Fractional Modeling of Neurotransmitter Transport in the presence of Receptor and Transporter

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***Abstract*— *Two major processes in central nervous system received the impulses from external and internal world are electrical and chemical in nature. The impulse transmission through synaptic cleft by the chemical process is the predominant type of communication. Here we present a fractional order model and its analysis for the transport of the neurotransmitter ACh (acetylcholine) in the synaptic cleft by the presence of finite number of receptors and transporters with different kinetic properties on the basis of Magleby [1] model.*

Keywords — *fractional model, differential equation, synaptic transmission, receptor, transporter, neurotransmitter, Magleby model*

1. INTRODUCTION

Synaptic transmission has been thoroughly investigated over a number of years ([2] - [5]) the roles of various transmitters as well as some of the pre and post synaptic events are well established. Introduction of neurotransmitter kinetics with mathematical foundation is described in different literature ([1] and [6]). Ordinary differential equations are used to describe the dynamics of neurotransmitter reactions in bio chemical systems.

Modeling of biological systems by fractional order differential equations has more advantages than classical order mathematical modeling. The fractional order differential equations (FODEs) models are more consistent with the biological phenomena than those of integer orders [7]. Fractional derivatives contain non local property that provides an excellent idea for describing the dynamical behavior of various chemical and bio chemical systems. In this article, we propose a novel neurotransmitter kinetic mathematical model of fractional order and we analyze it in the presence of finite number of receptors and transporters with different kinetic properties.

2. BASIC FUNCTIONS OF FRACTIONAL CALCULUS

In fractional calculus, the gamma function and beta function are the basic mathematical tools to understand the origin of its computational challenges.

2.1 THE GAMMA FUNCTION

The gamma function $\Gamma(z)$ is defined by the integral [8]

$$\Gamma(z) = \int_0^\infty e^{-t}\, t^{z-1} dt, Re\, z > 0 \qquad (1)$$

Which is the Euler integral of the second kind and converges in the right half of the complex plane $Re\, z > 0$.

2.2 BETA FUNCTION

The beta function $\beta(z, w)$ is defined by [9]

$$\beta(z,w) = \int_0^1 t^{z-1}\,(1-t)^{w-1} dt, Re(z) > 0,$$

$$Re(w) > 0 \qquad (2)$$

Which is the Euler's integral of first kind.

2.3 MITTAG-LEFFLER FUNCTION

The Mittag-Leffler function also plays a very important role in research of fractional calculus. The classical Mittag-Leffler function for one parameter is defined by [8]

$$E_\alpha(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k + 1)}, z \in C, Re(\alpha) > 0 \qquad (3)$$

The Mittag-Leffler function with two parameters α, β is defined by the series expansion as follows [9].

$$E_{\alpha,\beta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k + \beta)}, (\alpha > 0, \beta > 0) \qquad (4)$$

3. FRACTIONAL DERIVATIVE

To analyze the dynamical behavior of a fractional system it is necessary to use an appropriate definition of the fractional derivative. In fact, the definitions of the fractional order derivative are not unique and there exist several definitions, including Grunwald-Letnikov, Riemann-Liouville, Weyl, Riesz and the Caputo [9] representation.

Let $L^1 = L^1[a,b]$ be the class of Lebesgue integrable functions on [a,b] , $a < b < \infty$.

Definition 3.1. The fractional integral (or the Riemann-Liouville integral) of order $p \in \mathbb{R}^+$ of the function $f(t)$, $t > 0 (f : \mathbb{R}^+ \to \mathbb{R})$ is defined by [7]

$$I_a^p x(t) = \frac{1}{\Gamma(p)} \int_a^t (t-s)^{p-1} x(s) ds, t > a \qquad (5)$$

The fractional derivative of order $p \in (n-1, n)$ of $f(t)$ is defined by two (non equivalent) ways:

(i) $Riemann$ -Liouville fractional derivative: take fractional integral of order (n-p) and then take n^{th} derivative as follows:

$$D_*^p f(t) = D_*^n I_a^{n-p} f(t) \, , D_*^n = \frac{d^n}{dt^n}, n = 1,2 \qquad (6)$$

(ii) Caputo fractional derivative: take n^{th} derivative, and then take a fractional integral of order (n-p)

$$D^p f(t) = I_a^{n-p} D_*^n f(t), n = 1, 2, 3 \qquad (7)$$

We notice that the definition of time fractional derivative of a function $f(t)$ at $t = t_n$ involves an integration and calculating time fractional derivative that requires all past history, that is, all the values of $f(t)$ from $t = 0$ to $t = t_n$. For the concept of fractional derivative, we will adopt Caputo's definition which is a modification of the Riemann-Liouville definition and has the advantage of dealing properly with initial value problems.

4. THE FRACTIONAL ORDER MODEL

Typical simulation and optimization models for reactive biological systems do not include equations involving empirical or semi-empirical expressions ([10]) . Applying memory effect on the dynamics of such systems the kinetics of those reactive systems can also be accurately represented by using fractional calculus which are similar from those obtained by the law of mass action.

The instantaneous end-plate current voltage relationship is linear, and thus, for a fixed voltage, the end-plate current is proportional to the end-plate conductance. Hence it is sufficient to study the end plate conductance rather than the end plate current. Since the end plate conductance is a function of concentration of ACh, we restrict our attention to the kinetics of ACh in the synaptic cleft. We assume that ACh reacts with its receptor, R, in enzymatic fashion given as [11]

$$ACh + R \underset{K_2}{\overset{K_1}{\rightleftharpoons}} ACh.R \underset{\lambda}{\overset{\mu}{\rightleftharpoons}} ACh.R^*$$

And that the ACh receptor complex passes current only when it is in the open state $ACh.R^*$. Here the concentration of the reactants and products are denoted by lower case letters $c = [ACh]$, $y = [ACh.R]$, $x = [ACh.R^*]$. Where [ ] denotes the concentration of reactants and then it follows from the law of mass action that

$$\frac{dx}{dt} = -\lambda x + \mu y \qquad (8)$$

$$\frac{dy}{dt} = \lambda x + k_1 c(N - x - y) - (\mu + k_2) y \qquad (9)$$

$$\frac{dc}{dt} = f(t) - k_e c - k_1 c(N - x - y) + k_2 y \qquad (10)$$

Where N (the total concentration of ACh receptor) is assumed to be conserved, and ACh decays by a simple first order process at the rate $-k_e$. The postsynaptic conductance is assumed to be proportional to x, and the rate of formation of ACh is some given function of (t) .

The model equations in dimensional form can be non-dimensionalized by substituting $X = \frac{x}{N}$, $Y = \frac{y}{N}$, $C = \frac{k_1 c}{k_2}$ and $\tau = \lambda t$, then we get,

$$\frac{dX}{d\tau} = -X + \frac{\mu}{\lambda}Y \qquad (11)$$

$$\varepsilon\frac{dY}{d\tau} = \varepsilon X + C(1 - X - Y) - \left(\varepsilon\frac{\mu}{\lambda} + 1\right)Y \qquad (12)$$

$$\varepsilon\frac{dC}{d\tau} = \varepsilon F(\tau) - \frac{k_e}{k_2}C - \frac{N}{K}C(1 - X - Y)\frac{N}{K}Y \qquad (13)$$

Where $\varepsilon = \frac{\lambda}{k_2} << 1, \quad K = \frac{k_2}{k_1}, \qquad F(\tau) = \frac{f(t)}{\lambda K}$

Now we study the fractional order into the model of Magleby [1]. The new system is described by the following set of fractional differential equations.

$$\frac{d^\gamma X}{d\tau^\gamma} = -X + \frac{\mu}{\lambda}Y \qquad (14)$$

$$\varepsilon\frac{d^\gamma Y}{d\tau^\gamma} = \varepsilon X + C(1 - X - Y) - \left(\varepsilon\frac{\mu}{\lambda} + 1\right)Y \qquad (15)$$

$$\varepsilon\frac{d^\gamma C}{d\tau^\gamma} = \varepsilon F(\tau) - \frac{k_e}{k_2}C - \frac{N}{K}C(1 - X - Y) + \frac{N}{K}Y \qquad (16)$$

γ is a parameter describing the order of the fractional time derivative in Caputo sense and $0 < \gamma < 1$. The general response expression contains a parameter describing the order of the fractional derivatives that can be varied to obtain various responses. Obviously, the integer order system can be viewed as a special case from the fractional order system by putting the time fractional order of the derivative equal to unity. In other words, the ultimate behavior of the fractional system response must converge to the response equation of the integer order version of the equation.

Now we consider the following two cases.

4.1 Case :1

Upon setting ε to zero, we find the quasi -steady approximation.

$$Y = \frac{C(1 - X)}{1 + C} \qquad (17)$$

Eliminate 'Y' from equation (14) we get

$$\frac{d^\gamma X}{d\tau^\gamma} = -X + \frac{\mu}{\lambda}\frac{C}{(1 + C)}(1 - X) \qquad (18)$$

In the limit $C(t)$ is very very small equation (15) becomes

$$\frac{d^\gamma X}{d\tau^\gamma} = -X$$

$$\Rightarrow X = c_1 E_\gamma(-\tau^\gamma) \qquad (19)$$

Where E_γ is the Mittag-Leffler function ,

$$E_\gamma \tau = \sum_{k=0}^{\infty} \frac{\tau^k}{\Gamma(\gamma k + 1)}, \quad \tau \in \mathbb{R}$$

In original variables we get

$$x = N c_1 E_\gamma (-\lambda t)^\gamma \qquad (20)$$

Thus equation (20) explains that the post synaptic conductance decays exponentially in the synaptic cleft when c is small.

For $\frac{d^\gamma X}{d\tau^\gamma} = 0$, the quasi equilibrium state.

4.2 Case :2

If $F(\tau) = 0$, *and* $N << K$ then equation(16) becomes

$$\varepsilon\frac{d^\gamma C}{d\tau^\gamma} = -\frac{k_e}{k_2}C \qquad (21)$$

$$\frac{d^\gamma C}{d\tau^\gamma} = -\frac{k_e}{k_2 \varepsilon}C$$

$$C = C_0 E_\gamma (\frac{-k_e}{k_2 \varepsilon}\tau)^\gamma$$

This shows that ACh degrades exponentially in the synaptic cleft at the rate $-k_e$ so that c quickly approaches to zero.

For $\frac{d^\gamma X}{d\tau^\gamma} = 0$, the quasi equilibrium state equation (14) gives,

$$X = \frac{\lambda}{\mu} Y \tag{22}$$

Using (22) and limits $F(\tau) = 0$, $N << K$ in equation (15) and (16) we get,

$$Y = Y_0 E_\gamma (-\frac{1}{\varepsilon}\tau)^\gamma \tag{23}$$

$$C = C_0 E_\gamma (-\frac{k_e}{k_2 \varepsilon}\tau)^\gamma \tag{24}$$

Using equation (24) in equation (22) we get

$$X = \frac{\lambda}{\mu} Y_0 E_\gamma (\frac{1}{\varepsilon}\tau)^\gamma \tag{25}$$

Since the system is in quasi equilibrium state, and using the equation (22) in equation (15) we get,

$$x = \frac{N\mu k_1 c}{k_2\lambda + (\lambda + \mu)k_1 c}$$

Here we observe that when c is small, x would be approximately proportional to c. An exponential decrease of c caused by the decay term $-k_e$ would cause an exponential decrease in the post synaptic conductance.

5. CONCLUSION

The fractional order model is more realistic than the integer order model. The proposed fractional order model is more practical and can describe the dynamics of neurotransmitter kinetic system. Here we observe that if c is small, x would be approximately proportional to c. In this case an exponential decrease of c caused by the decay term $-k_e$ would cause an exponential decrease in the post synaptic conductance in the synaptic cleft and the decay of end plate current is due to conformational changes of the ACh receptor.

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