Abstract—For analyzing the electrical stimulations to achieve selective neural activation, it is computationally time-consuming to solve the electric fields coupled with nonlinear nerve models. The electric-field-based descriptor considering nerve dynamics is an effective tool for predicting neural firings and optimizing stimulation configurations. Based on the mathematical analysis of nonlinear nerve models, this paper explains the mechanism behind temporal interference stimulation and investigates the effects of field descriptors on the predictions of neural firing. Two field descriptors (electric and activation) derived from the 1st and 2nd order spatial derivatives of the electric potential for predicting neural activations are compared. The prediction results of both the electric and activation field descriptors are validated by published numerical and experimental results. While both predict the activation of different nerve fibers, the activation descriptor that requires a larger finite-element mesh-number than the electric field descriptor for the same computational accuracy is introduced. However, the intrinsic nonlinearity of nerves is responsible for TI stimulation of deep tissues. However, an explicit formulation of the nerve responses to the input currents is not available due to the high-order nonlinearity of a nerve model [8]. To understand and effectively utilize TI stimulation, a theoretical analysis of the nonlinear nerve models under different inputs is essential to guide further applications of FES.

Functional electric stimulation (FES) applies low frequency (LF) electrical current pulses to activate motor nerve fibers artificially, which causes muscle contraction to achieve functional movements. FES has been widely used in stroke rehabilitation [1] and voluntary-function restoration [2] because of its portable, harmless and cost-effective properties [3]. However, the difficulty to achieve selective FES has limited its application due to the complexity of modeling the nonlinear FES process. Built upon the concept of an electric field descriptor [4] that predicts spectral distribution of local electric fields, this paper investigates the role of nonlinear nerve dynamics on selective neuromuscular activation under stimulating fields.

Single high-frequency (HF) stimulations have been extensively studied for blocking nerve activations at suprathreshold levels (typically above 5kHz for human nerves) [5][6]. On the other hand, temporal interference (TI) stimulation, where two HF currents of kHz are inputted to surface electrodes, has recently been explored to stimulate deep brain (hippocampus) tissue in mice without disturbing the surrounding tissues [7]. According to our prior analyses [4], the intrinsic nonlinearity of nerves is responsible for TI stimulation of deep tissues. However, an explicit formulation of the nerve responses to the input currents is not available due to the high-order nonlinearity of a nerve model [8]. To understand and effectively utilize TI stimulation, a theoretical analysis of the nonlinear nerve models under different inputs is essential to guide further applications of FES.

Frankenhaeuser-Huxley (FH) model derived from experimental results [8] describes the dynamics of membrane voltage \( u_m \) and four state variables characterizing the sodium, potassium, and leakage membrane currents of myelinated nerve fibers. Due to the difficulty to mathematically solve the five-dimensional FH model, a simplified two-dimensional FitzHugh-Nagumo (FN) model [9] has been proposed for analyzing the nonlinearity of nerves. FN model has been proven as a projection from the high-dimensional nerve model and can produce various experimentally observed phenomenon. Using the FN model, the mechanism behind HF block has been analytically and numerically studied in [10], which provides a clue to model and analyze TI stimulation.

In our earlier study [4], an electric field descriptor was proposed for predicting local electric fields capable of driving neural activities. The field descriptor was derived from the norm of electric field intensity along the interest nerve-fiber direction, or alternatively the first-order spatial derivative of the electric potential. The field descriptor distributions can well predict the selective and steerable stimulations reported in TI experiments [7] and also explain the experimental results measured from human thigh under interferential currents [11]. As for the realistic neuron networks commonly encountered in deep brain stimulations where neurons are controlled by several excitatory or inhibitory synapses of other neurons [12], the generation and propagation sequences of action potentials (APs) in different neurons may change the temporal function of...
the networks. Thus, it is essential to determine the Ranvier nodes that initiate action potentials under electrical stimulation for determining the overall network states. In this paper, we analyze the effects of different methods on the effectiveness of a field descriptor based on mathematical analyses of the nonlinear neural dynamics. Specifically, we introduce a second-order spatial derivative in the field descriptor and show that the activation sequences of Ranvier nodes for given stimulation configurations can be identified. The remainder of this paper provides the following:

- Section II begins with the formulation of the nerve dynamics for analyzing a multi-compartment nerve model using a FN model solved by a multiple time-scale method to observe its HF and LF responses. 
- Based on a mathematical analysis, the input to the multi-compartment FH nerve model from an external stimulating electric field (2nd order spatial derivative) is utilized to design a field descriptor. 
- The effects of different methods on the effectiveness of the field descriptor are analyzed in Section III by comparing the predictions from the field descriptor distributions computed with (1st, 2nd) order spatial derivatives and the TI numerical/experimental findings [7] [13].

II. THEORETICAL BASIS

Consider the stimulation configuration shown in Fig. 1(a) where the current sources (i_{in}, i_{sh}) are applied at the electrodes (contact area A_i) relative to the reference (potential u_{ref}) and all other boundary surfaces are assumed electrically insulated. Figure 1(b) shows an equivalent circuit of a nerve membrane for the Frankenhaeuser-Huxley (FH) nerve model that describes the membrane ionic current i in nerve and change in membrane voltage u_m during a membrane AP. To optimize the activation of myelinated nerve fibers, a typical strategy is to solve the Maxwell equation with appropriately defined boundary conditions (Appendix A) numerically for an electric field solution as input to a multi-compartment nerve model to predict the directional AP propagation. The experiment-based FH nerve model [8] [14] has been widely accepted for simulating nerve’s excitability-oscillatory systems. For the two HF inputs defined in (4a–f) where η is a positive number close to 1 to ensure that the differential frequency |ω − ηω| is near to the system resonance frequency, the multi-compartment FH model (Appendix B) is analyzed analogously using the FN model (5) to solve for the membrane voltage u_m and the recovery variable w:

\[
\frac{dw}{dt} = \left[ u_m - u_m^3 / 3 - w \right] + \frac{\phi_m}{\xi(u_m + \beta - \gamma w)}
\]

Since the HF inputs provide an appreciable effect on the system dynamics only for sufficiently large amplitudes, the two input amplitudes are related to their frequencies with the ratio (a_1, a_2).

In (5), (ξ, γ) are the scaling parameters and β is set to adjust the unstable equilibrium corresponding to action threshold. The parameters are chosen to ensure that the neuron represented by (5) is in an excitatory regime [16].

A. Local 2nd Order Derivative

Generated by two sinusoidal currents with amplitudes (I_a, I_b) and frequencies (f, f + Δf) applied on the boundary as shown in Fig. 1, the potential u(r, t) at point r has the form (1) where (φ_a, φ_b) are the phases caused by the net effects of initial phase and phase-deviation on the permittivity ε:

\[
u(r,t) = u(r, t) \cos(2\pi ft + \phi_a) + u_b(r) \cos[2\pi(f + Δf)t + \phi_b]
\]

Since the external potential u_b at point r is equal to u(r, t), the external input to the Ranvier nodes of the multi-compartment model (Fig. 1b) formulated by the differential equation (B.1a) is the 2nd order difference of the electric potential:

\[
\delta^2 u \equiv u_{x,x} - 2\delta u_{x,n} + u_{x,n+1}
\]

Thus, the local 2nd order derivative of the potential along \( \hat{n} \) (Fig. 1a) is defined as the activation function (AF) [15]:

\[
\frac{\partial^2 u}{\partial n^2} = \frac{\partial^2 u_r}{\partial n^2} \cos(2\pi ft + \phi_a) + \frac{\partial^2 u_b}{\partial n^2} \cos[2\pi(f + Δf)t + \phi_b]
\]

In (3), \( \hat{n} \) is the coordinate variable along \( \hat{n} \).

B. Nonlinear Neural Dynamic Model

Because of the complexity involved in the FH model [8] for describing myelinated nerve fibers, the 2D FitzHugh- Nagumo (FN) model [16] that has been proven as a projection from the higher-order nonlinear nerve model (such as FH model), is widely used to characterize the nonlinear dynamics of nerve’s excitability-oscillatory systems. For the two HF inputs defined in (4a–f) where η is a positive number close to 1 to ensure that the differential frequency |ω − ηω| is near to the system resonance frequency, the multi-compartment FH model (Appendix B) is analyzed analogously using the FN model (5) to solve for the membrane voltage u_m and the recovery variable w:

\[
\omega = 2\pi f, \quad \eta \omega = 2\pi(f + Δf), \quad \phi_m = \phi_a = 0
\]

\[
\frac{d}{dt} u_m = \left[ u_m - u_m^3 / 3 - w \right] + \frac{\phi_m}{\xi(u_m + \beta - \gamma w)} + \left[ a_1 \omega \cos(\alpha t) + a_2 \eta \omega \cos(\eta \omega t) \right]
\]

(4a–d)

(4e, f)

(5)

Since the HF inputs provide an appreciable effect on the system dynamics only for sufficiently large amplitudes, the two input amplitudes are related to their frequencies with the ratio (a_1, a_2).

In (5), (ξ, γ) are the scaling parameters and β is set to adjust the unstable equilibrium corresponding to activation threshold. The parameters are chosen to ensure that the neuron represented by (5) is in an excitatory regime [16].
By applying the multiple time-scales method \cite{17} and defining a fast time \( \tau = \omega t \) (\( t \) is thus called a slow time) \cite{10}, the two time-scales \( t \) and \( \tau \) are used to expand the solution of (5) in powers of small parameter \( \omega^{-1} \):
\[
\begin{pmatrix}
 u_n(t) \\
 w(t)
\end{pmatrix} \approx \begin{pmatrix}
 u_{n0}(t, \tau) \\
 w_0(t, \tau)
\end{pmatrix} + \omega^{-1} \begin{pmatrix}
 u_{n1}(t, \tau) \\
 w_1(t, \tau)
\end{pmatrix} \tag{6}
\]

For HF stimulation (implying a small \( \omega^{-1} \)), the 1st term in the right-hand side of (6) is dominant. Due to the proximity between the frequencies \( \omega \) and \( \eta \omega \), we suppose that the functions \( u_{n0}, u_{n1}, w_0 \) and \( w_1 \) are \( 2\pi \) periodic in \( \tau \). Since \( \partial u / \partial t = \omega u \), the derivative of (6) gives
\[
\frac{d}{dt} \begin{pmatrix}
 u_n \\
 w
\end{pmatrix} = \left( \omega \frac{\partial}{\partial \tau} + \frac{\partial}{\partial t} \right) \begin{pmatrix}
 u_{n0} \\
 w_0
\end{pmatrix} + \left( \frac{\partial}{\partial \tau} + \omega^{-1} \frac{\partial}{\partial t} \right) \begin{pmatrix}
 u_{n1} \\
 w_1
\end{pmatrix} \tag{7}
\]

Substituting (6) and (7) into (5) followed by equating the terms proportional to \( \omega^0 \), we have
\[
\frac{\partial}{\partial \tau} \begin{pmatrix}
 u_{n0} \\
 w_0
\end{pmatrix} = \begin{pmatrix}
 a_1 \cos(\tau) + a_2 \eta \cos(\eta \tau) \\
 0
\end{pmatrix} \tag{8}
\]

The terms proportional to \( \omega^1 \) are obtained similarly:
\[
\begin{pmatrix}
 \partial u_{n0} / \partial t + \partial u_{n1} / \partial \tau \\
 \partial w_0 / \partial t + \partial w_1 / \partial \tau
\end{pmatrix} = \begin{pmatrix}
 u_{n0} - u_{n0} / 3 - w_0 \\
 \xi (u_{n0} + \beta - \gamma w_0)
\end{pmatrix} \tag{9}
\]

Since \( \partial \tau / \partial t = \omega^{-1} \approx 0 \), the solutions to (8) have the form in (10):
\[
\begin{pmatrix}
 u_{n0}(t, \tau) \\
 w_0(t, \tau)
\end{pmatrix} = \begin{pmatrix}
 \bar{u}_n(t) \\
 \bar{w}(t)
\end{pmatrix} + \begin{pmatrix}
 a_1 \sin \tau + a_2 \sin(\eta \tau) \\
 0
\end{pmatrix} \tag{10}
\]

The (1st, 2nd) terms in the right-hand side of (10) correspond to the (slow, fast) time responses, respectively. To solve for the unknown slow responses \( \bar{u}_n \) and \( \bar{w} \), (10) is substituted into (9) leading to (11a, b) which are then averaged over the range \([0, 2\pi]\) for \( \tau \) to eliminate the fast-time terms:
\[
\begin{pmatrix}
 \frac{d}{dt} \bar{u}_n \\
 \frac{d}{dt} \bar{w}
\end{pmatrix} = \begin{pmatrix}
 \bar{u}_n - \frac{1}{3} (\bar{u}_n + a_1 \sin \tau + a_2 \sin(\eta \tau)) \\
 \xi (\bar{u}_n + \beta - \gamma \bar{w}) + (a_1 \sin \tau + a_2 \sin(\eta \tau))
\end{pmatrix} + \begin{pmatrix}
 a_1 \sin \tau + a_2 \sin(\eta \tau) \\
 0
\end{pmatrix} \tag{11a}
\]

\[
\begin{pmatrix}
 \frac{d}{dt} \bar{u}_n \\
 \frac{d}{dt} \bar{w}
\end{pmatrix} = \begin{pmatrix}
 \bar{u}_n - \frac{1}{3} (\bar{u}_n + a_1 \sin \tau + a_2 \sin(\eta \tau)) \\
 \xi (\bar{u}_n + \beta - \gamma \bar{w}) + (a_1 \sin \tau + a_2 \sin(\eta \tau))
\end{pmatrix} \tag{11b}
\]

Noting that \( \eta \) is close to 1 and \( (u_{n1}, w_1) \) are \( 2\pi \) periodic in \( \tau \), we have (12a–d) with the integration constants \( (c_{n0}, c_{n1}) \) set to 0 by adjusting the unstable equilibrium via setting \( \beta \):
\[
\int_0^{2\pi} \sin \tau d\tau = 0, \quad \int_0^{2\pi} \sin \eta \tau d\tau \approx 0,
\int_0^{2\pi} \frac{\partial u_{n1}}{\partial \tau} d\tau = c_{n1} = 0, \quad \int_0^{2\pi} \frac{\partial w_1}{\partial \tau} d\tau = c_{n1} = 0 \tag{12a–d}
\]

With (12a–d), averaging (11a, b) over \([0, 2\pi]\) for \( \tau \) leads to
\[
\frac{d\bar{u}_n}{dt} \approx \frac{1}{6} (\bar{u}_n - \frac{1}{3} \bar{w} - \frac{1}{2} a_1 \bar{u}_n) \tag{13a}
\]

\[
\frac{d\bar{w}}{dt} \approx \xi (\bar{u}_n + \beta - \gamma \bar{w}) \tag{13b}
\]

Using trigonometric relations, the LF \( (1-\eta)\omega \) component in (13a) is derived from the cubic term in (11a). The coupled equations (13a, b) represent a parametric oscillation system about the slow variable \( \bar{u}_n \), where the damping term contains a varying parameter characterized by the LF \( (1-\eta)\omega \). Thus, the solution to \( \bar{u}_n \) contains this LF component oscillating in the characteristic timescale of the original FN system.

In summary, the membrane voltage \( u_{ad} \) is a nonlinear function of the HF input in (3) and contains LF components in its spectrum. As seen in (6), (10) and (13a, b), the membrane voltage response for TI stimulation can be decomposed to a slow \( \bar{u}_n(\tau) \) and a fast \( a_1 \sin \tau + a_2 \sin(\eta \tau) + \omega^{-1} u_{ad}(t, \tau) \) as illustrated in Fig. 2 (blue curves). In Eq. (B.4b–d) of FH model, the exponential terms can be expressed as a nonlinear polynomial of \( u_{ad} \):
\[
1 - a_1 e^{(\nu_{ad,n}-\nu)} \approx 1 - a_1 e^{\nu} \sum_{k=1}^{\infty} \frac{1}{k!} \lambda^k \mu_n \tag{14}
\]

which will also bring LF components \( k(1-\eta)\omega \) \((k=1, 2)\) to the membrane voltage response under TI stimulations.

\[\text{Fig. 2. Illustration of input and response of the FN nerve model.}\]

\[\text{C. Activation Field Descriptor}\]

The AF magnitude that is a nonlinear function containing infinite frequency components including \( \Delta f \) is chosen to derive the field descriptor. As an auxiliary process, the power density spectrum of AF is provided:
\[
\left( \frac{c_2 u^2}{\partial \tau^2} \right) = \sum_{m=\omega}\frac{1}{c_1} \left( \frac{c_1 u^2}{\partial \tau^2} \right) + \sum_{m=\omega} \left( \frac{c_1 u^2}{\partial \tau^2} \right) + \sum_{m=\omega} \left( \frac{c_1 u^2}{\partial \tau^2} \right)
\]

where \( c_0 = \frac{1}{2} \left( \frac{c_1 u^2}{\partial \tau^2} \right) + \sum_{m=\omega} \left( \frac{c_1 u^2}{\partial \tau^2} \right) + \sum_{m=\omega} \left( \frac{c_1 u^2}{\partial \tau^2} \right) \)
\[
f_1 = \Delta f, \quad f_2 = f, \quad f_3 = 2 f + \Delta f, \quad f_4 = 2 f + 2 \Delta f
\]

As indicated in (15c), the power density spectrum consists of a static and 4 frequency components including the low frequency \( \Delta f \) (coefficient \( c_1 \)) in addition to 3 HF components (coefficients \( c_2, c_3 \) and \( c_4 \)). Based on (15a), the AF magnitude can be expressed as a Fourier series in (16) where \( m^2 \) is the smallest integer such that \( m^2 \Delta f + 2nf \geq 0 \) and the numerically calculated coefficients \( (F_{m0}, \varphi_{m0}) \) are analyzed using Fast Fourier Transform (FFT) of \( \infty u^2/\partial \tau^2 \).
\[
\left( \frac{c_2 u^2}{\partial \tau^2} \right) = \sum_{m=\omega} \sum_{n=0} F_{\omega} \cos \left( \frac{2 \pi (m \Delta f + 2nf) \tau + \varphi_{m0}}{\lambda^2 \mu_n} \right) \tag{16}
\]
Since the resonance frequencies of the nerve models are within LF range [18], the LF amplitudes of (16) are summed up to compose the field descriptor $F_\lambda$:

$$F_\lambda = \sum |\hat{F}_{mn}| \text{ where } \hat{F}_{mn} = \begin{cases} F_{mn} & \text{if } f_{mn} < (m\Delta f + 2nf_0) < f_{max} \\ 0 & \text{Otherwise} \end{cases}$$  \hspace{1cm} (17)

The $(f_{min}, f_{max})$ values depend on the frequency range that can activate the nerves. For the cases considered, $(f_{min}, f_{max})$ are set at $(0, 500)$Hz according to the normal LF stimulation range [19] and HF inhibition frequency (normally in kHz) [6].

III. RESULTS AND DISCUSSION

Numerical investigations were conducted to evaluate the effectiveness of the field descriptor $F_\lambda$ for predicting neural activation by comparing results with that predicted using $F_E$ [4] based on 1st order derivative $\partial^2 u/\partial \phi^2$. The governing equation (Appendix A) of the electric fields and BCs for a homogenous media were solved using commercial FEM software COMSOL where the (element type, number of elements) are listed in Table I. The solutions to the FH model for a specified set of external potential $u_{ext}$ were numerically solved with parametric values in Table II and initial conditions: (B.1e), (B.3d–g). An activated state is identified using the procedure similar to [14] as follows: $u_{th}$ achieves a depolarization threshold (90mV between the values of subthreshold and suprathreshold stimulations) resulting an AP propagating along the fiber. Two shapes (Table I mimicking human limbs with different fiber directions are considered where the results are summarized in Figs. 3–5:

- **2D disk** (Fig. 3) for comparing with numerical results simulating an infinite homogeneous cylinder in [13].

- **3D cuboid** (Figs. 4 and 5) for comparing with published analyses and experimental results [4].

| Source configurations: $(L_0, L_1): (L_0, L_1) = (5, 5)$ mA |
| Frequency: $(f, f+\Delta f) = (1000, 1010)$Hz |
| Media: $\sigma = 0.015$ S/m, $\varepsilon_r = 1.1 \times 10^4$ |

### Table I. Parameters used in numerical studies

(a) Disk: $\theta = 25^\circ$, $R = 50$, $r = 4$ (mm)
Fiber angle: $0^\circ$, $25^\circ$, $45^\circ$, $90^\circ$
FEM (triangles, 6342 elements)

(b) Cuboid: $L = 15$, $h = 60$, $r = 2$
$d = 6$, $H = 40$, $\theta = 20^\circ$
$a_0 (0, 0, 0)$, $a_+ (+4, 0, 0)$ (mm)
FEM (tetrahedra, 354532 elements)
Nerve model: 61 nodes

For the 2D disk media, the $F_\lambda$ distributions for 4 fiber directions ($0^\circ$, $25^\circ$, $45^\circ$ and $90^\circ$ with respect to x axis) on the electrode plane are simulated in Fig. 3(a). To help quantitative visualization, Fig. 3(b) plots the $F_\lambda$ curves along the 4 fibers; showing that the $F_\lambda$ magnitudes are large for fibers oriented at $25^\circ$, $45^\circ$ and $90^\circ$ while zero for fiber oriented at $0^\circ$. As a basis for verifying the computation, Fig. 3(c) summarizes the numerical results reported in [13] where the fiber responses were computed by inputting the electric fields solved from Maxwell’s equations to multiple compartment Hodgkin-Huxley nerve model [20] with 11 Ranvier nodes. As revealed in Fig. 3(a, b), the $90^\circ$-oriented fiber is most easily activated (current threshold at 160μA) although the $F_\lambda$ magnitude on this direction is not the highest. However, the $F_\lambda$ integration along the $90^\circ$-oriented fiber is the largest among 4 fibers.

As shown in Table I schematically illustrating the 3D cuboid configuration where 61 Ranvier nodes $(n = -30)$ with internode length $L = 2$mm and central node $(n = 0)$ located at $a_0(0, 0, 0)$ or $a_+ (+4, 0, 0)$ were used in the FH neuron model, 3 fibers oriented at $a_0 (0, \cos 20^\circ, \sin 20^\circ)$ were simulated for verifying the mathematical analysis (Section II.B). Figures 4(a, b) show the membrane voltage responses $u_{th}(t)$ of node 0 for fiber at $(a_0, a_+)$ in the 3D cuboid along with their FFTs, where APs are generated periodically with a frequency of $\Delta f = 10$Hz under TI stimulation. Figure 5 compares the effects of two field descriptors ($F_\lambda$ and $F_E$) on the activation of the fibers. The activations of the field descriptors $F_\lambda$ and $F_E$ on the fiber plane and along fiber $(a_0, a_+)$ are compared in Figs. 5(a) and 5(b) respectively. Using the multi-compartment FH model, the computed membrane voltages of the three fibers are plotted in Fig. 5(c) with the axonometric and top views. The findings from Figs. 3–5 are summarized as follows:

- Figure 4 verifies the mathematical analysis in Section II.B, where the frequency peaks at around 10Hz and 1000Hz corresponding to the slow- and fast-time responses. The infinite frequency components of $u_{th}$ (right plot of Fig. 4) align with our analysis that the exponential terms in FH model bring LF components $k^2(\omega - \omega_0a)$ ($k = 1, \ldots$) to $u_{th}$. Nevertheless, it should be noted that the analysis using FN model only provide an approximate of the solution to FH equations since only a nonlinear cubic term is considered in FN model. Thus, the exact spectrum of $u_{th}$ and the amplitude of different frequencies still cannot be solved analytically.

- The activation field descriptor $F_\lambda$ (Section II.C) is verified by comparing published results with Figs. 3–5. The $F_\lambda$ predictions in Fig. 3(a) are consistent with the results [13] shown in Fig. 3(c) that only the fibers at $25^\circ$, $45^\circ$ and $90^\circ$ can be activated while the fiber at $0^\circ$ generates no AP. As compared to $F_\lambda$ peak value, $F_\lambda$ integration along the specific fiber is a better estimation of the stimulus threshold for considering the current redistribution between adjacent Ranvier nodes. In Fig. 4, the fiber at $a_0$ responses with periodic APs, while that at $a_+$ only generates the onset AP followed by HF oscillations, which can be predicted by the $F_\lambda$ distribution in Fig. 5(a). Both $F_\lambda$ and $F_E$ in Fig. 5(a) peak at the center area for TI stimulation, and maximize along the fiber at $a_0$, which coincides with the experimental results in [7] where the nerve in the central area between the two electrode pairs is activated while the fibers near the electrodes are silent.

- The significance of $F_\lambda$ on precise activation prediction is illustrated by comparing its distribution with that of $F_E$ in Fig. 5(a): While $F_E$ reaches a plateau at $(0, 0, 0)$, the field descriptor $F_\lambda$ reveals a valley. In both 1st and 2nd rows of Fig. 5(c), the APs propagated to node 0 are initiated at nodes $\pm 4$, whose coordinates coincide with the peak positions of $F_\lambda$ distribution in Fig. 5(b). These results suggest that while both ($F_\lambda$, $F_E$) predict the activation of different nerve fibers, $F_\lambda$ offers information on AP initiation of different nodes within a fiber, which is essential in practice where more realistic neuron networks are expected.
Fig. 3. Field descriptor along 4 directions. (a) $F_\alpha$ in the electrode plane. (b) $F_\alpha$ distribution along the fiber. (c) Current thresholds for fiber activation [13].

Fig. 4. Responses of $u_m$ (left) and their FFT (right) at (a) $\alpha_0$ and (b) $\alpha_n$.

Fig. 5. Verification. (a) $F_\alpha$ and $F_E$ distributions on fiber plane. (b) $F_\alpha$ and $F_E$ distributions on fiber ($\alpha_0$, $\alpha_n$). (c) Membrane voltages $u_m$ of the fibers at ($\alpha_0$, $\alpha_n$).

- Due to the noise brought by differential operator, the $F_\alpha$ curves computed from $2^{nd}$-order derivatives are much rougher than $F_E$ curves computed from $1^{st}$-order derivatives as shown in Fig. 5(b). Thus, the finite-element-mesh number required for computing accurate $F_E$ is much smaller than that required for computing accurate $F_\alpha$.

IV. Conclusion

By solving the FN nerve model under HF inputs using the multiple time-scales method, the frequency coupling phenomenon (behind TI stimulation) in nonlinear excitable oscillatory systems has been explained mathematically, which forms the basis to construct the field descriptor for predicting neural activations. Two field descriptors, $F_\alpha$ and $F_E$, based on the $1^{st}$ and $2^{nd}$-order spatial derivatives of the potential respectively, have been developed and compared. The results of both $F_\alpha$ and $F_E$ for predicting neural activations were validated by comparing with published TI numerical and experimental findings. Due to their computational advantages over complex nonlinear nerve models, both the field descriptor $F_\alpha$ and $F_E$ provide an effective tool for real-time FES applications where the neuron states need to be feedback. Although $F_\alpha$ derived from the $2^{nd}$ order spatial derivative of the potential field takes a larger finite-element mesh number than $F_E$ from the $1^{st}$ order spatial derivative of the same field for the same computational accuracy, it is superior to $F_E$ for being able to identify the activation sequence of Ranvier nodes. $F_\alpha$ can be further improved by considering the current redistribution between adjacent Ranvier nodes to estimate the stimulation thresholds of myelinated fibers [21].

Appendix A

Electric Field Modeling

The stimulating electric field $u(r, t)$ where $(r, t)$ are the (position vector, time) is governed by the current conservation law (A.1) where ($\sigma$, $\varepsilon_0$) denote (conductivity, relative permittivity) and $\varepsilon_0 = 8.85 \times 10^{-12} \text{F/m}$:

$$ \nabla \cdot \left[ \sigma + \varepsilon_0 \frac{\partial}{\partial t} \right] \nabla u(r, t) = 0 $$

(A.1)

As defined in Fig. 1(a), the Neumann (BC$_0$, BC$_1$) and Dirichlet BC$_2$ are given by (A.2a–c) where $n$ is the normal vector at the boundary and integration accounts for the shunt effect on BC$_2$:

Electric insulation at BC$_0$: $n \cdot \nabla u = 0$  \hspace{1cm} (A.2a)

Current source at BC$_1$: $\int_A (\sigma n \cdot \nabla u) dS = i_s$  \hspace{1cm} (A.2b)

Electric potential at BC$_2$: $u = u_{ref}$  \hspace{1cm} (A.2c)

Appendix B

Multiple Compartment Nerve Model [8] [14]

The membrane voltage $u_m$ during activation is related to the stimulating electric field (Fig. 1b). With the variables defined in Table II, the membrane current at node $n$ is given by the Kirchhoff's current law in (B.1a–d) where $u_{m,n}$ is the potential difference between the internal $u_{i,n}$ and external $u_{e,n}$ relative to resting $u_r$, $i_n$ is the ionic current, and $(G_m, C_m)$ are the (internodal conductance, membrane capacitance):

$$ \frac{du_{m,n}}{dt} = \frac{1}{C_m} \left[ G_m \left( u_{m,n-1} - 2u_{m,n} + u_{m,n+1} + u_{e,n-1} - 2u_{e,n} + u_{e,n+1} \right) - i_n \right]$$
\[ G = \frac{\pi d^2}{4 \rho L} \]

where \( G \), \( d \), \( \rho \), and \( L \) are defined.

The initial conditions are provided in (B.1e):

\[ u_{m.o}(0) = 0, \quad n = \cdots, -2, -1, 0, 1, 2, \cdots \]

(B.1e)

The FH model that describes the nodal nonlinear relation between \( u_{m.o} \) and \( \dot{i}_j \) is given in (B.2–5) where the node index \( n \) is omitted in the subscripts for simplicity:

\[
\begin{align*}
\dot{i}_n &= \pi d j, j \quad \text{where } j = j_{na} + j_p + j_{li} \\
\frac{d \gamma}{dt} &= \left( \eta_i(1 - \gamma) - \eta_j \right) \gamma = h \\
\eta &= \frac{A}{1 + e^{-\eta_i(1 - \gamma)} - \eta_j} \\
\gamma_{rel} &= \frac{A(u_{m} - B)}{1 - e^{-(u_{m} - B)}}.
\end{align*}
\]

(B.2a–d)

where \( \eta = \frac{A}{1 + e^{-u_{m} - B}} \) and \( \eta_j = \frac{A(u_{m} - B)}{1 - e^{-(u_{m} - B)}}. \)

(B.3b, c)

\[ m(0) = 0.0005, \quad l(0) = 0.8249, \quad n(0) = 0.0268, \quad p(0) = 0.0049 \]

(B.3d–g)

\[
\dot{j}_k = g_L (u_m - u_i) \]

(B.4a)

\[
j_k = (u_m + u_i) \frac{1 - a_F e^{i(u_m + u_i)}}{1 - e^{i(u_m + u_i)}} \frac{F \lambda}{k} \]  \[ \left( \frac{[\text{Na}]_n}{[\text{K}]_n} \right)^k \]  \[ \frac{k + K}{[\text{Na}]_n} \]

(B.4b–d)

where \( a_F = a_p \left( \frac{[\text{Na}]_n}{[\text{K}]_n} \right)^k \) and \( \lambda = \frac{F}{RT} \).

(B.5a–c)

**Table II. Symbols and values used in the FH model calculation.**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>((d, D))</td>
<td>(Axon, fiber) diameter</td>
<td>((14, 20)) μm</td>
</tr>
<tr>
<td>((l, L))</td>
<td>(Nodal gap, intermode) length</td>
<td>((2.5, 2000)) μm</td>
</tr>
<tr>
<td>(\rho)</td>
<td>Axoplasm resistivity</td>
<td>(110 \Omega) cm</td>
</tr>
<tr>
<td>(e_{ww}, e_{ww}, e_{ww})</td>
<td>(Sodium, potassium nonspecific) permeability constant</td>
<td>(8, 1.2, 0.54 \times 10^{-3}) cm/s</td>
</tr>
<tr>
<td>(c_m)</td>
<td>Membrane capacitance</td>
<td>(40 \mu F/cm^2)</td>
</tr>
<tr>
<td>(g_L)</td>
<td>Leak conductance</td>
<td>(0.0303 , \text{mho/cm}^2)</td>
</tr>
<tr>
<td>(u_c)</td>
<td>Leak current equilibrium potential</td>
<td>(0.026 , \text{mV})</td>
</tr>
<tr>
<td>(u_r)</td>
<td>Resting potential</td>
<td>(-70 , \text{mV})</td>
</tr>
<tr>
<td>([\text{Na}]<em>{in}, [\text{K}]</em>{in})</td>
<td>External (sodium, potassium) concentration</td>
<td>((114.5, 2.5) , \text{mM} /L)</td>
</tr>
<tr>
<td>([\text{Na}]<em>{in}, [\text{K}]</em>{in})</td>
<td>Internal (sodium, potassium) concentration</td>
<td>((13.74, 120) , \text{mM} /L)</td>
</tr>
<tr>
<td>(F)</td>
<td>Faraday's constant</td>
<td>(96.514 , \text{kJ/mol})</td>
</tr>
<tr>
<td>(R)</td>
<td>Gas constant</td>
<td>(8.314 , \text{J/(mol}K))</td>
</tr>
<tr>
<td>(T)</td>
<td>Absolute temperature.</td>
<td>(298.15 , \text{K})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(h (\eta_p, \eta_g))</th>
<th>(m (\eta_p, \eta_g))</th>
<th>(n (\eta_p, \eta_g))</th>
<th>(p (\eta_p, \eta_g))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0.5, 1.5)</td>
<td>(0.36, 0.4)</td>
<td>(0.02, 0.05)</td>
<td>(0.006, 0.09)</td>
</tr>
</tbody>
</table>

**REFERENCES**


