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Computation of Activating Fields for Approximation of the Orientation-Specific Neural Response to Electrical Stimulation

Conor Keogh, Francisco Saavedra, Brian Andrews and James J FitzGerald

***Abstract*— Computational methods of determining the response of neural tissue to electrical stimulation have demonstrated value for the development of novel devices and the programming of neuromodulation therapies. Detailed biophysical models are excessively computationally intensive for many applications; simple metrics to approximate activation can speed up progress in this area. The activating function provides such a useful metric. However, this measure, defined for a specific axon orientation, is not immediately applicable to computed electric fields to assess their effects. We demonstrate a method for computation of the activating function generalized to a field in order to allow rapid computation of the effects of stimulation on neural tissue while preserving information on axon orientation.**

***Clinical Relevance*— This demonstrates a useful method of approximating the effect of electrical stimulation on nervous tissue for the development of devices and the optimization of parameters for electrical neuromodulation.**

I. Introduction

Computational methods for determining the neural response to extracellular stimulation are of increasing importance, both in the development of novel devices [1]–[3] and the optimization of stimulation parameters for neuromodulation therapies [4], [5].

The biophysical response to extracellular stimulation can be modelled very accurately using multi-compartment neuron models with Hodgkin-Huxley dynamics [6]. However, this is computationally intensive and does not easily provide visualizations of the regions activated by stimulation. In scenarios where more rapid iterations of designs and parameters are required, more computationally efficient metrics are desirable.

The activating function provides a classic simplified metric for approximating the response to stimulation [7], [8]. A detailed neuronal model shows that current flow in the *n*th segment of the model is determined by a capacitive current, an ionic current and a current along the inside of the axon:

$$C_m\left(d\left(V_{i,n}-V_{e,n}\right)/dt\right)+I_{ionic,n}+G_a(V_{i,n}-V_{i,n-1}) \\ +G_a(V_{i,n}-V_{i,n+1})\ =\ 0$$

By introducing the reduced voltages

$$V_n = V_{i,n} - V_{e,n} - V_{rest}$$

We get:

$$\frac{dV_n}{dt} = \{G_a(V_{n-1}-2V_n+V_{n+1} \\ +V_{e,n-1}-2V_{e,n}+V_{e,n+1}) - I_{ionic,n}\}/C_m$$

We then insert $G_a = \pi d^2/4\rho_i\Delta x$ and $C_m = \pi d L c_m$ (where L is the active membrane length, i.e. the length of the nodes of Ranvier, or $L = \Delta x$ in the case of unmyelinated axons) and introduce the ionic current density $i_{ionic,n}$:

$$\frac{\mathrm{d}V_n}{\mathrm{d}t} = \{\frac{d\Delta x}{4\rho_i L}\ ((V_{n-1}-2V_n+V_{n+1})/\Delta x^2 \\ +\ (V_{e,n-1}-2V_{e,n}+V_{e,n+1})\ /\ \Delta x^2) - i_{ionic,n}\}\ /c_m$$

Examining the source term, we can see that the contribution of the extracellular field produced by stimulation is given by

$$f_n(t) = \left(V_{e,n-1}-2V_{e,n}+V_{e,n+1}\right)/\Delta x^2$$

The current flow in the *n*th segment is therefore proportional to this activating function, defined as the second difference of the extracellular potential along the axon. As $\Delta x \rightarrow 0$, this becomes the standard expression for the activating function:

$$f(x,t) = \left(\partial^2 V_e(x,t)\right)/\ \partial x^2$$

This simple metric provides a useful means of approximating the neural response to stimulation. However, this metric is defined as a second difference along a specific 1D trajectory (i.e. the length of the axon considered). It therefore only allows us to consider axons in specific locations with specific orientations, limiting the application to situations where we wish to compute the region likely to be activated by stimulation.

Metrics such as the volume of tissue activated [9] have attempted to overcome this issue for applications such as deep brain stimulation. However, these metrics either disregard axon orientation or assume a tangential orientation of the axon with respect to the electrode. These assumptions make these methods unsuitable for accurate evaluation of the effect of stimulating fields on axons with specific orientations, such as those encountered in peripheral nerve stimulation.

We therefore require the ability to calculate an activating function in a manner that can be generalized to a field, while

Conor Keogh is with the Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK (e-mail: conor.keogh@nds.ox.ac.uk). Francisco Saavedra is with the University of Concepcion, Chile (frsaaved@gmail.com).

Brian Andrews is with the Nuffield Department of Surgical Sciences, University of Oxford (brianandrews55@yahoo.com)
James J FitzGerald is with the Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK (email: james.fitzgerald@nds.ox.ac.uk)

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maintaining explicit representation of the axons' orientation. We consider the Hessian matrix (H) of the electric potential produced by stimulation, containing second derivative information for all directions at each point in the field; we then apply a rotation $R_n: x \rightarrow n$:

$$H' = R_n^{-1} H R_n$$

Where R_n is a rotation matrix that rotates the x-axis of the co-ordinate frame onto the orientation of the axon (n), defined by the angles between the x-axis and the axon of interest. We can then extract the first element of the rotated Hessian, giving us the second partial derivative along the axon's orientation, i.e. the activating function, defined for a field:

$$(H')_{11} = \partial^2 V / \partial n^2$$

We demonstrate that this metric can be computed and that it provides a computationally efficient method of approximating activation for fields with axons of specified orientations. It accurately predicts the level of neural activation as a function of axon orientation, with high measures of this rotated Hessian metric indicating a low activation threshold (i.e. only a small amount of current required to induce an action potential), and low levels of this metric predicting a high threshold, where a large current needs to be used to produce an action potential.

II. Methods

We calculated the electric field produced by stimulation using a simple geometric model of surface stimulation of a peripheral nerve. Activation of axons of varying orientations was assessed using detailed biophysical models and the rotated Hessian activating field. These metrics were compared to evaluate the ability of the rotated Hessian to approximate neural activation. The correlation coefficient between these measures was used to assess the ability of the rotated Hessian to capture the orientation-dependence of biophysical activation thresholds.

A. Electric field computation

A three-layer tissue model (skin, subcutaneous fat, muscle) was created. A bipolar electrode arrangement was simulated on the skin surface, with 5cm x 5cm electrodes separated by 5cm (figure 1). The physical properties, derived from a standard database [10], applied to each tissue type are shown in table 1.

TABLE I. Physical properties of tissue types

Tissue type	Physical properties	
	Conductivity (S/m)	*Relative permittivity*
Skin	$2E^{-4}$	$1.14E^{3}$
Fat	$3.77E^{-2}$	$5.03E^{6}$
Soft tissue	$2.02E^{-1}$	$2.57E^{7}$

The electric field produced by stimulation was computed by solving the Laplace equation with variable coefficients with homogeneous Dirichlet boundary conditions on the external air boundaries surrounding the volume using the finite element method with COMSOL Multiphysics [11]:

$$-\nabla \cdot \sigma \nabla V = 0 \text{ in } \Omega,$$
$$V = 0 \text{ on } \delta\Omega$$

where V is the electric potential generated by stimulation, σ is the tissue conductance, Ω is the domain modelled and δΩ is the external (air) boundary of the domain.

Additional Neumann boundary conditions were added to simulate the effect of current-controlled stimulation through the simulated electrodes:

$$\frac{\partial V}{\partial n} = J_n \text{ on } \Gamma_A,$$
$$\frac{\partial V}{\partial n} = -J_n \text{ on } \Gamma_R$$

Where J_n is the current density normal to the surface and Γ_A and Γ_G are the surfaces of the active and return electrodes respectively. J_n is computed such that $\int_{\Gamma_A} J_n = \mathrm{J}\, mA$, i.e. the total current normal to the electrodes is equal to the current (J) applied through the electrode.

B. Biophysical model

The effects of the computed electric field on an axon at 5cm depth under the electrodes was assessed by coupling the results of the finite element simulation to a biophysical model of a myelinated axon with Hodgkin-Huxley dynamics [6]. The orientation of the axon was varied in order to assess the effect of axon orientation.

The McIntyre-Richardson-Grill model of a myelinated axon was used to simulate stimulation of an 11.5µm axon of a peripheral nerve using the default parameters defined by McIntyre et al. [12]. All biophysical models were implemented in NEURON [13]. Extracellular fields were coupled using the cable equation with the extracellular field defined at each point of the axon. Simulations were run and whether the model generated an action potential was measured.

Thresholds for the amplitude required for activation were computed using a binary search algorithm. Stimulation amplitude was altered and simulations re-run until activation thresholds were identified to within 1mA.

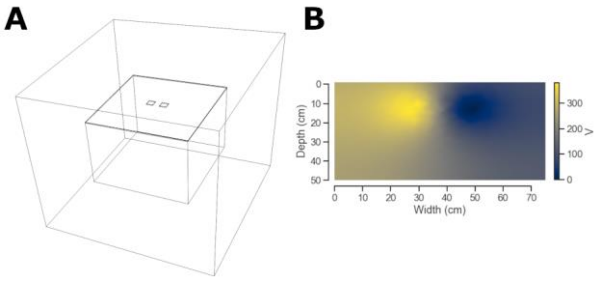

Figure 1. Geometry and sample electric field A. Simple three-layer model of tissue used for assessing activation metrics. B. A 2D slice through the computed field showing the potential produced by stimulation.

C. Computation of activation

The Hessian matrix of the electric potential produced by stimulation was approximated numerically by computing the second differences of the field at each point over a regularly spaced grid sampled every 0.05mm, producing a 3x3 matrix of second partial derivative information at each point in the field.

A rotation matrix was computed to rotate the x-axis of the original co-ordinate frame onto the trajectory of the axon of interest. This rotation matrix was then applied to the Hessian field.

The activating function for an axon with the given orientation was extracted from the Hessian matrix at each point in the field by taking out its first element, corresponding to the second partial derivative along the orientation of the axon, i.e. the activating function. This was performed for every point in the field, providing a metric over the whole field.

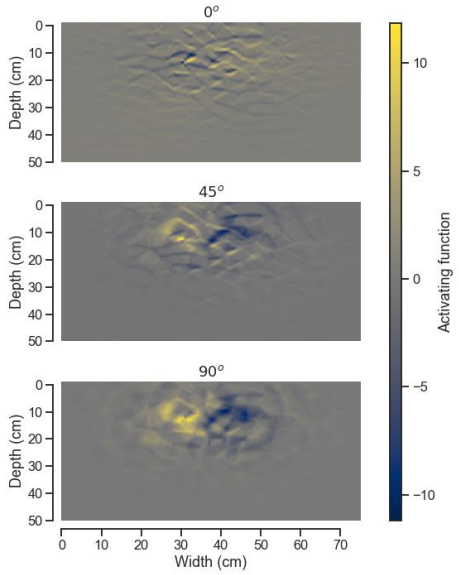

Figure 2. Rotated Hessian approximations for axons of varying orientations; slice taken through centre of electrodes. Yellow indicates high activation, blue indicates low activation. 90º to the x-axis,. 45º to the x-axis and 0º to the x-axis are shown. The pattern of activation differs for axons of differing orientations. This highlights the importance of using metrics for approximating activation the retain orientation information.

This approximation was then compared to the thresholds required for stimulation for axons with a range of orientations in order to evaluate its ability to approximate neural activation using a simple metric while maintaining orientation information.

III. Results

The geometric tissue model used is shown in figure 1. The electric field in the tissue model due to stimulation can be computed and visualized. These results were then used to compute the activation metrics assessed, demonstrating that the rotated Hessian approximation provides a computationally efficient, accurate method of assessing the effect of stimulation on neural tissue.

A. Orientation sensitivity

The rotated Hessian approximation can be computed for axons of arbitrary orientations, providing a metric defined everywhere on the domain modelled of the activation of an axon with that orientation at that position.

Activating fields for a selection of axons of differing orientations are shown in figure 2. The rotated Hessian approximation is able to capture the orientation selectivity of axons and to provide straightforward visualizations of the activating fields produced by stimulation.

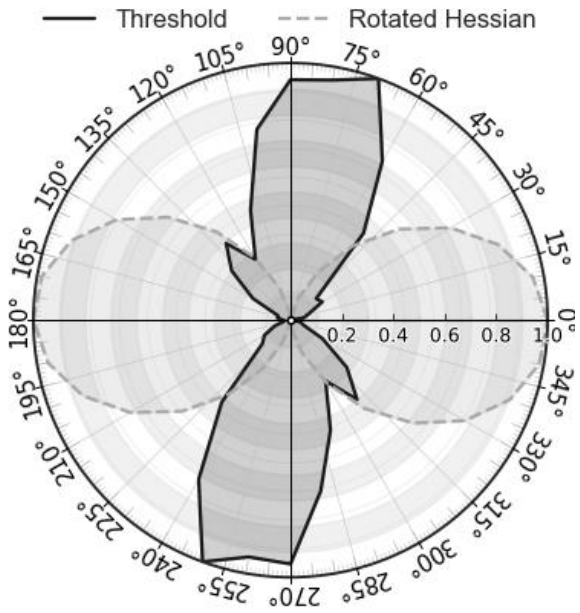

Figure 3. Polar plot of amplitude threshold and rotated Hessian approximation for a range of orientations. Angles represent the orientation of the axon of interest. The radius indicates the normalized magnitude of the activation metric for an axon of that orientation, i.e. the amplitude required to activate it and the rotated Hessian metric. The rotated Hessian successfully captures the orientation selectivity seen in the biophysical model. High rotated Hessian metrics occur where the amplitude threshold is lower.

B. Performance comparison

The rotated Hessian approximation shows a similar orientation selectivity to the biophysical models (figure 3). The amplitude required to induce an action potential in an axon model changes as a function of the orientation of the axon with respect to the electrodes. The rotated Hessian approximation captures this rotation and provides a computationally efficient means of evaluating the response to stimulation for axons with a specific orientation.

The amplitude required for producing an action potential in an axon model and the rotated Hessian approximation at the location of the axon are highly correlated (r = -0.92; p < 0.0001). The rotated Hessian provides an accurate means of approximating the orientation-specific neural response to electrical stimulation.

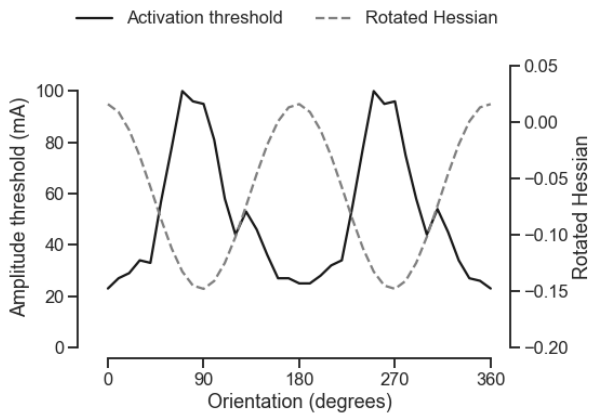

Figure 4. Amplitude threshold and rotated Hessian approximation shown over a range of axon orientations; the rotated Hessian captures the behaviour of the biophysical model, with high rotated Hessian metrics predicting low amplitude thresholds.

IV. Discussion

These results show that it is possible to rapidly compute a metric that predicts the neural response to electrical stimulation that can be generalized to a field and that accounts for the orientation selectivity of axons.

This method is, however, only applicable to fibres with a constant trajectory, i.e. regions where the fibres are locally straight. This is useful for cases such as the spinal cord or peripheral nerves or central tracts outside of local changes of orientation. Accounting for activation with locally complex morphology is more challenging – requiring, for example, projection of the field onto the trajectory of interest. These methods, while useful, lend themselves less well to generalization to a field.

Biophysical measures are useful and highly accurate, but are slow to compute and are not easily applied to the field produced by an extracellular electrode in order to evaluate the regions where activation is likely to occur. The metric presented here provides a simple means to generalize a classic approximation of the effect of stimulation on neural tissue to a field, while retaining information on orientation.

Approaches to calculating the volume of tissue activated in response to deep brain stimulation have provided a number of methods of computing the regions likely to be activated by stimulation on a field [14]. These include very simple metrics like the electric field norm, methods based on Rattay's activating function and complex methods based on detailed biophysical models. However, these methods are largely invariant to axon orientation. This provides a poor approximation for scenarios where local, directional axons are targeted, such as in the case of peripheral nerve stimulation. The orientation of axons with respect to the electric field is an important consideration, and any simplified metrics should maintain this relationship as much as possible.

The present work demonstrates a method derived from generalizing Rattay's activating function to a field. By using rotations of the Hessian matrix of the electric potential produced by stimulation, it is possible to compute the activation for axons of arbitrary orientation and to generalize this to the entire domain modelled. This allows rapid computation and simple visualizations of the regions of activation for axons of specific orientations.

This provides a useful, computationally efficient method for approximating activation for the development of novel neural interfacing techniques and the optimization of parameters for neuromodulation therapies.

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