International Journal of Research in Engineering and Science (IJRES)
ISSN (Online): 2320-9364, ISSN (Print): 2320-9356
www.ijres.org Volume 11 Issue 1 ǁ January 2023 ǁ PP. 180-188

A systematic study of the mathematical modeling of the strength-duration relationship

Burhan BEZEKCI[*1]
[*1]*Faculty of Engineering and Architecture, Kilis 7 Aralik University, Kilis 79000, Turkey,*
burhanbezekci@kilis.edu.tr

Abstract
The mathematical approaches that can be used to formulate the relationship between the strength of a stimulation pulse and its duration are examined in a spatially extended FitzHugh–Nagumo model. Apart from some known purely phenomenological methods specifically introduced to formulate the strength-duration curve, we also propose other mathematical empirical relationships widely used in optical science and optical industry for use in threshold curve fitting. The empirical theoretical predictions are compared with the numerical simulations, highlighting different qualitative agreement.

Keywords: *FitzHugh–Nagumo model, excitability, strength-duration, threshold, Lapicque*

Date of Submission: 02-01-2023 Date of acceptance: 14-01-2023

I. INTRODUCTION

Neurons are specialized cells in the body of living organisms and they are basically responsible for transmitting information to other nerve cells or other types of cells, such as muscles. Transient electrical signals are considered to be particularly important as they carry time-sensitive information over long distances and these electrical signals are produced by changes in the current flow into and out of the cell [1]. This ability of nerve cells to generate and propagate electrical activity is called excitability. Communication between electrically coupled cells refers to an excitable medium and it is usually defined as nonlinear reaction-diffusion system, where the reaction term defines how the constituents of the system are transformed into each other, and the diffusion part provides propagation of information [2] (see alsohttp://www.scholarpedia.org/article/Excitable_media for more detailed explanation).

In a single cell excitable system or in a spatially extended excitable system, strength-duration curve is a powerful tool for evaluating the excitability. One of the most successful mathematical models in the field of electrophysiology is FitzHugh-Nagumo model, a prototype of a single cell excitable system [3–5]. Therefore, we specifically choose FitzHugh-Nagumo (FHN) model to analyze the strength-duration throughout this paper.

There are many different forms derived from the original FitzHugh-Nagumo equation that have been used as to model the cardiac/neuron dynamics and considered as a prototype for excitable systems. One of which(in one spatially extended form) has been introduced in [6] as

$$\begin{aligned} u_t &= u_{xx} + f(u) - v, \\ v_t &= \gamma(\alpha u - v), \end{aligned} \tag{1.1}$$

where $f(u)$ is only nonlinear cubic polynomial function $f(u) = u\,(u-\beta)(1-u)$, the variables u and v represent the state of excitation of the medium and the recovery variable, respectively. The small positive parameter γ describes the ratio of time scales of the variables u and v, α is a constant, $\beta \in (0, 1/2)$ is threshold parameter.

We aim to study the asymptotic behaviour of the solution of (1.1) as $t \to \infty$ subject to the following initial and boundary conditions,

$$\begin{aligned} u(x,0) = u_r,\ v(x,0) = v_r, \\ u_x(0,t) = -I_s\Theta(t_s - t),\ v_x(0,t) = 0, \end{aligned} \tag{1.2}$$

where $(u_r, v_r) = (0{,}0)$ is the resting state for the system and $\Theta(\cdot)$is the Heaviside step function. The parameters I_s and t_s respectively represent the stimulus strength and duration of the stimulus. The solution of (1.1) with initial and boundary conditions given by (1.2) either approach the propagating pulse solution or the resting state as $t \to \infty$. The graphical representation of the relationship between $t_s$and $I_s$that separates these two outcomes is called a strength-duration curve.

II. ESSENTIAL NUMERICAL METHODS

From a mathematical point of view, numerical methods are necessary to study the boundary value problem since analytical results are not always possible to obtain explicitly. Even when analytical solutions are feasible it can be convenient to validate and estimate their accuracy by means of some numerical procedure. Thus, this section is devoted to numerical techniques for approximating strength-duration curve and the computation of the parameters in the analytical expressions.

2.1 DIRECT NUMERICAL SIMULATION

For numerical simulation of the FHN model we discretize the problem on a regular space grid on a finite interval $x \in [0, L]$ as an approximation of $x \in [0, \infty)$, with fixed space step Δ_x and a regular time grid with time stepΔ_t. In view of the discretization of the FHN model, u_i^j and v_i^j are denoted the numerical solutions at time $t = j\Delta_t$and position $x_i = i\Delta_x$such that$x_N = L$. We use explicit Euler forward difference in time whereas explicit second-order central difference approximation in space for the diffusion term is employed. Hence the discretization formula for the FHN model is

$$u_i^{j+1} = u_i^j + \frac{\Delta_t}{\Delta_x^2}\left(u_{i+1}^j - 2u_i^j + u_{i-1}^j\right) + \Delta_t f\left(u_i^j\right) - v_i^j, \tag{2.1}$$

$$v_i^{j+1} = v_i^j + \Delta_t \gamma\left(\alpha u_i^j - v_i^j\right),$$

where $f\left(u_i^j\right) = u_i^j\left(u_i^j - \beta\right)\left(1 - u_i^j\right)$. Meanwhile, considering that the initial condition is the unperturbed resting state and there is a constant current injected through the left boundary of the interval gives the followingdiscretization formula for initial and boundary conditions

$$u_i^0 = 0,\ u_0^0 = u_2^0 + 2\Delta_x I_s \Theta(t_s - t),\ u_{N+1}^0 = u_{N-1}^0, \tag{2.2}$$

$$u_0^{j+1} = u_2^{j+1},\ u_{N+1}^{j+1} = u_{N-1}^{j+1},$$

$$v_i^0 = 0,\ v_0^0 = v_2^0, v_{N+1}^0 = v_{N-1}^0,$$

$$v_0^{j+1} = v_2^{j+1},\ v_{N+1}^{j+1} = v_{N-1}^{j+1},$$

where no-flux Neumann boundary condition is applied at $x = 0$ and $x = L$.

Numerical procedure for identifying the threshold curve can be developed using the bisection method, an algorithm for finding the threshold values by means of some upper and lower estimates which are respectively known to be sufficient for ignition and to fail to ignite. The idea behind this shooting procedure is to numerically solve the FHN model (1.1) for initial and boundary conditions given by (1.2) using finite difference discretization formula described above, see (2.1) and (2.2).

Throughout this paper, we consider the FHN model with fixed values of the slow dynamics parameters $\gamma = 0.01$, $\alpha = 0.37$ and fixed value of the excitation threshold for the fast dynamics $\beta = 0.05$. Other parameters used for numerical computation are $\Delta_x = 0.03$ and $\Delta_t = 4\Delta_x^2/9$.

2.2 LEVENBERG-MARQUARDT ALGORITHM

The Levenberg-Marquardt algorithm is one of the most widely used standard iterative technique to solve nonlinear least-squares problems. This optimization algorithm, which was introduced firstly by Kenneth Levenberg in 1944 [7] and revised by Donald Marquardt in 1963 [8], provides a numerical solution to the following nonlinear least squares curve fitting problem:

$$S(\theta) = \sum_{i=1}^{m}[y_i - f(x_i, \theta)]^2, \tag{2.3}$$

where $(y_1, y_2, \cdots, y_m)$is the desired output vector, $f(x, \theta)$ is the function of an independent variable x and n parameters θ, and $S(\theta)$ is the function to be minimized.

The Levenberg-Marquardt algorithm is an iterative technique that starts with an initial guess for the n parameters θ that are updated at every iteration until a stopping criterion is satisfied, *i.e.*the absolute change in the parameter estimates between two consecutive iteration steps is less than a user-defined tolerance value. For each mathematical expression detailed below that can be used to describe the strength-duration relationship, the values of the parameters are obtained using the Levenberg-Marquardt algorithm.

III. MATHEMATICAL EXPRESSIONS FOR STRENGTH-DURATION CURVE

Due to the complex nature of the problem, it is not always possible to analytically investigate the behaviour of the solutions of the nonlinear reaction-diffusion systems. Therefore, several attempts have been made to establish the strength-duration relationship as experimentally tested theoretical models. Here we review some of these attempts that are dedicated to mathematically model electric current flow in excitable cells in (t_s, I_s)-plane along with some other theoretical formulas that have been originally proposed to describe the dispersion of optical materials.

3.1 LAPICQUE-WEISS (LW)

Phenomenological models dedicated to the studies of pulsed electrical stimulation goes as far back as 1901 when Weiss [9] experimentally derived a linear relationship between the threshold charge Q required to excite an axon and the pulse duration t_s, which is later on reformulated by Boston [10] in the following form

$$Q = I_{rh}(\tau + t_s), \tag{3.1}$$

where I_{rh} and τare considered to be coeff icients depending on the specimen type. This linear relation is known as the Weiss excitation law for the charge.

In 1907, French scientist Lapicque [11] (its translation version [12]) modeled the neuron using a capacitor and a resistor which are connected in parallel and proposed the following current law for excitation

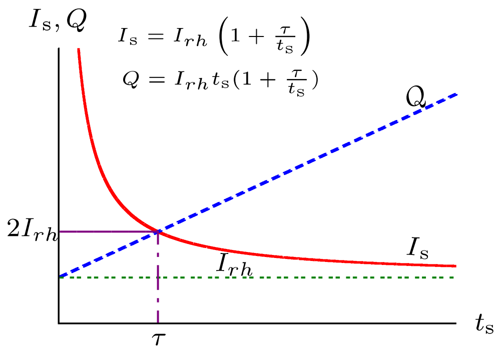

Figure 1:Lapicque hyperbolic strength-duration curve for current $I_s$and Weiss linear strength-durationrelationshipfor charge Q.

$$I_s = I_{rh}\left(1 + \frac{\tau}{t_s}\right), \tag{3.2}$$

which is equivalent to (3.1) as$Q = I_s t_s$.

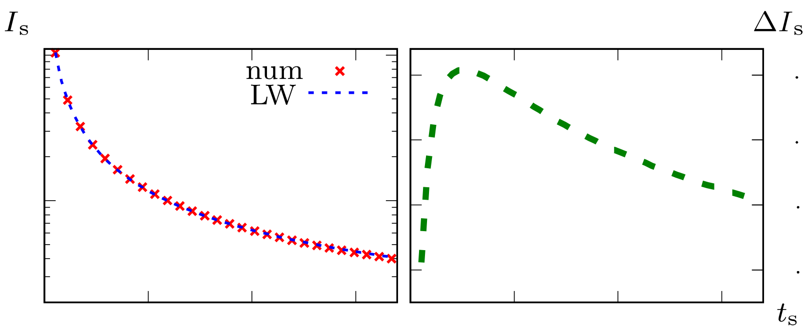

Figure 2:Comparison of direct numerical simulations and Lapicque-Weiss hyperbolic strength-duration curve along with the absolute difference between two curves.

The parameter I_{rh} is called rheobase referring to the minimal amount of intensity needed to reach spike threshold whereas the parameter τ is called chronaxie representing the value of the stimulus pulse duration when the current amplitude is equal to twice the rheobase current. The sketch of the Lapicque hyperbolic strength-duration curve and the Weiss linear charge-duration relationship is shown in Figure 1. The plot of the direct numerical threshold curve compared with Lapicque-Weiss theoretical strength-duration curve is depicted in

Figure 2. In all comparison figures, red stars denote numerical results of the FHN model which is the same for all cases, blue dashed lines denote the result of the theoretical approach considered and green dashed linesin the right panel of each represent the absolute difference between the two data sets. The values of parameters of the examined models are obtained using the Levenberg-Marquardt method and presented in Table 1.

3.2 LAPICQUE-BLAIR (LB)

The expression (3.2) is based on the idea that the stimulus strength $I_s$is inversely proportional to the time duration t_s. An alternative theoretical relation for the threshold mechanism is derived by Lapicque and Blair [13, 14] in the following exponentially decay form

$$I_s = \frac{I_{rh}}{1 - \exp(-t_s/\tau)}. \quad (3.3)$$

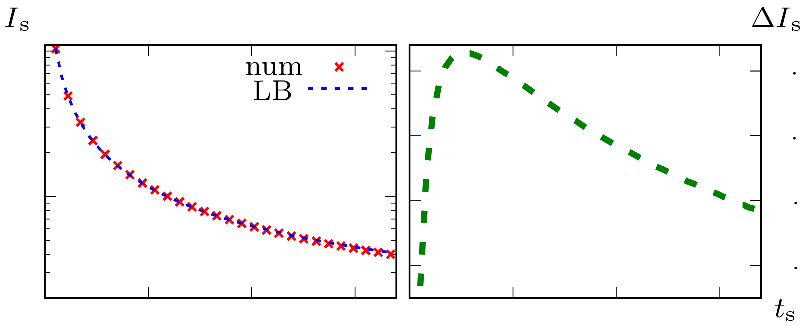

Figure 3:Comparison of the strength-duration curves obtained from Lapicque-Blair exponential function and the critical curve obtained by direct numerical simulations.

Comparison of this Lapicque-Blair exponential model with the direct numerical simulations is shown in Figure 3. As seen, reasonable agreement between the two data sets is observed as in the case of Lapicque-Weiss.

3.3 RASHEVSKY-MONNIER-HILL (RMH)

As Lapicque-Blair's model provides a reasonably good fit to experimental data, particular attention has been devoted to develop the idea that the nerve excitation can be described using two variables in which one refers to excited state and the other inhibition of excitation. Some of the leading studies of this approach have been independently conducted by Rashevsky [15], Monnier [16] and Hill [17] in the mid-1930s. The equations they considered are equivalent and so are their results. They calculated the strength-duration curve as a function of two time-constants

$$I_s = \frac{I_{rh}(1 - \kappa/\lambda)}{\exp(-t_s/\lambda) - \exp(-t_s/\kappa)}, \quad (3.4)$$

where κ is the time constant of excitation and λ is the time constant of accommodation, in which the term accommodation represents the membrane potential response to a sufficiently slow increase in the stimulating current without exciting [18]. Remark that when $\lambda \to \infty$ and $\kappa = \tau$, Hill's equation (3.4) reduces to Lapicque-Blair's equation (3.3).

Figure 4 shows this theoretical curve compared with the direct numerical simulations. As evident from the right panels of the above three figures, the formulas (3.2), (3.3) and (3.4) fit the numerical data well and the absolute differences between the data of (3.3) and (3.4) are not easily distinguishable. This is expected considering that the estimated value of the time constant of excitation is $\lambda = 6.6849e^{10}$.

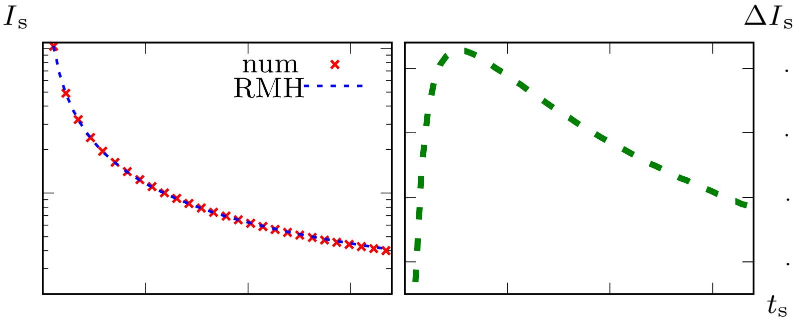

Figure 4:Comparison between strength-duration curve obtained by direct numerical iterations and analytical expression (3.4).

3.4 CAUCHY (C)

In the field of optical design, there have been extensive studies on the dispersion variations of optical material types that are currently used for optical manufacturing and refractive index and dispersion are two very important parameters for the application of optical materials. Apart from some exceptional cases, the refractive index increases as the wavelength decreases and therefore, it can be usually defined as a function of wavelength. In optical system design, it is usually desired to require the knowledge of the refractive index for unmeasured wavelengths. Therefore, to date, various well-known analytical closed expressions have been developed and introduced to compute the relationship between refractive index and wavelengths. This relation is named as dispersion formula. In terms of the behaviour of the resulted curves, these formulas can be also interpreted as an approximation to the strength-duration relationship and therefore they can be used to approximately describe the data considered throughout this paper. For convenience and brevity, similar notation will be adopted for all following models even though the problem itself is different.

The study of the index-wavelength relation was first carried out by Cauchy who derived following empirical formula [19]

$$I_s = A_1 + \frac{A_2}{t_s^2} + \frac{A_3}{t_s^4}, \tag{3.5}$$

where A_1 , A_2 and A_3 are unknown constants yet to be determined. This nonlinear interaction does not have a firm physical ground and thus, alternative expressions were later on developed. Indeed, results obtained by Cauchy formula (3.5) is not in close agreement with numerical results, not even comparable to those obtained by previous empirical approaches.

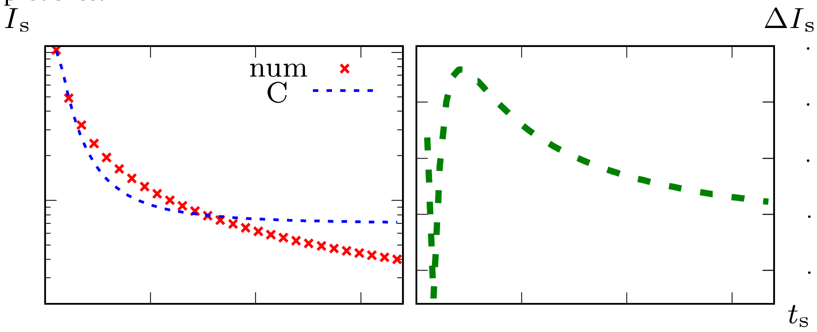

Figure 5:Approximation of the strength-duration curve compared with direct numerical simulations.

3.5 HARTMANN (H)

Cauchy's formula does not fit very well with direct numerical results as shown in Figure 5, and thus Hartmann [20] introduced the following formula for a better comparison and quantitative analysis

$$I_s = B_1 + \frac{B_2}{(t_s - B_3)^{B_4}}, \tag{3.6}$$

where the number of coeff icients is now 4.

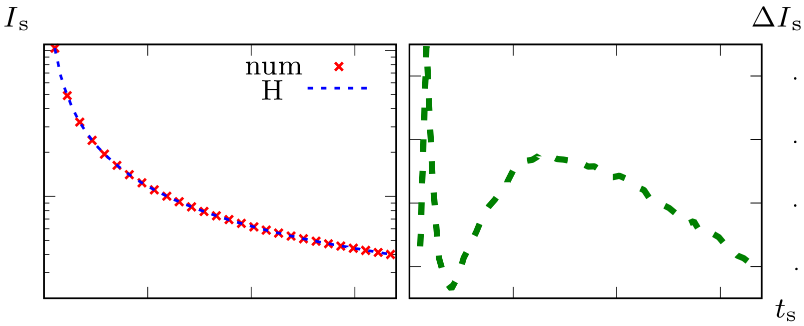

Figure 6:Illustration of the difference between numerical results and fitted data obtained from Levenberg-Marquard method using formula (3.6).

Figure 6 illustrates this theoretical strength-duration curve, compared to the direct numerical simulations. Remark that the performance of the resulting approximation based on the analytical expression (3.6) for the strength-duration curve produces significantly better results than all previous methods.

3.6 SELLMEIER (SE)

In 1871, Wolfgang von Sellmeier conducted another empirical study of index-wavelength relationship and came up with the following expression [21]

$$I_s^2 = C_1 + \frac{C_2 t_s^2}{t_s^2 - C_3} + \frac{C_4 t_s^2}{t_s^2 - C_5}. \tag{3.7}$$

Here, C_j are coefficients of the development in Laurent series that must be experimentally determined by the fitting process.

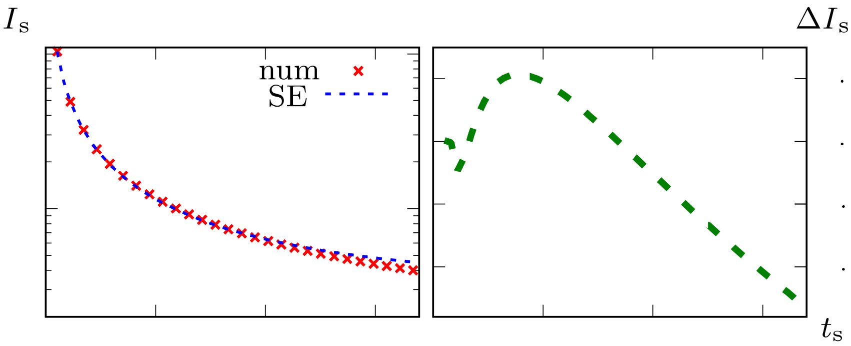

Figure 7:Sketch of the comparison between the analytical formula's result and numerical strength-duration curve where (3.7) is used.

The behaviour of the theoretical expression (3.7) compared with the numerical threshold curve is illustrated in Figure 7. Even though the number of parameters is more than that of Hartmann model, the estimated strength-duration curve has somewhat larger deviation.

3.7 SCHOTT (SC)

Due to widespread use of this formula and excellent fitting properties, there have been several attempts to recast the Sellmeier model. In 1966, Schott proposed another commonly used dispersion relation formula, which is later on named as Schott dispersion formula, written in the following form [22]

$$I_s^2 = D_1 + D_2 t_s^2 + \frac{D_3}{t_s^2} + \frac{D_4}{t_s^4} + \frac{D_5}{t_s^6} + \frac{D_6}{t_s^8}, \tag{3.8}$$

where D_1, D_2, D_3, D_4, $D_5$and $D_6$are coefficients that can be predicted based on measured data. This model is derived as a Laurent series expansion of the finite order of the Sellmeier formula.

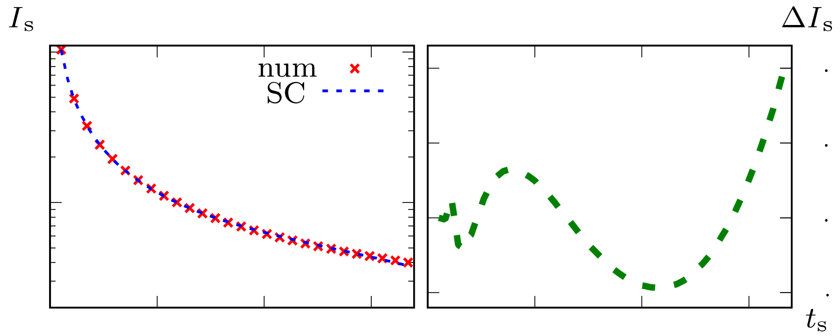

Figure 8:The plot of the comparison between numerical strength-duration critical curve and the analytical expression (3.8).

The result of Schott equation (3.8) behaves similarly to that of Sellmeier equation (3.7) to a certain degree in terms of agreement with the numerical result, as portrayed in Figure 8.

3.8 MODIFIED SCHOTT (MS)

After careful consideration of the above theoretical approaches, here we propose a mathematical model for the analytical description of the strength-duration threshold curve in the following form

$$I_s = E_1 + E_2 t_s^{E_3} + \frac{E_4}{t_s^{E_5}} + \frac{E_6}{\exp(-E_7 t_s)}, \tag{3.9}$$

where the number of coefficients is now 7. First 3 terms in this formula can be seen as a slight change version of the first 3 terms of Schott equation, with the difference that the powers of duration term t_s are also unknown coefficients instead of square. The last term, which is in the Lapicque-Blair form except that the denominator is now $exp(-E_7 t_s)$ is added as a correction term.

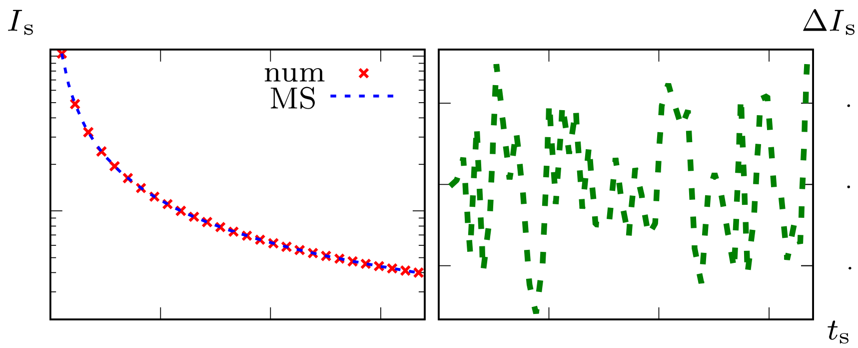

Figure 9:Approximation of the strength-duration curve for (3.9) compared with direct numerical simulations.

Figure 9 shows the comparison between this theoretical prediction and the numerical curve. As observed, these results indicate that the described method perform best since the absolute error is the smallest one.

Further analysis can be performed in order to compare the theoretical strength-duration curves described above in terms of accuracy. Two most widely-used error metrics are L_1 and L_2 norm defined as

$$L_1 = \sum_{i=1}^{n} |y_i - f(x_i)|, \quad L_2 = \sum_{i=1}^{n} \left(y_i - f(x_i)\right)^2, \tag{3.10}$$

where $y_i$refers to the data points of the numerical threshold curve for the FHN model and $f(x_i)$ refers to the data points of the estimated values of the theoretical threshold curve in our case.

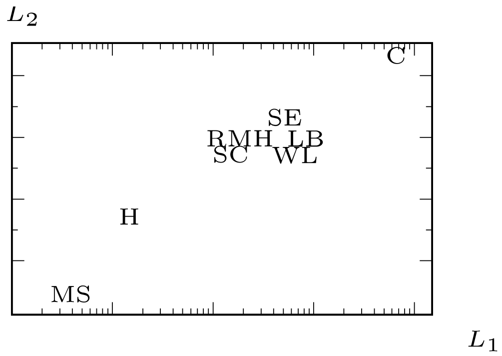

Figure 10:The sketch of the least absolute deviation L_1 versus least squares L_2.

Figure 10illustrates L_1 and L_2 norms of each empirical expression. It can be seen from this figure that Modified Schott equation achieves the best result, followed by Hartmann equation while the result for Cauchy equation is the worst by far and the others give more or less similar results as they are clustered and overlapping.

IV. DISCUSSION

In this work, mathematical formulations of the relationship between the minimum stimulus amplitude required to excite an axon and the duration for which the stimulus is applied are reviewed. Such formulations define strength-duration threshold curves that play an important role in nerve excitability studies. There have been some well-known theoretical models such as Lapicque-Weiss (3.2), Lapicque-Blair (3.3) and Rashevsky-Monnier-Hill (3.4) that specifically used to describe the strength-duration relationship. Apart from these formulations, we can also adopt some widely used dispersion relation introduced for the application of optical materials whose two very important parameters are refractive index and dispersion due to the similarities in graphical representation.

All above approaches were phenomenological and the parameters in the strength-duration relationships were to be fitted to experimental data. To measure and calculate the parameters of the closed-form of the analytical expressions for threshold stimulating current, we use Levenberg-Marquardt method, one of the most used nonlinear, least-squares fitting algorithm.

In this work, the strength-duration relationship is reviewed for the FHN model and there have been some well-developed semi-analytical approaches for the FHN model in the literature (see, for example [23–25]) and thus one may ask whether the empirical derivation is indeed necessary. However, these formulations can be adopted in practice to determine the equivalent curve for both simpler and more complex excitable media in which analytical analysis may not be possible.

Table 1: Computed coeff icients used in the analytical expressions

Model	Parameter Values
LW	$I_{rh} = 0.0086, \tau = 37.7243$
LB	$I_{rh} = 0.0162, \tau = 19.9995$
RMH	$I_{rh} = 0.0162, \lambda = 19.9995, \kappa = 6.6849e^{10}$
C	$A_1 = 0.1815, A_2 = 0.4492, A_3 = -0.0266$
H	$B_1 = 0.0060, B_2 = 0.3262, B_3 = 0.0062, B_4 = 0.9795$
SE	$C_1 = -5.5364, C_2 = 6.1822, C_3 = 0.0117, C_4 = -0.6448, C_5 = -0.0614$
SC	$D_1 = 0.0012, D_2 = -8.5885e^{-6}, D_3 = 0.1138, D_4 = -0.0037, D_5 = 6.9970e^{-4}, D_6 = -4.0354e^{-5}$
MS	$E_1 = 0.0024, E_2 = 0.3090, E_3 = 1.0136, E_4 = 0.0240, E_5 = -0.4371, E_6 = -0.0013, E_7 = -0.0339$

REFERENCES

[1]. Eric R Kandel, James H Schwartz, Thomas M Jessell, Steven A Siegelbaum, and AJ Hudspeth. Principles of neural science, volume 4. McGraw-Hill New York, 2000.

[2]. Y. Guo, Y. Zhao, S. A. Billings, Daniel Coca, R. I. Ristic, and L DeMatos. Identification ofexcitable media using a scalar coupled mapped lattice model. International Journal of Bifurcation and Chaos, 20(7):2137–2150, 2010.

[3]. Richard FitzHugh. Impulses and physiological states in theoretical models of nerve membrane. Biophysical Journal, 1(6):445–466, 1961.

[4]. Richard Fitzhugh. Thresholds and plateaus in the Hodgkin-Huxley nerve equations. The Journal of General Physiology, 43(5):867–896, 1960.

[5]. Jinichi Nagumo, SuguruArimoto, and Shuji Yoshizawa. An active pulse transmission line simulating nerve axon. Proceedings of the IRE, 50(10):2061–2070, 1962.

[6]. John C Neu, R Stephen Preissig, and Wanda Krassowska. Initiation of propagation in a one-dimensional excitable medium. Physica D: Nonlinear Phenomena, 102(3):285–299, 1997.

[7]. Kenneth Levenberg. A method for the solution of certain non-linear problems in least squares. Quarterly of Applied Mathematics, 2(2):164–168, 1944.
[8]. Donald W Marquardt. An algorithm for least-squares estimation of nonlinear parameters. Journal of the Society for Industrial and Applied Mathematics, 11(2):431–441, 1963.
[9]. Georges Weiss. Sur la possibilite de rendrecomparables entre eux les appareils servant a l'excitationelectrique. Archives Italiennes de Biologie, 35(1):413–445, 1990.
[10]. H Bostock. The strength-duration relationship for excitation of myelinated nerve: computed dependence on membrane parameters. The Journal of Physiology, 341(1):59–74, 1983.
[11]. Louis Lapicque. Recherchesquantitatives sur l'excitationelectrique des nerfs traiteecommeune polarization . Journal de physiologie et de pathologiegénérale, 9:620–635, 1907.
[12]. Nicolas Brunel and Mark CW Van Rossum. Quantitative investigations of electrical nerve excitation treated as polarization. Biological Cybernetics, 97(5-6):341–349, 2007.
[13]. Henry A Blair. On the intensity-time relations for stimulation by electric currents. i. The Journal of general physiology, 15(6):709–729, 1932.
[14]. Henry A Blair. On the intensity-time relations for stimulation by electric currents. ii. The Journal of general physiology, 15(6):731, 1932.
[15]. Nicolas Rashevsky. Outline of a physico-mathematical theory of excitation and inhibition. Protoplasma, 20(1):42–56, 1933.
[16]. Alexandre M Monnier and Louis ÉdouardLapicque . L'excitationélectrique des tissus : essaid'interprétation physique. Hermann &Cie, 1934.
[17]. AV Hill. Excitation and accommodation in nerve. Proceedings of the Royal Society of London. Series B, Biological Sciences, 119(814):305–355, 1936.
[18]. Walther Nernst. Zurtheorie des elektrischenreizes . Archivfür die gesamtePhysiologie des Menschen und der Tiere , 122:275–314, 2005.
[19]. Augustin-Louis Cauchy. Sur la réfraction et la réflexion de la lumière. Bulletin des sciences mathématiques, 14(6), 1830.
[20]. Johannes Hartmann. A simple interpolation formula for the prismatic spectrum. The Astrophysical Journal, 8:218, 1898.
[21]. Wilhelm Sellmeier. Zurerkarung der abnormenfarbenfolgeim spectrum einiger. substanzen. Annalen der Physik und Chemie, 219:272–282, 1871.
[22]. SCHOTT. Optical glass. SCHOTT catalog, 1966.
[23]. B Bezekci and VN Biktashev. Strength-duration relationship in an excitable medium. Communications in Nonlinear Science and Numerical Simulation, 80:104954, 2020.
[24]. B Bezekci and VN Biktashev. Fast-slow asymptotic for semi-analytical ignition criteria in fitzhugh-nagumo system. Chaos: An Interdisciplinary Journal of Nonlinear Science, 27(9):093916, 2017.
[25]. BBezekci. Analytical and Numerical Approaches to Initiation of Excitation Waves. PhD thesis, 2017.