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CLINICAL SIGNIFICANCE OF COMPUTATIONAL BRAIN MODELS IN NEUROREHABILITATION

ZNACZENIE KLINICZNE OBLICZENIOWYCH MODELI MÓZGU W REHABILITACJI NEUROLOGICZNEJ

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S u m m a r y

Despite quick development of the newest neurorehabilitation methods and techniques there is a need for experimentally validated models of motor learning, neural control of movements, functional recovery, therapy control strategies.

Computational models are perceived as another way for optimization and objectivization of the neurorehabilitation. Fully understanding of the neural repair is needed for simulation of reorganization and remodeling of neural networks as the effect of neurorehabilitation. Better understanding can significantly influence both traditional forms of the therapy (neurosurgery, drug therapy, neurorehabilitation, etc.) and use of the advanced Assitive Technology (AT) solutions, e.g. brain-computer interfaces (BCIs) and neuroprostheses [49, 50] or artificial brain stimulation.

There is a necessity of further common interdisciplinary effort of both medical staff and engineers.

S t r e s z c z e n i e

Pomimo szybkiego rozwoju najnowszych metod i technik rehabilitacyjnych istnieje potrzeba tworzenia eksperymentalnie weryfikowalnych modeli motorycznego uczenia się, nerwowej kontroli ruchu, funkcjonalnego powrotu do zdrowia oraz strategii terapeutycznych.

Modele obliczeniowe są uważanie za kolejny ze sposobów optymalizacji i obiektywizacji rehabilitacji neurologicznej. Pełne zrozumienie naprawy struktur nerwowych wymaga modelowania reorganizacji i przemodelowania sieci neuronowych następujących w efekcie rehabilitacji neurologicznej. Lepsze zrozumienie ww. procesów może znacząco wpłynąć zarówno na tradycyjne formy terapii (neurochirurgię, farmakoterapię, rehabilitację neurologiczną i inne), jak również użycie zaawansowanych rozwiązań technologii wspomagających, takich jak interfejsy mózg-komputer i neuroprotezy, jak również sztucznej stymulacji mózgu.

W omawianym obszarze istnieje potrzeba dalszego wspólnego interdyscyplinarnego wysiłku zarówno specjalistów medycznych, jak i inżynierów.

Key words: neurorehabilitation, brain plasticity, computational models
Słowa kluczowe: rehabilitacja neurologiczna, plastyczność mózgu, modele obliczeniowe

INTRODUCTION

Neurorehabilitation remains one of the most important parts of rehabilitation. Articles covering topics of neurorehabilitation constitute 41% of top-cited articles within rehabilitation [1]. Despite quick development of the newest neurorehabilitation methods and techniques there is a need for experimentally validated models of:

- motor learning,
- neural control of movements,
- functional recovery,
- therapy control strategies.

These topics are still underscored in contemporary scientific literature. They can influence important issues within core of the neurorehabilitation, e.g. impact of motor recovery and motor compensation to post-lesional functional recovery at the neuronal, motor performance, and functional levels [2] or debates concerning effectiveness of the robot-assisted repetitive exercises (repetitive practice, repetitive task training) [3]. These findings may have significant impact on understanding mechanisms underlying severe cognitive impairments [4, 5].

Computational models are perceived as another way for optimization and objectification of the neurorehabilitation. There is a necessity of further common effort of both medical staff and engineers. Highly sophisticated models of complex processes are more accessible thanks to significant increase of processing power [6] of computers based on Compute Unified Device Architecture (CUDA) technology, Tesla graphics processors (not only in supercomputers), and distributed computing (grid technologies) [7].

The aim of this paper is an assessment of the extent to which possible opportunities may be exploited, both in the area of neuroanatomical, theoretical and experimental computational neuroscience, and clinical applications within neurorehabilitation.

LOOKING FOR NEUROBIOLOGICAL BASEMENT OF SELF-ORGANIZED NERVOUS SYSTEM DYNAMICS

Understanding of the human nervous system seems be very difficult without simultaneous description of its processes on all levels: molecular, neuronal, system and behavioural. What is more, higher (cognitive, mental) cortical and sub-cortical processes [6] significantly depend on proper signals processing on the lower levels: brainstem (including Ascending Reticular Arousal System - ARAS), spine cord, and peripheral [8, 9]. Since direct (without scaling) models of human brain are beyond our possibilities, scientists try to approximate number of details needed for better understanding of clear, biologically plausible mechanisms.

Neural correlates of motor training induced by reorganization after nervous system damage may be investigated in animal models (with motor cortex lesions) and in humans (using functional magnetic resonance imaging - fMRI, transcranial magnetic stimulation - TMS, etc.). Despite continuous efforts of scientists and clinicians, it is hard to fully explain all mechanisms of neuroplasticity. What is more, there are a huge number of hypotheses existing in the area of nervous system neuroplasticity following recovery due to neurorehabilitation. In this situation computational models are perceived useful to increase knowledge and clinical experience, providing effectiveness and biological plausibility. Proper computational model (or even whole family of models) should provide:

- effective solution joining theoretical assumptions and experimental research,
- cheaper and quicker testing and selection of the hypotheses, even in the conditions not fully possible in the real world (e.g. due to medical, technical, ethical etc. causes),
- general insight into possible mechanisms,
- highlighting of the most important mechanisms, their features and limitations,
- simplifying mechanisms too complex to the direct simulation,
- possibility of various purposeful damages as representation of injuries/lesions in human nervous system.

It has to be admitted that construction of models well fitted to the assumptions is difficult, and needs a lot of trials and errors. Technical limitations of the used tools may significantly influence both construction process and its results. To smooth the path there is need for:

- formulate proper aims of the model,
- provide proper input signals and level(s) of processing associated with simulated function,
- provide (reliable) hypothetic assumptions, if exact facts are not known.

Lack of standardization and a few researches to compare makes nervous system modeling very hard in assessment.

According to remarks of Gazzaniga, understanding how every neuron operates is nothing - analysis of the neurons net to acquire and interpret whole information need for generation of particular function/behaviour is a true challenge [10, 11]. Details may be important, but the key role is played mechanisms providing connections between single neurons, emerging dynamics of neurons groups and activated by them higher representations/ functions/states. Thus, even the most advanced models of the central nervous system (CNS) may not necessarily help to understand the mind and consciousness [11].

BASIC APPROACHES AND TOOLS

There are defined at least two main approaches within contemporary human nervous system modeling: connectionism and functionalism. Connectionism states that even simplified models of the brain should be composed in a way similar to the origin: of large numbers of analogs of neurons connected together with weights measuring the strength of connections between them. Practical connectionists model of the brain is perceived by e.g. neural network. Alternative approach – functionalism - states that functional role, described by at least sensory inputs, causal relations among states and behavioral outputs, is more important than physical issues. Variability of physical systems providing practical realization of the same functions is perceived as a base for contemporary computer simulation. Despite usefulness of this approach, assumption that brain is physical device allowing computations producing behaviour may be simplified.

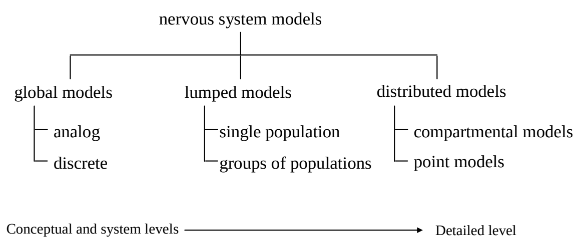

Fig. 1. *Basic kinds of nervous system models depending on the scale [12]*

Development of the aforementioned approaches has provided a lot of various types of software environments, but none is prevailing. Basic tools are as follows (in alphabetical order): Brian, Catacomb, Emergent, GENESIS, KInNeSS, MVA Spike, NCS, Nengo, NEST, NEURON, NSL, P(PSIM), SpikeNet, Topographica, XNBC, and XPP-Aut. Their features and possibilities are diverse. The most commonly used neural simulation software seems to be as follows:

- in models based on compartmental neurons: NEURON (developed primarily at Yale University and at Duke University), GENESIS (GEneral NEural SImulation System, developed at California Institute of Technology, and now at University of Texas at San Antonio) [13],
- in models based on point neurons: Emergent (formerly PDP++), developed at Carnegie Mellon University, and since 2010 University of Colorado at Boulder [14].

No doubts integrating studies joining computer simulation and experimental techniques are crucial to understand the complex details of neural structure and human nervous system function. Biocybernetics (according to the newest concept: neurocybernetics [15]) and bioinformatics have proposed techniques and tools for data acquisition, storage, analysis, visualization, and simulation. There is a need for further interdisciplinary co-operation and data sharing among medical specialists.

SINGLE NEURON MODELS

Primary building blocks for computational models of nervous system are usually single neuron models. Biological neurons are quite complex structures, so their computational features seem to be simplified. Biophysical models of true neurons are very complex so neurobiologically realistic models of single neurons are based on e.g. simplified Hodgkin-Huxley model (1952) [16]. Further efforts have provided additional solutions: FitzHugh-Nagumo model, Morris-Lecar model, Hindmarsh-Rose model, Wilson model, Izhikevich model, integrate-and-fire model, resonate-and-fire model, etc. [15]. Despite more than sixty years of development there is still a lot to discover in a single neuron simulation. Interesting model of pyramidal cell considering electrical activity of the individual synapses and glutamate receptors, cell nucleus activity, and the transport of receptors was proposed by Gorzelańczyk et al. [17]. Variable W proposed in the aforementioned model significantly simplifies chemical description of the secondary transmitters' concentration. None of existing models of neuron is perfect: features and limitations of various kinds of the popular integrate-anf-fire (IF) model (refractoriness, adaptation, subthreshold resonances, smooth spike initiation, lack of spatial structure, changes in length and shape of spikes) have been recently discussed by Naud and Gerstner [18]. Usefulness of the particular neuron model is limited primary by aim and area of the research: simplified models may be useful in psychology and (neuro)physiology (for simulation of very general mechanisms purposes), and the most advanced seem be neuron models used in pharmacological studies. Thus, chemical and enzyme kinetics and reaction thermodynamics [19] or cellular geometrics [20] may provide deeper insight into neuronal signal transduction

CORTEX FUNCTIONS SIMULATIONS

Models of cortex seem to be rather well described, but need further development towards more detailed one. 'Computational Explorations in Cognitive Neuroscience' book by O'Reilly and Munakata [14] shows a huge number of neural models of various cortical mechanisms, including lesions, etc. Despite the fact that it has been more than ten years since the book appeared, it is still the best on the market, even if cognitive architectures have developed thanks to supplemental research. Clinical significance of cortex functions modeling is hard to overestimate. Better understanding of how it may work influences the therapy and its efficacy e.g. in the area of (neuro)physiology, neurology, neurosurgery, neurorehabilitation, psychology, or even in such detailed issues like motor cortex stimulation (MCS). Computational models of MCS allows better preparation and prediction, including stimulus polarity, electrode position, and excitation thresholds [21]. Optimization of the therapy is achieved by joining effects of computer simulation and clinical evidence.

Consciousness is a perceived ability to be aware of oneself and environment. Assessment/measurement of consciousness in computational models seems to be very difficult. Research of Tononi et al. (*neural complexity*, *state-based Φ*) [22, 23], Seth et al. (*causal density*) [24], Gamez and Aleksander (*liveliness*) [25] have not changed this situation. Thus, each attempt aimed at simulation of consciousness and disorders of consciousness (DoC) should be carefully discussed and assessed.

Neural dynamics analysis is perceived as an important step toward better understanding of even the most complex brain processes. Attractors' analysis provides deeper insight into possible brain subnets states and ideas of solutions. But it needs deep knowledge in the area of simulated processes, since it may be rather hard to extract general mechanisms (rules of operation) based only on neural dynamics. What is more, scientists may do not know how many subspaces (subnets) with their own attractors play key role within particular process. A very useful Fuzzy Symbolic Dynamics (FSD) technique is developed in the Division of Applied Informatics NCU [26, 27, 28].

LOWER LEVELS SIMULATIONS

Continuous activation of the brain is provided by lower levels of processing through:

- bottom-up processes emerging from subliminal stimuli, physiological origin, etc.
- top-down causal processes,
- internal loops (e.g. dreams and imaginations) and context (e.g. emotions, memory) [11].

The problem lies in a huge number of data sets acquired simultaneously: sometimes we do not know exactly which of them are necessary for current (or even further) cortex dynamics reflecting subsequent brain states, and which of the aforementioned signals are "informational noise" (of course only from higher cognitive functions perspective) need for e.g. homeostasis, increased consciousness level, etc. Brainstem models developed in the Division of Applied Informatics NCU [7, 8] try to solve only several aforementioned problems, especially in the area of action of selected mechanisms or acquiring signals for level of consciousness control. The research is still being developed - its future results will be presented in subsequent articles.

MODELLING NEUROPLASTICITY

Power of brain plasticity and potential of the nervous system to recovery is enormously huge. Even patients with complete hemisphere lesion can show preserved motor, sensory and cognitive functions enough to lead a life without assistance, even with mild cognitive decline [29]. Scientists perceive that effective long-term plasticity simulation requires at least:

- realistic single neuron modeling including synaptic modeling, matching synaptic types,

coding strategy, axonal and dendritic sprouting, long term potentiation and depression etc.,
- neural network modeling including network connectivity,
- applied information theory rules [30].

On the lowest levels information can be contained e.g. in the mean speak rate or even in the timing of individual spikes. But higher levels require deep analysis of effective dynamic range (thus, influence of single neuron may not be distinguished). Recovery of higher functions depends mainly on plasticity of representations.

On the other hand, understanding of the neural repair needs simulation of brain injury, cell death, neurodegeneration, delayed repair, and then reorganization and remodeling of neural networks as the effect of neurorehabilitation. Neuronal, glial and vascular plasticity may have huge influence on recovery in damaged brain [31]. What is more, reorganization of CNS may be affected by:
- cause (stroke, traumatic brain injury – TBI, spine cord injury – SCI, metabolic disease, poisoning, etc.),
- time of the insult (biological age of the patient),
- characteristics of the lesion (structural properties, location, extent),
- type of reorganization (perilesional, remote) [29].

There may be a lot of significant issues. For this moment we do not know exactly how to translate into computational model e.g. better prediction for neurological patients with better functional outcome (clinimetrics) in admission. Functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS) and magnetoencephalography (MEG) proved their usefulness as non-invasive tools in the area of deeper understanding of neuroplasticity. Moreover, significant experience dependent structural changes have been found in both the gray matter and in the white matter (thanks to Diffusion Tensor Imaging - DTI) [26]. Aforementioned changes in white matter features were reflexed in axon caliber and myelination, providing improvement in the area of nervous signals conduction velocity and synchronization [32]. This situation may imply new class of more detailed models of neurons (with more precisely adjusted axon diameters, packing densities, etc.), useful in white matter plasticity modeling.

The most useful current solutions in post-lesional simulation of central nervous system (CNS) reorganization are as follows:
- Hebbian networks,
- Self-Organizing Maps (SOMs, Kohonen networks) with lateral inhibition,
- attractor networks (in selected cases) [33].

Current concepts: theory of dendritic branching [34, 35, 36] and synaptic plasticity [37, 38] should be key elements within computational models of neuroplastical processes.

FURTHER CONSIDERATIONS

Geometric features of nervous system may play a very important role in nervous signals processing [10]. Choice of particular software environment (e.g. Emergent based on point neurons) can limit possibilities of research and development in this area. From the other point of view, Emergent allows relatively quick and effective simulation of complex neuronal structures. Conclusions from Emergent studies may be developed using software with more advanced (multi)compartmental neurons. One of the most advanced solutions may provide models based on liquid state machines (LSMs). They proved their efficiency in mammalians visual system simulations [39, 40, 41, 42, 43]. Owing to diversity of elements (neurons, synapses, etc.), and variability of mechanisms and their characteristics (recurrent connections, time constants, etc.), LSMs are perceived as developing solution in simulation of nervous signal processing as distortions within “liquid” nature of the system.

Role of noise (random disturbances of signals [44]) in the nervous system seems to be highly underestimated. Huge number and diversity of noise sources within nervous system may play a significant role for information processing influencing all aspects of function. Noise, despite not always useful changes, may also provide favorable ones: activation, stochastic fluctuation, probabilistic differentiation, compensation, or stabilization, etc. and depends on both the level of processing (cellular, system, bahavioural) and timescale [44, 45, 46]. Noise may be the key element of complex variability mechanisms in both the real nervous system and their computational models. The most important role of noise in neurorehabilitation is perceived in perception of sensory signals, decision making and motor behaviour (e.g. generation of motor responses) [45]. We have to learn how to measure this noise, calculate it, and build it into our computational models. At present, Emergent software allows adding two kinds of Gaussian noise to the signals within neural net.

The most advanced computational models based on Emergent and GENESIS software developed in the Division of Applied Informatics NCU try to provide significant progress in autism and ADHD understanding [47]. Moreover, some of current efforts in computational brain simulation are a part of brain atlases development [48].

CONCLUSIONS

Computational neuroscience provides a lot of opportunities for whole nervous system studies. Interdisciplinary researches under computational models help to describe changes within nervous system as a result of damage and therapy. Presented approaches may be developed into larger projects providing more detailed models at all levels of nervous system processing, based on both point neurons and compartmental neurons. Better understanding can significantly influence both traditional forms of the therapy (neurosurgery, drug therapy, neurorehabilitation) and use of advanced Assitive Technology (AT) solutions, e.g. brain-computer interfaces (BCIs) and neuroprostheses [49, 50] or artificial brain stimulation. The latest solution (electrochemical neuroprostheses and robotic postural interfaces) was described recently [51, 52]. Particular research may be focused on the important (technical, scientific, ethical, e.g. quality of life, activities of daily living - ADLs) goals of human health care in general or the treatment/rehabilitation of selected disease. Moreover, biologically plausible neuronal models may provide second opinion according to the Evidence Based Medicine paradigm.

Despite advantages of computational models of nervous system, we should be aware that their interpretation is complex, the measures derived from computational models are indirect, and thus, clinical relevance is limited. No doubts future studies are required to determine the (neuro)biological basis of the observed changes/mechanisms. However, in the future this may imply another breakthrough in the therapy of patients with neurologic deficits: patient-tailored therapy (also called personalized medicine) [53].

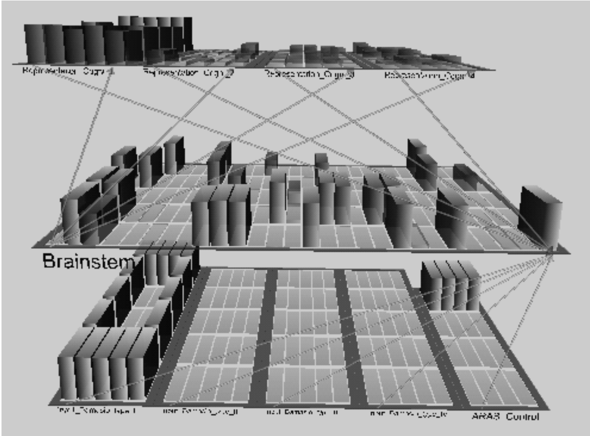

Fig. 2. *Simple model of information processing (software Emergent 4.19, example)*

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