The Effect of Modulatory Neuronal Input on Gastric Mill Frequency

Christina Ambrosio[1] Amitabha Bose[1] and Farzan Nadim[1,2]

1 Abstract

We study the crustacean stomatogastric nervous system to gain insight in the interaction of oscillators of different intrinsic frequencies. We show how fast inhibition from the pyloric network interacts with a slow modulatory input to control the frequency of the gastric mill rhythm. We deduce that the timing of the pyloric input is crucial in determining what affect it will have on the frequency of the gastric network. Over one set of timings, the modulatory input and the pyloric input work together to determine the frequency and over another set of timings, the affect of the pyloric input is mitigated by the modulatory input.

2 Introduction

Rhythmic movements are often controlled by central pattern generators (CPGs) that involve multiple oscillators of different frequencies. The crustacean stomatogastric nervous system, for example, contains multiple rhythmic subnetworks of different frequencies that interact with one another. Of these rhythms, two are generated within the stomatogastric ganglion: the gastric mill rhythm (frequency 0.1 Hz) that controls the movement of the gastric teeth and the pyloric rhythm (frequency 1 Hz) that operates the valves and filters of the pylorus [2]. Although the pyloric rhythm is always spontaneously active, the activity of the gastric mill rhythm requires input from modulatory command neurons. Activation of different types of modulatory neurons leads to different forms of the gastric mill rhythm and thus different movement sequences of the teeth. A gastric mill rhythm could, for instance, be elicited by activation of the Modulatory Commisural Neuron 1 (MCN1).

Earlier work has shown how the frequency of the slower gastric mill rhythm could be affected by synaptic input from the faster pyloric rhythm [4]. In particular, it was shown that the presence of the pyloric input drastically increases the frequency of the gastric mill rhythm, when MCN1 is tonically active. However, recent work has shown that MCN1 receives rhythmic inhibitory feedback from the pyloric network and under normal biological conditions is itself rhythmically active [5]. In this work, we report on the consequences of the rhythmic versus tonic activity of the modulatory neuron MCN1 on the frequency of the gastric mill rhythm. We show that this frequency is critically sensitive to the interaction between the pyloric input and the input from MCN1. Paralleling the study of Nadim et al [4], we consider two main cases; one where the pyloric input to the gastric mill network is absent and one where it is present. Our main finding is that the relative phase difference between the inputs from the pyloric rhythm and MCN1 to the gastric mill is critical in determining the gastric mill cycle frequency. In particular, for a certain range of phase differences, the presence of the pyloric input increases the gastric mill cycle frequency. In

[1]Dept. Mathematical Sciences, New Jersey Institute of Technology, Newark, NJ 07102; cla2@njit.edu, bose@njit.edu and farzan@njit.edu: corresponding author Christina Ambrosio

[2]Dept. Biological Sciences, Rutgers University at Newark, Newark, NJ 07102

contrast, for another range of phase differences the presence or absence of the pyloric input has no effect on the gastric mill cycle frequency.

Many central pattern generating networks are activated by modulatory command inputs from higher-up centers in the nervous system. In most cases, these modulatory command neurons themselves are rhythmically active, the significance of which is unknown. The current study suggests that the precise phase between a rhythmically active modulatory neuron and extrinsic input could provide an additional control mechanism for the frequency of the CPG. In particular, this study predicts for what range of phases the pyloric input is effective or ineffective in setting the gastric mill frequency.

3 Model

At the heart of the network-generated gastric mill rhythm is a reciprocally inhibitory pair consisting of the Lateral Gastric (LG) neuron and Interneuron 1 (Int1). In the presence of input from MCN1, this pair of neurons produces antiphase oscillations. The faster pyloric rhythm is generated by a single pacemaker Anterior Burster (AB) neuron, which provides rhythmic inhibition to Int1.

The model network in this study has four neurons as shown in Fig. 1. The pacemaker AB oscillates with a fixed period P and has duty cycle equal to 0.5. It sends an inhibitory synapse to both Int1 and MCN1, with the former synapse being delayed by m time units relative to the latter synapse where $0 \leq m \leq P$. In the absence of AB input, MCN1 is modeled to intrinsically rest at a high voltage. It has an excitatory synapse, with fast rise and decay rates, to LG. In return, LG provides pre-synaptic inhibition to this excitatory synapse. The inhibitory synapse has slow rise and decay rates. Finally, Int1 and LG are reciprocally connected by inhibitory synapses. Int1 and LG are modeled to have different intrinsic resting potentials. In the absence of either AB or MCN1 input, Int1 is tonically active (i.e., sits at a high membrane potential), continually suppressing LG.

To simplify the discussion, MCN1, LG and Int1 are modeled as passive neurons whose rhythmicity occurs only through network interactions as in [4]. The equations governing their activities are

$$\frac{dV_L}{dt} = -g_{leak,L}(V_L - E_{leak,L}) - g_{I\to L} m_{I\to L}(V_I)(V_L - E_{I\to L}) - g_s s(t)(V_L - E_s) \qquad (1)$$

$$\frac{dV_I}{dt} = -g_{leak,I}(V_I - E_{leak,I}) - g_{L\to I} m_{L\to I}(V_L)(V_I - E_{L\to I}) - \bar{g}_{AB\to I} s_{AB\to I}(t)(V_I - E_{AB\to I}) \qquad (2)$$

$$\frac{dV_M}{dt} = -g_{leak,M}(v_M - E_{leak,M}) - \bar{g}_{AB\to M} s_{AB\to M}(t)(V_M - E_{AB\to M}) \qquad (3)$$

$$\frac{ds_1}{dt} = \begin{cases} (1 - s_1)/\tau_{r1} & V_L \leq V_T \\ -s_1/\tau_{f1} & V_L > V_T \end{cases} \qquad (4)$$

$$\frac{ds_2}{dt} = \begin{cases} (1 - s_2)/\tau_{r2} & V_M \geq V_{Th(M)} \\ (.3 - s_2)/\tau_{f2} & V_M < V_{Th(M)} \end{cases} \quad (5)$$

where V_L is the voltage of LG, V_I is the voltage of Int1, and V_M is the voltage of MCN1. The values of the maximal conductances in units of mS/cm^2 are $g_{leak,L} = 1$, $g_{I\to L} = 5$, $g_s = 6$, $g_{leak,I} = .75$, $g_{L\to I} = 2$, $\bar{g}_{AB\to I} = .9$, $g_{leak,M} = 2$, and $\bar{g}_{AB\to M} = 15$ and the reversal potentials in units of mV are $E_{leak,L} = -60$, $E_{I\to L} = -80$, $E_s = 43$, $E_{leak,I} = 10$, $E_{L\to I} = -80$, $E_{AB\to I} = -60$, $E_{leak,M} = 10$, and $E_{AB\to M} = -60$. $m_{I\to L}(V_I)$ and $m_{L\to I}(V_L)$ are sigmoidal shaped gating functions given by $(1 + exp(\frac{-30-V}{4}))^{-1}$. $s_{AB}(t)$ is a half-sine function with period 1 second and a duty-cycle of 0.5 that models the inhibition from AB to the neuron to which it is coupled. In (3), $s_{AB\to M}(t) = s_{AB}(t)$ and in (2), $s_{AB\to I}(t) = s_{AB}(t - m)$ where m is a parameter that can range between 0 and P (=1000 ms) and is used to cause a delay between the timing of the AB input to MCN1 and Int1. In (1), $s(t) = s_1(t)s_2(t)$ controls the amount of excitation that LG receives from MCN1. The variable $s_2(t)$ models the direct effect of MCN1 excitation, while $s_1(t)$ models the effect of the pre-synaptic inhibition onto the excitatory synapse. Thus, when AB input to MCN1 is absent, $V_M \equiv V_{leak,M} > V_{Th(M)}$ and $s_2(t) \equiv 1$. Thus, $s(t)$ is controlled solely by the dynamics of s_1. In this case, when V_L is below the threshold V_T, the excitation grows with time constant τ_{r1} and when V_L goes threshold, the excitation decays with time constant τ_{f1}. When the inhibition from AB to MCN1 is intact, V_M goes above and below the threshold $V_{Th(M)}$ as the inhibition turns off and on. This causes s_2 to oscillate between 0 and 1. We choose the time constants τ_{r2} and τ_{f2} to be small compared with τ_{r1} and τ_{f1} so that we can consider s_2 to jump quickly between values near 0 and 1 each time MCN1 gets inhibited while s_1 slowly increases for $V_L < V_T$ and slowly decreases for $V_L > V_T$. This mimics rhythmic activity of MCN1 by creating a rhythmic MCN1 to LG excitation.

As described above, we now have two mechanisms controlling the MCN1 excitation to LG. The first mechanism provides the slow and constant rise and decay of the excitation through use of the inhibitory synapse from LG to the excitatory synapse from MCN1. The second mechanism forces the excitation to jump down to a smaller strength when the AB inhibition to MCN1 turns on and then allows the excitation to jump back up when the AB inhibition turns off. Hence, we have the MCN1 excitation growing and decaying with one time constant while jumping down and then back up with a much faster time constant and at a frequency fixed to that of the fast rhythmic AB inhibition. Thus the dynamics of the network evolve along two distinct time scales. One time scale is slow, corresponding to the slow pre-synaptic inhibition from LG to the excitatory MCN1 synapse. The other time scale is fast along which all other synapses and intrinsic properties evolve.

4 Results

In order to understand what controls the frequency of the gastric mill rhythm when MCN1 is rhythmic, we first quickly review the cases where AB input to MCN1 is removed. This corresponds to the situation where MCN1 is tonically active [3]. This study found that when MCN1 is tonically active, the presence of the AB input to Int1 increases the frequency of the gastric mill rhythm.

First, consider the situation where AB input to Int1 is removed. In this case, the only

outside input that the gastric mill receives is tonic excitation from MCN1 to LG ($s_2(t) \equiv 1$). Thus, the period of the gastric mill rhythm is controlled by the dynamics of $s(t) = s_1(t)$ Thus, for LG to escape Int1 inhibition, the excitation from MCN1 has to build up through removal of presynaptic inhibition as determined by the time constant τ_{r1}. Similarly, for Int1 to escape LG inhibition, the excitation that LG receives from MCN1 has to decrease through presynaptic inhibition as determined by the time constant τ_{f1}. These time constants are large and thus the period of the gastric mill is large in this case.

Next, consider the case where AB input to Int1 is present. Suppose Int1 is active, while LG is silent. MCN1 again provides a slowly rising and decaying amount of excitation to LG but now AB also periodically inhibits Int1. This periodic inhibition does not, however, immediately cause the voltage of Int1 to fall below $-30mV$, the threshold for synaptic inhibition of LG. However, the effect of the AB inhibition to Int1 is equivalent to periodically disinhibiting LG. Thus, when LG is suppressed by Int1, it receives a slowly increasing amount of excitation from MCN1 that increases its voltage and a periodic depolarization each time Int1 gets inhibited by AB. Thus at some point when the voltage of LG has increased high enough due to the MCN1 excitation, the periodic inhibition of Int1 due to AB will provide a sufficient amount of disinhibition to LG to enable it to burst. Therefore in this case, the AB input to Int1 allows LG to escape from Int1 inhibition at an earlier time compared to the previous case [3], i.e. $s(t) = s_1(t)$ is smaller when LG fires. When LG is in its active phase, the periodic inhibition of Int1 due to AB has little affect on the voltage of Int1 because, here, Int1 is already inhibited. Thus the period of the gastric mill rhythm is smaller than in the previous case, mainly due to a decrease in the LG interburst duration.

We now turn our attention to the cases where MCN1 is rhythmically active. The rhythmicity of MCN1 is achieved through the inhibitory synapse from AB which occurs with zero time delay. In case 1 below, AB input to Int1 will be removed. In case 2 below, AB input will be present but will be delayed by m time units relative to the timing of AB's input to MCN1. In the biological network, the delay between AB activity and MCN1 inhibition is approximately 20 ms (personal communication with M.P. Nusbaum) whereas the delay between AB activity and the peak of the LG neuron disinhibition could be as long as 400 ms [4]. The latter delay is believed to be due to slow synaptic rise times.

Case 1: AB input to Int1 is removed

In case 1, Int1 does not get periodically inhibited by AB but MCN1 does. The affect on the period of the gastric mill rhythm in case 1 can be seen by considering what happens when LG is at a high voltage and Int1 is suppressed. When LG is at a high voltage, $V_L > V_T$, the presynaptic inhibition from LG to MCN1 slowly increases and, therefore, slowly removes the MCN1 to LG excitation (s_1 decays). In addition, each time AB inhibits MCN1, the MCN1 to LG excitation rapidly decays (s_2 becomes small). The loss of excitation is not enough to immediately cause LG to fall below threshold. However the AB inhibition of MCN1 advances the end of the LG burst compared to the case where the MCN1 excitation is tonic (at the end of the LG burst, $s_1(t)$ is larger in the rhythmic case versus the tonic case). In this case, the timing of the AB input to MCN1, which indirectly affects s_2, together with the slower changing variable s_1, determine the gastric mill period.

Case 2: AB input to Int1 is present

Finally, in case 2, AB inhibits both Int1 and MCN1. Here, the timing of the inhibition

from AB to Int1 and to MCN1, determined by the parameter m, is critical in determining its affect on the gastric mill rhythm. In Fig. 2, we plot the gastric mill period versus the delay m for $\tau_{r1} = 4000msec$, $\tau_{f1} = 3500msec$, $\tau_{r2} = 50msec$, and $\tau_{f2} = 50msec$. Note that over a subset of m values between 0 and 210 and between 960 and 1000, the period of case 2 is identical to that of case 1. In other words, the presence of the AB synapse onto Int1 has no effect on period. Yet, for other values of m, the period of the gastric mill is dramatically reduced.

To understand this result, first suppose that there is no delay ($m = 0$) in the timing so that Int1 and MCN1 get inhibited by AB at the same time. Now when LG is in its interburst (Int1 is active), each time Int1 gets inhibited by AB (causing LG to get disinhibited), MCN1 also gets inhibited by AB. This inhibition of MCN1 removes the excitation from MCN1 to LG causing LG's voltage to be lowered. Therefore, each time LG gets disinhibited, its excitation from MCN1 gets reduced. These two affects oppose one another until the slow excitation from MCN1 builds up and at a time when the AB input is off, the voltage of LG becomes large enough to escape from the inhibition of Int1. This is equivalent to what happens in the case when the AB input to Int1 is not present. When Int1 is in its interburst and LG is active, we again assume that the AB input to Int1 has no affect on the voltage of Int1 since Int1 is already suppressed. Here, only the slow MCN1 excitation and the AB input to MCN1 affect the LG burst duration. Thus when $m = 0$, the AB input to MCN1 affects the period of the gastric mill rhythm by ending the burst duration of LG as in case 1. In this case, the period of the gastric mill remains the same as in case 1 when the AB input to Int1 is not present but the AB input to MCN1 is present. Fig. 2 compares the voltage traces of V_L and V_I for cases 1 and 2. For $m = 0$, the frequency of case 2 is the same as that of case 1. In case 1, the slow MCN1 excitation increases LG's voltage when LG is below threshold and decreases LG's voltage when LG is above threshold. However, each time AB inhibits MCN1, the excitation to LG is removed and the voltage of LG jumps down. The affect of the AB input to Int1 in case 2 can be seen when LG is in its interburst and Int1 is in its burst. Each time AB inhibits Int1, there is a sharp downward jump in the voltage of Int1 and a slight increase (disinhibition) in the voltage of LG. This same idea can be extended to other values of m near 0 where the timing of the AB input is such that at the point at which the slow MCN1 excitation has grown sufficiently large, at the next time at which Int1 gets inhibited by AB, the inhibition from AB to MCN1 prevents LG from crossing its threshold to fire an action potential.

Suppose next that $m = 500$ so that each time AB inhibits Int1, it does not inhibit MCN1 and each time AB inhibits MCN1, it does not inhibit Int1. Now when the voltage of LG is low, each time Int1 is inhibited by AB (MCN1 is not inhibited), LG is disinhibited. The timing of the AB input to MCN1 is such that it allows LG to escape Int1's inhibition at an earlier time compared with case 1. In this case, the slow MCN1 excitation does not have to grow as large as in case 1 for LG to enter its burst phase. When the voltage of LG is high, the AB input to Int1 again has no affect and, as in case 1, the AB input to MCN1 forces the LG burst to end. However, because the slow MCN1 excitation does not need to grow as large for $m = 500$ as in case 1, it takes less time for this excitation to decay back to the value that allows the burst duration of LG to end. This results in a shorter burst duration of LG compared with case 1. Thus when the voltage of LG is low, the AB input to Int1 allows the LG interburst to end earlier than in case 1, and when the voltage of LG is high, the AB

input to MCN1 allows the LG burst to end earlier than in case 1. Therefore, for m equal to half the period of AB, the period of the gastric mill rhythm is much shorter than in case 1 (see Fig. 2). The period is controlled by the slowly growing and decaying excitation from MCN1 and the fast periodic inputs from AB to Int1 and to MCN1. The above explanation also applies for a range of m values near 500. For these delay values, there is some amount of time that while the AB input to Int1 is on so that LG is disinhibited, MCN1 is not inhibited by AB and the slow MCN1 excitation to LG is large enough for LG to begin a burst.

In case 2, it is apparent that the period of the gastric mill rhythm is determined by m. If m is in a neighborhood of 500, the period is very short because both the AB input to Int1 and the MCN1 excitation to LG influence the LG interburst duration. This, in turn, influences the LG burst duration by shortening it. However, if m is in a neighborhood of 0, the period is large because only the MCN1 excitation to LG determines the interburst duration. In experimental findings, when the MCN1 excitation is tonic and the AB inhibition to Int1 is absent the period is long but when the AB inhibition is present the period is short. In the case when MCN1 is rhythmically active and the AB inhibition is absent, the period is also short but the addition of the AB inhibition does not further shorten the period [5]. This is consistent with our findings if m is chosen appropriately (see Fig. 3).

5 Discussion

Both modulatory and pyloric inputs are crucial for generating the gastric mill rhythm and determining its frequency. When the MCN1 excitation to LG is tonic, the presence of the pyloric input to Int1 decreases the period of the gastric mill oscillations by ending the LG interburst at an earlier time. However, when MCN1 is rhythmically active, the affect of the pyloric inhibition to Int1 is strongly dependent upon the phase of this input. In particular, this phase can be chosen in such a way that the gastric mill rhythm is fast regardless of the presence or absence of the AB inhibition of Int1. Thus, when MCN1 is tonically active, the AB input to Int1 increases the gastric mill frequency, but when MCN1 is rhythmically active, the AB input to Int1 need not change this frequency. Both of these cases have been observed experimentally. This indicates that although the AB inhibition of Int1 and the AB inhibition of MCN1 provide the same end result in setting the frequency, the different sections of the cycle for which these two inputs are applied can be chosen such that the AB input to MCN1 counteracts the affect of the AB input to Int1. This allows the rhythmic MCN1 input to solely set the frequency of the network with the AB input to Int1 having no influence. Thus, the timing of the AB inputs to MCN1 and to Int1 provide a degree of flexibility in controlling the gastric mill rhythm.

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Christina Ambrosio is currently a graduate student in the department of Mathematical Sciences at New Jersey Institute of Technology.

Amitabha Bose is currently an associate professor in the department of Mathematical Sciences at New Jersey Institute of Technology. He received his Ph.D. in applied mathematics from Brown University.

Farzan Nadim is currently an associate professor in the department of Mathematical Sciences at New Jersey Institute of Technology and the department of Biological Sciences at Rutgers University. He received his Ph.D. in mathematics from Boston University and was a post-doctoral fellow in neurobiology at Emory University and Brandeis University.

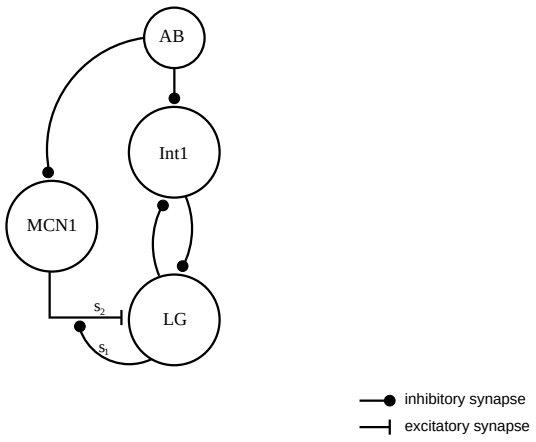

Figure 1: Schematic representation of the model of the MCN1 and AB elicited gastric mill rhythm.

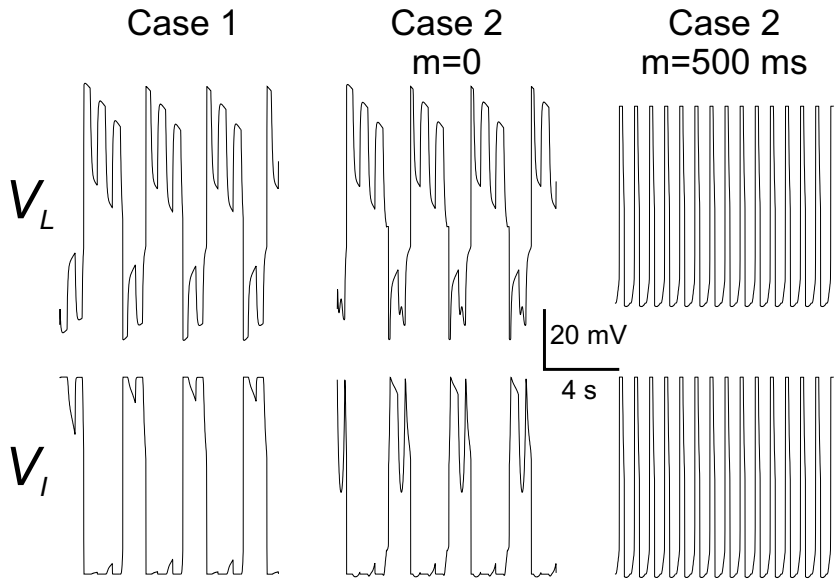

Figure 2: Voltage traces of V_L and V_I for case 1, case 2 ($m = 0$) and case 2 ($m = 500$). The frequency of the gastric mill rhythm is the same for case 1 and case 2 ($m = 0$) but dramatically increases for case 2 ($m = 500$).

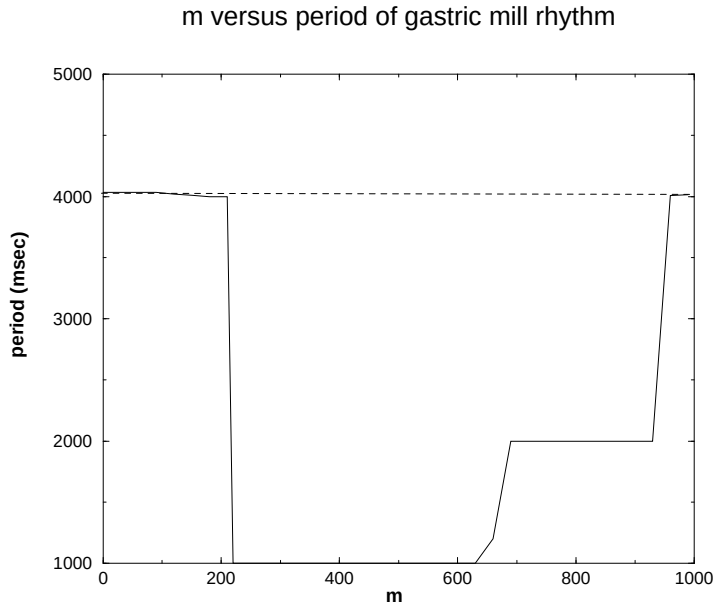

Figure 3: The period of the gastric mill cycle is plotted for different delay times, m, in case 2. The period of case 1 is marked by the dashed line. There is a small range of delays (for our chosen parameter values), $0 \leq m \leq 210$ and $960 \leq m \leq 1000$, for which the period of the gastric mill rhythm in case 2 is equal to the period of case 1.