Dariusz Mikolajewski[1,2] / Włodzisław Duch[2,3]

Brain stem modeling at a system level – chances and limitations

[1] Institute of Mechanics and Applied Computer Science, Kazimierz Wielki University, Bydgoszcz, Poland, E-mail: darek.mikolajewski@wp.pl
[2] Centre for Modern Interdisciplinary Technologies, Nicolaus Copernicus University – Neurocognitive Laboratory, Torun, Poland, E-mail: darek.mikolajewski@wp.pl
[3] Department of Informatics, Faculty of Physics, Astronomy and Informatics, Nicolaus Copernicus University, Torun, Poland

Abstract:
The topic of brain stem computational simulation still seems understudied in contemporary scientific literature. Current advances in neuroscience leave the brain stem as one of the least known parts of the human central nervous system. Brain stem lesions are particularly damaging to the most important physiological functions. Advances in brain stem modeling may influence important issues within the core of neurology, neurophysiology, neurosurgery, and neurorehabilitation. Direct results may include both development of knowledge and optimization and objectivization of clinical practice in the aforementioned medical areas. Despite these needs, progress in the area of computational brain stem models seems to be too slow. The aims of this paper are both to recognize the strongest limitations in the area of computational brain stem simulations and to assess the extent to which current opportunities may be exploited. Despite limitations, the emerging view of the brain stem provided by its computational models enables a wide repertoire of functions, including core dynamic behavior.

Keywords: brain stem, central nervous system, computational model, computational neuroscience, neural network

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Introduction

The topic of brain stem computational simulation seems understudied in contemporary scientific literature. Advances in brain stem modeling may influence important issues within the core of the neurology, neurophysiology, neurosurgery, and neurorehabilitation. Direct results may include both development of knowledge and optimization and objectivization of clinical practice in the aforementioned medical areas.

Brain stem lesions are particularly damaging to the most important physiological functions, including breathing. Their exact prevalence is not known yet [1]. Current brain stem disorder diagnostics aims at correlating clinical examination, imaging techniques, evoked potentials, brain stem reflexes, etc. [1], [2]. Computational models of the brain stem are another important step towards the improved understanding of brain stem functioning. Despite the aforementioned requirements, progress in the area of computational brain stem models seems too slow, especially when compared with the current achievements [3]. Studies on brain stem simulation, as a general rule of operation, on the system level were provided by various researchers [4], [5], [6], [7], [8], but none of them prevailed. The main leading hypotheses proposed in the area of general brain stem activity perceive the brain stem as (a part of) an action-selection device:

- model of Humphries et al.: reticular formation of brain stem as the cluster model of “small worlds” [9];
- model of Merker: brain stem as a device optimizing integration for action in real time (through target selection, action selection, and motivation) [10];
- model of Olmsted: brain stem reticular formation as supervised trial-and-error learning scheme with motivation modulation [11].

The aims of this paper are both to recognize the strongest limitations in the area of computational brain stem simulations and to assess the extent to which current opportunities may be exploited.

Dariusz Mikolajewski is the corresponding author.

Limitations of experimental studies

Uniquity of brain stem simulation from an experimental point of view [12] lies primarily in:

- very important: distinguishing the role of the brain stem in the nervous system (rather than low-level as compared with cortical functions);
- complex brain stem neuroanatomy (topography): the bigger variability of the brain stem structure, containing nuclei, pathways and other areas, including, e.g. widely discussed functional area of the ascending reticular arousal system (ARAS);
- both proper function of the brain stem and its disorders may result from a broad spectrum of causes at various levels (molecular, system, etc.) and are reflected in many associated clinical signs and symptoms (ranging from isolated signs to complex syndromes [1]);
- resulting distinguished signal structures and processing – brain stem behavior emerges from a relatively complex combination of intrinsic properties of neurons (nuclei or group of neurons) and synaptic interactions between them;
- variability of accessible diagnostic methods – modern functional magnetic resonance imaging and electrophysiological techniques have significantly improved the understanding of brain stem function;
- widely discussed state-of-the-art diagnostic imaging procedures for brain stem lesions: the major contribution of magnetic resonance imaging (MRI), relatively limited diagnostic value of computed tomography due to the low spatial resolution in the low contrast area, the wide use of electrophysiological tests (transcranial magnetic stimulation, early acoustic evoked potentials, somatosensory evoked potentials, vestibulocolic reflex, blink reflex, masseter reflex, etc.) [1];
- hypothetic structures, connections, and values of parameters resulting from the lack of knowledge in the area of brain stem neuroanatomy.

Experimental studies based on brain stem preparation of juvenile rats, for example, are perceived as the best current source of knowledge in the brain stem neuroanatomy area, but they are rather time consuming. They require precise chemical and pharmacological agents, sectioning of the brain, stimulation of the network activity, histological reconstruction, simultaneous electrophysiological recording, and reliable data analysis. Despite elicited biophysical properties and channel kinetics in neurons (populations of neurons) incorporated in the models, there are a lot of unknown issues, both hypothetical and widely discussed. This may influence both the reliability and the accuracy of the simulation. Heterogeneity of neurons within the brain stem creates further problems.

Because of the aforementioned needs for unique, distinguished approaches in computational modeling, building of a direct (without scaling) brain stem model is impossible now. So what can we learn from much simpler models, and how can we study complex systems this way? Analysis of simplified models may provide a plausible explanation of activities and mechanisms, both under normal conditions and, for example, during lesion simulation. More computational models bring together theoretical knowledge, experimental data (even obtained under various experimental conditions) and currently tested hypotheses. Thus, predictions useful in further research (simulational, experimental, etc.) planning may be achieved. This approach is called the data-driven modeling approach [13]. Multidimensional modeling tries to provide both neurobiological details and computational complexity of the brain stem and its parts.

Brain stem topography is complex. It consists of many brain stem nuclei, pathways connecting different brain areas and the spinal cord, and neural networks with specified coordinating tasks [1]; therefore, localization of the brain stem lesions and diagnosis of the associated brain stem disorders is a great challenge, even for experienced specialists. Proper matching of clinical and technical findings is crucial for correct diagnosis. The final result of this process may summarize the various methods for detecting functional disturbances in the brain's specialized structures (including the brain stem), correlations of aforementioned findings with morphologic criteria (e.g. MRI), and elaboration patterns of abnormal outcomes characteristic of small brain stem lesions [2].

Despite research, we do not know if reticular formation provides an integrative center in the human brain stem [14]. The most advanced parts of it seem to be models of respiratory rhythm [15], but the latest research [13], [16], [17] has not yet provided an ultimate solution. Despite efforts of researchers to link the properties of channels, synapses, and higher-level (higher-order) functions of nervous subsystems, they cannot be perceived as simply being correlative. The relationship between the current stimulus (and its parameters) and the responses of the nerves and different brain stem neurons, influences the function of cellular and membrane properties, and its assessment and resultant simulation [18]. Lack of well-known and widely accepted associations between input signals, brain stem functions, and its neural correlations makes research difficult, and even sometimes speculative.

Limitations of software environments

In our simulations we usually use two software environments:

- Emergent (formerly PDP++), based on point neurons – to build simplified conceptual models or a family of models and extract general structure and mechanisms using simplified neurons with three basic neurotransmitters, kWTA (k-Winners Take All) mechanism, accommodation, and the possiblity of adding noise (Carnegie Mellon University, Developer(s) University of Colorado at Boulder, License: GPL, https://grey.colorado.edu/emergent/index.php/Main_Page)
- GEneral NEural SImulation System (GENESIS: Dr. James M. Bower, License GPL, http://genesis-sim.org), based on compartmental neurons, to build more neurobiologically realistic "dimensional" neural networks.Our methodology of simultaneously developing compartmental and assessment models, created in the Emergent and GENESIS environments used in our "Spectrum of autism – integrated theory" project [19], [20], [21], involves a three-stage process (Figure 1):
- creation of general models based on point neurons (Emergent);
- more sophisticated and detailed models based on compartmental neurons (GENESIS);
- return to the model based on point neurons (Emergent), taking into consideration findings from previous models (particularly based on compartmental neurons in GENESIS), and neural dynamics analysis to provide all aspects of the network functionality.

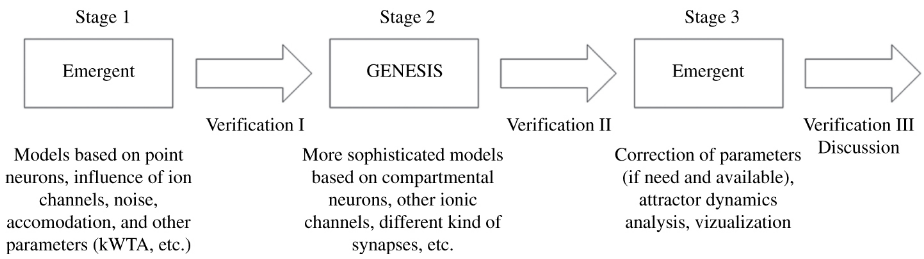

Figure 1: Concept of three-stage neurocomputational modeling using Emergent and GENESIS software [21].

The aforementioned methodology may be perceived as a distant development of computation in neocortical architecture proposed by Körner et al. [22], adopted to brain stem specificity.

Additionally, Emergent may be very useful in the construction of easy-to-develop complex models because of simpler neurons and incorporated useful computational mechanisms (e.g. kWTA). This solution provides the possibility of discrimination between various possible models and hypotheses.

Limitations of direct brain stem modeling

The modeling of brain stem functions has the same problems as many large systems simulations. Its full understanding is perceived as difficult due to the need for (if possible, simultaneous) analysis of information processing at all levels: molecular, neuronal, system, and behavioral. Generally (including ARAS) the brain stem influence is based on the activity of the brain stem's nuclei, which influence higher levels (sub-cortical and cortical levels) through modulation diffuse neuromodulatory projections. Neuron parameters should correspond to (neuro)physiological measurements, e.g. firing rates across neurons in each population as averaged properties of the model [23].

Both connectionism and functionalism require huge computational efforts of the origin (natural brain stem) and limitations of the units and number of loops in the model. Primary building blocks – neurons – have to be simplified to the primary Hodgkin-Huxley model (1952) or one of the many other solutions: FitzHugh-Nagumo model, Morris-Lecar model, Hindmarsh-Rose model, Izhikevich model, integrate-and-fire model, resonate-and-fire model, etc. Currently, each neuronal type/structure is usually represented by a population of at least

50–100 neurons. Because of this, even models of a very simplified brain stem structure take enormous effort. Furthermore, large-scale simulations of brain stem structures and signal processing as direct computational replication of experimental data [24] seem impossible due to the huge computational power required. This implies the following proposed way of developing brain stem models at the systematic level, from general mechanisms to detailed, as easier to build and develop.

"*Computational Explorations in Cognitive Neuroscience*" by O'Reilly and Munakata [12] describes many computational models of various cortical functions (including lesions), but experiences concerning cortex mechanisms are hard to replicate for brain stem modeling. Differences in structure, signals, and processing seem too big to overcome in any easy way. Despite the aforementioned problems, the research of O'Reilly and Munakata may provide a limited basis for further brain stem studies.

While studies on computational models of respiration [25], [26], [27], auditory [28], consciousness [29], and stress [30] functions of the brain stem have been successful, general concepts of brain stem activity remain unknown, or less-explored than other areas of brain stem function. Despite many types of breathing patterns having been recorded (using, e.g. brain spirographic techniques), their interpretations are widely discussed among specialists.

Figure 2 provides a general concept of the basic network. This idea was reflected in the family of models built based on the Emergent software (Figure 3).

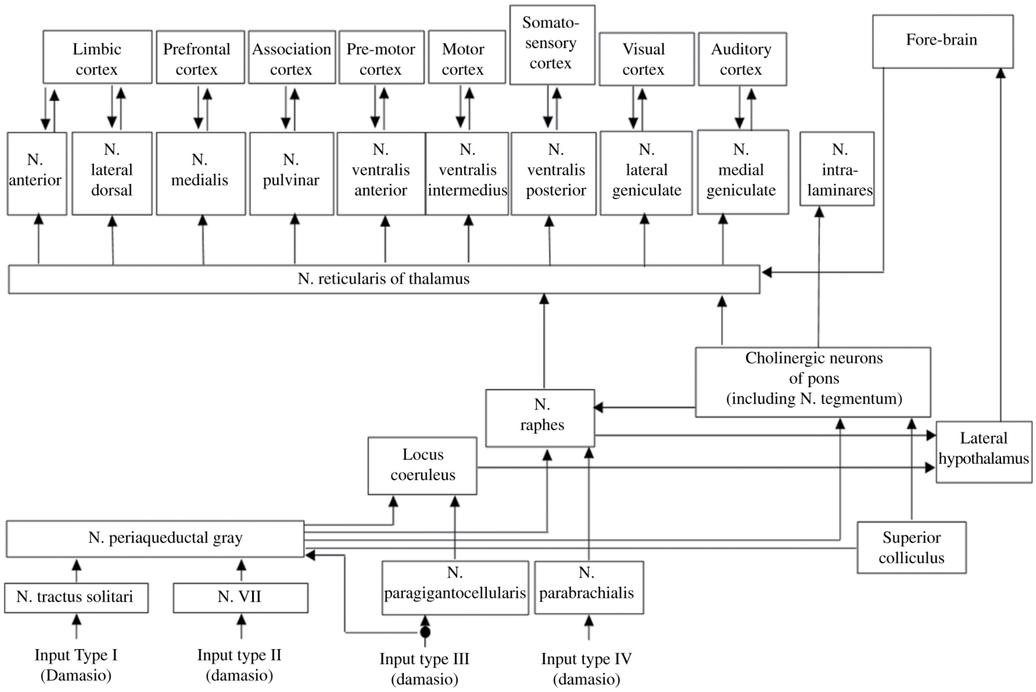

Figure 2: Simplified conceptual model of brain stem association to high-order levels/example.

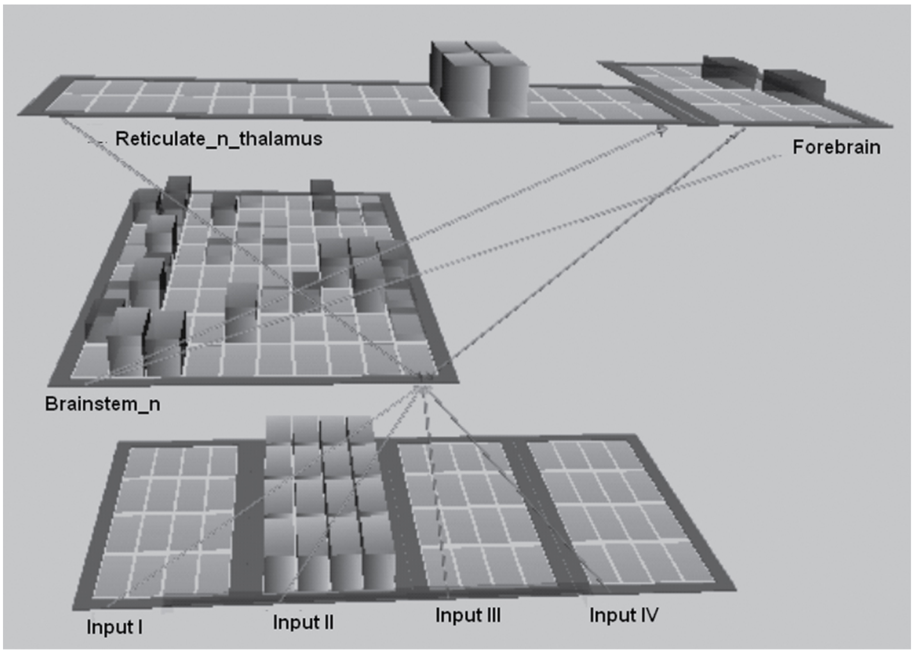

Figure 3: Practical realization of part of the conceptual model from Figure 1 using the Emergent software.

Experimental adjustment of both learning patterns (i.e. input signals) and neuron parameters may provide generalization and efficiency in general processing patterns. But due to increased variability of inputs (e.g. visual, auditory, etc.) the presented solution may not be optimal and may need additional readjustment. For example, signals for visual processing may require much higher resolution (depending on angular resolution of the particular human eye) which significantly influences the number of neurons and processing patterns at higher levels of neuronal nets. An additional problem may be a higher bit rate of selected inputs, difficult to interpret in neural networks, but important for further computational models. We focus rather on processed pictures and the information they provide for the nervous system. As a result of this simplified approach, binocular vision with advanced 3D effects (stereoscopic acuity) may be beyond our interest. But we should be aware of it and work for future solutions in this area.

Proposed directions of further research

At this moment, lack of general research standards in computational simulations of the brain stem activity and disorders makes objective assessment and compartmentalization of results between researches difficult. The main aforementioned limitations at a system level may be enhanced by:

- only partial explanation of processing levels;
- difference in signal inputs (both single signal features and possible multimodal signals);
- no full correlation of activation (even if pathologic) on neural, cellular, and system levels, response to the stimuli, neural network dynamics, and resulting behavior (usually possible in the real world thanks to simultaneous use of various diagnostic tools);
- limited (compared to cortex) neuroplastical features of the brain stem;
- underestimated role of noise in the nervous system, including brain stem;
- underestimated role of neuron accomodation and rivalry (partly);
- conscious and sub-conscious processing and associated phenomena;
- unknown role of the internal context of processing in the brain stem case (e.g. association between limbic functions and ARAS activity or damage).

Thus directions for further research in the area of computational models of brain stem at the systematic level are perceived as follows:

- theoretical, but biologically relevant assumptions based on experimental studies;
- standardized general procedures (patterns) of brain stem simulations, both in the area of whole families of general models and more sophisticated complex models;
- correlations between development, disorders, individual features, etc. and their influence on processing of information by brain stem structures;
- educational/scientific implementation of models (e.g. for demonstration or expert systems purposes).

An additional interesting direction of further research may be computational models of direct activation of the brain, e.g. during electroconvulsive therapy which found the brain stem also activated (using a right unilateral electrode configuration) [31].

There is no doubt that proper biologically relevant models may enhance research possibilities in the human nervous system. But aforementioned problems continue to present difficult challenges to researchers. Thus our efforts in the area of brain stem function simulation are going to continue. We hope the next set of results of our projects will be presented in subsequent articles.

Computational models may be useful tools to enhance our knowledge in the aforementioned area. Current efforts (return maps, fractal dimensions, independent components analysis, etc.) provide very limited success, so new approaches based on fuzzy symbolic dynamics (FSD) are being developed. The FSD provides analysis of emerging model dynamics depending on signal features, lesion characteristics, noise influence, neuron accommodation, and other network parameters [32], [33]. Moreover, complex models, with large groups of neurons and multiple interconnected subsystems, cause dynamics that are crucial to control for proper model function due to possible chaotic trajectories, for example. The nonlinearity of co-operating systems may provide the necessary lack of constraint. Areas of proper and stable functioning (depending on the model's so-called equilibrium point, local or global minima, etc.) may be relatively small, so it calls for careful exploration.

Conclusions

Despite limitations, the emerging view of the brain stem provided by its computational models enables a wide repertoire of functions, including core dynamic behavior. Current advances in neuroscience leave the brain stem as one of the least known parts of the human central nervous system [34], [35], [36]. Every effort and every tool, including computational approach, may be precious for deeper understanding of the mechanisms underlying normal brain stem activity and result of its damage. Due to large-scale models of brain stem structures requiring enormous computational power, simplified models described in this article will play a key role in further research, probably as a significant link between theoretical hypotheses and further research.

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