Neurons Tune Their Own Excitability When They Make A Decision

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Abstract

The brain is usually considered to be an extraordinarily complex object while a neuron is believed an ideal logical element. This idealization does not correspond to the real neural system properties. Experimental data give trustworthy evidence that a neuron is a microcosm of the brain. The firing threshold seems to be a dynamic property of an excitable membrane. Neurons appear to evaluate the most preferable consequence of their participation in the brain action, transiently change their excitability and only after that compare the magnitude of the input signal and threshold. This suggests a novel approach to understanding the neuron's role in controlling behavior. The model of a neuron has been developed on the basis of the supposed intracellular chemical reactions that are specific for a given input signal. The yield of chemical reactions was considered to affect the transition of sodium channels into an open state, as described in the Hodgkin-Huxley model, and to modulate neuronal excitability. However, for the given combination of inputs, the neuron model exhibits an all-or-none principle of spike generation when efficacy of the inputs changes. An increase in complexity of the neuronal model is more than compensated for by simplification of neural network tuning.

1 Necessity to modify the model of a neuron

Conventional neural network models based on a simple neuron related to the McCalloch and Pitts model [1] have many well-known remarkable properties and can solve some problems in line with algorithms of the networks operation. This approach is easier to analyze than the behavior of complex neuron units. However, irrespective of the physiological relevance of these models, they have some disadvantages [2]. The form of algorithms in general is determined by the model of the neuron, by the network structure and by the salient feature of the practical problem. The tuning is usually slow and sometimes accompanied by a network paralysis. Memory capacity is low and huge network creations are necessary. False images may appear and it is difficult to overcome local minima.

Properties of neural networks depend both on the network structure and on a model of neurons that is incorporated within the network. An artificial neuron is usually considered to make a summation of excitations and to generate an output reaction in accordance with its activation function. Neural networks consisting of such neurons store information, thus changing the efficacy of synaptic connections between neurons (Fig. 1).

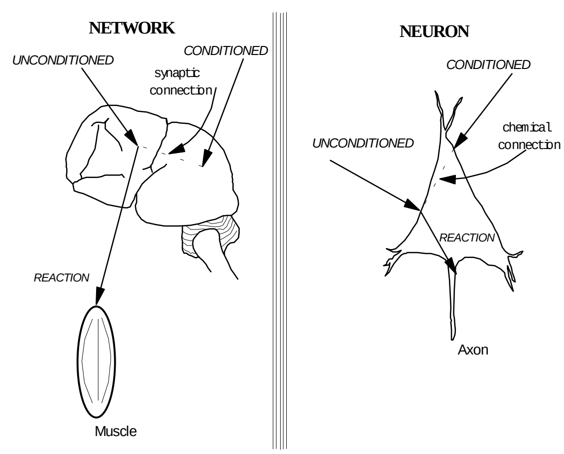

Figure 1 Alternative approaches. Left - trace of memory as a change in the physical connections between neurons, related to the conditioned and unconditioned stimuli. Right - learning as a change of chemical reactions between substances related to the conditioned and unconditioned stimuli.

An alternative approach considers a neuron as an object that makes predictions of the consequences of input signals and generates an output signal in conformity with these predictions [3,4]. The final level for decision-making is, apparently, molecular. The chemical substrate of memory can be satisfactorily described by the mixture of simple substances within neurons [5].

The idea that reorganization of synaptic connections constitutes a memory cannot answer some important questions [3]. If the function of a neuron is so simple, why is neuronal metabolism the most complex of all the cells of an organism? Why are informational macromolecules necessary for memorizing? Why are memory traces everywhere in the brain? Why is an art gallery of memory put up for only one painting? Why is temporary death much more damaging to memory than irreversible brain injury? Why can an isolated neuron learn? How does memory pass through a metamorphosis when neural structure reorganizes completely? Why is neural tissue defended by the brain-blood-barrier? These paradoxes signal the necessity to bring theory into line with the experimental data.

2 One neuron - two thresholds

Generally, the reactions of neurons to biologically important stimuli increase after learning, while they decrease to insignificant stimuli. A brain must decide which stimulus is more important in the current behavior. An elementary explanation is that synaptic efficacy changes for the specific input, i.e., the synaptic input corresponding to a more important signal becomes stronger.

Another possible explanation for neuronal plasticity is the change in properties of the excitable membrane [6-7]. Excitability usually increases during augmentation of the biological importance of a signal and decreases when it falls. The excitability changes transiently within the responses, since these alterations are selective for the significant and insignificant stimuli [3,9-12]. A neuron in some way evaluates the significance of a given signal and chooses an optimal excitability.

In our experiments, the activity of the neurons responsible for the defensive closure of the pneumostome was recorded intracellularly during elaboration of a classical conditional reflex and habituation. Tactile stimulation of different foot points was used as the conditioned and discriminated stimuli. Cutaneous electrical stimulation of a mollusk’s foot served as the unconditioned stimulus. The stimuli, which anticipated the appearance of dangerous irritation, induced an action potential (AP) which began at a low level of depolarization, as a contrast to the stimuli whose significance decreased as a result of learning (Fig. 2). After training neurons can reveal different excitability within different responses. The threshold within the responses to various stimuli changed similarly if the stimuli changed their meaning similarly. After learning, the neurons of one animal displayed a specific excitability within the responses. Selective changes in the AP threshold were related primarily to the first action potential within the response (Fig. 2). The thresholds of the second AP in responses were similar for responses to significant and insignificant stimuli. Therefore, AP threshold is the dynamic property of excitable membrane. The same neuron demonstrated different AP thresholds within responses depending on their significance. This implies that there is feedback not only between the organism and the environment, but also between a separate neuron and the environment.

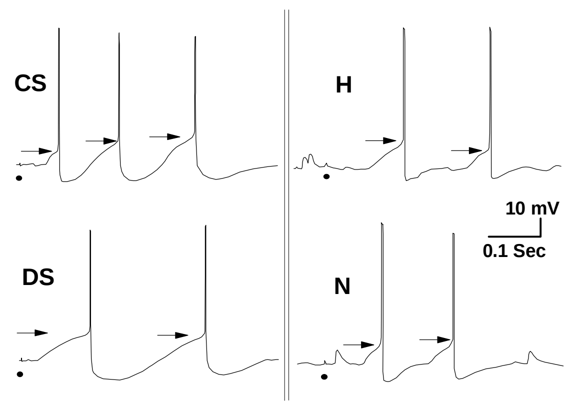

Figure 2 Selective change of the first AP threshold within the responses after learning. Left – an example of responses of the identified molluck neuron involved in the defensive pneumostome closure to the conditioned (CS) or discriminated (DS) stimuli after classical conditioning. Right - responses of such a neuron to a habitual (H) and novel (N) stimulus after habituation. Pointers - level of AP generation. Stimuli are indicated by black dots. Calibrations are shown in the plot. The experiments were carried out in semi-intact preparations of land snails, as previously described [13,14]. During classical conditioning, the contingency between tactile and painful stimuli changed and determined the significance of the conditioned stimulus. During habituation, the significance of a habitual tactile stimulus becomes smaller than the significance of a novel (rare) tactile stimulus.

3 Correspondence between plasticity of excitable membrane and synaptic plasticity

Reorganizations of both synaptic processes and excitability are essential for learning [15]. The primary appearance of APs during pairing in response to an initially ineffective stimulus does not correlate with the decrease in the AP threshold and is determined by an increase in the postsynaptic potential. However, prolongation of pairing after a rise in AP results in a decrease in the threshold in that response [11]. The presence of the AP in the response probably favors reorganization of excitability in the subsequent response.

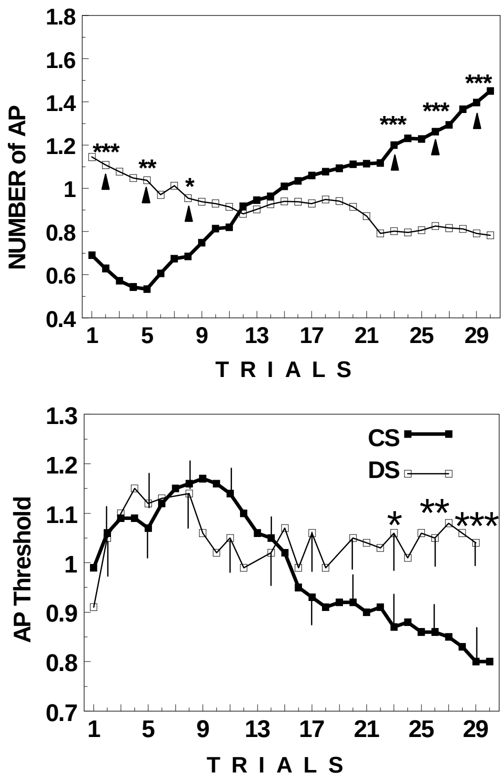

Figure 3 The behavior of neuronal activity evoked during conditional reflex acquisition. Symbols are denoted in the figure. Normalization was performed using the average of the responses of both the CS and the DS. Top - AP numbers in the response; medians and significance of the differences between the medians are shown (Mann-Whitney U test, significance of differences between responses to the CS and DS: * $p<0.05$, ** $p<0.01$, *** $p<0.001$). Bottom - thresholds of the first AP in the response. Means ± SE are shown. The values, standard errors and significance are calculated by means of a two-way ANNOVA with interactions between the trial number and the type of stimulus (CS and DS).

During training, a change in AP threshold corresponded to the AP number change (Fig. 3). AP latency and postsynaptic potential slope and amplitude after pairing also displayed selectivity for responses to the significant and insignificant stimuli. The changes in the AP threshold correlated with the efficacy of the corresponding stimulus for the AP generation.

Synaptic plasticity in the postsynaptic neuron may be accompanied by a change in excitability in the presynaptic neuron [7,9,16]. An AP evoked in the cells of a frog olfactory bulb during suppression of an inadequate signal action selectively decreased and inhibited the postsynaptic reaction in the target neuron [9]. The possibility that a change in the conduction velocity of an axon during learning may be the result of a change in cellular excitability cannot be excluded [17]. The waveforms of the APs in the single axon may also be different [18]. Therefore, the change in excitability within the response may affect synaptic efficacy in the target neuron.

Taking into account the above considerations, we may formulate the following basic principles of neuronal function:

1. A neuron evaluates the significance of the difference between a number of reinforcements that had been given following the generation and failure of the AP in the response to the current signal.
2. Excitability of neurons increases if a stimulus with a greater significance acts.
3. A neuron exhibits an all-or-none principle of AP generation for any given combination of inputs.
4. A neuron calculates the sum of input signals and compares this sum with the modified threshold.
5. The change in the excitability within a presynaptic neuron response is accompanied by changes in the monosynaptic response value in the postsynaptic target neurons.

The 1st principle identifies the biological significance of the signal, which is the statistical significance of the reward expectation. The 2st principle relates the signal significance evaluated by the neuron and it excitability within response to that signal. The all-or-none principle is not rejected; it remained valid for a given value of signal significance (principles 3 and 4). Lastly, the 5st establishes how a neuron transmits its decision to the target neuron. In correspondence with these 5 principles , we can express the state of activation function of a neuron as follows:

$$y = (1+P)\cdot\psi\left(\sum_{i=1}^{n} x_i - \vartheta_0\cdot(1-P)\right),$$

where threshold ϑ_0 is a positive constant; y is an output signal; x_i (i = 1, ..., n) are input signals of the neuron, which in general are gradual; $x_i = y^i$; y^i are output signals of corresponding presynaptic neurons; ψ (V) is computed by the Hodgkin-Huxley equation and in the simplest case is a binary threshold function; P is the significance of the difference between the number of reinforcements received after generation in the past and after failure of the AP in response to the current signal (punishment is considered to be a negative reinforcement). Neurons use prediction in order to tune their own excitability and modulate their own output signal (Fig. 4).

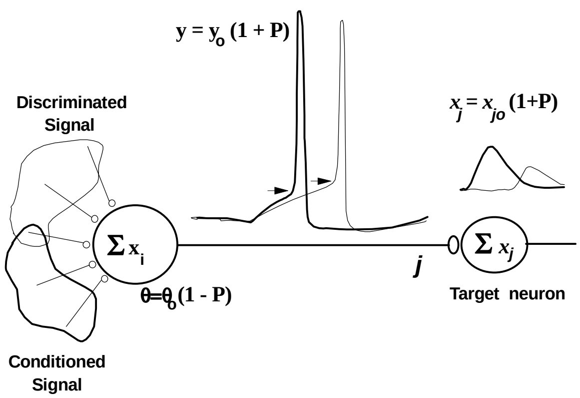

Figure 4 The forward propagation of prediction. A neuron decreases its threshold if a significant stimulus acts. The change in the excitability in a presynaptic neuron is accompanied by changes of the output reaction in its axon. A more powerful AP produces a more potent output signal and generates a stronger postsynaptic potential in the postsynaptic target neurons. Output reaction is a gradual function of the significance of an input signal. Therefore, the same magnitude of prediction P controls threshold, output reaction and response in the target neurons.

4 How a neuron chooses an appropriate excitability

Properties of neural cells in no-learning conditions can be described by the all-or-none principle [1], which means that the threshold for an action potential generation does not depend on the magnitude and quality of the input signal. However, following learning, neuronal behavior does not conform to such elemental logic. A neuron evaluates its own state and the state of its environment and makes a prediction concerning its future state. The past experience is the basis for this prediction. Our results mean that the all-or-none principle ought to be modified. I have developed a neuronal model that, after learning procedure, exhibits different excitability to stimuli, thus predicting different changes in the environment.

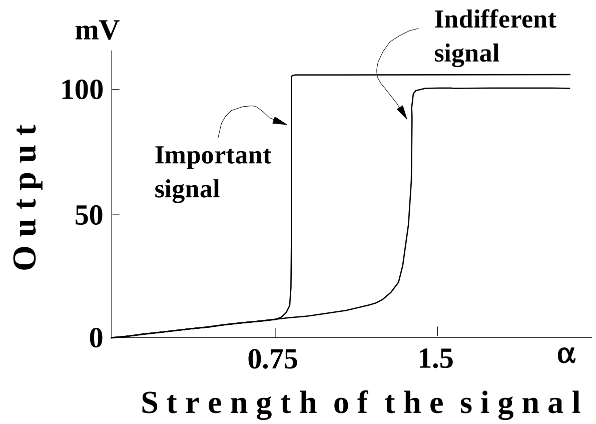

Figure 5 The activation function of the 10-synapsed neuron after learning. Important signal - conditioned stimulus after presentation of the20th combination with the unconditioned stimulus: 111111000. Indifferent signal - discriminated stimulus after its 20 isolated presentations: 0000111111. During the test, after learning, I used the important signal - αααααα0000 and the indifferent signal - 0000αααααα, where α changed in the limits 0<α<2. Abscissa - α value. Ordinate - maximum membrane potential deviation in response to the signal, calculated as described in the Hodgkin-Huxley model.

The properties of excitable membranes in our model were controlled by the supposed chemical reactions occurring in the neural cells. We can assume that chemical singularity during learning is generated by interactions of inner messengers specific for the corresponding excited synapses and for the rewarding input. This is in accordance with the possibility of a chemical blockade (by means of intracellular microiontophoresis of ribonucleoside diphosphates) of the AP threshold growth during habituation [5]. The kinetics of these supposed chemical reactions for paired interactions was described by a set of first order differential equations [4]. This allows for the simulation of changes in a neuron’s excitability during learning. The neuronal model exhibits different excitabilities after the learning procedure relative to the different input signals (Fig. 5). A neuron classifies the stimuli not only according to their strength but also according to their biological significances, and transiently changes its own excitability.

Suppose that one combination of excited synapses corresponds to a conditioned stimulus and another such combination corresponds to a discriminated stimulus. After conditioning, the thresholds within the response to this conditioned stimulus and this discriminated stimulus become different. However, for the given combination of inputs, the model neuron exhibits the all-or-none principle when the signal amplitude is varies while its significance stays even (Fig. 5).

A neuron cannot maintain a one-to-one correspondence between plausible predictions and its own states. Rather, it can only choose between two possible regimes of its function. As a result, the neuron transiently changes its excitability and generates the most preferable output reaction, either as the high or as the low excitable unit. The most preferable output reaction can be specific for different neurons.

Neurons make decision in two stages. First, they evaluate the importance of the current situation for maintenance of normal vital activity and, secondly, they consider the advantages of they own participation in the action. A neuron must decide whether to generate an AP or not. After learning, a neuron chooses the branch of the activation function (Fig. 5), which, presumably, leads to a healthy result. Evidently, a neuron makes independent decision, when it chooses between two possible activation functions (Fig. 5). This is a complex task for a neuron. A neuron uses complex molecular machinery for decision-making. This may explain the paradoxes mentioned in first paragraph.

Properties of such a model neuron resemble the properties of a live neuron. Tuning of each neuron in the network requires no other information than its inputs (which are modulated by means of predictions in the presynaptic neurons) and network error, which is the same in all neurons. A neuron transmits the prediction of a reward, that is a partially processed signal, into neuronal output. Therefore, heavy neuronal calculations do not disappear but are being used in the target neuron. Such neural networks do not depend on network structure and large neural networks may be easily constructed and extended.

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