

CHAOTIC SIGNAL PROCESSING IN NERVE CELLS

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Abstract

A model for the signal transmission between nerve cells is presented. The model is based upon the interplay between the electric nerve impulse and the intracellular concentration of calcium ions. It is demonstrated that a regular input to a single nerve cell can generate either a phase-locked situation or a chaotic output pattern. As a result the signal processing becomes ambiguous even for a single nerve cell. Neither the mean firing frequency nor the firing pattern follow a general input-output relation. Coupling even a few nerve cells enhances this ambiguity. It appears that the important parameter is not the firing frequency, but rather the mutual timing of the incoming and outgoing impulses.

Correlating the threshold variations - analogous to concentration changes - of the cells reveals a much richer template for information processing than correlating the impulses. The individual impulses function therefore more as strobes with the purpose to synchronize distant parts of a nerve cell. As a result even a simple information processing in the brain cannot be related to a logic, subroutine-like function of a small group of nerve cells. It must involve a noticeable background information distributed over many cells, perhaps the whole brain.

Introduction

The main function of the nervous system (NS) is information processing and communication, either between an organism and its surroundings or between different parts of the organism. Signals from the surroundings or from the body are registered by our senses and transformed to a nerve signal relayed to the central nerve system, CNS (brain and spinal cord). Output from the organism takes the form of muscular and secretory responses governed by nerve signals coming from CNS.

The nerve impulses to and from the CNS carries information of a rather simple type. Increased stimulus to a sensory cell gives a higher impulse frequency, and increased impulse frequency in the nerves to a muscle gives a stronger contraction. This is easy to investigate experimentally and is relatively well described. Regarding the communication inside the CNS the knowledge is more sparse. It is often assumed that the "signal" inside the brain resembles an electric system with the impulse frequency as the electric potential and the nerve branches as the wires.

In spite of a very extensive and still increasing research on NS function we are still far from understanding the information processing in the system. A possible explanation could be that our views were wrong. If the CNS internally operates with completely different signal forms, the conventional line of attack is bound to fail. It may resemble the belief that the amplifier of a rock band operates acoustically, because both input and output are sound.

It is now evident that the communication within the CNS can be of either electrical or chemical nature. The first is characterized by series of brief nerve impulses moving rapidly

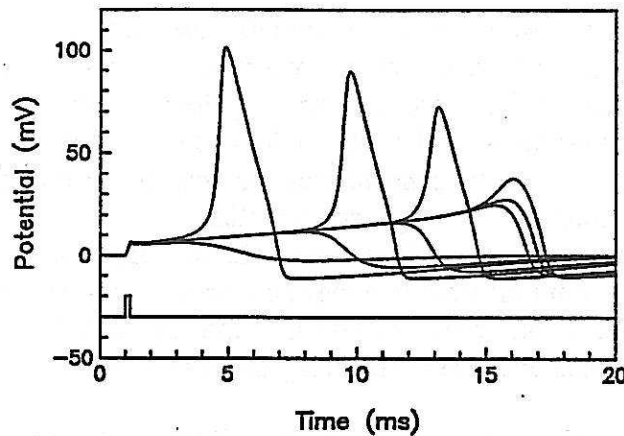


Fig. 1. Threshold. The figure shows the membrane potential as a function of the time for different stimuli (lower trace) close to threshold.

over large distances (many cm), the other is characterized by a local spread of chemical substances influencing the intracellular and extracellular milieu. A complete understanding of the interaction between these two forms is not yet in sight. Evidently the impulse pattern is strongly influenced by the chemical milieu, and that the chemical milieu is influenced by the impulse pattern. This complex interplay is apparently the crucial point in the information processing both in the single nerve cell and in groups of nerve cells.

1. The single nerve cell

Threshold

Hodgkin and Huxley (1952) demonstrated in a comprehensive mathematical description of the nerve impulse, a work that in 1963 won them the Nobel prize, that the threshold for firing a nerve impulse is extremely acute. With a subthreshold stimulus only a small potential deviation is seen that rapidly fades away, while a suprathreshold stimulus gives a full-blown impulse. As the stimulus approaches the threshold there is an increasing hesitation before the cell either gives an impulse or a dropout (Fig. 1). For a given stimulus strength the two responses coincide, but even with a relative difference in stimulus strength of 10^{-13} there is a distinct difference between them. Later experiments have shown that both the acute threshold and hesitation is a common finding in excitable systems.

The chemical milieu

With the acute threshold any small variation in the threshold can change the firing pattern of the cell and its information processing. Changes that will affect the threshold can occur in the cell's surroundings, in the cell membrane or inside the cell. In the surroundings the concentration of the ions participating in the electric impulse can change. More subtle are changes in the concentration of transmitters or hormones that influences ion channels. In the cell membrane the ion channels are embedded as large molecules stretching throughout the membrane. The number of channel molecules and their turnover is regulated by intracellular as well as extracellular control signals, so the amount of molecules and their distribution on the cell surface may vary with time. With nerve branches up to 1 m long differences also can arise between the many branches of a single nerve cell.

The latest decades have shown that the complex chemical processes inside the cell are coordinated by *second messengers*. An important example is the free calcium ions. Its role in the intracellular processes originates from an extremely low concentration at rest, around 10^{-5} times the outside concentration, so influx of few ions is sufficient to change the intracellular concentration noticeably. The low concentration is mainly sustained by a calcium pump extruding the incoming ions under energy consumption.

Most nerve cells have potential dependent calcium channels besides the sodium and potassium channels. Calcium ions flow into the cell during a depolarization, and the larger and longer the depolarization is, the more calcium gets into the cell. Calcium ions open a Ca^{2+} -sensitive K^+ -channel, which increases the firing threshold and diminishes the nerve cell's possibility of firing.

The removal of calcium ions is slow, so the effect of the calcium ions has a longer duration than the nerve impulse. New impulses can add to the effect, and the calcium concentration can rise more than 10 times with a concomitant increase in firing threshold. Both the incoming stimuli and the elicited impulses increase the threshold, varying it in a complex manner. With the acute threshold this variation has a dominating influence on future firing, so a nerve response depends on the past performance of the cell.

A simple model

Recently, a model for the impulse transmission between nerve cells was presented (Colding-Jørgensen, 1991) and compared with experimental results from nerve cell bodies of the snail *Helix pomatia*, which have a strong Ca^{2+} -dependent K^+ -conductance. The present model considers only silent cells. With a spontaneously oscillating cell the behavior is more complex as described by Colding-Jørgensen and Madsen (1991).

The synaptic input is simulated by equal-sized square current pulses of strength I_s and with a period T or a frequency $f = 1/T$. The influx of Ca^{2+} -ions during an impulse increases the firing threshold I_{th} by the amount i_t and during the stimulus by the amount i_s . Between stimuli, I_{th} decreases exponentially towards the resting value I_0 with the time constant τ . Both the impulse and the stimuli are considered to be short compared with τ . When I_s is larger than (or equal to) the actual threshold I_{th} , an impulse is elicited; when it is smaller, there is no impulse. To give dimensionless notation, the currents are given in units of i_t . The dimensionless stimulus S is then $S = (I_s - I_0)/i_t$ and the dimensionless threshold is $x = (I_{th} - I_0)/i_t$.

To elicit an impulse, it is necessary that $S \geq x$, but when the stimulus is close to the threshold the membrane stays depolarized for some time before the decision whether to fire or not is taken (Fig. 1). This hesitation can be several times the normal impulse duration, so a noticeable extra amount of Ca^{2+} -ions enters the cell. Consequently, the threshold is increased both when the cell fires an impulse and when it does not, so x becomes larger, when $|S - x|$ is small. This near-threshold behavior is very transient, and experimental results are sparse. A simple approximation is a fast exponential decay with $|S - x|$ giving the iteration scheme:

$$x_{n+1} = r[x_n + \delta_n], \quad (1)$$

$$\delta_n = \begin{cases} 0 + \varepsilon S + \beta_1 \cdot \exp(\gamma_1(S - x_n)) & \text{for } S < x_n \\ 1 + \varepsilon S + \beta_2 \cdot \exp(-\gamma_2(S - x_n)) & \text{for } S \geq x_n, \end{cases}$$

$$r = \exp(-T/\tau) = \exp(-v_{in}),$$

where ε , β_1 , β_2 , γ_1 , and γ_2 are positive constants, and where $v_{in} = \tau \cdot f$ is the dimensionless input

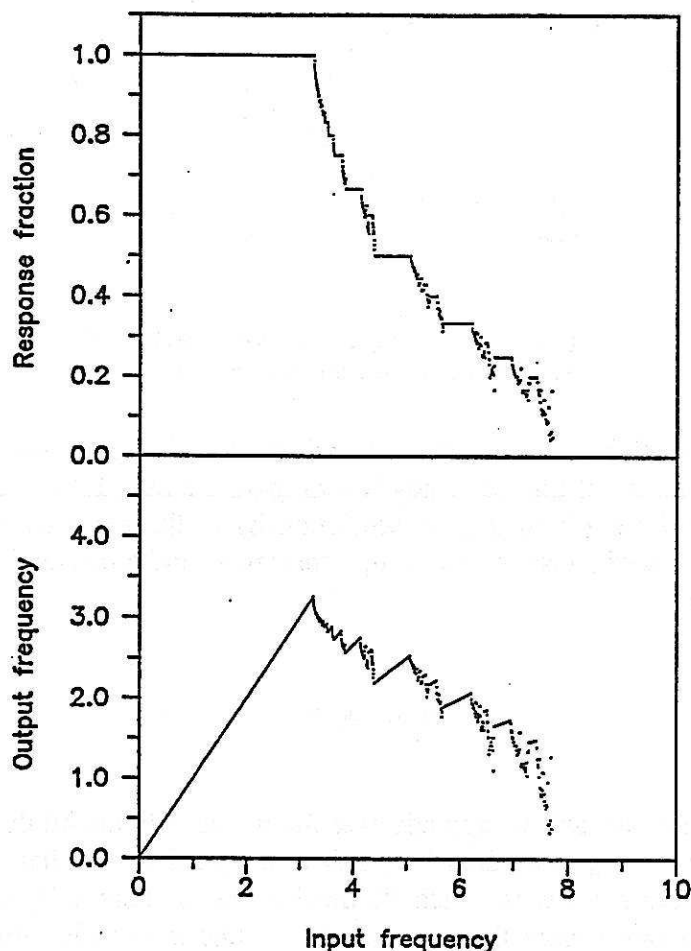
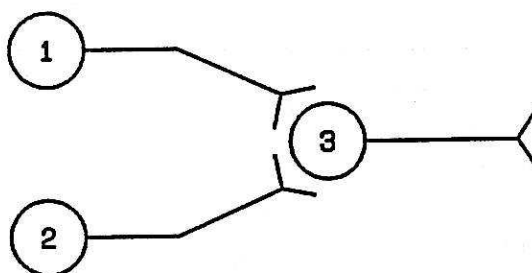


Fig. 2. Input-output relation for the model with $S=4$. The upper part shows the response fraction, Q , as a function of the input frequency, ν_{in} , and the lower part the output frequency, $\nu_{out}=Q \cdot \nu_{in}$. Other parameters are: $\varepsilon=0.1$, $\beta_1=0.4$, $\beta_2=0.2$, $\gamma_1=20$, $\gamma_2=40$.

frequency. The corresponding return map is a linear plot with a single gap at $x_n=S$ and a slope less than one, but close to $x_n=S$ there is an upward bend both for $x_n>S$ and $x_n<S$.

Of interest is the response fraction, $Q=m/N$, which is the number of impulses, m , elicited by a given number of stimuli, N . The relation between ν_{in} and Q is shown in the upper part of Fig. 2. It gives a broken-down "Devil's staircase" with regions of chaotic firing and regions of regular firing. Typically, the largest steps ($1/2$, $1/3$, $2/3$, etc.) survive the breakdown, while the smaller steps are absent. For large ν_{in} there is no firing, because the threshold increase caused by the stimulus is larger than the effect of the stimulus itself.

The input-output relation for the cell is shown in the lower part of Fig. 2 as the relation between the mean output frequency, $\nu_{out} = Q \cdot \nu_{in}$, and ν_{in} . For low frequencies the nerve cell acts as a follower ($\nu_{out}=\nu_{in}$), but around $\nu_{in}=3.26$ the relation breaks up and from then on there is no simple relation between input and output: Close input frequencies can give very different output frequencies. Moreover, the reverse relation between output and input is ambiguous, so it is not possible to find the input frequency from the output frequency. Finally, for large input frequencies there is no output at all, because the Ca^{2+} -influx during the stimulus abolishes all impulse activity, as demonstrated for the snail neuron (Colding-Jørgensen, 1991).



*Fig. 3. A simple coupling of three identical cells.
Cell 1 and 2 send synaptic input to cell 3.*

A similar alternation between regular and chaotic firing is seen, when the stimulus strength is varied instead of the frequency (Colding-Jørgensen, 1991), so in general the effect of the near-threshold stimuli adds an unpredictability to the response of the nerve cell. The result is a combination of a loss of incoming information and a production of new information added to the output.

2. Coupled cells

The synapse

When started, the impulse usually spreads over the whole cell and all the branches of an axon. The branches can be long, more than 1 m, and it is a golden rule that a long branch is used, whenever a firing pattern has to reach its destination unaltered. If, on the other hand, an information path includes more than one cell it is a fair implication that the impulse pattern should not be unaltered, but that information is to be added or removed. In this light it is no surprise that this is exactly, what the nerve cell does.

The impulse pattern is therefore only conserved within a single nerve cell, so the electric impulse is a means of communication between distant parts of the same cell. Communication between different cells is chemical. At the terminal endings a chemical transmitter is released. After diffusion across the synaptic cleft and reaction with postsynaptic membrane receptors of the receiving cell, second messengers are activated inside the cell as described previously. The amount of transmitter released depends on the chemical state of the nerve endings of the transmitting cell, and because the different parts of the cell can be far from each other, their chemical state can differ considerably. In this frame of view the nerve cell can be regarded as consisting of many distant chemical processors with a diffusion-reaction scheme operating on a scale of the order of micrometers and microseconds.

A simple coupling scheme

To study the effect of passing across a synapse the coupling scheme shown in Fig. 3 is used. Two cells, 1 and 2, converge on a third cell, 3, and it is assumed that an impulse in either 1 or 2 stimulates cell 3 with the strength $S=1$, so their impact on cell 3 is the same.

Fig. 4 shows a series of different firing patterns for cell 1 and 2 and the resulting firing of cell 3. The basic pattern is a 2:3 firing between cell 1 and 2 as shown in the left hand column. The upper row demonstrates the effect of a phase shift between the firing of cell 1 and 2. The mean frequency is the same, but cell 1 is phase-shifted 0, 10, and 20 per cent of its firing period from left to right. This results in a marked change in the firing frequency of

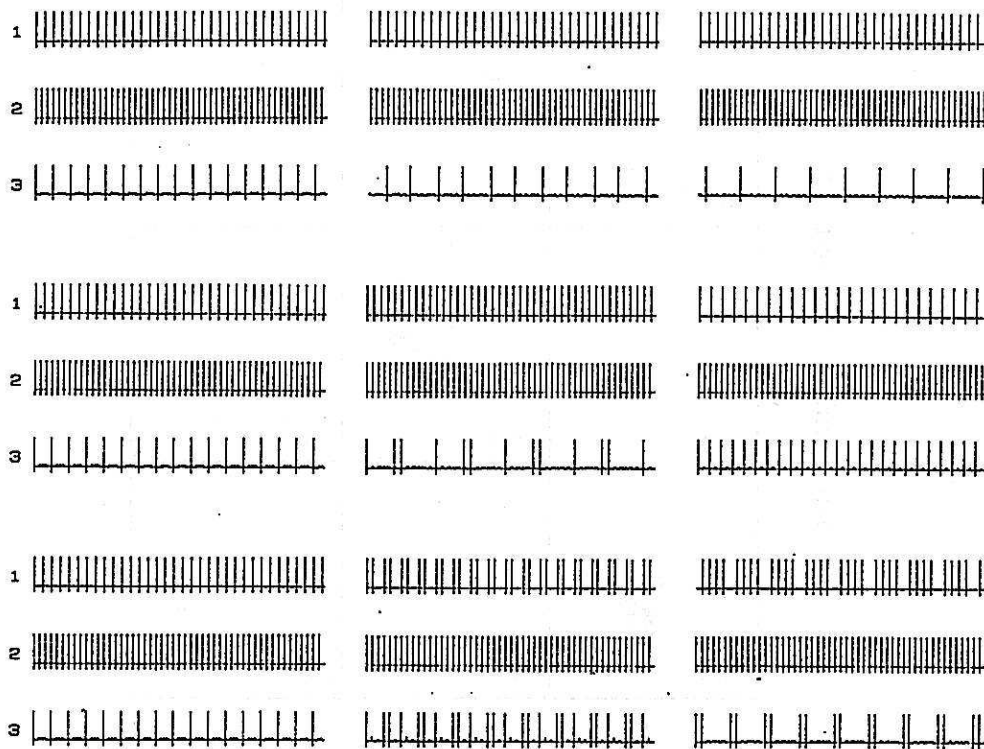


Fig. 4. Input-output patterns for the simple scheme shown in Fig. 3. For description see text.

cell 3. The middle row demonstrates a change in the input frequency. In the middle column the frequency of cell 1 is 25 per cent increased and to the right it is 33 per cent decreased with respect to the basic frequency. In the first case the frequency of cell 3 decreases and in the second case it increases, so the reaction of cell 3 is the opposite of what might be expected, if the firing frequency was the "signal". Finally, the bottom row demonstrates the effect of changing the input pattern without changing the mean frequency. Again there is a marked effect, both in the mean output frequency and in the output pattern.

These results show that even in a simple coupling scheme there is no simple relation between input and output. It appears that the important parameter in the signal transmission is not the firing frequency, but rather the mutual timing of the different incoming and outgoing impulses.

3. The ambiguous input-output relation

The chemical processor

Apart from an unpredictable impulse transmission, the concept of the electric impulse as the main signal suffers from another drawback: The information contents in a nerve signal is too small to account for the enormous information processing power of the brain. The conventional explanation is that the brain uses many parallel nerve signals for the processing. This is definitely the case in the complex senses as vision and hearing, but again this is only in the input to the CNS. Another logical, but often ignored, explanation is that the main

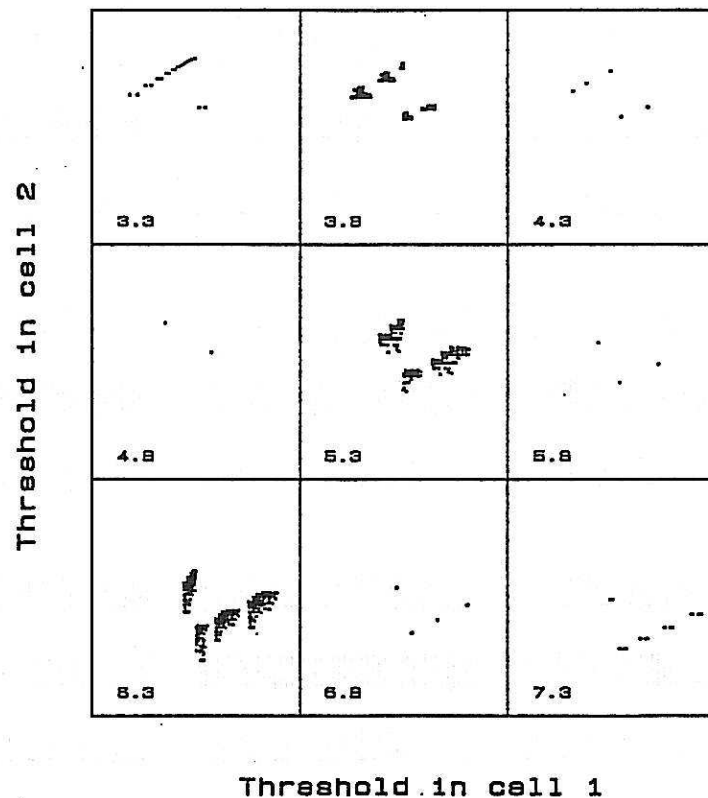


Fig. 5. A phase plot of the corresponding values of the firing threshold in cell 1 and cell 3 (cell 2 silent) for nine different values of v_{in} to cell 1 as indicated in the figures. The abscissa is in all cases $3 < x < 5$ and the ordinate $0 < x < 5$. For further description see text.

processing takes place in the chemical milieu in the different parts of the nerve cell. The concentration of the chemical substances may vary in a continuous manner, and due to a slow diffusion and the existence of intracellular compartmentarization large concentration differences can arise and survive locally. With concentration variations in both space and time, and with a variety of chemical substances the individual part of the nerve cell acts as a multi-dimensional processing unit, while the nerve impulses more serve as messengers between the different parts of the cell.

A cell-cell processor

To evaluate the synaptic transmission consider two cells, 1 and 3, coupled as in Fig. 3, but with cell 2 silent. Cell 1 is stimulated by a regular input with $S=4$ as in Fig. 2. Cell 3 is similar to cell 1 and is stimulated with $S=4$ every time cell 1 fires an impulse, otherwise $S=0$. With a given v_{in} cell 1 responds as in Fig. 2, and its firing threshold varies according to eqn (1). The firing pattern is fed into cell 3, and as the timing comes from v_{in} , the threshold variations of cell 3 are synchronous with those of cell 1. A logical way to view the synaptic transmission is therefore to make a phase plot of the two thresholds.

A sample of such phase plots is shown in Fig. 5 for different values of the input frequency, v_{in} . The chaotic firing of cell 1 begins around $v_{in}=3.26$ and the firing ceases for v_{in} a little less than 8 (Fig. 2). Between these limits the correlation between the two thresholds has the character of a chaotic attractor, where the shape of the attractor varies with v_{in} .

The figure also demonstrates that there is no simple input-output relation in the synapse. For a given input value there can be several possible output values and vice versa. The synaptic transmission is therefore not only unpredictable, it is also ambiguous. A consequence of the ambiguity is that the information flow in the NS is unidirectional, so a two-way communication requires two sets of wiring. This fundamental rule is obeyed almost everywhere in the CNS. Even the brain cortex is divided in areas sending impulses down to the spinal cord and areas where sensory input to the cortex is received from the spinal cord. The involved nerve branches are often spatially separated.

4. A chemical computer

The neural net

The development of neural nets has gained speed during the last decade. Initially, they were thought as electronic analogues to the nervous system, and there are many points of resemblance. The net operates with parallel information in contrast to the conventional computer, it must be trained to work, and it can make errors. Information stored in the net is distributed all over the net making it robust against damages.

The analysis of neural nets has improved our understanding of the nervous system. Particularly, the discovery of distributed information has been a landmark discovery. Unfortunately, seen from an experimentators view, this has also demonstrated the difficulty of gaining information about the actual function of a network by looking at one of its parts. The results presented in the previous sections adds to this disappointment. Looking at a single part of the network it is not only the actual function of the network that is hidden. It also appears that the flow of information through the selected part is random and ambiguous, and that the whole part can be destroyed without any noticeable change in the performance of the network.

Information and exformation

A key to the solution of this dilemma may be found in the dualism between electrical and chemical communication. Considering the chemical processors as the real working units, many such processors must be present to give the large information processing capacity of the CNS. This requires space, both because the processors have a finite volume, and because the maintenance of a concentration difference requires a certain distance. As the chemical communication over large distances is slow, the fast impulse is needed to coordinate the different parts of the system. The nerve impulse can therefore be regarded as a strobe or a synchronizing event. The information contained in the impulse pattern is limited and may have a very remote connection with the actual information processed.

This leads to the necessity of a distinction between the information quantity and the information quality in a signal. The quantity can be measured as demonstrated by Shannon and Weaver (1949), but the measure has many drawbacks. The most important can be demonstrated in the following way: Consider the present page. Take off all the letters on the page and put them back in a random order, but such that the distribution of the "words" is preserved. For an illiterate the page will look much the same, a rough Shannon measure will give the same value, but the meaning of the text is gone.

Instead of transmitting all the letters of the page it is simpler to use a symbol, for example the page number. The required information is then smaller. However, the receiver must have read the page to understand the message. Without this the information quality is gone. A large

amount of information can thus only be hidden in a short message, if both transmitter and receiver share a common background information. This background information is often called *exformation* to underline that it is excluded from the message transmitted, while the contents of the message, for example the page number, is called *information*.

In the CNS the exformation is distributed over the chemical processors. The processors are presumably coupled in self-organising, hierarchical structures, with different information processing functions, but with overlapping background information. A knowledge of this exformation and its symbols is necessary to understand the information processing of the nervous system.

Conclusion

The distributed background information and the ambiguous processing give a picture of a nervous system quite different from a conventional computer. A nagging question is, whether it in reality it the lack of precision and the ambiguous, associative information processing that is the secret behind the enormous capacity and fast processing of the CNS. In fact, when the difficulty of a stringent logic reasoning is compared with the intuitive understanding of the richness of nuances in art, poetry, or humor, the odds turn in favor of the intuition.

The presented results are to some extent discouraging, because an understanding of the information processing in the CNS is far from being in sight. However, more and more emphasis is laid on microenviromental chemistry, the development of intracellular fluorescence probes, microelectrodes sensitive to different chemical substances, and patch-clamp, etc. that will advance our understanding. The main stumbling-block is still how to deal experimentally with a background information distributed over many nerve cells, perhaps the whole brain.

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