Biomedical Reviews 2013; 24: 25-31

ISSN 1314-1929 (online)

COMPUTATIONAL MODELLING: MOONLIGHTING ON THE NEUROSCIENCE AND MEDICINE

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Computational modelling has emerged as a powerful tool to study the behaviour of complex systems. Computer simulation may lead to a better understanding of the function of biological systems and the pathophysiological mechanisms underlying various diseases. In neuroscience, modelling techniques have provided knowledge about the electrical properties of neurons, activity of ion channels, synaptic function, information processing, and signalling pathways. Using simulations and analysis in network models has resulted in greater understanding of the behaviour of neural networks and dynamics of synaptic connectivity. Moreover, the correlation between the neurobiological mechanisms and a cluster of physiological, cognitive, and behavioural phenomena may be explored by the computational modelling of the neuronal systems. In this context, a significant progress has been made in understanding of the neural network architectures including those with a high degree of connectivity between the units, information processing, performance of complex cognitive tasks, integration of brain signals, as well as the dynamic mechanisms and computations implemented in the brain for making goal-directed choices. Computational models are able to explore the interactions between the brain areas which are involved in predictive processes and high-level skills. In this review, the significance of computational modelling in the study of neural networks, decision-making procedure, nerve growth factor signalling, and endocannabinoid system along with its medical applications have been highlighted. ***Biomed Rev*** **2013; 24: 25-31**

Keywords: biological system, neural network, information processing, nerve growth factor, endocannabinoid system

INTRODUCTION

In recent years, the development of computational models has given the opportunity to study a wide range of complex systems *in silico*. The modelling approaches may also be used to make useful predictions. For example, important predictions from the computational models of the basal ganglia have been obtained which exhibit practical implications for neurological disorders such as Parkinson's disease (1). Meanwhile, the model selection and validation as well as the parameter estimation are necessary for improving model performance (2). In neuroscience, biophysical models have made a significant

Received 8 December 2013, revised 15 December 2013, accepted 20 December 2013.
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contribution to the understanding of the electrical properties of neurons. These models have also been used to investigate the signalling pathways underlying synaptic plasticity (3) leading to a deeper understanding of memory storage in neurons and information processing. From a historical point of view, Hodgkin and Huxley were the first who created the biophysical models. They developed equations in order to describe how the action potentials are propagated throughout the axons via the voltage-gated ion channels and employed the voltage-sensitive fast-acting sodium and the inward-rectifying potassium currents to predict the qualitative features and timing of the action potential (4). Although Hodgkin and Huxley's model provided an efficient explanation for the contribution of the aforementioned ion channels to the neuronal activity, other important features of the neural networks such as shunting and adaptation remained unpredictable. In fact, the complexity of neuronal dynamics and cellular signalling networks necessitates the development of descriptive, mechanistic, or interpretive models. The first multicompartmental neural modelling was designed by Wilfrid Rall using cable theory (2). Afterwards, modelling of complex cognitive processes was performed in order to explore the habitual and rule-governed features of human performance (5,6). Altogether, simulation experiments are designed to solve the complex problems and determine how a system may be affected by various conditions.

COMPUTATIONAL MODELS FOR NEURAL NETWORKS

Neurons are the complex and specialized cells which consist of differentiated domains for receiving and transmitting a flow of information. In human nervous system, several billion of neurons form intricate networks through which high-speed signals pass in a complex and dynamically changing pattern. Development of computational models has led to a better understanding of the complex interconnections between the neurons. Furthermore, computational modelling has provided knowledge about the neuronal development, axonal guidance, sensory processing, synaptic plasticity and memory, as well as the adaptive and discriminative properties of the brain in certain contexts (7). Although the organizational principles of the brain may be understood by other fields of science such as biology or psychology, the consolidation of these findings is performed through the unified descriptive models and databases as well as the quantitative modelling of brain activity (8). In the neural network model, the behaviour of individual neurons and dynamics of neural circuitry may be evaluated. In order to develop computational models to study the neural information processing, a special attention should be paid to the electric circuit analogies as well as the electro-dynamical variables including the current, resistance, and voltage. In addition, the designer of a neural network usually needs to simulate the synaptic transmission in the nervous system (9).

In a basic multiple-input computational model, each neuron is considered as a processor which has a dynamic connection with other neurons. The soma and dendrites receive the inputs and integrate the signals of pre-synaptic nerve terminals (10). In recent years, the interaction of different currents with geometric properties of neurons and the computational functions of dendrites have been under intense investigation (3,6). Moreover, several models have been designed in order to track the biochemical pathways at very small scales such as the spines or synaptic clefts (11). In transsynaptic neuronal changes due to the neurodegenerative processes (12), computational intelligence techniques including the neural network or evolutionary algorithms have been employed in medical imaging that may provide an efficient and reliable detection of structural damage in neurons. In this respect, computational modelling of cell replacement may be a promising approach for the treatment of neurological disorders (13). Computational models may also clarify the synapse function in response to the external stimulus at different time scales. Based on a stereochemical model, it has been shown that acetylcholine receptor-based synapse works at time scale of microseconds (14,15). The maintenance or change of the memory in multiple time scales is one of the major problems in neuroscience. In this context, significant effort has been made to develop the biologically relevant models (16). Several models have been designed to explore the interactions between the episodic and working memories in the hippocampus and prefrontal cortex, respectively (17,18).

APPLICATION OF COMPUTATIONAL MODELS IN DECISION-MAKING AND PROBLEM-SOLVING TECHNIQUES

In goal-directed choices, an action is usually chosen among others which are associated with costs and reward outcomes. In decision-making procedure, a series of computations are usually implemented in the brain (19). Combination of modelling and psychometrics may also be used for acquiring knowledge about the algorithms that are used by the brain to compare the action values (20). Human functional magnetic resonance imaging (fMRI) studies have provided evidence about the nature of brain function in a complex decision-making paradigm or sophisticated problem-solving (21). In this sense, a novel decision-making paradigm has been used to dissociate the basic decision-making computations including the stimulus values and prediction errors. Based on the findings, activation of the medial orbitofrontal cortex is correlated with stimulus values, while, activation of the ventral striatum is correlated with prediction errors (22). In making dietary decisions, models and algorithms have shown the critical role of the orbitofrontal cortex in self-control (23). Using a mathematical framework, it has been demonstrated that the anterior areas of prefrontal cortex are involved in making more complex decisions (24). An attempt for modeling the human cognitive procedures has been recently made through the simulated processes like acquired rule-based systems or manipulation of visual representations in decision-making (25). Computational modeling of cognitive functions has revealed that information from multiple sensory modalities are integrated in the frontal and parietal lobes of the brain (26,27).

COMPUTATIONAL MODELLING OF NERVE GROWTH FACTOR SIGNALLING

Nerve growth factor (NGF), the prototypic member of the neurotrophin family of growth factors, which was discovered by the Nobel Laureate, Rita Levi-Montalcini, plays a pivotal role in neuronal cell growth and differentiation in both peripheral and central nervous systems in health and disease (28,29). Furthermore, NGF is implicated in (*i*) the mechanism of action of a wide range of psychotropic agents (30-34), and (*ii*) the therapeutic effect in neuropsychiatric and cardiometabolic diseases (29,35-37). Since the mechanisms underlying the formation of complex neural networks have not been fully understood, the methods of statistical mechanics have been recently applied to extract predictions for cellular signalling networks. In this respect, NGF-induced neuronal differentiation has been modelled (38). In another modelling approach, the actions of NGF and epidermal growth factor (EGF) in rat pheochromocytoma cells have been investigated. Based on the findings, NGF and EGF stimulate extracellular regulated kinase phosphorylation with distinct dynamic profiles (39). These data give the opportunity to predict the cellular response to growth factors.

APPLICATION OF COMPUTATIONAL MODELS FOR THE STUDY OF THE ENDOCANNABINOID SYSTEM

The functionality of a neural network depends on the acquisition of morphological and functional polarization that begins with axonal specification and elongation. The endocannabinoid system (eCBs) which is implicated in the mechanism of action of psychotropic agents and regulation of hypothalamic-pituitary-adrenal axis activity (30-33,40,41), exerts a regulatory role on neuronal differentiation, dendritogenesis, and synaptogenesis (42). This ubiquitous signalling system mediates the inhibition of electric potentials (43), blocking of synapse stabilization (44), and short-term synaptic weakening (45). In fact, the eCBs is a neural network which plays a key role in the brain development processes and modulates brain functions (46), involving the cannabinoid CB_1 receptors. The neuromodulatory action of eCBs at network level is not yet fully understood. Using computational modelling, it has been shown that CB_1 receptors modulate the electrical activity in cortical neural networks (47). Modelling of the hippocampal neurons has revealed that CB_1 receptors play a critical role in the maturation of dendrites and assembly of axon initial segment (48). Neural network models have also demonstrated the modulatory effects of the eCBs on rapid eye movement (REM)-sleep. The activation of eCB-CB_1 signalling system results in the attenuation of brain activation during the REM-sleep (49). Moreover, neural network models have demonstrated the modulatory effects of CB_1 receptors on gamma-aminobutyric acid (GABA) transmission in the activated brain regions during REM-sleep (50).

MEDICAL APPLICATIONS OF COMPUTATIONAL MODELLING

Designing of drug delivery systems

In recent years, application of nanoparticles composed of discrete molecules and chemicals for targeted drug delivery has attracted a growing interest. The physical characteristics of nanoparticles enable them to deliver their contents directly to the disease site (51). In this context, computational models in which the fate of nanoparticles are simulated, have been developed to study the interactions of nanoparticles with the biological environments (52). This may result in the development of more precise drug delivery systems.

Predicting the adverse effects of drugs

In the early stages of drug discovery, computational models may be used to predict the potential side effects (53). This approach, other than the patient safety, may save time in drug approval process.

Tissue repair

A wide variety of diseases with multiple symptoms or disabilities have created demands towards the development of regeneration strategies or tissue replacement. Meanwhile, the limited efficiency and slow development of the currently available biomaterials limit their utility for regenerative applications. The modelling toolkits have been designed to predict the best composition for biomaterials leading to the optimized conditions for tissue repair (54).

Eye surgery

Computational modelling may be used to refine the technique of laser eye surgery for a better vision. In this sense, biomechanical models of human cornea have been developed to simulate the laser surgery. These models may be used in the virtual course for ophthalmologists-in-training (55).

Tuberculosis

Six months of treatment with several antibiotics may result in noncompliance in patients with tuberculosis. An experimental/computational approach has been recently used for modelling of the disease and patient's immune response that may lead to the prediction of treatment outcome and patient adherence (56).

Cardiometabolic diseases

Computational models have been used to improve the design of implanted devices including the coronary artery stents, artificial heart valves, the mechanics of blood vessel growth, blood flow, and heart valves (57). The models are also promising for further study of obesity therapy (58). Of note, a recent project designated multi-scale immune system simulator for the onset of type 2 diabetes (MISSION-T2D) aims to develop an integrated and patient-specific model, clustering multiple data for the simulation and prediction of the onset and progression of this cardiometabolic disease (59). Computational models have also provided decision-making tools which are based on the detailed analysis of the specific characteristics of patients leading to a more effective treatment (60).

Imaging

Development of the imaging techniques such as fMRI, PET, magnetoencephalography, and diffuse optical tomography has resulted in the remarkable advances in neuroscience. Simultaneous application of these techniques may provide more detailed information about the brain structure and its functional dynamics. Computational models in which several imaging modalities are combined have provided the opportunity to monitor the brain function during anaesthesia or sleep (61,62). Similar models may be used for a better understanding of the dynamics of brain function during the neurological disorders.

Biosensor technology

Biosensor is an analytical device which is made up of a specific biological element that recognizes a specific analyte, and a transducer which translates a biorecognition event into an electrical signal (63). Biosensors are widely used for clinical diagnostics and drug analysis (64-66). In order to optimize the configuration of a biosensor, computer-aided modelling may introduce various efficient designs. Thus, computational modelling of biosensors with perforated membranes has attracted an influential interest (67,68).

CONCLUSION

Computational models have provided a unique opportunity to develop novel hypothesis and solutions towards the challenging scientific problems. In this context, computational modelling for the neural system has resulted in a better understanding of the underlying physiological and biochemical events that mediate the key neuronal properties. Using the neural network computing and hybrid neural techniques, the complex analytical problems may be solved and the demands of modern neuroscience research be met. Noteworthy, the development of appropriate methods, algorithms, and software in the fields of mathematics, physics, chemistry, and biomedicine is critical for providing sufficient computational power. Such an *in silico* power may hopefully be transmitted to *in vivo* applications in biomedicine.

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