International Journal of Pure and Applied Mathematics
Volume 118 No. 6 2018, 295-303
ISSN: 1311-8080 (printed version); ISSN: 1314-3395 (on-line version)
url: http://www.ijpam.eu
Special Issue
ijpam.eu

Stability Analysis of Fractional order Neurotransmitter Kinetic model

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Abstract

This paper concerns the fractional order neurotransmitter kinetic model. Neural transmitters can generally exist in several states: stored, released, in combination with receptors and recycling to storage. A set of equations is proposed and analysed for such system. We consider the stability of the solution and discuss the physiological effect of the transport of the neurotransmitter ACh(acetylcholine) in synaptic cleft in the presence of finite number of receptors and transporters with different kinetic properties under certain limited conditions.

AMS Subject Classification:34A08.
Key Words and Phrases: fractional order model; differential equation; synaptic transmission; neurotransmitter; Mittag Leffler function;Jumarie fractional derivative.

1 Introduction

Synaptic transmission has been thoroughly investigated over a number of years ([1],[2],[3], [4]) and 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 ([5],[6]). Ordinary differential equations are used to describe the dynamics of neurotransmitter reactions in biochemical systems.
Modelling of biological systems by fractional order differential equations has more

advantages than classical order mathematical modelling. The fractional order differential equations (FODEs) model are more consistent with the biological phenomena than those of integer orders [7].
In this article, We have considered the stability of the solution and discussed the physiological effect of the transport of the neurotransmitter ACh(acetylcholine) in synaptic cleft in the presence of finite number of receptors and transporters with different kinetic properties under certain limited conditions.

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]

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

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]

$$\beta(z, w) = \int_0^1 t^{z-1}(1-t)^{w-1} dt, \; Re(z) > 0, \; Re(w) > 0 \tag{2}$$

which is the Euler's integral of first kind.

2.3 Mittag-Leffler function

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

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

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

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

3 Fractional Derivative

To analyse the dynamical behaviour 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 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]

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

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:

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

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

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

4 System of linear fractional differential equations

Consider the system of fractional order differential equations [10]

$$\begin{cases} {}^J D^p[x] & = ax + by \\ {}^J D^p[y] & = cx + dy \end{cases} \tag{8}$$

Here a,b,c and d are constants, the operator ${}^J D^\alpha$ is the Jumarie fractional derivative operator, call it for convenience ${}^J D^p \equiv \frac{d^p}{dt^p}$, and x and y are functions of t. The above system of equations can be rewritten as

$$\begin{cases} {}^J D^p[x] - ax - by = 0 \\ {}^J D^p[y] - cx - dy = 0 \end{cases} \tag{9}$$

It has the solution of the form

$$x = A_1 E_p(\lambda_1 t^p) + B_1 E_p(\lambda_2 t^p) \tag{10}$$

$$y = A_2 E_p(\lambda_1 t^p) + B_2 E_p(\lambda_2 t^p) \tag{11}$$

where A_1, B_1 are arbitrary constants and

$$A_2 = \frac{A_1(\lambda_1 - d)}{c}, \ B_2 = \frac{B_1(\lambda_2 - d)}{c}$$

5 Equilibrium points and their asymptotic stability

Here we describe the equilibrium points and their asymptotic stability of a fractional order linear system from [11]. Let $p \in (0,1)$ and consider the system

$$\begin{cases} D_*^p x(t) = f_1(x,y) \\ D_*^p y(t) = f_2(x,y) \end{cases} \tag{12}$$

with initial values $x_1(0) = x_0,\ y_1(0) = y_0$.
To evaluate equilibrium points, let

$$D_*^p x(t) = 0 \Rightarrow f_1(x^{eq}, y^{eq}) = 0$$
$$D_*^p y(t) = 0 \Rightarrow f_2(x^{eq}, y^{eq}) = 0$$

To evaluate asymptotic stability, let

$$x(t) = x^{eq} + \epsilon_1(t)$$
$$y(t) = y^{eq} + \epsilon_2(t)$$

then

$$D_*^p(x^{eq} + \epsilon_1) = f_1(x^{eq} + \epsilon_1, y^{eq} + \epsilon_2)$$
$$D_*^p(y^{eq} + \epsilon_2) = f_2(x^{eq} + \epsilon_1, y^{eq} + \epsilon_2)$$

which implies that

$$D_*^p \epsilon_i(t) = f_i(x^{eq} + \epsilon_1, y^{eq} + \epsilon_2),\ i = 1,2$$

but

$$\begin{aligned} f_i(x^{eq} + \epsilon_1, y^{eq} + \epsilon_2) &\simeq f_i(x^{eq}, y^{eq}) + \frac{\partial f_i}{\partial x}\Big|_{eq}\epsilon_1 + \frac{\partial f_i}{\partial y}\Big|_{eq}\epsilon_2 + \dots \\ \Rightarrow f_i(x^{eq} + \epsilon_1, y^{eq} + \epsilon_2) &\simeq \frac{\partial f_i}{\partial x}\Big|_{eq}\epsilon_1 + \frac{\partial f_i}{\partial y}\Big|_{eq}\epsilon_2 \end{aligned}$$

where $f_i(x^{eq}, y^{eq}) = 0$, then

$$D_*^p \epsilon_i(t) \simeq \frac{\partial f_i}{\partial x}\Big|_{eq}\epsilon_1 + \frac{\partial f_i}{\partial y}\Big|_{eq}\epsilon_2$$

and we obtain the system

$$D_*^p \epsilon = A\epsilon \tag{13}$$

with the initial values $\epsilon_1(0) = x(0) - x^{eq}$ and $\epsilon_2(0) = y(0) - y^{eq}$,
where

$$A\epsilon = \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \end{bmatrix}, \quad A = \begin{bmatrix} \frac{\partial f_1}{\partial x}\Big|_{eq} & \frac{\partial f_1}{\partial y}\Big|_{eq} \\ \frac{\partial f_2}{\partial x}\Big|_{eq} & \frac{\partial f_2}{\partial y}\Big|_{eq} \end{bmatrix}$$

We have $B^{-1}AB = C$, where C is a diagonal matrix of A given by

$$C = \begin{bmatrix} \lambda_1 & 0 \\ 0 & \lambda_2 \end{bmatrix}$$

where $\lambda_1$and λ_2 are the eigen values of A and B is the eigenvalue vectors of A, then $AB = BC, \quad A = BCB^{-1}$,
which implies that

$$D^p_* \epsilon = (BCB^{-1})\epsilon, \ D^p_*(B^{-1}\epsilon) = C(B^{-1}\epsilon),$$

then

$$D^p_* \eta = C\eta, \ \eta = B^{-1}\epsilon, \tag{14}$$

$$\eta = \begin{bmatrix} \eta_1 \\ \eta_2 \end{bmatrix},$$

i.e.

$$D^p_* \eta_1 = \lambda_1 \eta_1, \tag{15}$$

$$D^p_* \eta_2 = \lambda_2 \eta_2 \tag{16}$$

the solution of Eqs.15 - 16 are given by Mittag-Leffler functions [12]

$$\eta_1(t) = \sum_{n=0}^{\infty} \frac{(\lambda_1)^n t^{np}}{\Gamma(np+1)} \eta_1(0) = E_p(\lambda_1 t^p)\eta_1(0), \tag{17}$$

$$\eta_2(t) = \sum_{n=0}^{\infty} \frac{(\lambda_2)^n t^{np}}{\Gamma(np+1)} \eta_2(0) = E_p(\lambda_2 t^p)\eta_2(0) \tag{18}$$

Using the result of Matignon [13] then, if $|arg(\lambda_1)| > p\pi/2$ and $|arg(\lambda_2)| > p\pi/2$ then $\eta_1(t), \quad \eta_2(t)$ are decreasing and then $\epsilon_1(t), \ \epsilon_2(t)$ are decreasing.
So the equilibrium point (x_1^{eq}, x_2^{eq}) is locally asymptotically stable, if both the eigenvalues of the matrix A are negative ($|arg(\lambda_1)| > p\pi/2, \ |arg(\lambda_2)| > p\pi/2$).

6 The fractional order model

Applying memory effect on the dynamics of systems, the kinetics of those reactive systems can be accurately represented by using fractional calculus which are similar from those obtained by the law of mass action [14].
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

$$ACh + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ACh.R \underset{\lambda}{\overset{\mu}{\rightleftharpoons}} ACh.R^*$$

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 [15]

$$\frac{dx}{dt} = -\lambda x + \mu y \tag{19}$$

$$\frac{dy}{dt} = \lambda x + k_1 c(N - x - y) - (\mu + k_2)y \tag{20}$$

$$\frac{dc}{dt} = f(t) - k_e c - k_1 c(N - x - y) + k_2 y \tag{21}$$

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 post synaptic conductance is assumed to be proportional to x, and the rate of formation of ACh is some given function of f(t).
The model equations in dimensional form can be non-dimensioned by substituting $X = \frac{x}{N},\ Y = \frac{y}{N},\ C = \frac{k_1 c}{k_2}\ \ and\ \tau = \lambda t$, then we get,

$$\frac{dX}{d\tau} = -X + \frac{\mu}{\lambda}Y \tag{22}$$

$$\epsilon\frac{dY}{d\tau} = \epsilon X + C(1 - X - Y) - (\epsilon\frac{\mu}{\lambda} + 1)Y \tag{23}$$

$$\epsilon\frac{dC}{d\tau} = \epsilon F(\tau) - \frac{k_e}{k_2}C - \frac{N}{K}C(1 - X - Y) + \frac{N}{K}Y \tag{24}$$

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

Now we study the fractional order into the model of Magleby [6]. The new system is described by the following set of fractional differential equations.

$$\frac{d^\gamma X}{d\tau^\gamma} = -X + \frac{\mu}{\lambda}Y \tag{25}$$

$$\epsilon\frac{d^\gamma Y}{d\tau^\gamma} = \epsilon X + C(1 - X - Y) - (\epsilon\frac{\mu}{\lambda} + 1)Y \tag{26}$$

$$\epsilon\frac{d^\gamma C}{d\tau^\gamma} = \epsilon F(\tau) - \frac{k_e}{k_2}C - \frac{N}{K}C(1 - X - Y) + \frac{N}{K}Y \tag{27}$$

γ is a parameter describing the order of the fractional time derivative in Caputo sense and $0 < \gamma < 1$.

7 Stability analysis of the Model

We observe that the equations (26) and(27) are non autonomous simultaneous differential equations. By using $f(t)$ (the rate of formation of ACh) is equal to zero and N(the total concentration of ACh) is equal to $x + y$, then the original Magleby modelled equations reduce to a fractional order linear autonomous simultaneous equations as follows:

$$\frac{d^\gamma x}{dt^\gamma} = -\lambda x + \mu y \quad (28)$$

$$\frac{d^\gamma y}{dt^\gamma} = \lambda x - (\mu + k_2)y \quad (29)$$

$$\frac{d^\gamma c}{dt^\gamma} = -k_e + k_2 y \quad (30)$$

Equations (28 - 30) form linear autonomous system, so we can use phase plane analysis to analyse them. Equation (28) and (29) are coupled and independent of c.
Here the critical point of the system is x=0, y=0, c=0.
Consider the equations (28) and (29)
i.e,

$$\begin{cases} \frac{d^\gamma x}{dt^\gamma} = & -\lambda x + \mu y \\ \frac{d^\gamma y}{dt^\gamma} = & \lambda x - (\mu + k_2)y \end{cases} \quad (31)$$

where λ, μ, k_2 are constants.
Then its characteristic equation is as follows:

$$\Lambda^2 + (\lambda + \beta + k_2)\Lambda + \lambda k_2 = 0... \quad (32)$$

and its eigenvalues values are

$$\Lambda_1 = \frac{-(\lambda + \mu + k_2) + \sqrt{(\lambda + \mu + k_2)^2 - 4\lambda k_2}}{2}$$

and

$$\Lambda_2 = \frac{-(\lambda + \mu + k_2) - \sqrt{(\lambda + \mu + k_2)^2 - 4\lambda k_2}}{2}$$

A sufficient condition for the local asymptotic stability of the equilibrium point $(x_1^{eq}, x_2^{eq}) = (0, 0)$ is $|arg(\lambda_1)| > \gamma\pi/2$ and $|arg(\lambda_2)| > \gamma\pi/2$.
In the special case $\alpha = 1.5$,$\beta = 1.5$ and $k_2 = 4.5$ we get the system is asymptotically stable.

8 Conclusion

In this paper we have shown that the critical point of the system of fractional order is same as its integer order counterpart. In this neurotransmitter kinetic model, for $\alpha = 1.5$, $\beta = 1.5$ and $k_2 = 4.5$ we get the system is asymptotically stable, and we can conclude that fractional-order differential equations are, at least, as stable as their integer order counterpart.

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