

From Spreading Depression to Spatial Cognition

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Summary

The Laboratory of Neurophysiology of Memory started its existence in 1954 by systematic research into spreading depression of EEG activity of laboratory rodents and by the use of this remarkable phenomenon as a functional ablation method in behavioral research. Its main contributions were in the study of memory formation and consolidation, interhemispheric transfer, motor learning, conditioned taste aversion and spatial orientation and navigation. In the last five years it concentrated on navigation of rats in multiple reference frames, on electrophysiological evidence for the role of hippocampal place cells support of behavior in such dissociated frames, on the analysis of idiothetic and allothetic forms of navigation and on the mathematical methods allowing assessment of the contribution of goal directed locomotion to place cell activity. The methods used in spatial memory research in rats were used for examination of human subjects in a laboratory equipped with a tracking system for humans in the hospital Homolka. Animal models of Alzheimer disease were studied in transgenic mice with the human gene for the beta amyloid precursor protein.

Key words

Spreading EEG depression • Spatial memory • Place cells • Hippocampus • Alzheimer's disease

Historical introduction

The Laboratory of Neurophysiology of Memory belongs to the oldest research units of the Institute of Physiology ASCR in Prague. Its history is reviewed in more detail by Bureš (2003). It was informally started 50 years ago by publication of two papers on spreading depression (SD) of EEG activity (Bureš 1954a,b), reporting the possibility to elicit this remarkable phenomenon in non-anaesthetized rats. This finding stimulated the rather ambitious project to use local blockade of the depressed brain regions as a reversible functional ablation procedure (Burešová 1956, Bureš *et al.* 1958) and to organize a research group dedicated to this task. Such unit was officially established in 1958 as

the Laboratory of Physiology of Central Nervous System with Jan Bureš, Olga Burešová, Jiří Křivánek, Eva Fífková and Tomáš Weiss as the founding members. The method was widely used in the fifties and sixties to achieve reversible decortication for investigations concerned with the formation of localized engrams (Bureš and Burešová 1960a), analysis of their stability, accessibility and migration (Bureš and Burešová 1960b) and disruption of the memory consolidation process (Bureš and Burešová 1963).

In the late sixties this group pioneered research into the nature of network connectivity underlying classical conditioning at the level of single neurons (Bureš and Burešová 1967) by using electrical or iontophoretic stimulation of the recorded cell as the

unconditioned stimulus. In the early seventies, the laboratory concentrated its efforts on additional behavioral models, conditioned taste aversion (Burešová and Bureš 1973) and motor learning (Dolbakyan *et al.* 1977) and its name was changed to the Laboratory of Neurophysiology of Memory.

During the last two decades recognition of the importance of animal models of declarative memory has oriented the laboratory to spatial memory research (Bureš and Burešová, 1990). Relevant contributions concerned methodological development in this field (two-level radial maze, aversively motivated radial maze, on demand platform in the computerized water maze) and the role of neocortex and hippocampus in the mechanisms of spatial orientation.

Results of the above research form the bulk of almost 500 primary articles and chapters and three monographs (Bureš *et al.* 1974, 1988, 1998) published from 1949 to 2003. Throughout its 50-year-long history the laboratory served as training center hosting more than 100 graduate and postdoctoral students and visiting scientists from 27 different countries, who coauthored about 50 % of its publication output. The side products of the teaching activities were several books on neuroscience methods (Bureš *et al.* 1960, 1976, 1984) which appeared in repeated English editions and were translated into Russian and Chinese.

Present state

In the last five years, the research of our laboratory has concentrated almost exclusively on spatial memory of rats and mice while spreading depression, conditioned taste aversion, and motor learning have gradually been phased out. The inaugural PNAS article was an important publication for this period (Bureš *et al.* 1997). It formulated the assumption that place cells participate in navigation behavior and verifying it by experiments making it possible to record simultaneously place cell activity and place navigation. In the place avoidance task the rat foraging for food dispersed over a metal arena was punished by mild foot shock for entering a to be avoided region defined either in the coordinate system of the room (room frame) or of the arena (arena frame). When the arena was stable, both systems overlapped and yielded identical tracks. The rat rapidly learned a passive avoidance of the punished sector and concentrated its foraging to the safe part of the arena even when the shock was disconnected.

An interesting situation arises when the arena is made to slowly rotate at 1 rpm (Fenton *et al.* 1998). A trained rat is now exposed to an ambivalent state that may sometimes require different responses. It may be far from the part of arena floor, which was associated with shocks during pre-training in the stationary situation, but at the same time arena rotation may bring the rat into the punished room frame location. After 10 to 20 s the above conditions reverse: the rat is out of the dangerous zone according to its room frame position but inside it according to its arena frame position. Strong passive avoidance formed on the stable arena forces the rat to avoid two places: the room frame defined zone of punishment (e.g. the North-East sector of the arena) and the arena frame defined part of the floor delivering shocks. In the absence of punishment this “double place avoidance” extinguishes after 2 to 3 sessions, but can be changed into a permanent response, when the foot shock is applied as soon as the animal enters either the room frame-defined or the arena frame-defined sector of its surface. In the first case, the task cannot be solved by passive avoidance, because rotation of the arena would eventually transport the rat into the punished sector. Thus the rat has to move against the rotation of the arena and superimpose this active avoidance on the foraging in the safe part of the arena. In the second case, when the rat is punished for entering a specific segment of the arena floor the task can still be solved by passive avoidance. Finally, it was possible to punish the animal both for entering the room frame defined and the arena frame defined regions. This means avoidance of two different places on the rotating arena.

The passive avoidance run without foraging is not very suitable for place cell recording because it often elicits reduced activity in the parts of the arena most remote from the punished sector. From this point of view, the active avoidance on rotating arena is preferable because it forces the animal to move in circular paths around the center of the arena, but most of these trajectories are close to the periphery of the arena and are too narrow to represent standard firing fields. This disadvantage is absent in the appetitive place preference task (Rossier *et al.* 2000). Rats are trained to find a room frame or arena frame-defined place on the arena and stay there for 1 s. This triggers delivery of a food pellet to a random location on the arena. To get the food the rat has to leave the trigger point and search the arena. After the pellet has been found, the animal must return to the trigger point to release another one. The advantage of this

arrangement is that the whole surface of the arena is freely accessible to the foraging rat, which spends most time (more than 90 %) in random search of the invisible pellet. The straight goal-directed runs account for only 5 % of the 30-min session. The place preference task combines the foraging task routinely used for plotting firing fields of hippocampal place cells with navigation to a hidden location corresponding to the trigger point activating the feeder. In this way it is possible to verify the assumption that navigation requires activity of place cells implementing the cognitive maps that are presumably indispensable for successful navigation.

First results obtained with this method (Zinyuk *et al.* 2000) showed that in rats with long foraging

experience the most firing fields (58 %) recorded on stable arena dissipate on rotating arena. On the other hand, most firing fields (78 %) recorded in rats trained in the place preference task remained preserved during rotation of the arena. The fact that the rats were trained to navigate to a room frame-defined location on rotating arena was reflected in the ratio of room frame-defined and arena frame-defined firing fields which was 3/2 in foragers and 12/3 in navigators. The above results are consonant with the assumption that navigation to a room frame defined goal needs a support of room frame-dependent firing fields. Figure 1 shows results of a similar place cell activity recording performed during double place avoidance task (Klement *et al.* 2004).

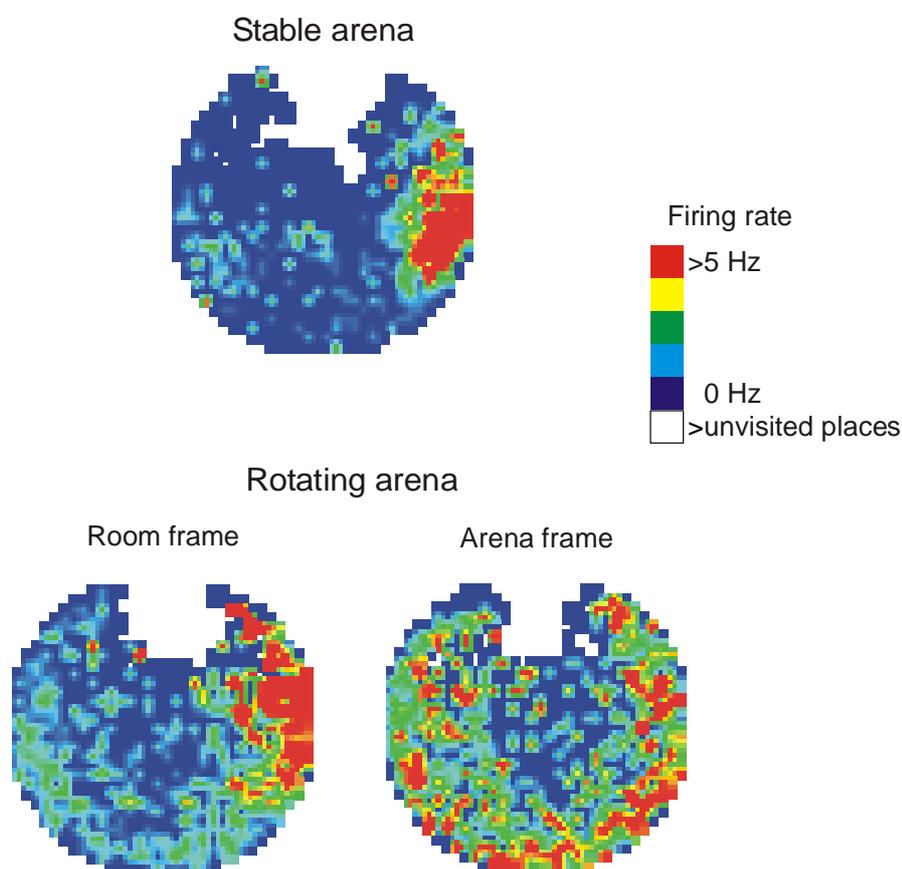


Fig. 1. Place cell activity correlates of a double place avoidance experiment. **Above:** distribution of spikes recorded during a 15-min session from a CA1 pyramidal cell of a rat trained to avoid the northern sector of the stationary arena. Efficient avoidance is indicated by the white (unvisited) part of the arena. Note the well delineated firing field at the eastern margin of the arena. **Below:** the same unit on the rotating arena when the rat was punished for visiting the segment of the arena pointing to the north and for visiting the part of the floor which was punished on the stable arena. The firing maps show cumulative spike activity generated by the particular unit during repeated visits of the rat in various positions plotted either in the room frame or in the arena frame. Note that the firing field is well preserved in the room frame but it fully dissipates in the arena frame. This indicates that this unit may help the rat to recognize its position relative to the punished northern sector but its activity does not help the rat to find the safe sector of the arena floor.

The finding that the arena frame dependent firing fields remain preserved in darkness suggested that they are supported by idiothetic and tactile or olfactory intramaze cues. This possibility was examined in experiments in which parts of arena not contacting the animal were shuffled so that the cues on arena floor were destabilized and made irrelevant for navigation (Stuchlík

et al. 2001). Active place avoidance in the darkness allowed the animal to stay outside the prohibited sector of the rotating arena for 10 to 20 min. This performance mediated by intramaze cue supported idiothetic deteriorated to 2 min when the surface of the arena was shuffled, probably because the cumulative errors of path integration could not be corrected by intra-maze

allothesis. Similar result was obtained when the arena was covered by 2 cm layer of water obliterating the local tactile and olfactory cues so that it was changed into a wading pool.

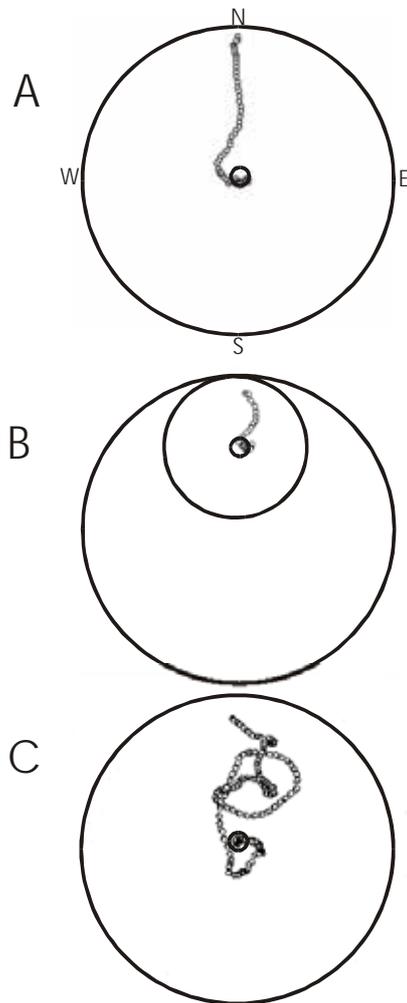


Fig. 2. Locomotion tracks tell what was on the mind of the subject solving the navigation task irrespective of whether it is an animal or a human being. This can be illustrated in a series of place navigation experiments in the water maze. The rat is trained for 5 days to swim 8 times per day from the wall of the small pool (diameter 90 cm) to the underwater escape platform in the pool center (B). Similar training continues to the center of the large pool (diameter 190 cm) (A). After both tasks are learned to asymptotic performance the animal is exposed to a situation requiring decision between several alternatives. It is placed into the pool in total darkness without knowing whether it is in a large pool, a small pool or a pool of completely different shape and size. Its track (C) is an eloquent expression of its changing assessment of the situation. It assumes first that it was placed into the small pool and starts its search in the expected location of the escape platform. When it finds nothing there, the rat rejects the small pool hypothesis and assumes that it is in the large pool and continues its centripetal swim to the presumed center of the large pool, where it eventually finds the goal (Wittnerová and Bureš 2004).

Critical role of hippocampus in place navigation has been demonstrated by lesions and functional ablation (Fenton and Bureš 1993). Whereas bilateral blockade is required for disruption of the water maze escape behavior or of the place avoidance task on stable arena, spatial behavior requiring dissociation of two reference frames is disrupted already by unilateral blockade elicited by injection of 5 ng of tetrodotoxin (TTX) into one dorsal hippocampus. A simple version of such behavior is avoidance of a room frame defined sector (e.g. North-East) of the rotating arena, which requires the rat to move against the movement of the arena in order to avoid mild foot shock (Cimadevilla *et al.* 2001) This active allothetic place avoidance (AAPA) task is disrupted by hippocampal TTX injection applied before training (blockade of acquisition), immediately after training (blockade of memory consolidation) or before retrieval testing (blockade of memory readout). It seems that AAPA sensitivity to disruption is due to the necessity to disregard one of the standard reference frames (arena frame) and pay attention only to the other one (room frame).

Sequential dissociation of memories activated by a rat solving complex navigational problems can also be demonstrated by the trajectory of the animal's movement in the water maze (Fig. 2). When the initial goal was not found, the search was directed to the subsequent goal showing a well conceived cognitive plan. Experiments of this type will be used in the research of electrophysiological correlates of the neural representation of the goal-directed locomotion.

The room frame and arena frame are not the only reference systems governing the spatial behavior of animals. In the nature animals must follow biologically important moving objects the locomotion of which may interfere with their access to food, endanger their pups or limit their home range. A simple model of predator avoidance (Paštálková and Bureš 2001) uses two rats, carrying different LED markers, engaged in foraging on a circular arena. Their locomotion is recorded with a computerized tracking system which delivers to one rat (the prey) mild foot shocks when it is closer than 20 cm from the other rat (the predator). In the no shock habituation period, the two rats prefer to be close together, about 10 to 15 cm from each other. After the shock is introduced, the prey rat rapidly learns to stay away from the predator rat, i.e. to keep a safe distance from the approaching predator. After 20 sessions the modal distance between the two rats increases to 40 cm.

The prey rat receives during a 20 min session only a few shocks, most of which were administered during sudden rapid approach of the predator to the inattentive prey. More predictable results can be obtained when a robot is

used instead of the predator, because it uses linear paths of constant velocity. Figure 3 shows the robot and the rat on arena and gives examples of the rat's reactions to the approaching robot.

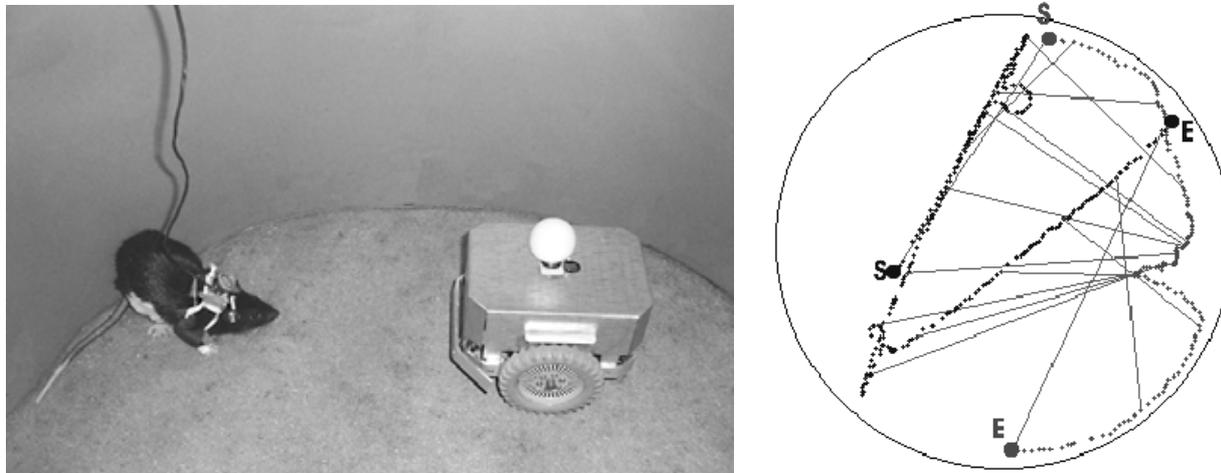


Fig. 3. Rat-robot avoidance. **Left:** The rat carefully observes the robot waiting at a distant section of the arena wall. **Right:** Tracks of the robot (straight) and of the rat (tortuous). The points indicate positions of the robot and of the rat at 100 ms intervals. The thin lines connecting the robot points and rat points indicate their mutual positions at selected times. The letters S and E indicate the positions of the robot and rat at the start and the end of the record. Note that the rat was immobile at the N section of the wall while the robot started to move from SW to N. When the rat-robot distance approached the shock delivery level, the rat moved to E and stayed there while the robot returned to SW. After the robot stopped at the wall, turned around and started to move to NE, the rat assessed the direction of the robot's next movement and made another rush to by-pass the robot at a safe distance and assumed a position at S (Svoboda and Telensky, unpublished results).

In a model of appetitive cooperation (Svoboda *et al.* 2003) two rats learn an operant approach-withdrawal task. When they approach to less than 10 cm to each other, the tracking system activates the feeder which delivers a pellet onto the arena. The rats disperse to find the food and to increase their mutual distance to more than 50 cm. When this condition is satisfied, the feeder is loaded with another pellet and prepared to deliver it when the rats come again together. After ten training sessions, the rats learned to synchronize their activities and perform a kind of dance, in which the approach-trigger pellet delivery was followed by departure in different directions and subsequent pellet search. The rat, which has found the food, estimates the distance from the other rat and when it is too short, it tries to increase it. The other rat is either continuing the search or cooperating by locomotion in opposite direction. When at least one rat decides that the critical distance has been reached, it will start the approach run which often coincides with an opposite movement of the partner rat. Whereas in the predation model only the prey learns to move in the reference frame formed around the predator, in the spatial cooperation task both animals can contribute to its

successful solution by assuming proper positions in the reference frame formed by both animals.

Several papers were devoted to place recognition during passive transport of the animal through familiar environment. Whereas in the AAPA task the passive transport of the immobile rat toward the shock sector of the room elicited recognition of the approaching danger and triggered protective locomotion, in the new experiments subject's recognition of a definite position in the environment indicated availability of reward and was manifested by increased activity in an operant task. In the first study (Klement and Bureš 2000) a rat in a Skinner box placed on the periphery of a rotating arena was trained to observe the experimental room through the transparent centrifugal wall of the box and to bar press when the long axis of the Skinner box passed through a 60° sector of the circular trajectory. The rats rapidly learned the task, started to bar press when the Skinner box approached to -30° from the reward sector, ceased bar pressing when eating the first pellet and when passing through the segments of the trajectory opposite the target zone. Under extinction conditions bar pressing culminated throughout the passage of the Skinner box

across the reward sector, but stopped shortly after the Skinner box had left the rewarded part of the trajectory.

The next step of the place recognition research addressed the question whether passive transport of the observer is an essential prerequisite of place recognition. Paštálková *et al.* (2003) placed the rat into a Skinner box, the transparent front wall of which overlooked a slowly rotating scene surrounded by a black curtain. The rat could observe the scene and bar pressing was only rewarded when the configuration of objects forming the scene assumed a specific position relative to the Skinner box. Rats learned in 20 sessions to concentrate bar pressing into a -30° angle anticipating the reward orientation and into the subsequent -15° segment of the reward zone. An important feature of this experiment is that the Skinner box was immobile and that absence of vestibular signals indicated to the animal that the movement of the scene was not produced by self-motion. When the conditions of the experiment were inversed (Skinner box rotated around the stationary scene), rats learned to recognize the rewarded scene orientation as efficiently as they did when observing the rotating scene.

Theoretical and methodological investigations were performed in addition to the experimental studies. The spontaneous firing activity of the place cells reflects the position of an experimental animal in its arena. The firing rate is high inside the firing field and low outside. It is a generally accepted concept that this is the way in which the hippocampus stores a map of the environment. This well-known fact was reinvestigated (Fenton and Muller, 1998) and it was found that while the activity was highly reliable in position, it did not retain the same reliability in time. The numbers of action potentials fired during different passes through the firing field were substantially different (overdispersion). This overdispersion indicates that place cells carry information in addition to position. We have presented a mathematical model based on a doubly stochastic Poisson process, which is able to reproduce the experimental findings (Lánský and Vaillant 2000, Lánský *et al.* 2001). This model enables us to propose specific statistical inference on the experiments in order to verify data and model compatibility. Furthermore, it permits to speculate about the neural mechanisms leading to the overdispersion in the activity of the place cells. Namely, the statistical variation of the intensity of firing can be achieved, for example, by introducing a hierarchical structure into the local neural network.

The informational content of the location-specific discharge of rat hippocampal cells is usually quantified by an average for the entire behaviorally accessible space. In contrast to this "global" information measure, we considered information that can be obtained from "local" spike counts at each position. The properties of these local information measures were illustrated on simulated data of location-specific spike counts. Next, the place cell data recorded from rats foraging in a cylindrical arena with two cue cards on its walls were analyzed. It was shown that information at the centers of firing fields is higher for fields nearer to the cues. Neither firing rates nor "global" information measure detects differences between fields near and far from the cues. Thus, analyses of the location-specific information provide a new tool for studying the location-specific activity. We found that while a rat is foraging in an open space, this additional information may arise from a process that alternately modulates the inputs to place cells by about 10 % with a mean period of about a second. It is argued that an additional signal carried by place cells is information about which navigation mode is currently being used (Olypher *et al.* 2002b, 2003).

While the bulk of our research was devoted to development of methods suitable for investigation of basic aspects of spatial cognition of animals, we have also examined possible application of our methods in clinically oriented studies. With the support of the McDonnell-Pew and GACR grants a neuropsychological laboratory equipped with a dry arena for navigation testing of human subjects and with a computerized tracking system was established in the hospital Na Homolce and used for examination of spatial memory of patients after hippocampal neurosurgery of intractable epilepsy (Bohbot *et al.* 1998). A battery of navigation tests was developed and used for examination of healthy people (Štěpánková *et al.* 2003), neurological and psychiatric patients as well as for evaluation of similar virtual tests, intended for early diagnostic of memory deficits heralding the first stages of Alzheimer's disease and other neurodegenerative disorders.

In collaboration with USA and Finland we examined spatial memory of transgenic mice expressing the human beta amyloid precursor protein (beta-APP) and demonstrated significant deterioration of water maze performance even in animals lacking amyloid plaques (Koistinaho *et al.* 2001). This research continues in pharmacological models of Alzheimer's disease in mice which develop several months after intracerebral

injection of beta amyloid precursor protein significant impairment of navigation behavior. It is hoped, that administration of antioxidants, anti-inflammatory drugs or drugs preventing aggregation of beta-APP into plaques may show directions for future causal therapy of this degenerative process.

Perspectives

Beside traditional experimental studies, we shall also apply theoretical and computational approaches in order to contribute to better understanding of information processes performed by neurons and neuronal nets. We will be primarily concerned with mechanisms that are crucial in information transfer from input activation to output signaling. The primary tool will be mathematical analysis based on the theory of stochastic processes and differential equations, supplemented by computer simulations.

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Currently most of the computational algorithms used in artificial systems are deterministic to ensure absolute reliability of the computational process. On the other hand, there is increasing evidence that the computational algorithms used by nervous systems are stochastic, which at the risk of marginal decrease of reliability are far more efficient than the deterministic ones. We will investigate these stochastic principles of information coding in nervous system and on the basis of the achieved results new computational algorithms for man-made devices, like computers or artificial sensors, can be proposed and/or computational processes in living systems influenced.

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Reprint requests

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