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FROM BIOLOGICAL NEURAL NETWORKS TO THINKING MACHINES: TRANSITIONING BIOLOGICAL ORGANIZATIONAL PRINCIPLES TO COMPUTER TECHNOLOGY

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ABSTRACT

The three-dimensional organization of the vestibular macula is under study by computer assisted reconstruction and simulation methods as a model for more complex neural systems. One goal of this research is to transition knowledge of biological neural network architecture and functioning to computer technology, to contribute to the development of "thinking" computers. Maculas are organized as weighted neural networks for parallel distributed processing of information. The network is characterized by non-modularity of its terminal/receptive fields. Wiring appears to develop through constrained randomness. A further property is the presence of two main circuits, highly channeled and distributed modifying, that are interconnected through feedforward-feedback collaterals and a biasing subcircuit. Computer simulations demonstrate that differences in geometry of the feedback (afferent) collaterals affects the timing and the magnitude of voltage changes delivered to the spike initiation zone. Feedforward (efferent) collaterals act as voltage followers and likely inhibit neurons of the distributed modifying circuit. These results illustrate the importance of feedforward-feedback loops, of timing, and of inhibition in refining neural network output. They also suggest that it is the distributed modifying network that is most involved in adaptation, memory and learning. Tests of macular adaptation, through hyper- and microgravitational studies, support this hypothesis since synapses in the distributed modifying circuit but not the channeled circuit are altered. Transitioning knowledge of biological systems to computer technology, however, remains problematical.

A major objective of neuroscience research is to understand the relationship between neural geometry and the coding of information. Neural geometry is defined here as the organization from the subcellular to the network and parallel systems level that permits the transfer of information from one site to another, so that some activity, whether that be an abstract thought or a motor response, results. While the goal of this kind of research is, more often than not, to gain knowledge of neural functioning as a basis for understanding normal and diseased states, the potential for spin-offs in computer technology is enormous. For what can emerge from work based in neurobiology is nothing less than a computer with "sense" as well as "knowledge"; that is, a computer that can "learn" and "think".

At the Biocomputation Center at NASA-Ames Research Center, my research team focuses on gaining an understanding of the fundamental properties of a simple mammalian neural network, the vestibular macula of the rat inner ear, as a model for more advanced neural systems. Maculas are linear bioaccelerometers that are organized similarly to engineered accelerometers: they have a test mass that is not tightly attached to the underlying detecting unit while the sensing part is anchored. It is thought that differences in the relative motions of the test mass and the detector during acceleration of the head provide the stimulus to the receptor cells, called hair cells. The signals are transduced into electrochemical activity by the hair cells, and macular neurons inform the central nervous system about the acceleration of the head in three-dimensional (3-D) space. The information, continuously transmitted, is integrated centrally with input from angular bioaccelerometers and other sensory systems, such as the visual and proprioceptive (joint and muscle sense), to keep the organism stable and in correct posture for the task at hand, whether the animal is at rest or in motion.

The sensing part of the linear bioaccelerometer is a neural network that, like retina and other parts of the brain, is organized for weighted, parallel distributed processing of information [1,2]. The test mass (otoconia) is not uniformly distributed over the sensory array, so that incoming signals are not passed identically to all parts of the network. Thus, in contrast to engineered systems, maculas are organized for parallel processing at both the input (test mass) and sensing (neural) levels.

The receptor hair cells of the macular neural network are of two types, I and II (Figure 1). Type I cells are almost completely enclosed by expanded terminals (calyces) of the nerve fibers and communicate only with calyces. Type II cells, in contrast, lie between calyces and synapse directly with them or with their collaterals. Type II cells also are under the influence of calyceal and nerve fiber activity from vesiculated collaterals of calyces and nerve fibers. Additionally, a system of very fine, unmyelinated nerve fibers provides presynaptic endings (efferents, [3]) for calyces, nerve fibers and type II hair cells. This efferent system may perform a biasing function in the network (see below).

One of the major features of the mammalian macula is the non-modular organization of its neural elements. No two terminal/receptive fields are identical. There is a spectrum of terminal field patterns ranging from those with a single calyx springing from the first heminode of a myelinated nerve fiber (M-type) to those with a branched pattern of two or three calyces and a long, unmyelinated segment distal to the heminode (U-type) [4,5]. An intermediate variety has one or two calyces and a short, unmyelinated preterminal segment (M/U-type). Similarly, the receptive fields differ in the number and arrangement of receptor cells. The morphological range from M-type to U-type innervation patterns is reflected in a physiological spectrum of discharge properties from highly irregular to regularly firing [6,7] that encode phasic to tonic head acceleration and positioning.

Our research with Monte Carlo simulations, using a matrix of measurements from the biological data and a random number generator, show that non-identical terminal/receptive fields could develop through a process of constrained randomness [8]. We were able to reproduce the patterns actually observed in the macular neural network by this computer method. Constrained randomness in wiring is very likely one way in which biological neural networks maintain robustness and the ability to degrade gracefully during aging while simultaneously ensuring variability and capability to meet unknown environmental challenges. Still, to my knowledge, constrained randomness has not been included in artificial neural networks and its advantages or disadvantages for computer technology are unexplored.

A further property that is coming under increased scrutiny for potential computer implementation is the fundamental organization of maculas and other biological neural networks into two main circuits. The first circuit consists of an input with relatively direct access to the output neurons while the second circuit distributes information to other cells and modifies the final output of the network. I have called these two circuits "highly channeled" and "distributed modifying" respectively (Figure 1) [8]. However, the two circuits correspond to those described for olfactory system and retina by Shepard [9] as "vertical" and "horizontal", and for cortex by Schmitt [10] as "direct" and "local".

The distributed modifying circuit involves cells that conform to the idea of interneurons. Interneurons are local cells that are inserted into conducting pathways to modify output of the transmission lines, but that do not conduct information over long distances. A distributed modifying circuit may include a single interneuron, as it does at the first stage of retinal processing, where horizontal cells take on this function; or it may consist of several interneurons and more complicated circuitry as it does in cerebral cortex. Although it is a novel use of the term "interneuron", type II hair cells should be considered to belong to this class since they are inserted into feedforward-feedback loops in the distributed modifying circuit. They function as a mixture of receptor cell and interneuron. In the retina, for example, a comparable cell would be a hybrid photoreceptor/horizontal cell.

In the macula, a portion of the distributed modifying circuit may have a biasing effect on neural elements of the network, as mentioned briefly above. This part consists of the highly vesiculated, button-like endings (boutons) that terminate on type II hair cells, calyces, intramacular nerve fiber branches, and collaterals (see Figure 1). Although all nerve fibers of this system are cholinergic [11], the morphology of the synapses made by their terminals suggests that they may have a dual function in the network that depends on subsynaptic features. For example, the boutons terminating on type II hair cells end opposite or near subsynaptic cisterns, which are part of smooth endoplasmic reticulum network of the cell. They thus correspond to c synapses [12] and likely function to hyperpolarize (inhibit) the cell via calcium release from the cisterns and resulting potassium extrusion [13] (see supporting evidence provided by Ohmori [14] for vestibular hair cells). (Efferent-type intramacular collaterals are considered here to hyperpolarize the type II hair cells because they, too, end opposite subsynaptic cisterns.) That some of the c synapses are involved in highly local processing is apparent because

~20% to 30% of them are reciprocal (there are both pre- and post-synaptic structures at the hair cell membrane) [8]. Synapses formed by other terminals on calyces, nerve fiber branches and collaterals are asymmetric synapses. The asymmetric synapses should have a depolarizing (excitatory) effect on these neural elements, keeping them at some state of activation depending on the number of synapses collectively transmitting at any given time. It is most interesting that many of these terminals form more than one junction with the postsynaptic element. Some terminals synapse with both a type II hair cell and a calyx where, on morphological grounds, they should bring about opposite effects. How common biasing circuits are in neural systems is unclear, but a comparable intrinsic cholinergic circuit has been described for optic tectum [15] where the circuit was shown experimentally to enhance retinotectal transmission.

Thus, the type II hair cell is inserted into feedforward-feedback loops in the network and some of its synaptic sites are morphologically organized to support highly localized neural processing. The type II cell also appears to function against both a transient inhibition from feedforward collaterals and a continuous biasing inhibition from the efferent terminals. This is in contrast to the type I cell, which is isolated from external influences except for those that might be transmitted through the calyx.

In order to begin to test the significance of the distributed modifying circuit, of local processing and of biasing in neural computation, we conducted a compartmental modeling study of collaterals using precise measurements from our serial sections and software called NEURON [16]. The question posed for this initial investigation was whether collaterals of differing morphologies would yield significantly different voltage contributions to neural activity, demonstrating a relationship between neural geometry and functioning.

Several collaterals with different morphologies were examined. Each terminal was converted into a matching geometric form which was subdivided into major segments depending on the taper rate (cylinder, frustrum, etc.) of each part. Each segment was partitioned into 30 compartments for modeling purposes, with the number of compartments deemed sufficient for the model determined empirically. The collaterals were all considered to arise from a nerve fiber with a diameter of 2.5 mm and a length of 2 l (1118 mm), divided into 200 compartments. Voltage changes were monitored at the input site (the distal end of the process), the base of the process, at a distance of 33.5 mm and at 145 mm along the nerve fiber branch. Following the initial study, simulations were conducted in which stem diameter was kept constant at 0.2 mm but the length was increased by factors of two, (or by the square root of two for the smaller lengths) from 0.5 mm to 16 mm. In other simulations, the stem length was kept constant at 0.8 mm (this was a real dimension), but the diameter was changed in the same manner from 0.07 mm to 1.6 mm.

Briefly, the results showed that when the collaterals and nerve fibers were considered to be passive and afferent functionally, the voltage changes at the base of the stem are very sensitive to changes in stem diameter but not as sensitive to changes in length. Interestingly, the size or shape of the head did not matter as much in terms of voltage changes delivered to the nerve fiber branch. Moreover, increasing the diameter of the stem not only resulted in increased voltage delivered to the base, but also shortened the time to peak delivery. The conclusion reached was that small changes in diameter of the collateral, anywhere this might occur, alter both the amount of voltage and its timing of delivery to the base of the collateral. This would mean that all afferent collaterals are not equivalent with respect to their influence on a calyx, or on the activity of other collaterals arising from nearby on the calyx. These results, based on biological data, support the concept that geometry affects both the timing of input and the magnitude of the voltage changes at the spike initiation zone in biological neural networks.

Results of similar simulations in which the collaterals were considered to be efferent in type showed that, in all cases, voltage changes were delivered to the type II hair cell quickly and without much diminution. Feedforward collaterals would thus seem capable of influencing type II cell activity, depending on the dynamic state of the calyx or nerve fiber branch, quickly and with minimal loss of current at the source. In the electronic sense, the efferent collateral is a voltage follower.

The degree of inhibition a type II experiences from moment to moment is a dynamic parameter. The level of inhibition depends on the timing of the *total* feedforward input from all the calyces and nerve fiber branches from which the type II cell receives efferent-type terminals and collaterals. Also, any individual calyx *simultaneously* regulates the transient inhibition of *all* the type II hair cells with which it communicates, whether they feed back to that calyx or to another. The dynamics of this inhibition in turn determine the amount of excitatory feedback provided to the calyces, since this depends on how much a type II cell's own excitatory activity overcomes imposed inhibition. Because of the short distances involved, the voltage changes in one part of the terminal array affect the entire array, so that there must be continuous fluctuation in transmembrane voltage, with the output reflecting the differing neural geometries of the terminal/receptive fields. This is an analog system that converts its output into a digital signal (discharge).

Our simulations, then, begin to tell us something about the possible importance of feedforward-feedback loops in biological neural networks, the necessity of timing, and the need for inhibition to control and refine output. The role of reciprocal synapses and of highly localized processing remain to be explored. Assuming that our interpretations of the basic circuitry are correct, it would be predicted that it is the distributed modifying circuit that would show most plasticity and adaptability to an environmental change. According to Shepard [9], it is this circuitry that would also be most involved in memory and learning.

This concept, if correct, has great relevance to the development of advanced, "thinking" computers. Although there is currently a great deal of research into neural plasticity and learning [see 17], the central idea that there are two fundamental circuits with one of them more susceptible than the other to adaptive change has, to my knowledge, not been specifically tested. However, a proposed explanation for neural modulation during learning in *Aplysia* [18] utilizes two basic circuits, one that is direct, or highly channeled, and the other that is routed through a modulating pathway. Additionally, the cerebellar circuitry is a classic example of a system with a highly channeled input (the climbing fiber) and a distributed modifying one (the parallel fibers), and research indicates that the latter circuit is the one that is more adaptive [19].

In contrast to many other neural networks, maculas are a perfect system to serve as a testbed for the concept of dual circuitry with non-equivalent plasticity. The macular network is simple compared to other more highly evolved systems, and it responds to transient linear acceleration and to steady-state gravitational stimuli. The gravitational environment can be manipulated through the use of the space shuttle and ground-based centrifuges. Additionally, changes in macular synaptic or collateral connectivities in response to an increase or decrease in gravitational bias can be determined more readily than ever before using computer-aided counting and reconstruction methods.

Early, preliminary findings in maculas from animals flown on SLS-2 for 9 days and from others subjected to 2-g centrifugation for two weeks indicate that synapses in type II hair cells decrease by ~30% in hypergravity and increase by ~25% as a consequence of spaceflight. Synapses in type I cells were not significantly affected when compared to controls. If these results hold up when the study is completed, we shall have demonstrated that the macula can adapt to an environmental change in linear acceleratory input, bidirectionally. Moreover, the conclusion will be almost inescapable that feedforward collaterals help regulate the excitatory output of the type II cell, including synapse formation and degradation. This would mean that some mechanism exists, even in these simple cells, for gene expression to alter the cell's structure in response to a differing pattern of activation. In other, central neural tissues, this is described as a form of learning (see discussions in [17]).

This brings us to another important issue: whether "memory" and "learning" are primitive attributes of every neuron finding highest expression in the human brain due to the enormous increase in association cortex, a distributed modifying type of neural circuitry. This would mean that although each neuron individually is still essentially an automaton, collective expression of individual mechanistic capablities, genetically assured, underpins emotional response, rational thought and creative ability.

How to interact best with industry to transition these and other insights emerging from biological research to computer technology remains problematical. My experience is that mechanisms to facilitate transitioning from science to industry are either not in place or do not work well. The vision of commercial payoff may be too short-sighted, or our hopes of assisting industry may be premature. What is required is closer interaction between theoreticians, experimentalists and implementers, but this kind of merger thus far appears easier to bring about in an individual laboratory than between science and industry, which often have disparate goals.

Nevertheless, I am certain that computer modeling of three-dimensional neural networks mimicking properties of biological systems will play an essential role in achieving knowledge of how to construct more intelligent computers. Indeed, one exciting prospect of our 3-D modeling effort is that one can begin with a simple system such as the vestibular macula and, by adding interneurons, build up to a retina or more complex cortex, even to parallel circuits that include an associative cortex, to learn what functional advantage is achieved by splitting cellular functions and increasing the complexity of distributed modifying circuits. While these simulations could aid in the understanding of vestibular maculas and of retina, they offer the additional promise of theoretical insights advantageous to computer technology and to the production of more sophisticated "thinking" machines. Rarely has there been so perfect an opportunity to reap biological, biomedical and technological advantage from a single nexus of science and industry; unfortunately for both players, we are still learning how to bring this bonding about.

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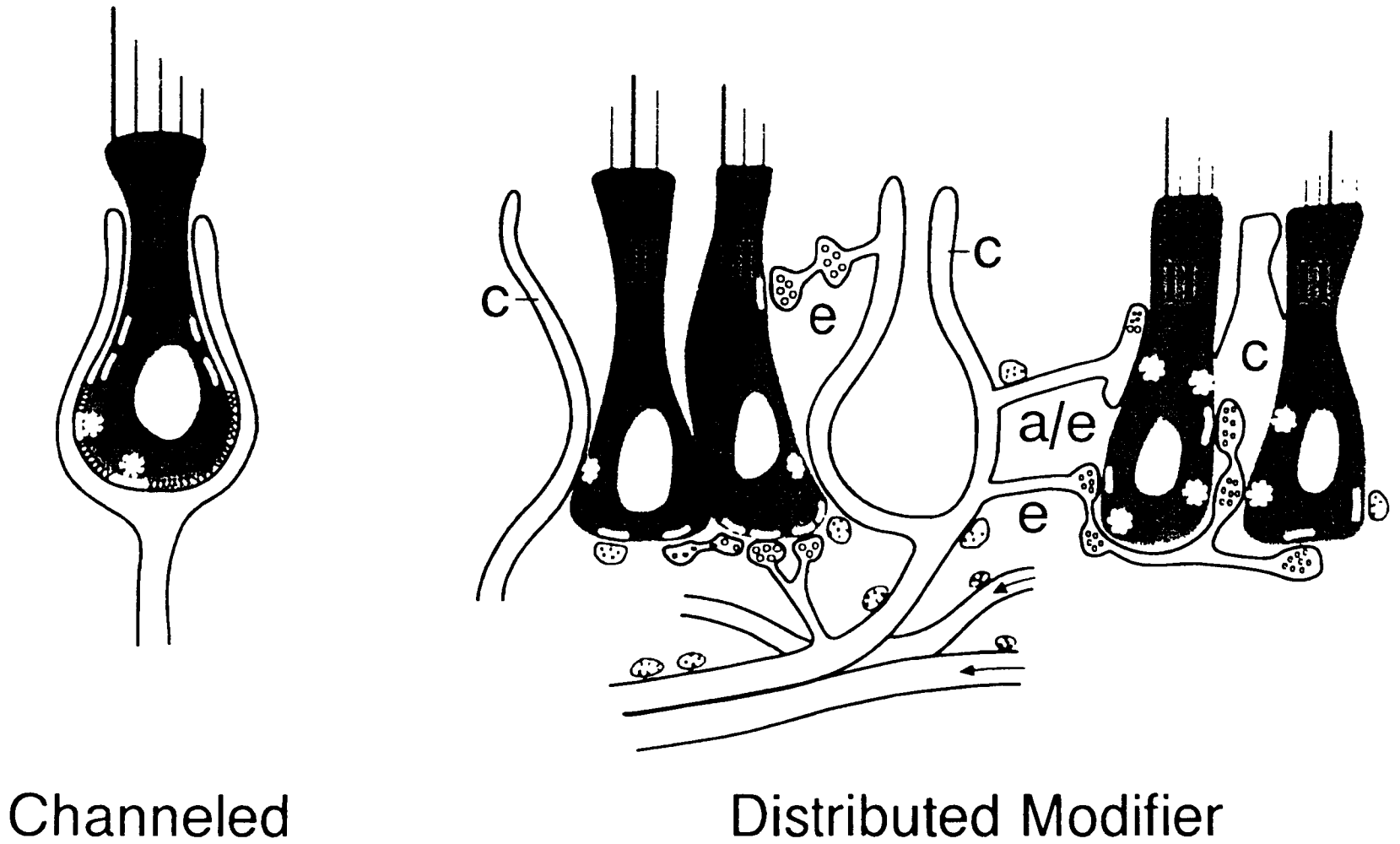

Figure 1. This diagram illustrates the two circuits, highly channeled (left) and distributed modifying (right) present in the vestibular macula. In the channeled circuit, input coming to the type I cell (I) is transduced and transmitted only to the calyx (C) nerve ending. All other parts of the macular neural network belong to the distributed modifying (modifier) circuit. Input to type II cells (II), once transduced, is subject to modification from calyceal and nerve fiber feedforward collaterals (e, efferent and a/e, mixtures of afferent and efferent morphologies) and to biasing from other vesiculated boutons (button-like endings, unlabeled). Type II cells distribute their output to more than one calyceal terminal by directly synapsing with a calyx (asterisk, far left, distributed modifying circuit) or by afferent collaterals (only an a/e collateral is drawn here). This feedback modifies the output that is sent from the macula to the central nervous system Arrows (lower center) indicate the direction of output flow. In the drawing, asterisk-like structures indicate afferent synapses and rod-like structures represent subsynaptic cisterns (see text).