

Use of ADNC in analyzing the firing patterns in central nervous system

Zoltán Attila Godó

Department of Electrical Engineering, University of Debrecen, Hungary

Department of Physiology, Medical and Health Center, Hungary

Egyetem tér 1, H-4010 Debrecen

Hungary

godoz@dragon.unideb.hu

Abstract - The digital surface of ADNC (Analog Digital Neural Computer) is constructed by five high-capacity microcontrollers. This artificial neural network controls an analog surface, to which a 128 microelectrode array connects. The server processor receives the instructions from a PC and it makes the client processors execute them. The analog surface is capable of recording and stimulating. The data flow from the microelectrode array and the processing instructions determine the route of the firing matrixes in the neural network. The analog surface fits closely into the RAS (Reticular Activating System) area of the central nervous system of the –in the current experiment- rat, where the RAS area is treated with stereotaxia. The point of attack of the neurolepticum medicines which are to be analyzed is the polysynaptical route system in this nervous system area, where these medicines evoke a characteristic synchronic firing pattern. It is unknown what kind of synchronic firing changes the conjugations of these GSH (glutathione) compounds cause in the RAS area, which can be in contact with their therapy efficiency. Because of its structure, ADNC can take closer to the more effective functional analysis of the central nervous system.

I. INTRODUCTION

The working of the central neural system and its functional analysis is unknown even today. One of its reasons is that the performance of the hardwares designed by man is far from the complexity and so from the performance of natural structure developed by the evolution. The neural networks consisting of more processors resemble very much the networks accomplished by nerve cells, so they model certain functions of them with good advancing. These networks are already capable of analyzing the working of smaller nervous system areas.

The former analyses were directed in order to understand the metabolism of neurolepticum medicines. It was shown that these compounds significant in human medicine increased the enzyme activity [1] of more tissue types (Wistar SPF Rat) GST (Glutathione-S-Transferase). Presumably its metabolism happens after conjugation with GSH (glutathione) [2-4].

The first point of attack of these medicines is presumably the *Formatio Reticularis*, certain nerve cell groups of the Reticular Activating System (RAS). Their effect is the characteristic synchronizing mechanisms in the firing pattern of the nervous route. This may be in connection with the effect that the pharmacological group evokes a characteristic tranquilant (sedative) effect. In later analyses it is to answer how the GSH conjugates of these medicines affects the RAS firing pattern, within that pattern the synoptical signal transfer and the synchronizing mechanisms are relevant. The role of metabolites in the therapy efficiency can be analyzed by this method.

RAS is the phylogenetically ancient network inner axis which forms a complex polysynaptical route system. Because of this, the functional analysis of its small surface needs building a high-capacity neural network. The partial mapping of collateralials in a given area can be especially important in the analysis because there is a synaptical connection between them, which is affected by the analyzed compounds. The mapping of collateralials is effective when the most routes are covered and they are analyzed at the same time [5]. The ADNC (Analog Digital Neural Computer), designed for this purpose connects to the central nervous system area [6] with stereotaxia with the help of a microelectrode array consisting of 128 electrodes.

It is constructed by closely cooperating analog and digital surfaces. The digital surface forms an artificial network. The system not only perceives the firing pattern of the nerve cells but it was necessary that the system could also be capable of stimulating them [7,8] in any kind of patterns, so it creates bidirectional communication.

II. GENERAL STRUCTURE

ADNC is made of two surfaces. The digital surface (DS) is to realize the working algorithm, to control and to read the analog surface (AS) and to maintain relations with the computer (PC). The DS consists of five high-capacity microcontrollers (Basic Stamp BS2 SX-IC, Parralax Inc.). The excellent laboratory application of this processor type was proved in former experiments [9]. One aspect of choice was that these processors have a much higher capacity, then the earlier versions (e.g. BS1-IC) [10-12]. These earlier versions were capable of complex microstimulation and they held on in spectacular experiments, such as rat navigation guided by remote control [13, 14].

The structure of the neural network that builds the DS is irregular. Not only equivalent units build it, but one of them has a special role, it is a server. The system forms star topology, so all data of client processors run through the server, too. The form is explained by the processing way how the special data flow in. The server is in connection with the PC, it takes over the command from the PC and it sends the results to the PC. The server processor gives the commands to the client processors, it receives their data; the server processor then evaluates the further steps and chooses a path way for the data flow. The client processors execute the commands, they are in connection with AS and they control it, they receive its data flow.

The AS connects directly to the nervous system of the experimental animal through a 128 unit microelectrode array. The (in this experiment from RAS) electrodes flowing in connect primarily to quad bilateral switch IC (CD4066BC, Fairchild Semiconductor Inc.) system. Through the switches analog stimulators and recorders can reach the microelectrodes. The DS controls the analog components through 4 byte demultiplexers (HEF4514B, Philips Semiconductors), so it multiplies the number of electrodes that can be reached by each digital output. The BS2 SX processors have namely only 16 I/O pin.

The third surface of ADNC is the living nervous system, because it connects organically to the AS. It receives signals from that and after "processing" because of its natural structure it sends back modified data flow, in form of action potential towards AS. Fig.1

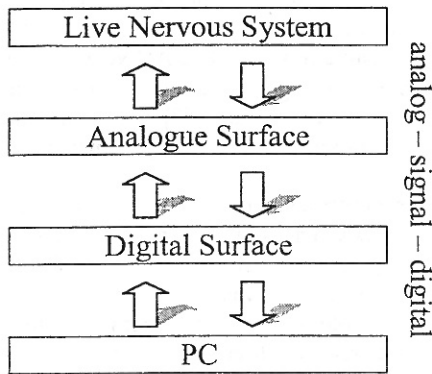


Fig. 1 The way of analog and digital signal. The connection of surfaces from PC towards nervous system area aimed by microelectrodes.

III. ANALOG SIGNAL PROCESSING

The standstill membrane potential of RAS nerve cells is usually -70mV. During the firing about +35mV overshoot is observable. So the action potential is easy and mainly rapid to digitalize on 1 or 0 byte signal. In the further analyses the task is to measure the analog value of standstill membrane potential. Its value influences the formation of action potential and so the firing pattern. So the analog surface was made to be capable of the punctual analog digital conversion over the strengthening of the signal. So it has two working states. One of them is the one byte binary overturning, the other is the more bytes quantating with A/D converter. The one byte recording is, of course, much faster, because only limit overturning must be perceived. In the most cases of present analyses this simpler method gave enough information, while it offered great amount of it.

The signals from nervous system through the microelectrodes flow in on an analog bidirectional switch IC. The switches carry out the connection to the stimulator and the recorder. Since they cannot be made separately for each electrode, they carry out multiplex function. DS controls this and also the stimulator and the recorder. Fig.2

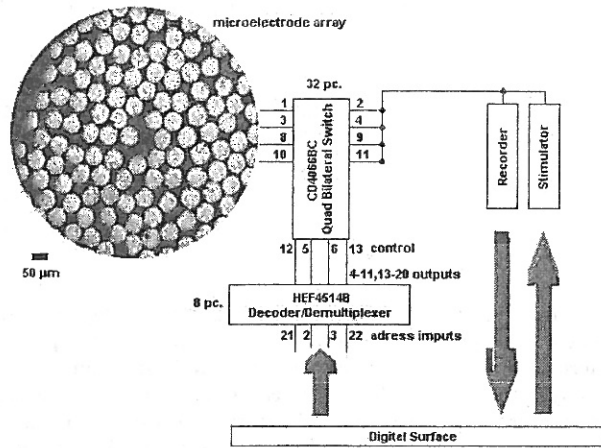


Fig. 2 AS connection to microelectrode array and DS

The action potential of the nervous system is of millivolt. This voltage gets through the switches into the recorders and from the stimulators through the microelectrodes into the RAS. The recorders send then TTL signals towards the DS and the DS controls the stimulators also with TTL signals. However, the switches and demultiplexers work on 15 volt, because the connection speed of the IC is significantly greater (CD4066BC and HEF4514B data sheets). The switches are at Propagation Delay Time Signal, Input to Signal Output TTL signals 55ns, whereas at 15 they halve. The demultiplexer Propagation Delays decrease from 260 ns to 65 ns by the application of higher voltage.

IV. DIGITAL SURFACE

The server in center position takes over the commands of a purpose oriented interpreter (ADNC-LI, ANDC-Language Interpreter) running on a PC with a simple synchronic signal transfer through the parallel port. The speed does not have a relevant role at this stage. The commands of the PC are processed by the server and the server gives the task to the client processors. There is an asynchronous serial data transmission between the server and the client processors with 9600 bound rate (Basic Stamp Programming Manual, Parallax Inc.). In the present day structure there are four client processors around the server. All of them control two demultiplexers through a 2x4 title line. They connect to the server with two PINs, with one of them they connect to a stimulator, with the other they connect to the recorder. The 2x16 output of the two demultiplexers enters to the controlling PINs of AS switches. So a client processor is able to control 32 microelectrodes, the four client processor controls altogether 128 microelectrodes.

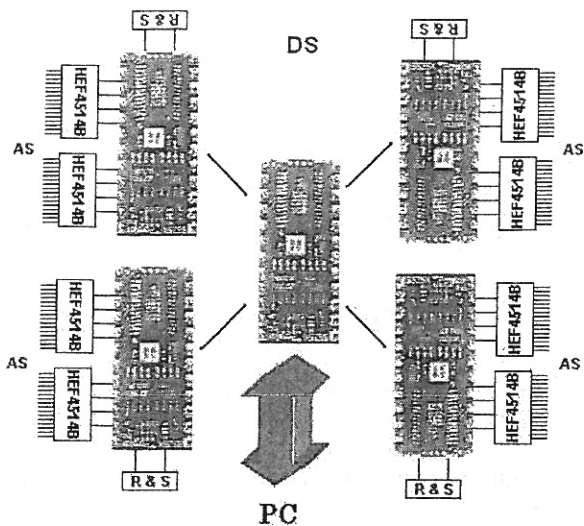


Fig. 3 Schematic structure of DS and its connection to PC and AS

Because a client processor has only one recorder and one stimulator, it has to address its own electrodes one after the other. The choice of microcontroller was the BS2-SX, because its speed executes 1000 instructions per second. According to the instruction to be executed the client processor does the stimulation or the recording and it sends the report or the whole data flow towards the server processor. So the total network works with four parallel processes at the same time.

V. DATA PROCESSING

The effect of GST conjugates to the RAS firing patterns can happen mainly after the modifying of the working of the embedded synapses. Among the nerve cell groups covered by certain electrodes of the microelectrode array there are polysynaptical connections with for us unknown complexity. So first it is necessary to record more firing patterns from the RAS area of the experimental animal. The continuous real time sampling of these create a three dimensional array.

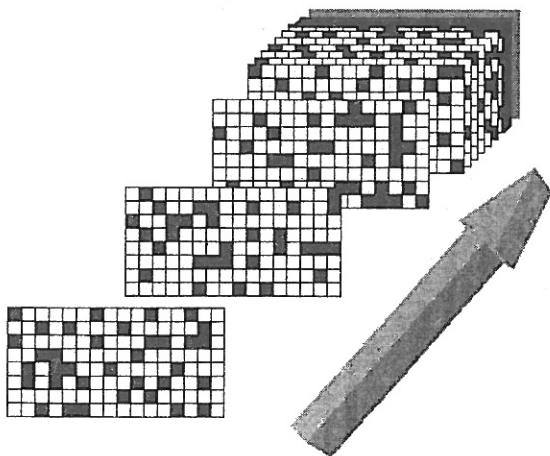


Fig. 4 The firing pattern entering through the microelectrode array creates firing matrixes. These assemble in a three dimensional array during the time indicated by the array.

With the help of cooperating client processors the microelectrodes can be found that cover the nerves firing significantly together. Since their positions can be far from each other, it is essentially necessary that the processors report the recorded firing patterns. So a rapid data flow starts through the neural network. Its direction is determined by the structure and functionality of the living nervous system covered by microelectrodes. The server processor determines namely on the basis of the patterns of the matrixes flowing in what nerve cell groups can stand together in a functional connection. The nerve cell groups are controlled by client processors and they stand under microelectrodes. The server processor controls the data flow by this way. So the artificial neural network and the nervous system form a closely collaborating unity. On certain directions of ADNC-LI the extract of synchronic firing matrixes can be returned to the RAS through the microelectrode array in form of stimulus. So the connection under certain electrodes can be reached. Of course, it must be taken into consideration that though the conduction of the axons can be an antidrome, however, the synapses as diodes make the data flow one directional.

Beside the approaching of the microelectrode array the synthesized GST-neurolepticum conjugates can be injected. The comparison of the new recorded matrix arrays with former ones helps in analyzing the efficiency of the conjugates. The change of synchronic firing patterns indicates unambiguously the medicine's effect on metabolite synapses.

The injection of the microelectrode array with stereotaxia is not always precise. Because of the complex nervous route system it can enter such areas where the synchronizing phenomena to be analyzed cannot be experienced. The ADNC produces results very fast because of its extreme quickness and easy application. So the experiment can be repeated with great efficiency in a new localization.

The server processor returns the firing matrix arrays to the PC where the good software supply helps in the further evaluation.

If the firing matrixes assemble in time, they can be shown as a film with the help of a program running on PC, with optional slowing. At this time the change of the patterns, the synchronization, and the desynchronization can be perceived apparently.

VI. CONCLUSION

The signals received from living nervous systems, especially if using hundreds of samplings they create a huge amount of data from the multielectrode array, can be processed only by an artificial neural network. This structure assimilates to the natural system, so it is evident to apply it in such analyses. The signal processing speed of the neural network stands closer to the nervous system to be analyzed, than being analyzed through I/O units of computers with general aims. The speed of BS2-BX microcontroller is very fast in indirect I/O operations. It must be taken into consideration that its expense is much less than in the case of PC microprocessors. The further evaluation is also comfortable because of the good

software supply, since the ADNC hands over the final data flow to the PC. The ADNC approaches the connection of artificial neural network and the living nervous system in a new way. It not only records or stimulates, but combining the two it communicates with the living nervous system. It handles the nervous system as a changing structural part of the neural network. The data flow of the neural network and its answer stimuli are determined partly by the natural structure of the nerve cells, partly by its synaptical connections and its working states affected by xenobiotics. The microcontroller-based neural network communicates with the nervous system and the microcontroller is controlled according to the processing aims with the help of an interpreter running on a PC. So the system is very user-friendly and efficient. Following one order an online data flow starts continuously from 128 electrodes. Following another order the system also returns the results of the operations (e.g. subtraction, addition, mapped synchronic firing patterns etc.) accomplished on the read matrixes through electrodes in form of stimuli. So, it creates bidirectional communication with the living nervous system. The ADNC, because of its structure, can take us closer to the more effective functional analysis of the central nervous system.

VII. REFERENCES

- [1] Zoltán Attila Godó, Zsolt Pirger, Gábor Nagy, Csaba Révész, Vince Varga „Glutathione-S-Transferase enzyme induction with psychoactive pharmacons” in XXXI. Membrane Transport Conference, Sümeg, Hungary, 2001, p. 84.
- [2] V. A. Catania, M. G. Luquita, E. J. Sánchez Pozzi, A. D. Mottino, Differential induction of glutathione S-transferase subunits by spironolactone in rat liver, jejunum and colon. *Life Science*, Vol. 63, No26. 1998.
- [3] Janáky, R., Varga, V., Oja S.S. and Saransaari, P., Release of [3H] GABA evoked by blutamate agonist from hippocampal slices: effects dithiootreititol and glutatione. *Neurochem.Int.* 24, (1994) 575-582.
- [4] G.D. Boccio, A. Pennelli, E. P. Whitehead, M. I. Bello, R. Petruzzelli, G. Federici, G. Ricci, Interaction of Glutathione Transferase from Horse Erythrocytes with 7-Chloro-4-nitrobenzo-2-oxa-1,3-diazole. *The journal of biological chemistry*. Vol. 266 (1991) No21.
- [5] Michael P. Maher, Jerome Pine, John Wright, Yu-Chong Tai, The neurochip: a new multielectrode device for stimulating and recording from cultured neurons. *J. Neurosci. Methods* 87 (1999) pp. 45-56.
- [6] Craig T. Nordhausen, Edwin M. Maynard, Richard A. Normann, Single unit recording capabilities of a 100 microelectrode array, *Brain Research* 726 (1996) pp. 129-140.
- [7] Yeomans JS. A brief history of brain stimulation. In: *Principles of brain stimulation*. Oxford University Press: New York; 1990. p. 3-19
- [8] D.A.Borkholder, J. Bao, N.I. Maluf, E.R. Perl, G.T.A. Kovacs, Microelectrode arrays for stimulation of neural slice preparations. *J. Neurosci. Methods*. 77 (1997) pp. 61-66.
- [9] Zoltán Attila Godó, “Applying microcontrollers to bioinformatics” in XXXIII. Membrane Transport Conference, Sümeg, Hungary, 2003, p. 21.
- [10] R. Bannatyne, G. Viot, Selecting a microcontroller, *Embedded Systems Programming* July (1998) 95 also pages 97-103.
- [11] J. Beil, Choosing a microcontroller, *Electronic Product Design* 17 (9)(1996) 61-66.
- [12] A.H.G. Al-Dhaher, Integrating hardware and software for the development of microcontroller-based systems. *Microprocessors and Microsystems*, 25 (2001) 317-328.
- [13] Shaohua Xu, Sanjiv K. Talwar, Emerson S. Hawley, Lei Li, John K. Chapin. A multi-channel telemetry system for brain microstimulation in freely roaming animals. *J Neurosci Methods*. accepted 12 September 2003.
- [14] Talwar SK, Xu S, Hawley ES, Weiss SA, Moxon KA, Chapin JK. Rat navigation guided by remote control. *Nature* 2002; 417:37-8.