Progress in Fractional Differentiation and Applications
An International Journal

http://dx.doi.org/10.18576/pfda/120111

On the Λ-Fractional Hodgkin-Huxley Model

Dimitrios Karaoulanis[1], Anastasios Konstantinos Lazopoulos[2,] and Konstantinos Anastasios Lazopoulos[3]*

[1] School of Electrical and Computer Engineering National Technical University of Athens, Greece 15780
[2] Mathematical Sciences Department, Hellenic Army Academy, Vari, Greece 16673
[3] Independent researcher

Received: 2 Nov. 2025, Revised: 2 Dec. 2025, Accepted: 22 Dec. 2025.
Published online: 1 Jan. 2026.

Abstract: In this study, the biological neuron is modelled as an electrical abstraction model. This structure is called the Hodgkin-Huxley (H-H) model. Using fractional calculus (F.C.), we can optimize this model to improve its accuracy and utility. Nevertheless, F.C. shows some unpleasant side effects. These drawbacks can only be tackled using Λ-Fractional Analysis (Λ-F.A). Therefore, the H-H model is optimized by the Λ-fractional H-H model, as presented.

Keywords: Biological neuron; Hodgkin-Huxley model; Fractional Calculus; Λ-Fractional Analysis.

1. Introduction

The neuron generates an action potential, which is propagated along the plasma membrane through specialized voltage-gated ion channels [1]. These channels remain closed when the membrane potential is near the cell's resting potential. Nevertheless, these channels open rapidly when the potential reaches a specific threshold. Then, an action potential is fired. Afterward, we enter the refractory period, during which the action potential decays and the membrane briefly hyperpolarizes, preventing the generation of further action potentials (Fig. 1).

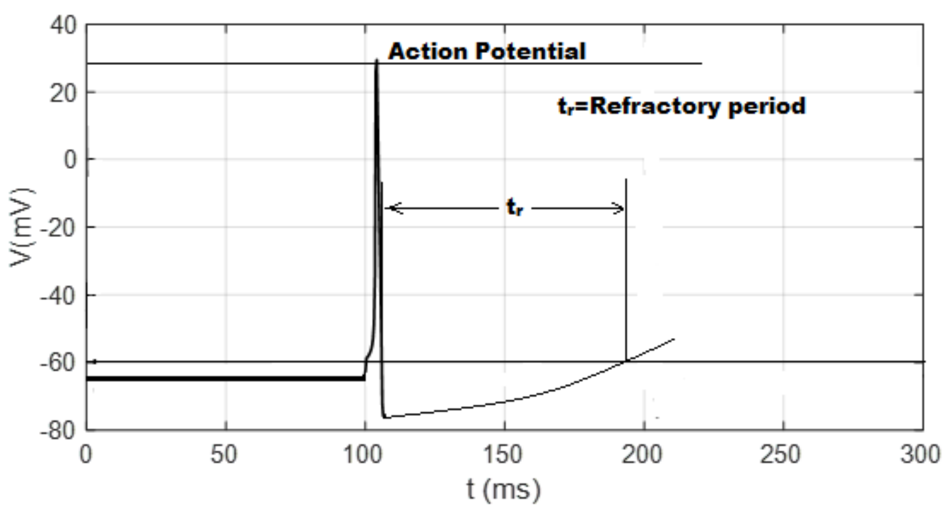

Fig. 1: The Action Potential.

The Hodgkin-Huxley model describes the above process. This theory explains the transport mechanism across a neuron's membrane using a set of linear ordinary differential equations. These equations explain the shape and propagation of the action potential, its sharp threshold, refractory period, and sub-threshold oscillations [1].

Nevertheless, the Hodgkin-Huxley model suffers from two grave weaknesses:

1) Dielectric losses in the membrane have been ignored.

2) The membrane capacitance has been assumed to be ideal.

These two statements open the gates for the Fractional Calculus approach. F.C. is a robust mathematical field that may optimize theories such as the Hodgkin-Huxley model. Nevertheless, operators in Fractional Calculus cannot be regarded as

*Corresponding author e-mail: orfeakos74@gmail.com

derivatives, which is a grave obstacle in solving F.C. problems [2].

The remedy to the abovementioned weakness is Λ-Fractional Analysis (Λ-F.A). Λ-Fractional Derivative (Λ-F.D) is the only operator that can be named "derivative" in Fractional Calculus: It has all the properties of a proper derivative, plus its order is a fraction [3].

In this article, we will first present the Λ-Fractional Derivative and then analyze the Hodgkin-Huxley model. Afterward, we will present the Λ-Fractional Hodgkin-Huxley model and show some applications. Finally, we will discuss it and extract conclusions.

2. The Λ-Fractional Analysis.

The Λ-Fractional Derivative was introduced by Lazopoulos and Lazopoulos in 2019 [3]. It is the ratio of two Riemann-Liouville derivatives, with the Λ-Fractional Space and the Λ-Transformation framing it.

Firstly, since $0<\gamma\leq 1$ applies, the Riemann-Liouville (RL) Fractional Derivatives are defined by (Kilbas [4]):

$$ {}_{a}^{RL}D_x^{\gamma} f(x) = \frac{d}{dx}\left({}_{a}^{RL}I_x^{1-\gamma}\ f(x)\right) \tag{1} $$

and

$$ {}_{x}^{RL}D_b^{\gamma} f(x) = -\frac{d}{dx}\left({}_{x}^{RL}I_b^{1-\gamma}\ f(x)\right) \tag{2} $$

where Eq. (1) defines the left and Eq. (2) the right Fractional Derivatives. At these equations, ${}_{a}^{RL}I_x^{1-\gamma}\ f(x)$ is the Riemann-Liouville Fractional Integral [3]. Moreover, the fractional integrals with the corresponding Riemann-Liouville FDs are related by the equation:

$$ {}_{a}^{RL}D_x^{\gamma}\left({}_{a}^{RL}I_x^{\gamma} f(x)\right) = f(x) \tag{3} $$

The main disadvantage of the Riemann-Liouville derivative is that it does not root out the derivative of a constant. To be more specific, if

$$ f(x) = C \tag{4} $$

Then,

$$ {}_{a}^{RL}D_x^{\gamma} f(x) = \frac{d}{dx}\left({}_{a}^{RL}I_x^{1-\gamma}\ f(x)\right) = \frac{d}{dx}\left(\frac{1}{\Gamma(1-\gamma)}\int_{a}^{x}\frac{C}{(x-s)^{\gamma}}ds\right) = \frac{C(x-a)^{-\gamma}}{\Gamma(1-\gamma)} \neq 0 \tag{5} $$

Now, we can define the Λ-Fractional Derivative as:

$$ {}_{a}^{\Lambda}D_x^{\gamma} f(x) = \frac{{}_{a}^{RL}D_x^{\gamma} f(x)}{{}_{a}^{RL}D_x^{\gamma} x} = \frac{\frac{d\,{}_{a}^{RL}I_x^{1-\gamma} f(x)}{dx}}{\frac{d\,{}_{a}^{RL}I_x^{1-\gamma} x}{dx}} = \frac{d\,{}_{a}^{RL}I_x^{1-\gamma} f(x)}{d\,{}_{a}^{RL}I_x^{1-\gamma} x} = \frac{dF(X)}{dX} \tag{6} $$

In the above equation, we can see that the Λ-FD ${}_{a}^{\Lambda}D_x^{\gamma} f(x)$ in the initial space (space (*x, f(x)*)) transforms to an ordinary derivative in Λ-Space (space (*X, F(X)*)). This fact is mostly important since this fractional operator in the initial space transforms to a proper derivative in Λ-Space, where all prerequisites for a proper differential are satisfied according to differential topology (Chilliworth [5]). Therefore, the Λ-Fractional Derivative is the only fractional operator in Fractional Calculus that can be considered as a proper derivative in Λ-Space and enjoys all the privileges of such a derivative. It is evident that the major role in this breakthrough is the exterior operator $\frac{d}{dx}$ of the R-L Derivative, which is crucial in transforming this fractional operator in the initial space to a proper derivative in Λ-Space. More detailed information about these terms can be found in [3] and [4].

3. The Λ-Fractional Hodgkin-Huxley model.

The circuit defined by the H-H equation is shown in Fig.2. The following equations describe the circuit [1]:

$$ C\frac{dV(t)}{dt} = -I_{Na} - I_K - I_L + I(t) \tag{7} $$

Where:

$$ I_{Na} = g_{Na} m^3 h(V - E_{Na}) \tag{8} $$

$$ I_K = g_K n^4 (V - E_K) \tag{9} $$

$I_L = g_L(V - E_L)$ (10)

The above set of equations is framed by the following equations:

$\frac{dh}{dt} = a_x - h(a_x + b_x)$ (11)

$\frac{dm}{dt} = a_x - m(a_x + b_x)$ (12)

$\frac{dn}{dt} = a_x - n(a_x + b_x)$ (13)

Parameters g_{Na} and g_K denote the maximum channel conductance. On the other hand, leakage channel conductance, g_L is constant. E_{Na}, E_K, and $E_L$are the reversal potential parameters. Variables m and h together give the probability of the Na^+ channel being open, and n gives the probability corresponding to the K^+ channel. (These variables depend on voltage and time). Finally, the functions αx(V) and βx(V) for x = n, m, h describe the transition rates between the open and closed states of the channels and are voltage-dependent (Table 1). These two functions are selected experimentally to match the experimental data obtained using the voltage-clamp technique.

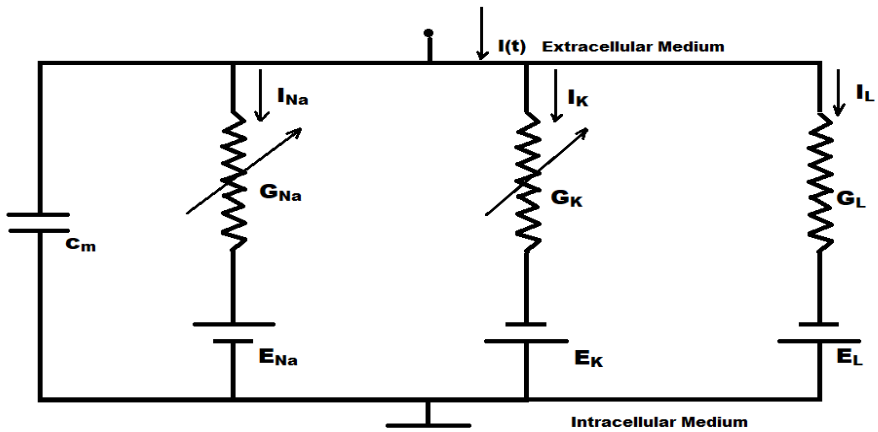

Fig. 2: The Hodgkin-Huxley model for the cell membrane. (G_{Na} and G_K vary with time and membrane potential)

Table 1: Values of $\boldsymbol{a_x}$ and $\boldsymbol{b_x}$ according to h,m,n.

	$\boldsymbol{a_x}$ (V)(s^{-1})	$\boldsymbol{b_x}$(V)(s^{-1})
h	$0.07e^{-\frac{V+65}{20}}$	$\frac{1}{e^{-\frac{V+35}{10}}+1}$
m	$0.1\frac{V+40}{1-e^{-\frac{V+40}{10}}}$	$4e^{-\frac{V+65}{18}}$
n	$0.01\frac{V+55}{1-e^{-\frac{V+55}{10}}}$	$0.125\,e^{-\frac{V+65}{80}}$

As already mentioned in the introduction, the Hodgkin-Huxley model has two significant shortcomings; the second is that the membrane capacitance is not ideal in practice.

The only way to address this problem is to use fractional calculus. Therefore, we base our approach on Jacques Curie's empirical law [1], which expresses the current as a fractional derivative of voltage:

$i(t) = C_f \frac{d^qV(t)}{dt^q}$ (14)

while the Eq.(7) takes the form:

$C_f \frac{d^qV(t)}{dt^q} = -g_{Na}m^3h(V - E_{Na}) - g_Kn^4(V - E_K) - g_L(V - E_L) + I(t)$ (15)

Consequently, the following equations frame it:

$\frac{d^qh}{dt} = a_x - h(a_x + b_x)$ (16)

$\frac{d^qm}{dt} = a_x - m(a_x + b_x)$ (17)

$$\frac{d^q n}{dt} = a_x - n(a_x + b_x) \tag{18}$$

These three fractional equations capture the imperfect nature of ion channels, which may in reality exhibit history dependence [6,7]. Therefore, the differential equations are fractional.

Eqs. (15-18) describe the circuit's behavior in the initial state according to the Hodgkin-Huxley model in Fig. 2. In Λ-space, these equations take the form:

$$C_f \frac{dV_\Lambda(t)}{dt} = -g_{Na} m^3 h(V_\Lambda - E_{Na}) - g_K n^4 (V_\Lambda - E_K) - g_L(V_\Lambda - E_L) + I(t) \tag{19}$$

$$\frac{dh_\Lambda}{dt_\Lambda} = a_{x_\Lambda} - h_\Lambda(a_{x_\Lambda} + b_{x_\Lambda}) \tag{20}$$

$$\frac{dm_\Lambda}{dt_\Lambda} = a_{x_\Lambda} - m_\Lambda(a_{x_\Lambda} + b_{x_\Lambda}) \tag{21}$$

$$\frac{dn_\Lambda}{dt_\Lambda} = a_{x_\Lambda} - n_\Lambda(a_{x_\Lambda} + b_{x_\Lambda}) \tag{22}$$

Where:

Table 2: Values of a_{x_Λ} and b_{x_Λ} according to h,m,n.

	a_x **(V)(s^{-1})**	b_x **(V)(s^{-1})**
h	$0.07e^{-\frac{V_\Lambda+65}{20}}$	$\frac{1}{e^{-\frac{V_\Lambda+35}{10}+1}}$
m	$0.1\frac{V_\Lambda+40}{1-e^{-\frac{V_\Lambda+40}{10}}}$	$4e^{-\frac{V_\Lambda+65}{18}}$
n	$0.01\frac{V_\Lambda+55}{1-e^{-\frac{V_\Lambda+55}{10}}}$	$0.125\,e^{-\frac{V_\Lambda+65}{80}}$

4. Numerical Methodology

To extract numerical results for the Λ-Fractional Hodgkin-Huxley model, we solve the system of differential equations (19)-(22) using the embedded algorithm ode45 in MATLAB 2021a [8]. We impose the two sparks I(t) at times t=100ms and t=200ms, and we use a characteristic set of constants for our problem, as given in the bibliography. The deduced values of V(T) refer to Λ-space.

These values of voltage V(T(t)) were transferred to the initial space by applying to these values the Riemann-Liouville fractional derivative of fractional order 1-γ. The numerical evaluation of the RL fractional derivative of V(T(t)) was performed using the so-called L1 algorithm, described thoroughly in the book by Changpin Li and Fanhai Zeng (page 44) [9].

5. Application of the Λ-Fractional Hodgkin and Huxley model in the cell membrane.

Eqs (19-22) are solved in Λ-space with the following values of constants and initial conditions:

g_{Na} = 120 mS/cm^2, g_K=36 mS/cm^2, g_L=0.3 mS/cm^2, V_{Na}=50 mV,V_K=-77 mV,V_L=-50mV and C=1μF/cm^2. The initial conditions for the differential equations are: V(0)=-45 mV, m(0)=0.1, n(0)=0.2, and h(0)=0.1.

The stimulation current I(t) is applied at the time moments t=100 ms, and t=200 ms (therefore, the stimulation period is 100 ms) with values I(100)=20μA/cm^2 and I(200)=44 μA/cm^2. The solution of Eqs(16-19) in Λ-space results in finding the function V(t), which afterward is transferred to the initial space via the transformation:

$$V(t) = {}^{RL}_{0}D_x^{1-\gamma} V_\Lambda(t) \tag{23}$$

In Figs. 3 and 4, we show the potential function v(t) as a function of time. We observe that as the order of the fractional derivative γ decreases, the potential curve shifts to the left. This shift of the potential curve is also observed in [1]. Moreover, as γ decreases, the amplitude of the action potential increases, as also noted in [1].

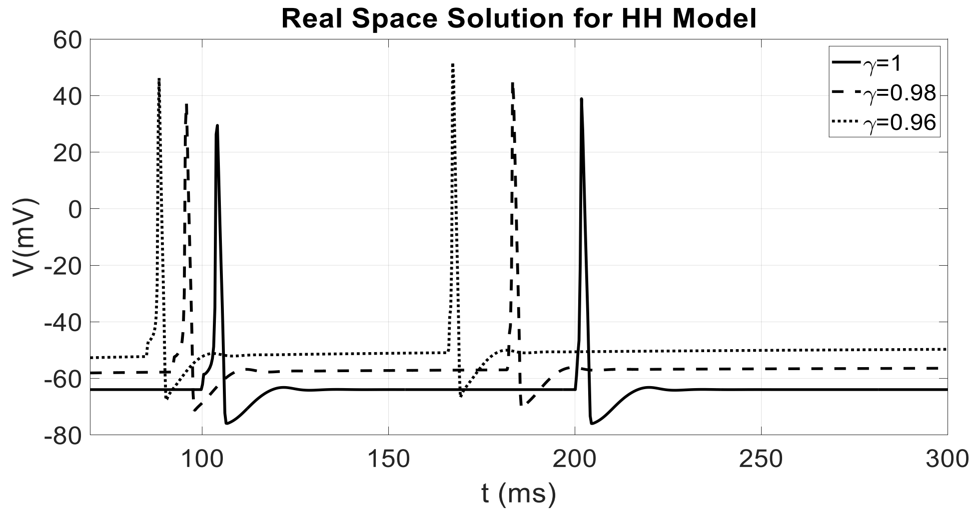

Fig. 3: The potential function v(t) versus time in the initial space for γ=1,0.98,0.96.

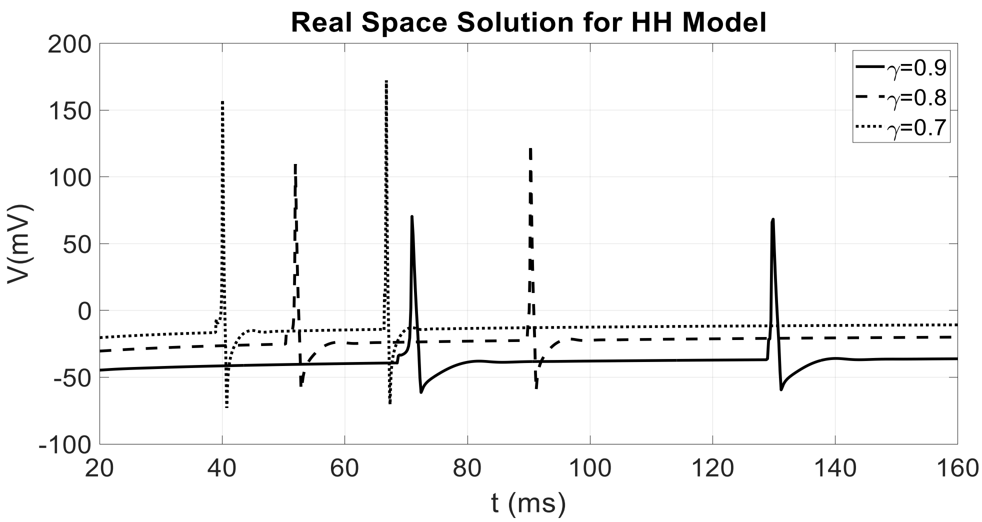

Fig. 4: The potential function v(t) versus time in the initial space for γ=0.9,0.8,0.7.

6. Discussion

The Hodgkin-Huxley model has some shortcomings that prevent it from accurately capturing the neuron's natural function: The membrane is modeled as an ideal capacitor, while the ionic channels are assumed to have no memory. The remedy to these imperfections is the fractional description of the neuron's function. Nevertheless, fractional calculus is not the "legitimate" method to cope with these kinds of problems. Due to differential topology, fractional "derivatives" are not suitable to build differential geometry, as they lack a differential. Therefore, Λ-Fractional Calculus is recalled for discussing the present model. It has been found that as the order of the fractional derivative γ decreases, the potential curve shifts to the left. This has been underlined in [1]. On the other hand, as γ decreases, the amplitude of the action potential increases. This is also shown in [1], which is a very important observation.

7. Conclusions

The Hodgkin-Huxley model is presented and implemented using the Λ-Fractional Analysis. The membrane is modeled using a non-ideal capacitor (fractional behavior), while the ionic channels are assumed to have memory, which again represents fractional behavior. Λ-Fractional Analysis is applied. It seems that as the order of the fractional derivative γ decreases, the potential curve is shifted to the left. This observation is also verified by [1]. Conversely, as γ decreases, the amplitude of the action potential increases. These remarks show the significant role of the fractional order in describing the phenomenon and the suitability of the Λ-Fractional derivative for modeling and solving such problems.

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