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

Literature Review of Master's Thesis

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1. Introduction

1.1 Overview

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) [12], [8]. This small network exhibits a ring topology, is said to be sufficient and necessary for the aerial respiration in the invertebrate *Lymnaea* [20]. With interest of understanding the production of rhythmic movement and the roles of each single neruon oscillator and coupled oscillatory circuits may paly in this procedure, we first build a model representing this real-word system to answer the questions raised.

Mathematical models usually adopt a variety of abstractions in order to describe complex oscillatory dynamics. 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. 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.

1.2 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 delayaiming to answer the questions including 1) why is the network of this structure able to function that way, 2) how do things work together, 3) what are the must-have components?

1.3 Significance

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 [37]. 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 [38].

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, both behavioral and neuronal components in the mollusk *Lymneaea Stagnalis* respiratory CPG are common with vertebrates, this model is the starting point to understand mechanisms underlying respiratory rhythmogenesis in both invertebrates and vertebrates [20].

2 Basic conceptions

2.1 Neurons and connections

Neurons are a type of cell distinguished from other cells by their unique complex shapes, particularly, the massive 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. 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 chemicals called neurotransmitters. Neurotransmitters are chemical messengers that either excite or inhibit neighboring cells by binding to receptors at the synapse.

In neural connectivity, synapses play the essential role. They function as intermedia between the axon of the presynaptic cell, 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 terms of the chemical and electrical processes in the synaptic contacts. Chemical synapses function by releasing vesicles, the tiny spheres of membrane that contain neurotransmitter substances, while for electrical synapses, ionic currents flow from one cell to another directly.

2.2 Oscillation

Oscillation is the basic kinetic model of both individual neurons and neural networks as oscillatory activity is ubiquitous in all levels of neural systems. At the cellular level, neurons can be regarded as cell-driven oscillators [9]. 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 that 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 [10] 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 [11], [13].

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], [39]. They are the theoretical foundation 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.

2.3 Symmety and Deley

Symmetry is generally 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. Moreover, symmetry is also a kind of complexity reduction by assuming some components are identical, this can save the computation resoucre dramaticaly and emphasize the critical part while blur non-critical in analysis. Symmetry, as a sense of geometric feature in a particular system, has been studied in many researching areas [51], such as protein structure [52], [53], supercomputer architecture [54], [55], neural networks [56], string theory [57], [58] etc., since it can lead to some special properties in a system [59], [60], [61], [62].

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, the propagation of action potentials along the axon or dendrite and bio-chemical reactions, 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 [14]. With the important role it plays in the connection of neurons, delays have been widely studied and used in both biological and artificial neural networks. In biological networks, delay can induce the synchronization of neural networks and its effect has been studied by Wang et al. [78], [79], [80]. Delay-coupled ring type networks composed of Hodgkin-Huxley type single-neurons have been analyzed via bifurcation theory [81], 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 [82] and how it can regulate the behavior of biological networks as an efficient biocompatible control tool [83].

2.4 Dynamical systems theory

The model developed will be systems of differential equations, which will be analyzed using both theoretical and numerical methods. With regard to both single-neuron [108], [109], [110] and neural network behavior [81], [95], dynamical systems theory, especially bifurcation theory, are commonly applied in the mathematical studies and analysis of a system decribed by differential equations. For dynamical systems, a bifurcation is like a transition, near which the neuron becomes excitable. Bifurcation theory can provide predictions of thresholds and other computational properties of a complex system [111], [112], [113]. Dynamical systems that have symmetries are called equivariant dynamical systems. Such systems can deal with the problem of coupled identical oscillators, and are very useful in the study of neural networks [114].

Delay-differential equations (DDEs) describe the behavior of systems with delays, and are characterized by derivatives of some unknown functions at the present being dependent on the values at previous times. Numerically solving most DDEs is no more difficult than solving ODEs [115]. Previous studies have shown the usefulness of DDEs in studing neural networks [116], [117], [118].

3. Ion channels and Hudgkin-Huxley mechanism

3.1 Electrophysiology of cell membrane and excitability

All living cells have a thin plasma membrane separating the intracellular components from the extracellular environment. The cell membrane is a phospholipid bilayer with proteins embeded, in, permeable to water molecules and a few other small, uncharged, molecules like oxygen (O_2) and carbon dioxide (CO_2). The consequence of this feature is that there exists a voltage difference across the membrane resulting from the difference of concentrations in and outside the cell due to the Ion Selective-Permeability of the cell membrane. This is the fundamental mechanism that endows cells the ability to use membrane potential for signaling by control of ionic transport.

Cells can be divided into 2 groups, excitable and non-excitable. "Excitable" means if the applied current is strong enough, the membrane potential generates the action potential which either responds in full to a stimulus or not at all. This is the well-known all-or-none or threshold phenomenon, as background noise is filtered out and signal can be transmitted reliably [21]. Most neurons are excitable, as seen in artificial neural networks, the most simplified neuron models only have 2 states, 0 and 1, but are capable to handle and solve different tasks when wired together, for instance, the Hopfield networks adapted in pattern recognition [86], [87], image segment [88], [89], [90].

3.2 The Hodgkin-Huxley Model

The ongoing impact of the idea from this famous model and its landmark role in computational neuroscience are too much to be mentioned as it revealed the mechanism of action potential generation both mathematically and biologically. With many others' continuing working and exploring, nowadays, thousands of channels are discovered, combining the studies of proteins and chemicals with respect to biochemistry. Also, there is access to many well established mathematical models, theories, methods and tools of analysis that provide the solid building block for building a particular neuronal system.

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) [22], known as the Hodgkin–Huxley-type models based on the mechanism that neurons generate electric signals by the flow of ions along their membranes. Such models can successfully reproduce the complex and rich behavior that biological neurons exhibit, as observed experimentally via intracellular electrophysiological measurements like current clamp and voltage clamp. The later, in contrast, are very simple models, i.e. Boolean, binary, on/off (McCulloch-Pitts [23], Hopfield [24], [25]) models, and have been well studied and widely used in artificial neural networks. There also exist some models between the two extremes such as FitzHugh Nagumo [26], [27], [28], Morris Lecar [29], [30], and Integrate-and-Fire (IF), [31], [32], [33]. These models can be viewed as simplifications 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 if transmembrane conductances have fast kinetics [28], along with fewer parameters allowing simulations of large-scale networks to run quickly [34], [35],.

The mathematical model built by Alan L. Hodgkin and Andrew F. Huxley [22], based on the assumption that conductance of ion channels is a function of time and membrane potential, results in a set of empirical differential equations along with tens of parameters obtained from experimental measurements. In this model, the membrane is expressed as a circuit (Figure 1)

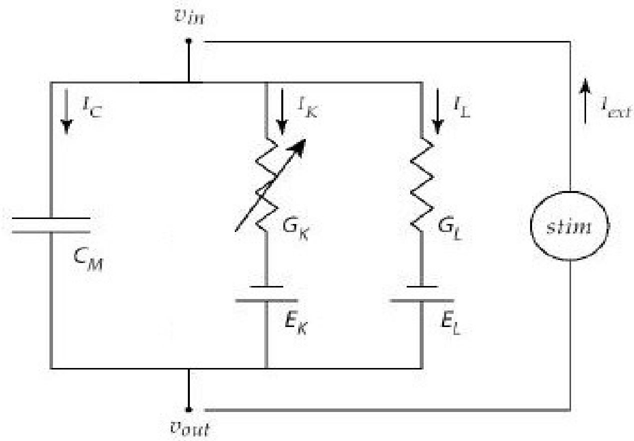

Figure 1 An electrical circuit resembles the cell membrane

By Kirchoff's law, we have

$$C_M \frac{dV}{dt} + I_{ion} + I_L = I_{ext}$$

where

$$I_{ion} = \sum_k I_k = \sum_k G_k (V - E_k)$$

is a combination of voltage-gated ion currents, G_k is the conductance describes the voltage and time dependence of ionic currents, usually not constant but a funcion of gating variables representing the degree to which channels are opened or closed. V is the membrane potential, E_k is the reversal potential for each channel. Plus the leak current I_L determines the passive properties of the cell, and I_{ext} is the external stimulus which can be an artificial injected current or synaptic input currents.

How this model describes the structural and functional role of ion channels, why it still remains its importance in neuroscience, and what else it can provide in studying the brain, are all well explained in [64].

3.3 Inhibition and excitation, neurotransmitters

The synaptic input term refers to the communication between cells, for electrical synapses (mediated by gap junction), it is a diffusive interaction that only depends on the difference of voltage between two neurons, the reaction is rapid, passive and bidirectional (symmetric).

In contrast, for chemical synapses, the reactions are neurotransmitter triggered, slow, active and unidirectional. Neurotransmitters are released by the presynaptic neuron, then bind to corresponding receptors of postsynaptic neuron, and change the open and close states of ion channels which results in the change of conductance and the membrane potential, this is the basis that a chemical synapse functions. Table1 lists the common neurotransmitters and their functions.

Table 1 Chemical Neurotransmitters

Groups	Neurotransmitters	Function
Acetylcholine	Acetylcholine	Excitatory
Amines	Epinephirine	Excitatory
	Dopamine	Excitatory and Inhibitory
	Norephinephrine	Excitatory
	Serotonin	Excitatory
Amino Acids	Glutamate	Excitatory
	Glycine	Mainly inhibitory
	g-Aminobutiric acid (GABA)	Inhibitory

A chemical synapse is either inhibitory or excitability regarding the effect on post-inhibitory neuron. The inhibitory effect is the less likelihood to fire an action potential while excitatory effect has more likelihood. A neuron may receive a large amount of inhibitory and excitatory inputs at the same time, after a complicated procedure of signal summation and processing, both the intrinsic properties and the inputs received will determine the output signal.

3.3 The richness of behavior of neurons

"Nature has evolved an astonishing diversity of neurons, each expressing only one set of ion channels out of billions of potential channel combinations. Each combination forms a complex dynamical system, capable of a wide range of behaviours, from fast spiking to slow spiking, from bursts of spikes to adapting spike trains, and even more complexity emerges when the spatial heterogeneity of ion channels in dendrites and axons is taken into account."- *The Hodgkin-Huxley Heritage: From Channels to Circuits, The Journal of Neuroscience, October 10, 2012 • 32(41):14064 –14073*

The Hodgkin-Huxley mechanism illustrated one thing that channels determine the behavior of neurons. Because of the richness and variety of ion channels, individual neurons show exceeding richness and complexity of spiking behavior. Looking at the neuro-computational features, as summarized and categorized in [65], 20 of the most prominent features of biological spiking neurons are discussed and analyzed (figure 2). It is unable to discuss all varieties of neuronal behaviors with the cellular and biophysical mechanisms behind in an adequate detail here, instead, only those observed in the CPG network in this study will be discussed further, which take place below chapters as part of the analysis on the respiratory neural network in *Lymnaea*.

One thing notable is that all the responses in Figure 2 were obtained by the same model [66] using different parameters, which shows the potential of adequate mathematical models in complexity reduction while still retain important intrinsic properties though the parameters may not be biophysically meaningful and measurable.

3.5 Modeling considerations

Regarding modeling part in this study, following the work in [70], the detailed, more realistic HH type model is preferred. However, it requires detailed knowledge of ion channels involved and large amount of analytic fits of data obtained experimentally in voltage clamp measurements to determine a particular ion channel. Moreover, it is very difficult to analyze as there is no analytical solution to these differential equations. Taken into account the data availability for each cell, and the needs of complexity reduction, approximating the behavior that a complex model exhibits via a reduced model is a better choice. For example, the spiking neuron model family of Integrate-and-fire models [75], [76] is well-established in theory and has been proved to give excellent spike timing predictions.

Though it is an ultimate goal to reproduce the realistic CPG as much as possible on a computer, and the most reasonable way is to reproduce all the essential channels, which may also need additional knowledge such as information of morphology, determination of channel types, channel density and distribution as it suggested the continuous deterministic HH model may not be enough to predict the voltage dynamics of cell membrane [77]. These requirements are far more beyond current source of availability for a focus on the cellular level of network, as of this research. Studying the rhythmic behavior of the whole neural network with respect to symmetry and delay, occupies the first priority here, the plausible approaches to compensate this may involve 1) a hybrid network consists of different mathematical models based on data availability of different cells and 2) an adaptation of general model with existing experimental data that exhibits similar behavior.

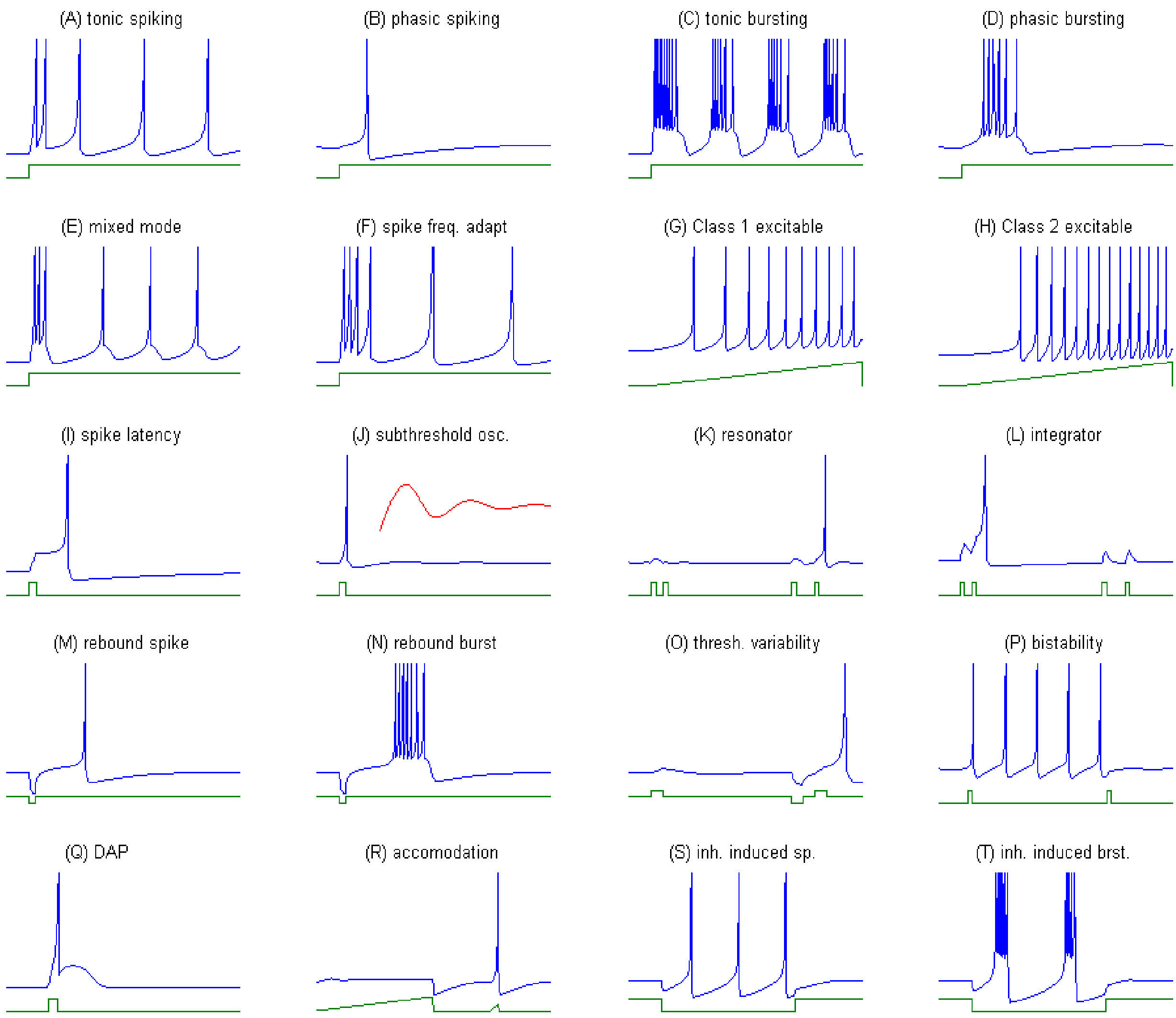

Figure 2. Behavior of biological spiking neurons in response to DC current stimulus [65], the MATLAB file generating the figure is from ModelDB, Artificial neuron model (Inhikevich 2003), Accession: 399948 (http://senselab.med.yale.edu/modeldb/showmodel.asp?model=39948)

4. Central Pattern Generator and rhythm generation

Central Pattern Generators are characterized as relatively small and autonomous neural networks, capable of generating rhythmic patterned output in the absence of sensory feedback, albeit sensory input is crucial to the alternation of patterns generated and the modulation of the whole network behavior. The term pattern is defined to be the oscillatory behavior of a network composed of coupled neurons. Mathematical models have shown that there usually exist more than one pattern of oscillation in a particular system [41], as a naturalistic system is capable to switch from one pattern to another, like a horse's gait can switch from walking to trotting to bounding to galloping, which allows animal to adapt its movement to changing needs. With such characteristecs, CPGs have been widely studied and an increasing amount of applications of bio-inspired CPGs in controlling system and robotics emerged in the past 2 decades for the demands of stable high-dimensional rhythmic output signals by only low-dimensional input, this also provides a good way to test computatioanal models embedded in a real environment [42].

Two baisic mechanisms are given pertaining to the mechanism of rhythm genertation in CPGs: 1) pacemaker driven, 2) as an emergent property of network behavior via synaptic connections [71]. Some examples of CPG in invetebrates are summarized in [72], such as pyloric thythm generator of cturatacean, a tipical pacemaker driven representive; *Clione* and *Xenopus* swimming and leech heartbeat systems, have pacemaking properties but subject to reciprocal inhibitory connections; and gastric mill rhythm of stomatogastric ganglion (STG) of lobster *Panulirus,* example of emergent process of network. Moreover, a discussion including pacemaker neurons, synaptic inhibition and the modulation of pacemaker properties by neuromodulators shows similarity in respiratory rhythm generation for mammalian [73]. All those above are more complicated systems including more neurons and synaptic connections, compared to the respiratory CPG in *Lymnaea*, but exihit similarities in the hierarchy of networks, output firing patterns and neural connections.

It is important to note that reciprocal inhibition is a core feature in almost every CPG, two reciprocally coupled neurons that produce rhythmic outputs form a half-center ocsillator (HCO), and functions as an elemental oscillator in the a neural network that may contain several such pairs. This conception is the key to understand rhythm generation in CPGs and the flexibility of CPGs to produce multiple output patterns [74].

5. A close look at the respiratory CPG in *Lymnaea*

5.1 The invertebrate mollusk *Lymnaea* and its respiration

Lymnaea stagnalis (Great Pond Snail) is a kind of mollusk, the population lives in stagnant water, has been a classic model to study the molecular and electrical properties of neurons. It is widely used in neurobiological experiments, [15], [16], [17], [18]; 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 [12], even on semiconductor chips [19].

The animal is a bimodal breathere, has a similar breathing pattern similar to that of amphibia reptiles and diving manmals. It is able to breath both cutaneoursly and aereally. The aerial respiration usually dominates in a hypoxic environment when the animal open and close of orifice (pneumostome) to obtain oxygen from the air. The frequency of aerial respiration dependes directly on the oxygen need [20], and this is reflected in the firing of neurons and neural networks, i.e. the CPG in this study. because such rhythmic behaviors controlled by a neural central pattern generator are inherently a reflection of changes in neuronal firing [8], [43].

5.2 Overlook at the whole network structure

The complete neural network is shown in figure 5, including the respiratory CPG that hypothesized to consist of only three interneurons: 1) right pedal dorsal 1 (RPeD1), 2) the input 3 interneuron (IP3I), 3) visceral dorsal 4 (VD4) and other neural connections that have influence on the aerial respiration [44]. These 3 neurons form a ring type network where in culture reconsturction has proved that all synaptic connections are chemical and monosynaptic. The VD4 neuron is connected via reciprocal inhibitory synaptic connections to both RPeD1 and Ip3I. The Ip3I neuron is excited by RPeD1 via postinhibitory rebound (PIR), which is a biphasic (inhibition followed by excitation) connection while RPeD1 connected to Ip3I via an excitatory synapse [12].

The modeling work of the whole network thus includes the construction of a ring of 3 neurons as well as 6 synaptic connections classified into 3 types: inhibition, excitation and a mixed PIR excitation. To some extent this structure can easily be transformed to system with property of symmetry, when treat some components as identical.

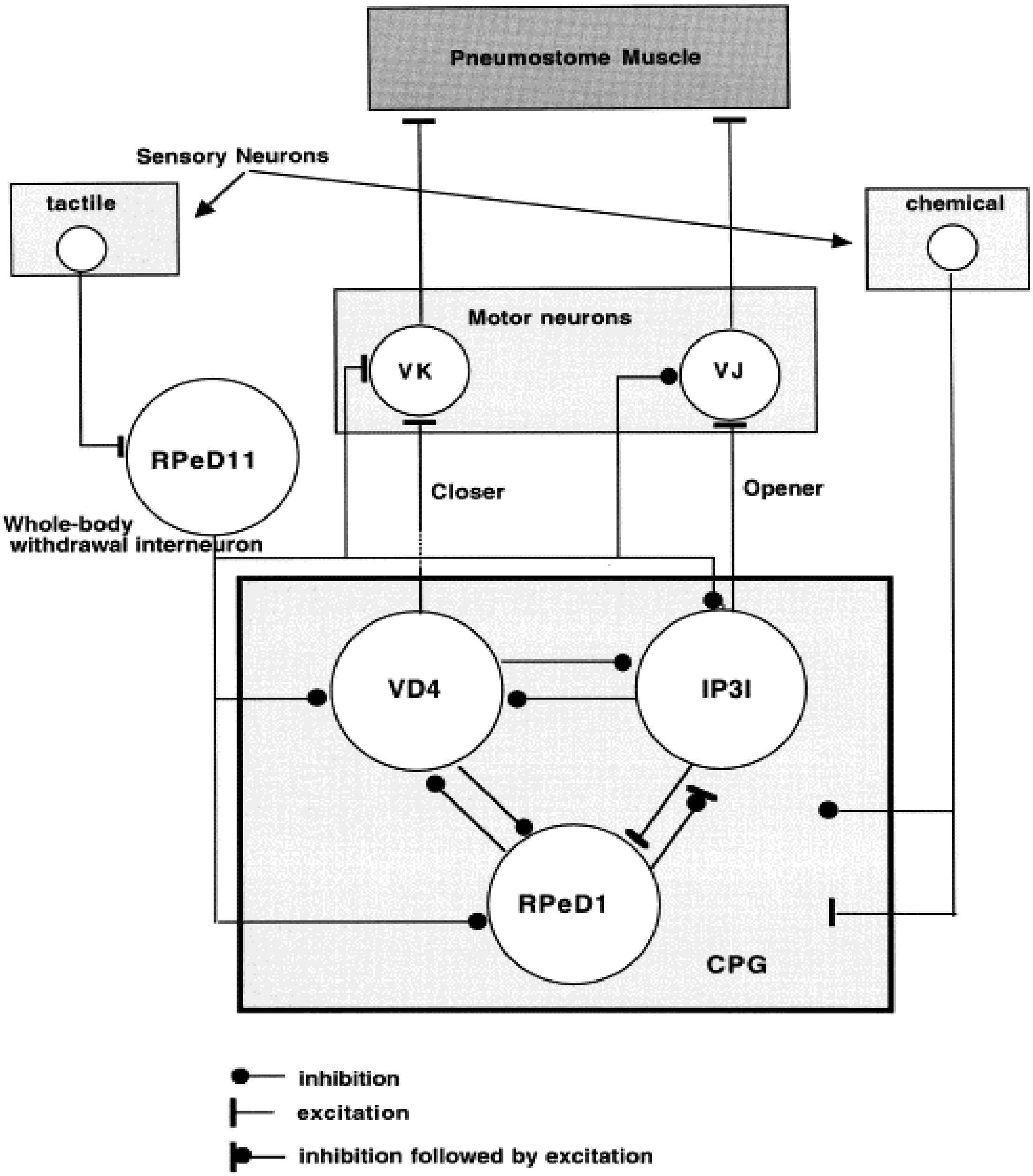

Figure 3. The complete neural circuit controlling aerial respiration (NOTE, this figure is copied directly from the original paper [44], it is only used as a quick preview in this draft, will be reproduced when I move to Latex with proper drawing tool which is still under practicing and evaluating.)

For instance,

1) radial symmetry (Figure 3), 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.

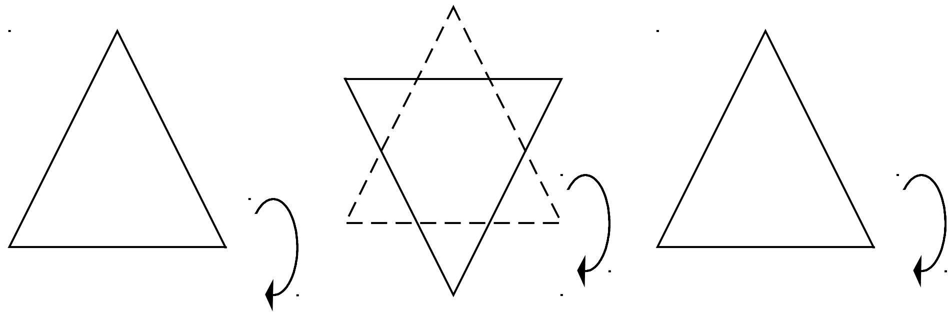

Figure 4. Rotating an equilateral triangle 120° leaves its appearance unchanged.

2) bilateral symmetry (Figure 5, also called mirror symmetry or reflection symmetry. An object exhibits bilateral symmetry, when broken if, into two parts, one part is the exact reflection of the other. In nature, it’s the most common appearance of animals, such as butter fly, rat, and even human beings.

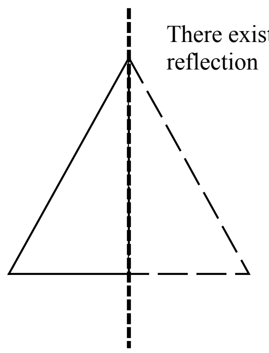

Figure 5. Symmetry with respect to reflection.

5.3 Determine the Function and Role of each neuron

Each neuron's response to DC current when cultured individually, and the behavior of pairs of co-cultured neurons, also the whole CPG both in vitro and in vivo are shown and discussed in [12], [20]. RPeD1, the giant Dapamine cell fires spontanously and functions as the initiator, V.D4 and I.P3.I are quiescent with no current injected but fire an alternating pattern of bursting when receive stimulus from RPeD1 and interestingly the phasic injection of dopamine can induce the similar phemomenon. Dopamine (DA) is a kind of neuron transmitters, and its effect is complicated, doesn't belong to inhibition or excitation, this increase the difficulty in analysis

Hypotheses of the fundermental network structure can be derived from above analysis on mechanisms of rhythym generation in CPGs and Half-center Oscillator. What need to be explored:

Can this CPG be regarded as

1) a Half-center oscillator driven by a pacemaker, such a system has naturally involved the property of bilateral symmetry, and is the most prospective answer as the alternating bursting of VD4 and IP3I shows similarity in the muturally inhibitory pairs in Leech heartbeat CPG [45].

2) coupled Half-center oscillators.

3) no Half-center oscillator involvement.

To determine the role of each neuron in this CPG, the classificaiton of neurons is also necessary to perform further analysis and this requires knowledge of *f-I* (frequency and current) response curve of neuron to determine which of the three types a neuron belongs to [46].

5.4 Arguments and controversies

It can be seen from figure 3 that the motor neusons VK and VJ control the pneumostome are not only connected to the CPG comprises 3 neurons, and in real neural system, neurons may receive inputs from many synapses as well as the influence from other tissue like glial cells [47], muscles and vessels, clearly, it is difficult to filter all the noise when attempt to perform electrophisiological recording, also the difficulties in controling experimental preparations may lead to more difficulties in the determination of relevant factors, even the necessity of the 3-neuron CPG in the respratory rhythm generation is argued mainly about the involvement of VD4 neuron [48]. The necessity means if any of the neurons in the CPG is removed then the pattern will be lost, and one of the interesting assumptions is given that the closure of pneumostome is a passive process if only RPeD1 and IP3I are required, which may be examined in this study by taking the advantage of modeling as hyposesis can be tested without a well-equiped lab, nor the diffiecultу of identifying a particular neuron and put electrode in to record. One thing must be recognized that a neuron is actually a very complicated living organism, plasticity endows the cell variant performance when temporal factor and spacial factor change, outside environment changes or even the aging of a neuron itself, for instance it was observed that freshely isolated VD4 can fire spontaneously action potentials while it is generally quiesenst in vivo [49].

Moreover, reports on the chemical synapse from RPeD1 to VD4 implied that the connection is either inhibitory (monophasic and hyperpolarizing) or biphasic (depolarizing followed by hyperpolarizing phases) rather than invariant due to two different receptors of Dapamine [50], this increases the uncertainty of modeling the synapses even the whole CPG network.

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