THE THORNY PATH TO AN ARTIFICIAL BRAIN
How to Build a Bridge between Neurophysiology and Network Modeling

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Abstract: Humanoid robots are created to imitate some of the tasks that humans undergo, but no current robot can emulate the cognitive capabilities of even the simplest mammals. One approach to developing computing platforms for cognitive robotics is to make use of experimental characterizations of the neurobiological substrate for action and perception systems and simulate brain functions designing real-time spiking neural networks. Biologically detailed network models are a powerful tool to understand how molecular and cellular mechanisms determine high level network processing. Recent advances in experimental and theoretical studies of the dynamic organization of neuronal populations suggest that our further success in creation of higher intelligence robots will depend on the ability to incorporate such basic principles of brain functioning as (i) stochastic dynamics and intrinsic nonlinearities in input-output transformation of neurons, (ii) structural and functional plasticity, (iii) signaling through neuromodulator networks.

1 INTRODUCTION

The adult human brain contains about 86 billion neurons (Azevedo, Carvalho, Grinberg, Farfel, Ferretti et al., 2009). The main function of neurons is to process and transmit information. This transmission occurs via roughly 10,000 chemical and, in few locations, electrical synapses. Both synapses and neurons have complex stochastic dynamic properties. The ability to learn and fulfill fine movements is achieved after an integration and representation in the brain of information from a large number of sensorimotor and cognitive signals. The human brain can rewire itself and change its structure and function in response to an experience, can pursue goals, think abstractly and creatively. Serious consideration to the possibility of building an electronic brain starts from the middle of the last century. However, the traditional artificial neural networks contain only very simplified (one-node) models of biological neurons with reciprocal interactions between all nodes and require a large diversity of training for real-world operations. In spite of immense calculation speeds, machines are much less effective than biological systems in real-world environments and cannot match the capabilities of the human brain. At the same time, a number of detailed network models representing diverse types of neurons with their complex morphology and distinct subsets of ion channels were simulated (see Markram, 2006 for review). These models are intended to fill the considerable gap in our understanding between the processes on the molecular level and on the level of network function. It is sufficiently difficult to build network models that incorporate realistic morphologies and asynchronous, dynamical and self-organizing changes in the synaptic connections and intrinsic properties. However, it is evident that understanding of the brain requires the development of realistic detailed models based on experimental description of all of their components that can be tested and refined through new experiments. Recently a large international project whose aim is to simulate in a supercomputer the brains of mammals with a high level of biological accuracy has been started (Markram, 2006). This may help to create a new generation of intelligent neuromorphic devices with the ability to form neural representations of their bodies and environment. Internal models will allow them to plan and prepare for future eventualities. I shall emphasize several aspects of neural functioning that may be important for biologically accurate brain simulations.

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2 REQUIREMENTS FOR BIOLOGICALLY ACCURATE BRAIN SIMULATIONS

2.1 Intrinsic Nonlinearities in Input-Output Transformation of Neurons

The most difficulty in accurately modeling signal flow in neural circuits arises from the fact that the electrical behavior of neurons is determined by a large number of non-linear elements, such as membrane ion channels with non-linear voltage-dependence and synapses with highly non-linear transmission. Moreover, most neurons have extensive dendritic trees, but the distribution and properties of dendritic ion channels still cannot be characterized experimentally. Dendrites integrate multiple synaptic inputs and translate them into axonal action potentials (APs). The spiking of neurons is usually driven by irregular synaptic inputs and stochastic flickering of voltage-gated channels. Physiological levels of channel noise can produce qualitative changes in neural dynamics (Dorval and White, 2005) and allow probabilistic synaptic integration (Cannon, O'Donnell and Nolan, 2010). However, synaptic transmission is often a major contributor to the voltage noise. Traditionally, it was thought that a neuron simply summates synaptic inputs, which it receives. When physiologically realistic patterns of synaptic inputs, as observed *in vivo*, were included in *in vitro* experiments, it was found that the slope of the relationship between mean input and output firing rates (gain) is fundamentally altered (Silver, 2010). For neurons that operate in coincidence-detection mode under sparse activation conditions (Olshausen and Field, 2004), synaptic noise results in the broadening of the time window for synaptic integration. The temporal fidelity of coincidence detection is influenced by shunting inhibitory conductances, which can be regulated by voltage-dependent membrane conductances (Pavlov, Scimemi, Savtchenko, Kullmann and Walker, 2011). In addition, neural gain can be controlled by active dendritic conductances under some conditions (Silver, 2010)

It is widely believed that activity-dependent change in synaptic plasticity is a fundamental mechanism for stably altering the function of neural networks. The standard models of memory in neuroscience are based on Hebb's postulate (Hebb, 1949) that repetitive co-activation of neurons strengthens the connection among them. These models assume that only the synaptic strength changes. However, short-term changes in the dynamics of the synaptic transmission introduce the frequency-dependent nonlinearity and modify the sensitivity of a neuron to the temporal coincidence of its inputs. These changes can be modulated by long-term plasticity. In result, the strengthening of synapses for different frequencies appears to be non-uniform and depends on prior activity (Silver, 2010; Markram, Gerstner and Sjöström, 2011). Changing the gain of neurons alters their responsiveness to input and, therefore, their functional connectivity in the network (Haider and McCormick, 2009). This is a mechanism by which functional neuronal assemblies can be formed and broken. Therefore, in order to understand the operating principles of network dynamics in the brain, it is necessary to include in the models realistic dynamics of synaptic transmission and the spatial and temporal patterns of synaptic activation observed *in vivo*.

Another important issue that has been paid insufficient attention in the past is that neural coding may be based on selective responses of neurons to some subsets of input interpulse intervals (Vartanian, Pirogov and Shabaev, 1986). Interpulse intervals can carry sufficiently higher stimulus-related information than either spike-timing precision or mean firing rate (Imaizumi, Priebe, Sharpee, Cheung and Schreiner, 2010). Specific classes of voltage-gated currents support subthreshold oscillations of the membrane potential and the intrinsic frequency preferences of neurons (Hutcheon and Yarom, 2000). Recently, experimental recordings have demonstrated a critical role of cell-specific subthreshold oscillations of membrane potential for spatial firing of grid cells in enthorhinal cortex (Giocomo, Zilli, Fransén and Hasselmo, 2007).

An additional complexity stems from the dependence of information transfer in neural circuits not only on synaptic transmission, but also on the diffusion of neurotransmitter molecules through the extracellular and cerebrospinal fluid. For example, hippocampal neurogliaform cells release the inhibitory neurotransmitter γ-aminobuteric acid (GABA) and do not require synapses to produce inhibitory responses in the majority of nearby neurons (Oláh, Füle, Komlósi, Varga, Báldi et al., 2009). The ambient levels of GABA can increase or decrease the neuron firing probability (Song, Savtchenko, and Semyanov, 2010). Spillover of the main excitatory neurotransmitter glutamate from the synaptic cleft prolongs the decay of synaptic currents, increasing the time window of synaptic integration and may activate presynaptic

metabotropic glutamate receptors at inhibitory neurons.

2.2 Multiple Forms of Experience-Induced Plasticity in the Brain

One of the central goals of computational neuroscience is to explain how learning and memory is achieved in the brain. Learning algorithms in existing models of neural nets use synaptic plasticity rules derived from already existing synapses to reorganize or to reconfigure the connectivity within a group of neurons. However, experience-dependent plasticity in adult neural circuits may involve formation and elimination of synaptic contacts, spines, and axonal boutons (Holtmaat and Svoboda, 2009). For example, in the neocortex, the induced appearance and disappearance of multiple synaptic contacts over a time scale of hours was directly shown in experiments after glutamate application (Le Bé and Markram, 2006). Spine and synapse densities can increase after training in enriched environment, after long-term sensory stimulation, and after induction of long-term potentiation (LTP), which is an artificial form of plasticity (Lambrecht and LeDoux, 2004). Nevertheless, the determinants of the location of new synaptic connections are not clear. Moreover, exposing animals to complex environment leads to rearrangement of axonal/dendritic arbors (Galimberti, Gogolla, Alberi, Santos, Muller et al., 2006). The actin cytoskeleton plays a major role in structural changes of neurons. It constantly rearranges in response to neuronal activity; and this leads to formation of new axonal varicosities and to changes in the head volume of dendritic spines (Dillon and Goda, 2005). The structural changes of the spine head result in changes of the calcium dynamics that controls, in its turn, the induction of synaptic plasticity. Besides, actin may contribute to synaptic transmission as it is involved in the trafficking of glutamate and GABA receptors and in vesicle translocation (Cingolani and Goda, 2008). A number of limitations preclude realistic modeling. Simulation environments for modeling individual neurons and neural circuits provide tools for spatial models with biologically realistic morphology and synaptic connections, but this morphology must be fixed. Solving of diffusion–reaction systems on domains with moving boundaries is challenging. So the techniques of multi-level simulations should be developed in which the model switches from dynamic structural changes to electrical activity.

On the other hand, it becomes more and more evident that learning cannot be completely equated with synaptic plasticity. For example, intrinsic plasticity in neurons can be considered as a cellular correlate of learning. Neuronal activity persistently regulates plasma membrane ion channels, which determine the ability of a neuron to generate an AP in response to a given input signal. Persistent changes in the intrinsic excitability of neurons elicited by modifications in the properties and/or number of ion channels can be produced by training in behaving animals or by activation of cellular preparations by definite artificial patterns. These changes may influence modifications in the synaptic strength in a defined time window following the training, function as a part of the engram itself, promote the consolidation of memory, and contribute to saving during reacquisition or to cross-modal acquisition (Zhang and Linden, 2003). The activity-dependent modulation of synaptic plasticity, the so-called metaplasticity (Abraham and Bear, 1996), can be caused by an alteration of the threshold for axosomatic spike generation or by a change of the properties of voltage-gated channels in a local domain of the dendritic tree. The latter is especially important since most neuronal types have a remarkable dendritic arbor onto which the majority of synaptic connections are made. Moreover, the properties and localization of dendritic voltage-gated channels can be altered by synaptic activity or neuromodulators and result in the qualitative change of the neuronal firing patterns (Remy, Beck and Yaari, 2010). Thus, both neurons and synapses are history-dependent, and learning occurs at multiple levels and time scales.

In addition, the brain responds to experience by adding new neurons, glial cells and capillaries (Grossman, Churchill, Bates, Kleim and Greenough, 2002). Induction of LTP at excitatory synapses depends on signalling molecules released by astrocytes (Henneberger, Papouin, Oliet and Rusakov, 2010). Therefore, the simulations should include the glial networks to capture neuron-glia interactions.

2.3 Neuromodulatory Control of Synaptic Transmission and Neuronal Excitability

The most difficult problem of neuroscience is to understand how system-level brain functions may arise from low level molecular and cellular mechanisms. The brain is connected with the body and the body and brain interact with the external environment. The behavior of an animal or human at

each given moment is hierarchically organized and directed towards the satisfaction of some need, which predominates over all other needs. Needs can be biological (e.g., for meals), social (e.g., for communication), and cognitive (e.g. for novelty). While a need induces active behavior, the acquired connections between a need and an object, which can it satisfy, makes the behavior and learning reward-mediated. The satisfaction of needs induces positive emotional states.

Neuromodulators, the substances that alter the function of other neurons at a slower time scale than neurotransmitters and diffuse through large areas, have a vital role in regulation of cognitive processes and behavior. They change intrinsic excitability of neurons, presynaptic release of neurotransmitters, and the conditions for induction of long-term synaptic plasticity (Schweighofer, Doya and Kuroda, 2004; Hasselmo and Sarter, 2011; Pawlak, Wickens, Kirkwood and Kerr, 2010). Neuromodulators are thought to be essentially required for induction of spike-dependent plasticity at specific synapses *in vivo* where there is a huge amount of constantly ongoing presynaptic and backpropagating spiking activity (Pawlak et al., 2010). Some neuromodulators, e.g. such as dopamine, noradrenaline, acetylcholine, serotonin, opioid peptides, are involved in behaviorally based learning and reward and play a particular important role in emotional responses. Thus, dopamine provides reward prediction errors and its release may be activated by reward-predicting stimuli (Schultz, 2010). However, it is still unclear how the specific neuronal activity around the reward event links to the behavioral outcome (Pawlak et al., 2010). A possible mechanism determining the crucial role of emotional reinforcement in formation of the functional connectivity between neurons could be gain modulation to sensory stimuli due to tonic changes in membrane potential. These changes may be evoked by the release of neuromodulators (Vartanian et al., 1986). To make matters more complicated, we know that certain brain structures process more specific reward information and predictions of future outcomes, but our general knowledge about how the reward systems are organized is very incomplete.

The majority of monoaminergic neurons do not make synaptic contacts and release neuromodulators for long-distance diffusion. Some other locally acting systems, such as endocannabinoids, metabotropic glutamate receptors, brain-derived neurotrophic factor (BDNF), and retrograde messengers also play an important role in synaptic plasticity. BDNF modulates synaptic transmission and membrane excitability and is thought to be necessary and sufficient for long-term memory retention in the hippocampus (Cunha, Brambilla and Thomas, 2010). Taking into consideration that a variety of neuromodulatory agents are released at different concentrations in behaving animals and may interact, realistic modeling can be a very challenging task.

One of the most intriguing issues is the role of activity-dependent plasticity in forming assemblies of neurons with pre-specified genetically determined connectivity. Recently it was shown that small clusters of pyramidal neurons in the neocortex containing about 50 neurons make predictable connections with predictable synaptic weights independently of individual experiences (Perin, Berger and Markram, 2011). Connection probability between any two neurons increases linearly with the number of their common neighbors. This synaptically organizing principle is genetically prescribed and applies across different animals. It was suggested that acquired memory relies on combining these microcircuits, which are fundamental building blocks of perception (Perin et al., 2011). The theory of neuronal group selection (Edelman, 1993) maintains that the brain gives repertoires of variant neuronal groups. The groups that emerged during embryonic development are selected to match the novelty and diversity of experience under control of inborn value systems producing neuromodulators. Experience could serve to combine these groups in a hierarchical manner.

3 FUTURE DIRECTIONS

Henry Markram, the founder of Brain Mind Institute in Switzerland, has claimed that with the right resources and strategy it would be possible to simulate the complete human brain at the cellular level within 12 years. The Human Brain Project proposes to integrate everything that we know about brain into computer models and use these models to simulate the actual working of the brain on a supercomputer (http://www.humanbrainproject.eu). It looks likely that the main constraint for this project may be not an insufficient power of supercomputer, which grows very quickly, but insufficient experimental data necessary for model development.

As it was mentioned above, one of the most crucial issues in neuroscience is to establish the functional role and mechanisms of neuromodulatory

control in cortical structures. For this, the combination of *in vitro* and *in vivo* techniques is required to bridge between cellular effects and behavioral functions. Most studies of neural dynamics and plasticity have been carried out *in vitro*. Systematic recordings *in vivo* are technically very demanding, they can be carried out only from the largest neuronal elements. Instead, optical and electrophysiological recordings are performed using reduced preparations, particularly acute brain slices, where controlled analysis of neuronal activity and cellular properties can be made. In *in vitro* slice preparations many synaptic connections are cut and natural neuromodulation does not occur at all. In result, the majority of experiments are conducted under conditions where high levels of stochastic voltage noise, which are observed *in vivo,* are significantly decreased and the degree of neuromodulation is negligible. However, both synaptic noise and changes in neural excitability evoked by neuromodulators alter the way the neuron transforms its synaptic input into output firing rate (Silver, 2010). Future optogenetic work might delineate the contributions of the different components of the cellular responses elicited by neuromodulators to behavioral learning and identify the particular forms of learning sensitive to these substances.

The appropriate level of physical detail required to understand how the behavioral function emerges from the observed effects at the molecular and cellular levels is unclear. Some phenomenological descriptions and simplifications are inevitable because of the limitations of realistic modeling, but it is clear that such a model may not replicate faithfully the neuron's dynamics under different conditions. If the prediction of the model does match experimental data, it does not guarantee the validity of the model, but should suggest new predictions that can be verified experimentally or other experiments that can test its validity under different conditions. This approach drew on the rich history of biophysical research and may be used for models at different levels of complexity.

Presently, our group is developing a large-scale computational model of the cerebellum based on some recent experimental data to show that learning in this brain structure can be regulated rather by neuromodulators and neuropeptides than by a climbing fiber error-driven teaching signal.

Many important details still remain to be specified. The involvement of long-term synaptic plasticity in learning and memory remains to be conclusively demonstrated. We still do know neither what cellular processes are necessary for the maintenance and retrieval of long-term memory nor what processes are central to the persistence of memory after recall. Recent finding of innate neural cortical assemblies (Perin et al., 2011) suggests that in order to construct neural microcircuits in the neocortex with realistic properties, it is necessary to create at first these assemblies using genetically determined connectivity principles and then to apply a learning rule to associate them. But we know a little about the topography of neurons in other brain areas. Interestingly, there is convincing evidence that the autoassociator theory of memory (Hebb, 1949) is incorrect for the hippocampus where the mutual synaptic interconnections are set up in early development (Colgin, Leutgeb, Jezek, Leutgeb, Moser et al., 2010).

The greatest challenges, however, appear when higher brain functions, such as cognition or consciousness are attempted to be reproduced. The subjective experience of each living being is unique and arises from the trinity of the brain, body, and environment. The brain works as a whole system, and only one percept at any time is possible. Each percept involves many brain areas simultaneously in order to update episodic memory, spatial maps, value systems, prefrontal planning, and motor preparation (Edelman, Gally and Baars, 2011). Our knowledge about the function and connections between different brain structures are still incomplete. For example, neuroscience inquires of such a basic human ability as creativity show a muddled picture. On the other hand, the construction of brain-based devices, which should incorporate the main principles of brain functioning and value system, can help us to explore how numerous biological mechanisms may interact to create new system properties.

4 CONCLUSIONS

Computer modeling is becoming a valuable tool for understanding how high brain functions arise from molecular and cellular mechanisms. The living brain is much more complex of any brain-based device, which it is possible to imagine. We only have begun to understand some basic operating characteristics of neural networks. Control of neural dynamics and connectivity by synaptic noise, a combination of biochemical networks of neuromodulators with neural networks to perform computations, the existence of multiple forms of plasticity are fundamental principles of their functioning. These

principles should be included in future models. Our basic knowledge about neural coding and brain functions on the systems level are still very insufficient. Hopefully, computational science and neuroscience will develop with a close interdependence, such that model predictions will inspire new experiments with discrepancies between theory and experiment serving as the impetus for model refinement.

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