Włodzisław DUCH[*]

THERAPEUTIC IMPLICATIONS OF COMPUTER MODELS OF BRAIN ACTIVITY FOR ALZHEIMER DISEASE.

Neural models of large-scale brain processes help to explain many features of neuropsychological syndromes and psychiatric disease. Two associative memory models useful to understand some aspects of cognitive impairments in Alzheimer disease are discussed. The first model is based on the synaptic deletion and compensation while the second on the synaptic runaway phenomenon. The models seem to be complementary, explaining different types of Alzheimer disease. They allow to draw several therapeutic suggestions that may help to slow down the development of the disease in its early stages.

1. INTRODUCTION

Neural networks and other computational intelligence models inspired by our understanding of the brain are widely used for medical diagnostics support, signal and image analysis, monitoring, search for carcinogenic agents and other data analysis tasks. In these applications neural networks compete with statistical, machine learning and other mathematical techniques. A qualitatively different area of neural modeling focuses on understanding of physiological responses of single neurons or small groups of neurons. Sophisticated biophysical models of compartmental neurons provide information directly related to neurophysiological parameters measured in experiments. Already in 1994 Callaway and collaborators modeling reaction times to different drugs stated: "Neural network models offer a better chance of rescuing the study of human psychological responses to drugs than anything else currently available" [3]. Classical methods of psychiatry and neuropsychopharmacology are restricted to observations of correlations between behavior and physiological responses of the organism to medical treatments. They do not provide any insights into the mechanisms leading to neuropathological behavior at the neural level. Simulations may provide understanding of neural responses to biochemical substances acting at the ionic channel levels.

A third area of neural modeling that slowly grows in importance concerns understanding of the large-scale processes going on in the brain. Brain processes are very complex and therefore neural networks based on biophysical, spiking neural models cannot be used for large-scale modeling. Simulations should capture casual relations between activity of brain

---

[*] Katedra Metod Komputerowych, Uniwersytet Mikołaja Kopernika, ul. Grudziądzka 5, 87-100 Toruń, Poland
http://www.phys.uni.torun.pl/~duch

structures and their general neuroanatomical features, in particular influence of lesions and neuropathological changes on changes of normal behavior and cognitive performance.

It is not *a priori* clear that simplified neural models will be sufficient to capture such casual relations (cf. [6] discussing hierarchical approach to modeling of brain functions at different levels of complexity). Convergence of the modeling process could be too slow to make them useful; for example some pathological effects could appear only in models based on complex integrated-and-fire spiking neurons. Fortunately there are some indications that the qualitative behavior of complex models based on spiking neurons [27] may also be obtained in simplified neural models [21]. Thus there is a chance that simple neural models may help to understand neurological and neuropsychological syndromes, providing some insight into the source of the pathologies and understanding of the effects of therapeutic procedures. A review article [23] and two books [18],[21] summarize results of such efforts to understand memory and language impairments, psychiatric disorders, Alzheimer and Parkinson disease, epilepsy and other neurological problems (see also [7]).

Brain simulations can complement traditional techniques in several ways. They provide insights into possible causal relations, allow for a full control of all aspects of experiments, they are inexpensive and are not restricted by ethical considerations. Such simulations are still in the initial stage of their development. They are usually based on oversimplified recurrent neural models with two-state neurons or feedforward models wit graded sigmoidal-response neurons. More biologically faithful networks based on simple spiking neurons should soon be introduced in such simulations (cf. [1], [7]).

In this article several therapeutic suggestions resulting from computational models of Alzheimer disease are made. Although several computational models of this disease have been published in the last decade few conclusions were drawn. Two such models are introduced here and directions for their further extensions are outlined. Assuming that computational models reflect real neural mechanisms leads to some therapeutic suggestions that should slow down the degeneration of synaptic connections and thus the development of the disease, at least in its early stages.

2. ALZHEIMER DISEASE

Alzheimer disease (AD) is the most common form of dementia gradually leading to a global cognitive dysfunction and death. The earliest symptoms involve memory degradation, both for learning new things and recalling known facts. This is followed by degradation of language skills, poverty of thoughts and associations, intellectual rigidity, loss of initiative and interest, disturbances in motor and executive functions. In advanced stages judgments are impaired, psychotic features may appear (such as paranoid delusions), and

personality is disintegrated. Prominent atrophy of predominantly frontal and temporal cortex is observed in neuroimaging studies and large amounts of senile plaques and neurofibrilliary tangles are found in the brain.

Although new discoveries related to possible AD causes are reported every month real causes and pathogenesis is still unknown and definitive diagnosis is made only after autopsy. The disease is always progressive, without remissions, and with great variability: life expectancy ranges between 1 and 25 years. Only a few drugs are available for Alzheimer treatment (for example Cognex and Aricept). They do not slow the progress of AD but are aimed at improving and stabilizing memory and cognitive state of the patient by helping to retain and utilize the neurotransmitter acetylcholine.

3. SYNAPTIC DELETION AND COMPENSATION MODEL

Two models of pathogenesis of AD have been proposed, both focusing on synaptic processes and their role in memory maintenance. The "synaptic deletion and compensation" model of Horn *et al.* [12] has been developed further by Ruppin and Reggia [25]. It is based on experimental observation that in the brains of AD patients the density of synaptic connections per unit of cortical volume decreases with progress of the disease, while the remaining synapses increase in size, perhaps trying to compensate for synaptic deletion. In feedforward neural models pruning is frequently used to delete weak synaptic connections at the expense of growing values of the remaining connections, necessary for realization of strongly non-linear behavior. How do these two processes – synaptic deletion and compensation – influence memory deterioration? What are the best compensation strategies that may slow down this process?

The simplest associative memory models are based on Hopfield networks. Assuming that the synaptic matrix W_{ij} determines the strength of connections between neurons i and j, each of the N neurons has threshold Θ_i for firing and is in one of the two states $V_i = \pm 1$, the external inputs are E_i, the simplest network dynamics is defined by

$$V_i(t+1) = \operatorname{sgn}\left(I_i(t+1)\right) = \operatorname{sgn}\left(\sum_{j=1}^{N} W_{ij}V_j(t) - \Theta_i + E_i\right) \tag{1}$$

Memory patterns are point-attractor stationary states of this dynamics corresponding to the minima of the energy function:

$$E(V) = -\frac{1}{2}\sum_{i \neq j}^{N} W_{ij}V_iV_j \tag{2}$$

The number of correctly memorized patterns (V_i vectors in the stationary states) in the fully connected Hopfield autoassociative memory model is $0.14N$. Deleting synaptic connections will cause forgetting of some patterns and distortion of others. Assume that a certain percentage d of synaptic connections is randomly deleted (zeroed in the model). The remaining connections may get stronger, $W'_{ij} = c(d,k)W_{ij}$, where the compensating factor $c(d,k)>1$ is a multiplicative factor depending on d and a parameter $k(d)$, called a compensation-strategy parameter, that is fitted to experimental data. Horn *et al.* [12] proved that taking $c(d,k) = dk/(1-d)$ significantly slows the memory deterioration. Depending on the compensation-strategy $k(d)$ after the same evolution period various degrees of deterioration are obtained. Thus failure of proper compensation for synaptic deletion may explain why patients with similar density of synaptic connections per unit of cortical volume show quite different cognitive impairments.

Hopfield networks require non-local learning and thus are not plausible from the neurobiological point of view. Ruppin and Reggia [25], Horn *et al.* [11], and Ruppin *et al.* [24] improved this model in several ways. Similar conclusions were obtained from other memory models (Willshaw, Hebbian, modified Hopfield networks), with over 1000 neurons used in simulations. Activity-dependent Hebbian models allow to study memory acquisition. Even in such simple models faster forgetting of more recent memories can be observed. This effect (called 'Ribbot gradient' in psychological literature) has been known since a long time in retrograde amnesia [16] and has also been observed in Alzheimer's patients. Temporal gradients of memory decline and several other experimental phenomena characterizing memory degradation in AD patients have been recreated in Hebbian models. Local compensatory mechanisms are sufficient [11] to maintain high capacity of the memory – there is no global error function that is optimized. The way deletion and compensation factors change in time has an influence on the final performance of the network. Cognitive impairments are therefore history-dependent in this model, leading to a broad variability of the AD symptoms despite similar levels of structural damage of the brain.

4. SYNAPTIC RUNAWAY MODEL

Hasselmo [9],[10] has focused on a different phenomenon observed in associative memory attractor networks. Storing a new pattern the activity of such networks goes through similar patterns and if certain memory capacity is exceeded interferes with them. This interference creates an exponentially large number of patterns that the system tries to store, bringing in effect pathological, exponential growth of the number and the strength of synaptic connections. This is called the "synaptic runaway" effect. If it does exist in real biological neural networks it should lead to very high metabolic demands of hyperactive

neurons, demands that in the longer time period cannot be satisfied. As a result toxic products should accumulate and neurons should die creating senile plaques.

Synaptic runaway may arise due to excessive memory overload, reduced synaptic decay or a low level of cortical inhibition. If external strength is large enough or if internal inhibition is sufficiently strong synaptic runaway may be prevented, but beyond critical storage capacity it is unavoidable. This model explains some intriguing experimental facts in AD:

- Enthorinal regions (involved in recognition memory) suffer greater degradation than cortical areas. These regions lack internal inhibition present in cortical modules.
- Cholinergic innervation in dentate gyrus in AD patients is sprouting.

Acetylcholine is a neurotransmitter that has complex functions. In dentate gyrus it does not influence external afferent synaptic transmission but it selectively suppresses the internal excitatory transmission, effectively increasing internal inhibition (experiments that proved this were inspired by theoretical considerations of Hasselmo [9]). Thus sprouting of cholinergic innervation may reflect the brain's attempts to stop the synaptic runaway by increasing internal inhibition.

Both these neural models complement rather than compete with each other. There may be at least two routes to development of Alzheimer Disease: synaptic loss and insufficient compensation should lead to AD cases with little structural damage of the brain, while synaptic runaway should eventually lead to death of the hyperactive neurons and significant structural damage. Both type of AD cases are indeed known.

5. THERAPEUTIC SUGGESTION FOR THE EARLY AD

Can we draw any therapeutic suggestions from these theoretical considerations? If synaptic runaway processes and failure of proper compensation are the cause of rapid memory impairment several suggestions can be made. These suggestions may be tested experimentally, although in view of high variability of the AD symptoms evaluation of efficiency of any new therapy is always difficult.

- Minimize new memory load.

Minimization of new memory load may involve a simple and regular daily routine and minimization of the number of new facts or items that should be remembered. Heavy memory load may contribute to the rapid progress of synaptic deletion. Patients should not be

allowed to follow visual, auditory or printed stories such as the TV news, soap operas or TV series requiring remembering of many new facts, names and interpersonal relations. Sedatives may have positive effect on the memory overload because in the absence of strong emotions the limbic neuromodulatory systems does not increase synaptic plasticity, preventing formation of new memories.

- Strengthen the old, well-established memory patterns.

A significant portion of time should be spent on recalling the stories and facts of patient's life, perhaps with the help of family members. These memories form a skeleton of the concept of 'self'. Antonio Damasio [5] expressed it this way: "... the endless reactivation of updated images about our identity (a combination of the memories past and planned future) constitutes a sizable part of the state of self as I understand it". These memories are probably based on strong synaptic connections between cortical columns, with little involvement from limbic inputs required by more recent memories (cf. Murre [16],[17]). Strengthening old memory patterns related to one's self is very much in line with the "Self-Maintenance-Therapy" (Selbst-Erhaltungs-Therapie) proposed by Romero [20] on quite different theoretical grounds and used in treatment of the early stages of Alzheimer's disease. In this therapy patients are required to tell stories recalling various events of their life as means to strengthen their self.

Compensation effects should selectively reinforce strong synaptic connections. This may be achieved through a combination of Self-Maintenance-Therapy (perhaps including family members) with drugs that allow for a short period of emotional arousal increasing synaptic plasticity.

- Simplify the brain dynamics to avoid memory interference.

Formation of new memory patterns or activation of existing memories requires repetitive high-frequency reverberations in the neocortex. For example, hearing and recognizing a real word leads to a noticeable rise in the EEG frequency, in comparison to a pseudoword, i.e. a meaningless combination of phonemes [19]. Integrated electrical activity of cortical columns gives a measure of the overall activity of the brain. The power spectrum obtained from the multi-electrode EEG measurements should allow, in the limit of a large number of electrodes, to evaluate this energy. In analogy to thermodynamics of systems far from thermal equilibrium one could thus define the "brain temperature" and think about the synaptic runaway processes as overheating the system.

'Cooling the brain', or reducing the average brain temperature, should decrease the synaptic runaway and synaptic deletion processes. It may be achieved with the help of biofeedback, yoga meditation or other deep relaxation techniques. In particular the alpha-

biofeedback is aimed at reducing the average EEG frequency [4], or achieving the 'alpha relaxation state'. Such mental activities as mantra repetition, chanting, visualization or contemplative absorption should lower the brain temperature, stopping the background thoughts and other processes that may lead to the synaptic runaway. Therefore in the early stages of AD it may be worthwhile to experiment with various relaxation techniques to slow down the development of the disease.

More detailed therapeutic suggestions related to an optimal compensation require more complex associative memory models. The existing models should be extended in several directions. Human memory involves interactions between hipocampal formation, neocortex and neuromodulatory systems, regulating plasticity of synapses depending on the emotional contents of the situation [2],[15]-[17]. Although such models have been created few years ago computational simulations have started only quite recently (Murre, private information). More realistic memory models that would allow studying the influence of different neurotransmitters on the inter-module inhibition and between-module excitation should help to evaluate potential benefits of new drugs. Models based on simplified spiking neurons [13] are needed to make direct connections with neurophysiology. Many associative memory models based on simplified models of spiking neurons have been created recently and should be used in a near future to study the Alzheimer disease and other memory-related diseases.

6. Conclusions

Small number of assumptions and simple neural models allow for qualitative understanding of experimental observations in case of Alzheimer disease and many other neurological and psychiatric disorders. Although therapeutic suggestions drawn here from AD models are speculative they may easily be tested. Computer simulations appeared only quite recently as tools for modeling real brain processes. In view of the great complexity of the brain and lack of detailed understanding of its functions skepticism towards such models may seem to be justified. There are many fundamental problems related to the convergence of computational models, hypothesis on which they based, selection of minimal neural models that capture relevant phenomena and are still amenable to computer simulations. Surprisingly, even very simple neural models of associative memory show a number of features that reflect many properties of real biological memories known from cognitive psychology [14]. The neural modeling process may not be so difficult after all.

Another interesting – and perhaps easier – area of neural modeling concerns reorganization processes following focal damages of neocortex (stroke, lesions) and damages to afferent pathways (amputation of limbs). Some therapeutic suggestions may be offered for faster recovery of sensorimotor competence after stroke [22], reduction of pain in phantom

limb phenomena [26] and even such strange neuropsychological syndromes as the body dysmorphia.

Neural models provide a new level of reasoning about brain diseases, level that cannot be adequately described in the language of psychiatry or psychopharmacology [6]. They show how difficult it is to draw conclusions about causal mechanisms if only behavior is observed. Although there are many computer programs for neural simulations only very few can be used for simulations of real memory processes. The situation is even worse on the hardware side, although the first integrated circuits suitable for "neurophysiological" experimentations have recently been announced [8]. We are at the beginning of a long way leading to understanding of pathologies of brain functions.

REFERENCES

[1] AMIT D.J., BRUNEL N., *Dynamics of a recurrent network of spiking neurons before and following learning*. Network, Vol. 8, pp. 373-404, 1997.

[2] BANQUET J.P, GAUSSIER P, CONTRERAS-VIDAL J.L, GISSLER A, BURNOD Y, LONG D.L., *A neural model of memory, amnesia and cortico-hippocampal interactions*. In [18], pp. 77-120, 1998.

[3] CALLAWAY E, HALLIDAY R, NAYLOR H, YANO L, HERZIG K., *Drugs and human information processing*. Neuropsychopharmacology, Vol. 10, pp. 9-19, 1994.

[4] CRISWELL, E., *Biofeedback and Somatics*. Freeperson Press, Novato, USA, 1995.

[5] DAMASIO A.R., *Descartes' Error: Emotion, Reason and the Human Brain*. Papermac, 1996.

[6] DUCH W., *Platonic model of mind as an approximation to neurodynamics*. In: Brain-like computing and intelligent information systems, eds. S-i. Amari, N. Kasabov (Springer, Singapore), chap. 20, pp. 491-512, 1997.

[7] DUCH W., *Sieci neuronowe w modelowaniu zaburzeń neuropsychologicznych i chorób psychicznych*. Biocybernetyka 2000, Tom 6: Sieci neuronowe (eds. W. Duch, J. Korbicz, L. Rutkowski i R. Tadeusiewicz), chap. II.18, pp. 589-616, 2000.

[8] FUSI S., DEL GIUDICE P., AMIT D.J., *Neurophysiology of a VLSI spiking neural network: LANN21*, NALS group preprint, Univ. Of Rome, 1999, http://jupiter.roma1.infn.it/

[9] HASSELMO M.E., *Runaway synaptic modification in models of cortex: Implications for Alzheimer's disease*. Neural Networks, Vol. 7, pp.13-40, 1991.

[10] HASSELMO M.E., *A computational model of the progression of Alzheimer's disease*. MD Computing, Vol. 14, pp. 181-191, 1997.

[11] HORN D, LEVY N, RUPPIN E., *Neuronal-based synaptic compensation: A computational study in Alzheimer's disease*. Neural Computation, Vol. 8, pp. 1227-1243, 1996.

[12] HORN, D, RUPPIN, E., USHER, M., HERRMANN, M., *Neural network modeling of memory deterioration in Alzheimer's disease.* Neural Computation, Vol. 5, pp. 736-749, 1993.

[13] MAASS W, BISHOP C., *Pulsed Neural Networks*. MIT Press, Bradford Book, Cambridge, MA, 1999.

[14] MCCLELLAND J. L., RUMELHART D.E., eds. *Parallel distributed processing: Explorations in the microstructure of cognition*, Vol. I, II, MIT Press, Cambridge, MA, 1987.

[15] MCCLELLAND, J.L., MCNAUGHTON, B.L., O'REILLY, R.C., *Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory.* Psychological Review, Vol. 102, pp. 419-457, 1995.

[16] MURRE J. M., *TraceLink: A model of amnesia and consolidation of memory.* Hippocampus, Vol. 6, pp. 675-684, 1996.

[17] MURRE J. M., *Implicit and explicit memory in amnesia: some explanations and predictions by the TraceLink model.* Memory, Vol. 5, pp. 213-232, 1997.

[18] PARKS R.W, LEVINE D.S, LONG D, eds. *Fundamentals of Neural Network Modeling*. MIT Press, Cambridge, MA, 1998.

[19] PULVERMUELLER F, PREISSL H, EULITZ C, PANTEV C, LUTZENBERGER W, ELBERT T, BIRBAUMER N., PSYCOLOQUY Vol. 5(48) , 1994. brain-rhythms.1.pulvermueller

[20] ROMERO B., *Self-Maintenance-Therapy (SMT) in early Alzheimer Disease*. European Archives of Psychiatry and Clinical Neuroscience, Vol. 248, pp.13-14, 1998.

[21] REGGIA J. A, RUPPIN E, BERNDT R.S, eds. *Neural Modeling of Brain and Cognitive Disorders*. World Scientific, 1996.

[22] REGGIA J, GOODALL S, CHEN Y, RUPPIN E, WHITNEY C., *Modeling Post-Stroke Cortical Map Reorganization*. In [21], pp. 283-302, 1996.

[23] RUPPIN E, *Neural Modeling of Psychiatric Disorders*. Network, Vol. 6, pp. 635-656, 1995

[24] RUPPIN E, HORN D, LEVY N, REGGIA J., *Computational Studies of Synaptic Alterations in Alzheimer's Disease*. In: J. REGGIA, E. RUPPIN, and R. BERNDT, Eds., *Neural Modeling of Brain and Cognitive Disorders*, World Scientific, 1996.

[25] RUPPIN, E, REGGIA, J., *A neural model of memory impairment in diffuse cerebral atrophy.* British Journal of Psychiatry Vol. 166, pp. 19-28, 1995.

[26] SPITZER M., *Phantom Limbs, Self-Organizing Feature Maps, and Noise-Driven Neuroplasticity*. In [21], pp. 273-282, 1996.

[27] XING J, GERSTEIN G.L, Networks with lateral connectivity. I. Dynamic properties mediated by the balance of intrinsic excitation and inhibition. II. Development of neuronal grouping and corresponding receptive field changes. III. Plasticity and reorganization of somato-sensory cortex. J. Neurophysiology, Vol. 75, pp. 184-232, 1996.