

MOLECULAR DYNAMICS OF SHORT-TERM MEMORY *

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Abstract

In the theory of context-sensitive associative memory (CSAM) described in [1, 2, 3, 4] a broad range of psychological phenomena of short-term memory (STM) and temporal context (mental set) can be naturally understood as implications of the states of "residual excitation" in neural elements. Such hypothetical states of analog dynamic memory were referred to as E-states. The usefulness of the phenomenological concept of E-states is suggested by a variety of psychological, neurobiological and information processing considerations. The mathematical models of the dynamics of such states can be derived from many different assumptions about microscopic cellular mechanisms [6]. One of the interesting possibilities [4] is to connect the dynamics of the macroscopic E-states with the statistical dynamics of the conformations of the protein molecules in neural membranes. The corresponding formalism can be viewed as a natural system-theoretical extension of the classical Hodgkin and Huxley [5] theory.

A single protein molecule is treated as a probabilistic finite-state machine. The probabilities of transitions between different conformations (states) of such a molecule (machine) are affected by different external inputs (membrane potential, concentrations of neurotransmitters, etc.). The average numbers of molecules in different conformations affect ionic currents, the rates of catalytic synthesis of second messengers, etc. These average numbers are identified with the E-states. Though the dynamics of a single molecule is discrete, the E-states change in a continuous fashion. This continuous dynamics can be highly nonlinear, because it is governed by a poten-

tially quite sophisticated logic within each molecule. The paper discusses some nontrivial possibilities of the outlined formalism.

0 INTRODUCTION

Trying to develop a neurobiologically plausible theory of context-sensitive associative memory, I was compelled to postulate that the brain has some sophisticated states of "residual-excitation-like" dynamic memory. I referred to such states as E-states [1, 2, 3, 4]. The study described in this paper is a result of my recent attempt to find possible neurobiological counterparts of such phenomenological states. Traditional models of neural elements consider the following sources of dynamic short-term memory (STM):

1. Accumulation of membrane charges.
2. Accumulation of neurotransmitters in synaptic gaps.
3. Accumulation of ions, second messengers, synaptic vesicles, etc. in cellular compartments.

This paper discusses another, potentially more sophisticated, source of cellular STM associated with statistical dynamics of the protein molecules in neural membranes. The corresponding formalism (Section 2) is a natural system-theoretical generalization of the classical Hodgkin-Huxley theory [5].

1 THE HODGKIN-HUXLEY MODEL

The Hodgkin-Huxley model is illustrated in Figure 1 a,b. The nerve membrane is permeable to three

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main types of ions: K^+ , Na^+ and Cl^- . Potassium and sodium permeabilities are determined by the properties of giant protein molecules embedded in the membrane. There are two main types of such molecules serving as potassium and sodium channels, respectively.

Internal concentrations of ions (particular Na^+) are maintained by metabolic pumps. In the case of the giant axon of the squid, which was used in Hodgkin and Huxley experiments, the concentrations of K^+ , Na^+ and Cl^- outside and inside the axon have the following approximate values:

Outside: $K_0 = 10mM$; $Na_0 = 460mM$; $Cl_0 = 540mM$

Inside: $K_i = 400mM$; $Na_i = 50mM$; $Cl_i = 40mM$

From the Nernst equation the corresponding equilib-

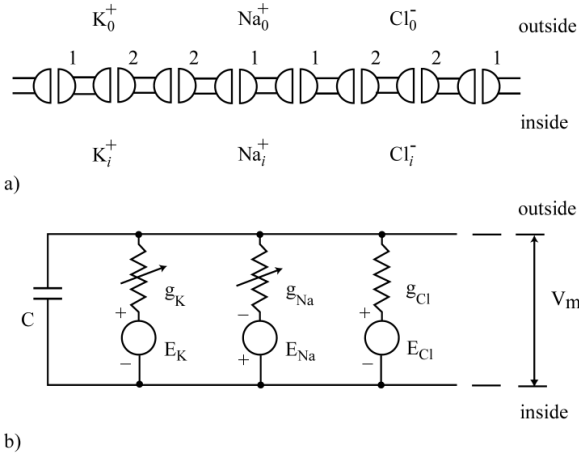


Figure 1: The mechanism of conductivity of nerve membrane

a)Giant protein molecules of two kinds (labeled 1 and 2) serve as potassium and sodium channels, respectively. b)Equivalent electrical circuit that can be used to calculate membrane currents and membrane potential. Potassium, g^K , and sodium g^{Na} , conductances are determined by the statistical distributions of the states of potassium and sodium channels.

rium potentials are equal to:

$$\begin{aligned} E_K &= 25 * \ln(K_0/K_i) = -92.2mV \\ E_{Na} &= 25 * \ln(Na_0/Na_i) = +55.5mV \\ E_{Cl} &= 25 * \ln(Cl_0/Cl_i) = -65.1mV \end{aligned}$$

According to the Goldman equation the resting membrane potential, V_m , is equal to:

$$V_m = 25 * \ln \frac{K_0 + (pNa/pK) * Na_0 + (pCl/pK) * Cl_0}{K_i + (pNa/pK) * Na_i + (pCl/pK) * Cl_i} = -69.9mV$$

$pNa/pK=.03$ and $pCl/pK=.1$, where pNa , pK and pCl are the resting permeabilities of the membrane to Na^+ , K^+ and Cl^- , respectively.

The main idea of the Hodgkin-Huxley theory is that potassium and sodium channel protein molecules change their conformations and, accordingly, their permeabilities as a result of the change of membrane potential, V_m . From their experiments with a clamp amplifier Hodgkin and Huxley found the following empirical expressions describing the change in time of the potassium and sodium conductances in response to a voltage step:

$$gK = gK_{max} * (1 - \exp(-t/t_n))^4 \quad (1)$$

where,

gK is the potassium conductance.

gK_{max} is the maximum potassium conductance reached for a particular voltage step.

t_n is the time constant for the opening of potassium channels (n-gate). In this formula both gK_{max} and t_n are voltage-dependant; t_n ranges between 4msec for small depolarizations, and 1msec for depolarizations to $V_m = 0$.

$$gNa = gNa_{max} * (1 - \exp(-t/t_m))^3 * \exp(-t/t_h) \quad (2)$$

where,

gNa is the sodium conductance.

gNa_{max} is the maximum sodium conductance for a particular voltage step.

t_m is the time constant for the opening of sodium channels (m-gate).

t_h is the time constant for the closing of sodium channels (h-gate).

gNa_{max} , t_m and t_h are voltage dependent. t_m ranges from .6msec near the resting potential, and .2msec at $V_m = 0$.

t_h is similar in magnitude to t_n in (1).

Expressions (1) and (2) combined with the data describing gK_{max} , gNa_{max} , t_n , t_m and t_h as functions of V_m allow one to calculate membrane currents and membrane potential as functions of time. The equivalent electrical circuit explaining the structure of such calculations is presented in Figure 1b.

2 SYSTEM-THEORETICAL FORMALISM

Empirical expressions (1) and (2) do not employ state variables, and, therefore, do not give a closed system-theoretical description of the dynamics of the discussed system. Such description, however, is suggested by the main idea of the Hodgkin-Huxley theory outlined in the previous section.

Let us treat a single protein molecule of a given kind as a microscopic probabilistic finite-state machine. The probabilities of transitions between different states (conformations) of such a machine are affected by different external inputs such as membrane potential, concentrations of neurotransmitters, etc. The average numbers of such machines in different states affect ionic currents, the rates of catalytic syntheses of second messengers, etc. These average numbers can be treated as some states of cellular STM (E-states). In the general case the macroscopic behavior of the outlined system can be described as follows:

The next E-state procedure:

$$\frac{dE_{ij}}{dt} = \sum_{j \neq k} (P_{ijk} * E_{ik}) - E_{ij} * \sum_{k \neq j} P_{ikj} \quad (3)$$

The input procedure:

$$P_{ijk} = FX(i, j, k, x) \quad (4)$$

The output procedure:

$$y = FY(x, E) \quad (5)$$

where,

- E_{ij} is the average number of the microscopic machines of the i-th kind in the j-th state,
- P_{ijk} is the probability of transfer from the k-th state of a microscopic machine of the i-th kind to the j-th state of this machine,
- x is the set of macroscopic input variables (membrane potential, etc.) affecting probabilities P_{ijk} ,
- y is the set of macroscopic output variables (ionic current, etc.),
- FX and FY are functions depending on a specific model $E = (E_{ij})$.

To illustrate a specific meaning of the proposed general formalism in the next section I use equations (3), (4), and (5) to reformulate the Hodgkin-Huxley model.

3 REFORMULATION OF THE HODGKIN-HUXLEY MODEL

To be able to use equation (3) we have to make some assumptions about the structure of the microscopic machines representing different kinds of protein molecules. In the case of the Hodgkin-Huxley theory there are two types of such machines corresponding to the potassium and sodium channels. Let us denote these microscopic machines as M1 and M2, respectively.

Let $n1$ and $n2$ be the numbers of states of M1 and M2, respectively. From the description of the Hodgkin-Huxley model we can assume $n1 = n2 = 5$. The following considerations lead to this assumption:

- In the case of the potassium channel (M1) we need one rest state, one high permeability state,

and at least 3 intermediate states to account for the fourth-order exponential in expression (1).

- In the case of the sodium channel (M2) we need one rest state, one high permeability state, one inactive state with a low (say, zero) permeability, and at least 2 intermediate states to account for the third-order exponential in expression (2).

After selecting the numbers of states we need to decide what transfers have nonzero probabilities. It is convenient to draw the state diagrams explicitly showing these transfers.

In the simplest case such diagrams for machines M1 and M2 may look as shown in Figure 2 a,b. More complex assumptions may lead to diagrams of Figure 2 c,d. Interestingly enough, even the simplest diagrams a) and b) are sufficient to account for most of the effects described in [6]. The results of computer simulation are discussed in Section 4.

After the state diagrams of machines M1 and M2 are selected we need to make assumptions defining equations (4) and (5). In the simplest model we can replace these equations by the expressions (6)–(10) presented below.

Potassium channel:

$$P_{110} = P_{121} = P_{132} = P_{143} = a_1 * f(V_m) \quad (6)$$

$$P_{104} = const$$

where,

$f(V_m)$ is a function describing the dependence of the probabilities of transfers on membrane potential; a_1 is a constant coefficient. For the sake of simplicity I assume that this dependence is the same for all transfers $0 \rightarrow 1, 1 \rightarrow 2, 2 \rightarrow 3$, and $3 \rightarrow 4$. I also assume that the probability of transfer $4 \rightarrow 0$ does not depend on membrane potential. Function $f(V_m)$, used in the computer simulation discussed in Section 4, is presented in Figure 3.

For the sake of simplicity it is assumed that the same function is applicable to all voltage-dependent transfers for both potassium and sodium channels.

NOTE. I do not suggest that these assumptions are necessarily correct. Most likely they represent a gross oversimplification of the biological reality. This is not essential, however, for the purpose of this work. My goal is to illustrate a formalism rather than to offer a precise description of the behavior of channels. In fact, I believe the experimental data required for such a description is not available at the present time. Obtaining such data may be a challenging task.

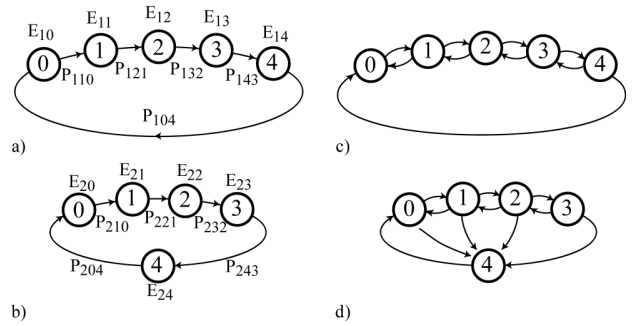


Figure 2: Protein molecules as microscopic machines

a) The simplest 5-stage model of potassium channel: 0 is a low conductivity rest state; 1, 2 and 3 are low conductivity intermediate states; 4 is a high conductivity state (n-gate is open). For the sake of simplicity only $0 \rightarrow 1, 1 \rightarrow 2, 2 \rightarrow 3, 3 \rightarrow 4$, and $4 \rightarrow 0$ transfers are assumed to have nonzero probabilities. b) The simplest 5-state model of sodium channel: 0 is a low conductivity rest state; 1 and 2 are low conductivity intermediate states; 3 is a high conductivity state (m-gate is open); 4 is a zero-conductivity inactive state (h-gate is closed). Only $0 \rightarrow 1, \dots, 4 \rightarrow 0$ transfers are taken into account. c) A more complex 5-state model of potassium channel taking into account the probabilities of backward transfers. d) A more complex 5-state model of sodium channel taking into account the probabilities of backward transfers, and assuming that there are nonzero probabilities of transfers from all states to the inactive state.

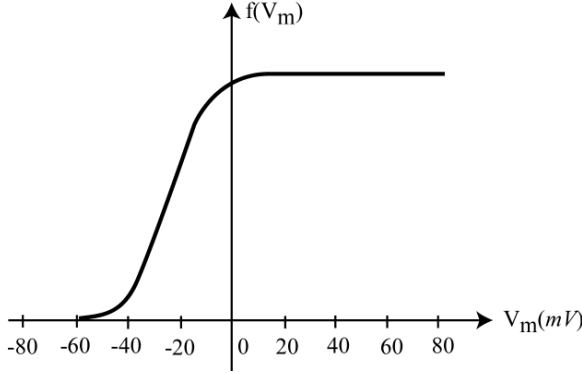


Figure 3: Function describing the dependence of the probabilities of transfers on membrane potential

Sodium channel:

$$P_{210} = P_{221} = P_{232} = a_2 * f(V_m) \quad (7)$$

$$P_{243} = const; P_{204} = const$$

I use the same function $f(V_m)$ as in the case of potassium channel. I assume the probabilities of transfers $3 \rightarrow 4$ and $4 \rightarrow 0$ are not voltage-dependent.

NOTE. The Hodgkin–Huxley model uses voltage-dependent conductivities of channels. In contrast, the formalism of Section 3 employs voltage-dependent probabilities of transfers. The effect of voltage-dependent conductivities is obtained as an implication of this formalism.

The total permeabilities of sodium and potassium channels (p_1 and p_2 , respectively) are the sums of the permeabilities of the corresponding protein molecules in different conformations (p_{1j} and p_{2j}) times the numbers of molecules in these conformations (E_{1j} and E_{2j}):

$$p_1 = \sum_{(j)} E_{1j} * p_{1j} \quad (8)$$

$$p_2 = \sum_{(j)} E_{2j} * p_{2j} \quad (9)$$

Let p_3 be permeability of membrane to Cl^- and let $p_3 = const$. Let us assume that ionic currents are described by the constant field diffusion equation:

$$i_k = p_k * z_k * F * V * \frac{c_{ko} - c_{ki} * exp(V)}{exp(V) - 1} \quad (10)$$

where,

$k=1, 2, 3$ correspond to K^+, Na^+ and Cl^- , respectively,

c_{ko} and c_{ki} are the outside and the inside concentrations of the ion of the k -th kind,

z_k is the valence of the ion,

F is the Faraday constant,

$V = V_m F / RT$, where R is the molar gas constant, and T is absolute temperature.

To complete the description of the model we need to define V_m as a function of the total ionic current.

$$\frac{dV_m}{dt} = \frac{(i_1 + i_2 + i_3)}{C} \quad (11)$$

where,

C is the membrane capacitance, i_1, i_2 , and i_3 are currents defined in (10). The time constant of this process is considerably smaller than those associated with variables E in equation (3), so it can be neglected.

Expression (11) is needed to simulate the behavior of the membrane in the absence of a clamp amplifier. If such amplifier is used, then $V_m = const$.

NOTE. Equations (3), (6)–(10) do not use phenomenological parameters $gK_{max}, gNa_{max}, t_n, t_m$, and t_h contained in equations (1) and (2). Accordingly, they do not require data describing these parameters as functions of V_m . The corresponding effects are produced automatically as the implications of the dynamic equations of the system. Another advantage of the formalism of Section 3 is that it can be extended to describe fluctuations of E -states and other macroscopic variables.

4 COMPUTER SIMULATION

Some results of computer simulation of equations (3), (6)–(11) are presented in Figures 4, 5, and 6.

The initial increase in sodium current in Figure 4 is a result of a rapid increase of a number of protein molecules in the high conductance state 3 (see Figure 3b). The three transfers ($0 \rightarrow 1, 1 \rightarrow 2, 2 \rightarrow 3$), leading to this state, determine the third-order of the curve. Transfer $3 \rightarrow 4$ leads to the inactivation of the sodium channels and decrease of the sodium current. Decreasing the probability of this transfer (P_{243}) increases the magnitude and the duration of the sodium current. The numbers on the curves are proportional to the probability P_{243} (coefficient a_2 in expression (7)). At $t=0$ membrane potential was stepped up from resting potential -70mV to 0 .

Figure 5 shows delayed potassium current caused by a step of membrane potential. The increase in the current is a result of transfers $0 \rightarrow 1, 1 \rightarrow 2, 2 \rightarrow 3$ and $3 \rightarrow 4$ leading to the high conductance state 4 (see Figure 2a). Unlike sodium channels, potassium channels do not have an inactive state, so potassium current does not decrease until membrane potential is stepped down. The four transfers leading to state 4 determine the fourth-order of the curve. The smaller the probabilities of these transfers, the slower the potassium current increase.

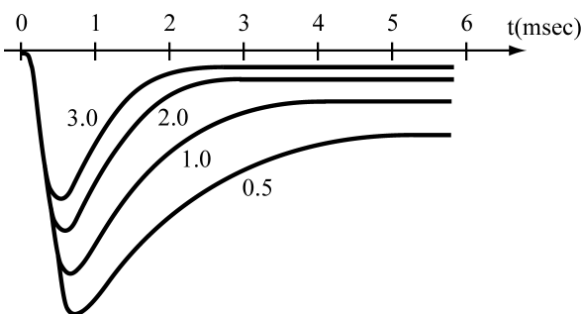


Figure 4: Sodium current as a function of time

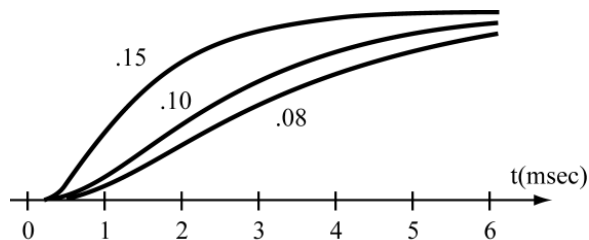


Figure 5: Potassium current as a function of time

The numbers on the curves in Figure 5 are proportional to the probabilities $P_{110} = P_{121} = P_{132} = P_{143}$ (coefficient a_1 in expression (6)). Membrane potential was stepped up at $t=0$ from -70mV to 0 .

The process of generation of spikes in response to short depolarizing pulses of different magnitude is shown in Figure 6. The threshold effect is a direct result of the dynamic equations of the model.

Depolarization above the threshold (in this case -34.13mV) produces a spike of membrane potential. In agreement with experimental data the shape and the magnitude of the spike do not depend on the level of depolarization, the latter affecting the delay of the spike. Depolarization below the threshold or hyperpolarization produce no spike.

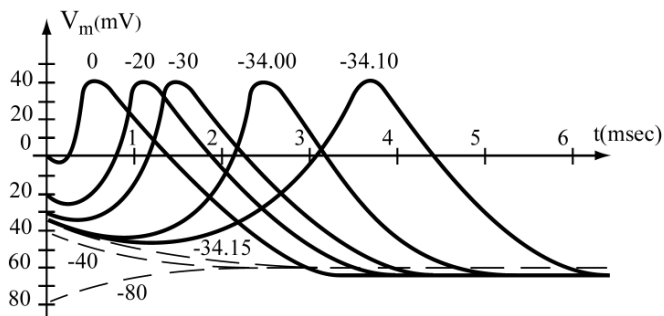


Figure 6: Membrane potential as a function of time

5 INERTIAL NEUROMODULATION

The formalism of Section 3 can be used to describe a broad range of different hypotheses about temporal processes associated with the statistical dynamics of protein molecules. In this section I show how equations (3)–(5) can be used to describe a simple effect of inertial neuromodulation. To avoid misunderstanding I must emphasize that the sole purpose of this model is to demonstrate the possibilities of a mathematical tool rather than to explain any specific neurobiological data. The model was used in [4].

The structure of the model is shown in Figure 7. In Figure 7a synapse S has channel protein molecules in the postsynaptic membrane. For the sake of simplicity, the model has only one kind of such molecules. The state diagram of the microscopic machine corresponding to this channel is shown in Figure 7b. In this diagram, 0 is the rest state. In this state, the channel has zero conductance. 1 is a "pre-active" state. The probability of transfer $0 \rightarrow 1$, P_{10} , is affected by neurotransmitter released through the presynaptic membrane in response to a modulating signal x_{mod} .

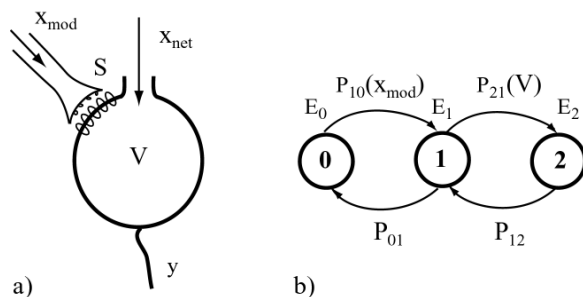


Figure 7: A model of inertial neuromodulation.

a) A neuron with a hypothetical modulating synapse. b) The state diagram of a microscopic machine corresponding to a channel protein molecule in the postsynaptic membrane of the modulating synapse.

The probability of transfer $1 \rightarrow 2$, P_{21} , is a function of membrane potential V . The probabilities of transfers $2 \rightarrow 1$, and $1 \rightarrow 0$ are constant. 2 is a high conductance state.

It can be shown that with different assumptions about functions $P_{10}(x_{mod})$ and $P_{21}(V)$ the described model produces the following effect of inertial neuromodulation: input x_{mod} temporarily sensitizes the neuron to the input x_{net} , representing the net postsynaptic current of other synapses.

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