Analysis of a 3-neuron network in *Lymnaea stagnalis*
– How symmetry and delay affect dynamics in neural networks

Master's
Thesis Proposal

Shanmei Liu

Department of Computer Science
Memorial University of Newfoundland

September 23, 2013

1. INTRODUCTION

Oscillation is the basic kinetic model of both individual neurons and neural networks. At the cellular level, it gives the elemental concept to study and illuminate functions and mechanisms of higher level such as cerebral cortex, thalamus, basal ganglia, cerebellum, the entire brain and central nervous system, where motion coordination, perceptions, cognition, memory, emotion etc. are generated. Evidence shows that oscillatory patterns are critical for cognitive states and sensory processing [1], [2], [3], [4], and even for the diagnosis and treatment of various mental diseases and brain disorders [5], [6], [7], seen in application of the scalp electroencephalography (EEG). Thus it is inherently a major area of research in neuroscience to determine how oscillations are generated and what their roles are.

Respiratory rhythmogenesis in the mollusk *Lymnaea stagnalis* is known to be controlled by a 3-neuron neural network known as a **central pattern generator (CPG)** [8], [9]. This relatively simple real-world case, which exhibits a ring topology, is an ideal system to analyze the generation of respiratory rhythm which is a result of the oscillation in the neural network.

Mathematical models usually adopt a variety of abstractions in order to describe complex oscillatory dynamics. Hence, in an attempt to measure how the mathematical abstraction conforms to experimental observations, and how modeling and simulation can verify hypotheses, analysis of a 3-neuron ring-type neural network focusing on features of symmetry and delay is proposed. Symmetry and delay affect the behavior of a network in spatial and temporal aspects, and both have a strong impact on the complexity of a system.

2. BACKGROUND

Neurons are a type of cell distinguished from other cells by their unique complex shapes and extensive branches. Specialized for intercellular communication, they are responsible for receiving and transmitting information, and are particularly sensitive to input stimuli especially when excitatory and inhibitory signals reach a balance, which can be reflected in oscillatory states.

In terms of morphology, a neuron can generally be decomposed into 3 parts: **Cell body** (**Soma**), **Axon** and **Dendrites** [10]. Dendrites are treelike thin appendages at one end of the cell (neuron); they receive impulses from other neurons and transmit **electrical stimulation** to the soma. The axon is a single elongated fiber that carries the nerve signal (impulse) away to other neurons. The electrical activity passing through the axon is called the **action potential**. The soma contains the **nucleus** and other structures that exist in other common living cells. The most important role of the soma is producing **neurotransmitters**. Neurotransmitters are chemical messengers that either excite or inhibit neighboring cells by binding to receptors.

In neural connectivity, **synapses** play the essential role. They functions as an intermedia between the presynaptic and the postsynaptic receptors. A synapse is actually a small gap (i.e. there is no physical continuity between these pre- and postsynaptic elements) at the end of a neuron that allows information to pass from one neuron to the next, through the process of **synaptic transmission**. Most synapses connect axons to dendrites, but other types of connections also exist, including axon-to-soma, axon-to-axon, and dendrite-to-dendrite. There are two types of synapses, **chemical synapses** and **electrical synapses**, which differ from each other in respect of chemical and electrical processes in the synaptic contacts [11]. Both chemical synapse and electrical synapse "decode" the information bring by action potential and pass the information on to the next cell.

Oscillatory activity is ubiquitous in all levels of neural systems, which means neural tissue can generate oscillatory activity in many ways. Basically, this can be seen on two levels, the microscopic and the macroscopic.

At the microscopic level, neurons can be regarded as cell-driven oscillators [12]. When they are completely isolated from any synaptic input, cellular membrane properties of individual neurons have the ability to produce rhythmic behavior that appears either in **membrane potential (**i.e. **transmembrane potential**, the difference of electronic potential between the inside and outside of a cell body, exists in all animal cells,**)** or **action potentials**. If neurons form a network, the oscillatory activity of the neural network often arises from **feedback connections** between the neurons connected with excitatory or inhibitory synapses, i.e. the network itself would produce bursts through synaptic interactions. This is a result of the synchronization of individual elements, and more complex phase relationships can arise. At the macroscopic level, synchronization of a large number of neuronal cells can give rise to macroscopic oscillations that generate EEG signals [13] with **non-linear dynamics,** like the well-known brain waves: Beta, Alpha, Theta and Delta, observed in states of consciously alert, physical and mental relaxation, somnolence with reduced consciousness, and deep sleep, respectively [14], [15].

Symmetry is a transformation that leaves an object invariant, which is one of the most common phenomena seen in nature. It has many fascinating characteristics in mathematics, linked to the field of **group theory** (a **group** is what allows mathematicians to perform a sort of "arithmetic" with non-number objectives [16]), which forms an important branch in mathematics. Moreover, symmetry is also a kind of complexity reduction. For instance, exploiting the symmetric property in **Discrete Fourier Transform** (DFT), we can save the source of storage and computation; this gives us the idea to take advantage of symmetry in simulation and implementation on a computer. In short, given that symmetry may bring some special properties, interest arises in how dynamics of neural networks may vary when symmetry is introduced.

In addition to symmetry, **delay** is also introduced to describe the temporal features of a system, which either arise directly in a model or be put in as a simplification to achieve particular dynamical effects. Delays exist everywhere due to different system response time and signal transmission speed between individual components. For example, we know both chemical and electrical signals are transmitted between neurons. The typical synaptic delay for a chemical synapse is about 2 ms, while for an electrical synapse it may be about 0.2 ms, since electrical synapse is the rapid transfer of signals [17]. With the important role it plays in the connection of neurons, delays are widely studied and used in both biological and artificial neural networks.

Lymnaea stagnalis (Great Pond Snail) is a kind of mollusk, the population lives in stagnant water, and are a classic model to study the molecular and electrical properties of neurons. It is widely used in neurobiological experiments, [18], [19], [20], [21]; for “its beautiful brightly-pigmented orange neurons” with the feature that they can be easily identified (since they are large in size) and the ability of *in vitro* reconstruction of synapses and neural circuits, i.e. to grow neurons in cell culture [8], [22]. Given the above information, *Lymnaea stagnalis* is a suitable example for modeling and simulation since the required experimental input data is available.

3. PROBLEM STATEMENT

Patterns of oscillation have a strong resemblance to the rhythmic behavior exhibited in respiration. Since rhythmic respiratory behavior is inherently a reflection of the oscillatory patterns in a neural network, the respiratory CPG of the mollusk *Lymnaea stagnalis* is chosen for modeling and simulation. Analysis will be applied on this ring-type network concentrating on the impact brought by features of symmetry and delay. Then, the questions such as why the breathing rhythm is generated as a particular mode, how it changes, and what factors play an important role in these processes, will be answered.

4. SIGNIFICANCE

Like vehicles are the extension of feet, computers are the extension of human brain. With increasing power of computing, numerous real-word phenomena are able to be simulated and analyzed through numerical methods on computer. The **blue brain project** [23] launched with an extreme ambition to build a virtual brain, using a supercomputer, that possesses the abilities of thinking, remembering, decision-making, cognition, consciousness and emotions, which are generally accepted as the unique virtues of a biological brain. Neuroscience, as a traditional empirical discipline, is pouring its influence in regions like artificial intelligence, machine learning and pattern recognition. Computational neuroscience is a relatively new field, originating from the mathematical model built by Alan L. Hodgkin and Andrew F. Huxley [24], [25] (the Hodgkin-Huxley formalism is still central to computational neuroscience [26]), it combines computational theory and technique with neuroscience, for furthering our understanding of brain function and translating this knowledge into potential technological applications.

People may be surprised to know that an exceedingly complicated system like the human brain can handle multiple problems and inputs by the same wiring since the repetitive architecture like interconnected homogeneous layers is common to see in nervous tissue [27]. A recent study also shows that the size of networks can affect information-energetic transmission efficiency: the smaller the size of network, the more efficiency it can gain [28]. Thus, the knowledge gained from study and research based on simple systems would be an essential foundation and clue for unlocking the complicated processes occur in the nervous systems of a variety of natural creatures, towards the goal of understanding ‘the most complex, sophisticated, and powerful information-processing device–known as the human brain” [29].

The main purpose of this study is an expectation that the analysis on small neural network can provide useful insight for understanding more complicated nerve structures and their functions. Also, as this is first attempt in modeling the whole respiratory CPG neural network in the mollusk *Lymneaea Stagnalis*, to illuminate the differences and similarities of respiratory mechanism in invertebrates and vertebrates is another motivation to commence this study.

5. LITERATURE REVIEW

5.1 Oscillation

The study of oscillation originates from classical mechanics, has a strong relation with mathematics since such phenomena are most likely to be described and analyzed by mathematical theories and techniques, especially in the area of **dynamical systems**. Several dynamical mechanisms that generate rhythmicity have been studied for years. Some common oscillators among those are **harmonic** (**linear**) oscillators, **weakly-coupled limit cycle** oscillators, **relaxation** oscillators and **delayed-feedback** oscillators derived from oscillatory phenomena in physics and have been widely used in the fields of both biological and artificial neural networks, [1], [30]. They are the theoretical foundation rely on which many classic neuron and neural network models are established, with each defined at a different level of abstraction and in an attempt to model different aspects of neuron and neural systems.

The term **pattern** is defined to be the oscillatory behavior of a network composed of coupled neurons. There usually exist more than one pattern of oscillation in a particular system [31], and systems may also be able to switch from one pattern to another, like a horse's gait can switch from walking to trotting to galloping, because such rhythmic behaviors controlled by a neural **central pattern generator** are inherently a reflection of changes in neuronal firing [32].

5.2 Symmetry

Symmetry, as a feature of geometry in a particular system, has been studied in many researching areas since it will lead to special properties in a system [33], [34], [35], [36]. Classifications of symmetry with a respect to system geometry include **radial symmetry**, **bilateral symmetry, spherical symmetry,** and **biradial symmetry**. Here we introduce two types that are more closely related to the model under consideration. The first is radial symmetry (Figure 1), also known as **rotational symmetry**. An object exhibits rotational symmetry if it appears unchanged when rotated through some angle. Examples of rotational symmetry can be seen in natural creations such as sea stars and daisies.

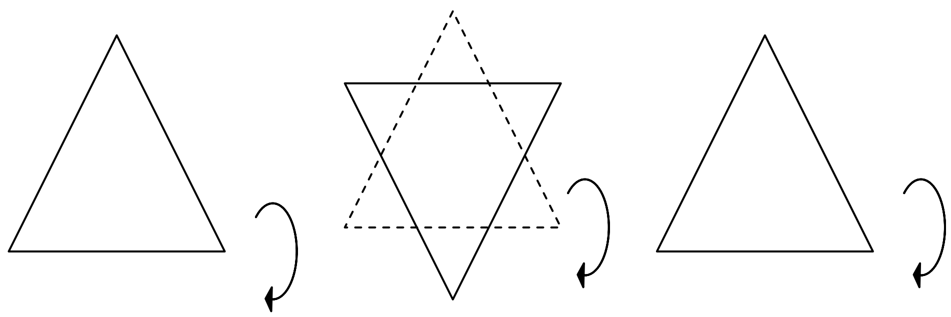

Figure 1. Rotating an equilateral triangle 120° leaves its appearance unchanged.

The second is bilateral symmetry, also called **mirror symmetry** or **reflection.** An object exhibits bilateral symmetry, if it can be broken down into two parts, one part is the exact reflection of the other (Figure 2). In nature, it's the most common appearance of animals, such as butter fly, and we human beings.

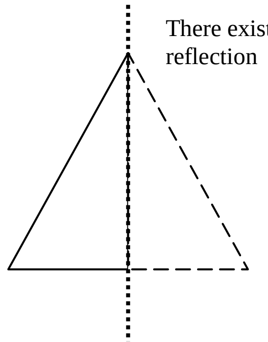

Figure 2. Symmetry with respect to reflection.

5.3 Neuron Models

To deal with the work of modeling an entire neural network, one must be taken into account that both single-neuron and whole-network behaviors hinge on modeling of individual components, i.e. the single neuron.

Single neuron models can be classified into two major categories: detailed biophysical models, and simple phenomenological models. The former include conductance-based (COBA) models following the work of Hodgkin and Huxley (1952) [24], known as the Hodgkin–Huxley-type models whose essence is the combination of different ion currents (based on the mechanism that neurons generate electric signals by the flow of ions along their membranes), can successfully reproduce the complex and rich behavior that biological neurons exhibit, as observed experimentally via intracellular electrophysiological measurements. However, simulation of a network built with such models is usually computationally expensive, analytically and computationally intractable. The later, in contrast, are very simple models such as Boolean, binary, on/off (**McCulloch-Pitts** [37], **Hopfield** [38], [39]) models, have been well studied and widely used in fields of artificial neural networks. There also exist some models between two extremes such as FitzHugh Nagumo [40], [41], [42], Morris Lecar [43], [44], and integrate-and-fire (IF), [45], [46], [47]. These models can be viewed as a simplification of Hodgkin–Huxley model by reducing the original four-dimensional model to fewer dimensions, since dynamics of membrane potential and voltage-gated conductances can be reduced as long as transmembrane conductances have fast kinetics [42], there are fewer parameters allowing simulations of large-scale networks to run quickly [48], [49], [50].

5.3.1 Hodgkin-Huxley (HH) Model:

The Hodgkin-Huxley (HH; Hodgkin & Huxley, 1952) model is known for the generation of the action potential**,** and the ability to capture a verity of complex dynamical features that real neurons can exhibit. However, its highly non-linear and multi-variable features make it difficult to analyze mathematically. The basic concept of Hodgkin-Huxley model is to treat the membrane as a circuit, then reconstruct the action potential by building equations for the ion channels [51], [52]. The blue brain project also adopted the detailed Hodgkin-Huxley Model in simulation performed on IBM's Blue Gene supercomputer. Their detailed multi-compartment model follows the **cable theory** of Rall**,** formed by segmenting the dendritic tree into electrically coupled Hodgkin-Huxley–type compartments, which results in the enormous requirement of computing power [53].

Information about the application of the HH model of interest in this study can be seen from two aspects:

1) The application of HH model in realistic systems closely related to this study.

   A HH-type model of a two-level mammalian central pattern generator (CPG) is constructed [54], which is a more complex realistic system compared with the respiratory CPG of the pond snail proposed in this study. The authors point out that lacking knowledge of the network mechanisms is the main difficulty in modeling; this gives support to the opinion that the network behavior, rather than single-neuron behavior plays the essential role in studying rhythmic activity of a system. The RPeD1 neuron in the *Lymnaea stagnalis* has been successfully modeled using HH-type model [55], providing the impetus for modeling the whole CPG in *Lymnaea stagnalis*.

2) The network behavior based on HH type models, with respect of spatiotemporal properties like delay, ring structure, symmetry, etc.

   Delay can induce the synchronization transition of neural networks and its effect has been studied in HH models by Wang et al. [56], [57], [58]. Delay-coupled ring type networks composed of HH type single-neurons have been analyzed via bifurcation theory [59], which also shows that a short-cut can destroys the rotational symmetry of the ring. Another study also shows how delay can affect the spatiotemporal periodic firing patterns of a feedforward loop comprised of oscillatory HH neurons [60] and how it can regulate the behavior of biological networks as an efficient biocompatible control tool [61]. Analysis on the bursting rhythm of several CPGs including the Lymnaea respiratory CPG is given in [62].

The information provided above shows the feasibility of applying Hodgkin-Huxley model in this study for realistic simulation.

5.3.2 Hopfield network model [63], [64]

The Hopfield model is one of the most successful models have been established, which can be seen in its prevalence of application in a vast region of research, from small systems to very large systems, from biological neural network to artificial neural network. As an artificial neural network model, it has been used to solve problems such as pattern recognition, image segment, etc. We also know that artificial neural network can be used to mimic the human brain structure and function. Studies on illuminating the origin and mechanism of cortex functions like cognition, memory etc. also adopt this model to simulate the network behavior of biological neurons [65], [66], [67], [68].

Also, a number of studies have used Hopfield model when model the effect of time delays in real-word problems [31], [69], [70], [71], [72], [73]. Several studies about CPGs based on the Hopfield model show its excellence in studying network behavior [74], [75], [76].

Since the Hopfield model can highlight the effect of neural coupling, downplay the role of sing-neuron dynamics, and give more focus on the network behavior, it corresponds with the concept of abstraction in this study. Moreover, its simplicity makes it suitable for applying theoretical/mathematical analysis.

6. METHODOLOGY

Consider the following steps for solving a scientific problem on a computer (Figure 3),

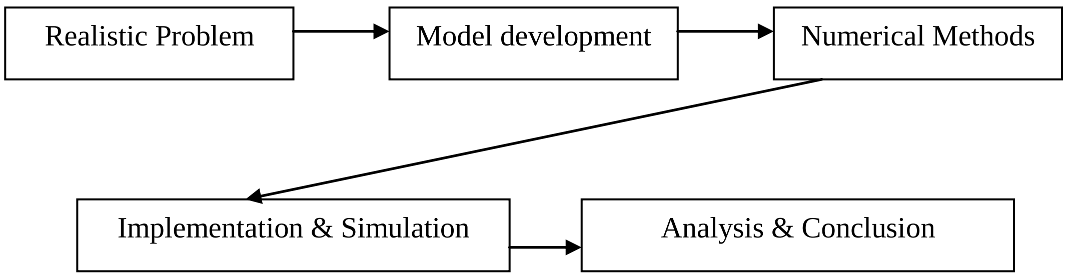

Figure 3. The procedure for problem solving on a computer.

Problems can be expected to arise in each step, and no doubt the first step-Model Development is the most difficult and critical among those to be faced.

It is difficult to build a good model with desirable abstraction, since: “A good theoretical model of a complex system should be like a good caricature: it should emphasize those features which are most important and should downplay the inessential details. Now the only snag with this advice is that one does not really know which are the inessential details until one has understood the phenomena under study.’’ [77]

As mentioned before, in the entire procedure of research, model development plays the most significant role, through which further analysis is able to commence, the following general scheme (figure 4) is given in [78].

Figure 4. Model development in 2 steps.

The conceptual modeling can be viewed as a collection of assumptions, algorithms, relationships, and data that describes the reality of a physical system, from which computational model can be constructed.

I. Conceptual Modeling

For reasons shown below, to understand of the oscillations and dynamics in a particular neural network, three preliminary partitions of modeling are presented based on the symmetric properties:

1. The respiratory rhythm of *Lymnaea stagnalis* is known to be controlled by a 3-neuron central pattern generator (CPG), including two identified **interneuron (**also known as **local circuit neuron,** a type of neuron with a feature of relatively short axons), Input 3 (I.P3.I) and Visceral Dorsal 4 (V.D4) controlling **expiration** and **inspiration** respectively, and the third, a giant **dopamine** cell of the right pedal ganglion (R.Pe.D1). Together, these neurons form a **ring** type network (Figure 5). The VD4 neuron is connected via reciprocal **inhibitory** synaptic connections (Chemical synapses are either inhibitory or excitatory, according to their impact on postsynaptic neuron) to both the RPeD1 neuron and the Ip3I neuron. The Ip3I neuron can be excited by RPeD1 via a **biphasic** (mixed inhibitory-excitatory) connection, i.e., excitatory via **postinhibitory rebound** (PIR) (PIR is an intrinsic property of many neurons that generates rhythmic electrical activity [79], [80]) [8].

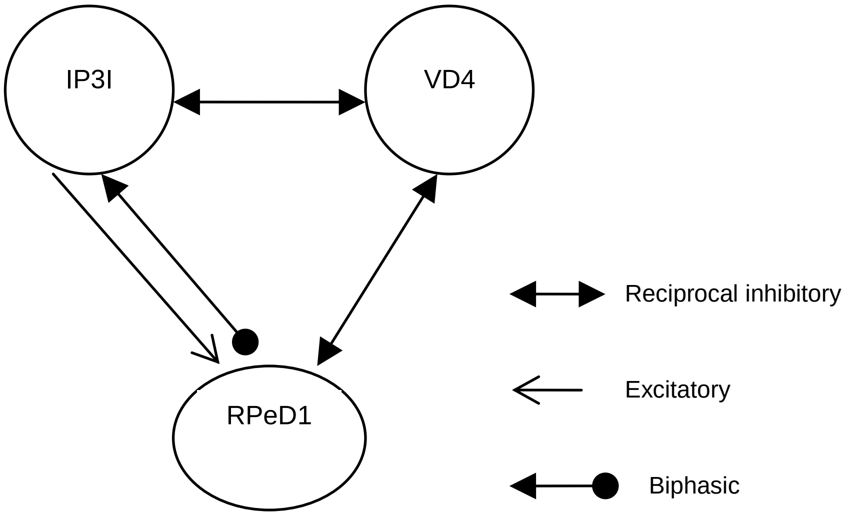

Figure 5. Central pattern generator that controls respiration in the Lymnaea stagnalis.

Therefore, in this neural network, treating the three different kinds of neural cells as identical, a network of rotational symmetry is founded (Figure 6). One thing that should be noted is that symmetric property does not only mean the neuron in a network is identical, the connection between individual elements is sometimes more important. With this basic structure, a further analysis of the oscillation of a system comprised of three identical oscillators could be applied, with delays considered as an additional feature.

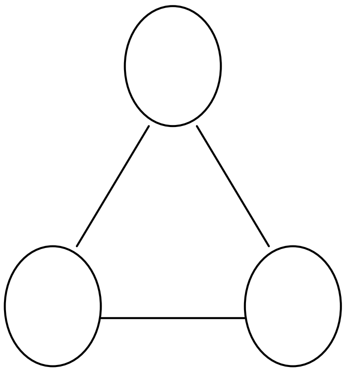

Figure 6. A ring of three identical neurons exhibits rotational symmetry.

2. By splitting the ring to a 2-indentical neurons and one distinct neuron, a bilateral symmetry is smoothly founded (figure 7), the split is based on following statements of [13] that

    1) These three neurons are sufficient for the generation of respiratory behavior.

2) Without RpeD1, the rest two interneurons failed to generate the respiratory rhythm but the phasic application of dopamine could elicit a similar burst though of higher frequency.
3) The continuous presence of dopamine cannot induce the rhythm generation of the two interneurons. Combined with the second statement, it means RPeD1 should be regarded as a special oscillator in this network.

And also that

4) "The R.Pe.D1 (Right Pedal Dorsal 1) neuron is spontaneously active and is responsible for the **initiation** of respiration, while the other two neurons, V.D4 and I.p3.I are quiescent except during active respiration." [55]

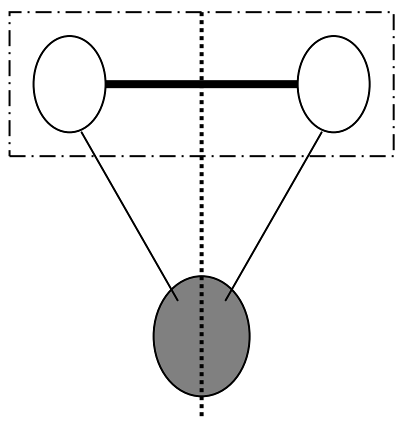

Figure 7. Bilateral symmetry derived from the previous rotational symmetry

The above statements imply that the similarity of functions in the two interneurons and a divergence in the third giant dopamine cell, RpeD1 more likely to be an initiator. This also leads to studies on the oscillation in a subsystem of 2 coupled identical neurons as in the dashed rectangle of Figure 7.

3. It is a natural sense that to validate a theory or hypothesis a contrast is needed, in this case, a model with asymmetry here. A recent survey of vertebrate provided evidence that inspiration and expiration are distinct and independent functions, but one of two dominates the behavior by generating a faster rhythm [81]. This hypothesis contradicts the common view that they are antagonistic phases of a unitary oscillator in the pattern of breathing, and gives the idea that the two neurons Ip3I and VD4 could also be regarded as distinct rhythm generators, with R.Pe.D1 functioning as an intermediary and initiator which regulates and synchronizes the whole network. Accordingly, this hypothesis

leads to the asymmetry show in Figure 8, which is suitable to examine this theory in the invertebrate mollusk.

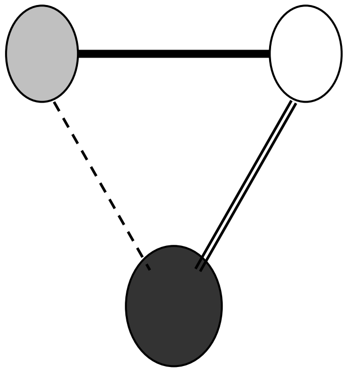

Figure 8. Asymmetry likely makes a system complex.

II. Theoretical Analysis Methods & Numerical Methods

Dynamical systems theory, especially **bifurcation theory,** which is commonly applied to the mathematical study on dynamical systems, will be the main method to apply theoretical/mathematical analysis on the dynamics exhibited by the model used in this study. In dynamical system, a bifurcation is like a transition, near which the neuron becomes excitable. Bifurcation theory can give prediction to threshold and other computational properties of a complex system [82], [83], [84].

Dynamical systems that have symmetries are called **equivariant dynamical systems**. Such systems can deal with the problem of coupled identical oscillators, and very useful in the study of neural networks [85].

The model developed will be system of, i.e. a system of **differential equations**, which will be analyzed using both theoretical and numerical methods. **Delay-differential equations** (**DDEs**) describe the behavior of systems with delays, characterized as the derivatives of some unknown functions at present time are dependent on the values of previous times. Numerically solving most DDEs is no more difficult than solving ODEs [86]. Previous studies have shown the usefulness of DDEs in study on neural networks [87], [88], [89], MATLAB also provides specific solver to deal with problems involving delay. Thus it is feasible to explore more about DDE in this study.

III. Computational Models

Computational tractability is also a factor that must be taken in to consideration, i.e. to measure the complexity (time, space requirements) of an algorithm and make sure the outcome in a reasonable amount of time that a computer could calculate. Therefore, two levels of modeling are preferred in this study: the first, for which theoretical/mathematical analysis can be done, provide clear results with respect to symmetry and delay in the network; the second, both single-neuron and whole-network behaviors with accurate biological/physiological properties, will provide result via numerical simulations.

The Hopfield-like model is chosen for theoretical/mathematical analysis on the dynamics of network due to its simplicity, while the Hodgkin-Huxley-type model is going to be used in simulations to verify the mathematical abstraction.

IV. Numerical Analysis tools and Simulators

MATLAB is currently the best environment for numerical analysis and simulation; it has a variety of packages for different particular computation requirements such as bifurcation analysis, ODE solvers, etc. Furthermore, in order to design, train, visualize, and simulate neural networks, it provides a Neural Network Toolbox which supports modeling complex dynamic networks with non-linear features.

Hodgkin-Huxley-type model can be simulated using NEURON [78], NEST [90], GENESIS [91], [92], XPP [93] or MATLAB [94] (the first 3 are tools designed for simulating realistic dendritic structures).

NEURON is a simulation environment for modeling neurons and neural networks, and is particularly well-suited for COBA models of cells with complex branched anatomy. Its purpose of design is trying to hide mathematical or computational issues and emphasize problems closely linked to experimental data [95]. These properties of NEURON make it an ideal environment for simulating the Hodgkin-Huxley type model. In addition, previous studies on solving problems related to delay by this simulator [96], [97], [98] have shown the feasibility to adopt NEURON as the simulation tool in this study.

In all, MATLAB and NEURON are chosen as simulation and analysis tools with the idea to simulate the complex Hodgkin-Huxley-type model in NEURON and the rest to be done in MATLAB.

V. Model Verification and Validation with Data Collection

Model verification and validation is a methodology for the development of computational models. Verification means building the model right, i.e. the program implements correctly on a computer. Validation means building the right model, i.e. to determine if a model is an accurate representation of the real system [98]. Particularly, refering to the model development process, we need to know 1) if the theories and assumptions underlying the conceptual model are correct, 2) if the programming and implementation of the conceptual model is correct, 3) if the model's output behavior reflects the designed purpose accurately, and 4) if the required data for model building, evaluation and testing, also experiments conducted on it, are adequate [100]. To answer the above questions is the role of model verification and validation. The process of model verification and validation according to the procedure of model development is given [101] and is shown in Figure 9.

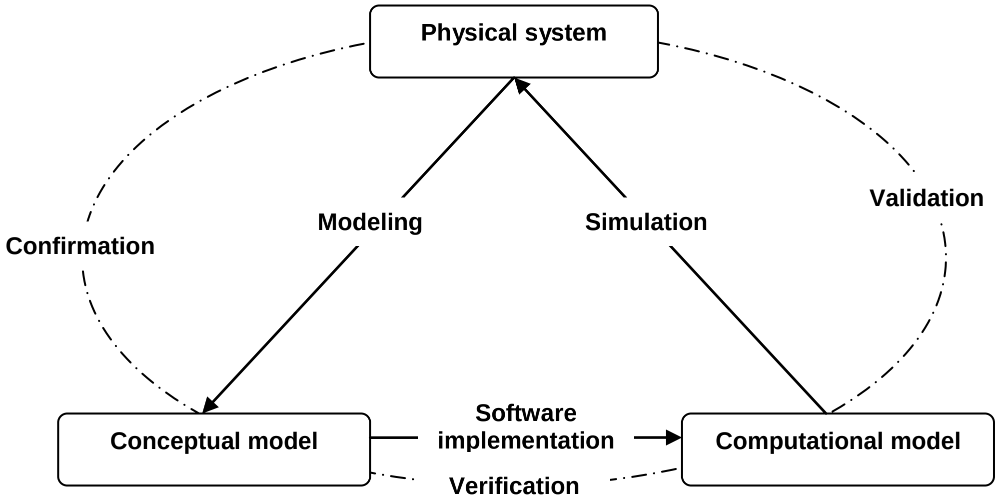

Figure 9, Verification and validation process.

Last but not least, to verify and validate a model, data from experiments is indispensable, such data will be used to obtain parameter values for simulation, as well as provide a standard for measuring results. There are numerous specific types of neurons with different shapes, sizes, shapes, structures, and functions. The difference can be reflected in various measurements [102], and the work of collecting experimental data in order to run an accurate simulation is something that should not be underestimated. Good data will make sure the modeling acting is in concert with simulations to achieve a desirable result.

7. TIMELINE

This research is expected to be done in a duration of 10-12 months:

1. Literature review – 1 month

2. Model development, data collection, simulation –2-3 months

3. Data analysis, model evaluating and improvement – 2-3 month

4. Model verification and validation – 1 month

5. Thesis writing – 4 months

8. BIBLIOGRAPHY

[1] Klimesch, Wolfgang. "EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis." *Brain research reviews* 29.2 (1999): 169-195.

[2] Ng, Benedict Shien Wei, Nikos K. Logothetis, and Christoph Kayser. "EEG phase patterns reflect the selectivity of neural firing." *Cerebral Cortex* 23.2 (2013): 389-398.

[3] Polanía, Rafael, Walter Paulus, and Michael A. Nitsche. "Noninvasively decoding the contents of visual working memory in the human prefrontal cortex within high-gamma oscillatory patterns." *Journal of cognitive neuroscience* 24.2 (2012): 304-314.

[4] Sauseng, Paul. "Brain oscillations: phase-locked EEG alpha controls perception." *Current Biology* 22.9 (2012): R306-R308.

[5] Gloor, P., and R. G. Fariello. "Generalized epilepsy: some of its cellular mechanisms differ from those of focal epilepsy." *Trends in neurosciences* 11.2 (1988): 63-68.

[6] Dauwels, Justin, et al. "A comparative study of synchrony measures for the early diagnosis of Alzheimer's disease based on EEG." *NeuroImage* 49.1 (2010): 668-693.

[7] Fingelkurts, Alexander A., et al. "EEG oscillatory states as neuro-phenomenology of consciousness as revealed from patients in vegetative and minimally conscious states." *Consciousness and cognition* 21.1 (2012): 149-169.

[8] N. I. Syed, A. G. M. Bulloch and K. Lukowiak (1990), "In vitro reconstruction of the respiratory central pattern generator of the mollusk Lymnaea", *Science* **250**, 282-285

[9] Syed, N. I., and W. Winlow. "Respiratory behavior in the pond snail Lynmaea stagnalis." *Journal of Comparative Physiology A* 169.5 (1991): 557-568.

[10] Purves, Dale. *Neuroscience*. Chapter 1, Sunderland, MA: Sinauer, 2008

[11] http://neuroscience.uth.tmc.edu/s1/introduction.html

[12] Selverston, Allen I., and Maurice Moulins. "Oscillatory neural networks." *Annual review of physiology* 47.1 (1985): 29-48.

[13] Klimesch, Wolfgang. "Memory processes, brain oscillations and EEG synchronization." *International Journal of Psychophysiology* 24.1 (1996): 61-100.

[14] Baars, Bernard J., and Nicole M. Gage. *Cognition, brain, and consciousness: Introduction to cognitive neuroscience*. Academic Press, 2010.

[15] Lopes da Silva, Fernando. "Neural mechanisms underlying brain waves: from neural membranes to networks." *Electroencephalography and clinical neurophysiology* 79.2 (1991): 81-93.

[16] *Mathematics Illuminated*: Unit 6- The beauty of symmetry http://www.learner.org/courses/mathilluminated/units/6/

[17] Hille, Bertil. *Ion channels of excitable membranes*. Vol. 507. Sunderland, MA: Sinauer, 2001.

[18] Vulfius, C. A., et al. "Phospholipases A2 isolated from snake venoms block acetylcholine-elicited currents in identified Lymnaea stagnalis neurons."*Biochemistry (Moscow) Supplement Series A: Membrane and Cell Biology* 7.3 (2013): 203-206.

[19] Murakami, Jun, et al. "Involvement of insulin-like peptide in long-term synaptic plasticity and long-term memory of the pond snail Lymnaea stagnalis." *The Journal of Neuroscience* 33.1 (2013): 371-383.

[20] Syed, N. I., et al. "Transplantation and functional integration of an identified respiratory interneuron in Lymnaea stagnalis." *Neuron* 8.4 (1992): 767-774.

[21] Feng, Z. P., et al. "Transcriptome analysis of the central nervous system of the mollusc Lymnaea stagnalis." *BMC genomics* 10.1 (2009): 451.

[22] http://www.scholarpedia.org/article/Lymnaea

[23] http://bluebrain.epfl.ch/

[24] Hodgkin, A. L. and Huxley, A. F. (1952). "A quantitative description of ion currents and its applications to conduction and excitation in nerve membranes. " *J. Physiol*. (Lond.), 117:500-544

[25] De Schutter, Erik. "Why are computational neuroscience and systems biology so separate?." *PLoS computational biology* 4.5 (2008): e1000078.

[26] Vandenberg, Jamie I., and Stephen G. Waxman. "Hodgkin and Huxley and the basis for electrical signalling: a remarkable legacy still going strong." *The Journal of Physiology* 590.11 (2012): 2569-2570.

[27] P Baldi, AF Atiya, "How delays affect neural dynamics and learning", *Neural Networks*, IEEE Transactions on, 1994

[28] Paprocki, Bartosz, and Janusz Szczepanski. "Transmission efficiency in ring, brain inspired neuronal networks. Information and energetic aspects." *Brain research* (2013).

[29] http://bcs.mit.edu/aboutbcs/

[30] Frank, T. D., et al. "Towards a comprehensive theory of brain activity:: Coupled oscillator systems under external forces." *Physica D: Nonlinear Phenomena*144.1 (2000): 62-86.

[31] Bungay, Sharene D., and Sue Ann Campbell. "Patterns Of Oscillation In A Ring Of Identical Cells With Delayed Coupling." *International Journal of Bifurcation and Chaos*17.09 (2007): 3109.

[32] Ermentrout, G., and C. Chow. "Modeling Neural Oscillations." *Physiology & Behavior* 77.4-5 (2002): 629-33

[33] Taylor, William R., and András Aszódi. *Protein geometry, classification, topology and symmetry: A computational analysis of structure*. CRC Press, 2010.

[34] Qi, Xiao-Liang. "Symmetry Meets Topology." *Science* 338.6114 (2012): 1550-1551.

[35] Tanaka, Yukio, Masatoshi Sato, and Naoto Nagaosa. "Symmetry and Topology in Superconductors-Odd-frequency pairing and edge states." *arXiv preprint arXiv:1105.4700* (2011).

[36] Tan, Jin Chong, Thomas D. Bennett, and Anthony K. Cheetham. "Chemical structure, network topology, and porosity effects on the mechanical properties of Zeolitic Imidazolate Frameworks." *Proceedings of the National Academy of Sciences* 107.22 (2010): 9938-9943.

[37] beim Graben, Peter, and James Wright. "From McCulloch–Pitts Neurons Toward Biology." *Bulletin of mathematical biology* 73.2 (2011): 261-265.

[38] Hopfield, John J. "Neural networks and physical systems with emergent collective computational abilities." *Proceedings of the national academy of sciences* 79.8 (1982): 2554-2558.

[39] Hopfield, John J. "Neurons with graded response have collective computational properties like those of two-state neurons." *Proceedings of the national academy of sciences* 81.10 (1984): 3088-3092.

[40] http://www.scholarpedia.org/article/FitzHugh-Nagumo_model

[41] Cattani, Anna, and Claudio Canuto. "FitzHugh-Nagumo to model a large number of diffusive coupled neurons." *BMC Neuroscience* 14.Suppl 1 (2013): P53.

[42] Izhikevich, Eugene M. *Dynamical systems in neuroscience*. Chapter 3, The MIT press, 2007

[43] Ditlevsen, Susanne, and Priscilla Greenwood. "The Morris–Lecar neuron model embeds a leaky integrate-and-fire model." *Journal of Mathematical Biology*(2012): 1-21.

[44] He, Ji-Huan, and Xu-Hong Wu. "A modified Morris–Lecar model for interacting ion channels." *Neurocomputing* 64 (2005): 543-545.

[45] Burkitt, Anthony N. "A review of the integrate-and-fire neuron model: II. Inhomogeneous synaptic input and network properties." *Biological cybernetics*95.2 (2006): 97-112.

[46] Keener, James P., F. C. Hoppensteadt, and J. Rinzel. "Integrate-and-fire models of nerve membrane response to oscillatory input." *SIAM Journal on Applied Mathematics* 41.3 (1981): 503-517.

[47] Brunel, Nicolas, and Vincent Hakim. "Fast global oscillations in networks of integrate-and-fire neurons with low firing rates." *Neural computation* 11.7 (1999): 1621-1671.

[48] Jolivet, Renaud, Felix Schürmann, Thomas K. Berger, Richard Naud, Wulfram Gerstner, and Arnd Roth. "The Quantitative Single-neuron Modeling Competition." *Biological Cybernetics* 99.4-5 (2008): 417-26.

[49] Abbott, L. F. and Kepler, T. B. (1990)." Model neurons: from Hodgkin-Huxley to Hopfield". In Garrido, L., editor*, Statistical Mechanics of Neural Networks*. Springer, Berlin.

[50] Brette, Romain, et al. "Simulation of networks of spiking neurons: a review of tools and strategies." *Journal of computational neuroscience* 23.3 (2007): 349-398.

[51] Schwiening, Christof J. "A brief historical perspective: Hodgkin and Huxley."*The Journal of Physiology* 590.11 (2012): 2571-2575.

[52] Catterall, William A., et al. "The Hodgkin-Huxley Heritage: From Channels to Circuits." *The Journal of Neuroscience* 32.41 (2012): 14064-14073.

[53] Markram, Henry. "The blue brain project." *Nature Reviews Neuroscience* 7.2 (2006): 153-160.

[54] McCrea, David A., and Ilya A. Rybak. "Modeling the mammalian locomotor CPG: insights from mistakes and perturbations." Progress in brain research 165 (2007): 235-253.

[55] Bungay, Sharene D., and Sue Ann Campbell. "Modelling a Respiratory Central Pattern Generator Neuron in Lymnaea stagnalis" *CANADIAN APPLIED MATHEMATICS QUARTERLY* Volume 17, Number 2, Summer 2009

[56] Wang, Qingyun, Xia Shi, and Guanrong Chen. "Delay-induced synchronization transition in small-world Hodgkin-Huxley neuronal networks with channel blocking." *Discrete Contin. Dyn. Syst., Ser. B* 16.2 (2011): 607-621.

[57] Wang, Qing Yun, et al. "Spatial coherence resonance in delayed Hodgkin–Huxley neuronal networks." *International Journal of Modern Physics B* 24.09 (2010): 1201-1213.

[58] Wang, Qingyun, Guanrong Chen, and Matjaž Perc. "Synchronous bursts on scale-free neuronal networks with attractive and repulsive coupling." *PLoS one*6.1 (2011): e15851.

[59] Kantner, Markus, and Serhiy Yanchuk. "Bifurcation analysis of delay-induced patterns in a ring of Hodgkin–Huxley neurons." *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*371.1999 (2013).

[60] Popovych, Oleksandr V., Serhiy Yanchuk, and Peter A. Tass. "Delay-and coupling-induced firing patterns in oscillatory neural loops." *Physical review letters* 107.22 (2011): 228102.

[61] Orosz, Gábor, Jeff Moehlis, and Richard M. Murray. "Controlling biological networks by time-delayed signals." *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* 368.1911 (2010): 439-454.

[62] Wojcik, Jeremy, Robert Clewley, and Andrey Shilnikov. "Order parameter for bursting polyrhythms in multifunctional central pattern generators." *Physical Review E* 83.5 (2011): 056209.

[63] Hagan, Martin T., Howard B. Demuth, and Mark H. Beale. *Neural network design*. Boston: Pws Pub., 1996.

[64] http://www.scholarpedia.org/article/Hopfield_network

[65] Akrami, Athena, Eleonora Russo, and Alessandro Treves. "Lateral thinking, from the Hopfield model to cortical dynamics." *Brain research* 1434 (2012): 4-16.

[66] Hotton, Scott, and Jeff Yoshimi. "Extending dynamical systems theory to model embodied cognition." *Cognitive Science* 35.3 (2011): 444-479.

[67] Shanahan, Murray. "The brain's connective core and its role in animal cognition." *Philosophical Transactions of the Royal Society B: Biological Sciences* 367.1603 (2012): 2704-2714.

[68] Asakawa, Shin-ichi, and Ikuko Kyoya. "Hopfield neural network model for explaining double dissociation in semantic memory impairment." *BMC Neuroscience* 14.Suppl 1 (2013): P233.

[69] Bungay, Sharene D., and Sue Ann Campbell. "Patterns of oscillation in a ring of identical cells with delayed coupling." *International Journal of Bifurcation and Chaos* 17.09 (2007): 3109-3125.

[70] Campbell, Sue Ann, Yuan Yuan, and Sharene D. Bungay. "Equivariant Hopf bifurcation in a ring of identical cells with delayed coupling." *NONLINEARITY-LONDON-* 18.6 (2005): 2827

[71] Zhang, Huaguang, et al. "Novel weighting-delay-based stability criteria for recurrent neural networks with time-varying delay." *Neural Networks, IEEE Transactions on* 21.1 (2010): 91-106.

[72] Kaslik, Eva, and Seenith Sivasundaram. "Impulsive hybrid discrete-time Hopfield neural networks with delays and multistability analysis." *Neural Networks* 24.4 (2011): 370-377.

[73] Li, Hongyi, et al. "Robust stability for uncertain delayed fuzzy Hopfield neural networks with Markovian jumping parameters." *Systems, Man, and Cybernetics, Part B: Cybernetics, IEEE Transactions on* 39.1 (2009): 94-102.

[74] Kleinfeld, D., and H. Sompolinsky. "Associative neural network model for the generation of temporal patterns. Theory and application to central pattern generators." *Biophysical journal* 54.6 (1988): 1039-1051.

[75] Felipe, M. G., F. Yang, and Zhijun Yang. "Building artificial CPGs with asymmetric hopfield networks." *Neural Networks, 2000. IJCNN 2000, Proceedings of the IEEE-INNS-ENNS International Joint Conference on*. Vol. 4. IEEE, 2000.

[76] Yang, Zhijun, and Qingbao Zhu. "A quadrupedal locomotion central pattern generator based on oscillatory building block networks." *Internet Computing & Information Services (ICICIS), 2011 International Conference on*. IEEE, 2011.

[77] M. E. Fisher. Scaling, university and renormalization group theory. *Springer Lecture Notes in Physics*, Vol. 186, 1983.

[78] Carnevale, Nicholas T., and Michael L. Hines. *The NEURON Book: Chapter 2,4* Cambridge: Cambridge UP, 2006.

[79] Jones, Bradley R., and Stuart H. Thompson. "Mechanism of postinhibitory rebound in molluscan neurons." *American zoologist* 41.4 (2001): 1036-1048.

[80] Angstadt, James D., et al. "Mechanisms of postinhibitory rebound and its modulation by serotonin in excitatory swim motor neurons of the medicinal leech." *Journal of Comparative Physiology A* 191.8 (2005): 715-732.

[81] Janczewski WA, Feldman JL (January 2006). "Distinct rhythm generators for inspiration and expiration in the juvenile rat". *J. Physiol. (Lond.)* **570** (Pt 2): 407–20

[82] Izhikevich, Eugene M. *Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting*. Preface, Cambridge, MA: MIT, 2007,

[83] Shlizerman, Eli, and Philip Holmes. "Neural dynamics, bifurcations, and firing rates in a quadratic integrate-and-fire model with a recovery variable. i: Deterministic behavior." *Neural Computation* 24.8 (2012): 2078-2118.

[84] Hashimoto, Sho, and Hiroyuki Torikai. "A novel hybrid spiking neuron: Bifurcations, responses, and on-chip learning." *Circuits and Systems I: Regular Papers, IEEE Transactions on* 57.8 (2010): 2168-2181.

[85] http://www.scholarpedia.org/article/Equivariant_dynamical_systems

[86] Kuang, Yang, ed. *Delay differential equations: with applications in population dynamics*. Academic Press, 1993.

[87] Coombes, Stephen, and Carlo Laing. "Delays in activity-based neural networks." *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* 367.1891 (2009): 1117-1129.

[88] Lu, Hongtao, Yongbao He, and Zhenya He. "A chaos-generator: Analyses of complex dynamics of a cell equation in delayed cellular neural networks."*Circuits and Systems I: Fundamental Theory and Applications, IEEE Transactions on* 45.2 (1998): 178-181.

[89] Pakdaman, K., et al. "Transient oscillations in continuous-time excitatory ring neural networks with delay." *Physical Review E* 55.3 (1997): 3234.

[90] http://www.scholarpedia.org/article/NEST_(NEural_Simulation_Tool)

[91] Bower, James M., and David Beeman. *The book of GENESIS: exploring realistic neural models with the GEneral NEural SImulation System*. Ed. Allan M. Wylde. Santa Clara, Calif: Telos, 1998.

[92] http://www.genesis-sim.org/

[93] http://www.math.pitt.edu/~bard/xpp/xpp.html

[94] http://www.mathworks.com/

[95] http://www.neuron.yale.edu/neuron/what_is_neuron

[96] Gómez, Leonel, Ruben Budelli, and Khashayar Pakdaman. "Dynamical behavior of a pacemaker neuron model with fixed delay stimulation." *Physical Review E* 64.6 (2001): 061910.

[97] Kovalsky, Yifat, Ron Amir, and Marshall Devor. "Simulation in sensory neurons reveals a key role for delayed Na+ current in subthreshold oscillations and ectopic discharge: implications for neuropathic pain." *Journal of neurophysiology* 102.3 (2009): 1430-1442.

[98] Schierwagen, A. and Claus, C.. Dendritic morphology and signal delay in superior colliculus neurons. Neurocomputing 38-40:343-350, 2001

[99] Carson, John S. "Model verification and validation." *Simulation Conference, 2002. Proceedings of the Winter*. Vol. 1. IEEE, 2002.

[100] Sargent, Robert G. "Verification and validation of simulation models."*Proceedings of the 37th conference on Winter simulation*. Winter Simulation Conference, 2005.

[101] Thacker, Ben H., et al. *Concepts of model verification and validation*. No. LA-14167. Los Alamos National Lab., Los Alamos, NM (US), 2004.

[102] Sengupta, Biswa, et al. "Action potential energy efficiency varies among neuron types in vertebrates and invertebrates." *PLoS computational biology* 6.7 (2010): e1000840.