

# The effects of varying the timing of inputs on a conditional oscillator

Christina Ambrosio<sup>(1)</sup>, Farzan Nadim<sup>(1,2)</sup>, Amitabha Bose<sup>(1)</sup>

<sup>(1)</sup> Department of Mathematical Sciences and  
Center for Applied Mathematics and Statistics  
New Jersey Institute of Technology, Newark, NJ 07102

<sup>(2)</sup> Dept of Biological Sciences, Rutgers University-Newark

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# The effects of varying the timing of inputs on a conditional oscillator

Christina Ambrosio\*      Farzan Nadim<sup>†</sup>      Amitabha Bose<sup>‡</sup>

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## Abstract

A conditional oscillator is one that requires input to oscillate. An example of such is the gastric mill network of the stomatogastric ganglion of the crab *Cancer borealis* which requires a modulatory input from outside the stomatogastric ganglion and input from the pyloric network of the animal in order to oscillate. Here we study how the frequency of the gastric mill network is determined when it receives rhythmic input from two different sources but where the timing of these inputs may differ. We find that over a certain range of the time difference one of the two rhythmic inputs plays no role whatsoever in determining the network frequency, while in another range, both inputs work together to determine the frequency. The existence and stability of periodic solutions to model sets of equations are obtained analytically using geometric singular perturbation theory. The results are validated through numerical simulations. Comparisons to experiments are also presented.

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## 1 Introduction

Many rhythmically active biological systems are conditional oscillators which require input from extrinsic sources to produce their activity. Such extrinsic inputs may arrive as a trigger signal thereby switching on the oscillation, or be continuously present as forcing or feedback for the duration of the oscillation [17, 18, 26]. The extrinsic input itself is often rhythmic and its frequency may or may not

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\*Department of Mathematical Sciences, New Jersey Institute of Technology, Newark, NJ 07102: cla2@njit.edu

<sup>†</sup>Department of Mathematical Sciences, New Jersey Institute of Technology, Newark, NJ 07102 and Department of Biological Sciences, Rutgers University at Newark, Newark, NJ 07102: farzan@njit.edu

<sup>‡</sup>Department of Mathematical Sciences, New Jersey Institute of Technology, Newark, NJ 07102: bose@njit.edu

match that of the target oscillator. Often, the oscillating network receives multiple inputs simultaneously, for example a central command input and a sensory feedback input. Such inputs are readily identified in central pattern generators (CPGs), neural networks within the central nervous system (CNS) that are responsible for generating rhythmic motor behaviors such as locomotion, swimming or breathing [13, 15, 17]. However, even in cases where the extrinsic inputs to a biological oscillator are known, the significance of the rhythmicity of such inputs or the consequences of having multiple inputs is largely unknown: often a non-rhythmic (tonic) input or only one of multiple inputs is sufficient to produce the biological oscillation. For instance, the CPG responsible for swimming in lower species of fish consists of chains of oscillators in the spinal cord [14]. This CPG receives rhythmic command input from the brain as well as multiple rhythmic and tonic sensory feedback inputs from the body. Without these inputs the CPG is inactive and the animal does not swim. However, the isolated spinal cord, in the presence of a chemical stimulant (tonic input) produces “fictive swimming”, rhythmic patterns which appear identical to those responsible for swimming in the intact animal [12].

In this paper, we use mathematical analysis to investigate the significance of the timing of multiple inputs to a conditional biological oscillator. We focus on the rhythmically active crustacean gastric mill CPG located within the stomatogastric ganglion (STG). The STG is one of several ganglia in the crustacean CNS that control feeding and digestion behaviors [24]. As in many invertebrate systems, the small number of neurons in the STG makes it amenable to both experimental and modeling studies of neuronal networks responsible for generating behaviors.

The gastric mill rhythm is generated by a subset of neurons in the STG. At the heart of this rhythm are two neurons, lateral gastric (*LG*) and interneuron 1 (*Int1*), which make reciprocally inhibitory synaptic connections and (when the gastric mill rhythm is activated) oscillate in antiphase with a frequency of 0.1 Hz. The gastric mill CPG, however, is a conditional oscillator: its activity depends on (modulatory) input from central command neurons located in other CNS ganglia [18, 24]. One such neuron, the modulatory commissural neuron 1 (*MCN1*), when excited, elicits a sustained gastric mill rhythm [8]. Previous studies have shown that input from the much faster pyloric CPG (frequency 1 Hz; also located in the STG) is crucial in setting the frequency of the *MCN1*-elicited gastric mill rhythm [3, 21]. This input comes in the form of an inhibitory synapse to *Int1* from the pyloric pacemaker neuron anterior burster (*AB*). Although tonic excitation of *MCN1* is sufficient for eliciting a gastric mill rhythm, it is known that, in the intact CNS, *MCN1* is itself rhythmically active [29]. The rhythmicity of *MCN1* is also due to a synaptic input it receives from *AB*. Thus, there are two pathways by which the pyloric pacemaker neuron *AB* influences the gastric mill network: the direct synaptic connection from *AB* to *Int1* and the indirect synaptic influence exerted by inhibiting *MCN1* which, in turn, excites the gastric mill neurons. Recent experimental findings show that the presence of either or both of the two pathways of *AB* influence results in a gastric mill rhythm of similar frequency [29]. However, when both pathways are removed (and thus the *MCN1* activity is tonic) the gastric mill rhythm slows down significantly. Although the mechanism through which the direct pyloric input influences the gastric mill frequency is understood, it is not known how the rhythmic activity of *MCN1* provides an apparently redundant mechanism for maintaining

the gastric mill frequency.

We expand on the techniques of Manor et al. [16] and build a simplified, biophysically-based model of the gastric mill network incorporating the effects of both *MCN1* and *AB*. Using this model, we show that the time difference between the two distinct *AB* influences on the gastric mill is critical in determining the gastric mill frequency. When  $m$ , the time delay between the *AB* inhibition of *Int1* and *MCN1*, is small, the gastric mill frequency is determined solely by direct modulatory effects of *MCN1* on the gastric mill neurons. However, when  $m$  is large, the gastric mill rhythm operates at a higher frequency and is determined by both the *MCN1* and *AB* inputs. Throughout this work, we use geometric singular perturbation theory to examine the behavior of our model on low-dimensional manifolds. We also use phase plane analysis as a means of geometrically understanding the behavior of the network. Using these mathematical tools, we prove the existence and stability of periodic solutions of the model when the activity of *MCN1* is either tonic or rhythmic. Furthermore, we confirm our findings through numerical simulations in which we change the delay parameter  $m$  and numerically calculate the period. We then compare our results with the experimental findings of [29]. The results from our model match the experimental results only when  $m$  is either 0 or small. Thus, we show that the time difference between inputs to an oscillatory network serves as a mechanism to control the network frequency. Our analysis, therefore, gives a possible explanation for the experimental results which could be tested in future experiments.

The remainder of the paper is organized as follows. In section 2, we derive a model set of equations and show how it can be reduced into sets of fast and slow equations. The effect of various synaptic inputs on relevant nullclines are illustrated with the goal of showing how fixed points of the fast set of equations depend on these inputs. In section 3, we prove the existence, uniqueness and stability of period solutions for four different cases of the gastric mill rhythm. These cases are considered so that we may parallel the study of Wood et. al. [29]. In section 4, we derive an analytic formula for the period of the solutions for cases 1 through 4. We then check our analytic results against simulations. In section 5, we discuss the impact of making a certain synapse (that from *MCN1* to *LG*) voltage dependent. Section 6 contains a Discussion to conclude the paper.

## 2 Model

Our model consists of the gastric mill network composed of *Int1* and *LG*, the pacemaker neuron *AB* of the pyloric network and the modulatory commissural neuron *MCN1*; see Fig. 1. *LG*, *Int1*, and *MCN1* are modeled as passive neurons (*LG* having a subthreshold resting potential and both *Int1* and *MCN1* having suprathreshold resting potentials). *LG* and *Int1* have reciprocally inhibitory synapses between them. *Int1* and *MCN1* receive inhibitory input from the pacemaker neuron *AB*. *AB* and *MCN1* both fire in pyloric time with a period denoted  $P_{AB}$ . *AB* sends an inhibitory synapse to *Int1* and *MCN1* sends a slow excitatory synapse to *LG*. In addition, *LG* presynaptically inhibits *MCN1* each time it fires, thus removing the excitation from *MCN1* to *LG*.

Through this circuitry, the voltage of  $LG$  is able to increase above threshold (due to the excitation it receives from  $MCN1$  and the disinhibition it receives from  $AB$ ) causing  $Int1$  to become suppressed and then decay back below threshold (due to the presynaptic inhibition), thereby producing the antiphase oscillations of the gastric mill rhythm [9][16].

## 2.1 Equations

We do not explicitly model the pacemaker neuron  $AB$ , but instead incorporate its effect on  $MCN1$  and  $Int1$  through a synaptic variable  $s_{AB}(t)$ . This variable is modeled as a square wave with period  $P_{AB}$ . Let  $D_c$  denote the duty cycle of  $AB$  (the ratio of its active time to its period). During one period of  $AB$ , the variable  $s_{AB}$  is equal to 1 for a time  $D_c P_{AB}$  and equal to 0 for a time  $P_{AB}[1 - D_c]$ .

The dynamics of the system evolve along two distinct time scales. One is a slow time scale corresponding to the effect of pre-synaptic inhibition from  $LG$  to the slow excitatory component of the  $MCN1$  synapse. The voltage of  $MCN1$  will also evolve on the slow time scale, although its evolution will be substantially faster than that of the pre-synaptic inhibition. The other is a fast time scale along which all other synapses and intrinsic properties evolve. We use a small parameter,  $\epsilon$ , to demarcate these two time scales.

The equations to describe the activity of  $LG$ ,  $Int1$ , and  $MCN1$  are:

$$\epsilon \frac{dV_L}{dt} = -g_{leak,L}[V_L - E_{leak,L}] - \bar{g}_{I \rightarrow L} n_\infty(V_I)[V_L - E_{I \rightarrow L}] - g_s(V_L)s(t)[V_L - E_{exc}] \quad (1)$$

$$\epsilon \frac{dV_I}{dt} = -g_{leak,I}[V_I - E_{leak,I}] - \bar{g}_{L \rightarrow I} n_\infty(V_L)[V_I - E_{L \rightarrow I}] - \bar{g}_{AB \rightarrow I} s_{AB \rightarrow I}(t)[V_I - E_{AB \rightarrow I}] \quad (2)$$

$$C \frac{dV_M}{dt} = -g_{leak,M}[V_M - E_{leak,M}] - \bar{g}_{AB \rightarrow M} s_{AB \rightarrow M}(t)[V_M - E_{AB \rightarrow M}] \quad (3)$$

where  $V_L$  is the voltage of  $LG$ ,  $V_I$  is the voltage of  $Int1$ , and  $V_M$  is the voltage of  $MCN1$ .  $g_{leak,L}$ ,  $g_{leak,I}$ , and  $g_{leak,M}$  are the conductances of the leak currents in  $LG$ ,  $Int1$ , and  $MCN1$ .  $E_{leak,L}$ ,  $E_{leak,I}$ , and  $E_{leak,M}$  are the reversal potentials of the leak currents in  $LG$ ,  $Int1$ , and  $MCN1$ . The parameter  $C$  is  $O(1)$  with respect to  $\epsilon$ . Denote the right hand sides of equations (1) and (2) by  $f(V_L, V_I, s)$  and  $g(V_I, V_L, s_{AB \rightarrow I})$ , respectively.

The parameters of the reciprocally inhibitory synapses between  $Int1$  and  $LG$  are  $g_{I \rightarrow L}$  and  $g_{L \rightarrow I}$  (the maximal conductances) and  $E_{I \rightarrow L}$  and  $E_{L \rightarrow I}$  (the reversal potentials).  $n_\infty(V_I)$  and  $n_\infty(V_L)$  are sigmoidal shaped gating functions lying between 0 and 1:

$$n_\infty(V_x) = \left(1 + \exp \frac{v_x - V_x}{k_x}\right)^{-1} \quad (4)$$

where  $v_x$  is the half-activation voltage and  $k_x$  is inversely related to the slope at this point.

The fast, periodic inhibitory input from  $AB$  to  $MCN1$  is described by  $\bar{g}_{AB \rightarrow M} s_{AB \rightarrow M}(t)[V_M - E_{AB \rightarrow M}]$  where  $s_{AB \rightarrow M}(t) = s_{AB}(t)$ ,  $\bar{g}_{AB \rightarrow M}$  is the conductance of the synapse, and  $E_{AB \rightarrow M}$  is the

reversal potential which is chosen to be less than  $E_{leak,M}$  so that the input from  $AB$  to  $MCN1$  is inhibitory. The periodic, inhibitory input from  $AB$  to  $Int1$  is given by  $\bar{g}_{AB \rightarrow I} s_{AB \rightarrow I}(t)(V_I - E_{AB \rightarrow I})$ .  $\bar{g}_{AB \rightarrow I}$  is the conductance and  $E_{AB \rightarrow I}$  is the reversal potential. An important aspect of this work is to highlight the fact that different timing relationships of  $AB$  input to  $MCN1$  and  $Int1$  lead to dramatically different frequencies of the gastric mill rhythm. To this end, we will use the parameter,  $m$ , to delay the  $AB$  input to  $Int1$  relative to  $MCN1$ . In other words,  $s_{AB \rightarrow I}(t) = s_{AB \rightarrow M}(t - m)$ . The parameter  $m$  is a constant which can range between 0 and  $P_{AB}$  (the period of  $s_{AB}(t)$ ).

The effect of the excitation that  $LG$  receives from  $MCN1$  is given in (1) by  $g_s(V_L)s(t)[V_L - E_{exc}]$  where  $g_s(V_L) = \bar{g}_s s_\infty(V_L)$  is the voltage dependent conductance of the synapse,  $E_{exc}$  is the reversal potential and  $s(t)$  models the amount of excitation  $LG$  receives. The function  $s_\infty$  is a sigmoidal gating function similar in form to  $n_\infty$ ; its exact form will be discussed later in Section 5. We express  $s(t) = s_1(t)s_2(t)$  as the product of two different effects.  $s_2(t)$  models the effect of the  $AB$  inhibition of  $MCN1$  on the fast excitatory component from  $MCN1$  to  $LG$ .  $s_1(t)$  models the effect of the presynaptic inhibition of the slow excitatory component of this synapse. We let  $V_{Th(M)}$  and  $V_T$  denote the activation thresholds for these two synapses. The relevant equations are:

$$\frac{ds_1}{dt} = \begin{cases} [1 - s_1]/\tau_{r1} & V_L \leq V_T \\ -s_1/\tau_{f1} & V_L > V_T \end{cases} \quad (5)$$

$$\epsilon \frac{ds_2}{dt} = \begin{cases} [1 - s_2]/\tau_{r2} & V_M \geq V_{Th(M)} \\ [s_{2min} - s_2]/\tau_{f2}(s_2) & V_M < V_{Th(M)} \end{cases} \quad (6)$$

The time constants  $\tau_{r1}$ ,  $\tau_{f1}$ , and  $\tau_{r2}$  in (5) and (6) are  $O(1)$  with respect to  $\epsilon$  while

$$\tau_{f2}(s_2) = \begin{cases} 1 & s_2 \geq s_{2min} \\ 1/\epsilon^2 & s_2 < s_{2min}. \end{cases} \quad (7)$$

To understand which parameters are important in controlling the gastric mill frequency, we use phase-plane analysis along with geometric singular perturbation theory to reduce the full flow to a study of flow on lower dimensional slow manifolds. From equations (1)-(3) and (5)-(7), we see that  $V_L$ ,  $V_I$ ,  $V_M$ , and  $s_2$  evolve on a faster time scale than  $s_1$ . Setting  $\epsilon = 0$  in the equations yields the slow equations:

$$0 = f(V_L, V_I, s) \quad (8)$$

$$0 = g(V_I, V_L, s_{AB \rightarrow I}) \quad (9)$$

$$C \frac{dV_M}{dt} = -g_{leak,M}[V_M - E_{leak,M}] - \bar{g}_{AB \rightarrow M} s_{AB \rightarrow M}(t)[V_M - E_{AB \rightarrow M}] \quad (10)$$

$$\frac{ds_1}{dt} = \begin{cases} [1 - s_1]/\tau_{r1} & V_L \leq V_T \\ -s_1/\tau_{f1} & V_L > V_T \end{cases} \quad (11)$$

$$0 = \begin{cases} [1 - s_2]/\tau_{r2} & V_M \geq V_{Th(M)} \\ [s_{2min} - s_2]/\tau_{f2}(s_2) & V_M < V_{Th(M)}, s_2 \geq s_{2min} \end{cases} \quad (12)$$

$$\frac{ds_2}{dt} = 0 \quad V_M < V_{Th(M)}, s_2 < s_{2min} \quad (13)$$

The set of points satisfying  $f(V_L, V_I, s) = 0$  and  $g(V_I, V_L, s_{AB \rightarrow I}) = 0$  are called the  $V_L$  and  $V_I$  nullclines, respectively. In slow time, equations (8) and (9) imply that any trajectory is forced to lie on the  $V_L$  and  $V_I$  nullclines while  $s_1$  slowly evolves and  $s_2$  instantaneously jumps between  $s_{2min}$  and 1 whenever  $V_M$  crosses the threshold  $V_{TH(M)}$ .  $V_M$  crosses the threshold  $V_{TH(M)}$  as a function of  $s_{AB \rightarrow M}(t)$ . From (10), when  $s_{AB}(t) = 0$ , then  $V_M \rightarrow E_{leak,M} > V_{TH(M)}$  with rate proportional to  $1/C$ . When  $s_{AB \rightarrow M}(t) = 1$ , then  $V_M \rightarrow V_M^*$  where

$$V_M^* = \frac{g_{leak,M} E_{leak,M} + \bar{g}_{AB \rightarrow M} E_{AB \rightarrow M}}{g_{leak,M} + \bar{g}_{AB \rightarrow M}}, \quad (14)$$

with rate again proportional to  $1/C$ . While  $C$  is  $O(1)$  with respect to  $\epsilon$  it is chosen to be substantially smaller than the time constants  $\tau_{f1}$  and  $\tau_{r1}$ . Using this assumption, for simplicity of our analysis later, we shall assume that the time it takes for  $V_M$  to increase under (10) from  $V_M^*$  to  $E_{leak,M}$  is  $T_C$ , and that the time it takes to decrease between these two points is instantaneous with respect to the slow time scale. In short,  $T_C$  is the time it takes  $V_M$  to cross threshold once it is released from  $AB$  inhibition.

Note that when  $\bar{g}_{AB \rightarrow M} = 0$ , then  $V_M$  is always greater than  $V_{TH(M)}$ , and we refer to *MCN1* as being tonically active. Alternatively when  $\bar{g}_{AB \rightarrow M}$  is sufficiently large then  $V_M$  goes above and below  $V_{TH(M)}$  in pyloric time and we say that *MCN1* is rhythmically active. We note that  $V_M$  may cross  $V_{Th(M)}$  several times before  $V_L$  crosses  $V_T$  because the period of  $s_{AB \rightarrow M}(t)$  is small compared with the rates of rise and decay of  $s_1(t)$ .

To define fast equations, let  $\zeta = t/\epsilon$  in equations (1)-(3) and (5)-(7), then set  $\epsilon = 0$  to obtain:

$$\frac{dV_L}{d\zeta} = f(V_L, V_I, s) \quad (15)$$

$$\frac{dV_I}{d\zeta} = g(V_I, V_L, s_{AB \rightarrow I}) \quad (16)$$

$$\frac{dV_M}{d\zeta} = 0 \quad (17)$$

$$\frac{ds_2}{d\zeta} = \begin{cases} [1 - s_2]/\tau_{r2} & V_M \geq V_{Th(M)} \\ [s_{2min} - s_2]/\tau_{f2}(s_2) & V_M < V_{Th(M)} \end{cases} \quad (18)$$

$$\frac{ds_1}{d\zeta} = 0. \quad (19)$$

Therefore, in fast time  $V_L$  and  $V_I$  evolve according to the dynamics of  $f(V_L, V_I, s)$  and  $g(V_I, V_L, s_{AB \rightarrow I})$  and  $s_2$  increases and decreases between 1 and  $s_{2min}$  while  $s_1$  remains constant. These equations govern transitions between the different branches of the  $V_I$  and  $V_L$  nullclines.

## 2.2 Geometry of nullclines

In the previous subsection, we derived reduced fast and slow equations which govern the flow of trajectories in relevant phase spaces. For the slow equations (8)-(13), the slow variables  $V_M$  and

$s_1$  evolve according to equations (10)-(11), while the activity of the fast variables  $V_L$ ,  $V_I$ , and  $s_2$  is constrained through the algebraic equations (8), (9), (12) and (13). For the fast equations (15)-(19), the slow variables act as parameters. Fixed points of the fast equations correspond to situations where the  $V_I$  and  $V_L$  nullclines intersect. We will be interested in situations where the existence and stability of fixed points of the fast subsystem changes. Generally speaking, this may occur because the slow variable  $s_1$  causes the fast system to undergo a saddle-node bifurcation, or if  $s_{AB}$  changes causing the position of the nullclines to change on the fast time scale in phase space. Below, we show geometrically how these situations may arise.

We shall first consider the case when the synapse from *MCN1* to *LG* is not voltage dependent. We do this by letting  $s_\infty(V_L) \equiv 1$ . The effect of the voltage dependency of this synapse is considered in Section 5. We find the explicit equations for the nullclines by solving (8) for  $V_L$  and (9) for  $V_I$  to find that

$$V_L = F(V_I, s) = \frac{g_{leak,L}E_{leak,L} + \bar{g}_{I \rightarrow L}n_\infty(V_I)E_{I \rightarrow L} + \bar{g}_s s(V_L)E_{exc}}{g_{leak,L} + \bar{g}_{I \rightarrow L}n_\infty(V_I) + \bar{g}_s s s_\infty(V_L)} \quad (20)$$

and

$$V_I = G(V_L, s_{AB \rightarrow I}) = \frac{g_{leak,I}E_{leak,I} + \bar{g}_{L \rightarrow I}n_\infty(V_L)E_{L \rightarrow I} + \bar{g}_{AB \rightarrow I}s_{AB \rightarrow I}(t)E_{AB \rightarrow I}}{g_{leak,I} + \bar{g}_{L \rightarrow I}n_\infty(V_L) + \bar{g}_{AB \rightarrow I}s_{AB \rightarrow I}(t)} \quad (21)$$

A simultaneous solution to (8) and (9) can be found graphically by plotting  $F(V_I, s)$  versus  $G(V_L, s_{AB \rightarrow I})$ . An intersection of these two nullclines corresponds to a fixed point of the fast equations. However, the position of the nullclines in  $V_I - V_L$  phase space changes as a function of  $s$  and  $s_{AB}$ ; see Fig. 2. In general, increases (decreases) in  $s$  move the  $V_L$  nullcline to the right (left), either in slow time due to changes in  $s_1$  or in fast time due to changes in  $s_2$ . The  $V_I$  nullcline has two possible positions in phase space depending on whether  $s_{AB \rightarrow I} = 0$  or 1. The nullcline corresponding to  $s_{AB \rightarrow I} = 1$  is lower in phase space than the one for  $s_{AB \rightarrow I} = 0$ . We note that the left branch of the  $V_I$  nullcline shifts down much more than the right branch since on the right branch  $V_I$  is already close to  $E_{AB \rightarrow I}$  independent of  $s_{AB \rightarrow I}(t)$ . The number and stability of fixed points also changes as a function of  $s$  and  $s_{AB \rightarrow I}$ . We identify four important values of  $(s, s_{AB \rightarrow I})$  as  $(s_L^{off}, 0)$ ,  $(s_L^{on}, 1)$ ,  $(s_R^{off}, 0)$  and  $(s_R^{on}, 1)$ ; see Fig. 3. The superscripts *off* and *on* refer to the *AB* input to *Int1* which can either be absent (*off*) or present (*on*). These points correspond to values when the two nullclines intersect tangentially resulting in the loss (or gain) of two fixed points through a saddle-node bifurcation. Because  $s_1$  is increasing on the left branches and decreasing on the right, the ordering of these bifurcation points is  $s_R^{on} < s_R^{off} < s_L^{on} < s_L^{off}$ . These values can be calculated analytically; see the Appendix.

On the slow time scale, the solution trajectory must lie at the intersection of the  $V_I$  and  $V_L$  nullclines, i.e. at a fixed point of the fast subsystem. Thus to understand the evolution of trajectories in the  $V_I - V_L$  phase space, we need to understand how the position of fixed points changes as a function of  $s$  and  $s_{AB}$ .

Let us first consider the case when  $s_{AB}(t) \equiv 0$ . Then *MCN1* is tonically active and sits at a value of  $E_{leak,M}$ .  $E_{leak,M}$  is chosen to be larger than  $V_{Th(M)}$  which we see from (12) allows  $s_2 = 1$ .

As a result, we have  $s(t) = s_1(t) * 1$  which means that  $s(t)$  increases toward 1 with time constant  $\tau_{r1}$  when  $V_L < V_T$  and decreases toward 0 with time constant  $\tau_{f1}$  when  $V_L > V_T$  (see Fig. 4A).

From (20), as  $s$  slowly increases, the  $V_L$  nullcline slowly shifts to the right, thus causing the position of the stable fixed point to shift to the right. This continues until the  $V_L$  nullcline shifts far enough to the right so that the stable fixed point on the left branches of the nullclines is lost through a saddle node bifurcation when  $s = s_L^{off}$ ; see Fig. 5. Once the fixed point is lost, the trajectory is forced to jump on the fast time scale (equations (15)-(16)) to the only remaining stable fixed point which is on the right branches of the nullclines. This jump pushes  $V_L$  above  $V_T$  causing  $s(t)$  to begin to decrease. When  $s$  decreases, the  $V_L$  nullcline slowly shifts to the left until the stable fixed point on the right branches of the  $V_L$  and  $V_I$  nullclines similarly undergoes a saddle-node bifurcation at  $s = s_R^{off}$ . The trajectory then makes a jump back to the left branches of the nullclines which forces  $V_L$  below  $V_T$ . Similar dynamics occur when  $s_{AB \rightarrow I}(t) \equiv 1$  except now the trajectory would pass through the bifurcation points  $s_L^{on}$  and  $s_R^{on}$  during its transition between left and right branches.

When *MCN1* excitation to *LG* is rhythmic instead of tonic,  $s_2$  changes on the fast timescale between 1 and  $s_{2min}$  as  $V_M$  crosses over  $V_{Th(M)}$  while  $s_1$  increases toward 1 when  $V_L \leq V_T$  and decreases toward 0 when  $V_L > V_T$  on the slow timescale. This causes  $s(t)$  to generally have a shape as shown in Fig. 4B. Notice that the envelope of  $s(t)$  activity is the same as in the tonic excitability case seen in Fig. 4A, but now there are rapid changes in  $s(t)$  due to the rapid changes in  $s_2(t)$ . The jump of  $s_2$  between  $s_{2min}$  and 1 causes the  $V_L$  nullcline to instantaneously jump to the right when  $s_2$  jumps to 1 and instantaneously jump to the left when  $s_2$  jumps to  $s_{2min}$ . The distance of these jumps in the  $V_L$  nullcline, calculated from (20), is  $F(V_I, s_1 * 1) - F(V_I, s_1 * s_{2min})$ . Note that in the *MCN1* rhythmic case, fixed points can be lost in two different ways. They may be lost as before through a saddle-node bifurcation as  $s$  is slowly changing due to changes in  $s_1$ ; see Fig. 6A. Or they may be lost when  $s_2$  changes on the fast time scale. For example, on the left branches, it may be that  $s_1 * s_{2min} < s_L^{off}$ , but  $s_1 * 1 > s_L^{off}$ . In this case, the fixed point would be lost if  $s_{2min}$  changed to 1 due to a change in *MCN1* activity; see Fig. 6B. On the right branches, it may be that  $s_1 * 1 > s_R^{off}$ , but  $s_1 * s_{2min} < s_R^{off}$ . In this case, the fixed point would be lost when  $s_2$  changes from 1 to  $s_{2min}$ .

In the case where  $s_{AB \rightarrow I}(t)$  is a square wave, the trajectory will always lie on a nullcline with either  $s_{AB \rightarrow I} = 0$  or  $s_{AB \rightarrow I} = 1$ . Now fixed points can be lost in three different ways. Consider the left branches. As before, a fixed point can be lost as  $s$  increases slowly through a bifurcation point or instantaneously as  $s_2$  changes from  $s_{2min}$  to 1. The third way it can be lost is if  $s_L^{off} > s > s_L^{on}$  and  $s_{AB \rightarrow I}$  switches from 0 to 1; see Fig. 6C (see Fig. 6D for the analogous loss of a fixed point on the right branches.)

### 3 Different cases for the gastric mill frequency

To understand how the two different inputs of *AB* and *MCN1* modulate the gastric mill frequency, we parallel the study of Wood et. al. [29] by considering four different cases (see Fig. 7):

**Case 1.** Tonic *MCN1* excitation with the *AB* input to *Int1* absent

**Case 2.** Tonic *MCN1* excitation with the *AB* input to *Int1* present

**Case 3.** Rhythmic *MCN1* excitation with the *AB* input to *Int1* absent

**Case 4.** Rhythmic *MCN1* excitation with the *AB* input to *Int1* present

In each case, we shall prove the existence, local uniqueness and stability of a periodic solution and then calculate the period of this solution. The proofs of existence, local uniqueness and stability of periodic solutions exploit the different time scales. In Cases 2 through 4, this will reduce to finding fixed points of appropriate one-dimensional maps. The proofs construct singular periodic solutions which are valid at  $\epsilon = 0$ , whose existence, local uniqueness and stability can be extended to the  $\epsilon$  sufficiently small case [20].

In the biological circuit it is known that the synapse from *MCN1* to *LG* is dependent on the voltage of *LG*. For mathematical clarity, we shall postpone discussing the voltage dependent case until section 5. Instead, we shall first concentrate on the voltage independent case where we set  $s_\infty(V_L) \equiv 1$ .

**Case 1: Tonic *MCN1* excitation with the *AB* input to *Int1* absent**

When considering Case 1, we set  $\bar{g}_{AB \rightarrow I} = 0$  and  $\bar{g}_{AB \rightarrow M} = 0$  in equations (2) and (3) so that all input from *AB* is absent. When  $\bar{g}_{AB \rightarrow M} = 0$ ,  $V_M > V_{Th(M)}$  for all  $t$  and *MCN1* is tonically active. This allows us to set  $s_2 \equiv 1$  so that  $s = s_1 * s_2$  will only follow the dynamics of  $s_1$ .

In Case 1, the only way a fast transition between branches can occur is by  $s_1$  passing through the bifurcation points  $s_L^{off}$  or  $s_R^{off}$ . To construct a periodic solution, let  $s_1(0) = s_R^{off}$  such that the trajectory at  $t = 0^-$  is at the bifurcation point on the right branches at the intersection of the  $V_I$  and  $V_L$  nullclines; see Fig. 8. At  $t = 0^+$ , the trajectory jumps back to the left branches at the intersection of the nullclines; see Fig. 8A. On these branches,  $V_L < V_T$  and thus  $s_1$  will increase until it reaches the bifurcation point  $s_L^{off}$  at  $t = T_1$ ; see Fig. 8B-C. The trajectory will jump back to the right branch and since  $V_L > V_T$ ,  $s_1$  will now decrease until it comes back to  $s_R^{off}$  at  $t = T_2$ ; see Fig. 8D. Thus the value of  $s_1$  will have returned to its original value at time  $T_2$ . Since all the fast variables are slaved through equations (8) and (9) to the behavior of  $s_1$ , we do not explicitly need to check their evolution during the time interval  $[0, T_2]$ . In this sense, proving the existence of this periodic solution has been reduced to proving that the single variable  $s_1$  is periodic. Thus it is seen that there exists a singular periodic solution whose period is  $T_2$ . In section 3.2, we will both analytically and numerically calculate  $T_2$ .

The solution is unique and stable since if  $s_1(0) > s_R^{off}$  and the trajectory was on the right branches of the nullclines, for example, then the solution can be flowed forward a time  $\hat{t}$  such that  $s_1(\hat{t}) = s_R^{off}$ . From here the solution trajectory would follow the dynamics described above and return to  $s_R^{off}$  at time  $t = T_2 + \hat{t}$ . Thus, by flowing backward in time, it is seen that  $s_1(T_2) = s_1(0)$ .

**Case 2: Tonic MCN1 excitation with the AB input to Int1 present**

In Case 2,  $\bar{g}_{AB \rightarrow M} = 0$  so that  $s_2 \equiv 1$  and thus the MCN1 to LG excitation is tonic. Now the AB to Int1 inhibition is present ( $\bar{g}_{AB \rightarrow I} > 0$ ). Without loss of generality, let  $m = 0$  in (2). Hence,  $s$  causes the  $V_L$  nullcline to slowly shift to the right and left as in Case 1 and  $s_{AB \rightarrow I}(t)$  causes the  $V_I$  nullcline to instantaneously jump down when  $s_{AB \rightarrow I}(t)$  goes to 1 and to jump back up when  $s_{AB \rightarrow I}(t)$  returns to 0.

To understand the control of frequency in Case 2, we again consider the nullclines in the phase-plane. When  $V_L > V_T$ , the  $V_L$  nullcline moves to the left slowly because  $\tau_{f1}$  is large. The AB input to Int1, on the other hand, is fast and periodic so that the  $V_I$  nullcline shifts up and down repeatedly and instantaneously compared with the shift of the  $V_L$  nullcline. Thus, on the right branches of the nullclines, three cases arise for the loss of the fixed point. The first possibility is that while  $s_R^{on} < s < s_R^{off}$ ,  $s_{AB \rightarrow I}(t)$  switches from 1 to 0, forcing the  $V_I$  nullcline to jump up causing the stable fixed point to be immediately lost. This forces the trajectory to jump directly to the stable fixed point on the left branches of the  $V_I$  and  $V_L$  nullclines; see Fig. 6D.

The second possibility is that when  $s_{AB \rightarrow I}(t) = 1$ ,  $s$  decreases until the fixed point is lost through the saddle-node bifurcation at  $s = s_R^{on}$ . The third possible way for the fixed point on the right branches to be lost is as in Case 1. That is, while  $s_{AB \rightarrow I} = 0$ ,  $s$  decreases to  $s_R^{off}$ ; see Fig. 8D. Which of these cases occurs depends upon the amount of time that  $s_{AB \rightarrow I}(t)$  spends in its active and inactive phases and the timing of the AB input to Int1. In other words, the timing of the periodic jumps in  $s_{AB \rightarrow I}$  affects the timing of the shifts in the  $V_I$  nullcline which in turn determines which case occurs. The fixed point on the left branch can be lost similarly to the ways discussed above. Let us say that a periodic solution obeys Property A if the associated trajectory jumps from the right to left branches when  $s_{AB \rightarrow I}(t)$  switches from 1 to 0 and from left to right branches through the bifurcation point  $s_L^{on}$ ; see Fig. 9.

Recall that the pyloric period is much smaller than the gastric mill period. Thus, while LG is inactive ( $V_L < V_T$ ),  $s_{AB}$  can oscillate several times, say  $j$  times, between 0 and 1. The exact number of times depends on the time constant  $\tau_{r1}$ . Similarly when LG is active ( $V_L > V_T$ ), the number of oscillations,  $k$ , of  $s_{AB}$  depends on the time constant  $\tau_{f1}$ . This implies that the periodic solution in case 2 depends on the relationship between  $\tau_{r1}$ ,  $\tau_{f1}$  and the pyloric input frequency of AB. In the following theorem we will derive a relationship which  $\tau_{r1}$  and  $\tau_{f1}$  need to satisfy in order to find a periodic solution with Property A. This involves fixing the integers  $j$  and  $k$  first. To that end define

$$h(k) = \frac{D_c}{\ln \left( \frac{1 - s_R^{off} (s_R^{off} / s_L^{on})^{D_c/k}}{1 - s_R^{off}} \right)} \ln \left( \frac{1 - s_R^{off}}{1 - s_L^{on}} \right) + D_c - 1. \quad (22)$$

**Theorem:** *Let  $k$  and  $j$  be integers which satisfy  $j < h(k)$ . There exists values  $\tau_{r1}(j)$ ,  $\tau_{f1}(k)$  and  $\bar{g}_{AB \rightarrow I}$  large enough such that equations (1)-(3) and (5)-(6) possess a locally unique, asymptotically stable periodic solution obeying Property A with period  $P = (j + k + 1)P_{AB}$  where  $j$  is the number*

of times  $s_{AB}$  oscillates between 0 and 1 while  $V_L < V_T$  and  $k$  is the number of time  $s_{AB}$  oscillates between 0 and 1 when  $V_L > V_T$ .

**Proof:** We shall construct a Poincare map  $\mathcal{P}$  of a certain interval  $\mathcal{I}$  into itself. Existence and stability of the periodic solution is determined by showing that  $\mathcal{P}$  is a contraction on  $\mathcal{I}$ , thereby also yielding local uniqueness of the periodic solution. To construct the periodic solution in question we will show that the associated trajectory will jump from the left to the right branches from the bifurcation point  $s_L^{on}$ . It will jump from the right to the left branches from a point  $s^* \in \mathcal{I}$  at one of the times while  $s_{AB \rightarrow I}$  switches from one to zero.

To construct  $\mathcal{I}$ , consider the points  $s_R^{off}$  and  $s_R^{on}$  corresponding to the bifurcation points along the right branches of the  $V_I$ - $V_L$  nullclines when  $s_{AB \rightarrow I} = 0$  ( $AB$  off) and  $s_{AB \rightarrow I} = 1$  ( $AB$  on), respectively. By choosing  $\bar{g}_{AB \rightarrow I}$  and  $\tau_{f1}$  sufficiently large, we can guarantee that the time distance between  $s_R^{on}$  and  $s_R^{off}$  under the dynamics  $s' = -s/\tau_{f1}$  is larger than  $D_c P_{AB}$ . Indeed the time  $\Delta t$  between these two points on the right branches is  $\tau_{f1} \ln(s_R^{off}/s_R^{on})$ , where  $s_R^{on}$  is a decreasing function of  $\bar{g}_{AB \rightarrow I}$ . Moreover, there exists  $\hat{s}$  such that  $\hat{s} = s_R^{off} \exp(-D_c P_{AB}/\tau_{f1})$ . Thus the time distance between  $\hat{s}$  and  $s_R^{off}$  on the right branches is exactly  $D_c P_{AB}$ . We let  $\mathcal{I} = [\hat{s}, s_R^{off}]$ ; see Fig. 10. Note that at this point, we are only stating that we need  $\tau_{f1}$  sufficiently large. Below, we will be more specific.

We next show that  $\mathcal{I}$  maps into itself under the flow if  $\tau_{r1}$  and  $\tau_{f1}$  are chosen appropriately. We flow the endpoints of the interval  $\mathcal{I}$ ,  $s_R^{off}$  and  $\hat{s}$ , through one cycle of the  $V_I$  and  $V_L$  oscillation and show that these endpoints are mapped into  $\mathcal{I}$ . Thus by continuous dependence on initial conditions, all points in  $\mathcal{I}$  will map into  $\mathcal{I}$ .

First consider a trajectory  $s_a(t)$  where  $s_a(0) = s_R^{off}$  and the trajectory is on the right branch. Next let  $s_{AB \rightarrow I}(0^-) = 1$  and  $s_{AB \rightarrow I}(0^+) = 0$ , so that the trajectory jumps back to the left branch at  $t = 0^+$ . The dynamics of  $s_a$  on the left branches obey  $s' = (1 - s)/\tau_{r1}$ . By choosing

$$\tau_{r1}(j) = (j + 1 - D_c)P_{AB} / \ln([1 - s_R^{off}]/[1 - s_L^{on}]), \quad (23)$$

we can guarantee that  $s_a([j + 1 - D_c]P_{AB}) = s_L^{on}$ . This means that the trajectory which starts at  $s_R^{off}$  will leave the left branches of the nullclines through the bifurcation point  $s_L^{on}$  along the  $s_{AB \rightarrow I} = 1$  nullcline at time  $t = (j + 1 - D_c)P_{AB}$ .

Next consider a trajectory  $s_b(t)$  with the initial condition given by  $s_b(0) = \hat{s}$ . Recall that the time distance from  $\hat{s}$  to  $s_R^{off}$  on the right branches is given by  $\tau_{f1} \ln(s_R^{off}/\hat{s})$ . On the left branches, the time between these points is governed by  $\tau_{r1}$  and is equal to  $\tau_{r1} \ln([1 - \hat{s}]/[1 - s_R^{off}])$ . Thus if

$$\tau_{r1} < \tau_{f1} \frac{\ln(s_R^{off}/\hat{s})}{\ln([1 - \hat{s}]/[1 - s_R^{off}])} \quad (24)$$

then the time between these points on the left branches will be less than that on the right branches, and, in particular, will be less than  $D_c P_{AB}$ . Thus the trajectory starting with initial condition at

$\hat{s}$  at  $t = 0$  will reach  $s_L^{on}$  when  $s_{AB \rightarrow I} = 1$  at a time  $T_1$  bounded between  $(j + 1 - D_c)P_{AB}$  and  $(j + 1)P_{AB}$ . Therefore, any trajectory with  $s(0) \in \mathcal{I}$  will do the same.

Note that the time between any two trajectories remains invariant while they both evolve on the left branches and even across the jump back to the right branches. That the trajectories remain the same time distance apart on the left branches follows from the fact that they both obey the same differential equation ( $s' = (1-s)/\tau_{r1}$ ). Moreover, since they leave the left branches through the same point  $s_L^{on}$ , the time distance between them when the leading cell reaches the bifurcation point is the same as the time distance apart when the trailing cell reaches this point. When both trajectories are on the right branches, the time distance, again remains invariant since both trajectories evolve under  $s' = -s/\tau_{f1}$ . In particular, the time distance between  $s_a(T_1)$  and  $s_b(T_1)$  is less than  $D_c P_{AB}$ .

Consider again the trajectory  $s_a(t)$  which had  $s_a(0) = s_R^{off}$  and  $s_a([j + 1 - D_c]P_{AB}) = s_L^{on}$ . We want this trajectory to spend  $k$  oscillations of  $s_{AB}$  on the right branches. We also want the trajectory to be in a position to jump back to the left branches when  $s_{AB \rightarrow I}$  switches from one to zero. Finally, since we want  $\mathcal{I}$  to map into itself, we choose

$$\tau_{f1}(k) = \frac{(k + D_c)P_{AB}}{\ln(s_L^{on}/\hat{s})}, \quad (25)$$

such that  $s_a([j + k + 1]P_{AB}) = \hat{s}$ . Note that by substituting  $\hat{s} = s_R^{off} \exp(-D_c P_{AB}/\tau_{f1})$  into (25), and solving for  $\tau_{f1}$ , we obtain

$$\tau_{f1} = \frac{kP_{AB}}{\ln(s_L^{on}/s_R^{off})} \quad (26)$$

In other words, with the choices of  $\tau_{r1}$  and  $\tau_{f1}$  that we have made, the trajectory with initial condition  $s_R^{off}$  is mapped back to  $\hat{s}$  at a time  $T_2^- = (j + k + 1)P_{AB}$ .

Next consider the trajectory  $s_b(t)$  where  $s_b(0) = \hat{s}$  and  $s_b(T_1) = s_L^{on}$ . To construct the Poincare map, we need  $s_b(T_2^-) \in \mathcal{I}$ . Thus we need  $\hat{s} < s_b(T_2^-) < s_R^{off}$ . That  $\hat{s} < s_b(T_2^-)$  follows by continuity since  $\hat{s} = s_a(T_2^-) < s_b(T_2^-)$ . The value  $s_b(T_2^-) < s_R^{off}$  since the time between  $s_a(T_2^-) = \hat{s}$  and  $s_R^{off}$  is  $D_c P_{AB}$ , whereas the time between  $s_a(T_2^-)$  and  $s_b(T_2^-)$  is less than  $D_c P_{AB}$ .

We have just shown that the trajectories whose  $s$  values are associated with the end points of the interval  $\mathcal{I}$  have  $s$  values mapped back to  $\mathcal{I}$  after a time  $T_2^-$ . Thus by continuity with respect to initial conditions, any trajectory with  $s(0) \in \mathcal{I}$  will end up with  $s(T_2^-) \in \mathcal{I}$  at a time when  $s_{AB \rightarrow I}$  will switch from one to zero. Therefore we can define a one-dimensional Poincare map  $\mathcal{P} : \mathcal{I} \rightarrow \mathcal{I}$  where  $\mathcal{P}(s) = s(T_2^-)$ .

To show that  $\mathcal{P}$  is a contraction mapping on  $\mathcal{I}$  let  $s_a(0) > s_b(0) \in \mathcal{I}$  be arbitrary. Let  $\Delta t$  denote the time on the right branch between them. At  $t = 0^+$ , the trajectories jump back to the left branch. Because of our choice of time constants  $\tau_{r1}(j)$  and  $\tau_{f1}(k)$ , the new time between these points is less than  $\Delta t$ . As before the time distance between these trajectories remains invariant as they evolve along the left branches, across the jump to the right branches and then back to  $\mathcal{I}$ . Since this new time is less than the original time,  $s_a(T_2^-) - s_b(T_2^-) < \alpha[s_a(0) - s_b(0)]$ , where  $\alpha < 1$

is dependent on  $\tau_{r1}$  and  $\tau_{f1}$ . Therefore  $\mathcal{P}$  is a contraction. As a result, there exists a unique value  $s_{Case\ 2}^* \in \mathcal{I}$  such that  $\mathcal{P}(s_{Case\ 2}^*) = s_{Case\ 2}^*$ . This value is asymptotically stable, and corresponds to a locally unique periodic solution of equations (1)-(3) and (5)-(6).

Equation (24) provides a condition on the time constants  $\tau_{f1}$  and  $\tau_{r1}$  for which the theorem holds. This condition can be translated into a relationship between the integers  $j$  and  $k$ . Namely, by substituting  $\hat{s} = s_R^{off} \exp(-D_c P_{AB}/\tau_{f1})$  into the fraction on the right hand side of (24), we see that the numerator of that expression reduces to  $D_c P_{AB}/\tau_{f1}$ , while the denominator reduces to

$$\ln \left( \frac{1 - s_R^{off} \exp(-D_c P_{AB}/\tau_{f1})}{1 - s_R^{off}} \right). \quad (27)$$

Now substituting (26) into (27) and then substituting the resulting expression into (24), we obtain

$$\tau_{r1} < \tau_{f1} \frac{(D_c P_{AB}/\tau_{f1})}{\ln \left( \frac{1 - s_R^{off} (s_R^{off}/s_L^{on})^{D_c/k}}{1 - s_R^{off}} \right)}. \quad (28)$$

Canceling  $\tau_{f1}$  from the right-hand side, substituting  $\tau_{r1}$  from (23) and solving for  $j$ , we obtain

$$j < \frac{D_c}{\ln \left( \frac{1 - s_R^{off} (s_R^{off}/s_L^{on})^{D_c/k}}{1 - s_R^{off}} \right)} \ln \left( \frac{1 - s_R^{off}}{1 - s_L^{on}} \right) + D_c - 1. \quad (29)$$

The right-hand side of (29) is what we called  $h(k)$  in the statement of the theorem.

**Remark:** Note that if (29) is not satisfied, then we cannot find time constants  $\tau_{r1}$  and  $\tau_{f1}$  for which a periodic solution satisfying Property A exists. However, by choosing  $\tau_{r1}$  and  $\tau_{f1}$  differently, we could instead have easily constructed a periodic solution whose  $s_1$  value passed through the bifurcation point  $s_R^{off}$  on the transition from right to left branches and which jumped back to the right branches with  $s_1 \in (s_L^{on}, s_L^{off})$  when  $s_{AB \rightarrow I}$  switched from one to zero.

### Case 3: Rhythmic MCN1 excitation with AB input to *Int1* absent

In Case 3, the input from *AB* to *MCN1* is present ( $\bar{g}_{AB \rightarrow M} > 0$ ) so that the *MCN1* elicited excitation to *LG* is rhythmic. Once again, we set  $\bar{g}_{AB \rightarrow I} = 0$  so that the  $V_I$  nullcline remains at a fixed position. In this case,  $s_2$  jumps instantaneously between  $s_{2min}$  and 1 while  $s_1$  increases with rate  $1/\tau_{r1}$  and decreases with rate  $1/\tau_{f1}$ , thus, causing the activity of  $s$  to be rhythmic.

Again, consider the nullclines. Suppose, the trajectory is at the stable fixed point on the right branches of the nullclines. When  $V_L > V_T$  and  $V_M > V_{Th(M)}$ , the  $V_L$  nullcline slowly shifts to the left due to  $s_1$  and then jumps further to the left when  $V_M < V_{Th(M)}$  due to  $s_2$ . The distance that the trajectory jumps depends on  $\tau_{f2}$  and the amount of time that *AB* inhibits *MCN1*. At this point,  $s_1$  is still slowly pushing the  $V_L$  nullcline to the left. When  $V_M$  goes back above  $V_{Th(M)}$ ,  $s_2$  forces the  $V_L$  nullcline to jump back to the right, returning the nullcline to the position it would have been

at if  $V_M$  had never gone below  $V_{Th(M)}$ . The trajectory eventually jumps to the fixed point on the left branches of the nullclines when **(a.)**  $s_2 = 1$  and  $s_1$  moves the fixed point to the position where the nullclines are tangent i.e.  $s_1 = s_R^{off}$  or **(b.)** when  $s_2 = s_{2min}$  and  $s_1$  decreases to  $s_R^{off}/s_{2min}$  moving the fixed point to the position where the nullclines are tangent or **(c.)** when  $s_2$  jumps to  $s_{2min}$  resulting in an instantaneous shift of the  $V_L$  nullcline past the point of bifurcation of the fixed points. Which case occurs depends on the speed at which  $s_1$  decreases ( $\tau_{f1}$ ), the amount of time the  $V_L$  nullcline spends being shifted to the left by  $s_2$  (the amount of time that  $s_{AB \rightarrow M}(t)$  spends in its active or inactive phases), and the timing of the instantaneous shifting of the  $V_L$  nullcline (timing of the  $AB$  input to  $M CN1$ ).

Once the trajectory has jumped to the left branches of the nullclines, the  $V_L$  nullcline slowly shifts to the right due to  $s_1$  and then instantaneously jumps to the left when  $V_M < V_{Th(M)}$ . Again, the trajectory eventually jumps to the fixed point on the right branches of the nullclines when **(a'.)**  $s_2 = 1$  and  $s_1$  moves the fixed point to the position where the nullclines are tangent (i.e.  $s_1 = s_L^{off}$ ); see Fig. 6A or when **(b'.)**  $s_2 = s_{2min}$  and  $s_1$  moves the fixed point to the position where the nullclines are tangent or when **(c'.)**  $s_2$  jumps to 1 resulting in an instantaneous shift of the  $V_L$  nullcline past the point of bifurcation of the fixed points; see Fig. 6B.

We shall establish the existence of the periodic solution which follows the subcases **(c)** and **(a')** above. Namely, the trajectory will jump from the left to the right branches through the bifurcation point  $s_L^{off}$  and from the the right to the left branches when  $s_2$  jumps down from 1 to  $s_{2min}$ ; see Fig. 11.

Recall that  $s(t) = s_1(t) * s_2(t)$  where we consider  $s_2(t) = 1$  when  $V_M \geq V_{Th(M)}$  and  $s_2(t) = s_{2min}$  when  $V_M < V_{Th(M)}$ . When  $s_{AB \rightarrow M}(t)$  jumps to 1,  $V_M$  instantaneously jumps below  $V_{Th(M)}$ . Thus,  $s_2(t)$  instantaneously jumps to  $s_{2min}$ . However, when  $s_{AB \rightarrow M}(t)$  jumps to 0,  $V_M$  requires a a small amount of time,  $T_C$ , to go above  $V_{Th(M)}$ . This amount of time is controlled by the value of  $C$  in equation (3). In our model, we set  $C = P_{AB}/20$  which fixes  $T_C$  to be approximately  $P_{AB}/20$ . Consequently, when  $s_{AB \rightarrow M}$  jumps to 0 at time  $t_0$ ,  $s_2$  jumps to 1 at time  $t_0 + T_C$ . Hence, for one cycle of  $AB$  activity,  $s_2(t) = s_{2min}$  for time  $D_c P_{AB} + T_C$  and  $s_2(t) = 1$  for time  $(1 - D_c)P_{AB} - T_C$ .

As in Case 2, we can construct a Poincare map  $\mathcal{P}$  of an interval of  $s$  values on the right branch,  $\mathcal{I} = [\tilde{s}, s_R]$ , into itself. Here  $s_R = s_1^R * 1$  where  $s_1^R = s_R^{off}/s_{2min}$ . Next let  $\tilde{s} = [s_1^R \exp([D_c - 1]P_{AB} + T_C)/\tau_{f1})] * 1$  so that the time distance between  $s_R$  and  $\tilde{s}$  is  $[1 - D_c]P_{AB} - T_C$ . Let  $\tilde{s}_1 = [s_1^R \exp([D_c - 1]P_{AB} + T_C)/\tau_{f1})]$ ; see Fig. 12.

We consider a trajectory  $s_a(t)$  where  $s_a(0^-) = s_1^R * s_2(0^-)$  and the trajectory is on the right branch of the nullclines. Let  $s_{AB \rightarrow M}(0^-) = 0$  and  $s_{AB \rightarrow M}(0^+) = 1$  so that  $s_2(0^-) = 1$  and  $s_2(0^+) = s_{2min}$ . Thus the trajectory jumps back to the left branch at  $t = 0^+$  when  $s_2$  jumps from 1 to  $s_{2min}$ . We then choose  $\tau_{r1}(j) = ((j + D_c)P_{AB} + T_C)/\ln([1 - s_1^R]/[1 - s_L^{off}])$  which guarantees that  $s_a((j + D_c)P_{AB} + T_C) = s_L^{off}$  so that the trajectory which starts at  $s_R$  at  $t = 0^-$  will leave the left branches of the nullclines through the bifurcation point  $s_L^{off}$  at  $t = (j + D_c)P_{AB} + T_C$ . Using the same argument as in Case 2 with an equivalent condition on  $\tau_{r1}$  as in (23), the trajectory  $s_b(t)$  with initial condition  $s_b(0) = \tilde{s}_1 * s_2(0)$  will be forced to reach  $s_L^{off}$  at a time  $T_1$  bounded between  $(j + D_c)P_{AB} + T_C$  and  $(j + 1)P_{AB}$ . Therefore, any trajectory with  $s(0) \in \mathcal{I}$  will also reach  $s_L^{off}$

during these times.

Next, we choose  $\tau_{f1}(k)$  so that  $s_a(t)$  gets mapped back to  $\mathcal{I}$ , particularly to  $\tilde{s}$  at the instant before  $s_{AB \rightarrow M}(t)$  jumps from 0 to 1. Therefore, we let  $\tau_{f1}(k) = \lceil [k + [1 - D_c]]P_{AB} - T_C \rceil / \ln(s_1^L / \tilde{s}_1)$ . Thus, at  $s_a(T_2^-)$  where  $T_2 = (k + j + 1)P_{AB}$ ,  $s_a(t)$  lies in  $\mathcal{I}$ . In a similar argument to that of Case 2, the trajectory  $s_b(t)$  with  $s_b(0) = \tilde{s}_1 * s_2(0)$  and  $s_b((j + 1)P_{AB}) = s_L^{off}$  will also lie in  $\mathcal{I}$  at  $t = T_2^-$  with  $\tilde{s} = s_a(T_2^-) < s_b(T_2^-) < s_R$ .

We define a one-dimensional Poincare map  $\mathcal{P}: \mathcal{I} \rightarrow \mathcal{I}$  where  $\mathcal{P}(s) = s(T_2)$ . The argument showing that  $\mathcal{P}$  is a contraction mapping on  $\mathcal{I}$  is the same as in Case 2. Consequently, there exists a locally unique, asymptotically stable value  $s_{Case\ 3}^* \in \mathcal{I}$  such that  $\mathcal{P}(s_{Case\ 3}^*) = s_{Case\ 3}^*$ .

**Remark:** The period of the constructed solutions in Cases 2 and 3 are both  $(j + k + 1)P_{AB}$ . Note that this occurs since the values of  $\tau_{r1}(j)$  and  $\tau_{f1}(k)$  are chosen to be different in both cases. In general, if *a priori*,  $\tau_{r1}$  is chosen to have the same value for both Cases 2 and 3, and similarly for  $\tau_{f1}$ , then the periods of Cases 2 and 3 need not be the same.

#### Case 4: Rhythmic MCN1 excitation with AB input to Int1 present

In case 4, the MCN1 to LG excitation is rhythmic ( $\bar{g}_{AB \rightarrow M} > 0$ ) and AB inhibits Int1 ( $\bar{g}_{AB \rightarrow I} < 0$ ). Consequently, the  $V_L$  nullcline shifts to the right and left with slow changes in  $s_1$  and with quick jumps of  $s_2$  between 1 to  $s_{2min}$ . The  $V_I$  nullcline jumps up and down instantaneously due to the  $s_{AB \rightarrow I}$  oscillations between 0 and 1.

Suppose the trajectory lies at the stable fixed point on the left branches of the  $V_L$  and  $V_I$  nullclines. Here,  $V_L < V_T$  which allows  $s_1$  to increase. When  $s_{AB \rightarrow M}(t) \rightarrow 1$ , the  $V_L$  nullcline jumps to the left. Similarly, when  $s_{AB \rightarrow I}(t) \rightarrow 1$ , the  $V_I$  nullcline jumps down. Recall that the time difference between when the  $V_L$  and  $V_I$  nullclines shift is controlled by the parameter  $m$ . For example, if  $m = 0$ , the  $V_L$  nullcline jumps to the left at the same time that the  $V_I$  nullcline jumps down. However if  $m = D_c P_{AB}$  then when the  $V_L$  nullcline jumps to the left, the  $V_I$  nullcline jumps up. This creates several possibilities for the length of the period.

To provide more insight into the role of  $m$ , suppose again that  $m = 0$ . In case 2, the jumping down of the  $V_I$  nullcline allowed the fixed point to bifurcate at smaller values of  $s_1$  relative to Case 1. However, for  $m = 0$ , whenever the  $V_I$  nullcline jumps down, the  $V_L$  nullcline jumps back to the left. If this jump to the left is large enough ( $1 - s_{2min}$  is large) and the jump down in the  $V_I$  nullcline is not extremely large, there will still exist a stable fixed point on the left branches. In this case, the trajectory will have to wait until  $s_2 = 1$  and  $s_1$  has grown large enough so that the fixed point occurs where the nullclines intersect tangentially for  $s_{AB \rightarrow I}(t) = 0$  (Fig. 6A) or when  $s_2$  jumps to 1 ( $s_{AB \rightarrow M}(t)$  jumps to 0) and the fixed point is instantaneously lost (Fig 6B). This is equivalent to (a.) and (c.) in Case 3. If the jump to the left of the  $V_L$  nullcline is not large and/or the jump down in the  $V_I$  nullcline is extremely large, the fixed point will be lost and the trajectory will immediately jump to the stable fixed point on the right branches of the nullclines. This is equivalent to case 2. The above result also extends to the situation in which  $m \in (0, T_C]$  because for  $0 < m \leq T_C$ , each time the  $V_I$  nullcline is in the downward position, the  $V_L$  nullcline

is shifted to the left. Therefore, the fixed point can not be lost until  $s_1$  grows large enough for the bifurcation to occur while  $s_2 = 1$ .

Next suppose that  $m = D_c P_{AB}$ . For  $m = D_c P_{AB}$ , each time the  $V_I$  nullcline is shifted in the downward position, the  $V_L$  nullcline remains to the right. Therefore, as opposed to the situation in which  $m = 0$ , the fixed point on the left branches of the nullclines can be lost due to the jump down of the  $V_I$  nullcline as in Case 2; see Fig. 6C. This same idea extends to values of  $m$  lying in a neighborhood,  $[R_1, R_2]$ , of  $D_c P_{AB}$  where  $R_1 > T_C$ ,  $R_2 < P_{AB}$ . For  $m \in [R_1, R_2]$ , there is always some amount of time for which the  $V_L$  nullcline is to the right while the  $V_I$  nullcline is shifted downward, thus allowing the fixed point to be lost at an earlier time than in Case 3.

We now consider the existence of a periodic solution for Case 4 with  $\tau_{r1}(j)$  and  $\tau_{f1}(k)$  defined as in Case 3. For  $m \in (0, T_C]$ , the periodic orbit will be defined in exactly the same way as Case 3. Consider the interval  $\mathcal{I}$  on the right branches as defined in Case 3 with  $s_{AB \rightarrow M}(0^-) = 0$  and  $s_{AB \rightarrow M}(0^+) = 1$  where  $s_{AB \rightarrow I}(t) = s_{AB \rightarrow M}(t - m)$ . Let  $s_a(t)$  be a trajectory with  $s_a(0) = s_1^R * s_2(0)$ . At  $t = 0^+$ ,  $s_{AB \rightarrow M}$  jumps to 1 and  $s_{AB \rightarrow I}$  remains equal to 0 because of the small delay  $m$ . Thus,  $s_2$  instantaneously jumping to  $s_{2min}$  forces the trajectory to the left branches in the same way as Case 3 because the  $V_I$  nullcline remains in the upward position at  $t = 0^+$ .

On the left branches with  $m \in (0, T_C]$ , each time  $s_{AB \rightarrow I} = 1$ , pushing the  $V_I$  nullcline down,  $s_2 = s_{2min}$  and the  $V_L$  nullcline is forced to the left. Thus, the trajectory with initial conditions as stated above can not jump from  $s_L^{on}$  as in Case 2 because each time the  $V_I$  nullcline is in its downward position, the  $V_L$  nullcline is shifted too far to the left for  $s$  to reach  $s_L^{on}$ . Therefore, the only time at which the fixed point of the left branches can be lost is when  $s_2 = 1$ . At  $t = (j + D_C)P_{AB}$ ,  $s_{AB \rightarrow M}(t)$  will jump to 0. However,  $s_2$  will not jump to 1, returning the  $V_L$  nullcline to the right, until  $t = (j + D_C)P_{AB} + T_C$ . Hence, at  $t = (j + D_C)P_{AB} + T_C$ ,  $s_{AB \rightarrow I}$  will already be equal to 0 since  $m \leq T_C$  and the trajectory will reach  $s_L^{off}$  tangentially as in Case 3. By choosing  $\tau_{f1}(k)$  as in Case 3,  $s_a(t)$  gets mapped to  $\tilde{s}$  at  $t = T_2^-$ .

With the same argument as in Case 3, the trajectory  $s_b(t)$  with  $s_b(0) = \tilde{s}_1 * s_2(0)$  and  $s_b(T_1) = s_L^{off}$  (where  $T_1 \in ((j + D_c)P_{AB} + T_C, (j + 1)P_{AB} + T_C)$ ) will also be mapped back to  $\mathcal{I}$  at  $t = T_2^-$  with  $\tilde{s} = s_a(T_2^-) < s_b(T_2^-) < s_R$ . Therefore, the one-dimensional Poincare map  $\mathcal{P}: \mathcal{I} \rightarrow \mathcal{I}$  where  $\mathcal{P}(s) = s(T_2)$  is established exactly as in Case 3. Thus for  $m \in (0, T_C]$ , the same arguments apply to show that there exists a unique, asymptotically stable periodic orbit in Case 4 and the periodic orbits of Cases 3 and 4 have the same period.

For  $m \in [R_1, R_2]$ , the period of the solution trajectories in Case 4 is locked to the period of  $s_{AB}$  oscillations and is, therefore, much shorter than the period of solution trajectories in Case 3. For  $m \in [R_1, R_2]$ , as stated above, on the left branches of the nullclines, the inhibition from  $AB$  to  $MCN1$  and to  $Int1$  is timed such that while the  $V_I$  nullcline is shifted downward,  $s_2 = 1$  which places the  $V_L$  nullcline to the right. Thus,  $s_1$  does not need to grow very large for the  $LG$  interburst to end. Once on the right branches, the burst of  $LG$  is ended during the first time  $s_2$  jumps to  $s_{2min}$  because  $s_1$  is sufficiently small (due to the fact that the  $LG$  interburst was ended for a small value of  $s_1$ ) to push the  $V_L$  nullcline far enough to the left to cause a loss in the fixed point. Similarly, once the solution trajectory is back to the left branches,  $s_1$  is large enough (because  $s_1$  did not decay a

long time on the right branches) so that the first jump in  $s_2$  back to 1 causes a loss in the fixed point and an end to the  $LG$  interburst. In the regions  $T_C < m < R_1$  and  $R_2 < m \leq P_{AB}$ , the solution trajectories remain periodic but are slightly more complicated to describe than those outside of these regions. For example, with the parameters fixed as above, when  $m \in (0, T_C]$  or  $m \in [R_1, R_2]$  consecutive  $LG$  bursts have exactly the same length as do consecutive  $Int1$  burst. However, when  $m$  is not in these regions, consecutive  $LG$  bursts and consecutive  $Int1$  bursts need not have the same length. Instead, several cycles of  $LG$  and  $Int1$  oscillations may be required before the  $LG$  (and  $Int1$ ) burst duplicates its length. We further explain this in the next section.

## 4 Determining the frequency of solutions

The period of the gastric mill rhythm can be computed as the sum of the  $LG$  burst and the  $LG$  interburst. During the interburst,  $s_1$  increases toward a maximum value which we shall denote  $s_{max}$ . Similarly, during the burst,  $s_1$  decreases toward a minimum value  $s_{min}$ . The periodic solutions in Cases 1-4 are then computed by finding out how much time is needed for  $s_1$  to evolve between the values of  $s_{max}$  and  $s_{min}$  on the left (during the interburst) and right (during the burst) branches. Using equation (5), it is straightforward to see that

$$P = \tau_{r1} \ln \left( \frac{1 - s_{min}}{1 - s_{max}} \right) + \tau_{f1} \ln \left( \frac{s_{max}}{s_{min}} \right) \quad (30)$$

The main question now is to determine the values  $s_{min}$  and  $s_{max}$  for each of the four cases. However, these values have already been determined in the construction of the periodic solutions above. In particular, for Case 1,  $s_{min} = s_R^{off}$  and  $s_{max} = s_L^{off}$ . For Case 2,  $s_{min} = s_{Case\ 2}^*$  and  $s_{max} = s_L^{on}$ . Note that  $s_L^{on} < s_L^{off}$ . Since the  $AB$  inhibition does not affect the right branches of the  $V_I$  nullcline too much,  $s_{Case\ 2}^* \approx s_R^{off}$ . Thus from equation (30), it is seen that the period of Case 2 is smaller than the period of Case 1 since the interburst of  $LG$  is shorter. This result is consistent with what was found by Manor et al. [16].

In Case 3,  $s_{min} = s_{Case\ 3}^*$  and  $s_{max} = s_L^{off}$ . Here  $s_{Case\ 3}^* \in [s_1^R \exp([D_c - 1]P_{AB} + T_C)/\tau_{f1}], s_1^R]$ . Finally, for Case 4, when  $m \in (0, T_c]$ , the periodic solution is different than the one constructed in Case 3 due to the shifting of the  $V_I$  nullcline. However, the period of the solutions in Cases 3 and 4 are the same because the values of  $s_{min}$  and  $s_{max}$  are the same. When  $m > T_c$ ,  $s_{min} \in [s_1^R \exp([D_c - 1]P_{AB} + T_C)/\tau_{f1}], s_1^R]$  and  $s_{max} \in [s_L^{on}, 1 + (s_L^{on} - 1)\exp(-(D_C P_{AB} + T_C)/\tau_{r1})]$ . Calculations of  $s_L^{off}$ ,  $s_R^{off}$ ,  $s_L^{on}$ , and  $s_R^{on}$  can be found in the Appendix. Using (30), we calculated values for the period for Cases 1 through 4. The analytic results are shown in Table 4 for Cases 1 through 3. There, we assumed for Case 2 that  $s_{min} = s_{Case\ 2}^*$  equals the average of  $s_R^{off}$  and  $s_R^{on}$ , while for Case 3,  $s_{min} = s_{Case\ 3}^* = s_R^{off}/s_{min}$ .

To confirm the validity of our analytic computations of the period using (30), we also numerically solved the set of equations in our model using XPP [11]. For Cases 1 through 3, these results are

Period Calculation for $\tau_{r1} = 4900$ msec, $\tau_{f1} = 4000$ msec		
Case	XPP Simulation	Analytic Formula
Case 1	Period=10,140 msec	Period=10,075 msec
Case 2	Period=5,000 msec	Period=4,688 msec
Case 3	Period=4,000 msec	Period=3794 msec

Table 1: Determining the period in Cases 1-3.

also given in Table 4 and show a close correlation between the calculation of the periods obtained analytically and numerically.

In Figure 13 we show the results of numerically calculating the period in Case 4 as a function of the delay parameter  $m$  with  $\tau_{r1} = 4900$  and  $\tau_{f1} = 4000$ . We see that for  $0 < m \leq 60$ , the period of the gastric mill rhythm for Case 3 is equal to that of Case 4. For  $350 < m \leq 760$ , the period of the gastric mill is equal to the period of  $AB$  activity. For  $60 < m \leq 350$ , there is a transition between having a period equal to that of case 3 to the much shorter period of  $AB$  activity. Similarly, for  $760 < m \leq 1000$ , the period begins to increase from 1 *sec* up to the period found in Case 3. As stated in the previous section, for  $60 < m \leq 350$  and for  $760 < m \leq 1000$ , it may take several cycles of  $LG$  and  $Int1$  oscillations before the  $LG$  and  $Int1$  burst lengths duplicate themselves. In these situations, the period is calculated as the time it takes to have two duplicate  $LG$  burst lengths divided by the number of cycles of  $LG$  oscillations occurring in that time. Figure 14 shows the gastric mill rhythm frequency as found in experiments by Wood et al. [29] for Cases 1-4. In this work, Wood et al. [29] artificially replicate the affect of  $AB$  activity to  $MCN1$  through computer controlled stimulation of  $MCN1$ . We see that for  $MCN1$  tonic, the frequency of the network is much higher when the  $AB$  input to  $Int1$  is present. For  $MCN1$  rhythmic, the frequency of the network is higher than when  $MCN1$  is tonic, however, there is no change in frequency when the  $AB$  input to  $Int1$  is added to the network. Figure 15 shows that our model accurately replicates the behavior of the actual gastric mill when  $0 < m \leq 60$ . Thus, the time mismatch between the pyloric and modulatory inputs to the gastric mill network is critical in establishing the correct frequency of the system.

## 5 Voltage Dependent $MCN1$ to $LG$ synapse

We now consider the effect of having voltage dependent coupling between  $MCN1$  and  $LG$  as opposed to a constant conductance synapse. Therefore, we return to equation (1) with  $g_s(V_L) = \bar{g}_s s_\infty(V_L)$  where  $s_\infty(V_L)$  is a sigmoidal gating function varying between 0 and 1 of the form

$$s_\infty(V) = \left(1 + \exp\frac{v_k - V_k}{k}\right)^{-1} \quad (31)$$

Due to this voltage dependency, the amount of excitation that *LG* receives from *MCN1* will depend upon the voltage of *LG* causing *LG* to receive less excitation when it, itself, is at a low voltage. Thus, when *LG* is in its interburst, the strength of the synapse will be weaker than in the voltage-independent case. When *LG* is in its burst, the strength of the synapse will increase to a value near to that of the previous section. As a consequence of the weaker conductance, in all of the Cases 1-4, the voltage dependency will increase the *LG* interburst duration because  $s$  will be required to grow to a larger value of  $s_{max}$  for the fixed point to be lost on the left branches of the nullclines. On the right branches of the nullclines, where *LG* is in its burst,  $s_\infty(V_L)$  is closer to 1 and, therefore, the burst duration of *LG* will not be affected as significantly as the interburst duration. However, the value of  $s_{min}$  will be slightly larger than when the conductance is not voltage dependent because as  $V_L$  decreases on the right branches,  $s_\infty$  also decreases. Therefore,  $s$  will not need to decrease as much to cause a loss of the fixed point and an end to the *LG* burst. The increase in the burst duration in all Cases 1-4, however, is larger than the decrease in interburst duration, resulting in an increase in the period of the solutions.

Upon relaxing the conditions that  $s_2$  and  $s_{AB \rightarrow I}$  jump between their minimum and maximum values instantaneously, in addition to increasing the period in Cases 1-4, the voltage dependency also increases the range of  $m$  over which the period of Case 3 equals the period of Case 4. When  $s_2$  rises and decays exponentially, for example,  $s_2$  moves continuously between its maximum and minimum values. Regardless of whether the conductance of the *MCN1* synapse to *LG* is constant or voltage dependent, the same condition must be satisfied for the period of Case 3 to equal the period of Case 4. This condition is that the fixed point on the left branches of the nullclines must be lost through  $s_L^{off}$ . That is,  $m$  must be chosen to live in a certain interval, say  $[M_1, M_2]$ , such that once  $s_1$  has grown large enough for  $s$  to reach  $s_L^{on}$  while  $s_{AB \rightarrow I} = 1$ , the  $V_L$  nullcline must be shifted far enough to the left by  $s_2$  when  $s_{AB \rightarrow M} = 1$  so that the saddle-node bifurcation does not occur at  $s_L^{on}$ . This situation persists until  $m$  becomes just larger than  $M_2$ . For  $M_2 < m < D_c P_{AB}$ , when  $s_{AB \rightarrow I}$  jumps to 1,  $s_{AB \rightarrow M}$  will already equal 1 so the  $V_L$  nullcline will already be to the left. However, before  $s_{AB \rightarrow I}$  returns 0,  $s_{AB \rightarrow M}$  will return 0. Consequently, the  $V_L$  nullcline will move to the right and the fixed point will not be lost through  $s_L^{on}$ .

When  $s_2$  rises and decays exponentially and  $m$  is slightly too large as described above, the loss of the fixed point through  $s_L^{on}$  often occurs while  $s_2$  is increasing toward 1 but has not yet reached its maximum value of 1. As a specific example, for  $\tau_{r1} = \tau_{f1} = 4000$ ,  $\tau_{r2} = \tau_{f2} = 325$ , and conductance of the *MCN1* to *LG* synapse constant ( $s_\infty(V_L) = 1$ ), the periods of Cases 3 and Cases 4 are the same for  $80 \leq m \leq 275$ . Note the lower bound on the interval is 80, not 0, since we have relaxed the condition that  $s_2$  and  $s_{AB \rightarrow I}$  change instantaneously. Once  $m > 275$ , the saddle-node bifurcation occurs through  $s_L^{on}$  instead of  $s_L^{off}$ , thus, causing the period of Case 4 to be smaller than the period of Case 3.

Now let us consider the effect of the voltage dependent conductance on the position of the  $V_L$  nullcline and, therefore, the role it plays in altering the interval of  $m$  over which the period in Case 3 equals that in Case 4. When  $LG$  is at a low voltage,  $s_\infty(V_L)$  is close to 0. Thus, on the left branches of the nullclines, when  $s_2$  decreases to its minimum, there is a much larger jump to the left of the  $V_L$  nullcline than when the conductance is constant. Furthermore, even as  $s_2$  increases back to 1, the  $V_L$  nullcline remains significantly far to the left until  $s_2$  gets very close to 1. Therefore, even as  $m$  increases to the range  $[M_2, D_c P_{AB}]$  where  $s_{AB \rightarrow M}$  jumps back to 0 (forcing  $s_2$  to increase back to 1) just before  $s_{AB \rightarrow I}$  returns to 0, the  $V_L$  nullcline will remain too far to the left (because it takes some amount of time for  $s_2$  to grow close enough to 1) for the saddle-node bifurcation to occur at  $s_L^{on}$ . Hence, the fixed point can not be lost through  $s_L^{on}$  while  $s_2$  is growing toward 1 as occurs when the conductance is constant. Furthermore, when  $s_{AB \rightarrow I}$  is a half-sine function as in Manor et al. [16], the  $V_I$  nullcline spends less time in the downward position. Consequently, there is again a smaller range of time for  $s$  to reach  $s_L^{on}$  when the  $V_I$  nullcline is in the downward position. Accordingly, a larger interval of  $m$  will exist for the fixed point on the left branches of the nullclines to be lost from  $s_L^{off}$  as in Case 3 when the conductance is voltage dependent than when the conductance is constant. Returning to the example in the above paragraph but now allowing the conductance of the  $MCN1$  to  $LG$  synapse to be voltage dependent, the interval of  $m$  for which the period of Case 3 equals the period of Case 4 extends to  $80 \leq m \leq 350$ . When  $s_2$  has instantaneous kinetics, there is no significant difference in the range of  $m$  between the voltage dependent and non-voltage dependent cases because  $s_2$  is always either equal to 1 or 0 so the fixed point on the left branches can not be lost while  $s_2$  is increasing toward 1.

## 6 Discussion

Networks involved in the generation of rhythmic movements often involve sets of reciprocally inhibitory neurons that rely on external stimuli to trigger oscillations or to set the appropriate frequency of the rhythm [2][6][25]. It has been observed that while tonic stimulation may often times be sufficient to elicit the network activity, the synaptic inputs driving these circuits are themselves rhythmic [5][28]. An example of this is the pyloric network of the lobster stomatogastric nervous system which receives rhythmic excitatory input. The same effects of this rhythmic input, however, can be achieved through tonic firing of the input cells [19].

Furthermore, it has been noted in many cases that although one source of input is sufficient to produce oscillations in the target network, multiple inputs act together to generate and set the frequency of the network. The heartbeat of the leech, for example, is controlled by pairs of reciprocally inhibitory neurons. These oscillators receive inhibitory input from interneurons that act to coordinate the activity of the separate oscillators [7]. Einum et al [10] also recently showed that reticulospinal neurons of the lamprey brain stem receive both excitatory and inhibitory rhythmic inputs from neurons in the spinal cord during locomotor activity.

The stomatogastric nervous system of the crab provides a good example of a system containing

a conditional oscillator, made up of an asymmetric half-center oscillator, that receives multiple rhythmic synaptic inputs in order to oscillate. The interactions between the gastric mill network and pyloric network have been extensively studied to show how each network acts to influence one another's frequency [3, 4, 27]. In their work, Nadim et al. [21] and Manor et al. [16] considered how the frequency of the gastric mill rhythm is generated and controlled in the presence of both a slow modulatory input and a much faster periodic input.

In this paper, we continued upon the work of Nadim et al. [21] and Manor et al. [16] with the aim of mathematically explaining the experimental results of Wood et al. [29]. Specifically, we addressed the effect of having a rhythmic modulatory input versus a tonic input drive the network oscillations and then how two simultaneous rhythmic inputs work together to determine the network frequency. In order to do this, we incorporated the rhythmicity of the modulatory projection neuron on the existing model of Manor et al. [16]. We then derived conditions on the parameters that dictate the strength and rise and decay rates of the synaptic currents to ensure the existence, local uniqueness, and stability of periodic solutions. Once periodic orbits were established, we derived a formula to estimate the period of such orbits in the presence and absence of pyloric input to the gastric mill network for both tonic and rhythmic modulatory input.

Using geometric, singular perturbation theory, the five-dimensional system is reduced to studying the position of the nullclines in the  $V_L - V_I$  phase plane with the variable controlling the amount of excitation provided from the modulatory projection neuron to the gastric mill treated as a parameter. The model shows that the rhythmicity of the projection neuron speeds the gastric mill rhythm by allowing the loss of a relevant stable fixed point to occur at an earlier time than when the input is tonic. Thus, although tonic stimulation of the gastric mill network can generate the gastric mill rhythm, the rhythmicity of the input speeds the frequency of the gastric mill rhythm as in seen by Wood et al. [29].

In the presence of the rhythmic modulatory excitation and fast pyloric inhibition, the timing of the jump of the  $V_L$  and  $V_I$  nullclines in response to the  $AB$  input to  $Int1$  and to  $MCN1$  determines how the loss of the stable fixed point on either the left or right branches of the nullclines will occur. This, in turn, determines the length of the  $LG$  and  $Int1$  interburst and burst durations. The frequency calculated from this model, matches the experimental results of Wood et al. [29] only when there is either a short delay or no delay in the timing of the two pyloric inputs. In this case, the position of the  $V_L$  nullcline in response to the  $AB$  inhibition of  $MCN1$  prevents the  $AB$  disinhibition of  $LG$  from ending the  $LG$  interburst. Thus, it is as if there is only one source of synaptic input to the gastric mill network. Therefore the analysis gives a possible biological mechanism by which the effect of the two simultaneous synaptic inputs can overlap to result in a frequency equivalent to that of having only one of the inputs present. If the delay is chosen differently, however, the gastric mill rhythm has a higher frequency than when only one of the inputs is present because the position of the  $V_L$  nullcline does not prevent  $LG$  from getting disinhibited by  $AB$ . Thus, the timing of the inputs can be used as a tool to switch between different modes of firing frequency. This may serve as a means by which different chewing patterns are elicited.

The biological and mathematical reductions of the full, compartmental model of Nadim et al.

[21] implemented by Manor et al. [16] and extended to this work have proven to be instrumental in understanding the frequency regulation of the gastric mill rhythm and intercircuit coordination with the pyloric network. The reduced model neglects all intrinsic currents and models the neurons in this network as having only leak currents. Despite the severity of the reductions, the reduced network is able to accurately model the gastric mill rhythm and its response to the slow, modulatory and fast, pyloric inputs. In [1], Ambrosio shows that the results found through analysis of the reduced model do extend to the full model. The reduced model, also, clarifies the relationship between the synaptic rise and decay times of the  $AB$  inhibition of  $MCN1$  in the full model necessary to obtain the experimentally observed behavior. Furthermore, because the reduced model consisting of passive neurons is able to accurately reproduce the qualitative behavior of the full model, it is clear that the synaptic currents and their timing with respect to one another are the primary components responsible for the dynamics of the gastric mill rhythm. This is important because the ability to ignore the intrinsic dynamics of each of the neurons results in significantly simpler equations. This makes mathematical analysis much more accessible. For example, in this network, we were able to reduce the study of our system to the study of a one-dimensional map. This then allowed us to define a Poincare map to prove the existence and stability of periodic orbits which would have been much more difficult if working in higher dimensions.

Such techniques can be extended to numerous other models whose intrinsic and synaptic currents act on multiple timescales. The leech heartbeat mentioned above, for example, is controlled by a network of reciprocally inhibitory neurons that are dependent upon both synaptic and intrinsic currents. These currents exhibit both fast and slow dynamics and a biophysically detailed model of this network exists [22][23]. Although this model was shown to accurately reproduce many of the behaviors of the real network, some properties have not yet been able to be reproduced and the significance of certain currents is not yet clearly understood. In particular, the reduced model may give some insight into the extreme sensitivity of the oscillations to the leak current parameters seen in the more detailed models. More generally, a reduced version of this model that is more amenable to mathematical investigation in terms of allowing for a reduction to lower dimensions and phase plane analysis is likely to more clearly reveal many of the underlying properties responsible for such things as the network oscillations and sensitivity to synaptic and intrinsic inputs.

## Appendix A

We describe how to calculate the bifurcation points  $s_L^{off}$ ,  $s_L^{on}$ ,  $s_R^{off}$  and  $s_R^{on}$ . On the left branch, when the two nullclines intersect tangentially for  $s_{AB \rightarrow I}(t) = 0$ , then  $s = s_L^{off}$ . Similarly, on the right branch when  $s = s_R^{off}$  and  $s_{AB \rightarrow I}(t) = 0$  the fixed point occurs when the two nullclines intersect tangentially. Thus, to calculate  $s_L^{off}$  and  $s_R^{off}$ , we use the equations for the  $V_L$  and  $V_I$  nullclines:

$$V_L = F(V_I, s) = \frac{g_{leak,L}E_{leak,L} + \bar{g}_{I \rightarrow L}n_\infty(V_I)E_{I \rightarrow L} + \bar{g}_s s E_{exc}}{g_{leak,L} + \bar{g}_{I \rightarrow L}n_\infty(V_I) + \bar{g}_s s} \quad (32)$$

and

$$V_I = G(V_L, s_{AB \rightarrow I}) = \frac{g_{leak,I} E_{leak,I} + \bar{g}_{L \rightarrow I} n_\infty(V_L) E_{L \rightarrow I} + \bar{g}_{AB \rightarrow I} s_{AB \rightarrow I}(t) E_{AB \rightarrow I}}{g_{leak,I} + \bar{g}_{L \rightarrow I} n_\infty(V_L) + \bar{g}_{AB \rightarrow I} s_{AB \rightarrow I}(t)} \quad (33)$$

We rewrite (33)

$$\begin{aligned} V_L &= -k_L l n \left[ -1 + \frac{\bar{g}_{L \rightarrow I} (V_I - E_{L \rightarrow I})}{-g_{leak,I} (V_I - E_{leak,I}) - \bar{g}_{AB \rightarrow I} s_{AB \rightarrow I}(t) (V_I - E_{AB \rightarrow I})} \right] + v_L \\ &\doteq \tilde{G}(V_I, s_{AB \rightarrow I}) \end{aligned} \quad (34)$$

We find the equation for the tangent point by solving

$$\frac{dF(V_I, s)}{dV_I} = \frac{d\tilde{G}(V_I, s_{AB \rightarrow I})}{dV_I} \quad (35)$$

From (35), we obtain a quadratic equation for  $s$

$$\begin{aligned} \bar{g}_s^2 s^2 &+ s \left[ 2\bar{g}_s [g_{leak,L} + \bar{g}_{I \rightarrow L} n_\infty(V_I)] - \bar{g}_{I \rightarrow L} E_{I \rightarrow L} \frac{dn_\infty(V_I)}{dV_I} g_s \frac{dV_I}{d\tilde{G}} \right. \\ &+ \left. \bar{g}_{I \rightarrow L} \frac{dn_\infty(V_I)}{dV_I} \bar{g}_s E_{exc} \frac{dV_I}{d\tilde{G}} \right] + [g_{leak,L} + \bar{g}_{I \rightarrow L} n_\infty(V_I)]^2 \\ &- \frac{dV_I}{d\tilde{G}} \left[ g_{leak,L} \bar{g}_{I \rightarrow L} E_{I \rightarrow L} \frac{dn_\infty(V_I)}{dV_I} - \bar{g}_{I \rightarrow L} \frac{dn_\infty(V_I)}{dV_I} [g_{leak,L} E_{leak,L} \right. \\ &+ \left. \bar{g}_{I \rightarrow L} n_\infty(V_I) E_{I \rightarrow L}] \right] = 0 \end{aligned} \quad (36)$$

Next, we use the restriction that the tangency of the nullclines must occur at a fixed point. Therefore, we use the equations for the  $V_L$  and  $V_I$  nullclines to determine the fixed points for different values of  $s$ . We rewrite (32) as

$$s = (-g_{leak,L} (V_L - E_{leak,L}) - \bar{g}_{I \rightarrow L} n_\infty(V_I) (V_L - E_{I \rightarrow L})) / g_s (V_L) (V_L - E_{exc}) \quad (37)$$

We then plug (34) into (37) to obtain an equation for  $s = S(V_I)$ . This equation says that for each value of  $V_I$  there exists a unique value of  $s$  which will cause the nullclines to intersect. We then check to see if this value of  $s$  also satisfies the quadratic equation (36). If it does, we have found a bifurcation point of the fast subsystem. There are two values of  $s$  which satisfy the equations above. The smaller valued one corresponds to  $s_L^{off}$ , the larger corresponds to  $s_R^{off}$ . To calculate  $s_L^{on}$  and  $s_R^{on}$ , we follow the same steps as above but with  $s_{AB \rightarrow I}(t) = 1$  in (33).

We used the analytically calculated values of the bifurcation points to obtain the results given in section 4. In Case 2, we assume that  $s_{max} = s_L^{on}$  and  $s_{min}$  is the average of  $s_R^{off}$  and  $s_R^{on}$ . In Case 3, we assume the maximum value that  $s$  takes is  $s_L^{off}$  while  $s_2 = 1$  which implies that  $s_{max} = s_L^{off}$  and the minimum value  $s$  assumes is  $s_R^{off}$  when  $s_2 = s_{2min}$ . Therefore,  $s_{min}$  is  $\frac{s_R^{off}}{s_{2min}}$ . In Case 4, the

values of  $s_{max}$  and  $s_{min}$  depend on  $m$ . For  $m$  near 0, for example,  $s_{max}$  and  $s_{min}$  are calculated as in Case 3.

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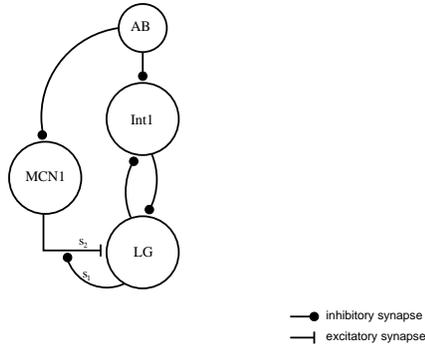


Figure 1: Schematic representation of the *MCN1* and *AB* elicited gastric mill rhythm.

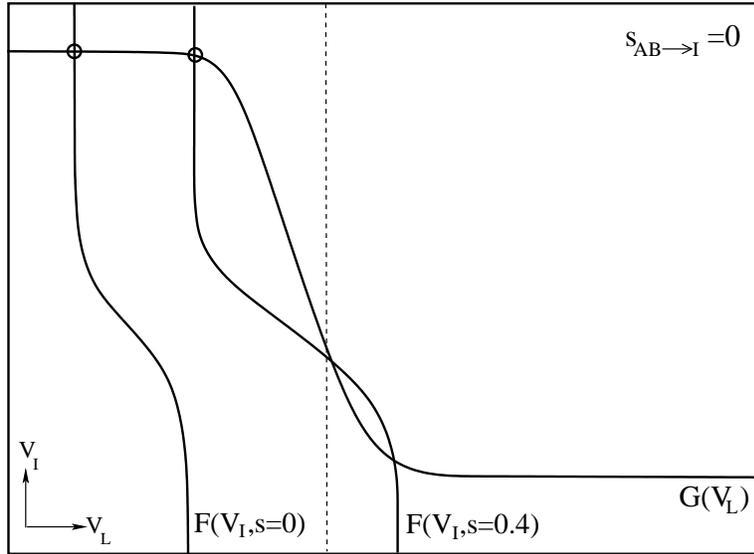


Figure 2: The  $V_L$  and  $V_I$  nullclines plotted in phase space for two different values of  $s(t)$ . The  $V_L$  nullcline is labeled  $F$  and the  $V_I$  nullcline is labeled  $G$ . When  $s = 0$ , the  $V_L$  nullcline is to the far left. As  $s$  increases, the  $V_L$  nullcline shifts to the right.

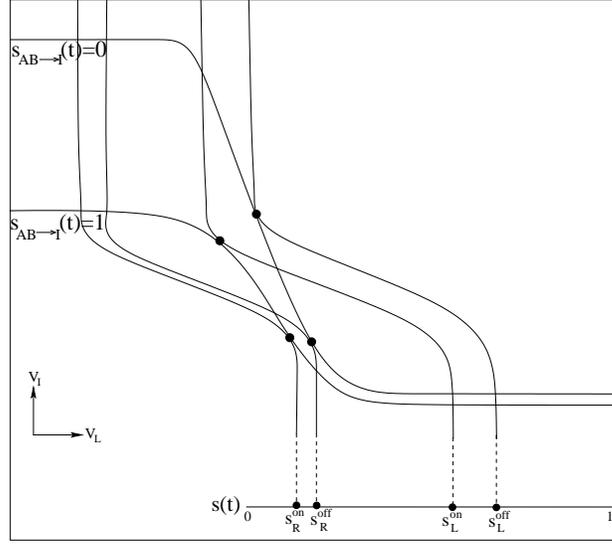


Figure 3: Position of the  $V_L$  and  $V_I$  nullclines for  $(s, s_{AB \rightarrow I}) = (s_R^{on}, 1), (s_R^{off}, 0), (s_L^{on}, 1),$  and  $(s_L^{off}, 0)$ . At these four points, the nullclines intersect tangentially, resulting in the loss (or gain) of two fixed points through a saddle-node bifurcation.

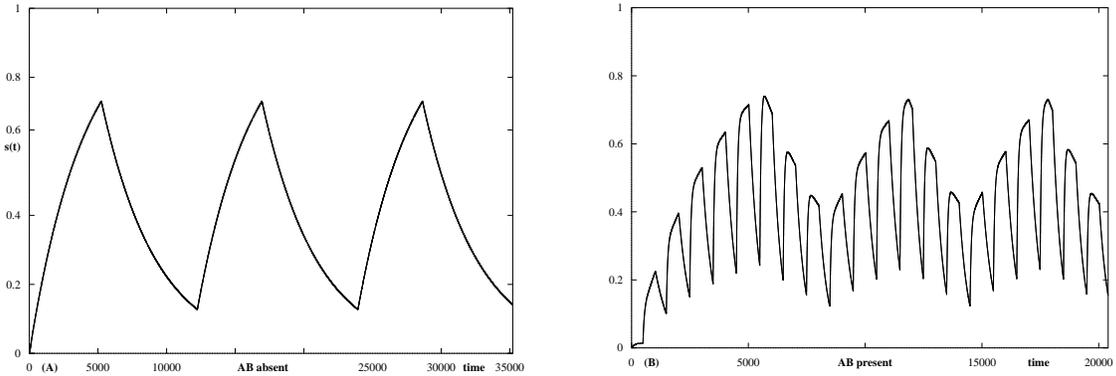


Figure 4: (A)  $s$  versus time for the case when the  $MCN1$  to  $LG$  excitation is constant ( $s_2 = 1$ ).  $s$  increases to 1 with rate  $1/\tau_{r1}$  when  $V_L \leq V_T$  and  $s$  decreases to 0 with rate  $1/\tau_{f1}$  when  $V_L > V_T$ . (B)  $s$  versus time for the case when the  $MCN1$  to  $LG$  excitation is bursting. When  $V_L \leq V_T$ ,  $s_1$  increases to 1 with rate  $1/\tau_{r1}$  and  $s_2$  jumps between 1 and  $s_{2min}$  when  $s_{AB \rightarrow M}(t)$  jumps between 0 and 1. When  $V_L > V_T$ ,  $s_1$  decreases to 0 with rate  $1/\tau_{f1}$  and  $s_2$  jumps between 1 and  $s_{2min}$  when  $s_{AB \rightarrow M}(t)$  jumps between 0 and 1.

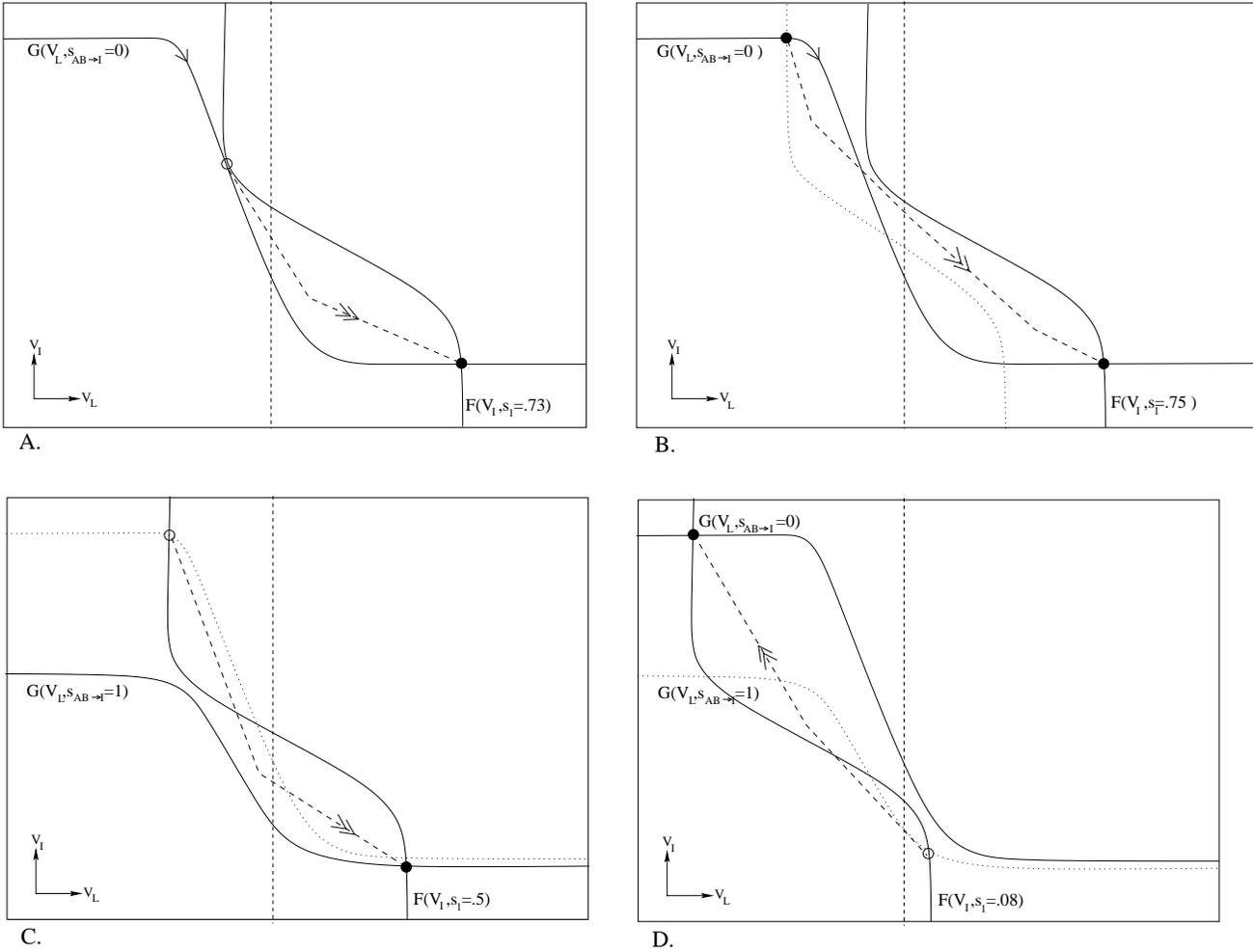


Figure 5:  $V_L$  and  $V_I$  nullclines for different values of  $s$  when  $s_{AB \rightarrow I}(t) = 0$ . The dotted horizontal line is  $V_L = V_T$ . When  $s = 0.5$ , the fixed point is on the left branches of the  $V_L$  and  $V_I$  nullclines ( $V_L$  nullcline dotted). When  $s = s_L^{off}$ , the fixed point undergoes a saddle-node bifurcation at  $\bullet$ . The trajectory is therefore, forced to jump to the stable fixed point on the right branches of the nullclines where  $V_L > V_T$ .

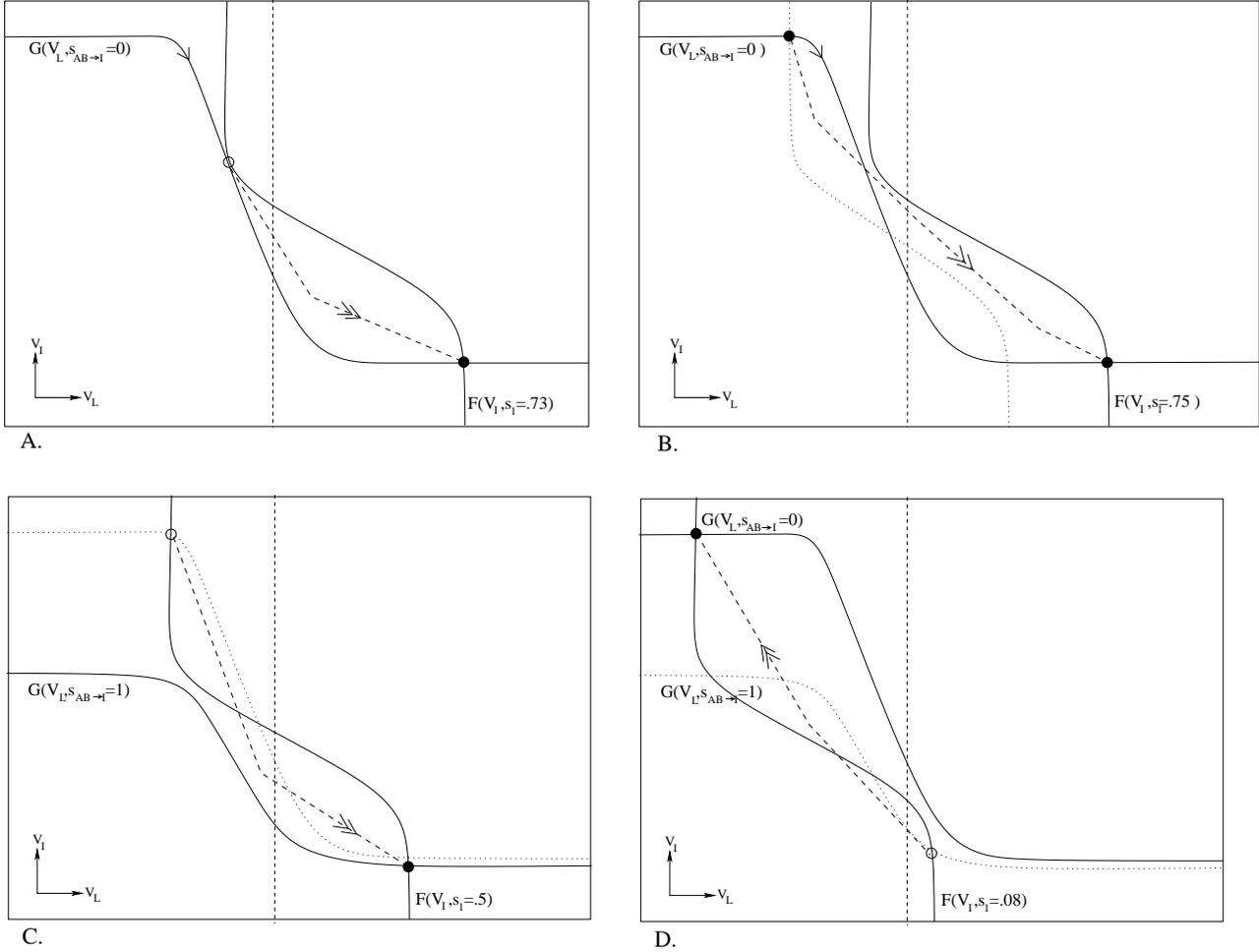


Figure 6: For *MCN1* rhythmic, fixed points can be lost in two ways: through a saddle-node bifurcation as  $s$  slowly changes due to  $s_1$  or when  $s_2$  changes on the fast timescale. (A.) On the left branches of the nullclines,  $s_2 = 1$  and  $s_1$  moves the  $V_L$  nullcline to the right resulting in a saddle-node bifurcation of the fixed point at  $\circ$  once  $s = s_L^{on}$ . The trajectory is forced to jump to the stable fixed point on the right branches of the nullclines (shown by  $\bullet$ ). This can also occur when  $s_{AB \rightarrow I} = 1$  and  $s_1$  reaches  $s_L^{on}$ . (B.) When  $s_2$  jumps from  $s_{2min}$  to 1, the fixed point on the left branches of the nullclines is instantaneously lost because  $s > s_L^{off}$  and the trajectory will jump to the fixed point on the right branches of the nullclines (shown by  $\bullet$ ). This can also occur when  $s_{AB \rightarrow I} = 1$  and  $s_2$  jumps to 1 when  $s > s_L^{off}$ . (C.) When *MCN1* is rhythmic and  $s_{AB \rightarrow I}(t)$  oscillates between 0 and 1, the fixed point can be lost in another way. While  $s_2 = 1$  and  $s_{AB \rightarrow I}(t)$  jumps from 0 to 1, the fixed point on the left branches of the nullclines (shown by  $\circ$ ) is instantaneously lost because  $s > s_L^{on}$  and the solution trajectory is forced to jump to the fixed point on the right branches of the nullclines ( $\bullet$ ). (D.) On the right branches of the nullclines for *MCN1* tonic, when  $s_{AB \rightarrow I}$  jumps from 1 to 0, the fixed point (shown by  $\circ$ ) is instantaneously lost because  $s_R^{on} < s < s_R^{off}$  and the solution trajectory must jump to the fixed point on the left branches of the nullclines ( $\bullet$ ).

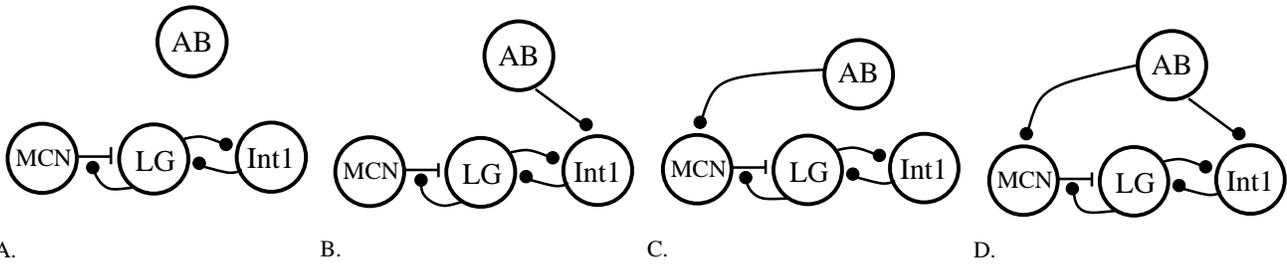


Figure 7: Circuitry for cases 1-4. (A.) The  $AB$  input to  $MCN1$  and to  $Int1$  is absent. (B.) The  $AB$  input to  $Int1$  is present but the  $AB$  input to  $MCN1$  is absent. (C.) The  $AB$  input to  $MCN1$  is present but the  $AB$  input to  $Int1$  is absent. (D.) The  $AB$  input to  $Int1$  and to  $MCN1$  is present.

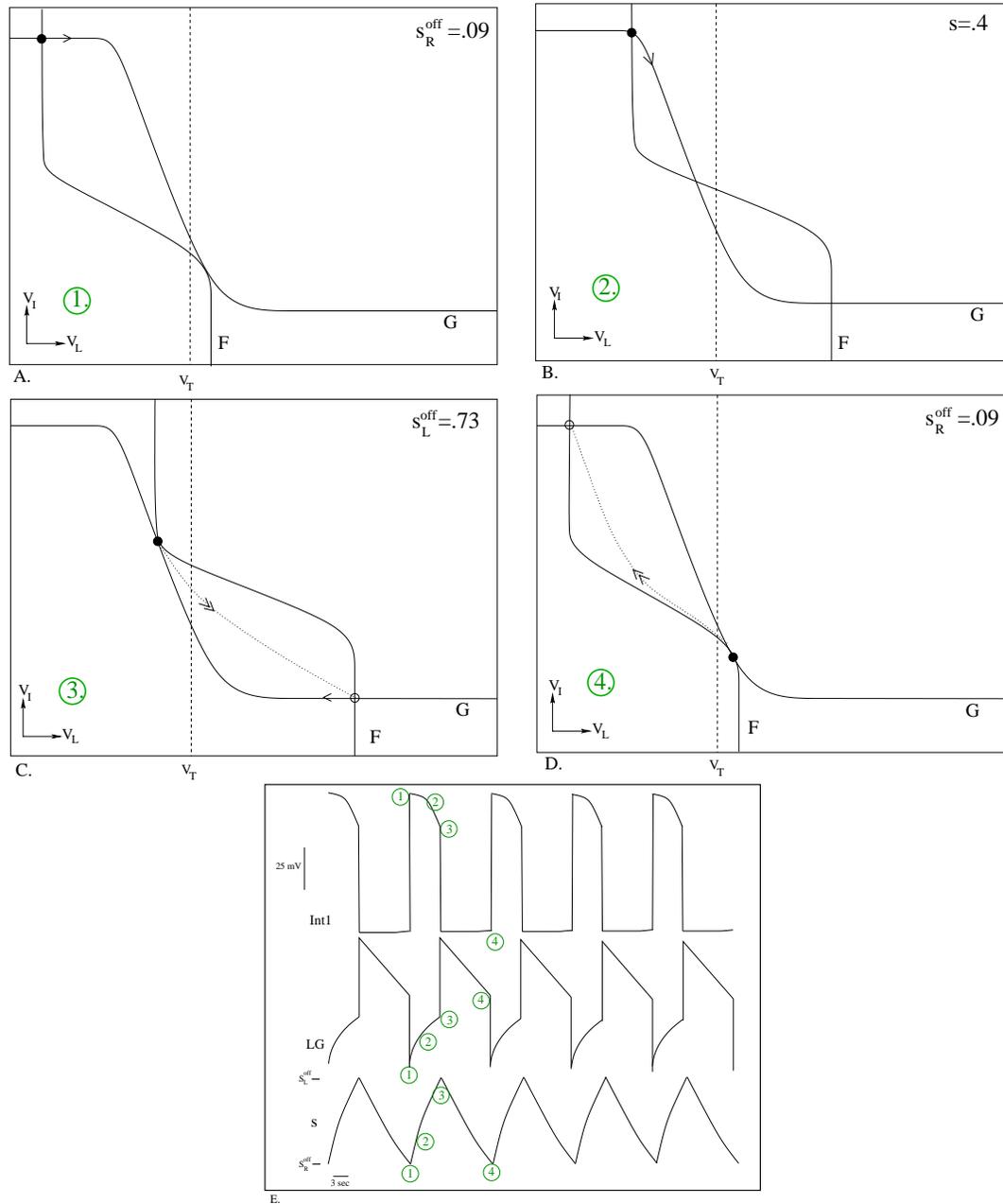


Figure 8: Plots of the  $V_I$  and  $V_L$  nullclines for different values of  $s$  in case 1.  $\bullet$  marks the position of the trajectory at a stable fixed point,  $\circ$  marks the point to which the trajectory will jump when the stable fixed point bifurcates (solid square), and the dotted lines indicate the position of the trajectory during the jumps. The arrows show the direction that the trajectory is moving and the dashed vertical line marks the threshold,  $V_T$ . In (A.),  $s = s_R^{off}$  which is the point at which the saddle-node bifurcation occurs on the right branches of the nullclines. Thus, the trajectory will be forced to lie on the stable fixed point on the left branches of the nullclines. (B.) On the left branches of the nullclines,  $V_L < V_T$  which means that  $s$  will begin to increase toward 1. (C.)  $s$  continues to increase until it reaches the value  $s_L^{off}$  where the stable fixed point on the left branches of the nullclines undergoes a saddle-node bifurcation. The trajectory is, therefore, forced to jump to the fixed point on the right branches of the nullclines. This jump causes  $s$  to cross above  $V_T$  so that  $s$  begins to decrease. (D.)  $s$  has decreased to  $s = s_R^{off}$  at which the fixed point on the right branches is again lost through a saddle-node bifurcation and the trajectory is forced to return to the upper left branches of the nullclines. Therefore, the solution trajectory lies on a periodic orbit. (E.) The voltage traces of  $LG$  and  $Int1$  are plotted as  $s$  increases and decreases between  $s_L^{off}$  and  $s_R^{off}$ .

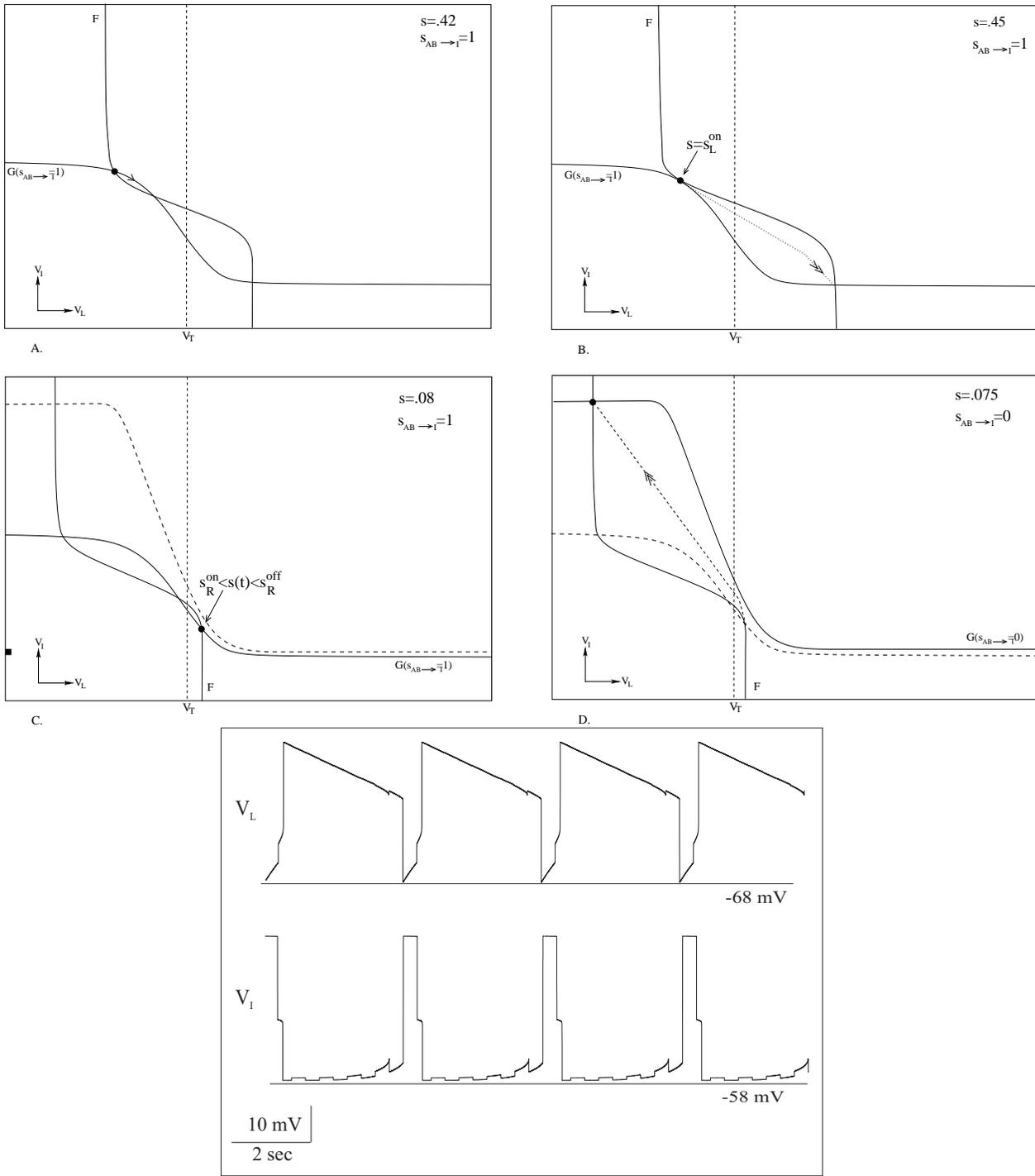


Figure 9: In Case 2, a periodic orbit obeying property A jumps from the left to right branches and from the right to left branches of the nullclines in the following way. (A.) The trajectory lies at the stable fixed point (●) on the left branches of the nullclines where  $s_{AB \rightarrow I} = 1$  and  $s_1$  increases toward 1. (B.) While  $s_{AB \rightarrow I}$  remains equal to 1,  $s_1$  increases sufficiently large for a saddle-node bifurcation to occur through  $s_L^{on}$ . (C.) On the right branches of the nullclines, while  $s_{AB \rightarrow I} = 1$ ,  $s_1$  decreases below  $s_R^{off}$  but does not reach  $s_R^{on}$ . (D.) As soon as  $s_{AB \rightarrow I}$  jumps back to 0, the fixed point on the right branches of the nullclines is instantaneously lost because  $s_1 < s_R^{off}$ . (E.) Voltage traces of  $V_L$  and  $V_I$  for a periodic orbit obeying property A

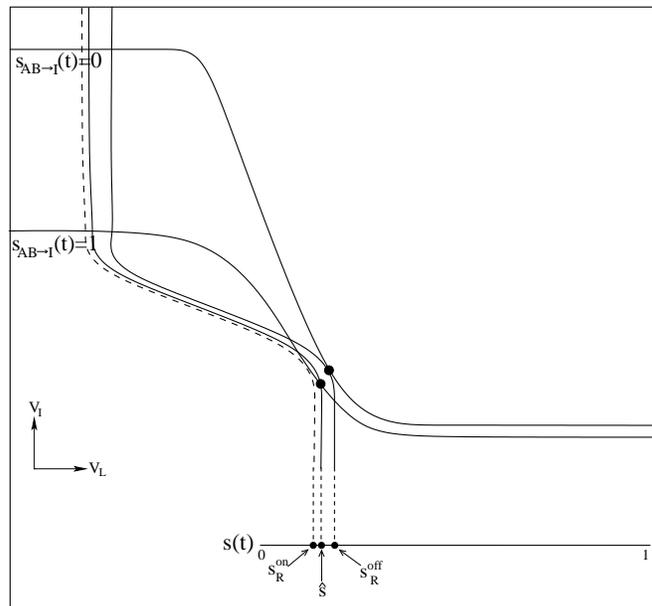
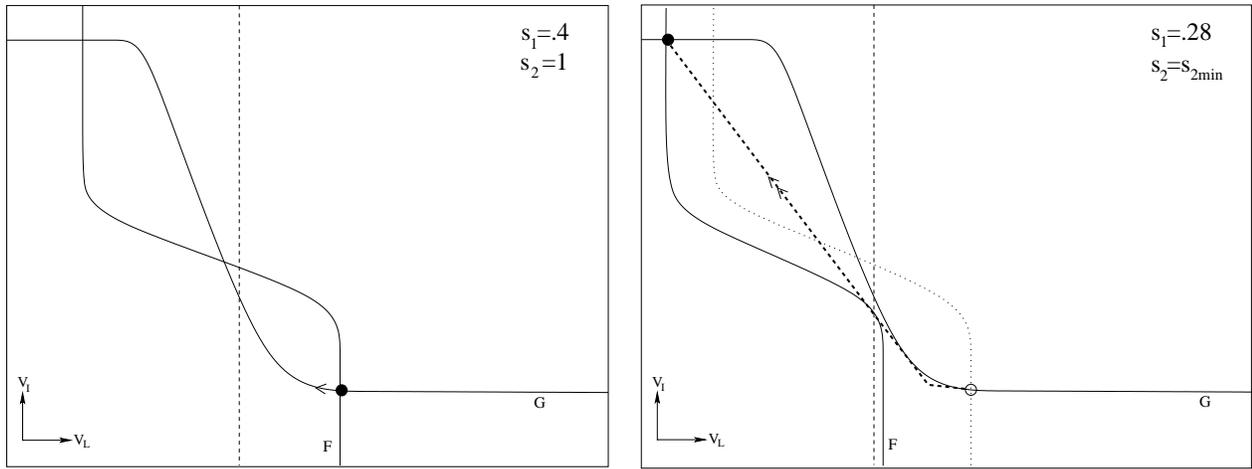
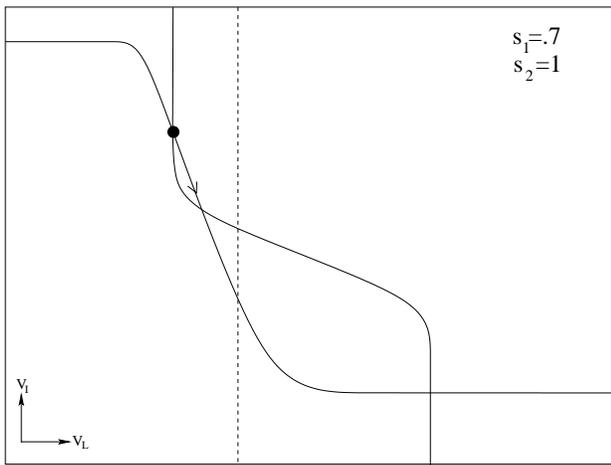


Figure 10: To define the Poincaré map for Case 2, we let  $I = [\hat{s}, s_R^{off}]$  where  $\hat{s} = s_R^{off} \exp(-D_c P_{AB} / \tau_{f1})$ . Note that  $\tau_{f1}$  is chosen sufficiently large to ensure that  $\hat{s} > s_R^{on}$ .

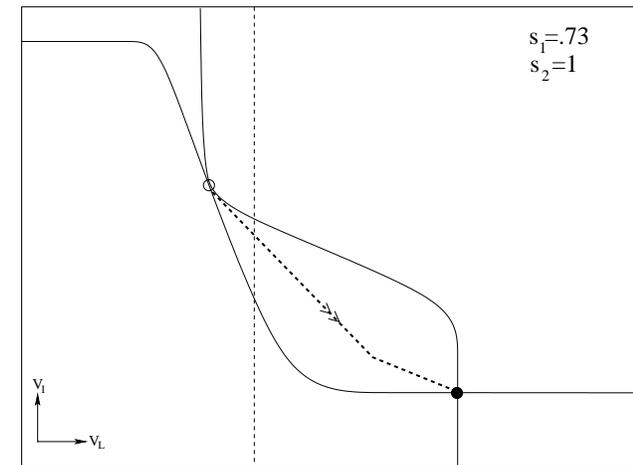


A.

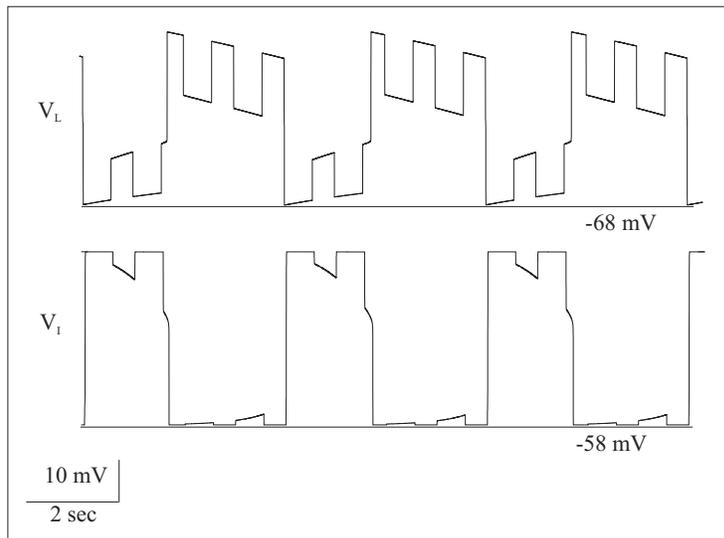
B.



C.



D.



E.

Figure 11: Case 3 solution trajectory and nullclines. (A.) The trajectory lies at the stable fixed point ( $\bullet$ ) on the right branches of the nullclines where  $s_{AB \rightarrow I} = 0$  and  $s_2 = 1$ . (B.) When  $s_2$  jumps to  $s_{2min}$ ,  $s$  instantaneously goes below  $s_R^{off}$  and the fixed point is lost. (C.)-(D.) On the left branches of the nullclines, the fixed point is lost while  $s_2 = 1$  and  $s_1$  increases large enough for the saddle-node bifurcation to occur.

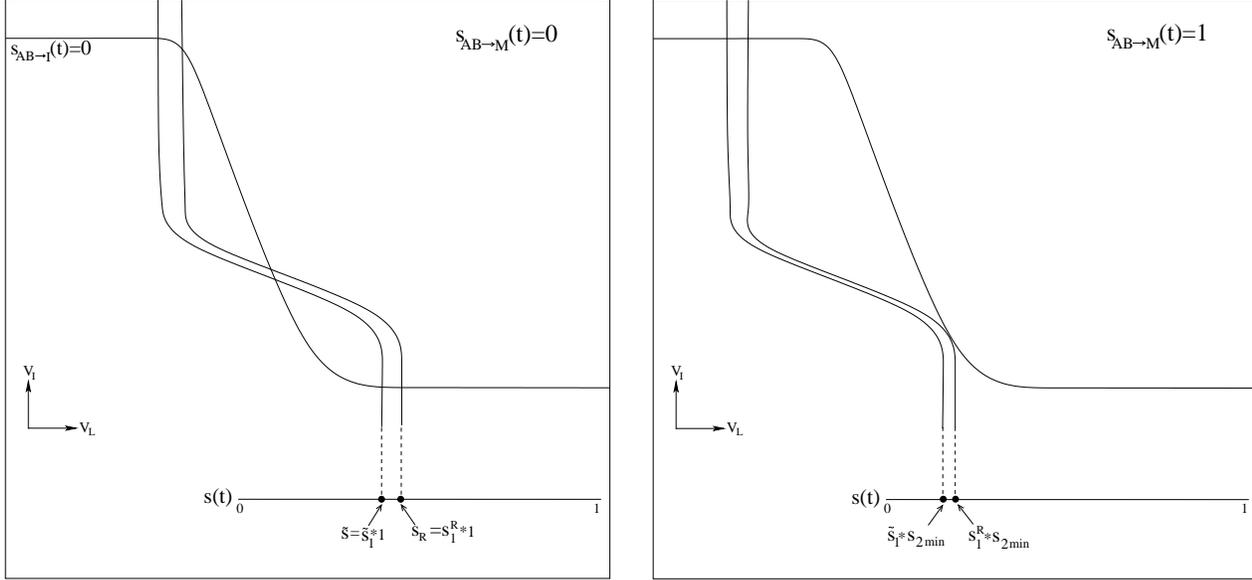


Figure 12: (A.) To define the Poincare map for Case 3, we let  $I = [\tilde{s}, s_R]$  where  $s_R = s_1^R * 1$ ,  $s_1^R = s_R^{off} / s_{2min}$  and  $\tilde{s} = [s_1^R \exp([(D_c - 1)P_{AB} + T_C] / \tau_{f1}) * 1$ . (B.) For  $s = s_R$ , when  $s_2$  jumps from 1 to  $s_{2min}$ ,  $s$  jumps to  $s_R^{off}$ . Similarly, for  $s = \tilde{s}$ , when  $s_2$  jumps to  $s_{2min}$ ,  $s$  jumps to  $\tilde{s}_1 * s_{2min}$ .

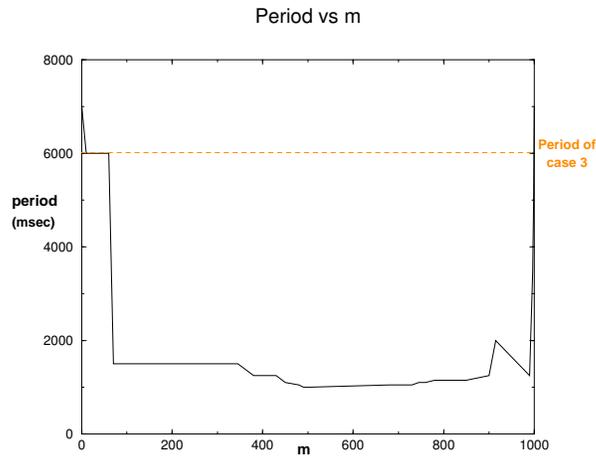


Figure 13: The period of the gastric mill cycle is plotted for different delays,  $m$ , in Case 4. The period of Case 3 is marked by the dashed line. There is a small range of delays,  $0 < m \leq 60$ , for which the period of the gastric mill rhythm is equal for Cases 3 and 4.

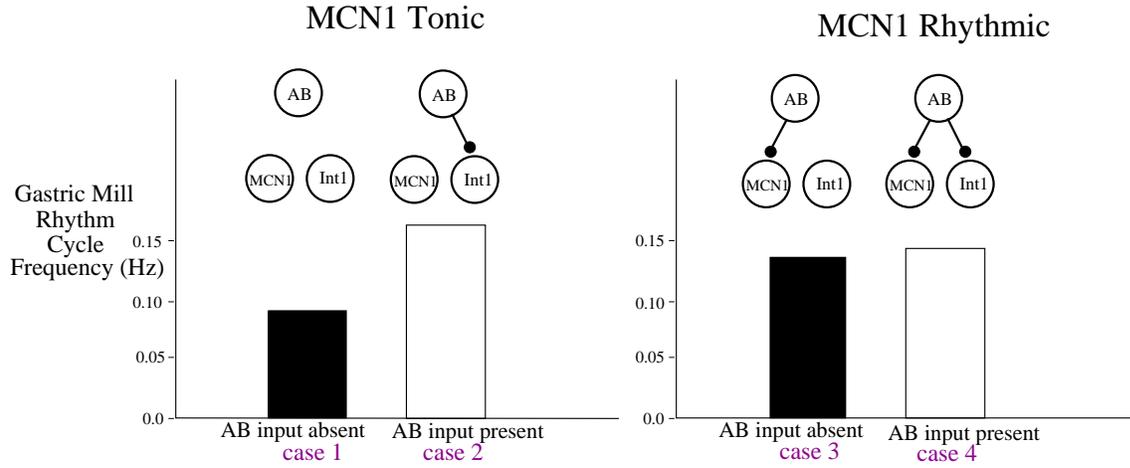


Figure 14: Experimental findings of the gastric mill rhythm cycle frequency for Cases 1-4 [29].

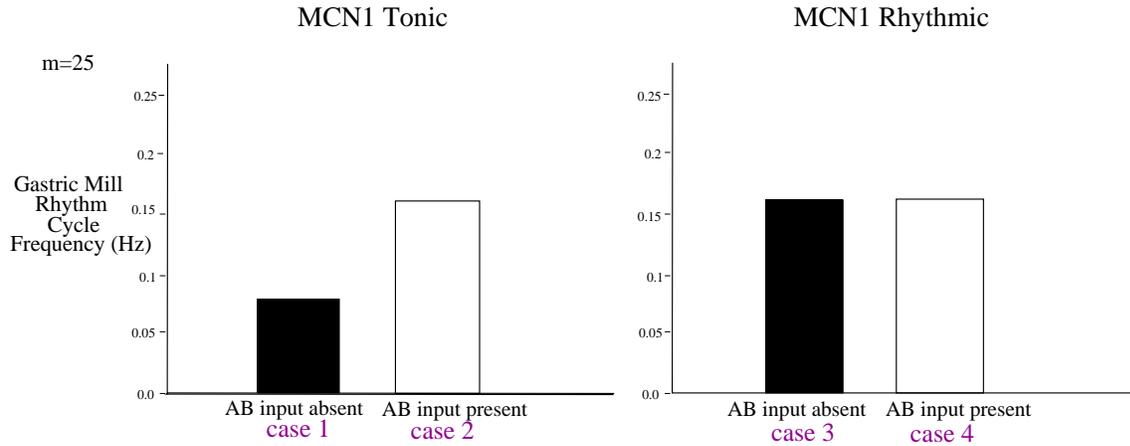


Figure 15: Calculations of the gastric mill rhythm cycle frequency for cases 1-4 using our model with  $\tau_{r1} = 7200msec$ ,  $\tau_{f1} = 5500msec$ ,  $\tau_{r2} = 1msec$ ,  $\tilde{\tau}_{f2} = 1msec$ , period of  $s_{AB} = 1sec$ ,  $m = 25msec$ , and  $g_s = 6mS/cm^2$  in Cases 1 and 2 and  $g_s = 7mS/cm^2$  in Cases 3 and 4.