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Computation of Time-dependent Probabilities of Vesicle Release and Binding of Neurotransmitters of Postsynaptic Neuron

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When a postsynaptic neuron receives a spike from the axon, its synapse releases neurotransmitters to the synaptic cleft. The probability of vesicle release depends on the amount of calcium ions. The concentration of calcium ions keeps on changing with time. The opening and closing of these channels is controlled by the calcium ion gates operating at different rates. Similarly, the binding of neurotransmitters to the membrane depends on the number of receptors. The existing literature considers probabilities of vesicle release and binding of neurotransmitters as constants. In practice, these two probabilities are time-dependent. This issue is addressed in this paper and new derivations of the time-varying nature of these two probabilities are obtained from simulation study and analysis. The present investigation of estimation of these two time-dependent probabilities will help to develop improved nanoscale neuronal communication models.

Keywords: Vesicle release probability, Binding probability, Neuronal Communication

Introduction

The existing literature[1,2] deals with the fact that the vesicle release probability is constant which is, in reality, is time-dependent. In the current paper, this problem is addressed and expression for time-varying vesicle release probability is derived and its characteristics are analyzed. This value depends on the number of receptors in an open state and hence varies with time. In addition, the existing reported literature does not consider the value of binding probability to be time-dependent. Thus to derive an expression for the time-varying binding probability is important and required for developing a realistic nano-scale molecular communication system.

Materials and methods

In this section, the details of materials and methods used for investigation of the proposed problem are outlined. The materials used in this investigation are: background information on release and binding probabilities related to the synapse of a biological neuron. In addition, the experimental data used for the simulation study is provided in a tabular form (Table 1). The method employed in this study constitutes the derivation of the time-varying probabilities of vesicle release and binding of neurotransmitters.

Vesicle Release and Binding Probabilities

In a recent paper[1], the authors have provided a theoretical study on quantification of information received by the post-synaptic neuron from a pre-synaptic neuron. They have analyzed a bipartite synapse considering reliable and unreliable vesicle release probability and neurotransmitter binding probability. A recent study[2] reveals that the release probability is controlled by the size of the readily releasable vesicle pool and the release probability per vesicle. After the arrival of action potentials, the vesicle release probability regulates the release of

Table 1 — Data used for performing simulation based experiments

Sl No	Symbols	Stands for	Values in $ms^{-1}\times \mu M^{-1}$
1	k_1^+	opening rate of first gate	3.75×10^{-3}
2	k_1^-	closing rate of first gate	4×10^{-4}
3	k_2^+	opening rate of second gate	2.5×10^{-3}
4	k_2^-	closing rate of second first gate	1.0×10^{-3}
5	k_3^+	opening rate of third gate	5.0×10^{-4}
6	k_3^-	closing rate of third gate	0.1
7	k_4^+	opening rate of fourth gate	0.75×10^{-3}
8	k_4^-	closing rate of fourth gate	10.0
9	M	No of spikes	40
10	N	No of neurotransmitters in a vesicle	1000

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neurotransmitters. In another paper[3], the authors have analyzed the source of reception noise generated due to ligand receptor binding of a diffusion-based molecular communication system. The ligand receptor binding is made using two different approaches. It is reported that during recovery from synaptic depression reduction in release probability of releasable vesicles is observed. The authors have presented a mathematical model[4] of synaptic transmission of a tripartite synapse. It predicts the inter-event internal distribution of currents activity mediated by a synaptic astrocyte. It also explains the mechanism of plasticity in which the low fidelity synapse through the astrocytic coupling. The various noise effects which cause uncertainty in the cardiovascular process have been analyzed by the authors.[5] They have derived the capacity of the particulate drug delivery systems considering end-to-end noise effects and time-varying blood flow. In the literature, the relation between [Can] and the probability of release is reported by developing a four gate model of the vesicle release process. The model consists of four gates with different opening and closing times. When the presynaptic neuron receives a signal, it is forwarded to synapse through the axon. The synapse then releases the neurotransmitters which are enclosed in the vesicles into the synaptic cleft. From the literature survey, it is observed that the probability of vesicle release is considered as constant and depends on many factors. One of the factors is the presence of calcium ions. The amount of vesicle release approximated is proportional to the amount of calcium ions in the synapse. The concentration of calcium ions keeps on changing with respect to time. The movement of these ions in and out of neurons through calcium channel constitutes the calcium current. The opening and closing of these channels are controlled by the calcium ion gates. The binding of the neurotransmitters to the membrane of the post-synaptic neuron is governed by the legend -binding mechanism. The probability associated with such binding refers to the binding of neurotransmitters to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors of the membrane of the receiving post-synaptic neuron.[1] To the best of our knowledge, no previous authors have addressed this problem. In this paper, this task is taken up and a closed-form equation of time-dependent binding probability $P_b(t)$of neurotransmitters is derived and its characteristics are also studied. The typical experimental data obtained from references[1,4] is presented in Table 1.

Method

The methodology adopted to obtain the closed form expression of time-dependent vesicle release and binding probabilities is through derivation. In this section, starting from basic equation of concentration of calcium ions and probability expression of open gates, the expression for time-dependent vesicle release probability is derived. Further, using the basic equations of reaction rate of a chemical system of neuro-transmitters and the expression for time varying binding probabilities is derived. In this case it is assumed that the concentration of calcium ion is a function of time. The probability of Vesicle Release depends on the presence of calcium ions in the synapse. Since the concentration of calcium ions changes with respect to time, the Vesicle Release probability also should change with respect to time. The binding probability depends on the legend-binding mechanism which is a time varying phenomenon. Hence, this probability is also time dependent in nature.

Derivation of Expression of Time Varying Vesicle Release Probability

The Bertram-Sherman-Stanley four-gate model of vesicle release process consists of four gates which are independent to each other and operate at different opening and closing times. It is reported that the gate S_1 opens more rapidly where the opening rate of $S_4$is the slowest. The relationship[4] between calcium ion and the number of calcium ions is given by

$$\frac{d[Ca_n](t)}{dt} = -0.13C_a - 0.075\,[Ca_n] \quad \ldots (1)$$

where $[Ca_n]$ denotes the concentration of calcium ion and I_{ca} is the calcium current. Assuming that the calcium current is constant for the purpose of obtaining a close form solution, the concentration of the calcium ion is obtained as

$$[Ca_n](t) = 013\, e^{0.075t}.I_{ca}e^{\frac{-0.075t-c(0.075)}{0.075}} \quad \ldots (2)$$

where c is a constant of integration.

The time varying vesicle release probability, ($P_r(t)$) can be represented[1] as

$$P_r(t) = P_1(t).P_2(t).P_3(t).P_4(t) \quad \ldots (3)$$

where $P_j(t), 1 \leq j \leq 4$are the open gates probabilities associated with S_j gate. This probability can be expressed as

$\frac{dP_j(t)}{dt} = k_j^+[Ca_n](t) - \frac{P_j(t)}{\tau_j(t)}$, j=1,2,3,4 … (4)

where $\tau_j = \frac{1}{k_j^+[Ca_n](t)+\overline{k_j}}$, k_j^+ and k_j^- represent opening and closing rates of any jth gate. Solving equation-2 gives

$[Ca_n](t) = k + m\, e^{0.075\, t}$ … (5)

where k = A constant – $1.73I_{ca}$ and m = A constant = (-0.13I_{ca}) c . Substituting the values of $[Ca_n](t)$fromequation-5 in equation-4 and solving, the expression of $P_j(t)$ is obtained as

$P_j(t) = \frac{I_j(t)}{IF_j(t)}$ … (6)

where, $IF_j(t) = integrating\ factor = e_j^{ct+d_j e^{0.075t}}$, $c_j = k_j^+ + k_j^-$ and $d_j = mk_j^+$ and $I = \int IF(t)[Ca_n](t)dt$

Solution of equation-6 gives

$$P_j(t) = -0.075\frac{\frac{k\tau(c_{1j}-c_3(t))}{-1^{c_{1j}}d^{c_{1j}}} - \frac{m\tau(c_{2j}-c_{3j}(t))}{-1^{c_{2j}}d_j^{c_{2j}}}}{e^{ct}+c_{3j}(t)} \quad \ldots (7)$$

where $c_{1j} = 0.075\, c_j$, $c_{2j} = \frac{40}{3}(c_j + 0.075)$, $c_{3j}(t) = d_j.e^{0.075t}$

Derivation for expression for Time-varying Binding Probability

The reaction rate equation (RRE) of a chemical system related to neuro transmitters is expressed[3] as

$\frac{dn_b(t)}{dt} = k^+ + C_R(t)\big(N_R - n_b(t)\big) - k^- n_b(t)$ … (8)

where $C_R(t)$ is the concentration of neuro transmission, $n_b(t)$ is the number of bound receptors, k^+ is the rate of neurotransmitters binding, N_R is total receptors at the receiver, k^- is the rate of neurotransmitters release. In this paper,$C_R(t)$, which depends on time, is approximated by a polynomial function $A\,t^2 + Bt + C$ of time, where A, B and C are constants to be determined by interpolation.

From reference[3], using k^+ = 0.2 and k^-= 10, it is observed that $k^+C \gg k^-$. Using this approximation and taking integrating factor (IF) as $\int(k^+C_R(t) + k^-)\,dt$, equation-8 is solved to obtain the expression of $n_b(t)$ as

$n_b(t) = N_R + c_1 e^{-k^+[At^3 + B\frac{t^2}{2} + C]}$ … (9)

According to reference[1], the time varying binding probability,$P_b(t)$ is given as

$\frac{dP_b(t)}{dt} = C_R(t)k^+ + (N_R - n_b(t))$ … (10)

The terms used in equation-10 have been explained after equation- 8. Substituting the values of $C_R(t)$ and $n_b(t)$ from equation-10, the expression for $P_b(t)$ is expressed as $e^{c_1 e^M} + c_2$, where M is given as $-k^+(A\frac{t^3}{3} + B\frac{t^2}{2} + C)$. Finally, the time dependent binding probability is found to be $P_b(t) = e^{c_1 e^{-k^+(A\frac{t^3}{3} + B\frac{t^2}{2} + C)}} + c_2$.

where c_1 and c_2 are constants of integration.It represents the derivation of time varying binding probability of neurotransmitters in the synapse of a biological neuron.

Results and Discussions

This section deals with the steps required for computing each of the time varying vesicle release and binding probabilities using various typical values of constants and other relevant parameters which are presented in Table 1.

Steps for Finding the Time Varying Values of Vesicle Release Probability

Step-1: Equation-11 is computed for each of the four calcium ion gates using the data provided in Table 1.

Step-2: Equations 3 and 7 are computed to find the time varying vesicle release probability using the time varying probability value of each of the four gates obtained in Step-1.

Steps for Finding the Time Varying Values of Binding Probability

Steps for finding out the values of A, B and C used in equation-11 are:

Step-1: Find probability of release for all time between 0 to t secs.

Step-2: Compute concentration of neuro-transmitters for each time interval using, where M and N represent the number of spikes and neurotransmitters of a vesicle respectively.

Step-3: Since, the values of A, B and C are found by using interpolation method by using the values of $C_R(t)$ at various time intervals.

Step-4: The values obtained from time varying $C_R(t)$ in step-3 is used in equation-11 to compute the time varying values of binding probability.

The vesicle release probability with variation in time for 11 values of calcium current is obtained following Step-2 of Section 3.1 and using data of Table 1 and is shown in Fig. 1. It is observed from this figure that the vesicle release probability value exhibits exponential decay characteristics with increase in time. Further, for the same instant, if the

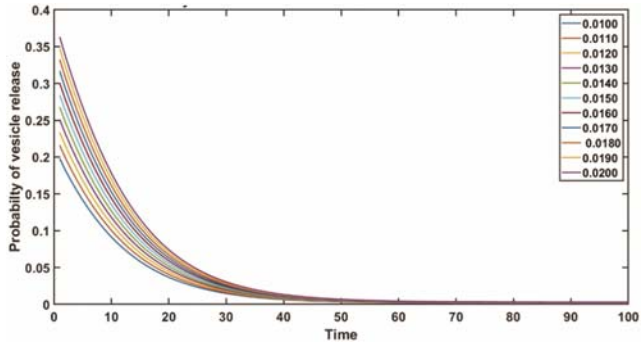

Fig. 1 — Plot of time-dependent vesicle release probabilty for different calcium currents

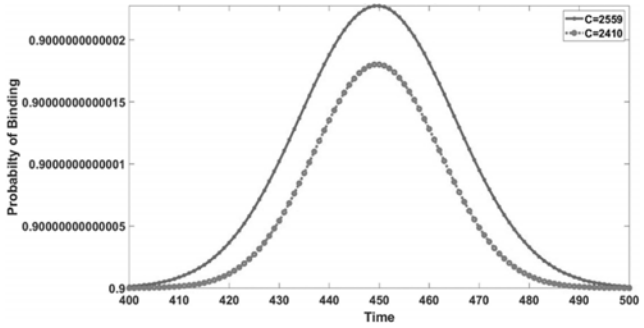

Fig. 2 — Plot of variation of Binding probability with time for different C values

Table 2 — Salient feature of plot of Time dependent binding probability of Fig. 2

S No.	Values of C In the expression of $C_R(t)$	Time in seconds at which Peak occurs	Peak value of $P_b(t)$
1	2559	451	0.900
2	2410	441	0.721

calcium current increases, the probability value correspondingly decreases. The smaller is the time instant, the higher is the *Pr(t)*. When the time value reaches 100 seconds, the corresponding probability value almost becomes zero for all calcium currents.

The variation of binding probability with time for two different values of C is shown in Fig. 2.

The characteristic of the variation of binding probability is similar to the plot of Gaussian distribution.

In Table 2, the features of time dependent binding probability of Fig. 2 are presented. From this table it is observed that the lesser is the value of C, the smaller is the value of binding probability. For a C value of 2559, the peak value of binding probability is 0.9 which occurs at 451 second. But for a C value of 2410, the peak value becomes 0.721 at 441 seconds which is smaller than the previous case.

The spiking response of synapse depends on the binding and vesicle release probabilities. The characteristics of vesicle release probabilities show that it is exponentially decaying in nature with respect to calcium currents. However, the binding probability exhibits bell shape characteristics. It is observed that in the middle of the time its value is maximum.

Conclusion

The vesicle release and binding probabilities are two important factors which contribute to the development of realistic nanoscale neuronal communication systems. But the time-varying characteristics of these two probabilities are not considered in previous literature. This paper has investigated this issue and expressions of time dependent vesicle release and binding probabilities are presented. Further, using these expressions the exact probabilities at any given time can be computed and used for improved estimation of spike generation of postsynaptic neuron. A nearly exponential decay characteristic of vesicle release probability is observed with variation of time and for different calcium currents. In case of binding probability, the plot is of bell shape type with respect to time variation. Further study can be made to develop improved molecular communication models using these time dependent probabilities which are not considered earlier.

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