Pulse-Coupled Belousov-Zhabotinsky Oscillators with Activity Dependent Coupling Strengths

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by
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Abstract

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A thesis presented to the Department of Biochemistry
Graduate School of Arts and Sciences
Brandeis University
Waltham, Massachusetts

By Malia McAvoy

Central pattern generator (CPG) networks produce characteristic repetitive firing patterns that drive motor motions such as that of the pylorus of the lobster. Maintaining the physiological activity of these networks under various conditions is important. Synaptic plasticity, the tuning of the strengths of synapses, may take place based on the activity of the network. Calculations using a simple model featuring the three main neuron types of the lobster pyloric network CPG have shown that simple activity dependent rules can ensure the physiological activity. The tuning of connection strengths based on the activity of the members in the network is a generic idea that may be tested in other systems as well. In this work we studied tri-membered networks of pulse-coupled Belousov-Zhabotinsky oscillators both in numerical simulations and experiments. We first established the characteristic behaviors of the networks with different topologies. We found that the pyloric network topology is unique because it has a preference for triphasic oscillations in a specific peak order when the coupling strengths are equal and the cycle lengths of the oscillators match. We have found that other behaviors may appear when cycle lengths differ more than 4%. After establishing the main characteristics of two tuning mechanisms, we found that a method using a common target activity may be sufficient to secure the preferred triphasic behavior even if the natural activities differ 14%. Our findings support that activity dependent modification of interaction strength may ensure the stability of network dynamics in CPGs as well as other systems.
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List of Abbreviations

ADC Activity Dependent Coupling
BZ Belosouv-Zhabotinsky chemical reaction
CPG Central Pattern Generator
CSTR Continuously-fed Stirred Tank Reactor
CW Clockwise directionality of triphasic oscillations (1, 2, 3 peak order)
CCW Counterclockwise directionality of triphasic oscillations (3, 2, 1 peak order)
i-CW The initial directionality of the network is clockwise
i-CCW The initial directionality of the network is counterclockwise
i-(IP 2-3) Oscillators 2 and 3 are initially in-phase
IP 1-2 Oscillators 1 and 2 are in-phase
IP 1-3 Oscillators 1 and 3 are in-phase
IP 2-3 Oscillators 2 and 3 are in-phase
IP 1-2-3 All oscillators are in-phase
ODE Ordinary Differential Equation
PSU Power Supply Unit
STG Stomatogastric Ganglion
VAC Vacuum generated by an aspirator pump
How nervous systems produce movement has intrigued neuroscientists for many years. Repetitive movements, such as walking and breathing, are driven by rhythmic patterned outputs generated by certain networks of neurons. Some of these networks can produce this rhythmic patterned output when completely isolated from sensory feedback. Such networks are called central pattern generators (CPGs). A frequently used animal model for studying CPGs is the pyloric network of the stomatogastric ganglion (STG) within the digestive system of the lobster. The pyloric network controls striated muscles that dilate and constrict the pyloric region of the stomach in a cyclic three phase rhythm.

This network can be represented as a simplified three cell model. Results from this numerical model have shown that when the pyloric network is subject to activity-dependent plasticity, the synaptic strengths can assemble to produce a rhythmic triphasic motor pattern [1]. Two activity dependent rules, global and local, allow for convergence from random initial synaptic strengths into a set that causes the network to produce the physiological triphasic motor pattern. This capability illustrates that complex circuits can be tuned via simple activity dependent rules to achieve a certain rhythmic patterned output. We have been motivated by this phenomenon to address the following question: can activity dependent coupling drive a simpler network comprised of a different type of oscillators to produce a stable temporal pattern from a wide range of initial conditions? These question will be addressed using networks of three pulse-coupled Belousov-Zhabotinsky (BZ) chemical oscillators. We are studying a system which shares some of the fundamental dynamical properties of neurons. This system is interesting in the field of
nonlinear dynamics because it utilizes both theory and experiments. By studying this system, we have gained some insight into why the specific topology in the pyloric network evolved and the dynamical features necessary to produce the patterns.
2

Introduction

A brief overview of the fundamentals of neuroscience will be presented in order to highlight the common characteristic features of neural systems and pulse-coupled chemical oscillators, which will be presented in the subsequent section.

2.1 Neuroscience Fundamentals

Individual neurons are the basic units of the nervous system. They have four morphologically defined regions: (1) the cell body, (2) dendrites, (3) axon and (4) axon terminal (Figure 2.1).

![Figure 2.1: Typical morphology of a neuron](image)

Neurons produce electrical signals that can be measured across the cell membrane through transient changes in the electrical current that flows into and out of the cell. This current arises from the potential difference across the cell membrane which at rest is about -70 mV.
2. INTRODUCTION

When the membrane potential reaches a threshold of about -55 mV, a peak in the potential occurs, called an action potential (Figure 2.2).

![Figure 2.2: Action potential](image)

The impulse propagates down the axon away from the cell body arriving at the axon terminal where the signal is passed onto another cell. The cell sending the signal is called the presynaptic cell while the cell receiving the signal is called the postsynaptic cell (Figure 2.3).

![Figure 2.3: Presynaptic and postsynaptic cells](image)

Synaptic transmission may be either electrical or chemical. Electrical synapses establish communication between cells via gap-junctions that directly connect the cytoplasms of the two cells. This type of synaptic transmission allows for rapidly transfer of signals. Chemical synapses have a small space between the presynaptic and postsynaptic cells called the synaptic cleft. Synaptic vesicles within the cytosol of the axon terminal contain chemical transmitters. When an action potential arrives at a synapse, the vesicles fuse with the cell membrane and release their contents into the synaptic cleft. Many transmitter molecules bind to the receptors located
on the postsynaptic membrane and activate them, others are removed from the cleft actively, preparing the synapse for the next transmission. Though chemical transmission is not as fast as electrical transmission, it has an important capability of selectively modifying biochemical pathways through specific reactions and amplification may occur through signal transduction cascades. A single synaptic vesicle may release several thousand molecules of transmitters that can in turn open many ion channels in the target cell. The sensitivity of the neuron to incoming signals may change through various cellular mechanisms, which is known as plasticity.

While a single neuron may have an important function in a network, it is incapable of generating higher order functionality of an organism by itself. A simple example of a network of neurons is one that mediates the flexion-withdrawal spinal reflex in humans. Tapping the kneecap with a hammer stimulates a sensory neuron within the spinal cord which excites extensor motor neurons causing the quadriceps to contract while another pathway simultaneously inhibits motor neurons that innervate flexor muscles (Figure 2.4).

![Figure 2.4: Circuit that drives the flexion-withdrawal reflex](image)

Some motor circuits are regulated through synaptic plasticity modifying the strength of individual synapses. Changes in inhibitory synaptic strengths may alter the motor patterns produced dramatically [3].
Certain periodic movements such as walking, breathing, flying and swimming are called rhythmic motor patterns. Due to their functional and physiological importance, neuroscientists are interested in describing the fundamental concepts of the self-organization of neural networks that produce rhythmic motor patterns. Some rhythmic motor patterns, such as the leech heartbeat, are isolated from sensory feedback. Other movements can be altered to deal with changing environmental conditions by receiving sensory feedback. For instance, sensory input received by the box jellyfish *Tripedalia cystophora* modifies its swimming [4]. These rhythmic motor patterns are driven by the rhythmic patterned outputs mediated by small neural networks. It has been shown that most rhythmic patterned outputs are produced endogenously (i.e. without rhythmic sensory or central input) by neural networks called CPGs [5]. CPGs generate rhythmic patterned outputs to drive a wide variety of rhythmic motor patterns.

2.2 Synaptic Plasticity in the Pyloric Network

Our motivation for investigating pulse-coupled oscillators with activity dependent coupling strength arises from a theoretical study [1] in which a set of activity dependent rules that tune inhibitory synapses were implemented into a three cell model of the pyloric network of the STG. A brief overview of the fundamental concepts of the study by Soto-Treviño et al. will first be presented.

Pyloric Network of the STG as an Animal Model for CPGs

The digestive system of the lobster is a frequently used animal model for studying CPGs. Crustaceans do not have teeth in their mouths, therefore particles of food are swallowed whole. A central tooth with rows of tooth-like denticles immediately before the stomach, called gastric teeth, grind the food into smaller particles. Rhythmic contractions of the gastric teeth and stomach are controlled by the STG (Figure 2.5) which has two CPGs: the pyloric and the gastric mill networks.

The pyloric network controls striated muscles that dilate and constrict the pyloric region of the stomach in a cyclic, three phase rhythm, called the pyloric rhythm, while the gastric mill
network produces a slower six phase rhythm that controls muscles which produce chewing by the gastric teeth. The STG is often used as an animal model to study rhythmic motor patterns because the ganglion has neuronal and synaptic properties similar to that of more advanced animals like mammals [5].

Model of the Pyloric Network

The pyloric rhythm depends on a pacemaker consisting of a single anterior burster (AB) neuron coupled electrically to two pyloric dilator (PD) neurons such that these three cells always fire synchronously; therefore a single "pacemaker" neuron called AB/PD was implemented in the model. The lateral pyloric (LP) and pyloric (PY) neurons both fire on rebound from inhibition. The same set of Morris-Lecar differential equations extended by the terms which describe the activity dependent plasticity were used for each type of cell [1]. However, the intrinsic membrane properties of each type of neuron are different in the animal and therefore slightly different model parameters were used for each neuron in the model.

This model implements the pyloric network with five inhibitory synaptic connections (Figure 2.6). The LP and PY neurons are inhibited by two different neurons but the pacemaker receives feedback from the LP neuron only. When the model neurons are connected with this topology and possess the appropriate synaptic strengths, an alternating triphasic pattern is generated that mimics the pyloric rhythm in the order AB/PD, LP, then PY.
Activity Dependent Modification of the Synaptic Strengths

The goal of the theoretical study by Soto-Treviño et al. [1] was to propose a simplistic mechanism by which the network self regulates in order to produce the appropriate synaptic strengths and generate the physiological pattern from random initial synaptic strengths. Two sets of rules were used to implement the plasticity of the inhibitory synapses: (1) global rules tune the synaptic strengths according to the difference between the activities of the neurons and their target activity that is physiological and (2) local rules modify particular synapses based on the activity difference between the presynaptic and postsynaptic cells. These rules allowed all five synaptic strengths to converge from random initial synaptic strengths onto a fixed point at which the circuit oscillated in the physiological triphasic pattern.

Notably, it was shown that because the global rule preserves the ratio of the strengths of those synapses that terminate at the same cell, any synaptic tuning that does not differentially regulate individual synapses is incapable of generating the desired triphasic rhythm from any random initial condition. For instance, when the PY to LP synapse is five times the strength of the AB/PD to LP synapse and the AB/PD to PY synapse is five times as strong as the LP to PY synapse, the global rules produce two behaviors which are physiologically undesired: one or more oscillators are suppressed and entrainment but in the undesired order (AB/PD, followed by PY, and then LP) [1]. The local rules were added in order to differentially regulate the individual synapses and thus prevent these undesired behaviors from occurring.

We have been motivated by this study to address the following question: can activity dependent coupling drive a simpler network comprised of a different type of oscillator to produce a stable temporal pattern from a wide range of initial conditions? This question was addressed using numerical models of a network of three pulse-coupled BZ oscillators.
2.3 A Brief History of Nonlinear Chemical Dynamics

The first report of oscillations in a chemical system was published by Gustav Fechner in 1828. Fechner described an electrochemical cell that produced an oscillating current. Then, in 1899 Wilhelm Ostwald observed that the rate of chromium dissolution in acid periodically increased and decreased. Before the 20th century, oscillating chemical reactions did not receive much attention. There was no accepted scientific way to describe how a chemical reaction proceeds over time since chemical kinetics was not yet an accepted branch of science. In 1921, William C. Bray had discovered the first homogeneous chemical oscillator, the iodate-catalyzed decomposition of hydrogen peroxide [7] but his experimental work was criticized by the chemical community. The majority of chemists were skeptical of oscillating chemical reactions because they believed that the Second Law of Thermodynamics prohibited such oscillations. Many viewed an oscillating reaction as an analog of a pendulum which passes through its equilibrium point during each cycle of oscillation. This view is indeed in conflict with the Second Law of Thermodynamics as an oscillating behavior would require the free energy of the system to oscillate as the reactants were converted to products and then back to the original reactants (Figure 2.7a).

![Graphs showing earlier and current views of chemical oscillations](image)

Figure 2.7: (a) An earlier view of chemical oscillations (b) Current view of chemical oscillations
As a result of this view, the underlying causes of all chemical oscillations were attributed to heterogeneous processes or simply to technical errors. However, a chemical oscillator is rather different from a pendulum. Chemical oscillations occur far from equilibrium and are governed by non-equilibrium thermodynamics in which the free energy declines monotonically while the concentrations of certain intermediates increases and decreases periodically, thus the Gibbs free energy of the system does not pass through its equilibrium point. (Figure 2.7b).

The beginning of modern nonlinear chemical dynamics emerged in the early 1950s when Boris Belousov, a Soviet biophysicist, was trying to construct an inorganic chemical system that is analogous to the Krebs cycle proceeding in living organisms. Belousov was investigating a solution of sodium bromate, citric acid and ceric ions (Ce$^{4+}$). He expected the citric acid to monotonically reduce the yellow cerium (IV) into colorless cerium (III) but instead he observed that the solution alternates between colorless and yellow.

Belousov had tried to publish his results but because the editors did not believe that such phenomenon was possible, his paper was repeatedly rejected by the Soviet peer reviewed chemical journals. Belousov’s work received no attention until Anatol Zhabotinsky, a graduate student at Moscow State University, began studying the system. In Belousov’s original recipe, citric acid was oxidized yielding products which precipitated out of solution. By replacing citric acid with malonic acid, Zhabotinsky produced a homogeneous bromate oscillator which we now call the Belousov-Zhabotinski reaction. At least ten papers on the BZ reaction were published in Russian before the first came out in English.

The cerium (IV) catalyst can be replaced by other metal ions or complexes with similar redox potentials. One particular catalyst, tris(1,10-phenanthroline) iron(4) (ferroin), was initially used by Belousov to enhance the color changes in the cerium-catalyzed system. However, when Ce$^{4+}$ is used along with ferroin, the patterns are disrupted because CO$_2$ is produced. In 1970, Albert Zaikin and Zhabotinsky [10] identified conditions under which ferroin alone catalyze the BZ reaction, allowing them to study spatial patterns (Figure 2.8).

In 1977, Ilya Prigogine and Gregoire Nicolis [11] described the theoretical requirements of all chemical oscillators. First, the chemical system must be sufficiently far from the state of thermodynamic equilibrium. Second, the reaction mechanism must include reactions which
allow for both positive and negative feedback. Third, specific parametric requirements must be met; for instance, the chemical concentrations, temperature and, in a flow reactor, flow rates must be within the correct range for the oscillations to occur.

For a long time the iodate-catalyzed decomposition of hydrogen peroxide and BZ reaction were the only known chemical oscillators besides living organisms and there was no known systematic method to create them. In 1981, De Kepper, Kustin and Epstein [12] were the first to construct a systematically designed oscillating chemical reaction comprised of arsenite, iodate and chlorite in a continuously-fed stirred tank reactor (CSTR). Their methodology has led to the growth of the number of chemical oscillators from two accidently discovered systems to dozens of new systems. Oxohalogen chemistry, which characterizes the Bray and BZ systems, is the most common source of chemical oscillators although sulfur [13], phosphorous [14], cobalt [15,16] and manganese [17] varied oscillators as well as organic reactions also can give rise to oscillatory dynamics.

### 2.4 Oscillatory Dynamics in the BZ Reaction

Chemical oscillations are defined as the periodic or nearly periodic variation of the concentrations of chemical species over time. This exotic behavior provided the initial motivation for
the development of nonlinear chemical dynamics and it continues to be a thoroughly studied phenomenon [8]. The BZ reaction is a prototype system producing chemical oscillations and these oscillations may be observed by color oscillations or using instruments displaying traces of redox potential over time (Figure 2.9).

![Figure 2.9: Typical time series for the BZ reaction](image)

By surveying and evaluating the literature, Field, Koros and Noyes at the University of Oregon [18] proposed a chemical mechanism in which the system is considered to oscillate between the reduced and oxidized state. This model is referred to as the FKN mechanism which consists of three processes which comprise reactions proceeding at different stages of the entire BZ reaction.

Process A involves the consumption of the inhibitory chemical species, $\text{Br}^-$, by $\text{BrO}_3^-$ with a low steady state concentration of $\text{HBrO}_2$. The stoichiometric steps along with their rate laws are as follows:
2.4. OSCILLATORY DYNAMICS IN THE BZ REACTION

\[
\begin{align*}
BrO_3^- + Br^- + 2H^+ & \rightarrow HBrO_2 + HOBr & v_1 = k_1[BrO_3^-][Br^-][H^+]^2 \quad (2.1) \\
HBrO_2 + Br^- + H^+ & \rightarrow 2HOB & v_2 = k_2[HBrO_2][Br^-][H^+] \quad (2.2) \\
HOBr + Br^- + H^+ & \rightarrow Br_2 + H_2O & v_3 = k_3[HOBr][Br^-][H^+] \quad (2.3) \\
Br_2 + CH_2(COOH)_2 & \rightarrow BrCH(COOH)_2 + Br^- + H^+ & v_4 = k_4[Br_2][CH_2(COOH)_2] \quad (2.4)
\end{align*}
\]

where the overall reaction is

\[
BrO_3^- + 2Br^- + 3H^+ + 3CH_2(COOH)_2 \rightarrow 3BrCH(COOH)_2 + 3H_2O \quad (2.5)
\]

Process A ceases when \([Br^-]\) falls below a critical value allowing the autocatalytic \(BrO_3^- / HBrO_2\) reaction to take over in Process B.

In process B there is an autocatalytic production of \(HBrO_2\) and simultaneous oxidization of the redox catalyst. The stoichiometric steps of Process B with their empirical rate laws are:

\[
\begin{align*}
HBrO_2 + BrO_3^- + H^+ & \rightarrow 2BrO_2^* + H_2O & v_5 = k_5[HBrO_2][BrO_3^-][H^+] \quad (2.6) \\
BrO_2^* + M^{n+} + H^+ & \rightarrow HBrO_2 + M^{(n+1)+} & v_6 = \text{fast} \quad (2.7) \\
2HBrO_2^* & \rightarrow BrO_3^- + HOBr + H^+ & v_7 = k_6[HBrO_2^*]^2 \quad (2.8) \\
HOBr + CH_2(COOH)_2 & \rightarrow BrCH(COOH)_2 + H_2O & v_8 = k_7[HOBr][CH_2(COOH)_2] \quad (2.9)
\end{align*}
\]

where the overall reaction is

\[
BrO_3^- + 5H^+ + CH_2(COOH)_2 + 4M^{n+} \rightarrow BrCH(COOH)_2 + 4M^{(n+1)+} + 3H_2O \quad (2.10)
\]

The catalyst system is generally represented as a \(M^{n+}/M^{(n+1)+}\) couple. This couple can be, for instance, a Ce\(^{3+}/Ce^{4+}\) couple or catalysts such as ferroin(II)/ferroin(III) and Mn\(^{2+}/Mn^{3+}\). The concentration of \(HBrO_2\) increases approximately six order of magnitude above the value in process A. When the reduced catalyst is oxidized, the autocatalytic cycle ends and process C takes over.

Process C is called the "clock resetting" process in which the redox catalyst is reduced by the brominated malonic acid and \(Br^-\) is regenerated:

\[
4M^{(n+1)+} + BrCH(COOH)_2 + 2H_2O \rightarrow 4M^{n+} + 2CO_2 + HCOOH + 5H^+ + Br^- \quad (2.11)
\]
The net reaction of all processes is:

$$3\text{BrO}_3^- + 5\text{CH}_2(\text{COOH})_2 + 3\text{H}^+ \rightarrow 3\text{BrCH(COOH)}_2 + 2\text{HCOOH} + 4\text{CO}_2 + 5\text{H}_2\text{O} \quad (2.12)$$

The BZ reaction can be summarized as the oxidative bromination of malonic acid by sodium bromate. The Gibbs free energy change of the net reaction is negative, thus this reaction proceeds spontaneously; however, in the absence of a catalyst the net process is very slow and does not produce oscillations.

\section*{2.5 Coupling of BZ Oscillators}

Coupling of chemical oscillators can be achieved in numerous ways such as diffusively \cite{19-22}, electrically \cite{23,24}, using pumps \cite{25-27} or light \cite{28,29}. One method of coupling involves diffusional mass exchange which occurs through a medium shared by adjacent systems \cite{8}. A recent example is the coupling of BZ emulsion droplet arrays in which BZ reactants are in the form of droplets separated by oil gaps as shown in Figure 2.10 \cite{30}.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{diffusively_coupled_bz_droplets.png}
\caption{Diffusively coupled BZ droplets}
\end{figure}

These droplets are diffusively coupled through the inhibitory intermediate, Br$_2$, which dissolves in the oil gaps.

Another type of coupling that is more analogous to synaptic transmission is pulse-coupling recently implemented with chemical oscillators. Pulse-coupling of two BZ oscillators is achieved by computer controlled chemical perturbations which resemble spike-mediated neurotransmission \cite{31,32}. Since the oxidized and reduced states of the BZ depend on [Br$^-$], one method of coupling
2.5. COUPLING OF BZ OSCILLATORS

may be achieved by perturbing the oscillators using KBr solution. The addition of KBr into the reaction mixture of oscillator 2 is triggered when a spike is detected in the signal of oscillator 1. KBr extends the length of the cycle in which the addition occurred and thus delays the next peak. Excitatory coupling may be achieved by injecting a solution of AgNO$_3$ to lower [Br$^-$] through formation of AgBr precipitate. One study investigated the dynamics of two pulse-coupled BZ oscillators in which the coupling was equal and constant. In-phase oscillators were observed under excitatory coupling (Figure 2.11) and anti-phase oscillations were observed under inhibitory coupling (Figure 2.12) [31].

![Figure 2.11: Initially anti-phase oscillations switch to in-phase upon excitatory coupling [31]](image)

![Figure 2.12: Anti-phase oscillations with inhibitory coupling](image)

The effect of KBr pulses on the dynamics of BZ oscillators is analogous to the effect of inhibitory synapses. Modulation of the strength of inhibitory synapses can be implemented in this chemical analog of neurons. In our work, pulse-coupled BZ oscillators will be studied using experiments and numerical models.
3 Experimental Methods

3.1 Chemicals

The following chemicals were dissolved in deionized water without further purification: NaBrO₃ (99+%, Acros Chemicals), tris-(1,10-phenantroline)iron(II) solution (ferroin) (0.025 M, Ricca Chemical Company), malonic acid (MA) (99%, Acros Chemicals), H₂SO₄ (10N, Fisher), KBr (99+%, Jassen Chimica), Triton X-100 (Acros Chemicals).

3.2 Experimental Setup of the BZ Oscillators

Four physically isolated BZ oscillators were used each according to the following scheme [31,32]:

![Figure 3.1: Arrangement of each BZ oscillator](image)

*Figure 3.1: Arrangement of each BZ oscillator*
3.2. EXPERIMENTAL SETUP OF THE BZ OSCILLATORS

Black arrows indicate the continuous flow of reagents into the reactor and the outflow of the excess reaction mixture. Red and green arrows indicate data acquisition and control processes, respectively. The dotted lines show the intermittent control signal to the solenoid valve controlling when a perturbation occurs and the resulting flow of perturbing solution.

CSTRs

The CSTRs were each constructed of 15.0 mL beakers sealed with custom made silicon stoppers. There were two reagent feed stocks: one containing NaBrO$_3$ and H$_2$SO$_4$ and the other containing MA and ferroin. These two solutions were continuously pumped into four CSTRs using two peristaltic pumps (Gilson Minipuls 3). The reagents of each oscillator were supplied by two channels of the 4-channel peristaltic pump. The flow rates of each channel were measured at the beginning of each experimental day ($k_0 = 6.30 \times 10^{-4}$ s$^{-1}$) with a maximum relative deviation of 0.5%. The CSTRs were kept at room temperature and stirred at rates between 500-800 rpm using magnetic stirrers (Scinics Instruments, Multistirrer MC 301). The reagent concentrations maintained after dilution and mixing within the CSTRs were as follows: $[\text{NaBrO}_3]_0 = 0.2$ M, $[\text{H}_2\text{SO}_4]_0 = 0.25$ M, $[\text{MA}]_0 = 0.05$ M and $[\text{ferroin}]_0 = 1.0 \times 10^{-3}$ M. These regent concentrations produce oscillations with a cycle length of around 60 s and amplitude of around 200 mV when uncoupled. The volumes of the reaction mixtures were kept constant by removing excess solution out of overflow holes on the top of the reactors through Teflon (PTFE) tubes connected to suction flasks under vacuum generated by an aspirator pump (VAC, Cole Parmer - 75301). The CSTRs were nearly identical: when uncoupled, the cycle lengths of oscillations, volume of the CSTR and total inflow rate of reagents varied by no more than 5%.

Monitoring Oscillations in the BZ Reaction Mixture

The BZ oscillations were followed by measuring the redox potential ($E$) using a Pt (Radiometer M241PT)-reference (Radiometer 321, Ag/AgCl/KCl) electrode pair connected to a pH meter (Oakton pH-510). The reference electrode was chemically isolated from the reaction mixture using a glass junction (radiometer AL-100) filled with saturated K$_2$SO$_4$ solution. Acquired data were analyzed using a high precision multichannel data acquisition board (National Instrument
3. **EXPERIMENTAL METHODS**

NI-6310) connected to the analogue output of the pH meter to a personal computer. A custom designed application using LabView acquired the redox potential signal at a rate of 2 Hz.

### 3.3 Pulse-Coupling

**KBr Perturbing Solution**

The KBr perturbing solution was kept in four reservoirs mounted 1.5 m above the reactors. This solution was acidified using H$_2$SO$_4$ in order to keep the [H$^+$] of the perturbing solution the same as the reaction mixtures (typically [H$_2$SO$_4$] = 0.25 M). This step is necessary because the cycle lengths of each oscillator depend on the [H$^+$] of the reaction mixture. The flow of KBr solution through the Teflon tubes was driven by gravity.

**Preparations before Coupling**

The periods of the oscillators were monitored in order to ensure that the variation was less than 5% and there was no drifting for at least five cycles. Three of the four constructed oscillators were chosen based on which oscillators varied the least in their cycle lengths. The periods were fine-tuned by adjusting the stirring rates. The positions of the initial peaks relative to each other were adjusted by injecting KBr into the reaction mixtures in order to push the peaks in the desired positions before coupling.

**Perturbations**

Coupling of the oscillators was accomplished by computer-controlled chemical perturbations. A spike detected in the redox potential of one oscillator triggers the addition of a small volume (10-100µL) of inhibitor (KBr) into the reaction mixture of another (other) oscillator(s) (Figure 3.2). The coupling strength is expressed as the concentration of KBr added ([KBr]$_{\text{inj}}$) after dilution to the total volume of the reaction mixture. The Pt electrode potential for signal initiation was 0.960 with a positive dV/dt. Upon detection of a spike in the BZ reaction, the computer sent a signal to the reed relay (RB, COTO-9007-05-0000-1032) using the 5V TTL digital outputs of the NI-6531. The reed relay closed the circuit between the 10V DC
3.3. PULSE-COUPLING

Figure 3.2: Inhibitory chemical perturbation

output of the power supply unit (PSU, Extech 382260) and the solenoid valve. This caused the valve to open for a brief period time ($t_{\text{open}}$). The amount of discharged solution ($V_{\text{pulse}}$) depended linearly on $t_{\text{open}}$. The flow rates of perturbing solution were around 100 $\mu$Ls$^{-1}$. The LabView application controlled perturbations through the 5 V digital output channels of the data acquisition board. A block scheme of the pulse-coupling application is shown in Figure 3.3 [31].

Figure 3.3: Application used to control the perturbations
The gray blocks represent units of the application used to control the perturbations. The blocks in blue represent input variables. The "Potentials" are measured independently and continuously for each CSTR while the other three variables ("Thresholds", "Delay settings" and "Pulse lengths") are defined by the user. The only output variable is the open states of the valves shown in yellow.
Numerical Model

An eight variable model was used to describe the behavior and parameters of the three BZ oscillators in a CSTR. The model consists of the following ordinary differential equations (ODEs):

\[
\begin{align*}
\frac{dx}{dt} &= -k_1 h y + k_2 h^2 y - 2k_3 x + k_4 h ax \frac{(z_t - z)}{z_t - z + c_{\text{min}}} - k_0 x - k_v x \\
\frac{dy}{dt} &= -k_1 h y - k_2 h^2 y + k_9 v z - k_{10} b z - k_0 y + c_{\text{inh}} \\
\frac{dz}{dt} &= 2k_4 h ax \frac{(z_t - z)}{z_t - z + c_{\text{min}}} - k_9 v z - k_{10} b z - k_0 z - k_v z \\
\frac{dv}{dt} &= 2k_1 h y + k_2 h^2 y + k_3 x^2 - k_9 v z - k_{13} v + k_0 v - k_v v \\
\frac{dh}{dt} &= (h_0 - h)k_0 - k_v h \\
\frac{da}{dt} &= (a_0 - a)k_0 - k_v a \\
\frac{db}{dt} &= (b_0 - b)k_0 - k_v b \\
\frac{dz_t}{dt} &= (z_0 - z_t)k_0 - k_v z_t
\end{align*}
\]

where the variables corresponding to concentrations are as follows: \( h = [H^+] \), \( a = [\text{NaBrO}_3] \), \( b = [\text{MA}] \) (malonic acid), \( x = [\text{HBrO}_2] \) (activator), \( y = [\text{Br}^-] \) (inhibitor), \( z = [\text{ferruin}] \) and \( v = [\text{BrMA}] \) (bromomalonic acid). The coupling strength \( y_{\text{inh}} = c_{\text{inh}} \Delta t \) corresponds to the experimental parameter \([\text{KBr}]_{\text{inj}}\). The values of \( c_{\text{inh}} \) and \( \Delta t \) were \( 1 \times 10^{-5} \text{ M} \) and \( 1 \text{ s} \) in all numerical simulations. The model parameters used are: \( k_1 = 2 \times 10^6 \text{ M}^{-2}\text{s}^{-1} \), \( k_2 = 2 \text{ M}^{-3}\text{s}^{-1} \), \( k_3 = 3 \times 10^3 \text{ M}^{-1}\text{s}^{-1} \), \( k_4 = 42 \text{ M}^{-2}\text{s}^{-1} \), \( k_9 = 20 \text{ M}^{-1}\text{s}^{-1} \), \( k_{10} = 0.05 \text{ M}^{-1}\text{s}^{-1} \), \( k_{13} = 0.004 \text{ s}^{-1} \),
Numerical Model

\[ c_{min} = (3k_r k_{10} z_t)^{1/2}/k_{red}, \] 
\[ k_r = 2108 \text{ M}^{-1}\text{s}^{-1} \text{ and } k_{red} = 5106 \text{ M}^{-1}\text{s}^{-1}. \]

The inflow concentrations are: 
- \([\text{NaBrO}_3]_0 = 0.20 \text{ M}, \] 
- \([\text{MA}] = 0.1 \text{ M}, \] 
- \(z_t = [\text{ferroin}]_0 = 3 \text{ mM}, \) 
- \(k_0 = 0.0005 \text{ s}^{-1}, \) 
- \([H^+] = 0.25 \text{ M} \text{ and } k_v = 6.666 \times 10^{-3} \text{ s}^{-1} \text{ yielding oscillations with } T = 168 \text{ s}. \)

4.1 Implementation of Noise

Noise is introduced by perturbations of \([H^+]\) with a random amplitude at the beginning of each cycle which alters the cycle lengths randomly. The random change in the concentration of hydrogen in the solution is given by the following differential equation:

\[
\frac{dh}{dt} = k_0 (h_0 + h_0 \frac{\text{rand}}{100} - h) - k_v h \quad (4.9)
\]

where \(h = [H^+]\) in solution, \(h_0 = [H^+]_0\) in flow and \(\text{rand}\) is a uniformly distributed pseudorandom number between the interval \((-0.5, 0.5)\). The term \(h_0 \frac{\text{rand}}{100}\) is applied only when there is a peak or at the beginning of the cycle as a single change in the value of \(h\).

4.2 Analysis of the Numerical Results

The preferred behavior of a network of three oscillators under various initial conditions is quantified by running a 33 \times 33 \text{ (map) array of the initial phases for oscillator 2 and 3 for 15,000 s. Each time series was analyzed at the end if the order was } 1 \to 2 \to 3 \text{ (clockwise, } \text{"CW"}, \) 3 \to 2 \to 1 \text{ (counter-clockwise, } \text{"CCW"}, \) 1 \to 2 & 3 \text{ (2 and 3 in-phase, } \text{"IP 2-3"}, \) 1 & 3 \to 2 \text{ (1 and 3 in-phase, } \text{"IP 1-3"}, \) 1 & 2 \to 3 \text{ (1 and 2 in-phase, } \text{"IP 1-2"}) \text{ or } 1 & 2 & 3 \text{ (1, 2 and 3 in-phase, } \text{"IP 1-2-3"}). \) These data are then analyzed statistically by calculating both the percentage of initial conditions that resulted in a particular final behavior (listed as \text{"final" in the tables). In addition, the percentage of total cycles that the system has spent producing a particular behavior is calculated to see if that behavior was predominant over time (i.e. developed early on) (listed as \text{"development" in the tables).}
Before investigating networks of three BZ oscillators under activity dependent coupling, we wanted to establish an understanding of the behaviors produced by tri-membered networks with different topologies under static coupling in order to determine if the topology of the pyloric network itself favors a particular behavior. We also wanted to show what the limitations of static coupling are and later determine what advantages the activity dependent modification of the coupling may possess. We first studied whether the topology of the pyloric network has any advantage over other tri-membered networks since the pyloric network of the STG specifically generates one behavior that is physiological, the triphasic pattern [1].

This was accomplished by determining which networks have a preference for the tri-phasic pattern with a certain order that the oscillations peak and which ones have no preference. In addition, noise tolerance was tested to show if a behavior is robust. The term directionality will be used to refer to the order which the oscillators fire when the topology is represented as a circular network in the order 1, 2, 3. Oscillators may fire in two orders 1, 2, 3 or 3, 2, 1 which appear as clockwise (CW) and counter-clockwise (CCW) in the circular representations respectively. Preference for the correct direction is an important characteristic of the pyloric network because there is a physiological one (AB/PD, followed by LP, and then PY) while the other is undesired. In our model system, we do not specify a particular direction as preferred in our study, but we attempt to determine if a particular behavior is preferred by the different
5. NETWORKS OF THREE OSCILLATORS: STATIC COUPLING

5.1 Dynamics of Networks of Three Oscillators with Different Topologies

**Definition of Phase Difference ($d\phi$)**

The parameter we use to describe the phase relation at the peaks of pulse-coupled BZ oscillators is the phase difference ($d\phi$) with respect to a reference oscillator which is defined as oscillator 1. The phase difference is calculated as

$$d\phi = \frac{t_2 - t_1}{T_1}$$  \hspace{1cm} (5.1)

where $t_1$ is the time at which a peak occurs in the reference oscillator, $t_2$ is the time at which the other oscillator(s) peak(s) and $T_1$ is the cycle length of the reference oscillator at the final stable state (Figure 5.1).

![Figure 5.1: Definition of the phase difference](image)

**Experimental Parameters**

The reaction mixture contained the following chemicals: $[\text{NaBrO}_3]_0 = 0.20$ M, $[\text{H}_2\text{SO}_4]_0 = 0.30$ M, $[\text{MA}]_0 = 0.05$ M, $[\text{Ferroin}]_0 = 0.001$ M and Triton X-100 (0.1 g/L). The coupling strengths were constant. The initial cycle lengths were around 60 seconds ($\pm 10$ s). The exact natural cycle lengths at the beginning of each experiment are specified in the results. We forced the peaks to be in the desired order at the beginning of each experiment by injecting the reaction mixtures with KBr ($[\text{KBr}]_{\text{inj}} = 3.3 \times 10^{-6}$ M). Once the peaks were in the desired initial pattern,
5.1. DYNAMICS OF NETWORKS OF THREE OSCILLATORS WITH DIFFERENT TOPOLOGIES

Pulse-coupling was initiated and the peaks develop into the final pattern. The final pattern is defined as a pattern which is stable for at least five cycles. Each experiment ran for about 800 s.

**Linear Network**

The connection diagram of the first network that was studied, called the "linear network", is shown below:

![Linear network topology](image)

**Figure 5.2: Linear network topology**

The map of the final patterns produced by the linear network is shown in Figure 5.3.

![Linear network map of the longest patterns](image)

**Figure 5.3: Linear network map of the longest patterns**

The following statistics were generated by the linear network:
Table 5.1: Linear network statistics

<table>
<thead>
<tr>
<th></th>
<th>CW</th>
<th>CCW</th>
<th>IP 1-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Development</td>
<td>5.18%</td>
<td>5.27%</td>
<td>89.55%</td>
</tr>
</tbody>
</table>

From these data, it is clear that there is a strong preference for oscillators 1 and 3 to become in-phase (out-of-phase with oscillator 2) both after stabilization and during development in this network.

In order to test whether this arrangement is robust, noise was added to the system. When a significant amount of noise (30) is introduced, this network will still have a preference for the in-phase arrangement both during development and at the final state (Table 5.2).

Table 5.2: Linear network with noise (30) statistics

<table>
<thead>
<tr>
<th></th>
<th>CW</th>
<th>CCW</th>
<th>IP 1-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final</td>
<td>0.28%</td>
<td>0.47%</td>
<td>99.25%</td>
</tr>
<tr>
<td>Development</td>
<td>15.25%</td>
<td>14.45%</td>
<td>70.29%</td>
</tr>
</tbody>
</table>

Table 5.3 shows the experimental results with the linear network topology under static coupling.

Table 5.3: Linear network experimental results

<table>
<thead>
<tr>
<th></th>
<th>[KBr]_{inj} / M</th>
<th>Initial Cycle Length (T) / s</th>
<th>Initial Behavior</th>
<th>Final Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.3 \times 10^{-6}</td>
<td>T_1 = 68.5, T_2 = 58.2, T_3 = 66.0</td>
<td>CW</td>
<td>IP 1-3</td>
</tr>
<tr>
<td>2</td>
<td>6.7 \times 10^{-6}</td>
<td>T_1 = 61.3, T_2 = 59.5, T_3 = 62.6</td>
<td>CW</td>
<td>IP 1-3</td>
</tr>
<tr>
<td>3</td>
<td>3.3 \times 10^{-6}</td>
<td>T_1 = 62.5, T_2 = 59.3, T_3 = 64.9</td>
<td>IP 2-3</td>
<td>IP 1-3</td>
</tr>
<tr>
<td>4</td>
<td>3.3 \times 10^{-6}</td>
<td>T_1 = 63.3, T_2 = 60.3, T_3 = 63.8</td>
<td>CCW</td>
<td>IP 1-3</td>
</tr>
</tbody>
</table>

The experimental results for the linear network agree with the simulated results.

This IP 1-3 behavior is an example of zero-lag synchronization of pulse-coupled oscillators when they communicate through a relay oscillator [33]. The central oscillator (no. 2) can be viewed as the relay oscillator. When a peak occurs in oscillator 1, a perturbation to oscillator 2 occurs, then when oscillator 2 peaks oscillator 3 becomes perturbed. A similar sequence of
5.1. DYNAMICS OF NETWORKS OF THREE OSCILLATORS WITH DIFFERENT TOPOLOGIES

Events take place in the reverse direction. The time between the peak of oscillator 1 and the perturbation of oscillator 3 appears as a delay, therefore oscillator 1 and 3 will produce the same dynamics as if they were coupled directly with a delay; that is, in-phase oscillations [31].

Circular Unidirectional Network

The next network studied has all of the connections pointing in the clockwise direction (Figure 5.4).

![Circular unidirectional network topology](Image)

Figure 5.4: Circular unidirectional network topology

The following map and statistics were obtained:

![Circular unidirectional network map](Image)

Figure 5.5: Circular unidirectional network map of the final patterns
Table 5.4: Circular unidirectional network statistics

<table>
<thead>
<tr>
<th></th>
<th>CW</th>
<th>CCW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final</td>
<td>37.67%</td>
<td>62.31%</td>
</tr>
<tr>
<td>Development</td>
<td>17.27%</td>
<td>82.49%</td>
</tr>
</tbody>
</table>

This network has a preference for the counter-clockwise direction. This preference remains when noise (10 units) is applied (Table 5.5).

Table 5.5: Circular unidirectional network with noise (10) statistics

<table>
<thead>
<tr>
<th></th>
<th>CW</th>
<th>CCW</th>
<th>IP 1-2</th>
<th>IP 1-3</th>
<th>IP 2-3</th>
<th>IP 1-2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final</td>
<td>37.78%</td>
<td>62.21%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Development</td>
<td>25.67%</td>
<td>74.11%</td>
<td>0.095%</td>
<td>0.11%</td>
<td>0%</td>
<td>0.16%</td>
</tr>
</tbody>
</table>

The experimental results with the circular network topology under static coupling are shown in Table 5.6.

Table 5.6: Circular unidirectional network experimental results

<table>
<thead>
<tr>
<th></th>
<th>[KBr]_{inj} / M</th>
<th>Initial Cycle Length (T) / s</th>
<th>Initial Behavior</th>
<th>Final Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.7 \times 10^{-6}</td>
<td>T_1 = 61.8, T_2 = 60.6, T_3 = 62.8</td>
<td>CCW</td>
<td>CCW</td>
</tr>
<tr>
<td>2</td>
<td>6.7 \times 10^{-6}</td>
<td>T_1 = 61.0, T_2 = 59.0, T_3 = 61.0</td>
<td>CW</td>
<td>CW</td>
</tr>
</tbody>
</table>

The experimental results for the circular network agree with the simulated results, though there is no instance of CCW transition to CW. This network has a stronger preference for the triphasic oscillations with peaks in the CW order than those in the CCW order. Some initial conditions that are CCW may lead to CW, however we have not seen these in experiments.

Circular Plus One Connection Network

Another network analyzed has one more connection than the previous network (Figure 5.6). The map of the final patterns generated by the circular plus one connection network is displayed in Figure 5.7, and the statistics are shown in Table 5.7.
5.1. DYNAMICS OF NETWORKS OF THREE OSCILLATORS WITH DIFFERENT TOPOLOGIES

There is a preference for the clockwise direction though there are spots of 3:4:4 entrainment, unstable oscillations and other patterns. In the 3:4:4 entrainment, oscillator 1 (blue) completes 3 cycles during the time oscillators 2 and 3 (red and green) complete 4 cycles, and this keeps repeating (Figure 5.8).
The following table summarizes the preferred behaviors of the circular plus one network with noise:

<table>
<thead>
<tr>
<th></th>
<th>CW</th>
<th>3:4:4</th>
<th>Other patterns</th>
<th>Unstable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Final</strong></td>
<td>90.24%</td>
<td>5.49%</td>
<td>4.63%</td>
<td>2.46%</td>
</tr>
<tr>
<td><strong>Development</strong></td>
<td>89.68%</td>
<td>4.54%</td>
<td>1.24%</td>
<td>4.54%</td>
</tr>
</tbody>
</table>

The circular plus one network with noise does not differ quantitatively from the results with no noise. The preferred behavior was still CW and there were some instances of 3:4:4 entrainment and other patterns. The prevalence of the 3:4:4 entrainment pattern upon addition of noise decreased by 2.84% for the final patterns and by 5.21% for the patterns predominant over the time of the simulations. This decrease in the relative occurrence of the 3:4:4 pattern with noise may indicate that the 3:4:4 pattern is more noise sensitive than the CW pattern which increased by 1.33% for the final patterns and decreased by 0.76% over the development of the patterns.

The experimental results with the circular network topology under static coupling are shown in Table 5.9. In both experiments and numerical simulations, we observed entrainment when the initial behavior is IP 2-3; however, in experiments we saw a 1:2:2 entrainment whereas in simulations we observed 3:4:4 entrainment. This difference between experiments and simulations may be resolved by considering their differences in the values of $[\text{KBr}]_{\text{inj}}$. In numerical simulations, $[\text{KBr}]_{\text{inj}} = 1.0 \times 10^{-5}\text{M}$ while in the experiment, $[\text{KBr}]_{\text{inj}} = 3.3 \times 10^{-5}\text{M}$ (row 3, Table 5.9). We know from previous studies with two oscillators [32] that the final
5.1. DYNAMICS OF NETWORKS OF THREE OSCILLATORS WITH DIFFERENT TOPOLOGIES

Table 5.9: Circular plus one network experimental results

<table>
<thead>
<tr>
<th>[KBr]_{inj} / M</th>
<th>Initial Cycle Length (T) / s</th>
<th>Initial Order</th>
<th>Final Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$3.3 \times 10^{-6}$</td>
<td>$T_1 = 61.4$, $T_2 = 65.3$, $T_3 = 61.8$</td>
<td>CW</td>
</tr>
<tr>
<td>2</td>
<td>$6.7 \times 10^{-6}$</td>
<td>$T_1 = 60.1$, $T_2 = 60.9$, $T_3 = 62.1$</td>
<td>CCW</td>
</tr>
<tr>
<td>3</td>
<td>$3.3 \times 10^{-6}$</td>
<td>$T_1 = 61.5$, $T_2 = 61.5$, $T_3 = 62.6$</td>
<td>IP 2-3</td>
</tr>
</tbody>
</table>

Behaviors depend on the value of [KBr]_{inj}. Therefore, we anticipate some deviations in the behaviors between experiments and simulations.

**All-to-All Network**

The all-to-all topology is shown below:

![All-to-All Network Topology](image)

Figure 5.9: All-to-all network topology

The map for this network is completely symmetrical (Figure 5.10). The network maintains its initial behavior even in the areas where the oscillations are nearly in-phase initially. The statistics demonstrates that there is an equal occurrence of the clockwise and counter-clockwise directions; however, it appears that CCW stabilizes sooner (Table 5.10).

Table 5.10: All-to-all network statistics

<table>
<thead>
<tr>
<th></th>
<th>CW</th>
<th>CCW</th>
<th>IP (1, 2)</th>
<th>IP (1, 3)</th>
<th>IP (2, 3)</th>
<th>IP (1,2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final</td>
<td>43.66%</td>
<td>43.66%</td>
<td>4.36%</td>
<td>4.36%</td>
<td>3.98%</td>
<td>0%</td>
</tr>
<tr>
<td>Development</td>
<td>39.71%</td>
<td>39.78%</td>
<td>7.71%</td>
<td>7.71%</td>
<td>5.09%</td>
<td>1.19%</td>
</tr>
</tbody>
</table>
When noise (10) is applied to this system, the size of the in-phase regions decrease and the final states seem to be more or less the same as the initial ones (Table 5.11).

<table>
<thead>
<tr>
<th></th>
<th>CW</th>
<th>CCW</th>
<th>IP (1, 2)</th>
<th>IP (1, 3)</th>
<th>IP (2, 3)</th>
<th>IP (1, 2, 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Final</strong></td>
<td>48.48%</td>
<td>51.33%</td>
<td>0%</td>
<td>0.095%</td>
<td>0.095%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Development</strong></td>
<td>48.03%</td>
<td>49.33%</td>
<td>1.06%</td>
<td>1.10%</td>
<td>0.47%</td>
<td>1.07%</td>
</tr>
</tbody>
</table>

There is preference for the CCW pattern in the model but the preference seems statistically insignificant. The following are the experimental results with the all-to-all network topology under static coupling:

<table>
<thead>
<tr>
<th>[KBr]_{inj} / M</th>
<th>Initial Cycle Length (T) / s</th>
<th>Initial Order</th>
<th>Final Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 $3.3 \times 10^{-6}$</td>
<td>$T_1 = 61.6, T_2 = 66.5, T_3 = 64.9$</td>
<td>CCW</td>
<td>CCW</td>
</tr>
<tr>
<td>2 $3.3 \times 10^{-6}$</td>
<td>$T_1 = 63.8, T_2 = 69.6, T_3 = 66.8$</td>
<td>CW</td>
<td>CW</td>
</tr>
<tr>
<td>3 $3.3 \times 10^{-6}$</td>
<td>$T_1 = 63.8, T_2 = 69.6, T_3 = 66.8$</td>
<td>IP 2-3</td>
<td>CW</td>
</tr>
<tr>
<td>4 $3.3 \times 10^{-6}$</td>
<td>$T_1 = 63.8, T_2 = 69.6, T_3 = 66.8$</td>
<td>IP 1-3</td>
<td>CCW</td>
</tr>
</tbody>
</table>

In numerical simulations, the initial peak order and the in-phase behavior were maintained. In
experiments, when the initial pattern was in-phase, the final pattern was always triphasic. This may be due to the light variation in cycle lengths that we see as noise.

Network with the Pyloric Topology

The connectivity diagram of the network with the pyloric topology is shown in Figure 5.11.

![Network with the pyloric topology](image)

Figure 5.11: Network with the pyloric topology

The behaviors that this network produces are shown in Table 5.13.

<table>
<thead>
<tr>
<th></th>
<th>CW</th>
<th>CCW</th>
<th>IP (1, 2)</th>
<th>IP (1, 3)</th>
<th>IP (2, 3)</th>
<th>IP (1,2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final</td>
<td>0%</td>
<td>98.39%</td>
<td>0%</td>
<td>0%</td>
<td>1.61%</td>
<td>0%</td>
</tr>
<tr>
<td>Development</td>
<td>5.70%</td>
<td>92.29%</td>
<td>0.020%</td>
<td>1.01%</td>
<td>0.99%</td>
<td>1.67%</td>
</tr>
</tbody>
</table>

This network has a strong preference for the CCW triphasic oscillations. Table 5.4 shows the behaviors when noise (50) is introduced.

<table>
<thead>
<tr>
<th></th>
<th>CW</th>
<th>CCW</th>
<th>IP (1, 2)</th>
<th>IP (1, 3)</th>
<th>IP (2, 3)</th>
<th>IP (1,2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Development</td>
<td>1.57%</td>
<td>98.32%</td>
<td>0.014%</td>
<td>0%</td>
<td>0.92%</td>
<td>0.19%</td>
</tr>
</tbody>
</table>

This network is very noise tolerant. When very high noise (50) is applied, the counter-clockwise direction is still strongly preferred and the IP 2-3 pattern disappears which suggests that the IP 1-2 pattern was not as stable as the CCW triphasic oscillations.
The strong preference for the triphasic oscillations with CCW peak order can be explained as follows. Oscillator 1 only has one incoming connection, while other oscillators have two. In a triphasic pattern the two incoming links produce two perturbations: one at lower phase and another at higher phase. The later the perturbation occurs within a cycle the longer delay it causes in the appearance of the next peak. In a triphasic pattern oscillator 1 receives only one perturbation, whenever oscillator 2 peaks. If the peak order is CCW this perturbation occurs at a higher phase as opposed to the CW order where it occurs at a low phase. In order to have triphasic behavior the cycle lengths of the oscillators must match. Therefore, the stable phase differences of oscillator 2 and 3 are 0.72 and 0.36 respectively. The perturbations to oscillator 1 occur at a slightly higher phase than those in the CCW behavior of the all to all network ($\delta \phi_2 = 0.66$). In the CCW order all three oscillators receive a perturbation at higher phase, while in the CW order oscillator 1 would receive one at a low phase. The resulting cycle length difference means that this peak order is unstable, therefore the initial conditions where the peak order is CW eventually produce CCW oscillations.

To verify this reasoning, a control calculation was performed where $g_{2\rightarrow 1}$ was increased. When $g_{2\rightarrow 1}$ was 15 times stronger than the other coupling strengths the system had a preference for the triphasic behavior with CW peak order (Figure 5.12).

![Figure 5.12: Network with the pyloric topology produced CW triphasic oscillations when $g_{2\rightarrow 1} = 15$](image)

The experimental results for the network of the pyloric topology with when the initial pattern is CW (i-CW), CCW (i-CCW) and IP 2-3 (i-(IP 2-3)) are shown in tables 5.15, 5.16 and 5.17, respectively.
5.1. DYNAMICS OF NETWORKS OF THREE OSCILLATORS WITH DIFFERENT TOPOLOGIES

Table 5.15: Network with the pyloric topology experimental results (i-CW)

<table>
<thead>
<tr>
<th>[KBr]_{inj} / M</th>
<th>Initial Cycle Length (T) / s</th>
<th>Initial Phase</th>
<th>Final Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 3.3 × 10^{-6}</td>
<td>T_1 = 62.8, T_2 = 60.0, T_3 = 62.8</td>
<td>[0 0.37 0.57]</td>
<td>IP 1-3</td>
</tr>
<tr>
<td>2 3.3 × 10^{-6}</td>
<td>T_1 = 64.5, T_2 = 58.6, T_3 = 63.5</td>
<td>[0 0.25 0.35]</td>
<td>IP 1-3</td>
</tr>
<tr>
<td>3 3.3 × 10^{-6}</td>
<td>T_1 = 62.9, T_2 = 58.5, T_3 = 62.6</td>
<td>[0 0.34 0.45]</td>
<td>IP 1-3</td>
</tr>
<tr>
<td>4 3.3 × 10^{-6}</td>
<td>T_1 = 69.3, T_2 = 54.4, T_3 = 66.1</td>
<td>[0 0.15 0.35]</td>
<td>IP 1-3</td>
</tr>
<tr>
<td>5 1.67 × 10^{-5}</td>
<td>T_1 = 63.0, T_2 = 53.8, T_3 = 67.6</td>
<td>[0 0.65 0.75]</td>
<td>CCW, IP 1-3 switching</td>
</tr>
<tr>
<td>6 1.67 × 10^{-5}</td>
<td>T_1 = 63.6, T_2 = 53.6, T_3 = 64.6</td>
<td>[0 0.35 0.70]</td>
<td>IP 1-3</td>
</tr>
</tbody>
</table>

Table 5.16: Network with the pyloric topology experimental results (i-CCW)

<table>
<thead>
<tr>
<th>[KBr]_{inj} / M</th>
<th>Initial Cycle Length (T) / s</th>
<th>Initial Phase</th>
<th>Final Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 6.7 × 10^{-6}</td>
<td>T_1 = 62.0, T_2 = 59.3, T_3 = 61.9</td>
<td>[0 0.87 0.05]</td>
<td>CCW</td>
</tr>
<tr>
<td>2 3.3 × 10^{-6}</td>
<td>T_1 = 63.4, T_2 = 59.9, T_3 = 63.5</td>
<td>[0 0.68 0.25]</td>
<td>CCW</td>
</tr>
<tr>
<td>3 1.67 × 10^{-5}</td>
<td>T_1 = 63.4, T_2 = 55.1, T_3 = 66.3</td>
<td>[0 0.75 0.55]</td>
<td>Unstable</td>
</tr>
<tr>
<td>4 3.3 × 10^{-5}</td>
<td>T_1 = 63.9, T_2 = 54.5, T_3 = 67.3</td>
<td>[0 0.70 0.40]</td>
<td>1:2 entrainment</td>
</tr>
<tr>
<td>5 2.5 × 10^{-5}</td>
<td>T_1 = 68.0, T_2 = 59.5, T_3 = 78.2</td>
<td>[0 0.80 0.10]</td>
<td>1:2 entrainment</td>
</tr>
<tr>
<td>6 3.3 × 10^{-6}</td>
<td>T_1 = 57.8, T_2 = 51.6, T_3 = 62.6</td>
<td>[0 0.60 0.40]</td>
<td>Unstable</td>
</tr>
<tr>
<td>7 3.3 × 10^{-6}</td>
<td>T_1 = 67.7, T_2 = 56.7, T_3 = 66.6</td>
<td>[0 0.95 0.20]</td>
<td>Unstable</td>
</tr>
<tr>
<td>8 3.3 × 10^{-6}</td>
<td>T_1 = 68.0, T_2 = 55.9, T_3 = 68.2</td>
<td>[0 0.85 0.79]</td>
<td>Unstable</td>
</tr>
<tr>
<td>9 6.7 × 10^{-6}</td>
<td>T_1 = 67.0, T_2 = 56.0, T_3 = 66.6</td>
<td>[0.0 0.95 0.20]</td>
<td>Unstable</td>
</tr>
</tbody>
</table>

Table 5.17: Network with the pyloric topology experimental results (i-(IP 2-3))

<table>
<thead>
<tr>
<th>[KBr]_{inj} / M</th>
<th>Initial Cycle Length (T) / s</th>
<th>Initial Phase</th>
<th>Final Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 1.0 × 10^{-5}</td>
<td>T_1 = 63.0, T_2 = 58.3, T_3 = 61.6</td>
<td>IP 2-3</td>
<td>IP 1-3</td>
</tr>
<tr>
<td>2 3.3 × 10^{-6}</td>
<td>T_1 = 64.8, T_2 = 56.1, T_3 = 71.3</td>
<td>All in-phase</td>
<td>IP 1-3</td>
</tr>
<tr>
<td>3 3.3 × 10^{-6}</td>
<td>T_1 = 63.0, T_2 = 62.6, T_3 = 63.6</td>
<td>IP 1-3</td>
<td>IP 1-3</td>
</tr>
</tbody>
</table>
According to the simulations, the network with the pyloric topology is the only network which produces the triphasic behavior with a preferred directionality. However, in experiments, due to the difference in natural cycle lengths, we have observed that when the initial pattern is clockwise, the final pattern is IP 1-3. When the initial pattern is CCW, the final pattern is IP 1-3 switching with CCW, CCW or unstable and when the initial pattern is two oscillators in-phase, the final pattern is IP 1-3. We speculate that the IP 1-3 behavior is stable because the perturbations through the 1 to 3 connection are made when oscillator 3 is at a low phase; when it is insensitive to additions. This would render the network with the pyloric topology essentially identical to the topology of the linear network. This may underline the need for activity dependent modification to achieve triphasic oscillations when the coupling is pulse-like.

Summary

The results of the characterization of the preference of different networks with static coupling may be summarized as follows:

1. The linear network of three oscillators with reciprocal coupling between neighbors has a strong preference for in-phase behavior but it is noise sensitive.

2. The network possessing connections pointing in one direction has a slight preference for the counter-clockwise order and is noise tolerant.

3. The network with connections pointing in one direction plus one inhibition connection that coupled two neighbors reciprocally has a preference for oscillators to peak in the clockwise direction but it also produces entrainment which has not been seen in other networks.

4. There is no preference for a particular behavior in the network where the coupling topology is all-to-all and coupling strengths are equal. The network maintains the initial peak order.

5. According to the simulations, the network with the pyloric topology is the only network which produces the triphasic behavior with a preferred directionality. However, in experiments we have observed that when the initial pattern is clockwise, the final pattern is IP
1-3. When the initial pattern is CCW, the final pattern is IP 1-3. We believe this may be due to the difference in the natural cycle lengths in experiments.

In conclusion, the topology is sufficient to produce the triphasic behavior with a preferred directionality in simulations. In addition, the behavior produced by the network with the pyloric topology is more noise tolerant than the behaviors of the other networks studied. In addition, the preferred directionality of this network in our system is opposite of that in the biological system. The preferred directionality was reversed to match the biological system by making the $g_{2 \rightarrow 1}$ connection significantly higher than the others. Another important observation is that certain initial conditions do not lead to a triphasic rhythm but may be an arrangement where two oscillators peak in-phase and the third one is oscillating at the same frequency but out of phase like the IP 1-3 pattern in the linear network or the 3:4:4 entrainment in the "one direction plus one" network.

The IP 1-3 patterns produced by the linear network in both simulations and experiments and by the pyloric network in experiments, may be stable because the injection is made on oscillator 3 from oscillator 1 is it has low phase and therefore the effect is negligible and the network is identical to the linear network. All of the networks described thus far consisted of oscillators which had the same cycle lengths. However, one important property of the pyloric network in the animal model is that each neural cell has a different characteristic frequency. The behaviors produced by the network with the pyloric topology when the natural cycle lengths are different in simulations will be discussed next.

5.2 Non-equal Cycle Lengths in the Network with the Pyloric Topology

We sought to account for this discrepancy between numerical simulations and experiments by varying the cycle lengths of the oscillators in numerical simulations.
\( T_1 > T_2 > T_3 \)

We varied the cycle lengths of the oscillators by creating a 10% difference in which oscillator 1 is 10% slower than oscillator 2 and oscillator 3 is 10% faster than oscillator 2. This set of cycle lengths is referred to as a 20% "spread" in the cycle lengths. With this spread in the cycle lengths under static coupling, the IP 1-3 behavior is produced (Table 5.18).

Table 5.18: \( T_1 > T_2 > T_3 \) statistics

<table>
<thead>
<tr>
<th>Spread</th>
<th>Pattern</th>
<th>Relative occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>CCW</td>
<td>55.6%</td>
</tr>
<tr>
<td></td>
<td>IP 1-3</td>
<td>44.4%</td>
</tr>
<tr>
<td>14%</td>
<td>CCW</td>
<td>100%</td>
</tr>
<tr>
<td>10%</td>
<td>CCW</td>
<td>100%</td>
</tr>
<tr>
<td>4%</td>
<td>CCW</td>
<td>100%</td>
</tr>
</tbody>
</table>

According to the map (Figure 5.13), the IP 1-3 pattern is generated when the peak order was CW initially.

These results agree with the experiments shown previously (Table 5.15). The simulations also
show that the CCW pattern was maintained with i-CCW which agrees with some experimental results (rows 1 and 2, Table 5.16).

\[ T_3 > T_2 > T_1 \]

Table 5.19 shows the patterns and their relative occurrences for the network with cycle lengths in the order \( T_3 > T_2 > T_1 \).

<table>
<thead>
<tr>
<th>Spread</th>
<th>Pattern</th>
<th>Relative occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>3:2:2</td>
<td>100%</td>
</tr>
<tr>
<td>14%</td>
<td>3:2:2</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td>4:3:3</td>
<td>4%</td>
</tr>
<tr>
<td>10%</td>
<td>4:3:3</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>3:2:2</td>
<td>2%</td>
</tr>
<tr>
<td>4%</td>
<td>CCW</td>
<td>100%</td>
</tr>
</tbody>
</table>

All 3:2:2 patterns are identical with three peaks in the order 3, 1, 2 bunched very closely followed by four peaks in the order 1, 3, 2, 1 (Figure 5.14), but how closely the peaks are bunched together depends on the spread. The 4:3:3 patterns are identical and always begin with oscillators 1 and 3 in-phase (Figure 5.15).
5. NETWORKS OF THREE OSCILLATORS: STATIC COUPLING

Figure 5.14: Time series of $T_3 > T_2 > T_1$ (14% spread)

Figure 5.15: Time series of $T_3 > T_2 > T_1$ (10% spread)

The triphasic CCW pattern with the 4% spread when oscillator 1 is slowest and oscillator 3 is fastest looks identical to the triphasic CCW pattern with the 4% spread when oscillator 3 is slowest and oscillator 1 is fastest.
5.2. NON-EQUAL CYCLE LENGTHS IN THE NETWORK WITH THE PYLORIC TOPOLOGY

\[ T_2 > T_3 > T_1 \]

The patterns observed for the network with cycle lengths in the order \( T_2 > T_3 > T_1 \) are shown in Table 5.20.

<table>
<thead>
<tr>
<th>Spread</th>
<th>Pattern</th>
<th>Relative occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>3:2:2</td>
<td>100%</td>
</tr>
<tr>
<td>14%</td>
<td>3:2:2</td>
<td>100%</td>
</tr>
<tr>
<td>10%</td>
<td>4:3:3</td>
<td>100%</td>
</tr>
<tr>
<td>4%</td>
<td>CCW</td>
<td>100%</td>
</tr>
</tbody>
</table>

The 3:2:2 pattern observed with both a 20\% (Figure 5.16) and 14\% spread in the cycle lengths when oscillator 2 is slowest and oscillator 3 is fastest is different than the 3:2:2 pattern previously discussed (Figure 5.14).

![Figure 5.16: Time series of both a \( T_2 > T_3 > T_1 \) (20\% spread)](image)

Both 3:2:2 patterns consist a cluster of three peaks followed by four peaks but the order is different. Instead of a 3:2:2 pattern with three peaks in the order 3, 1, 2 bunched very closely followed by four peaks in the order 1, 3, 2, 1, the three peaks are in the order 2, 1, 3 followed by four peaks in the order 1, 2, 3, 1.
5. NETWORKS OF THREE OSCILLATORS: STATIC COUPLING

$T_2 > T_1 > T_3$

The patterns observed for the network with cycle lengths in the order $T_2 > T_1 > T_3$ are shown in Table 5.21.

Table 5.21: $T_2 > T_1 > T_3$ statistics

<table>
<thead>
<tr>
<th>Spread</th>
<th>Pattern</th>
<th>Relative occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>Unstable</td>
<td>55.8%</td>
</tr>
<tr>
<td></td>
<td>IP 1-3</td>
<td>37.4%</td>
</tr>
<tr>
<td></td>
<td>15:10:13</td>
<td>4.0%</td>
</tr>
<tr>
<td></td>
<td>14:9:12</td>
<td>1.4%</td>
</tr>
<tr>
<td></td>
<td>6 others</td>
<td>1.4%</td>
</tr>
<tr>
<td>14%</td>
<td>CCW</td>
<td>98.01%</td>
</tr>
<tr>
<td></td>
<td>CW</td>
<td>1.04%</td>
</tr>
<tr>
<td></td>
<td>IP 1-3</td>
<td>0.47%</td>
</tr>
<tr>
<td></td>
<td>IP 1-2</td>
<td>0.38%</td>
</tr>
<tr>
<td></td>
<td>IP 2-3</td>
<td>0.10%</td>
</tr>
<tr>
<td>10%</td>
<td>CCW</td>
<td>100%</td>
</tr>
<tr>
<td>4%</td>
<td>CCW</td>
<td>100%</td>
</tr>
</tbody>
</table>

There were many entrainment patterns observed with a 20% spread but most time series show an unstable behavior. The most frequent stable pattern, IP 1-3, occurred when the initial peak order was CW appearing as a separate region within the unstable part of the map (Figure 5.17).
5.2. NON-EQUAL CYCLE LENGTHS IN THE NETWORK WITH THE PYLORIC TOPOLOGY

Figure 5.17: Map of $T_2 > T_1 > T_3$ (10% spread)

$T_3 > T_1 > T_2$

The final patterns for the network with cycle lengths in the order $T_3 > T_1 > T_2$ are displayed below:

Table 5.22: $T_3 > T_1 > T_2$ statistics

<table>
<thead>
<tr>
<th>Spread</th>
<th>Pattern</th>
<th>Relative occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>7:7:5</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>4:3:3</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td>15:15:11</td>
<td>19%</td>
</tr>
<tr>
<td>14%</td>
<td>4:3:3</td>
<td>100%</td>
</tr>
<tr>
<td>10%</td>
<td>CCW</td>
<td>100%</td>
</tr>
<tr>
<td>4%</td>
<td>CCW</td>
<td>100%</td>
</tr>
</tbody>
</table>

$T_1 > T_3 > T_2$

The table below shows the patterns observed with cycle lengths in the order $T_1 > T_3 > T_2$. The variation in the cycle length when the order is $T_1 > T_3 > T_2$ does not alter the preferred behavior.

Stable triphasic behavior can only occur when oscillators can achieve matching cycle lengths.
Table 5.23: $T_1 > T_3 > T_2$ statistics

<table>
<thead>
<tr>
<th>Spread</th>
<th>Pattern</th>
<th>Relative occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>CCW</td>
<td>100%</td>
</tr>
<tr>
<td>14%</td>
<td>CCW</td>
<td>100%</td>
</tr>
<tr>
<td>4%</td>
<td>CCW</td>
<td>100%</td>
</tr>
</tbody>
</table>

The cycle length of an oscillator in the pyloric network depends on both the natural cycle length and the timing of the perturbations. We have shown in section 5.1 that when the natural cycle lengths match and the coupling strengths are equal the only stable peak order is CCW. When natural cycle lengths are not equal, triphasic oscillations with CCW peak order may become impossible to achieve by this system when the spread of the cycle lengths is greater than 4%. Interestingly, the threshold at which the tri-phasic behavior breaks down is different for the different cycle length orders. It highlights once again that in this network topology each oscillators have different impact on the dynamics of the network which may be why this topology evolved in the biological system.

Summary

The initial motivation for studying the behaviors generated by the network with the pyloric topology with non-equal cycle lengths was to account for a discrepancy between experiments and simulations. According to the simulations with equal cycle lengths, the network with the pyloric topology is the only network which produces the triphasic behavior with a preferred directionality. However, in experiments, where the cycle lengths do not match, we observed another prevalent behavior which is the IP 1-3 pattern. This pattern was generated in simulations when there is a spread in the cycle lengths that is greater than 8% where oscillator 1 is the slowest and oscillator 3 is the fastest. In order to be physiological, the pyloric network in the STG must produce the triphasic pattern reliably. All previous results used static coupling and equal coupling strengths. Activity dependent modification of the coupling strengths may produce the necessary conditions for the triphasic oscillations when there are different cycle lengths.
Networks of Three Oscillators with Activity Dependent Coupling Strength Modification

6.1 Implementation of ADC

A global rule was implemented in order to apply activity dependent coupling to the network of three reciprocally coupled BZ oscillators. We defined the change in the coupling strength \( \Delta g \) as a function which is determined by the oscillator's own previous cycle length (\( T_{\text{actual}} \)) and a target cycle length which all oscillators develop toward (\( T_{\text{target}} \)). This function is applied to all couplings pointing at the oscillator when it completes a cycle (Figure 6.1).

When \( T_{\text{actual}} \) changes, the \( \Delta g \) is added to the connection matrix which defines the topology and
the relative strength of each connection. For example, the topology of three reciprocally coupled oscillators in an all-to-all network (Figure 5.9) is represented by the following connection matrix:

\[
\begin{pmatrix}
0 & g_{1\rightarrow2} & g_{1\rightarrow3} \\
g_{2\rightarrow1} & 0 & g_{2\rightarrow3} \\
g_{3\rightarrow1} & g_{3\rightarrow2} & 0
\end{pmatrix}
\]

Each row represents the oscillator that triggers perturbations to the oscillator in the corresponding column index where the non-zero value is written. The sum of \(\Delta g\) and the connection matrix value determines the value of \(c_{\text{inh}}\) (Eq. 6.2) at the moment of adjustment.

\[
c_{\text{inh}} = \Delta g + \text{conmatrix}(\text{row}, \text{column})
\]  

(6.1)

Using this function, we began our investigation to gain a general understanding of how this system develops under ADC and determine what parameters may be used to characterize its behavior. We used two forms of \(\Delta g\) function: a linear and an exponential function.

### 6.2 Linear Function

The tuning function \(\Delta g\) was first defined as the following linear function:

\[
\Delta g = \left( \frac{T_{\text{target}} - T_{\text{actual}}}{T_{\text{target}}} \right) k
\]  

(6.2)

**Initial Phases**

We first checked if the results depend on the initial phase difference in a network possessing a completely symmetric "all-to-all" topology. When ADC is applied to three oscillators with this topology, the pair of incoming connections to one oscillator are modified simultaneously by the same global rule. Therefore, \(g_{2\rightarrow1} = g_{3\rightarrow1}, g_{1\rightarrow2} = g_{3\rightarrow2}\) and \(g_{1\rightarrow3} = g_{2\rightarrow3}\). A scan of the different values for the initial phases of the three oscillators was performed with \(k = 0.5\) and \(T_{\text{target}} = 200\) s with a duration of 30,000 s. Each resulted in generation of the triphasic behavior and the same final phase difference \(d\phi = [0.0 \ 0.25 \ 0.45]\) for oscillators 1, 2 and 3,
respectively. The only points that deviated from this behavior were those with initial phases close to in-phase ($\phi_0 = [0.0 0.15 0.20-0.45]$) (Figures 6.2).

![Figure 6.2: Scan of initial phases under ADC](image)

**Tuning Factor**

Next, we tested how the tuning factor (k) affects the final phase arrangements when fixed initial phases and $T_{\text{target}}$ were used ($\phi_0 = [0.10 0.20 0.30]$, $T_{\text{target}} = 200$ s) in a tri-membered network with all-to-all coupling. We noticed that changing the tuning factor changed how far apart or close together the peaks were spread at the end. The data was evaluated by calculating the phase difference between the pair of oscillators that were closer together and the pair of oscillators that were further apart as shown in Figure 6.3.

The results demonstrated that for smaller values of the tuning factor, the oscillators had the ideal $2\pi/3$ triphasic arrangement and diverged from this arrangement as the value of the tuning factor increased and approached $d\phi = 0.27$ for the large difference and $d\phi = 0.11$ for the small difference (Figure 6.4); thus, the peaks were very close to each other.
6. NETWORKS OF THREE OSCILLATORS WITH ACTIVITY DEPENDENT COUPLING STRENGTH MODIFICATION

The trend of the tuning factor vs. final phase difference is expected because smaller values of the tuning factor change the coupling strength less dramatically which allows the oscillators to adopt the most stable arrangement gradually. If the tuning factor is too high \( (k \geq 5.0) \), then the oscillators will not reach a final stable state (Figure 6.5).
6.2. LINEAR FUNCTION

Similar calculations were carried out by adjusting the values of the $T_{\text{target}}$ with the same initial phases as in 3.2 and fixed $k = 0.5$ (Figure 6.6).

The ideal $(2\pi/3)$ triphasic behavior is generated at higher values of the $T_{\text{target}}$. This observation seems reasonable because the tuning function depends on the reciprocal of the $T_{\text{target}}$ value (see Eq. 6.1); however, it may not be that obvious because the tuning function makes changes in the value of the coupling strengths, and therefore the final coupling strengths and the cycle lengths are not directly related.

Changes in the initial phases have little effect on the final phase arrangement, and triphasic oscillations were observed. Therefore, it seems that the triphasic behavior may deviate from the ideal $2\pi/3$ triphasic phase relation at high values of the tuning factor and low values of the $T_{\text{target}}$. 

Figure 6.5: Unstable phase relation for $k = 5.0$

**Target Cycle Length**

Figure 6.6: Phase differences as a function of $T_{\text{target}}$
Initially Asymmetric Coupling Strengths

We were then interested in revisiting our main question: what are the limits within activity dependent coupling to adapt and maintain the triphasic pattern? To answer this question, we adjusted the values of the coupling strengths in the connectivity matrix and tested whether the system was able to adapt to this asymmetry. The initial phases were fixed ($\phi_0 = [0 \ 0.2 \ 0.4]$) as well as the tuning factor ($k = 0.5$) and the target cycle length ($T_{\text{target}} = 300$ s). The initial coupling strength of the 3 to 1 connection was increased by 1 up to 10. The network still generated the triphasic behavior consistently, and the small difference and large difference remained fairly constant (average small difference: $d\phi = 0.45$, average large difference: $d\phi = 0.20$) (Figure 6.7).

![Phase differences as a function of the coupling strength of the 3 to 1 connection](image)

Figure 6.7: Phase differences as a function of the coupling strength of the 3 to 1 connection

Then, we varied the factor while keeping the coupling strength of the 3 to 1 connection at 5. Above $k = 1.5$ the stronger connection would silence the other connection.

6.3 Exponential Function

In order to address the issue of silencing connections at high $k$ values under initially asymmetric coupling strengths, we examined the modifier function more closely. We found that with the asymmetric connectivity, there is a fundamental mathematical problem with the linear function. The linear function may be rewritten in the form:
6.3. EXPONENTIAL FUNCTION

\[ g(T_{\text{target}}, t) = g_0 + u(T_{\text{actual}})t \]  \hspace{1cm} (6.3)

where \( g(T_{\text{target}}, t) \) is a function of a sub-function \( u(T_{\text{actual}}) \) that is the actual cycle length referenced to the target cycle length as follows:

\[ u(T_{\text{actual}}) = \frac{T_{\text{target}} - T_{\text{actual}}}{T_{\text{target}}} k \]  \hspace{1cm} (6.4)

If the \( T_{\text{target}} \) is kept constant (300 s), a linear plot is obtained at various values of \( k \) when \( T_{\text{actual}} \) is varied (Figure 6.8). When \( k \) is constant (2.5) and \( T_{\text{actual}} \) and \( T_{\text{target}} \) are varied, a different plot is obtained (Figure 6.9).

Figure 6.8: Sub-function \( u(T_{\text{target}}) \) with constant \( T_{\text{target}} \)
In both cases, the sub-function $u(T_{\text{target}})$ returns zero when $T_{\text{actual}} = T_{\text{target}}$. Variation of $k$ or $T_{\text{target}}$ generates only slight differences since similar $u$ values are returned, though with different slopes and maximum values.

However, when an initial coupling strength asymmetry is introduced, the weaker coupling strength may decay to zero. Because the modifier $u$ values are absolute, they will be the same for both the strong and the weak connections. The coupling strength ratio will change as:

$$\frac{g_1}{g_2} = \frac{g_0 + u(T_{\text{target}})t}{g_0 + u(T_{\text{target}})t}$$

(6.5)

For all positive $u(T_{\text{target}})$ values, the limit of the ratio is 1 because the relative difference between $g_1$ and $g_2$ becomes negligible as $t$ approaches infinity. For negative $u(T_{\text{target}})$ values and $g_{01} < g_{02}$, the ratio becomes negative. Negative coupling strength is not meaningful in our system because it would signify a negative volume of inhibitory solution. Therefore, zero was set as the lower limit for all $g_{i \rightarrow j}$. As a consequence, if one connection is significantly stronger and the resulting cycle length is longer than the target, the weaker connection may be reduced to zero as the activity dependent tuning function regulates the inhibition to match $T_{\text{target}}$.

This problem can be resolved by including the actual coupling strength itself into the function as shown below:

$$\Delta g = \left(\frac{T_{\text{target}} - T_{\text{actual}}}{T_{\text{target}}}\right)(k)(g).$$

(6.6)
The integrated form of the coupling strength ratio as a function of time for this function is:

\[
\frac{g_1}{g_2} = \frac{g_{01} e^{u(T_{\text{target}})t}}{g_{02} e^{u(T_{\text{target}})t}}
\]

which can be simplified to:

\[
\frac{g_1}{g_2} = \frac{g_{01}}{g_{02}}.
\]

Therefore, in theory, the exponential function does not show any dependence on the parameters and the coupling strength ratio will remain fixed, meaning that $g_1$ will not be reduced to zero as long as $g_2$ is not zero.

**Initial Phases**

The dependence of the final phases on the initial phases was tested using the exponential function, and the results were the same as the observed ($d\phi = [0.0 \ 0.45 \ 0.75]$ or $d\phi = [0.0 \ 0.25 \ 0.45]$) for the linear function. Then, the dependence of the final phases on the tuning function was observed with fixed initial phases $d\phi = [0.0 \ 0.20 \ 0.40]$ and $T_{\text{target}} = 300$ s. As before with the linear function, the oscillators generated the ideal $2\pi/3$ triphasic behavior for smaller values of the tuning function, but the oscillators approached $d\phi = 0.39$ for the small difference and $d\phi = 0.16$ for the large difference (Figure 6.10).

![Figure 6.10: Phase differences as a function of the tuning factor using the exponential function](image-url)
The dependence of the final phases on the $T_{\text{target}}$ was also studied at fixed initial phases ($\phi_0 = [0.0 0.20 0.40]$) and $k = 0.5$. As before with the linear function, the ideal $2\pi/3$ triphasic pattern was generated at larger values of the $T_{\text{target}}$ (Figure 6.11).

![Figure 6.11: Phase differences as a function of the $T_{\text{target}}$ using the exponential function](image)

### 6.4 Non-equal Natural Cycle Lengths

Under static coupling, there were six natural cycle length combinations that led to stable, preferred behaviors that are not triphasic (section 3.4). Since the pyloric network produces the physiological behavior when ADC is introduced, we first wanted to determine whether the global rule could tune the coupling strengths to develop into a set that would produce a specific behavior with preference for the triphasic pattern.

Then we determined whether there was a set of adjustable parameters, $k$ and $T_{\text{target}}$, that led to stable, non-zero coupling strengths with various initial cycle lengths. Once the optimal values of the adjustable parameters were found, we tested whether these values of the adjustable parameters would produce the triphasic pattern for a wide range of initial conditions (section 5.2).

### Coupling Strength Development Over Time

The global rule tunes the coupling strengths of each connection for each oscillator to achieve the target cycle length ($T_{\text{target}}$) according to Equation 6.7. The development of the coupling
6.4. NON-EQUAL NATURAL CYCLE LENGTHS

strength is shown by plotting the coupling strength over time. In these plots, each connection is labeled as shown in Figure 6.12.

![Figure 6.12: Coupling strength labels](image)

Connections $g_{1\rightarrow2}$ and $g_{3\rightarrow2}$ will develop together since they are both tuned according to the activity of oscillator 2 as a consequence of the method (section 6.2). Therefore, on a plot of the coupling strength development over time, the coupling strengths of $g_{1\rightarrow3}$ and $g_{1\rightarrow2}$ will overlap. The same is true for connections $g_{1\rightarrow3}$ and $g_{2\rightarrow3}$ which are tuned according to the activity of oscillator 3.

**Adjustable Parameters: $k$ and $T_{\text{target}}$**

The optimal values of adjustable parameters were defined as those which produced 1) stable coupling strengths before 50,000 s and 2) stable triphasic pattern. The particular value of the adjustable parameter was considered optimal if the time taken to produce the final pattern ($t_{\text{final}}$) was low relative to that of the other parameter values. We determined the optimal set of adjustable parameters for the networks which produced three different patterns: triphasic oscillations, 4:3:3 and 3:2:2 entrainments and IP 1-3. These networks had the following cycle lengths: $T_1 > T_2 > T_3$ (20% spread), $T_3 > T_2 > T_1$ (20% spread) and $T_3 > T_1 > T_2$ (14% spread), respectively (section 5.2). The values of the optimal adjustable parameters, $k$ and $T_{\text{target}}$, were found by setting one parameter constant while changing the other.
T_1 > T_2 > T_3 with a 20% spread in the natural cycle lengths

Since the final behavior of the T_1 > T_2 > T_3 (20% spread) network depends upon whether the initial directionality of the peaks under static coupling is either CW or CCW (section 5.2), the optimal values of adjustable parameters were found for both initial conditions.

**i-CW** The optimal set of k values was between 0.05 - 3 (Figure 6.13) and the optimal set of T_{target} values was 250-300 s (Figure 6.14).

![Figure 6.13: T_1 > T_2 > T_3 (20% spread, i-CW): k vs. t_{final}, T_{target} = 265s](image1)

Figure 6.13: T_1 > T_2 > T_3 (20% spread, i-CW): k vs. t_{final}, T_{target} = 265s

![Figure 6.14: T_1 > T_2 > T_3 with a (20% spread, i-CW): T_{target} vs. t_{final}, k = 0.1](image2)

Figure 6.14: T_1 > T_2 > T_3 with a (20% spread, i-CW): T_{target} vs. t_{final}, k = 0.1
The final pattern for all optimal values of the k and T_{target} parameters was IP 1-3 (Table 6.1).

Table 6.1: Optimal values of adjustable parameters for T_1 > T_2 > T_3 (i-CW)

<table>
<thead>
<tr>
<th>Adjusted parameter</th>
<th>Optimal range</th>
<th>Fixed Parameter</th>
<th>Final pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>k</td>
<td>0.05 - 5</td>
<td>T_{target} = 265 s</td>
<td>IP 1-3</td>
</tr>
<tr>
<td>T_{target}</td>
<td>250-350 s</td>
<td>k = 0.1</td>
<td></td>
</tr>
</tbody>
</table>

The magnitudes of the coupling strengths after stabilization were in the following order:

\[ g_{2\rightarrow1} > g_{1\rightarrow2} = g_{3\rightarrow2} > g_{1\rightarrow3} = g_{2\rightarrow3} \]  
(Figure 6.15).

Figure 6.15: T_1 > T_2 > T_3 (20% spread, i-CW): coupling strengths vs. time with k = 0.5, T_{target} = 265 s

Another observation made about the coupling strengths is the initial overshoot (Figure 6.16) at \( k > 0.9 \). This initial overshoot can be understood by considering the fact that the inhibitory effect on each oscillator depends both on \( g_{i\rightarrow j} \) and \( \phi_{i\rightarrow j} \) (phase at which the perturbation occurs). As the perturbation occurs later in the cycle, the time taken for the next cycle to occur will be longer. At larger \( k \) values, the tuning function increases the coupling strengths more rapidly which causes the peaks to change position and to achieve a different arrangement than in the final state.
Figure 6.16: $T_1 > T_2 > T_3$ (20% spread, i-CW): coupling strengths vs. time with $k = 1$, $T_{\text{target}} = 265$ s

**i-CCW** The optimal $k$ values (0.1 - 3) and $T_{\text{target}}$ values (265 - 280 s) are shown in Figures 6.17 and 6.18, respectively.

Figure 6.17: $T_1 > T_2 > T_3$ (20% spread, i-CCW): $k$ vs. $t_{\text{final}}$, $T_{\text{target}} = 265$ s
6.4. NON-EQUAL NATURAL CYCLE LENGTHS

Figure 6.18: $T_1 > T_2 > T_3$ (20% spread, i-CCW): $T_{\text{target}}$ vs. $t_{\text{final}}$, $k = 0.1$

This network produces CCW triphasic oscillations for all optimal values of $T_{\text{target}}$ and $k$ (Table 6.2).

Table 6.2: Optimal values of adjustable parameters for $T_1 > T_2 > T_3$ (i-CCW)

<table>
<thead>
<tr>
<th>Adjusted parameter</th>
<th>Optimal range</th>
<th>Fixed Parameter</th>
<th>Final pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k$</td>
<td>0.1 - 3</td>
<td>$T_{\text{target}} = 265\text{s}$</td>
<td>CCW</td>
</tr>
<tr>
<td>$T_{\text{target}}$</td>
<td>265s - 280 s</td>
<td>$k = 0.01$</td>
<td></td>
</tr>
</tbody>
</table>

All of the coupling strengths develop closely together and there is no initial overshoot below $k = 0.5$ (Figure 6.19).
6. NETWORKS OF THREE OSCILLATORS WITH ACTIVITY DEPENDENT COUPLING STRENGTH MODIFICATION

Figure 6.19: $T_1 > T_2 > T_3$ (20% spread, i-CCW): coupling strengths vs. time with $k = 0.1$, $T_{\text{target}} = 265$ s

$T_3 > T_2 > T_1$ with a 20% spread in the cycle lengths

The range of optimal $k$ values was 0.3 - 7 (Figure 6.20) and the range of optimal $T_{\text{target}}$ values was 250-280 s (Figure 6.21).

Figure 6.20: $T_3 > T_2 > T_1$ (20% spread): $k$ value vs. $t_{\text{final}}$, $T_{\text{target}} = 265$ s
The final pattern for all optimal k and $T_{\text{target}}$ values was CCW (Table 6.3).

Table 6.3: Optimal values of adjustable parameters for $T_3 > T_2 > T_1$.

<table>
<thead>
<tr>
<th>Adjusted parameter</th>
<th>Optimal range</th>
<th>Fixed Parameter</th>
<th>Final pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k$</td>
<td>0.3 - 0.7</td>
<td>$T_{\text{target}} = 265$ s</td>
<td>CCW</td>
</tr>
<tr>
<td>$T_{\text{target}}$</td>
<td>250-280 s</td>
<td>$k = 0.1$</td>
<td></td>
</tr>
</tbody>
</table>

The coupling strength $g_{2\rightarrow 1}$ is the greatest at all optimal k and $T_{\text{target}}$ values (Figure 6.22). This difference in the magnitude can be accounted for by considering both the topology of the network and the $T_1 > T_2 > T_3$ cycle length order. In the network with the pyloric topology, oscillator 1 receives only one perturbation (from oscillator 2) while oscillators 2 and 3 each receive two perturbations. Therefore, in order for oscillator 1 to have the same cycle length as the other oscillators, oscillator 1 must receive the most inhibition.
6. NETWORKS OF THREE OSCILLATORS WITH ACTIVITY DEPENDENT COUPLING STRENGTH MODIFICATION

Figure 6.22: $T_3 > T_2 > T_1$ (10% spread): coupling strengths with $k = 0.1$, $T_{\text{target}} = 265$ s

$T_3 > T_1 > T_2$ with a 14% spread in the cycle lengths

The optimal set of $k$ values was between 0.1 - 0.5 (Figure 6.23), and the optimal set of $T_{\text{target}}$ values was 250-300 s (Figure 6.24).

Figure 6.23: $T_3 > T_1 > T_2$ (14% spread): $k$ vs. $t_{\text{final}}$, $T_{\text{target}} = 265$ s
The final pattern for all optimal k and \( T_{\text{target}} \) values was CCW (Table 6.4).

**Table 6.4:** Optimal values of adjustable parameters for \( T_3 > T_1 > T_2 \).

<table>
<thead>
<tr>
<th>Adjusted parameter</th>
<th>Optimal range</th>
<th>Fixed Parameter</th>
<th>Final pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k )</td>
<td>0.1 - 0.5</td>
<td>( T_{\text{target}} = 265 \text{ s} )</td>
<td>CCW</td>
</tr>
<tr>
<td>( T_{\text{target}} )</td>
<td>250s - 300s</td>
<td>( k = 0.1 )</td>
<td></td>
</tr>
</tbody>
</table>

The coupling strength development follows the same trend as \( T_1 > T_2 > T_3 \) (20% spread, \( i\text{-CCW} \)).

**Adjustable Parameters under a Wide Range of Initial Conditions**

After finding the values of adjustable parameters that lead to stable all non-zero coupling strengths with triphasic oscillations, we wanted to determine whether the values of adjustable parameters would work for a wide range of initial conditions such as initial phase differences and initial cycle lengths. Therefore, we ran a \( 33 \times 33 \) array of all of the different initial cycle length settings studied under static coupling which produced one stable pattern (section 3.4), but we added the global rule with the following parameters: \( k = 0.1 \) and \( T_{\text{target}} = 280 \text{ s} \). These parameters were selected because they were within the optimal range of \( k \) and \( T_{\text{target}} \) values for
all of the cycle lengths tested. The following table summarizes the results for all initial cycle lengths:

<table>
<thead>
<tr>
<th>Natural Cycle Lengths</th>
<th>CCW / %</th>
<th>IP (1, 3) / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₃ &gt; T₂ &gt; T₁ (20% spread)</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>T₁ &gt; T₂ &gt; T₃ (20% spread)</td>
<td>55.49</td>
<td>44.51</td>
</tr>
<tr>
<td>T₂ &gt; T₃ &gt; T₁ (20% spread)</td>
<td>0.05</td>
<td>99.95</td>
</tr>
<tr>
<td>T₂ &gt; T₁ &gt; T₃ (20% spread)</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>T₃ &gt; T₁ &gt; T₂ (14% spread)</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>T₁ &gt; T₃ &gt; T₂ (14% spread)</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

All initial cycle length conditions except T₁ > T₂ > T₃ (20% spread) and T₂ > T₃ > T₁ (20% spread) produced the CCW triphasic behavior under ADC. We can conclude that some natural behaviors that were not triphasic were corrected by the global rule; however, the IP 1-3 pattern is still produced with the addition of the global rule. Perhaps the IP 1-3 pattern is a point of local stability as the network samples through all possible arrangements during development, and this point of local stability is more easily achieved under certain initial conditions such as when the oscillators begin in the CW triphasic arrangement with initial cycle lengths T₁ > T₂ > T₃ (20% spread) or if the initial cycle lengths are T₂ > T₃ > T₁ (20% spread). The global rule alone cannot change the ratios between the coupling strengths, and the appropriate coupling strengths to produce the triphasic pattern from certain initial conditions may not be achieved. Therefore, addition of the local rule may be necessary in order to drive these networks out of the IP 1-3 pattern.
Discussion

In this study we have explored the dynamics that various topologies (linear, uni-directional circular, circular plus one, all to all, the pyloric topology) prefer when all coupling is of equal strength and when the coupling is inhibitory in tri-membered networks of pulse coupled BZ oscillators. By exploring the dependence of the stable dynamics on the initial peak order, we established the behaviors favored by each network. Most notably, the pyloric network constructed by pulse-coupled BZ oscillators is a different physical system than its biological construct yet both clearly favor a behavior that is similar: the triphasic oscillations with a specific peak order.

The neurons that the biological system comprises of have different dynamical characteristics; therefore we checked if the preferred behavior depends on the natural cycle lengths of the oscillators. We have observed that each symmetric cycle length combination displays a different preferred behavior, the order $T_1 > T_2 > T_3$ being the most resilient producing triphasic behavior even if the lowest and highest cycle lengths differ by 20%.

We tested if the behaviors seen in the model occur in the experimental system. We have found a fair agreement between the experimental observations and simulations, but further work is necessary to address the source of the discrepancies: in particular, why the experimental system with pyloric topology prefers the in-phase behavior, while in calculations CCW was preferred. We have established the fundamental characteristics of two tuning mechanisms that resemble the global rules in the model of the biological system. By using the exponential tuning function and the optimal tuning parameters, we tested whether this mechanism can help the
network to achieve the triphasic behavior under the conditions where static coupling yields undesired behaviors. We have shown that the global rule itself is sufficient when the cycle lengths do not differ more than 14%. However, this tuning mechanism is insufficient when the network dynamics lead to in-phase oscillations of oscillators 1 and 3.

We have also shown that certain analogous undesired behaviors such as in-phase oscillations and entrainment patterns may occur in the chemical analog as well as when the cycle lengths of the oscillators are different.

Our work highlights a few key differences between the biological system that served as our motivation and the chemical system. In systems where the coupling is pulse-like, initial peak orders may significantly affect the final stable state that the system achieves. This discreet, pulse-like, interaction affects the tuning of the coupling strengths as well in a complex way that requires further work to characterize. In the model of the biological system, synapses were implemented as current flows in a Morris-Lecar model; thus the coupling and tuning of the synapses was taking place continuously over time during calculations. The most significant difference in dynamics is the preferred directionality of the peak order. In the chemical system, the preferred directionality is the reverse of that in the biological system, however the coupling strengths are not equal in the latter. When the connection $g_{2 \rightarrow 1}$ was significantly higher than others the chemical analog was able to produce the reverse (equivalent of the physiological) peak order as well which suggests that the right combination of natural cycle lengths and tuning mechanism may allow for analogs of the lobster pyloric network to produce analogous pattern generating behavior.
References


REFERENCES


