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DYNAMICAL MODEL OF CHOLINERGIC SYNAPSE TRANSMISSION

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Abstract The diffusion and conversion of ACh from one form into another responsible for the transmission of nerve impulses in the cholinergic synapses is described by means of five simultaneous ordinary differential equations.
Key words: Dynamical mathematical model, cholinergic synapse transmission, computer simulation

MODELE DYNAMIQUE DE LA TRANSMISSION DE LA SYNAPSE CHOLINERGIQUE

Résumé La diffusion et la conversion de ACh de l'une de ses formes dans une autre responsable pour la transmission des impulsions nerveuses dans les synapses cholinergiques est décrite au moyen de cinq équations différentielles simultanées et ordinaires.
Mots-clefs: Modèle mathématique dynamique, transmission synaptique cholinergique, simulation à l'ordinateur

INTRODUCTION

The following basic hypotheses with respect to the transmission of nerve impulses in the cholinergic synapses are assumed in the present model:

(i) There exist two forms of acetylcholine (ACh) in the presynaptic area: 'free' ACh and ACh bound to the synaptical vesicles (Israel *et al.*, 1970; Marchbanks, 1975; Israel *et al.*, 1979).

(ii) The nerve impulses reach the presynaptic membrane and change its permeability, resulting in release of 'free' ACh into the synaptic cleft (Dunant *et al.*, 1974; MacIntosh and Collier, 1976). By intensive activity of the synapse the decrease of 'free' ACh in the presynaptic zone leads to the decline of vesical ACh which participates in the transmission process.

(iii) The 'free' ACh released in the cleft binds the specific ACh receptors on the postsynaptic membrane (Nachmansohn, 1962). ACh produces a conformational change of the receptor protein and the resulting shift of charge triggers a sequence of reactions responsible for the permeability of the postsynaptic membrane (Heidmann and Changeux, 1978).

(iv) The next step is an almost instantaneous hydrolysis of the ACh by the enzyme acetylcholinesterase (AChE). The products of the hydrolysis diffuse back to the presynaptic zone and are used for a new synthesis of ACh (Silver, 1974).

Our first purpose is to describe mathematically the diffusion and conversion of ACh in the synaptic area.

MATHEMATICAL MODEL

Figure 1 shows a schema of the synaptic area; imagine a circular cylinder H perpendicular to the plane of the synaptic membranes, bound by the plane section M of the postsynaptic membrane and the plane section N which outlines the beginning of the presynaptic zone. The rectangule on Fig. 1 presents a plane section of H. The volume of H can be considered as sum of three volumes $V_0 + V_1 + V_2$; V_0 is the volume of all the vesicles in H, $V_0 + V_1$ is the volume of the presynaptic zone, and V_2 is the volume of the synaptic cleft. Since the volumes V_1, V_2, V_3 are small we may consider average concentrations in every volume instead of concentrations in every point of H. This saves the necessity of introducing partial differential equations in the model.

Consider first the rate of change of the quantity of the vesical acetylcholine (A_v) with time. Assuming that A_v converts only into 'free' acetylcholine (A_f), i.e. the

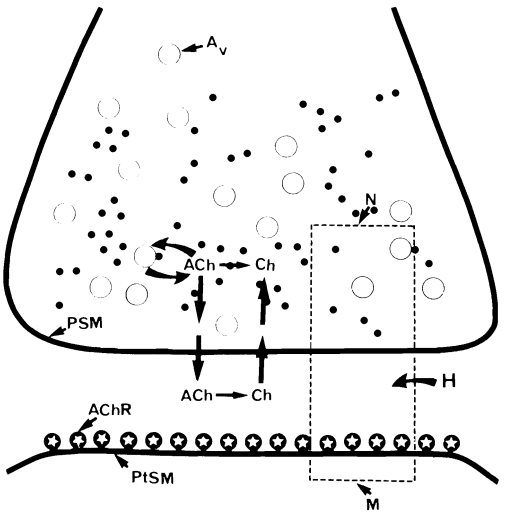


Fig. 1. Synapse. The space of consideration is denoted by H.

vesicles do not pour out directly into the cleft, we may write

$$(1) \qquad d(V_0[A_v])/dt = \bar{K}_v([A_f] - [A_v]).$$

where $\bar{K}_v$ is a parameter characterizing the permeability of the vesical membranes.

Noticing that A_f increases by the quantity of A_v, which is poured out from the vesicles, we have

$$d(V_1[A_f])/dt = -\bar{K}_v([A_f] - [A_v]) + \ldots.$$

In the right-hand side we must also subtract a term accounting for the decrease of A_f caused by the diffusion of A_f through the presynaptic membrane into the cleft. This term is proportional to the difference of the concentrations of A_f and of ACh released in the cleft A_r with some coefficient $\bar{K}_p$ characterizing the permeability of the presynaptic membrane and hence of the form $\bar{K}_p([A_f] - [A_r])$. Finally we add a term P, accounting for the new synthesis of ACh in the presynaptic area. Thus the equation for A_f obtains the form

$$(2') \qquad d(V_1[A_f])/dt = -\bar{K}_v([A_f] - [A_v]) - \bar{K}_p([A_f] - [A_r]) + P.$$

The quantity $V_2[A_r]$ of ACh released in the synaptic cleft increases by the quantity of ACh diffusing through the presynaptic membrane, which is equal to $\bar{K}_p([A_f] - [A_r])$, and diminishes by the quantity Q of ACh bounding the receptor R on the postsynaptic membrane:

$$(3) \qquad d(V_2[A_r])/dt = \bar{K}_p([A_f] - [A_r]) - Q.$$

Equations (1)–(3) describe the diffusion of ACh through the membranes. Next we describe the interaction of the ACh in the cleft with the receptor R on the postsynaptic membrane, producing the complex RA and the subsequent dissociation of RA. The complex RA dissociates into the receptor R and some products S from which ACh is produced in the presynaptic zone later on:

$$A + R \underset{K_{-1}}{\overset{K_{+1}}{\rightleftarrows}} RA \underset{K_{-2}}{\overset{K_{+2}}{\rightleftarrows}} R + S.$$

Here K_{+1} and K_{-1} denote the rate constants for bounding and dissociation of the complex RA, K_{+2} is the rate constant for the reaction $RA \to R + S$; K_{-2} is assumed to be zero according to the fact that the reaction $R + S \to RA$ is of very low rate and can be neglected.

Thus we have

$$d[RA]/dt = K_{+1}[A_r]([R] - [RA]) - (K_{-1} + K_{+2})[RA],$$

where $[R] = \text{const.}$ is the concentration of all receptors and hence $[R] - [RA]$ is the concentration of the free receptors.

In the following we assume that the volumes V_1, V_2, V_3 are constant in time. Multiplying the last equation by V_2 yields

$$(4) \qquad V_2 d[RA]/dt = d(V_2[RA])/dt = V_2 K_{+1}[A_r]([R] - [RA]) - V_2(K_{-1} + K_{+2})[RA].$$

Equation (4) shows that the quantity of ACh bounded to R increases by $V_2 K_{+1}[A_r]([R] - [RA])$. This should be equal to the quantity Q in equation (3) since ACh in the cleft diminishes by the quantity Q.

$$Q = V_2 K_{+1}[A_r]([R] - [RA]).$$

Consider now the rate of variation of the quantity S of the products obtained from the dissociation of the complex AR. The concentration of these products in the synaptic cleft at time t will be denoted by $[S](t)$. Then $S = V_3[S]$. According to the mass-conservation law the quantity S is equal to the quantity of the newly-synthesized ACh. The increase of S is as great as the decrease of the ACh bounded to the receptors on the postsynaptic membrane. The decrease of S is as great as the quantity of the newly-synthesized ACh in the

presynaptic zone. These arguments lead to the equation:

$$(5') \quad d(V_3[S])/dt = V_2(K_{-1} + K_{+2})[RA] - P,$$

where P is the term appearing in (2).

Clearly P is proportional to the difference $[S] - [A_f]$ with a coefficient $K_w > 0$ denoting the rate of diffusion of the products S of the dissociation of AR on the postsynaptic membrane to the presynaptic membrane. Thus (5′) may be written

$$(5) \quad d(V_3[S])/dt = V_2\bar{K}_d[RA] - \bar{K}_w([S] - [A_f]),$$

wherein $\bar{K}_d = K_{-1} + K_{+2}$.

Equation (2′) obtains the form

$$(2) \quad \begin{aligned} d(V_1[A_f])/dt = &- \bar{K}_v([A_f] - [A_v]) \\ &- \bar{K}_p([A_f] - [A_r]) \\ &+ \bar{K}_w([S] - [A_f]). \end{aligned}$$

With some approximation we further assume that $V_0 = V_1$. Denoting further K_{+1} by K_s and $V_2/V_0 = r$ we arrive at the system

$$(6) \quad \begin{cases} \dfrac{d[A_v]}{dt} = K_v([A_f] - [A_v]), \\ \dfrac{d[A_f]}{dt} = -K_v([A_f] - [A_v]) - K_p([A_f] \\ \qquad - [A_r]) + K_w([S] - (A_f]), \\ \dfrac{d[A_r]}{dt} = \dfrac{K_p}{r}([A_f] - [A_r]) - K_s[A_r]([R] \\ \qquad - [RA]), \\ \dfrac{d[RA]}{dt} = K_s[A_r]([R] - [RA]) - K_d[RA], \\ \dfrac{d[S]}{dt} = K_d[RA] - \dfrac{K_w}{r}([S] - [A_f]), \end{cases}$$

where $K_v = \bar{K}_v/V_0$, $K_p = \bar{K}_p/V_0$, $K_w = \bar{K}_w/V_0$ and all the concentrations are taken at the moment t.

Next we give some explanations with respect to the parameters K_v and K_p.

The parameter K_v characterizes the permeability of the vesicle memoranes. We may assume that K_v can take two different values depending on the magnitude of the difference $[A_f] - [A_v]$ between the concentrations of the bounded and free ACh in the presynaptic zone. If this difference is too great the activity of the synapse increases and K_v takes a greater value b in comparison with its normal value a. Thus we put

$$K_v = K_v(t) = \begin{cases} a, \text{ if } |[A_f](t) - [A_v](t)| \le \varepsilon, \\ b, \text{ if } |[A_f](t) - [A_v](t)| > \varepsilon, \end{cases}$$

where ε is a threshold value.

The parametre K_p characterizes the permeability of the presynaptic membrane with respect to ACh. We assume that K_p depends linearly on the frequency V of the arriving nerve impulses, $K_p(t) = K_v(t) + K_{p,0}$.

The function v is an input function for the system (6). The output function is the concentration $[RA]$ responsible for the potential generated on the postsynaptic membrane as a result of the binding of ACh to $[R]$.

Let us look now at the mathematical problem. We have the system (6) of five ordinary differential equations with unknown positive parameters $a, b, \varepsilon, K, K_{p,0}, K_s, K_d, K_w$ and $[R]$. The problem is to find values for these parameters so that the output function $[RA](t)$ reacts to the input function $v(t)$ in a reasonable way. Thus we have a parameter identification problem for the system (6). There are no convenient methods for solving this problem because the coefficients K_v and K_p are nonlinear functions. We have treated our problem by means of computer simulation.

COMPUTER SIMULATION

We shall first find the equilibrium state of the system (6) corresponding to a minimal activity of the synapse. At equilibrium the impulses transmitted through the nerve have some minimal frequency to which corresponds a minimal value $K_{p,0}$ of $K_p(t)$, such that $K_p(t) \ge K_{p,0}$ for all $t \ge t_0$. At equilibrium it holds $K_v = a$ as well. The stable state $[A_v]_0$, $[A_f]_0$, $[A_r]_0$, $[RA]_0$, $[S]_0$ of system (6) annihilates the derivatives and thus satisfies the algebraic equations

$$(7) \quad \begin{cases} a([A_f]_0 - [A_v]_0) = 0, \\ -a([A_f]_0 - [A_v]_0) - K_{p,0}([A_f]_0 - [A_r]_0) \\ \qquad + K_w([S]_0 - [A_f]_0) = 0, \\ \dfrac{K_{p,0}}{r}([A_f]_0 - [A_r]_0) - K_s[A_r]_0([R] \\ \qquad - [RA]_0) = 0, \\ K_s[A_r]_0([R] - [RA]_0) - K_d[RA]_0 = 0, \\ K_d[RA]_0 - \dfrac{K_w}{r}([S]_0 - [A_f]_0) = 0. \end{cases}$$

This system reduces to four equations, so in order to determine the stable state we need one more equation. Such can be the normalizing condition

$$(8') \qquad V_0[A_r]_0 + V_1[A_f]_0 + V_2([A_r]_0 + [RA]_0 + [S]_0) = \text{const.}$$

expressing the fact that the whole quantity of ACh is constant in the volume H of consideration. In view of $V_2/V_1 = r$, $V_0/V_1 = 1$ (8') becomes

$$(8) \qquad [A_r]_0 + [A_f]_0 + r([A_r]_0 + [RA]_0 + [S]_0) = \text{const.} = 1.$$

From (8) we have

$$(9) \quad \begin{cases} [A_r]_0 = \dfrac{K_d}{K_s} \cdot \dfrac{[RA]_0}{[R] - [RA]_0}, \\ [A_r]_0 = [A_f]_0 = [A_r]_0 \times \left\{1 + r\dfrac{K_s}{K_{p,0}}([R] - [RA]_0)\right\}, \\ [S]_0 = [A_f]_0 + r\dfrac{K_d}{K_w}[RA]_0. \end{cases}$$

Substituting (9) in (8) we get the following quadratic equation for $[RA]_0$:

$$(10) \qquad \alpha[RA]_0^2 - \beta[RA]_0 + [R] = 0,$$

wherein

$$\alpha = r\left\{\left(r\frac{K_d}{K_w} + 1\right) + r\frac{K_d}{K_{p,0}}(r+2)\right\},$$

$$\beta = \alpha[R] + 2(r+1)\frac{K_d}{K_s} + 1.$$

It is easily seen that the root $u_0 = (\beta - \sqrt{\beta^2 + 4\alpha[R]})/(2\alpha)$ of (10) is always in the interval $(0, [R])$, whereas the root $u_0^* = (\beta + \sqrt{\beta^2 + 4\alpha[R]})/(2\alpha)$ is always greater than $[R]$. Therefore we have

$$(11) \qquad [RA]_0 = (\beta - \sqrt{\beta^2 + 4\alpha[R]})/(2\alpha).$$

The values for $[A_r]_0$, $[A_f]_0$, $[A_r]_0$, $[RA]_0$ and $[S]_0$ thus obtained determine the stable state of the system.

In order to get a numerical solution of (6) we use the improved Euler's method. Denoting for brevity $[A_r](t_j) = x_j$, $[A_f](t_j) = y_j$, $[A_r](t_j) = z_j$, $[S](t_j) = w_j$, $[RA](t_j) = u_j$, $K_p(t_j) = K_{p,j}$, we obtain the following system of difference equations:

$$\begin{cases} x_{j+1} = x_j + (h/2)[K_{r,j}(y_j - x_j) + K_{r,j}(\gamma_j^{(2)} - \gamma_j^{(1)})], \\ y_{j+1} = y_j + (h/2)[K_{r,j}(x_j - y_j) - K_{p,j}(y_j - z_j) + K_w(w_j - y_j) + K_{r,j}(\gamma_j^{(1)} - \gamma_j^{(2)}) - K_{p,j}(\gamma_j^{(2)} - \gamma_j^{(3)}) + K_w(\gamma_j^{(5)} - \gamma_j^{(2)})], \\ z_{j+1} = z_j + (h/2)[K_{p,j}(y_j - z_j)/r - K_s(c - u_j)z_j + K_{p,j}(\gamma_j^{(2)} - \gamma_j^{(3)})/r - K_s(c - \gamma_j^{(4)})\gamma_j^{(3)}], \\ u_{j+1} = u_j + (h/2)[K_s(c - u_j)z_j - K_d u_j + K_s(c - \gamma_j^{(4)})\gamma_j^{(3)} - K_d\gamma_j^{(4)}], \\ w_{j+1} = w_j + (h/2)[K_d u_j - K_w(y_j - w_j)/r + K_d\gamma_j^{(4)} - K_w(\gamma_j^{(2)} - \gamma_j^{(5)})], \end{cases}$$

where

$$\gamma_j^{(1)} = x_j + hK_{r,j}(y_j - x_j),$$

$$\gamma_j^{(2)} = y_j + h[K_{r,j}(x_j - y_j) - K_{p,j}(y_j - z_j) + K_w(w_j - y_j)],$$

$$\gamma_j^{(3)} = z_j + h[K_{p,j}(y_j - z_j)/r - K_s(c - u_j)z_j],$$

$$\gamma_j^{(4)} = u_j + h[K_s(c - u_j)z_j - K_d u_j],$$

$$\gamma_j^{(5)} = w_j + h[K_d u_j - K_w(y_j - w_j)/r],$$

and the initial values x_0, y_0, z_0, w_0 and u_0 have already been computed by means of (9) and (11). h is a properly chosen step. We recall that $K_{p,j} = Kv_j + K_{p,0}$, $j = 1, 2, \ldots$, depend on the input sequence $v_j = v(t_j)$ and $K_{r,j}$ are defined by

$$K_{r,j+1} = \begin{cases} a, & \text{if } |x_j - y_j| \le \varepsilon, \\ b, & \text{if } |x_j - y_i| > \varepsilon. \end{cases}$$

Our algorithm is as follows:

(1) Give arbitrary input values to the unknown parameters a, b, ε, K, $K_{p,0}$, K_s, K_d, K_w and $[R]$.

(2) Determine the root $u_0 = [RA]_0$ of (10) by means of (11).

(3) Using u_0 determine $x_0 = [A_r]_0$, $y_0 = [A_f]_0$, $w_0 = [S]_0$ and $z_0 = [A_r]_0$ by means of (9).

(4) Using an input function $v_j = v(t_j)$ solve the system (12) with a properly chosen step h.

(5) Observe whether the function $u(t) = [RA](t)$

function $v(t)$. If this is not the case then go to (1) with other values of the parameters.

After a great number of such experiments the computer simulation approach gave finally very good results. Some of them are presented below.

The following input values are common for many experiments: $a = 0.1$, $b = 0.5$, $\varepsilon = 0.01$, $K = 2.0$, $K_{p,0} = 0.5$, $r = V_2/V_1 = 0.2$, $r_1 = V_0/V_1 = 1.0$, $K_d = 0.5$, $K_s = 2.5$, $[R] = 1$, $h = 0.05$.

In our examples the input function $v(t)$ is defined by

$$v(t) = \begin{cases} 0, \; t \in [t_0, t_1], \\ (1/2)K_{p,0}c_0 e^{\varepsilon_1(t-t_1)}/(c_0 + K_{p,0} - K_{p,0}e^{\varepsilon_1(t-t_1)}), \\ \quad t \in [t_1, t_2], \\ v(t_2), \; t \in [t_2, t_3], \\ (1/2)K_{p,0}c_0 e^{\varepsilon_2(t_4-t)}/(c_0 + K_{p,0} - K_{p,0}e^{\varepsilon_2(t_4-t)}), \\ \quad t \in [t_3, t_4]. \end{cases}$$

The conductivity of the presynaptic membrane is $K_p(t) = Kv(t) + K_{p,0} = 2v(t) + 0.5$. The form of this function is clear from Figs. 2a and 3a.

Example 1. Here the parameters are $r = 0.2$, $[R] = 2$, $K_s = 2.5$, $K_d = 0.5$, $K_w = 0.5$, $a = 0.1$, $b = 0.5$, $K_{p,0} = 0.5$, $\varepsilon_1 = \varepsilon_2 = g$, $c_0 = 2$.

The graphs of the functions K_p and $[RA]$ are presented on Figs. 2a and 2b respectively. It is clearly seen that both functions have similar behaviour. The maximum value of $[RA]$ is reached a little later than the maximum value of K_p. This reflects the fact that due to the chemical mechanism of the impulse transmission, the train of impulses appears at the 'exit' with some retardation.

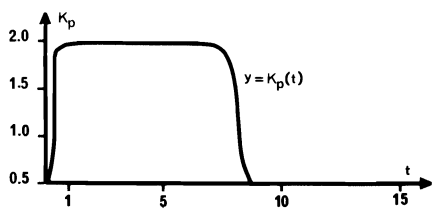
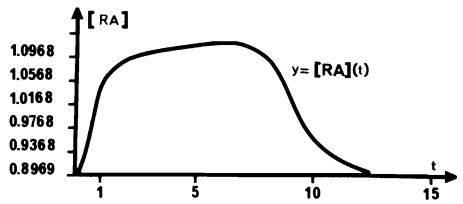


Fig. 2a. Input function $K_p(t)$ used in example 1.



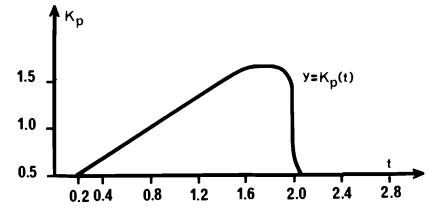


Fig. 3a. The input function used in example 2.

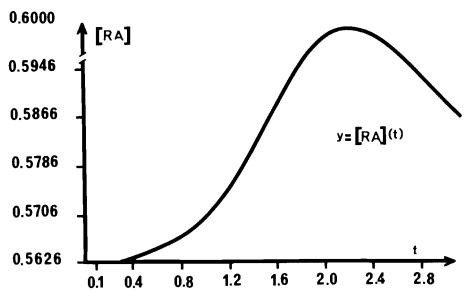


Fig. 3b. The output function obtained in example 2.

Example 2. In this example we have chosen the following values for the parametres: $r = 0.5$, $[R] = 1$, $K_s = 2.5$, $K_d = 0.5$, $K_w = 0.5$, $a = 0.1$, $b = 0.5$, $K_{p,0} = 0.5$, $\varepsilon_1 = 1$, $\varepsilon_2 = 5$, $c_0 = 10$.

The input function $v(t)$ in this example increases slowly and falls down quickly (indeed we have $\varepsilon_1 = 1$ in (t_1, t_2) and $\varepsilon_2 = 5$ in (t_3, t_4).

Figures 3a and 3b show the curves $K_p(t)$ and $[RA](t)$, respectively. The observation of the forms of these curves leads us to the same conclusions as in example 1.

The computer experiments show that the assumptions outlined in the introduction give the basis of a plausible mechanism for the transmission of impulses through the synapse. The results of the simulation qualitatively match with the results in real experiments.

We hope that it is possible to model different physiological, extreme and pathological states of the nerves and other systems on the basis of the proposed mechanism. The results of such a modeling can be compared with available data of real experiments. The model can also be used for simulation of the structural

REFERENCES

Dunant, Y., Gautron, J., Israel, M., Lesbats, B. and Manaranche, R., Evolution de la décharge de l'organe électrique de la torpille et variations simultanées de l'acétylcholine au cours de stimulation. *J. Neurochem.* **23,** 635–643 (1974).

Heidmann, T. and Changeux, J. P., Structural and functional properties of the acetylcholine receptor protein in its purified and membrane-bound states. *A. Rev. Biochem.* **47,** 317–357 (1978).

Israel, M., Gautron, J. and Lesbats, B., Fractionnement de l'organe électrique de la Torpille; localisation subcellulaire de l'acétylcholine. *J. Neurochem.* **17,** 1441–1450 (1970).

Israel, M., Dunant, Y. and Manaranche, R., The present status of the vesicular hypothesis. *Prog. Neurobiol.* **13,** 237–275 (1979).

Marchbanks, R. M., Biochemistry of cholinergic neurones. *Handbook of Psychopharmacology, Basic Neuropharmacology*, Vol. 3, Biochemistry of Biogenic amines. Iversen, L. L., Iversen, S. D. and Snyder, S. H. (Eds), pp. 247–326. Plenum Press, New York, London (1975).

MacIntosh, F. C. and Collier, B., *Neurochemistry of Cholinergic Terminals*, Vol. 42, Zaimis, E. (Ed.). Springer, Berlin, Heidelberg, New York (1976).

Nachmansohn, D., Chemical and molecular basis of nerve activity, in: *Neurochemistry*, Elliott, K. A. C., Page, I. H. and Quastel, J. H. (Eds), pp. 522–557. Thomas, Springfield, Illnois (1962).

Silver, A., The Biology of Cholinesterase, *North-Holland Research Monographs*, Vol. 36, North-Holland, Amsterdam, (1974).