculated with Equ. 3 and the model is solved with a direct solver, UMFPACK.

3.2 2D model of human thigh

A 2D domain representing a simplified human thigh is created. On the domain one point electrode or two surface electrodes are placed, simulated by Dirichlet-boundary conditions (Fig. 2).

In the thigh a 1D fiber model is embedded. This is done by adding a line, representing the fiber in the 2D domain. Then a 1D geometry is added to the model and the 1D model of the fiber is implemented in this geometry. The two models are coupled with extrusion coupling variables. This procedure is repeated up to three fibers.

The coupling is done in both directions. On the one hand from the 2D potential distribution to the line model of the fiber and on the other hand back from the 1D model of the fiber to the 2D model of the thigh. Therefore the direct feedback of both models on each other can be simulated.

At last a rectangular stimulation impulse is applied to the electrodes and the potential distributions in the domain and the fiber(s) are calculated using the direct solver UMFPACK.

3.3 Coupling

On the inner boundary, representing a muscle fiber, the two models are coupled (Equ. 6) using Extrusion coupling variables and Neumann boundary conditions (Fig. 2).

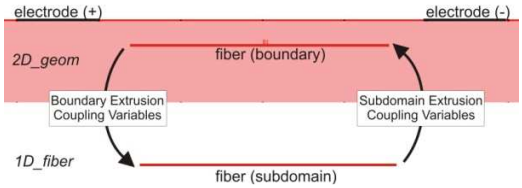

Fig. 2. Schematic illustration of the coupling of the two geometries (*2D_geom* and *1D_fiber*). The coupling is mainly done by the use of Extrusion Coupling Variables, Equ. 6 and the Neumann boundary condition on the inner boundary.

More precisely: The model consists of two different geometries. On the one hand there is a 2D geometry (*2D_geom*) representing the human thigh. In this geometry the potential distribution is calculated (Equ. 3). The second geometry is a 1D geometry (*1D_fiber*), representing a muscle fiber with the implemented Hodgkin-Huxley model (Equ. 1, 2). In *2D_geom* there is a line embedded. This line is coupled by "Boundary Extrusion Coupling Variables" to the subdomain of 1D_fiber. The coupled value is inserted as V_e in Equ. 6 and therefore in the Hodgkin-Huxley model.

The resulting *V* of the solved Hodgkin-Huxley line model is coupled by "Subdomain Extrusion Coupling Variables" to the line, the inner boundary representing the fiber, of *2D_geom*. The influence of the potential travelling along the fiber is simulated by Neumann boundary conditions on the inner boundary in *2D_geom*.

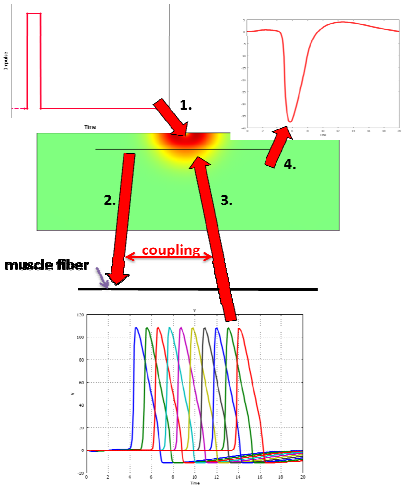

Fig. 3. "Coupling": A rectangular square pulse (1) applied to a 2D domain induces a potential distribution in this domain. Every muscle fiber placed in the domain is exposed to the potential (2). The muscle fiber's response is an action potential (3). The transmembrane currents of the propagating action potential disturbs the external potential and can be displayed as an EMG like graph (4).

3.4 Influence of coupling

To examine the effects of the "recoupling" of the fiber potential on the potential distribution in the 2D geometry and therefore the other fibers, the model is extended with the following assumptions: 3 fibers (*Fiber1*, *Fiber2* and *Fiber3*) are embedded in the 2D geometry representing a simplified human thigh (Fig. 4.). They are embedded, but not all of them are coupled as described before.

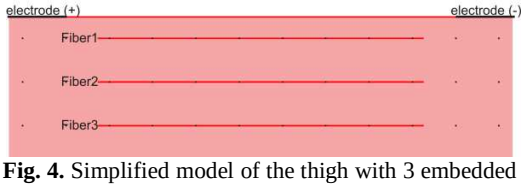

Fig. 4. Simplified model of the thigh with 3 embedded fibers and 2 surface electrodes.

A definition of "*active*" and "*inactive*" fibers is made. Active fibers are coupled as described before. Inactive fibers are not coupled and therefore have no influence on the surrounding potential distribution.

3.5 Influence of electrodes position

Based on the 2D thigh model a more complex model for evaluating the influence of electrode positions on potential distribution and the excitation of fibers is designed (Fig 5).

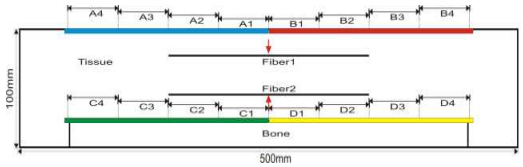

Fig. 5. Simplified model of the thigh with 2 embedded fibers and different electrode positions.

The model is defined with different active electrodes on the surface and also on the bone, e.g. A2 and B2 or B2 and D2 (Fig. 5). The size of the model electrodes is typical for patients with denervation. In the thigh 2 fibers were embedded and the coupled interaction of electrode and membrane currents are studied. Using Dirichlet boundary conditions two electrodes were set active. On one electrode a positive square pulse (+) and on another electrode a negative square pulse (-) was set.

4. Experimental Results

4.1 1D model of muscle fiber

The 1D model of the fiber was first used to evaluate the model and to study the influences of stimulation and fiber parameters.

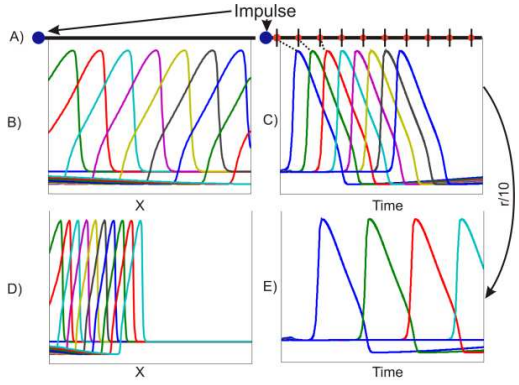

Fig. 6. A) 1D fiber: injected stimulation impulse at the left end of the fiber; B & D) propagation of the action potentials along the fiber (every line represents a snapshot of transmembrane voltage along the fiber); C & E) action potentials as functions of the time at different places. Between B&C and D&E the radius is reduced to a tenth, demonstrating essentially reduced spike propagation.

Figure 6 shows the excitation process of a fiber as response to a single current pulse injected at the left fiber ending with two different radii.

4.2 2D model

Now two 1D fiber models are embedded in a 2D area in order to calculate the potential distribution in the 2D domain and the resulting intracellular potential when stimulated with an external current source. The most interesting part is the "recoupling" of the intracellular potential to the surrounding tissue area.

First this simulation was done using a model with a single point source (Fig. 7).

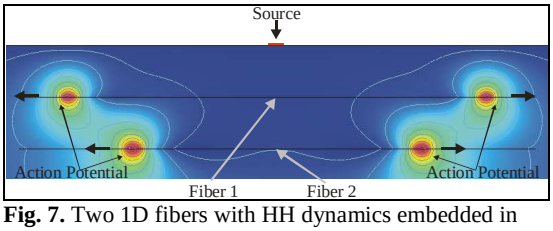

Fig. 7. Two 1D fibers with HH dynamics embedded in a 2D area. At the source a rectangular 5ms pulse is applied. The resulting action potentials and their moving direction are shown at time = 20ms. Note the delayed response of the more distant fiber which needs more time to reach the threshold.

The results of the activation of the two coupled 1D line models are comparable to the 1D model (Fig. 6). The model with two surface electrodes instead of the point source delivers nearly the same results, which are also conform to other simulations and literature [9]. Due to the coupling a disturbance of the potential distribution of the 2D geometry can be observed (Fig. 7).

4.3 Influence of coupling

For analysis of the effects of the coupling several fibers are set active or inactive and the potential distribution is calculated. The effect on the other fibers is observed. The change of the potential distribution in the 2D geometry (Fig. 7) caused by the membrane currents of the coupled ("active") fibers has an influence on the embedded and coupled fibers. The influence is not very big, but in some cases it can be observed that the influence is big enough to activate a fiber, that without coupling was not activated (Fig. 9).

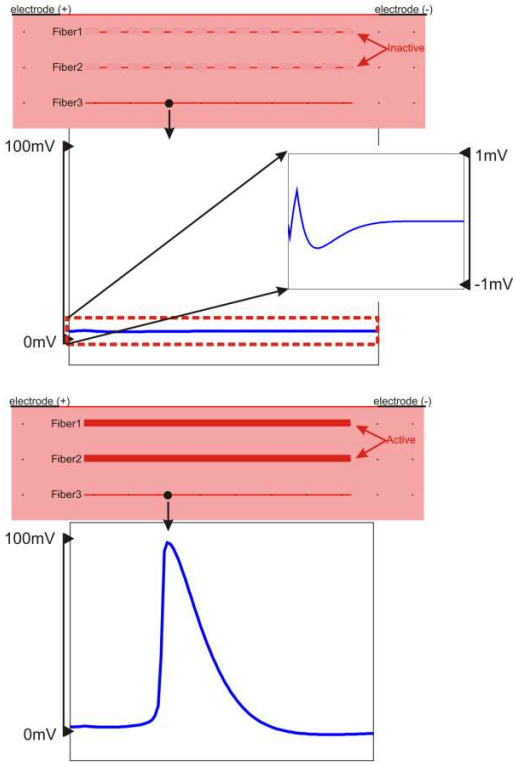

Fig. 8. 2D geometry with three embedded fibers: To simulate the influence of the coupling two fibers are "Inactive" (not coupled) or "Active" (coupled). The membrane potential of the third fiber is examined. It can be seen that the coupling of the two fibers has an influence on the third fiber and the generation of action potentials.

4.4 Influence of electrodes position

To gain comparable results of the influence of different electrode configurations on the fibers the following assumption was made: The time (ms) from starting the impulse till an action potential is initiated reflects the excitability of the fiber. If there is no action potential, no time is entered in the diagram (Fig. 10).

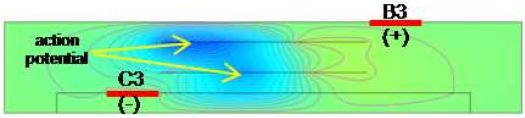

Fig. 9. Potential distribution in the thigh 3 ms after the stimulation impulse, caused by propagating action potentials in fiber 1 and 2. Electrodes C3 (-) and B3 (+) are active.

As a first result of this simulation it can be seen that the initiation of the action potential takes place under the cathode, if the fiber is situated beneath the electrodes (Fig. 9). If the fiber is not underneath the electrode the excitation arises at the fiber ending located closer to the cathode.

Furthermore it can be observed, that the relative position of the electrodes compared to the fibers / regions is very important for the excitation process. The greater the distance between the electrodes the deeper is the activated area. On the other side the closer the electrodes are placed together the faster is the activation of the fibers close to the electrodes (Fig. 10).

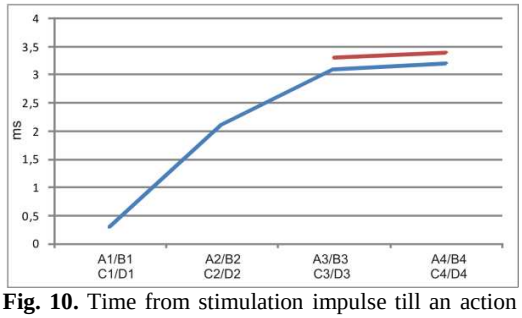

Fig. 10. Time from stimulation impulse till an action potential is initiated. The diagram shows the excitation time of different electrode positions at the surface and implanted electrodes (Fig. 5). The red line represents the fiber placed closer to the electrodes. The blue line is representing the more distant fiber.

5. Discussion

The results gained from the simulation of the 1D fiber model are in accordance with Hodgkin-Huxley standard compartment model (lumped circuit model) evaluations based on space discretization with constant Δx [2]. The influence of the radius of the fiber on the propagation of action potentials is a well known fact [14].

When embedding and coupling the 1D line model of the muscle fiber in a 2D geometry the results of the HH-like excitation are comparable to the simple 1D model (Fig. 6) and therefore to literature.

The influence of the intracellular potential of the fiber model to the extracellular potential can be seen on the one hand by action potentials propagating along the fiber. On the other hand, it causes changes of the potentials in the surrounding area caused by the changed membrane currents. These changes are quite similar to a simplified EMG signal (Fig. 11).

The results gained from the simulations with different electrode positions show, that the relative position of the electrode compared to the muscle fiber is very important for the excitation process.

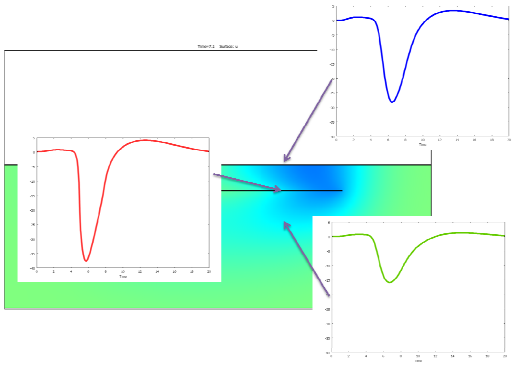

Fig. 11. Simplified thigh with embedded muscle fiber: After a stimulation impulse an action potential is traveling along the fiber. This causes changes in the surrounding area. These changes are quite similar to EMG recordings.

Investigating the influence of activated fibers on their surrounding area it can be seen that the "disturbance" of the potential distribution, caused by an activated muscle fiber, leads to an earlier activation of nearby fibers. Nevertheless this effect should not be overestimated. In this simulation the effect is just as big that it can be observed in the direct neighborhood of the fiber. And only fibers where the membrane potential is already shifted very close to the threshold are affected by this effect. Based on previous simulations [9] there was the assumption that a disturbance in the potential distribution of the tissue surrounding the fiber facilitates the activation of the fiber. This assumption seems to be approved a little more by first results of the simulations using Comsol Multiphysics.

6. Conclusion

With Comsol Multiphysics it is possible to evaluate Hodgkin-Huxley like excitation processes in conducting 2 dimensional media. Once the model is implemented into the software it can be easily adapted to different geometries and parameters of fibers as well as those of the extracellular regions. The Hodgkin-Huxley model is very appropriate as "proof of concept" because it is the basis for many other models like that of Henneberg [3] or Plonsey [15].

The coupled model makes it possible to calculate simultaneously the external field caused by active electrodes and its disturbance caused by the membrane currents from the responding fibers, whereas, up to now calculations of action potentials were mostly done in two steps: (i) calculation of the extracellular potential distribution and (ii) using this distribution the excitation of the fiber was calculated with a compartment model.

The presented coupled model is predestinated to analyze the effects of Functional Electrical Stimulation in the human thigh. In "real" life coupling is omnipresent. For example measuring EMG data [16] is the feedback of muscle fiber excitations on the tissue surrounding the fiber. However, up to now many models only allow to simulate the coupling in one direction, either by calculating the excitation of a fiber as response to an external field or by simulation the EMG as an answer of a fiber.

Because of the coupling the effects of the stimulation, the influence of activated muscle fibers and the effect of different electrode positions can be observed directly in one model. This can lead to a better understanding of the effects of functional electrical stimulation and therefore to an improvement of the stimulation parameters in real life.

The next steps will be an enhancement of the model with new parameters and the implementation of a modified Henneberg model to simulate denervated human muscles. Another improvement will be an extension of the model to the third dimension to get a more realistic simulation.

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