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Analytical and Numerical Study of a Mathematical Model of Neurotransmitter Transport in the Presence of Receptors and Transporters

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Abstract

Passage of impulses from the receptors of external and internal world towards peripheral and central nervous system take place in respect of two major processes which are electrical and chemical in nature. Electrical process in the end part of the axon which called axon terminal leads to the chemical process that is responsible for impulsive transmission through synaptic gap or cliff. This chemical transmission is a predominant type of communication through the nervous system. We present some analytical and numerical solutions of Magleby [1] model for the transport of the neurotransmitter ACh (acetyl choline) in synaptic cleft in the presence of finite number of receptors and transporters with different kinetic properties.

Keywords*:* synaptic transmission, neurotransmitter, receptors, transporters, differential model, synapse model, Magleby Model.

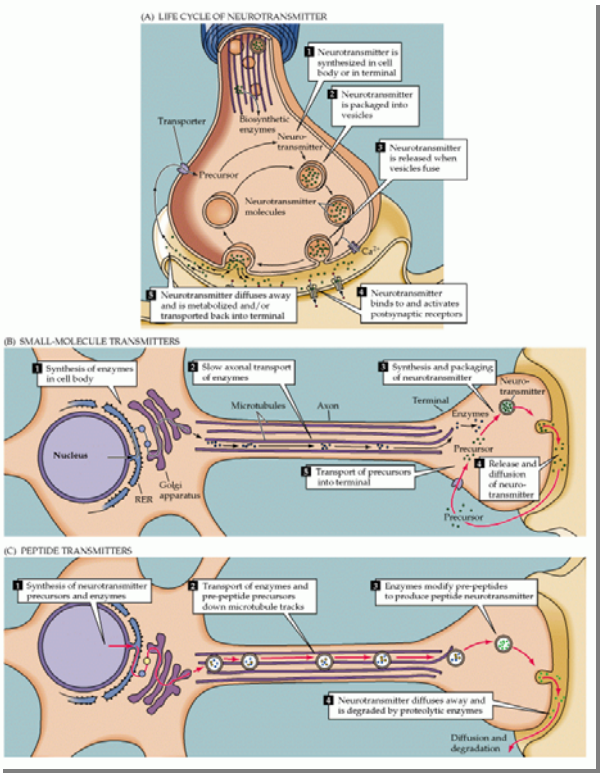
Introduction

Electrical synapse and chemical synapse are two primary ways that cells communicate with neighbours. Chemical synapses are typically small and inaccessible and are crowded together in very large numbers in the brain. Neurons also make synapses with skeletal muscle cells, and these are usually much easier to isolate and study. For this reason a great deal of experimental and theoretical work on synaptic transmission was performed on neuromuscular junction, where the axon of a motor neuron forms a chemical synapse with a skeletal muscle fibre. Synaptic transmissions have been thoroughly investigated over a number of years (Eccles [2],

Katz [3], Bennett [4], Krnjevic [5], Chalyi [6]) and the roles of various transmitters as well as some of the pre and post synaptic events are well established. Magleby [1] have studied end-plate currents in glycerol treated frog sartorius nervous muscle preparations with the voltage clamp techniques. Leibovic [7] have analysed the boundedness and stability of solutions of a system of nonlinear differential equations which represent kinetics of neural transmitters which can generally exist in several states (stored, released, in combination with receptors, recycling storage). Kouki.et.al [8], have studied the effects of memantine, an adamantane derivative, on neuromuscular transmission in the frog sartorius muscle preparation by measuring the end-plate current (EPC) by the voltage clamp method. Memantine (0.5–50 μM) reduced the peak amplitude and shortened the duration of the EPC, and the membrane voltage-peak EPC relationship became non-linear. Andrzej [9] have presented a methodology of mathematical description of the storage and release of the neurotransmitter during the fast synaptic transmission. In this paper we analyse the mathematical properties of one of the models of neuronal stimulus.

Physiological Description of Model

Here we give a small introduction for the synthesis, packaging, secretion, and removal of neurotransmitters in the synaptic cleft through pictures (Dale [10])



(A)The life cycle of transmitter agents entail (1) neurotransmitter synthesis, (2) packaging into vesicles, (3) fusion of vesicles resulting in neurotransmitter release, (4)

activation of postsynaptic receptors, and (5)neurotransmitters are then removed from the synaptic cleft. In many cases, the neurotransmitter and/or a breakdown product is reused for neurotransmitter synthesis.
(B)Small-molecule neurotransmitters are synthesized at nerve terminals. (1)The enzymes necessary for neurotransmitter synthesis are made in the cell body of the presynaptic cell and (2) transported down the axon by slow axonal transport. (3) Precursors are taken up into the terminals by specific transporters, and neurotransmitter synthesis and packaging take place within the nerve endings. (4)After vesicle fusion and release the neurotransmitter may be enzymatically degraded. (5) The reuptake of the neurotransmitter (or its metabolites) starts another cycle of synthesis, packaging, release, and removal.
(C)Peptide neurotransmitters, as well as the enzymes that modify their precursors, are synthesized in the cell body (1) Enzymes and propeptides are packaged into vesicles, (2) fast axonal transport of these vesicles to the nerve terminals, (3) the enzymes modify the propeptides to produce one or more neurotransmitter peptides, (4) after vesicle fusion and exocytose, the peptides diffuse away and are degraded by proteolytic enzymes

Mathematical Formulation

Magleby [1] showed that 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

$$ACh + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ACh.R \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} ACh.R^*$$

and that the ACh receptor complex passes current only when it is in the open state ACH.R*.

Let $c = [ACh], y = [ACh.R], x = [ACh.R^*]$

$$\frac{dx}{dt} = \alpha x + \beta y, \tag{1}$$

$$\frac{dy}{dt} = \alpha x + k_1 c(N - x - y) - (\beta + k_2) y, \tag{2}$$

$$\frac{dc}{dt} = f(t) - k_e c - k_1 c(N - x - y) + k_2 y, \tag{3}$$

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 $f(t)$. To solve the equations in Magleby [1] model we consider some simplifying assumptions. First assume that the kinetics of ACh binding to its receptor is much faster than the other reactions in the scheme so that y is in instantaneous equilibrium with c .

The model equations in the dimensional form can be non-dimensionalized by substituting $X=\frac{x}{N}, Y=\frac{y}{N}, C=\frac{k_1 c}{k_2}$ and $\tau=\alpha t$ in terms of which equations (1), (2 ,(3) become

$$\frac{dX}{d\tau}=-X+\frac{\beta}{\alpha}Y \tag{4}$$

$$\varepsilon\frac{dY}{d\tau}=\varepsilon X+C(1-X-Y)-\left(\varepsilon\frac{\beta}{\alpha}+1\right)Y \tag{5}$$

$$\varepsilon\frac{dC}{d\tau}=\frac{1}{\varepsilon k_2{}^2 K}F(\tau)-\frac{k_e}{k_2}C-\frac{N}{K}C(1-X-Y)+\frac{N}{K}Y \tag{6}$$

Where

$$\varepsilon=\frac{\alpha}{k_2}\ll 1 \text{ and } K=\frac{k_2}{k_1}, F(\tau)=\frac{f(t)}{\alpha k} \tag{7}$$

Case 1: For ε = 0

Using the quasi –steady approximation that is $\varepsilon=0$ in equation (5) we get

$$Y=\frac{C(1-X)}{1+C}. \tag{8}$$

Eliminate' Y' from equation (4) we get

$$\frac{dX}{d\tau}=-X+\frac{\beta}{\alpha}\frac{C}{1+C}(1-X). \tag{9}$$

In the limit C (t) is very very small equation (9) becomes

$$\frac{dX}{d\tau}=-X\Rightarrow X=c_1 e^{-\tau} \tag{10}$$

.

In original variables we get

$$x=N c_1 e^{-\alpha t} \tag{11}$$

.

Thus equation (11) explains that the post synaptic conductance decays exponentially in the synaptic cleft when c is small.

For $\frac{dX}{d\tau} = 0$, the quasi equilibrium state

Case 2: If $F(\tau) = = 0,\ N << K$

Equation (6) becomes

$$\varepsilon \frac{dC}{d\tau} = -\frac{k_e}{k_2} C. \tag{12}$$

Integrating (12) we get

$$C = C_0 \exp(-\frac{k_e}{\varepsilon k_2} \tau).$$

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

For $\frac{dX}{d\tau} = 0$ the quasi equilibrium state equation (4) gives

$$X = \frac{\beta}{\alpha} Y. \tag{13}$$

Using (13) and limits $F(\tau) = = 0,\ N << K$ in equation (5) and (6) we get

$$Y = Y_0 \exp(-\frac{1}{\varepsilon} \tau), \tag{14}$$

$$C = C_0 \exp(-\frac{k_e}{\varepsilon k_2} \tau). \tag{15}$$

Using (14) in (13) we get

$$X = \frac{\beta}{\alpha} Y_0 \exp(-\frac{1}{\varepsilon} \tau) \tag{16}$$

Thus we get

$$x = -\frac{N \beta k_1 c}{\left(k_2 \alpha^2 + \alpha(\alpha + \beta) k_1 c\right)}. \tag{17}$$

Here we observe that if 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 postsynaptic conductance.

Thus Keenar [11] tried to solve the system of equations (1), (2), (3) in various limiting cases but still the whole system remains unsolved. We are giving here phase-plane analysis of the complete system in limiting case $f(t)=0$ and $N=x+y$ and also solving the system by power series.

Methodology

Phase-Plane Analysis

We observe that the equations (1) and (2) are nonlinear and 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 plus y, equations (1), (2) and (3) and they reduce to a linear autonomous simultaneous equations.

Consider $f(t)=0$, $N=x+y$ and substitute this in equations (1), (2),(3) we get

$$\frac{dx}{dt}=-\alpha x+\beta y, \tag{18}$$

$$\frac{dy}{dt}=\alpha x-(\beta+k_2)y, \tag{19}$$

$$\frac{dc}{dt}=-k_e c+k_2 y. \tag{20}$$

Equations (18) to (20) form linear autonomous system, so we can use phase-plane analysis to analyse them. Equation (15) and (16) are coupled and independent of c so we apply phase-plane analysis to this system as below.

The critical point of the system (18) - (20) is

$$x = 0,\ y = 0,\ c = 0. \tag{21}$$

Auxiliary equation of (15) - (16) is

$$m^2-(\alpha+\beta+k_2)m+\alpha k_2=0. \tag{22}$$

Roots of (19) are

$$m_1=k_2,\ m_2=\alpha+\beta, \tag{23}$$

where m_1 & m_2 are real and distinct. If k_2 and $(\alpha+\beta)$ are of same sign the critical point is a nodal point (fig1) and if k_2 and $(\alpha+\beta)$ are of opposite sign it is a saddle point (fig.2).

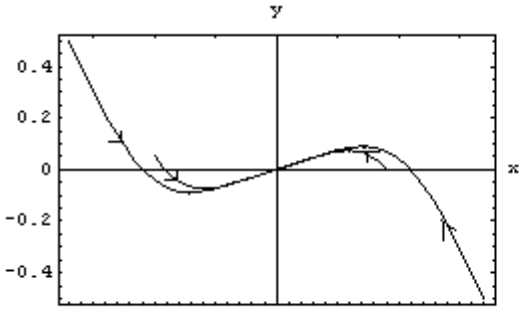


Fig 1. α=1.5, β=1.5, k_2=4.5

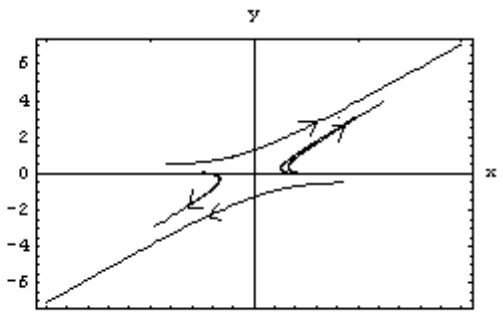


Fig 2.α=1.5, β=1.5, k_2=-4.5

Power Series solution

Now we want to solve equations (18) - (20) with the following initial conditions

$$x = 1, y = 1, c = 0 \tag{24}$$

Consider the series solutions of (18), (19), and (20) as follows

$$x = \sum_{n=0}^{\infty} a_n t^n \ , \ y = \sum_{n=0}^{\infty} b_n t^n \ , c = \sum_{n=0}^{\infty} d_n t^n \ , \tag{25}$$

Substituting (25) in (18)-(20) and equating the coefficients of the same powers we get the recurrence relations as below

$$a_{n+1} = \frac{-\alpha a_n + \beta b_n}{n+1}, \ b_{n+1} = \frac{\alpha a_n - (\beta + k_2) b_n}{n+1} \ , d_{n+1} = \frac{-k_e d_n + (k_2) b_n}{n+1} \tag{26}$$

By (24) we get

$$a_0 = 1, b_0 = 1, d_0 = 0 \tag{27}$$

$$a_1 = -\alpha + \beta, b_1 = \alpha - (\beta + k_2) \ , d_1 = (k_2), \tag{28}$$

$$a_2 = \frac{(-\alpha)^2 - \beta^2 - \beta k_2}{2}, \quad b_2 = \frac{-(\alpha)^2 - k_2 \alpha + (-\beta)^2 + 2\beta k_2 + (k_2)^2}{2} \ ,$$

$$d_2 = \frac{\alpha k_2 - \beta k_2 - (k_2)^2 - k_e k_2}{2}, \tag{29}$$

$$a_3 = \frac{(-\alpha)^3 - \alpha\beta^2 - \alpha^2\beta + \beta^3 - 2\beta^2 k_2 + {k_2}^2 \beta}{6} \ ,$$

$$b_3 = \frac{(\alpha)^3 - \alpha\beta^2 - \alpha\beta k_2 + \alpha^2\beta + (-\beta)^3 - 3(k_2)^2 \beta + k_2\alpha^2 - 3k_2\beta^2 + (k_2)^2 \alpha - (k_2)^3}{6} \ ,$$

$$d_3 = \frac{{k_e}^2 k_2 - \alpha^2 k_2 - k_e \left(k_2\right)^2 - k_e k_2 \alpha + k_e k_2 \beta + \beta^2 k_2 + 2\beta {k_2}^2 - \alpha^3 {k_2}^2}{6}, \tag{30}$$

and so on.

Substituting the values of a_i, b_i and d_i in (25) and rearranging the terms we get

$$x(t) = e^{(-\alpha)t} - \left(e^{-(\beta t)} - 1\right) + \frac{-\beta k_2}{2} t^2 + \frac{\alpha\beta\left(\beta - \alpha\right) + \beta {k_2}^2 + 2\beta^2 k_2}{6} t^3 \ldots\ldots, \tag{31}$$

$$y(t) == e^{(-\beta)t} - \left(e^{-(\alpha t)} - 1\right) - k_2 t + \frac{-k_2\alpha + +2\beta k_2 + \left(k_2\right)^2}{2} t^2 + \ldots\ldots, \tag{32}$$

$$c(t) = \left(e^{k_2 t} - 1\right) - \frac{k_2}{k_e}\left(e^{-k_e t} - \frac{{k_e}^2}{k_2} t - \frac{k_e}{k_2}\right) + \frac{\left(k_2\alpha - k_2\beta\right)t}{2} + \ldots\ldots \tag{33}$$

We observe that the solutions given by (31) - (33) exactly match with the solutions obtained by Keener [12] in limiting cases.

Modified power series

We apply a new approach for power series solution as given by Nuran.at.el [12] to the system (18) - (20) with the initial condition (24) as follows.

Let us consider the first order approximation

$$x = 1 + e_1 t, \tag{34}$$

$$y = 1 + e_2 t, \tag{35}$$

$$c = e_3 t. \tag{36}$$

Substituting equations (34)-(36) in (18) – (20) we get

$$e_1 = -\alpha\left(1 + e_1 t\right) + \beta\left(1 + e_2 t\right), \tag{37}$$

$$e_2 = \alpha\left(1 + e_1 t\right) - \left(\beta + k_2\right)\left(1 + e_2 t\right), \tag{38}$$

$$e_3 = -k_e\left(e_3 t\right) + k_2\left(1 + e_2 t\right). \tag{39}$$

Equations (37)-(39) can be written as

$$e_1 = -\alpha + \beta + o(t), \tag{40}$$

$$e_2 = \alpha - \beta - k_2 + o(t), \tag{41}$$

$$e_3 = k_2 + o(t). \tag{42}$$

The system (40) – (42) can be expressed as $Ae = B$ where

$$A=\begin{bmatrix}1 & 0 & 0\\ 0 & 1 & 0\\ 0 & 0 & 1\end{bmatrix},e=\begin{bmatrix}e_1\\ e_2\\ e_3\end{bmatrix},B=\begin{bmatrix}-\alpha+\beta\\ \alpha-\beta-k_2\\ k_2\end{bmatrix}. \tag{43}$$

Solving equation (43) we get

$$e_1=-\alpha+\beta, \tag{44}$$

$$e_2=\alpha-\beta, \tag{45}$$

$$e_3=k_2. \tag{46}$$

Using (44)-(46) in equation (34)-(36) and including second order approximation we get

$$x(t)=1+(-\alpha+\beta)t+e_1(t^2), \tag{47}$$

$$y(t)=1+(\alpha-\beta-k_2)t++e_2(t^2), \tag{48}$$

$$c(t)=(k_2)t+e_3(t^2). \tag{49}$$

Substituting (47)-(49) in (18) - (20) and solving we get

$$x(t)=1+(-\alpha+\beta)t+\frac{1}{2}\left[(-\alpha)^2-\beta^2+\beta k_2\right](t^2)+e_1(t^3),$$

$$y(t)=1+(\alpha-\beta-k_2)t+\frac{1}{2}\left[(-\alpha)^2-\beta^2+k_2(\alpha-\beta)+\beta k_2+{k_2}^2\right)t^2+e_2(t^3),$$

$$c(t)=(k_2)t+\frac{1}{2}\left[(-k_e)^2-k_ek_2+k_2(\alpha-\beta-k_2)\right)(t^2)+e_3(t^3).$$

Proceeding like this we get

$$x(t)=e^{(-\alpha)t}-\left(e^{-(\beta t)}-1\right)+\frac{-\beta k_2}{2}t^2+\frac{\alpha\beta(\beta-\alpha)+\beta{k_2}^2+2\beta^2k_2}{6}t^3......, \tag{50}$$

$$y(t)=e^{(-\beta)t}-\left(e^{-(\alpha t)}-1\right)-k_2t+\frac{-k_2\alpha+2\beta k_2+(k_2)^2}{2}t^2+....., \tag{51}$$

$$c(t)=\left(e^{k_2t}-1\right)-\frac{k_2}{k_e}\left(e^{-k_et}-\frac{{k_e}^2}{k_2}t-\frac{k_e}{k_2}\right)+\frac{(k_2\alpha-k_2\beta)t}{2}+\ldots\ldots \tag{52}$$

Thus the first approximations of modified power series method exactly matches with the solution obtained using Taylor's series method and in limiting cases with

Keener's [12]. This method gives us more accurate and exact solution.

Discussion

In this paper Magleby and Stevens's neurotransmitter model is considered. The analysis is done by Phase plane and it has been shown that the observations exactly match with the Keener [12]. Power series method supports the same result. That is 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.

We have also obtained the solution for the system of equations given by (1)-(3) for some limiting cases by power series and modified power series solution. The obtained solutions are entirely new and can be used to predict the exact conductance of the model.

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