Agent-based Exploration ofWirings of 
Biological Neural Networks: Position Paper

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Abstract
The understanding of human central nervous system (CNS) depends on knowledge of its wiring. However, there are still gaps in our understanding of its wiring due to technical difficulties. While some information is coming out from human experiments, medical research is lacking of simulation models to put current findings together to obtain the global picture and to predict hypotheses to lead future experiments. Agent-based modeling and simulation (ABMS) is a strong candidate for the simulation model. In this position paper, we discuss the current status of “neural wiring” and “ABMS in biological systems”. In particular, the paper discusses that the ABMS context provides features that require for exploration of wiring of biological neural networks.

1 Introduction
The understanding of the brain and the central nervous system (CNS) depends on knowledge of their wiring. Since direct recording from individual human neurons is impossible, indirect methods are used. In indirect methods, a particular group of nerve fibres or cells is stimulated and the responses of neurons that are affected by the stimulus (reflexes) are recorded. Up until 1994, the wiring of the human CNS was estimated by counting the number of neuron discharges that occur at specific times following a stimulus. But this indirect method is open to numerous methodological errors both in the stimulation and in the recording processes. Error free indirect estimation of wiring in the human CNS has recently been tested and now used in Ege University labs to reassess previously ‘established’ wiring in the CNS.

Although, neuroscientists are performing various experiments to explore wirings, there are still gaps in our understanding of CNS because of technical difficulties. For example, direct stimulation of nerves is very difficult in some regions, since they are located deep. And yet, there is no satisfactory theory on how these unknown parts of CNS operate. Therefore, neuroscientists rely upon the knowledge that is obtained in animal studies. Apparently, there is a strong need to predict the characteristics of these gaps in the knowledge by putting together information that is available from both human and animal experiments. And such a prediction can be done using computational simulation techniques.

Agent-based modeling and simulation (ABMS) seems as a strong candidate for the simulation work and hence the solution to the problem of putting information together to predict hypotheses for future studies. ABMS is a new approach to modelling systems and is composed of interacting, autonomous agents. It is a powerful and flexible tool for understanding complex adaptive systems such as biological systems.

Biological systems are highly robust, flexible and has ability to adapt to the changing circumstances. They are composed of bio-entities that operate in naturally dynamic environments. It is widely accepted that ABMS coordinated by self-organization and emergence mechanisms are an effective way to design biological systems. Because it is possible to associate different elements of a biological process to independent computing entities (agents). Furthermore, ABMS allows explicitly modeling the environment in which bio-entities operate.

Biological neural networks can be understood in terms of complex networks. Characterizing structure and function of complex networks is an interdisciplinary approach called network science. Recent collaborative studies in network science and neuroscience show that CNS have features of complex networks such as small-world topology, highly connected hubs and modularity. In another work, it has been shown that an initially random wiring diagram can evolve to a functional state characterized by a small-world topology of the most strongly connected nodes and by self-organized critical dynamics. Thus, it seems that neural wiring problem can be reduced to network formation problem in which each node has discretion in forming...
its links in the network relationship. In this sense, abstractions of neurodevelopmental mechanisms [van Ooyen, 2003] of biological nervous systems can be used to form networks.

We believe that the use of ABMS and self-organizing dynamics, along with the adoption of neuroscience and network science knowledge will make it possible to harness the complexity of this problem domain by delegating software agents to simulate bio-entities.

Additionally, we wish to use ABMS in neuroscience as an adjunct to laboratory and theoretical research. Simulation can be seen as a substitute for an experiment that is impossible to perform in reality, where impossibility can be either theoretical or pragmatic [Hartmann, 1996]. Thus, an ABMS tool to investigate neural wiring can also be used to make “in-machina” experiments and to test hypothesis.

This paper is organized as follows. The next section explains the wiring problem of biological neural networks. In Section 3 ABMS in biology is discussed. Section 4 states how ABMS can be used for exploration of neural wiring. Related work is given in Section 5 and finally, Section 6 concludes the paper.

2 Wiring of Biological Neural Networks

The primary aim of neuroscientist working on neural wiring research is to investigate functional connections in between biological neural networks. This way we will have a better understanding about how CNS works. This primary aim can be broken into the following specific aims:

• To produce satisfactory explanations for the current situation.
  - To be able to summate information available from different resources for different pathways.
  - To be able to pinpoint gaps in the system as the final working of the system is known.

• To be able to bring out testable hypotheses for the unknown sections of the system.

With its multiplicity of cell types and complex patterns of cellular interactions, the nervous system represents the most complex organ of animals. Understanding how neuronal circuits are wired is one of the holy grails of neuroscience. Besides many experimental advances in determining the cellular machinery, theoretical approaches have also proven to be useful tools in analyzing this machinery. A quantitative understanding of neural wiring can allow us to make predictions, generate and test hypotheses, and appraise established concepts in a new light.

The nervous system is a network of specialized cells that communicate information about an organism’s surroundings and itself. It processes this information and generates reactions in other parts of the body. It is composed of neurons and other specialized cells called glial cells that aid in the function of the neurons. A neuron is an excitable cell in the nervous system that processes and transmits information by electrochemical signalling. A typical neuron can be divided into three functionally distinct parts, dendrites, soma and axon. Roughly speaking, the dendrites play the role of the “input device” that collect signals from other neurons and transmits them to the soma. The soma is the “central processing unit” that performs an important non-linear processing step (called “integrate & fire model”): If the total input exceeds a certain threshold, then an output signal (spike) is generated [Gerstner and Kistler, 2002]. The output signal is taken over by the “output device”, the axon, which delivers the signal to other neurons. Furthermore, neurons respond to stimuli, and communicate the presence of stimuli to the central nervous system, which processes that information and sends responses to other parts of the body for action.

A number of specialized types of neurons exist: sensory neurons respond to touch, sound, light and numerous other stimuli affecting cells of the sensory organs that then send signals to the spinal cord and brain. Motor neurons receive signals from the brain and spinal cord and cause muscle contractions and affect glands. Each sensory neuron receives information from a special ending, receptor. There are many receptors in the skin, in the muscle, in the joints and within the viscera.

Figure 1 shows a simplified wiring diagram of human masticatory system during no mastication. This diagram is a result of various experiments established in Ege University labs [Naser-Ud-Din et al., 2010, Lobbezoo et al., 2009, Sowman and Türker, 2008, other past experiments and animal studies (reviewed in detail in Türker, 2002)]. The reason for using animal studies is: direct electrical stimulation of nerves is very difficult in some parts of the jaws region, since these nerves are located deep in the face and close to numerous blood vessels [Scutter et al., 1997]. Even though the dashed lined neurons are represented like a single neuron in the figure, there may be a few (oligosynaptic) or many (polysynaptic) neurons (each one connected to several other ones) in that part of the wiring diagram.

Using human reflex research [Türker, 2002] neuroscientists are carrying on finding pathways as much as possible, but as mentioned above investigating some parts of the picture is almost impossible to obtain using current techniques. Consequently, there must be computational tools (and techniques) that allow combining the current findings to predict the wiring of the pathways that are impossible to obtain in human subjects.

3 Agent-based Modeling and Simulation in Biology

Agent-based modeling and simulation (ABMS) has increasingly been adopted as a suitable approach for analyzing complex systems and evaluating theories and...
models of complex systems (especially for social or biological systems). ABMS is used in a broad range of domains, including social and economical simulation, biological systems, traffic and crowd simulation and in other domains [Macal and North, 2006].

Since ABMS allows biological systems to be decomposed into several independent but interacting entities, usage of ABMS for biological systems is widespread [Amigoni and Schiaffonati, 2007; Merelli et al., 2007]. Each day, more promising evaluations of ABMS for solving biological problems are being developed (e.g.: Maniadakis and Trahanias, 2009; Folcik et al., 2007; Christley et al., 2007). Basically, the reasons for using ABMS in biology are twofold [Amigoni and Schiaffonati, 2007]:

- ABMS in biology can be used to support information gathering, processing and integration. In other words, ABMS can be used to summate information gathered from various experiments and can help us to understand biological processes.
- ABMS can be used to simulate the behavior of biological systems. As Hartmann says [Hartmann, 1996]: “Simulation can be seen as a substitute for an experiment impossible to make in reality, where impossibility can be either theoretical or pragmatical”. Hence, by simulating the behavior of biological systems it becomes possible produce testable hypotheses for the unknown parts of the system.

Following there paragraphs explain the features provided by ABMS that support these reasons.

Biological systems are self-organized in their nature [Camazine et al., 2001]. A system is said to be “self-organizing” if it is able to reorganize itself by managing the relations between components, either topological, structural or functional, upon environment perturbations solely via the interaction of its components, with no requirement of external forces [Gardelli et al., 2009]. Self-organization allows us to reduce the complexity of problem by concerning not the overall system, but the behaviors of individual agents. It is widely accepted that ABMS is well suited for simulating self-organizing systems [Macal and North, 2006]. For instance, when simulating biological systems an agent is a good abstraction for representing bio-entities which represents a global phenomena when put together.

Environment also plays an important role when simulating biological systems. There are two roles of the environment when simulating biological systems [Klügl et al., 2004]. Firstly, simulation can be used for modelling environment. Real bio-entities can operate in naturally dynamic complex biological environments. Thus, when simulating the behavior of biological systems this dynamism should be explicitly modeled [Helleboogh et al., 2007]. Secondly, environment can be used for simulation. Since ABMS can be seen as simulated multi-agent systems situated in a simulated environment, in simulations the modelled environment should always be a first class entity that is as carefully developed as the agents themselves [Klügl et al., 2004]. This is especially true for self-organizing multi-agent systems, as the agents’ environment guides the selection and self-organization process. Furthermore, the study of biological systems needs experiments to explore their behaviors. Similarly, simulation models of such systems must be run many times to explore if they behave as expected. Eventually, to be able to assess simulation results, data generated by the simulation runs and data collected from experiments should be compared. In such a situation, environment can be used as a regulator for sake of calibration in order to obtain results that can be analyzed and compared to actual data [Bandini and Vizzari, 2006].

However, running an agent-based model is an easy task, but the analysis is not [Richiardi et al., 2006]. Even for simple scale simulations, we must cope with vast parameter space of the model. Thus, parameters should be tuned in order to find the optimal behavior of an agent performs. This optimal behavior is going to influence the global behavior of its collective. Nevertheless, even if supported by a reference tool, the tuning process can be quite time-consuming. It is apparent that theories and tools allowing automatic tuning of parameters are needed. Recent studies address the problem of automatic tuning of parameters of agent-based simulation models [Bonjean et al., 2009; Montagna and Rolli, 2009; Gardelli et al., 2009; Terano, 2007; Fehler et al., 2006].

Besides the aforementioned clear advantages, the main problem when using ABMS in biology is the level of trust to the outcome obtained using ABMS [Amigoni and Schiaffonati, 2007]. In other words, the weak validation of the results obtained makes ABMS hard to trust. The reason for that is the lacking of a governing theory. Moreover, experimental data obtained are sparse and thus a direct comparison to the results obtained in simulation is sometimes difficult. Overcoming this drawback requires developments of aforementioned calibration mechanisms and, closer collaborations between biologists and computer scientists.
4 Using ABMS for Exploration of Neural Wiring

ABMS can be effectively used to tackle exploration of neural wiring problem due to its aforementioned advantages. In this section we propose that the use of ABMS and self-organizing dynamics, along with the adoption of network science and neuroscience knowledge, would lead us to highlight neural wiring problem.

4.1 Proposed Approach

There is considerable amount of knowledge about developmental neuroscience. The study of neural development aims to describe the cellular basis of brain development and to address the underlying mechanisms. The science of studying neural development by computational and mathematical modeling is relatively new [van Ooyen, 2003]. Neural development models are used to study the development of the nervous system at different levels of organization and at different phases of development, from molecule to system and from neurulation to cognition.

Neurodevelopmental processes can be broadly divided into two classes: activity-independent mechanisms and activity-dependent mechanisms. Activity-independent mechanisms are generally believed to occur as hardwired processes determined by genetic programs played out within individual neurons. These include differentiation, migration and axon guidance to their initial target areas. These processes are thought of as being independent of neural activity and sensory experience. Once axons reach their target areas, activity-dependent mechanisms come into play. Although synapse formation is an activity-independent event, modification of synapses and synapse elimination requires neural activity. Activity-independent mechanisms are said to be self-organizing dynamics of neurons. There is no information at a higher level of organization than the individual neuron, so all the organization in central nervous system and brain is an ‘emergent property’ of the interaction of large numbers of individual neurons.

Besides, the small-world architecture have been found in several empirical studies of brain networks in humans and other animals and it is shown that CNS have features of complex networks - such as small-world topology, highly connected hubs and modularity [Bullmore and Sporns, 2009]. More than that, it has been shown that an initially random wiring diagram can evolve to a functional state characterized by a small-world topology of the most strongly connected nodes and by self-organized critical dynamics [Siri et al., 2007].

To this end, inspiring from the above information gathered from neuroscience and network science studies, we may develop an agent-based model.

An important consideration when we use ABMS to simulate a system is deciding the level of abstraction to model the system. We can describe a system using different levels, aspects, or representations. As Prem [Prem, 1993] suggests, the level should be the one where the prediction of the behavior of the system is easiest; in other words, where we need least information to make predictions [Shalizi, 2001]. In this sense, in our biological neural network model, agents will represent bio-entities at cell and tissue level: neuron agents, receptor agents, and muscle agents.

Neuron agents will implement the activity independent (self-organizing) mechanisms of neural development. An apt learning algorithm will then be applied to make the network evolve to a small-world topology. Meanwhile, environment will control neural development using global parameters and characteristics. Since activity dependent mechanisms require neural activity, they will be modeled using experimental data obtained to calibrate the model together with receptor agents and muscle agents.

5 Related Work

Schoenharl et. al. [Schoenharl, 2005] developed a toolkit for computational neuroscientists to explore developmental changes in biological neural networks. This toolkit develops complex network topologies in neural networks using pruning. However, details of the methodology used (e.g. how the initial random network is constructed) and of simulation parameters (e.g. how the threshold parameter for pruning is obtained) are not clear.

Mano et. al. [Mano and Glize, 2005] presents an approach to self-organization in a dynamic neural network by assembling cooperative neuro-agents (CNA). The network is initialized with only unconnected CNAs and then during a learning period, the network self-organizes. The network of CNAs they presented is able to define criteria for adapting the genotypic transfer function, node strengths, connectivity between nodes, neuron proliferation, and even neuron deaths.

Maniadakis et. al. [Maniadakis and Trahianas, 2009] addresses the development of brain-inspired models that will be embedded in robotic systems to support their cognitive abilities. They introduce a novel agent-based coevolutionary computational framework for modeling assemblies of brain areas. They specifically employ self-organized agent structures to represent brain areas. Moreover, they introduce a “hierarchical cooperative coevolutionary” scheme that effectively specifies the structural details of autonomous, yet cooperating system components. However, this work focuses on brain slices rather than reflex pathways and aims to improve cognitive capabilities of robotic systems. But, introduced mechanisms may be used to support research efforts in the field of psychology and neuroscience.

Apart from agent-based approaches there are biological neural network simulators. They are used primarily to simulate spiking neural networks which are present in the biology to study their operation and characteristics. In this group we can find sophisticated simulators such as GENESIS [Bower et al., 2003] and NEURON [Hines and Carnevale, 1997]. They are de-
signed to provide biologically realistic models of electrical and chemical signalling in neurons and network of neurons. They support the simulation of complex neural models with a high level of detail and accuracy. However, this research into electrical signalling ignores the fascinating problem of wiring of biological neural networks.

6 Conclusion and Prospects

In this paper we have shown that neuroscientists working on neural wiring has a strong need of computer scientists. Then we have provided a critical outlook on agent-based modelling and simulation in solving their problems.

The literature shows that, day by day, ABMS is getting more mature for biological systems. However, although ABMS is a pioneering and powerful approach in biology, research into the design and use of agent-based models is still in its infancy and requires closer collaborations between biologists and computer scientists. The inherent differences between biological and computational models, along with the difficulty of obtaining precise biological data, make both approaches indispensable [Fisher and Henzinger, 2007].

Up to now, we have established a “core” biological model involving various simplifications and assumptions (Section 2). We proposed then a preliminary agent-based simulation model (Section 4). Next step will be enhancing, implementing and calibrating the proposed model. We will then compare in silico experiments with in vitro biological experiments. As a result of comparison we will either adjust our computational model or develop new/improved biological experiments to revise the biological model. This cycle will proceed until we get satisfactory results.

We see this study as the first step for understanding neural circuits. Within the scope of the goals of neural wiring research, we are planning to develop an agent-based simulator that combines currently available bits of data into a manageable format. So that the working of the entire nervous system can be tested. The simulator will be used to explore the wiring of, possibly dynamic, black box networks. This will probably lead us produce new techniques to construct and test network development inspiring from developmental neuroscience as well as we will use existing network development techniques. Furthermore, the developed simulator will be used for predicting future human reflex findings in via putting forward workable hypotheses about human CNS. Meanwhile, we will demonstrate the power of the developed simulator through a series of case studies.

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