Memory neuron: Synapse microchemistry for the memory component of a neuroconnective brain model*

(neuron circuits/membrane pores/recording/erasing/synapse regeneration)

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ABSTRACT This paper examines the synaptic microchemistry required if a memory neuron is to have the operating characteristics previously attributed to it [Wooldridge, D. E. (1980) Proc. Natl. Acad. Sci. USA 77, 2305-2308]. It is concluded that the requirements can be met by a combination of membrane mechanisms not very different from those that are commonly postulated to explain the properties of known types of neurons.

In a preceding paper (1), a neuron designed for use as the principal memory component of a brain model was specified to have the following properties.

i. The memory neuron carries multiple—perhaps as many as 100 or more—"recording connections," each consisting of synapses on the body or large dendrites of the memory neuron by the terminations of a single "input" axonal fiber. These recording synapses and the connections they form are inhibitory in type and are capable of assuming either of two states: "effective" or "ineffective." Only the effective synapses are able to respond to input nerve current.

ii. The memory neuron carries a single "biasing connection," consisting of enough excitatory synapses (of fixed strength) so that the neuron itself spikes at a nearly maximal rate if its only synaptic input is nerve current of similar high spiking rate coming in on the single biasing fiber.

iii. There are enough inhibitory synapses on the memory neuron so that high-rate nerve current is required to no more than one or a few recording connections, when they are in their effective state, to prevent the neuron from spiking despite high-rate current in the biasing fiber.

iv. All the recording synapses of a memory neuron, whether effective or ineffective, respond to an "erasing command" by going into a common prerecording condition characterized by absence of any influence of previous recordings. The erasing command is a sustained high-rate nerve current in an output fiber of a neural circuit that serves the "memory unit," an aggregation of components that includes all the cooperating memory neurons needed to accomplish the storage of a complete sensory stimulus description.

v. After being put in the prerecorded condition, all the recording synapses of a memory neuron respond to a subsequently arriving "recording command" consisting of the appearance of a short train of closely spaced spikes in an output fiber of a circuit serving the entire memory unit. The response to the recording command consists of the acquisition of a persisting state of effectiveness by the synapses of recording connections whose input fibers are active (carry no nerve current) and of a persisting state of ineffectiveness by the synapses of recording connections whose input fibers are active, when nerve current appears in the recording command fiber. The chemical events that determine whether a synapse is left in its effective or ineffective state are completed within 30 msec of triggering by the recording command.

vi. The chemistry of recording synapses is of such a nature as to provide a "synapse regeneration" feature that continuously and actively counteracts any decay of effectiveness of synapses that have been left by recording in an effective state as well as any acquisition of effectiveness by synapses that have been left in an ineffective state.

The objective of this paper is to describe a set of plausible, although necessarily speculative, synaptic microchemical mechanisms capable of giving recording connections the specified properties.

Model of the recording synapse: General features

The more conspicuous features of my model of the recording synapse, and of the related erasing and recording command circuits, can be quickly described. To begin with, much of the usual synaptic mechanism is assumed to operate. Thus, molecules of transmitter substance, released from vesicles on the input side of the synaptic gap by the effect of spiking activity in the connecting fiber, float across the gap and attach themselves to conductivity receptor sites on the postsynaptic membrane, to be detached again after a few milliseconds by effects of thermal agitation or destructive enzymes in the fluid (2). However, in my model, attachment of a molecule of transmitter substance to a receptor site does not always open a local region of the memory neuron membrane to the passage of polarizing ions. Instead, the local membrane region remains closed if a molecule of something I will call "blocking substance" has previously been incorporated in the atomic configuration of the receptor site. Such incorporation of blocking substance is specified to occur when the complex molecule constituting a conductivity receptor site interacts with a molecule of "erasing substance." This substance, in turn, is put into the interneuronal fluid and hence into the synaptic gaps by chemoemissive fibers coming from a set of auxiliary neurons that serve the entire memory unit. These neurons are activated by the sustained presence of the erasing command on their excitatory input connections. Their chemoemitting terminations are disposed closely around the memory neurons of the one memory unit. This, together with the limited lifetime of erasing substance before it is destroyed by some enzyme in the fluid, prevents the erasure of one memory unit from causing more than a small concentration of erasing substance to appear in the neighboring

* This is the second paper in a series. Paper no. 1 is ref. 1.
memory units. The effects of the residual leakage are dealt with below, in connection with synapse regeneration.

In general, it is simply the absence or presence of blocking substance in most of the conductivity receptor sites of the synapses that determines whether a recording connection is effective or ineffective in the sense of item 1 of the properties listed above. An implication of this statement is that the blocked configuration of the receptor site is a relatively stable one, at least to the extent that thermal agitation alone has a probability of detaching the blocking substance and restoring effectiveness to the receptor sites that is small compared with the probabilities of other reactions that are about to be dealt with. However, there is no requirement for great rapidity in the blocking reaction: the erasing command-triggered preparation of a memory unit for the acceptance of a fresh record does not share with the recording command-triggered events the necessity of completion within 30 msec.

Through operation of the specified blocking mechanism, the recording synapses of a memory neuron emerge from the erasing experience in a common state of ineffectiveness. Moreover, the memory neuron itself is caused to be inactive on the completion of erasure; this is accomplished by designing the erasing command-generating circuit of the memory unit so that it turns off biasing current to the memory neurons. This in turn makes it possible to limit greatly the responsibility assigned to the subsequently emitted recording command. All this command must do to cause a new stimulus description record to be laid down in a freshly prepared memory unit is to restore biasing current to the memory neurons. There follows a general description of a set of synaptic reactions that yields such recording consequences.

First it should be noted that, when excitatory biasing current is switched back on by the recording command, all the inhibitory connections are ineffective and therefore there is nothing to keep the memory neuron from going promptly into rapid spiking. This makes it possible to use the appearance of spiking activity in the memory neuron as the actual trigger for the synaptic recording reactions. In my model these reactions are then as follows.

i. The large change in the internal electrical potential of the memory neuron, accompanying spiking, completes the activation of a system of "catalysis receptor sites" on the postsynaptic membrane which have been put temporarily in a potentially effective molecular configuration by reaction with erasing substance; at such sites, ingredients normally present in the interneuronal fluid are then rapidly combined or fragmented to return new complex molecules of "unblocking substance" to the synaptic gap.

ii. If the input fiber is inactive so that there is little if any transmitter substance in the synaptic gap, unblocking substance reacts with the conductivity receptor sites to remove their blocking molecules. Nearly all conductivity receptor sites are cleared in this way and the entire synapse thereby is restored to a state of effectiveness in less than 30 msec.

iii. If the input fiber is active so that transmitter substance is attached to nearly all of the conductivity receptor sites, restoration of the synapse to effectiveness does not occur because the unblocking reaction at a receptor site is prevented by the attachment of transmitter substance.

It is easy to confirm that these reactions have the desired result in that restoration of excitatory bias to the memory neurons by recording command switching is sufficient to impose on the recording connections of an erased memory unit a pattern of persistent effectiveness and ineffectiveness that reflects the momentary pattern of inactivity and activity in the input fibers.

The microchemical events that constitute the postulated synaptic reactions are given more detailed consideration below.

Molecular configuration changes in the receptor sites: General features

In my own speculation about the microchemistry of the neural membrane, I have found it helpful to use a physical picture in which the tiny conductivity receptor sites responsible for the polarizing effect of an active recording synapse are thought of as complex molecular "outer gates" to "conductivity pores" in the memory neuron membrane; through the transmembrane "channels" of these pores, ions of a special type 1 may move from the synaptic gap to the interior of the memory neuron or vice versa, but only if the gates are in an "open" rather than a "closed" molecular configuration (4). Catalysis receptor sites are similarly considered to be outer gates of "catalysis pores" through the memory neuron membrane. In this case there is no neuron polarizing or depolarizing requirement, so it is not obvious that passage of ions through the channels of the pores is called for, but this capability turns out to be useful and is therefore attributed to the catalysis pores.

The discussion of the foregoing section has indicated that from time to time the outer gates (that is, the catalysis receptor sites and the conductivity receptor sites) must participate in reactions that change their molecular configuration and therefore their chemical properties. (In my model of the recording synapse, the inner gates of the pores—those on the internal surface of the memory neuron—as well as the transmembrane channels are assigned fixed properties and do not participate in the chemical reactions of interest.) Of these reactions, those involving the conductivity pores—in which erasing substance installs a molecule of blocking substance in the outer gate, unblocking substance removes such a blocking molecule, or transmitter substance changes the gate configuration to make it immune to the effects of unblocking substance—are similar enough to events generally attributed to membrane sites as to require no detailed justification at this stage of model building. However, there are questions of interest with respect to the chemical reactions that involve the catalysis pores.

Molecular configuration changes in the catalysis pores

The outer gate of a catalysis pore is assumed to have no capability of generating unblocking substance except after reaction with erasing substance. This reaction is thought of as one detaching a molecular fragment that, when present, prevents the gate from achieving the particular atomic arrangement required for it to be an effective catalyst. But detachment of the incapacitating fragment is specified to be only the first of two steps essential to the acquisition of catalytic effectiveness and may therefore be said only to make the gate "eligible" for participation in the remaining catalysis-forming reaction. This remaining reaction is the one said earlier to be triggered by spiking of the memory neuron on the appearance of the recording command, by means of a postulated strong dependence of the reaction on the transmembrane potential. Such dependence is exhibited by the reaction if it involves the participation of an ion that must travel through the membrane to reach the gate. Hence I attribute to the channels of the catalysis pores the property of permeability to Ca2+, suggested by the similar permeability that played an important role in an earlier development of a quantitative theory of spiking (4). In the present case, however, the Ca2+ enter the channels only from the in-

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1 Possibly, but not necessarily, Cl− (3).
terior of the neuron, by way of the persistently open inner gates, rather than from the surrounding fluid by way of the persistently closed outer gates. A Ca$^{2+}$ coming through the channel and approaching closely enough to the under side of the outer gate of a catalysis pore—if the gate has first been made eligible as described above—is specified to be able to enter into and change the gate molecule to a catalytic configuration. Only when it is in this “effective” state is the outer gate of a catalysis pore able to direct the formation of unblocking substance by the combination or fragmentation of molecular ingredients always present in the fluid of the synaptic gap.

The basic reason why the rate of generation of unblocking substance in a recording synapse depends strongly on the state of activity of the parent neuron may now be simply stated: the probability that a Ca$^{2+}$ in a channel gets near enough to the outer gate to engage in an attachment reaction is strongly dependent on the potential across the membrane. Thus, very few of the Ca$^{2+}$ that diffuse into the pores through the inner gates succeed in traversing the channels against the field caused by the normal negative resting potential of the neuron, but when the interior of the neuron is given a positive increment of 75–100 mV during the formation of a spike, many more of the entering Ca$^{2+}$ reach the outer gates. The exponential factor in the pertinent probability calculations leads to rates of formation of the catalytic configuration of the outer gates that are hundreds of times greater during the approximately 1-msec half-width of each spike than when the neuron is in an inactive condition (4). Hence, despite the fact that even a rapidly spiking neuron is near its resting potential most of the time, the average rate of creation of catalytic configurations of the outer gates may be 100 times higher for a spiking than for a nonspiking neuron.

However, this is not the whole story. The concentration of unblocking substance developed in the synaptic gap depends not only on the rate of conversion of eligible to effective gates but also on how the gates regain their normal condition of ineligibility and thus ineffectiveness. Because of the requirement for rapid recording, the period of effectiveness of a catalysis gate must be short. This can be ensured most simply if, in addition to causing the formation of unblocking substance, the effective configuration of the gate is allowed to react with some ingredient of the adjacent fluid in such a way as to return to its ineligible configuration, by casting off the attached Ca and recovering an incapacitating fragment. If this reaction is assigned a time constant of not more than 10 or 15 msec, the rapid recording requirement can be met (the allowable time constant would need to be shorter than this if it were not for the effect of synapse regeneration).

Thus, the normal course of events is that the outer gate of a catalysis pore that has reacted with erasing substance remains eligible although inert until a Ca$^{2+}$ makes the gate effective by coming through the channel and attaching to its under side, after which the gate supervises the formation and emission of molecules of unblocking substance into the synaptic gap for a period that averages no more than 10 or 15 msec before a final reaction restores the gate to its normal ineligible state.

Requirement for a bimolecular unblocking reaction

Unfortunately, when recovery of ineligible by the catalysis pores is provided for in the way just described, it is not clear that the memory neuron has the previously specified recording characteristics. It now appears that, although formation of unblocking substance proceeds rapidly in a spiking neuron and slowly in a nonspiking neuron, the total amount finally formed is the same in the two cases (because all eligible catalysis pores must eventually acquire Ca$^{2+}$ and experience a 10- to 15-msec interval of effectiveness). So far, there is no reason to expect that a given amount of unblocking substance, during whatever time it has in the synaptic gap before it is either destroyed or escapes to the surrounding interneuronal fluid, will encounter and react with any more blocked conductivity gates in one case than in the other. Thus, something additional must be done to cause the reactivity of unblocking substance to increase with increase in its concentration.

The obvious addition to the model is to specify that the unblocking reaction at a conductivity gate that contains blocking substance (and is not shielded by transmitter substance) is bimolecular with respect to unblocking substance. Specifically, we may assume that, on close enough approach to a blocked but unshielded conductivity gate, a first molecule of unblocking substance can attach itself loosely and survive for a short period of time before it is dislodged by thermal agitation; but the unblocking reaction is able to take place only if a second molecule of unblocking substance is supplied, by its own close approach within the short interval of attachment of the first molecule. Under these circumstances, it can be seen that the probability that a specific molecule of unblocking substance will trigger an unblocking reaction is high in the high-concentration situation caused by spiking of the parent neuron and is low in the low-concentration situation characteristic of a nonspiking neuron.

The unblocking process must meet two more requirements.

1. Substantially all of the catalysis gates of each recording synapse left, by erasing, in an eligible but ineffective state must be converted to the catalytic configuration by Ca$^{2+}$ within 10–15 msec of the initiation of memory neuron spiking by the recording command.

2. The number of catalysis pores must be large enough to yield, during the above interval and the additional 10- to 15-msec life of the effective gate configuration, a concentration of unblocking substance that restores most of the conductivity gates of the synapse to their unblocked condition (provided that the synapse is an inactive one, with no shielding transmitter substance).

With these additional specifications, it may be seen that the memory neuron has recording characteristics that are at least close to those sought, in that: the synapses that are active when the recording command is received are left after 30 msec in about the same state of low inhibitory effectiveness as that imposed by the erasing process; the synapses that are inactive are left in a state of high inhibitory effectiveness; and these synaptic states remain nearly invulnerable to change unless erasing substance appears again around the memory neuron.

To be sure, there are imperfections in the specified process. Thus, an active connection is not left completely ineffective after the 30-msec recording interval allowed to a stimulus description; and, because of the persistence of some residue of eligibility in the catalysis gates, the synaptic effectiveness can increase still more if in the immediately following stimulus description the connection becomes inactive. These imperfections, as well as the imperfection wherein nominally effective connections are degraded by leakage of erasing substance from nearby memory units, are presented from having serious consequences by the synapse-regeneration properties of the model.

Synapse regeneration additions to the microchemistry

After being recorded, a memory neuron spends the large majority of the time in a nonspiking condition, with its own and nearby memory units free from the kind of chemoemissive activity that is triggered by erasing and recording commands.
It is under such a "resting" condition that synapse regeneration chemistry must normally operate, so as to compensate for the imperfections of the recording process.

For synapse regeneration, three additions are made to the microchemical details of the memory neuron. Oddly enough, despite the fact that a principal concern is the leakage of small amounts of erasing substance between memory units, one of the three additions has the purpose of ensuring that a small concentration of erasing substance is always present in the interneuronal fluid (and hence in the synaptic gaps of the recording connections). This can easily be provided for just by letting the chemoemissive terminations of the erasing circuit discharge at a low rate even in the absence of triggering nerve current in the supplying fibers.

It is also necessary to specify that the generation of unblocking substance is not the sole prerogative of catalysis gates but is also caused by the outer gates of conductivity pores, when they are in their unblocked configuration. However, the catalytic activity of a conductivity gate can be small compared with that of an eligible and effective catalysis gate.

Finally, it is necessary to give the eligible configuration of the catalysis gate, as well as the effective configuration, a limited lifetime. However, this can be measured in seconds instead of milliseconds. Because the control circuits can be designed to issue the recording command and complete the laying down of a memory record promptly upon the completion of erasing, the new mode of return to the normal ineligible state by an eligible-but-ineffective gate has a negligible effect on the recording events. This return can be attributed to the same kind of reaction with ingredients in the fluid as that which returns the effective gates, with the reaction rate much slower for the ineffective configuration.

Now let us explore the consequences of these new provisions. First, consider the most obvious effect of the non-zero resting state concentration of erasing substance in the synaptic gap. This is a continuing conversion to ineffectiveness of any effective conductivity pores, as erasing substance reacts with them to install blocking substance in their outer gates. If the average resting state concentration of erasing substance is 1% of the concentration achieved during erasing, a time constant of the order of 1 min for this reaction is consistent with the allocation of a few seconds for the erasing interval itself.

Opposing the tendency toward decay of synaptic effectiveness are two effectiveness growth processes. One arises out of the conversion, by resting state erasing substance, of outer gates of catalysis pores from the ineligible to the eligible state followed by the acquisition by some of these gates of Ca²⁺ and an ensuing period of catalytic effectiveness which in turn supports a continuing non-zero concentration of unblocking substance in the synapse and a correspondingly continuous conversion of conductivity pores from the ineffective to the effective configuration. However, the quantitative importance of this effectiveness growth process is limited: during the few seconds that eligibility of a catalysis gate is allowed to persist (by the third of the listed additions to the microchemistry), the low resting state concentration of erasing substance can build the fraction of eligible gates to only a few percent; because the memory neuron does not spike during the resting state, conversion of the already small fraction of eligible gates goes very slowly also; hence, the number of effective gates and the resulting concentration of unblocking substance established in the synaptic gap remains very low, and the bimolecular nature of the unblocking reaction further reduces the resulting rate of conversion of ineffective conductivity pores to a point of negligibility by comparison with the effectiveness decay rate attributable to resting state erasing substance.

The second synaptic effectiveness growth process caused by resting state erasing substance involves the catalytic property now attributed to an unblocked outer gate of a conductivity pore. The rate of generation of unblocking substance due to this property is evidently proportional to the unblocked fraction of the conductivity pores of the synapse. Hence, the quantitative expression for the resulting rate of unblocking of blocked pores, because of the bimolecular nature of the reaction, contains a factor proportional to the square of the concentration of the unblocked fraction. This is the important effectiveness growth principle. It is by its interplay with the effectiveness decay caused by direct reaction of resting state erasing substance with unblocked conductivity pores that the desired synapse-regeneration properties are bestowed on the memory neuron.

Although it probably is obvious from what has been said already that this interplay has a tendency to make weak synapses weaker and strong synapses stronger, it may be worthwhile to illustrate the point in a more quantitative fashion. The difficulty of computing the change, with time, of the effectiveness of a recording synapse depends on what assumption is made about the disappearance of the unblocking substance that is introduced into the synaptic gap at unblocked conductivity gates. Certain diffusion-related complications are avoided, with little if any loss of plausibility, if a short lifetime is attributed to this substance. Specifically, I assume that most of the molecules react with some ingredient of the fluid and effectively "disappear" by losing their unblocking capability, without ever engaging in an unblocking reaction, and that they do this before they have diffused very far along the postsynaptic membrane from their place of origin. The important consequence of this assumption is that it makes both the unblocked fraction of conductivity pores and the concentration of unblocking substance the same in all parts of the synapse. The governing equation for synapse regeneration, neglecting the very small effect of the catalysis pores, then becomes:

\[ \frac{dE}{dt} = -E/T + E^2(1 - E)/cT, \]

in which \( E \) is the effectiveness of the synapse as measured by the fraction of its conductivity pores that are unblocked, \( T \) is the time constant that characterizes the direct blocking of unblocked pores by resting state erasing substance (suggested earlier to be of the order of 1 min), and \( cT/E^2 \) is the effectiveness-dependent time constant of the bimolecular reaction that unblocks blocked conductivity pores.

In Fig. 1 the synapse-regeneration equation is plotted for various initial values of \( E \), with \( c = 0.16 \). For this value of \( c \), each curve is asymptotic either to a standard high effectiveness \( E_h \) of 0.8 or to a standard low effectiveness, \( \approx 0 \). It is easy to show that, in general,

\[ E_h = 0.5 + \sqrt{0.25 - c^2}. \]

The important feature of Fig. 1 is that, if the synapse effectiveness is initially higher than \( 1 - E_h \), it will asymptotically approach \( E_h \), but if the initial effectiveness is lower than \( 1 - E_h \) it will decrease to a value very close to 0.

To judge the effectiveness of such a mechanism in protecting a stored record against cumulative degradation by chemical leakage during erasing/recording events in nearby memory units, it must be borne in mind that such nearby events are relatively rare and of short duration—a recorded memory neuron spends the large majority of its time in the undisturbed resting state during which synapse regeneration can quietely

\[ c, \text{ which represents the fraction of } T \text{ to which the time constant of the unblocking reaction descends as } E \to 1, \text{ must stay } < 0.25 \text{ if decay is not always to exceed growth and erase all synapses.} \]
operate. Therefore, rather substantial temporary imperfections in the stored record can be accepted, with the practical consequence that the design of the memory system need only hold the leakage of reactive molecules to a moderately low rather than to an extremely low level.

The addition of the synapse regeneration scheme to the model evidently also compensates for imperfections in the memory system other than chemical leakage. Thus, it is no longer troublesome if at the end of the erasing/recording sequence the recording connections that are supposed to be effective are of substantially less than full strength and those that are supposed to be ineffective retain an appreciable residue of effectiveness; such initial imperfections, if not too large, are soon removed by synapse regeneration. Similarly tolerable is a moderate amount of disturbance of a new recording due to continuation of some of the molecular recording events past the point of significant change in the incoming stimulus description.

In short, by the means described there is continual correction of small errors that creep into the recordings from any source, which might otherwise accumulate to make long-term memory impossible.

Use of the postulated memory neuron in neuroconnective modeling

The argument at the end of the first paper of this series (1), relating to the difficulty of experimentally confirming the presence in the brain of components with operating characteristics like those attributed to the memory neuron, applies with even greater force to underlying microchemical processes such as those suggested in this paper. Thus, it may be a long time yet before experiment succeeds in identifying the actual memory components of the brain and determining their operating characteristics and microchemistry. Meanwhile, the memory neuron of these papers is offered to the neuroconnective brain modeler as a temporary stand-in for the real thing. If the arguments given for the choice of its properties are sound, it may be reasonable to hope that a theory of sensory memory will not be seriously compromised by being based on such a speculative component.

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