A Static Distributed-parameter Circuit Model Explains Electrical Stimulation on the Neuromuscular System

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Abstract

Finite Element Modeling (FEM) has been widely used to model the electric field distribution, to study the interaction between stimulation electrodes and neural tissue. However, due to the insufficient computational capability to represent neural tissue down to an atom-level, the existing FEM fails to model the real electric field that is perpendicular to neuron membrane to initiate an action potential. Thus, to reveal the real electrode-tissue interactions, we developed a circuit to model transmembrane voltage waveforms. Here, we show a distributed-parameter circuit model to systematically study how electrode-tissue interaction is affected by electrode position, input current waveform, and biological structures in the neuromuscular system. Our model explains and predicts various phenomena in neuromuscular stimulation, guides new stimulation electrode and method design, and more importantly, facilitates a fundamental understanding of the physical process during electrode-tissue interaction. In our model, myelin is assumed to be inductive. The voltage waveform resonance caused by this inductive myelin accounts for the much lower stimulation threshold to activate motoneurons than muscle fibers, which is observed with in vivo measurements. These findings confirmed the feasibility of studying electrode-tissue interaction using a proper distributed-parameter circuit. Our current application on the neuromuscular system also raises the possibility that this distributed-parameter circuit model could potentially be applied to study other neural tissues, including the Peripheral Nervous System (PNS) and the Central Nervous System (CNS).

Significance

Finite Element Modeling (FEM) has been conventionally used to study electrode-tissue interaction. However, FEM fails to model the real electric field with the correct orientation that excites a neuron. Here, we adopt the idea of using a circuit to model voltage waveforms. We show a distributed-parameter circuit model to systematically study how electrode-tissue interaction is affected by electrode position, input current waveform, and biological structures in the neuromuscular system. Based on our hypothesis of inductive myelin sheath, we proposed that the resonance in voltage waveform accounts for the much lower stimulation threshold of motoneurons as compared to muscle fibers. These findings confirmed the feasibility of studying electrode-tissue interaction using a proper distributed-parameter circuit model.
Electroceuticals, where electrical stimulation is delivered to the nervous and neuromuscular system, are becoming widespread therapeutic solutions to people with neurological disorders and neuromuscular disabilities. For example, people with spinal cord injury (SCI) above the sixth cervical vertebra are unable to control extant limbs due to the interruption to the motor pathway (1). Functional electrical stimulation (FES) could benefit these people by restoring functional actions, like voluntary grasp, via the electrical stimulation of specific muscles. However, despite its application and medical promise, the electrophysiology of electrical stimulation is neither precise nor well understood.

The history of electrophysiology dates to 1770, when Luigi Galvani first discovered bioelectricity as he made a frog muscle twitch by accidentally creating a battery from surgical instruments (2). The mechanism of electrical stimulation remained elusive until 1952, when Alan Hodgkin and Andrew Huxley proposed a quantitative description of membrane current on the unmyelinated squid giant axon (3). In 1976, Donald McNeal first applied the established nerve axon models to explain excitation of nerve tissue, by bringing in the concept of shared electric field between the stimulation electrodes and the excitable tissue (4). With increased computing power, modern computational models further improved McNeal’s method, by accounting for additional parameters, such as the anisotropic extracellular conductivity in electric field modeling and non-linear response of neuronal cells and axons. Such modern computational models include the field-neuron model, which has been applied to analyze electrical stimulation on the peripheral nervous system (5-7) and the central nervous system (8, 9).

Despite the development of these computational models, there are large discrepancies between these computational models and experimental observations. Firstly, the tissue should not be considered as purely resistive (5-9), as recent indirect (10-12) and direct (13) evidence suggests that extracellular medium consists of non-resistive components. Secondly, the deterministic gating property assumed in the computational models (5-9) contradicts the stochastic gating property as observed in single ion channel recording (14-18). In addition, there lacks a complete model that can systematically study how the interaction between stimulation electrode and tissue is affected by electrode position, input current waveforms, and biological structures of the neural tissue. In this paper, we aim to achieve such a complete model that explains and predicts various phenomena in neuromuscular system stimulation.

In our previous work (19), composite biological structures in the tissue are neglected for circuit simplification. In this study, by considering motoneurons, muscle fibers and extracellular medium, the previous lumped-parameter circuit is expanded to a distributed-parameter circuit, enabling a more detailed investigation of the interaction between stimulating electrode sites and excitable tissues. This model can qualitatively explain the following phenomena:

1. With different locations of stimulation electrode sites relative to the target motoneuron (motoneuron-electrode position), stimulation efficiency can either increase or decrease with respect to the spacing between the two electrode sites.

2. Motoneuron-electrode position determines the polarity of transmembrane voltage waveform, which is an unsolved issue using the previous lumped-parameter circuit.

3. Force mapping curves (a measured curve of the generated force with respect to input current amplitude or pulse width) measured with increasing current amplitude may form a certain shape with multiple curvatures, which has been reported by others as well (20, 21). A conventional explanation for this phenomenon is that multiple groups of motoneurons are sequentially recruited when the current amplitude is increased (20, 21). But in our model, this phenomenon can be theoretically derived and numerically calculated.

4. Instead of forming a force mapping curve with multiple curvatures, we observed that the recruitment of multiple motoneuron groups will induce an unstable output force at the transition current, showing an abnormally high error bar in the force mapping curve. This phenomenon is reflected in the measurement data. It helps us to tell when an additional group of motoneurons is recruited during the experiment.
Based on a comprehensive understanding of the above phenomena, we propose an effective design of stimulation electrode and stimulation method to precisely control stimulation efficiency and reduce muscle fatigue. Firstly, a two-sided multiple-channel polyimide electrode design is proposed to reduce stimulation fatigue by alternatively activating motoneurons on frontside and backside of the electrode. Secondly, a comprehensive calibration of force mapping curves using different combinations of the electrode sites is necessary because stimulation efficiency and linearity of force control is determined by motoneuron-electrode location, meaning that a universal parametric force control method does not exist.

Lastly, we demonstrate that the resonance in voltage waveform accounts for the much lower stimulation threshold of motoneurons as compared to muscle fibers. In this study, we provide a theoretical and experimental exploration of excitability differences between myelinated motoneurons and unmyelinated muscle fibers.

**Concept of distributed-parameter circuit model**

In our previous work, the target motoneuron is modeled as a parallel RLC circuit, while extracellular medium is simplified as parallel impedance and integrated within leakage resistor of the parallel RLC circuit (19). In this paper, the entire muscle tissue, including the target motoneurons and extracellular medium, is modeled as a distributed-parameter circuit network (Fig. 1). The detailed circuit configuration of each block in this network is determined by its biological features. Here, myelin is modeled as inductor \((L)\), and cell membrane is modeled as capacitor \((C)\). In this way, myelinated motoneurons are represented by parallel RLC components (green blocks in Fig. 1). Unmyelinated muscle fibers are represented by RC components (blue blocks). Extracellular medium is modeled as resistive components \((R_s)\) connecting each block.

This circuit network can be further expanded by adding more functional components (e.g. fat tissue and skin as the peripheral circuits) and revised when studying different experimental scenarios (e.g. different configurations and implantation positions of stimulating electrodes). In this study, a custom-made two-sided multiple-channel polyimide electrode was implanted in the muscle belly, transversal to muscle fibers of the Tibialis Anser (TA) muscle, and the force generated by stimulation was measured by a force gauge tied to the ankle (Fig. 2A). Thus, the corresponding circuit network is revised as Fig. 2B. Each electrode site (e1 to e6 refer to the frontside; e1’ and e6’ refer to the backside) is connected to a node (E1 and E6 refer to the frontside; E1’ and E6’ refer to the backside). The non-conducting polyimide layer is modeled as broken connections between the frontside and backside. By connecting a current source to an arbitrary electrode sites and a voltage meter to a capacitor in an arbitrary block, voltage waveform at any position in the tissue can be calculated. Then, the probability of motoneuron excitation is calculated from the effective voltage waveform that exceeds threshold voltage.

**Results**

**Influence of motoneuron-electrode position on voltage waveforms.** Apparently, the exact voltage waveform on each block in Fig. 2B is determined by the block position and the electrode sites selected to deliver current input. This motoneuron-electrode position affects amplitude, shape and polarity of voltage waveform on each block. Since there are many motoneuron-electrode combinations, two simplified situations are modeled (Fig. 3A and Fig. 3B), to qualitatively investigate the effect of this motoneuron-electrode position upon voltage waveform.

In Fig. 3A, fixed electrode sites (positive electrode site between P3 and P4; negative electrode site between P9 and P10) are selected to deliver negative-first biphasic square current input. Voltage waveforms upon different blocks (P1 to P12) are modeled and shown in Fig. 3C. For these different blocks, voltage amplitude changes, and the polarity also switches. The blocks which are next to the
electrode sites (P3 and P4; P9 and P10) have the largest voltage amplitude. Meanwhile, voltage polarity gradually changes from negative-first to positive-first when the position changes from P1 to P12.

In another situation (Fig. 3B), two motoneuron blocks are fixed (P1 and P2) while the spacing between electrode sites is increased (positive electrode site between P1 and P2 is fixed; negative electrode site changes from E1 to E8). The voltage waveforms on P1 and P2 (Fig. 3D and Fig. 3D’) show an opposite changing trend. Peak amplitude of the block outside electrode sites (P1) and between electrode sites (P2) increases and decreases with increasing electrode spacing, respectively.

Changing trends of peak amplitude and polarity (green lines in Fig. 3C, Fig. 3D and Fig. 3D’) agree with the results using conventional method of electric field distribution modeling. However, our model can also reveal information about the voltage waveform, which is critical in determining neuron excitation. Thus, understanding this voltage waveform and its relationship to motoneuron-electrode distance can help us understand more phenomena, such as the multi-curvature force mapping curve and the polarity with respect to the stimulation electrodes, which will be discussed subsequently.

Influence of voltage waveform on force mapping curve: An explanation of multi-curvature phenomenon. Firstly, we discuss the phenomena of multi-curvature force mapping curves. For muscle stimulation using square wave current, it is widely observed that force mapping curves measured with increasing current amplitude may show multiple curvatures (20, 21). A conventional explanation for this phenomenon is that multiple groups of motoneurons are sequentially recruited when current amplitude is increased. In our model, this phenomenon can be quantitatively derived from the distributed-parameter circuit model. Using the same circuit configuration as Fig. 3A, voltage waveforms of block P1 to P12 in Fig. 3C are shown in Fig. 4A and Fig. 4B, along with an estimated threshold voltage. Due to voltage oscillations induced by RLC components, area A in Fig. 4A contributes to the first curvature in the neuron excitability probability mapping curves in Fig. 4A’, and area B contributes to the second curvature. Thus, the two effective voltage areas in Fig. 4A account for the two curvatures in neuron excitation probability mapping curves (Fig. 4A’). But this phenomenon will not always happen. For the voltage waveforms with only one area exceeding voltage threshold (indicated as C in Fig. 4B), their corresponding neuron excitation probability mapping curves show a single curvature (Fig. 4B’). These two types of force mapping curves, with and without multiple curvatures, were observed in our experiments.

Two conclusions can be reached from the above modeling results and validated by force mapping experiments in two in vivo experiments (Fig. 4C, Fig. 4C’). Firstly, due to the unknown motoneuron-electrode position after electrode implantation, stimulating efficiency using the same electrode pair will vary in different experimental trials. In Fig. 4C, electrode sites with the largest spacing (e1 and e6) show minimum stimulation efficiency. However, in another experiment (Fig. 4C’), electrode sites of e1 and e6 show medium stimulation efficiency. Secondly, multi-curvature phenomenon will not always happen in the force mapping curves. Whether the curve has multiple curvatures is determined by the shape of voltage waveform. When motoneurons are close to the stimulation electrodes, the high-amplitude voltage waveform tends to result in multi-curvature neuron excitation probability curve. The blue curve in Fig. 4C and the purple curve in Fig. 4C’ clearly show multi-curvature pattern, while other curves don’t show such a pattern. Apart from the multi-curvature force mapping curves, the orange curve in Fig. 4C’ shows an abnormally high error bar. We will discuss the reason for this high error bar in the following session.

Activation of multiple groups of motoneurons. When expanding the area of excited motoneurons with increasing current amplitude, we predict an unstable force output during a transition period. This unstable force output accounts for the abnormally high error bar observed in the orange force mapping curve in Fig. 4C’.
Two force mapping curves (e2e5, orange and e3e4, purple) are selected from Fig. 4C’ and plotted in Fig. 5A (orange and purple curve). There is a sudden force increment accompanied by an abnormally large error bar for the orange curve. We speculate this error bar is a sign of an additional group of motoneurons starting to be recruited with increasing current amplitude. In our experiments (Fig. 1A), the force measured is the summed-up force generated by multiple groups of activated motoneurons. When an additional group of motoneurons starts to be recruited by stimulation, although the total force will be higher than activating one group alone, the force generated by this second group of motoneurons is still low and unstable at this stage. Therefore, the measured force curve will show a large error bar at this current. Then, when current amplitude further increases, the stimulation strength of this second group of motoneurons will be higher, which results in a stable force output, making the error bar return to a normal level. This abnormal high error bar only occurs within a certain current range. Fig. 5B shows the force profile measured at this transition range (1000 µA to 1200 µA) of the orange curve in Fig. 5A. When current amplitude is high enough (1200 µA), the force profile will recover to a stable condition.

In addition to the measured force mapping curves, a good curve fitting with distributed-parameter circuit modeling helps us to understand the spatial distribution of these motoneurons within the muscle. Here a simple modeling case is demonstrated. The neuron excitation probability curves are shown in Fig. 5C and Fig. 5C’, using the distributed-parameter circuit model in Fig. 5D. The corresponding electrode pairs of these two curves are modeled in the circuit network (e3e4 in Fig.2B as E1+E1- in Fig. 5D; e2e5 in Fig. 2B as E2+E2- in Fig. 5D). The locations of the two target motoneurons (P1 and P2) are captured to fit the force mapping curves. At low stimulation current, both E1 and E2 electrode pairs can only stimulate P1. However, when current increases to around 1600 µA, E2 starts to stimulate another motoneuron P2, while E1 has no influence on P2. From this modeling, the relative locations of the two motoneurons with respect to the electrode sites can be roughly estimated. This simple case demonstration shows the potential to apply this model for an in-depth investigation of biological structure in the future.

**Influence of input current waveform polarity on motoneuron activation.** This distributed-parameter circuit model not only helps us understand force curves, but also allows us to analyze voltage waveform polarity. As shown in Fig. 3C, the polarity of voltage waveforms at different positions will not be the same. This polarity is not only determined by motoneuron position and input current waveform, but also determined by which electrode is connected to the positive terminal of current source. Fig. 6A uses a distributed-parameter circuit model to demonstrate this principle. Two electrode sites (E1 and E2) are connected to current source, which deliver monophasic square wave current pulses of different pulse widths. Voltage waveform by applying positive pulses from E1 and negative pulses from E2 are the same (Fig. 6B). Similarly, voltage waveform by applying negative pulses from E1 and positive pulses from E2 are the same (Fig. 6B’). Although the voltage waveforms in Fig. 6B and Fig. 6B’ are just of opposite polarity, changing trend of the effective voltage area with increasing pulse width is completely different. According to the voltage waveform modeling, we predicted that the force mapping curves will form two groups (one group: positive pulses from E1, and negative pulses from E2; another group: negative pulses from E1, and positive pulses from E1).

Force mapping curves measured in the two independent *in vivo* experiments are consistent with our prediction (Fig. 6C, Fig. 6D). One force mapping curve was measured at small pulse width range (100-300 µs), and the other was measured at large pulse width range (100-800 µs). Two electrode sites (e1 and e6) of the furthest distance on our polyimide electrode were used. Force mapping curves are the same when e1 delivers positive current or e6 delivers negative current (blue and orange curves, with Fig. 6B’ type activation). Force mapping curves are also the same when e1 delivers negative current or e6 delivers positive current (purple and green curves, with Fig. 6B type activation). In each measurement, the four recruitment curves form two groups of different changing trend with increasing pulse width.
The flipping of voltage waveform polarity (Fig. 6B and Fig. 6B’) causes the voltage waveforms to exceed threshold voltage in different patterns, so that the two groups have totally different changing trends with increasing pulse width.

**Independent activation of motoneurons using two-side polyimide electrode.** Based on a comprehensive understanding of the above phenomena, we proposed an effective design of custom-made stimulation electrode and stimulation method to reduce muscle fatigue. In Fig. 7A, due to the non-conducting polyimide layer, there will be broken connections between frontside and backside of the electrode. Thus, when current is applied from the frontside electrode sites, motoneurons on the backside won’t be activated. In other words, electrode sites on one side can only cause limited motoneuron activations on the other side of the electrode.

A modeling demonstration is shown in Fig. 7A-C. Two electrode sites (E+ and E-) on the frontside of electrode are selected for current delivery. F1, F2, F3 are three motoneuron positions on the frontside, while B1, B2, B3 are three motoneuron positions on the backside of the electrode. The overall voltage amplitude on the frontside motoneurons is much larger than the backside motoneurons (Fig. 7B, Fig. 7B’). Neuron excitation probability curves show that only with much larger current, the backside motoneurons can be activated by frontside electrode sites (Fig. 7C).

*In vivo* experiments demonstrated the independent activation of motoneurons using two-side polyimide electrode. At the beginning of the experiment, force mapping curves for both frontside and backside electrode sites were measured (blue curves in Fig. 7D and Fig. 7D’). Then, the frontside electrode sites were used for a long-time electrical stimulation to induce fatigue. The stimulation lasted for 2.5 min, and the force profile can be found in Fig. 7E. This force profile shows signs of muscle fatigue at the end of the 2.5 min stimulation, as the force drops to half of the initial value. Right after this 2.5 min stimulation, force mapping curve using frontside electrode sites was measured (orange curve in Fig. 7D). At that moment, because of the muscle fatigue on the frontside, the force mapping curve was much lower than the one measured at the beginning. Then, the force mapping curve using backside electrode sites was also measured (orange curve in Fig. 7D’). It was only slightly lower than the one measured in the beginning. Lastly, after 5 min resting, the force mapping curve using the frontside electrode sites was measured again (purple curve in Fig. 7D), which showed recovery of muscle fatigue but was still much lower than the measurement in the beginning. Thus, frontside electrode sites stimulate frontside motoneurons, but barely stimulate backside motoneurons. These experiments confirmed our prediction of independent activation of motoneurons using the two-sided polyimide electrode sites.

**Difference in excitability between motoneurons and muscle fibers: a theoretical explanation.** There are two types of excitable cells in the muscle tissue: motoneurons and muscle fibers. They show distinctive excitability properties for electrical stimulation. In our model, these differences can be theoretically predicted and confirmed by *in vivo* experiments. The experiments targeting motoneurons and muscle fibers are conducted on healthy muscle and denervated muscle, respectively.

Here, two distributed circuits are built to model the healthy muscle and denervated muscle. Myelin sheath is proposed as an inductor, and the equivalent circuit of a myelinated motoneuron is modeled as a RLC component (Fig. 8A). Unmyelinated muscle fiber is modeled as a RC component (Fig. 8B). To make a fair comparison, the block representing the target motoneuron or muscle fiber is placed at the same position in the circuit network. The modeling parameters are set based on two reasonable considerations as follows:

1. Due to the lack of myelin sheath, muscle fibers have a larger exposed cell membrane surface and more leakage channels, which can be modeled as a larger capacitor ($C_2 \gg C_1$) and a lower leakage resistor ($R_p_2 \ll R_p_1$), respectively.
2. It has been reported that the conductance and gating properties of the sodium channels in
motoneurons and muscle fibers are nearly the same (22), and the muscle fiber sodium channels only
require a slightly more negative potential to activate than the motoneuron sodium channels (23, 24). 
Therefore, in our modeling, the motoneurons and muscle fibers share the same parameters for ion
channel excitation probability calculus, among which the most important is the same threshold voltage.

Firstly, voltage waveforms are compared when the same negative monophasic current pulse (100 µs
pulse width) is applied (Fig. 8C1). The voltage waveform of a RC component shows a typical charging
and discharging curve as a capacitor, while the voltage waveform of a RLC component shows voltage
oscillation, resulting in a much higher peak amplitude. Thus, to exceed the threshold voltage and
activate muscle, the threshold current required for RLC component is much lower than RC component. 
The ion channel excitation probability mapping curves by changing current amplitude in Fig. 8C2 show
the difference in threshold current. The probability mapping curves with increasing pulse width in Fig.
8C3 show that an RC circuit requires a much higher current to achieve the same force. This phenomenon
is also observed in previous report (25) and confirmed by our in vivo experiments (Fig. 8C4). To achieve
the similar force output, healthy muscle requires only 1 mA while the denervated muscle requires 10
mA.

Then the changing trend of voltage waveforms with increasing pulse width is compared in Fig. 8D1
and Fig. 8D2. Voltage waveforms of a RC component show a simple charging and discharging process as
a capacitor. Although the slope of the curve, which represents the charging rate, varies with the circuit
parameters, the general shape will not change. Thus, the effective voltage area, which is the part
exceeding threshold voltage, will always have a monotonically increasing trend. As a result, the
corresponding probability mapping curves (Fig. 8D3) and measured force mapping curves (Fig. 8D4) also
increase with respect to pulse width monotonically. However, the changing trend of the effective
voltage area of the RLC component is quite complex. Many factors, such as current amplitude, circuit
parameter and extracellular environment, can induce nonlinear effect upon the effective voltage area
and finally result in various probability mapping patterns, as discussed in Fig. 4. Fig. 8D2 just shows a
typical voltage waveform of the RLC component. With different current amplitudes, the effective
voltage waveform will be completely different.

In summary, due to the lack of myelin sheath, muscle fiber is not very easily stimulated being pure
RC, but because of the branching motoneurons coordinating the impulse it is able to be activated with
lower current in healthy muscles. While the force mapping curves produced by changing pulse width in
muscle fiber stimulation always follow a monotonically increasing trend, the force mapping curves of
motoneuron stimulation will have a complex pattern (19).

Discussion

A static system-level distributed-parameter circuit model to study electrical stimulation on
neuromuscular system. In this paper, we thoroughly studied the interaction between the stimulation
electrodes and muscle tissue. This interaction is affected by different parameters in the system,
including motoneuron-electrode position, input current waveforms (amplitude, pulse width, frequency,
and polarity), circuit properties of the tissue components (motoneuron, muscle fiber, and extracellular
medium).

Here, we demonstrate a modified distributed-parameter circuit to study a specific electrode
implantation: intramuscular implantation of a two-side multiple-channel polyimide electrode. There are
many electrode designs for muscle stimulation, including the epimysial electrode and skin surface
electrode. These electrodes also come in different structures, like flexible strip electrodes, wire
electrodes and large-area patch electrodes. By including circuit components representing additional
tissue layers (fat layer, skin) and properly assigning the motoneuron-electrode positions, modified
distributed-parameter circuit can be applied to study these implantations.
A new explanation of cathodal make, cathodal break, anodal make, and anodal break stimulation phenomena. It has been observed that cardiac tissue can be electrically stimulated with the onset (make) or termination (break) of an input current that is delivered with either a negative (cathodal) or positive (anodal) electrode (26, 27). These phenomena can be easily explained with our model. In the case of unipolar stimulation configuration, where only one electrode delivers input current, the effectiveness of cathodal make can be intuitively understood, as it will depolarize the tissue surrounding the electrode. However, considering the dramatic resonance caused by the RLC component, cathodal break, anodal make, and anodal break may also generate voltage waveforms with a certain area sufficiently negative to exceed the voltage threshold. This explains the capability of cathodic and anodic tissue stimulation, while accounting for the different required threshold at the same time. It also indicates how to design stimulators and neural implants to better utilize this principle for tissue stimulation.

The gap between static and dynamic distributed-parameter circuit model. Here, we assigned static values to parameters of both the circuit components (resistance, inductance, and capacitance) and neuron excitation probability calculation (threshold voltage). By using static parameters of circuit components, we indeed assumed that the electrical properties of the muscle tissue remain unchanged during applied electrical stimulation. Similarly, by using static parameters of neuron excitation probability calculation, we assumed that external electrical stimulation won’t affect the resting potential and threshold voltage of motoneurons. This adoption of static parameters limits our capability to study some specific issues. One example is the quantitative description of muscle fatigue during electrical stimulation, which is characterized as change in force output. During muscle fatigue, the same current input is applied, but the output force is different. It means something have changed, either the generated voltage waveform affected by circuit parameters, or the response of the nerve fibers, neuromuscular junctions, and muscle fibers.

Thus, to quantitatively study these dynamic processes in electrical stimulation, further studies are required to establish a bridge between the parameters in our model and the dynamic change of muscle tissue.

Reason for using voltage waveforms modeled with a distributed-parameter circuit, instead of electric field distribution modeled with the existing Finite Element Modeling (FEM). In electrical stimulation, transmembrane electric field opens ion channels. Considering the neuron membrane is partially permeable to ions, charged ions accumulate on both sides of the neuron membrane. Thus, electric field generated by these local ions is perpendicular to the membrane. To model the effect of this perpendicular transmembrane electric field \( E \) on the neuron, we calculate the voltage across the capacitor \( V \) in our model. This \( V \) is the path integral of the electric field \( E \) in the direction perpendicular to the capacitor plates (neuron membrane) as described by the equation \( \Delta V = E \times \Delta d \) (\( \Delta V \) is a change of \( V \), \( \Delta d \) is a change of membrane thickness). Thus, in our model, the voltage across the capacitor can be used to characterize electric field perpendicular to membrane, which then opens an ion channel. However, electric field modeled with the existing FEM is only determined by physical boundary condition and electrode positions, which is irrelevant to the electric field perpendicular to neuron membrane.

In our model, by calculating the voltage across the capacitor (neuron membrane), we can model the nonlinear relationship between \( V(t) \) (transmembrane voltage at time point \( t \)) and \( I(t) \) (input current at time point \( t \)). In response to an external input current \( I(t) \), the local ions on both sides of the neuron membrane will move. This local ion movement is not only affected by the charging and discharging process of the neuron membrane, but also affected by the surrounding tissue environment. We have built a distributed-parameter circuit network to account for the influence of the other parts of the tissue.
However, in the existing FEM, the tissue is modeled as a medium. In this way, the existing FEM is always assuming a linear relationship between $V(t)$ and $I(t)$.

**Methods**

**Animal statement.** All experiments were conducted according to protocols approved by the Institutional Animal Care and Use Committee at the National University of Singapore.

**Preparation of denervated muscles.** Sprague-Dawley rats (around 450 g) were used for the sciatic nerve transection. Anesthesia (Aerrane®, Baxter Healthcare Corp., USA) was induced with isoflurane. Buprenorphine (Ilum Temvet Injection®, Troy Laboratories, Australia) was injected for pain relief before the surgery. After the rat was anesthetized, a shaver was used to gently remove the fur on the left leg. Then, the skin was disinfected with 70% ethanol wipes, and an incision was made to expose the bicep femoris muscle. An incision was then made on this bicep femoris muscle to expose the sciatic nerve. The sciatic nerve was transected on the site before it branches into three smaller nerves. Then the bicep femoris muscle and the skin were both sutured back. Right after the surgery, enrofloxacin was injected. During the first five days after the nerve transection surgery, buprenorphine was injected twice a day and enrofloxacin (Baytril®, Bayer Global Corp. German), was injected once a day.

**Electrode implantation.** The fabrication of the custom-made flexible electrode can be found in our previous publication (28). The custom-made flexible electrode was folded to form a loop on the tip. A suture was threaded through this loop. Then, this suture was threaded through the center of the exposed TA muscle belly. Pulling by the suture, the interface was also threaded into the muscle belly. The interface was sutured to the muscle surface for fixation. Then, the skin was sutured back. All the in vivo measurement results were obtained using this custom-made flexible electrode, except for the results in Fig. 8D4. The measurements for Fig. 8D4 used two stainless steel wires to deliver the long stimulation current pulses. These two stainless steel wires were sutured perpendicular to the muscle fiber direction, with a separation distance of around 1 cm and a depth into the muscle of 2-3 mm.

**Electrical stimulation.** An isolated high-power stimulator (A-M SYSTEMS model 4100, USA) was used for electrical stimulation. Every one second, a train of 10 negative-positive biphasic pulses was applied. Every 16.7ms, a biphasic pulse was delivered. In the experiment of comparing four waveforms, positive-negative biphasic pulses, negative-positive biphasic pulses, positive monophasic pulses, and negative monophasic pulses were applied.

**Force data collection and analysis.** The anesthetized rat was fixed on a stand, and the ankle of the left leg was connected to a dual-range force sensor (Vernier, USA). This force sensor was connected to a laptop through a data acquisition device (National Instruments, USA). LabView (National Instruments, USA) was used for on-site result visualization during the measurements. After the measurements, MATLAB (MathWorks, USA) was used for data analysis. The recorded forces exceeding a certain amplitude threshold were used for assessing the strength of the excitability. If the forces were below this amplitude threshold, then the muscle was considered as not activated.

**Distributed-parameter circuit modeling.** The modeling was performed on MATLAB (MathWorks, USA). Firstly, a circuit description was performed in Simulink (MathWorks, USA). Then, current inputs of different waveforms were recursively fed to the circuit model, and the voltage responses of the targeted RC or RLC component were collected. Lastly, these voltage responses were fed into the probability equation to calculate the probability of excitation under these current inputs.

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**Fig. 1.** Distributed-parameter circuit modeling concept. Rs represents the resistor of extracellular media. L represents the inductor of myelin. C represents the capacitor of cell membrane. RLC components (green blocks) model the motoneurons distributed in the healthy innervated muscle tissue. RC components (blue blocks) model muscle fibers.
Fig. 2. *In vivo* measurement setup and the corresponding distributed-parameter circuit concept. (A) Our custom-made two-side multiple-channel polyimide electrode is sutured in the muscle belly, transversal to muscle fibers of the Tibialis Anterior (TA) muscle. When electrical stimulation was delivered to the TA muscle, leg freely kicked forward. Force was measured from the ankle. (B) The corresponding distributed-parameter circuit with broken connections between two sides of electrode sites to represent the insulating polyimide substrate, and RLC components (green blocks) to represent distributed motoneurons.
Fig. 3. Influence of motoneuron-electrode position on voltage waveform. (A) Distributed-parameter circuit of fixed electrode site location and changing targeted motoneuron positions (green blocks P1-P12). (B) Distributed-parameter circuit of fixed positive electrode site location and changing negative electrode site locations (E1-E8). Two targeted motoneuron positions (P1, P2) are studied, P2 is between the electrode sites, and P1 is outside. (C) Voltage waveforms on motoneuron positions in (A). The amplitude of the voltage waveforms is largest for motoneurons close to the two stimulation electrodes. The polarity of the voltage waveforms shifts from P1 to P12. (D, D') Voltage waveforms on P1 (D) and P2 (D') with negative electrode positions in (B).
Fig. 4. Force mapping curves with multiple curvatures are explained with the voltage waveforms. (A, A’) Voltage waveforms (A) and corresponding neuron excitation probability curves (A’) of P1-P6 in Fig. 3c. (B, B’) Voltage waveforms (B) and corresponding neuron excitation probability curves (B’) of P7-P12 in Fig. 3c. For voltage waveforms with two areas exceeding the threshold (area A and area B), the probability curves have two corresponding curvatures. For voltage waveforms with only one area exceeding the threshold (area C), the probability curves also only show one curvature. (C, C’) Quantification of force at different current measured in two *in vivo* experiments. Data are means ± s.d. (n=15 per group).
Fig. 5. Activation of multiple groups of motoneurons. (A) Quantification of force at different current. (B) Force profile at four current corresponding to the transition points in (A). Data are means ± s.d. (n=15 per group). (C) Neuron excitation probability curves using two groups of stimulation electrodes E1 and E2. (C) Neuron excitation probability curves of two groups of electrode sites on P1 and P2 separately. (D) Distributed-parameter circuit with two groups of electrode sites (E1+ and E1-, E2+ and E2-) and two targeted motoneuron positions (P1, P2).
Fig. 6. Influence of input current waveform polarity on motoneuron activation. (A) Distributed-parameter circuit with two electrode sites (E1 and E2) and a targeted motoneuron (green block). (B, B’) Modeled voltage waveforms of different pulse width. E1 delivers positive monophasic current or E2 delivers negative monophasic current (B). E1 delivers negative monophasic current or E2 delivers positive monophasic current (B’). (C, D) Quantification of force at different pulse width in two experiments. Data are means ± s.d. (n=15 per group).
Fig. 7. Independent activation of motoneurons using two-side polyimide electrode. (A) Distributed-parameter circuit with broken connections to represent the non-conducting polyimide substrate. E- and E+ are electrode sites on the frontside of the polyimide electrode. F1, F2, F3 are motoneurons on the frontside, and B1, B2, B3 are motoneurons on the backside of the polyimide electrode. (B, B’) Voltage waveforms on F1-F3 (B) and B1-B3 (B’) when current input is delivered from frontside electrode sites. The scale of the front motoneuron waveforms are much larger than the back motoneuron waveforms. (C) The corresponding probability curves. (D, D’) In vivo measurement results. Quantification of force at different current during frontside stimulation (D) and backside stimulation (D’). (E) Force profile of 2.5 min electrical stimulation to induce fatigue on frontside. Data are means ± s.d. (n=15 per group).
Fig. 8. The inductive myelin accounts for the difference in excitability of motoneurons and muscle fibers. (A) Distributed-parameter circuit with RLC component (green block) representing the target motoneuron in healthy muscle stimulation. (B) Distributed-parameter circuit with RC component (blue block) representing the target muscle fiber in denervated muscle stimulation. (C1, C2) Modeled voltage waveforms (C1) and probability curves (C2) on RLC component and RC component. (C3, C4) Modeled probability curves (C3) and quantification of force (C4) at small pulse width. (D1, D2) Modeled voltage waveforms of RC (D1) and RLC (D2) component at different pulse width. (D3, D4) Modeled probability curve (D3) and quantification of force of a denervated muscle (D4) at large pulse width. Data are means ± s.d. (n=15 per group).