A COMPUTER MODEL
OF ESOPHAGEAL
ELECTRICAL ACTIVITY

by

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ESOPHAGEAL ELECTRICAL ACTIVITY

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ABSTRACT

A chain of 42 bidirectionally coupled relaxation oscillators was used to model electrical activity in the smooth muscle portion of the opossum esophagus. Each oscillator was represented by two first order nonlinear differential equations. The equations were programmed on a Nova 830 minicomputer to develop the model and to test the responses to various stimuli.

The model simulated distally, proximally and bidirectionally propagated contractions (represented by oscillations at 2.5 Hz) when the pulse representing direct muscle stimulation was applied at the beginning, end or in the middle of the chain. Contractions were not present in the absence of a stimulus. The velocity of propagation increased from 3.6 cm/sec among oscillators representing the upper part of smooth muscle to 1.85 cm/sec among distal oscillators representing the lower part of the smooth esophageal muscle.

The model showed "ON" and "OFF" responses upon depolarization or hyperpolarization of the oscillators. The velocity of propagation of "ON" responses was variable and depended upon the amplitude of the stimulus which was applied to all of the oscillators simultaneously. The velocity of propagation of the "OFF" responses was much faster than that of the "ON" responses when the stimulus was applied to all oscillators. The number of spikes in a burst of "OFF" responses was variable and depended

upon the amplitude and the duration of the stimulus applied.

In conclusion, the model simulated all of the characteristics observed in the smooth muscle portion of the opossum esophagus. This includes those which were observed on vagal stimulation and balloon distension. The model also elucidates the mechanism of functioning of the myogenic control system and its modulation by the neuronal control system.

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INTRODUCTION

The presence of electrical activity in the esophagus, its origin, nature and role in governing peristalsis have been studied extensively for the last two decades by many researchers - Christensen (2), Christensen et al (4), Doods et al (7,8), Sarna et al (24). The results from experiments on opossums, humans and monkeys showed several differences between the electrical activity in the striated and the smooth esophageal muscle portions. The peristaltic movement in the striated muscle is controlled entirely by the central nervous system located in the brain - Jansen (12). Vagotomy which abolishes peristalsis in this part of the esophagus has very little effect on peristalsis in the smooth muscle portion of the esophagus - Jansen (12).

In the smooth muscle portion of the esophagus the independent myogenic control system together with intrinsic and extrinsic neuronal control systems play a major role in esophageal motility - Sarna et al (24).

The aim of this thesis was to develop a computer model of the esophageal myogenic electrical activity so as to elucidate its functioning and organization.

In chapter II,general information about the esophagus and the mechanisms that regulate primary and secondary peristalsis are discussed. Chapter III discusses the electrical activity of the striated and smooth muscle portion of the esophagus and the characteristics of responses obtained during distension and electrical stimulation. Chapter IV describes the computer model for the electrical activity and makes a comparison between the results from model and the data reported in chapter III. Chapter V is a proposed electronic representation of the relaxation oscillators used to build the computer model. Chapter VI presents mathematical analysis of equations used to simulate the electrical activity in the smooth muscle portion of the esophagus. The conclusions derived from the experimental results and suggestions concerning the applicability of the model to further studies of electrical events in the esophagus are proposed in Chapter VII. Two Appendixes are included: Appendix I presents a list of parameters used in all of the 42 oscillators in the model. Appendix II shows the use of interactive computer program to develop such models.

CHAPTER II

ESOPHAGUS

2.1 General Information

The main function of the esophagus is to transport the bolus of food from the pharyngeal sphincter into the stomach. The esophageal tube extends from the pharynx to the stomach. The upper end is protected from easy access of air by the upper esophageal sphincter. The lower end is protected from gastric content by the lower esophageal sphincter. These are depicted in Fig. 2.1. Between the sphincteric areas, the esophagus in humans is divided into thirds - the upper or cervical third, the middle third which lies between the base of the neck

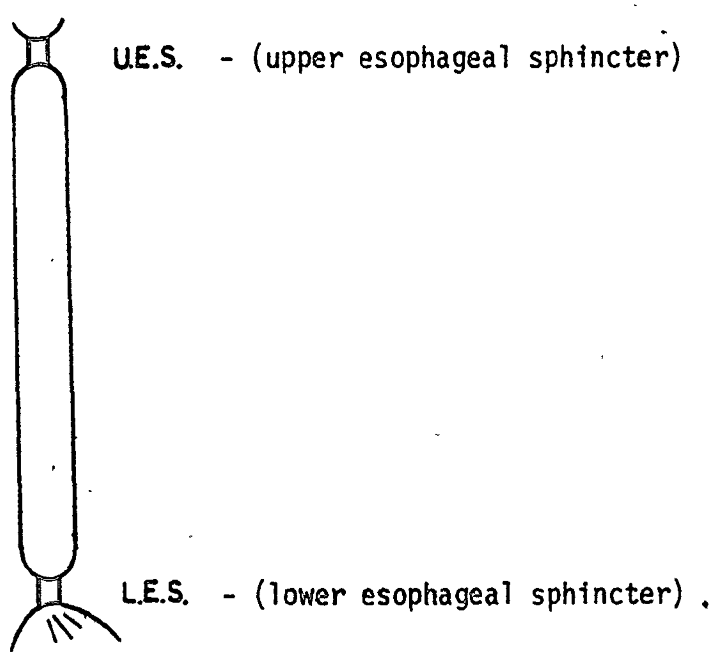

Fig. 2.1. Diagram of the esophagus.

and aortic arch and the lower or distal third. The middle and lower thirds make up the thoracic esophagus. The walls of the esophagus are composed of four coats (1) an external or fibrous coat, (2) a muscular coat, (3) a submucous coat, (4) an internal or mucous coat. The muscular coat consists of an external longitudinal and internal circular layer. The submucous coat serves to connect the muscular and mucous coats and to carry the larger blood and lymph vessels. The mucous membrane is arranged in longitudinal folds which disappear when the esophagus is distended by the passage of food. The nerve fibers from the vagus and thoracolumbar nervous system form a plexus between the layers of the muscular coat and the submucous coat.

In mammals the esophagus is composed of striated and smooth muscles. Christensen et al (4) have shown that the esophagus in common opossums (Didelphis Virginianna) has an orange coloured striated muscle occupying 5 to 6 cm of the total length of 15 to 18 cm, and a pink smooth muscle which makes up the remainder. Microscopic examination of the excised organ shows muscularis mucosae - smooth muscle throughout the esophagus, and muscularis propria containing fibers which have a smooth muscle in the distal two thirds of the esophagus and striated muscle in the proximal one third.

In humans the esophagus has a length 23 to 25 cm and a tube diameter of 2.5 to 3.0 cm. The upper 2 to 6 cm of the esophagus contain only striated muscle fibers. The lower third consists of a smooth muscle type and there is a transitional zone in between the two. A similar distribution of striated and smooth muscle types has been found in cat and monkey esophagii. The dog esophagus is composed entirely of striated muscle except for the gastroesophageal sphincter which contains smooth muscle.

The active transport of food in the esophagus is carried out by primary peristaltic contractions initiated by swallowing or by secondary peristalsis initiated by distension of the esophageal wall. The primary and secondary peristalsis are propagative in nature whose velocity of propagation depends upon the consistency of the food. Solid and semisolid foods require 4 to 8 sec for passage from mouth to stomach. About half of this time is taken up in passage through the esophagus. Liquid and very soft foods arrive at the lower esophagus sphincter in about 1 sec. Depending upon the condition of the lower sphincter the food may pass into the stomach at once or it may be temporarily held in the esophagus. Repeated deglutition causes the tension of the muscles of the lower esophageal sphincter to diminish progressively until it is completely relaxed and food passes into the stomach. After this the relaxation disappears, the sphincter becomes more contracted and remains contracted for a considerable time.

The mechanism which regulates the progress of esophageal peristalsis has been studied extensively ever since the pioneering work of Meltzer and Mosso over one hundred years ago - Jansen (12).

2.2 Primary Peristalsis

The primary peristaltic contraction which is initiated by deglutition starts up in the pharynx and progresses down until it reaches the cardia. For a long time the central controlling system in the brain was considered to be the only regulating factor in the production and progression of primary peristalsis. Experiments carried out by Longhi et al (18) indicated that swallowing is not adequate to generate primary peristalsis without the presence of an intraluminal bolus. Many experiments were than undertaken to establish whether the initiation and the progression of primary peristalsis is bolus dependent. The results obtained by Jansen et al (14) from the canine esophagus indicated that two mechanisms are involved in the production of the primary peristalsis - the central control mechanism in the brain and the afferent information which originates in the esophagus caused by the presence of a bolus.

The primary peristalsis in the striated esophageal muscle of the opossum, the rabbit and the rhesus monkey is mainly controlled by the central regulating mechanism in the brain. The information from the swallowing center arrives through vagal nerves. Bilateral vagotomy abolishes peristaltic activity in the striated muscle portion of the esophagus - Jansen (12).

The initiation and progression of primary peristalsis in the smooth muscle portion of the esophagus is controversial. The existence of at least two nervous control systems has been shown by many studies. For the peristalsis initiated by deglutition the central control mechanism in the brain emits electrical discharges to more distal parts of striated and smooth muscles. The vagotomy of the nerves in this area temporarily abolishes peristalsis or greatly reduces it. This indicates that peristalsis can occur without the help of the central nervous system. Mukhopadhyay's (20) results also support the hypothesis that the peristalsis in the smooth part of esophagus is controlled by local mechanisms rather than by the central nervous system. He also showed that bilateral vagotomy and stimulation of the distal cut end initiated perisaltic contractions in the opossum esophagus. The velocity of propagation of contractions in the opossum esophagus decreased gradually from 3.2 cm/sec as measured in a region at 70-80% of length to 1.85 cm/sec at 90-100% of length. The administration of atropine did not abolish the peristalsis and the changes in velocity of propagation were not significant.

The existence of a peripheral control mechanism in the wall of smooth muscle which can function independently of central control was suggested by Christensen (2) and Christensen et al (4). They demonstrated that peristalsis can be produced in an esophagus which has been removed and placed in an organ bath.

Evidence for the existence of a myogenic control system which may bring about the esophageal peristalsis in the smooth muscle of the esophagus has been suggested by recent studies of Sarna et al (24). These studies showed that direct muscle stimulation resulted in propagated contractions after the nervous inputs had been blocked by tetrodotoxin (TTX).

2.3 Secondary Peristalsis

The secondary peristalsis is initiated by local stimulation of the esophageal wall. The progression of secondary peristalsis is regulated by two systems, the central mechanism in the brain and the afferent information originated by the presence of an intraluminal bolus. The contribution of these two mechanisms differs at different levels of the esophagus. Studies done by Jansen et al (15) suggest that the central control must be involved in the initiation of the secondary peristalsis since the secondary wave is initiated above the level of the stimulus and not at the level. According to their results the central regulating system should be considered as a predominant factor in the thoracic part of the esophagus. The presence of an intraluminal bolus is necessary for the progression of the secondary peristaltic contractions at the cervical level of the esophagus.

CHAPTER III

ELECTRICAL ACTIVITY OF STRIATED AND SMOOTH MUSCLE OF THE ESOPHAGUS

3.1 General Information

Many investigators have attempted to define the characteristics of the electrical activity in the striated and the smooth muscle portions of the esophagus. Helleman et al (11) recorded the electrical activity in dogs, cats and monkeys in the resting state and after deglutition. According to their observation no electrical activity was present in the smooth muscle of the resting esophagus but some spiking activity of low amplitude was recorded in the striated muscle.

There was a remarkable difference in the electrical activities recorded from the smooth and striated muscle after deglutition. This resulted in a burst of spikes progressing distally. In the striated muscle of the dog esophagus the initial phase of the burst of electrical activity was composed of single spikes which had identical shape and amplitude. The amplitude and the number of spikes per unit of time rapidly increased. The individual spikes were difficult to distinguish from each other. Then the spike activity decreased again and died out slowly. The recorded frequency of spikes was about 46/sec close to the upper esophageal sphincter and decreased distally to 30/sec. The duration of an individual action potential was 4 to 6 msec.

In the smooth muscle portion, the number of spikes in a burst of oscillation was much smaller than that observed in the striated muscle.

The duration of action potential was much longer (16 to 40 msec) and the amplitude was several times larger. The shape of the spikes was often irregular; but, the burst occasionally showed spikes of identical configuration with a rhythm of 2 to 8/sec. The deglutive spike activity in the smooth muscle portion of the esophagus did not increase or decrease in amplitude nor frequency and the bursts of oscillations were separated by short periods of inactivity. The results of Hellemans et al (11) suggest that the wave of relaxation precedes the primary and secondary peristaltic contractions and that deglutition results in inhibition of the primary and secondary peristalsis. The findings of Ueda et al (27) in cat esophagus agree with those of Helleman that the action potential of the smooth muscle is characterized by a long duration, high amplitude and a lower frequency.

Since an esophagus does not have an omnipresent electrical control activity - Sarna (26), the peristaltic movement has been assumed to be primarily a neurogenic phenomenon. Sarna et al (24) evaluated the hypothesis that the myogenic control system, the existence of which has been proved in the rest of the gastrointestinal tract, has a role to play in esophageal motility and does exist as an independent system in the smooth muscle portion of the esophagus. The interaction of the myogenic system with the intrinsic and extrinsic neuronal control systems in controlling the peristaltic movement was also determined .

3.2 Myogenic Control System and Electrical Responses to Direct Muscle Stimulation in the Smooth Esophageal Muscle

The results from studies done on anesthetized opossums by Sarna et al (24) explained the role of the myogenic control system in esophageal motility. Direct muscle stimulation at 20 to 40V with 100 to 400 msec pulse widths resulted in the propagation of contractions. The direction of propagation depended upon the site of stimulus. If the stimulus was applied distally the propagation was proximal, if it was applied proximally the propagation was distal and if it was applied in the middle, the propagation was bidirectional (swallows normally propagate only distally). The contractions were associated with propagating electrical oscillations in the frequency range of 2 to 10 Hz. In some opossums single direct muscle stimulation did not produce any propagating contractions. Instead it produced local contractions. Repeated direct muscle stimulation produced larger local contractions and initiated their propagation.

The velocity of propagation observed during direct muscle stimulation was similar to velocity during spontaneous swallows and less than 5 cm/sec. According to Sarna et al (24) the myogenic control system is capable of producing and propagating contractions, however the functioning of the myogenic control system can be modulated by the neural system.

3.3 Characteristics of Electrical "ON", "OFF" and "Duration" Responses

Experimental studies of the electrical responses existing in the smooth muscle portion to distension of the esophagus and cervical vagal stimulation were undertaken independently by many researchers. Christensen (2) and Christensen et al (4) examined the responses to electrical stimulation of various smooth muscle preparations and distension of the esophagus. Doods et al (6,7,8) evaluated the vagal control mechanism governing peristalsis in the esophageal smooth muscle by checking responses of the feline and the opossum esophagus to cervical vagal stimulation.

3.3.1 Electrical responses to distension of the esophagus

The data obtained by Christensen (2) in vivo indicated that the balloon inflation by 1 ml for 5 to 10 sec at various levels of the esophagus caused two kinds of responses. A burst of action potentials indicating contractions of the circular muscle occurred just above or at the point of stretch after inflation of the balloon with a delay of 0.29 to 0.36 sec. These were called "ON" responses. The "OFF" responses occurred as a result of the deflation of the balloon and they were represented by a burst of oscillations which started below the point of stretch with a delay of 0.96 to 1.08 sec. The existence of "Duration" responses was suggested by Christensen et al (4). Since the maintenance of distension produces shortening of the esophagus for the duration of distension - they classified the observed responses as "Duration" responses.

3.3.2 Esophageal responses to cervical vagal stimulation

The responses to cervical vagal stimulation were observed in the feline and the opossum esophagus by Doods et al (6,7,8). The results of their observations in the smooth muscle portion of the feline esophagus showed the existence of circumferentially and longitudinally oriented contractions.

The circumferential contractions in the smooth muscle were recorded as "ON" and "OFF" responses. Both types of responses were bell-shaped in configuration and the stimulation frequency had almost no affect on the wave form. The "ON" contractions occurred 0.5 to 1 sec after vagal stimulus onset, regardless of stimulus length. The latency of the "ON" type responses was not affected by intensity, frequency or the duration of the stimulus. The "OFF" responses occasionally occurred in the feline esophagus with a delay of 0.5 to 2 sec. after stimulus cessation. The circumferential esophageal contractions elicited by the low frequency vagal stimulus often demonstrated a velocity of propagation similar to primary peristalsis. For the high frequency stimulus, the contractions were more simultaneous. The duration of circumferential "ON" and "OFF" responses was independent of stimulus duration.

The observed longitudinal contractions were also bell-shaped Their latency was very close to that of "ON" contractions and was not affected by changing the frequency or the duration of stimulus. The duration of longitudinal contractions was longer than that of circumferential contractions and it was directly related to the value of the stimulus. They developed about 1 sec after stimulus onset and lasted throughout the stimulus. The magnitude of the longitudinal contraction was dependent upon the stimulus strength.

3.4 Effect of Drugs on Esophageal Contractions

The effect of drugs on electrical responses to direct muscle stimulation, on "ON", "OFF" and "Duration" responses in the smooth esophageal muscle were examined by many researchers - Sarna et al (24), Doods et al (6,8), Lund et al (17), Christensen et al (4) and many others.

The contractions obtained by direct muscle stimulation were not blocked by intraarterial atropine nor tetrodotoxin indicating that the myogenic system is capable of generating and propagating contractions independent of neural input (24).

The "ON" responses were blocked by atropine but they were unaffected by any of the other drugs (24,17,4). This may indicate that they may have resulted from contractions of the longitudinal muscle. Atropine also caused the disappearance of the "Duration" responses in feline esophagus (6) and decreased the magnitude of "Duration" responses in opossums (8).

"OFF" responses were abolished in all experiments by tetrodotoxin indicating that the responses are nerve mediated.

In conclusion, although the investigation of the electrical activity in the smooth esophageal muscle does not answer all the unknowns about esophageal motor function it has helped in explaining the physiological equivalent of peristalsis of smooth esophageal muscle.

CHAPTER IV

A COMPUTER MODEL OF ESOPHAGEAL ELECTRICAL ACTIVITY

4.1 General Information

A chain of 42 bidirectionally coupled relaxation oscillators is proposed as a model of the electrical activity in the smooth muscle portion of the opossum esophagus. The total length of the esophagus in the opossum is 15 to 18 cm, of which the striated muscle occupies the upper one third, the transitional zone occupies the second third and the smooth muscle occupies the remaining part. For our model a hypothetical smooth muscle of the esophagus of 5 cm in length is assumed.

Each oscillator in a chain is represented by a set of two first order nonlinear differential equations (4.4), (4.5). The equations are a generalized form of the van der Pol equation (4.1)

$$\ddot{x} - \alpha(1 - x^2)\dot{x} + \omega x = 0 \tag{4.1}$$

where x is a dependent variable representing the amplitude

α is a damping coefficient

ω is the undamped frequency

$\dot{x}$ and $\ddot{x}$ are the first and the second derivatives of x.

Fitzhugh (9) using Lineards transformation generalized the Van der Pol equation by the addition of terms to form a pair of nonlinear differential equations (4.2) (4.3) which can have a stable singular point "P" or a limit cycle in the phase plane.

$$\dot{x} = c(y + x - \frac{x^3}{3} + zz) \tag{4.2}$$

$$\dot{y} = -\frac{1}{c}(x + by - a) \tag{4.3}$$

The above system of equations was used by Fitzhugh to build the model of a nerve membrane. Its properties are visualized in fig. 4.1. The x

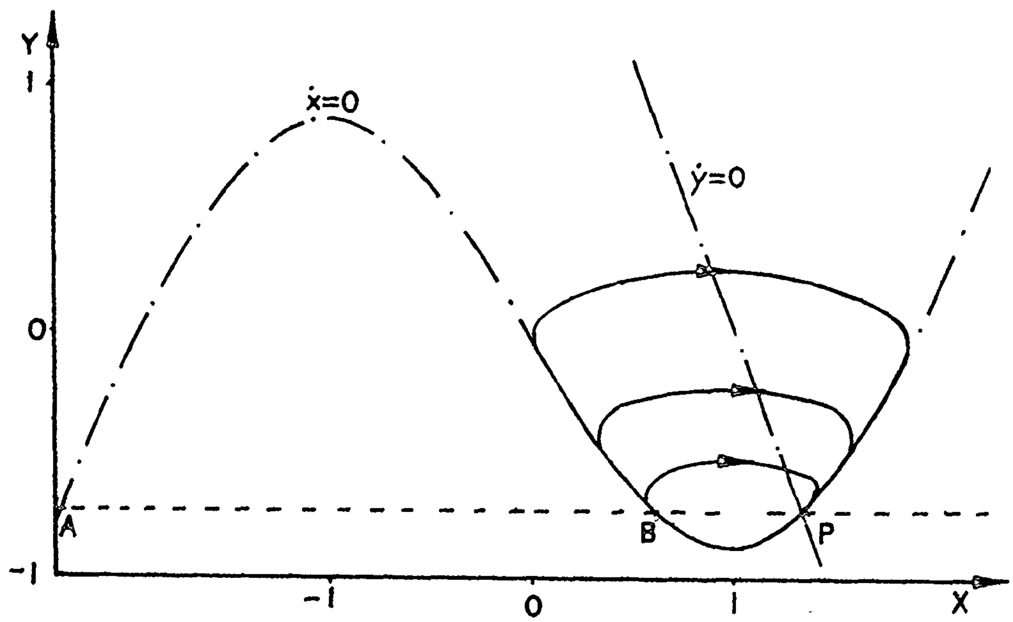

Fig. 4.1. The phase plane of the Fitzhugh equations.

and y nullclines shown in fig. 4.1 are obtained by setting $\dot{x} = \dot{y} = 0$ in equations (4.2)(4.3). The y nullcline is a straight line with a slope $-\frac{1}{b}$, and the x nullcine is a N shaped curve having a slope of -1 at the origin. The phase line x (dotted) going through the resting point

"P" has three singular points (A,B,P) where it intersects the three branches of the x nullcline. The left most point "A" is a stable excited point, the middle point "B" is an unstable point representing the threshold phenomenon and the point "P" to the right is a stable quiescent point. "P" can move spontaneously in the plane along the curves with the arrowheads. For a sufficiently large negative stimulus it can be displaced across the threshold separtrix and result in excitation.

In phase plane analysis of the nerve, Fitzhugh derived the conditions so that a system resting at a single stable point would exhibit an oscillation when excited by an external stimulus. The Fitzhugh system of equations was further modified for our application by adding "ω" - the coefficient for the undamped frequency thus giving the following

$$\dot{x} = c(y + x - \frac{x^3}{3} + zz) \tag{4.4}$$

$$\dot{y} = -\frac{1}{c}(\omega^2 x - a + by) \tag{4.5}$$

By referring to Fitzhugh's phase plane analysis the necessary conditions for the existence of a singular point "P", resting in a stable state or exhibiting several oscillations when excited, were determined. Sections 6.1 and 6.2 show the determination of the above conditions for our system of equations by setting $\dot{x} = \dot{y} = 0$ and using a Taylor series for two variables.

The stable point "P" is obtained if:

$$a_{MIN} \geq \omega^2 - \frac{2}{3} b , \qquad b < c^2 , \qquad \omega^2 > b \tag{4.6}$$

The stimulus "zz" which moves the stable point beyond the separtrix is described by equation (4.7). The determination of the conditions for "zz" is shown in section 6.3

$$-[(\frac{a-\omega^2}{b}) + \frac{2}{3}] \leq zz \leq -[(\frac{a+\omega^2}{b}) - \frac{2}{3}] \tag{4.7}$$

The proposed model has two types of coupling between oscillators - forward coupling and backward coupling. These are shown in fig. 4.2.

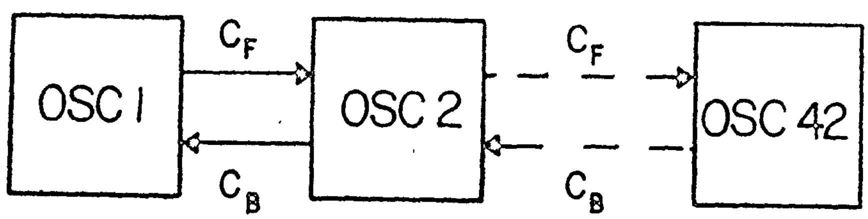

Fig. 4.2. Block diagram illustrating the arrangement of oscillators used in esophageal electrical activity model.

The forward and backward couplings are referred to as bidirectional couplings. Forward coupling indicates that the output of one oscillator is feeding into the next distal oscillator, backward coupling indicates that an oscillator is affecting the next proximal oscillator. The physiological analog of bidirectional coupling in the smooth muscle of the esophagus may be that the proximal cell is affecting the membrane potential of next distal cell and vice versa.

Due to the use of bidrectional coupling between oscillators in our model the proposed equations (4.4), (4.5) are modified to include the coupling factors. Therefore in a chain of coupled oscillators the equations for an nth oscillator are as follows:

$$\dot{x}_n = c\left(y_n + x_n - \frac{x_n^3}{3} + C_F x_{n-1} + C_B x_{n+1} + zz\right) \tag{4.8}$$

$$\dot{y}_n = -\frac{1}{c}\left(\omega^2 x_n - a + by_n\right) \tag{4.9}$$

where C_F is the factor for forward coupling

C_B is the factor for backward coupling

zz is the stimulus intensity

x and y are state variables

ω is the frequency coefficient

a,b,c are the parameters determining the location of the stable point "P" .

The proper selection of parameters used in equations (4.8) and (4.9) allowed the authors to obtain the wave shape, the frequency of oscillation and the velocity of propagation, similar to those observed in the opossum esophagus on swallowing. In all the oscillators of the chain parameters "a", "b", "c" were chosen subject to conditions (4.6). The location of the stable point "P" in the first oscillator was chosen to be close to the boundary of the unstable region, therefore "a" was set close to "a_{MIN}". The distally decreasing velocity of propagation was obtained in the model by using slightly different locations of the stable point "P" for each oscillator and by changing the coupling factors throughout the chain.

The oscillations in most of the biological systems are bell-shaped.

This was achieved in our model by setting parameter "c" > 30.

According to the observation of Helleman et al (11), Jansen (12) and others the esophagus does not show any electrical acitivity in the resting state. Deglutition results in contractions which progress distally as a burst of oscillations at a frequency in the range of 2 to 10 Hz.

The model proposed in this thesis also does not show any oscillations in the absence of an external stimulus. However, when excited the phase point "P" of the stimulated oscillator is shifted to the unstable region. There it oscillates at a frequency of 2.5 Hz and keeps doing so until "P" moves out of the unstable region. The propagative nature of oscillations is achieved by using bidirectional coupling between oscillators.

The model simulates responses obtained during direct muscle stimulation and responses obtained upon vagal stimulation and balloon distension.

4.2 Direct Muscle Stimulation

Direct muscle stimulation described in section 3.2 was simulated in the model by the application of a rectangular stimulus to one oscillator of the chain. To check the responses of the model several rectangular stimuli differing in width of the pulse and amplitude were applied to the beginning, the middle and the end of the chain.

The distally progressing contractions recorded by Sarna et al (24) were simulated by a burst of oscillations of frequency 2.5 Hz progressing distally. These were elicited when the stimulus was applied at the beginning of the chain. A rectangular stimulus of 0.4 sec pulse width and -10 V amplitude when applied to oscillator #4 elicited two oscillations within the duration of the stimulus and a burst of four spikes after stimulus cessation - fig. 4.3a and 4.3b. The number of spikes propagating throughout the chain changed as the amplitude of the stimulating pulse was increased. The stimulus of 0.4 sec pulse width and -20 V amplitude when applied to oscillator #4 elicited two oscillations within the duration of the stimulus and a burst of eight oscillations after stimulus cessation - fig. 4.4a and 4.4b. The decrease in the width of applied stimulating pulse resulted also in a change of the number of spikes generated. The stimulating pulse of the same amplitude -20 V and 0.1 sec pulse width when applied to oscillator #4 resulted in one oscillation at the time of stimulus application and five spikes after stimulus cession - fig. 4.5a and 4.5b.

In all of the above cases the frequency of the generated spikes and the velocity of propagation were not affected by changes in amplitude or width of the applied stimulus. Fig. 4.6 shows the velocity of propagation obtained upon the stimulation of distally propagating responses to direct muscle stimulation. The velocity of propagation was calculated from the results plotted in fig. 4.4a as a time lag between the first peak of oscillation being propagated through the chain in successive oscillators. The decreasing number of spikes generated in each case was caused by different location of the working point of each oscillator in the chain.

The proximally propagating contractions were simulated in our model by the application of the stimulating pulse near the end of the chain. A rectangular pulse of 0.4 sec pulse width and -10 V amplitude was applied to oscillator #39 - fig. 4.7a and 4.7b. One oscillation was

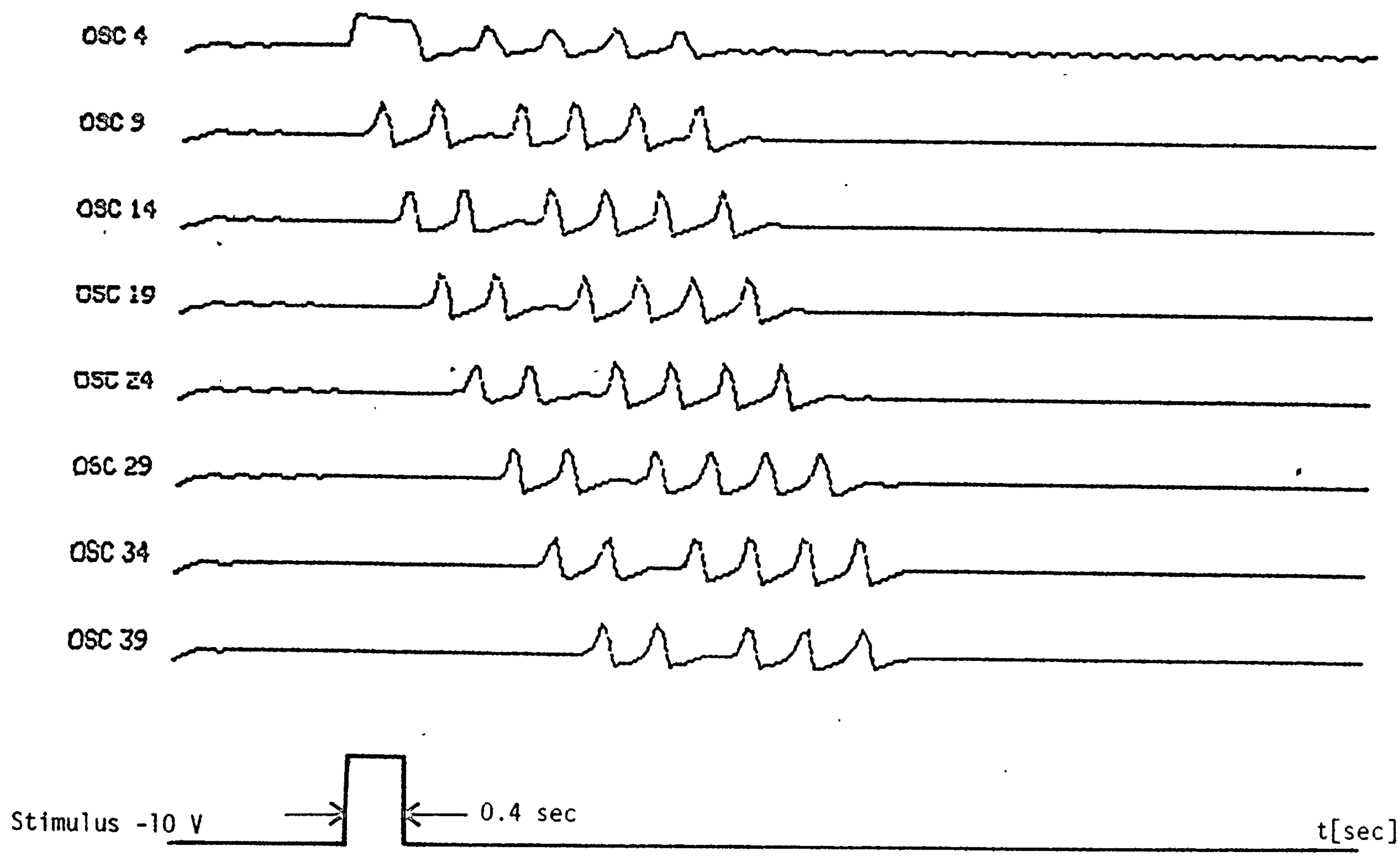

Fig. 4.3a. Distally propagating burst of direct muscle responses obtained when a stimulus of -10 V amplitude and 0.4 sec pulse width was applied to oscillator #4. Responses were recorded throughout the chain of oscillators.

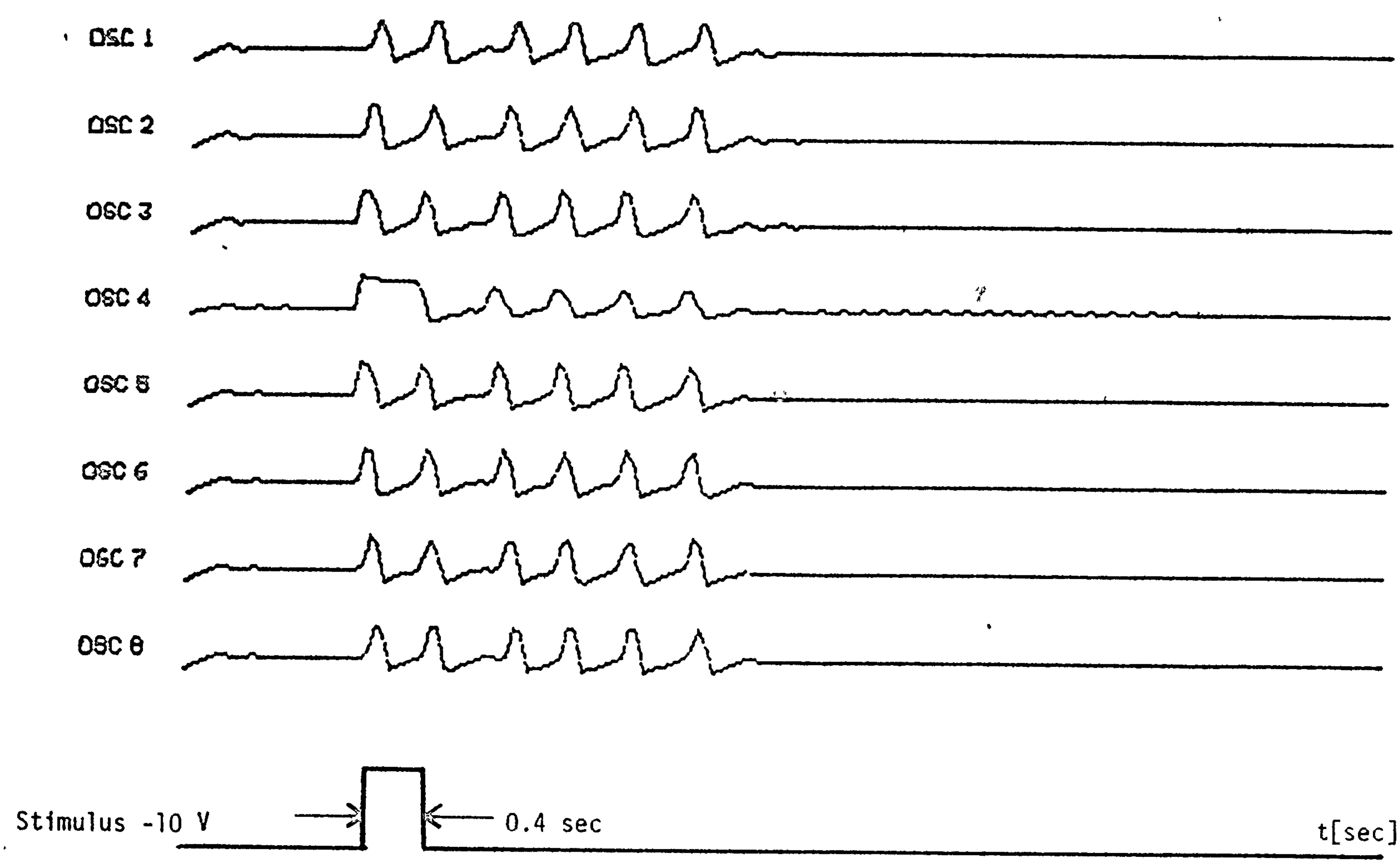

Fig. 4.3b. Direct muscle responses obtained when a stimulus -10 V amplitude and 0.4 sec pulse width was applied to oscillator #4. The oscillations shown are at the neighbouring oscillators.

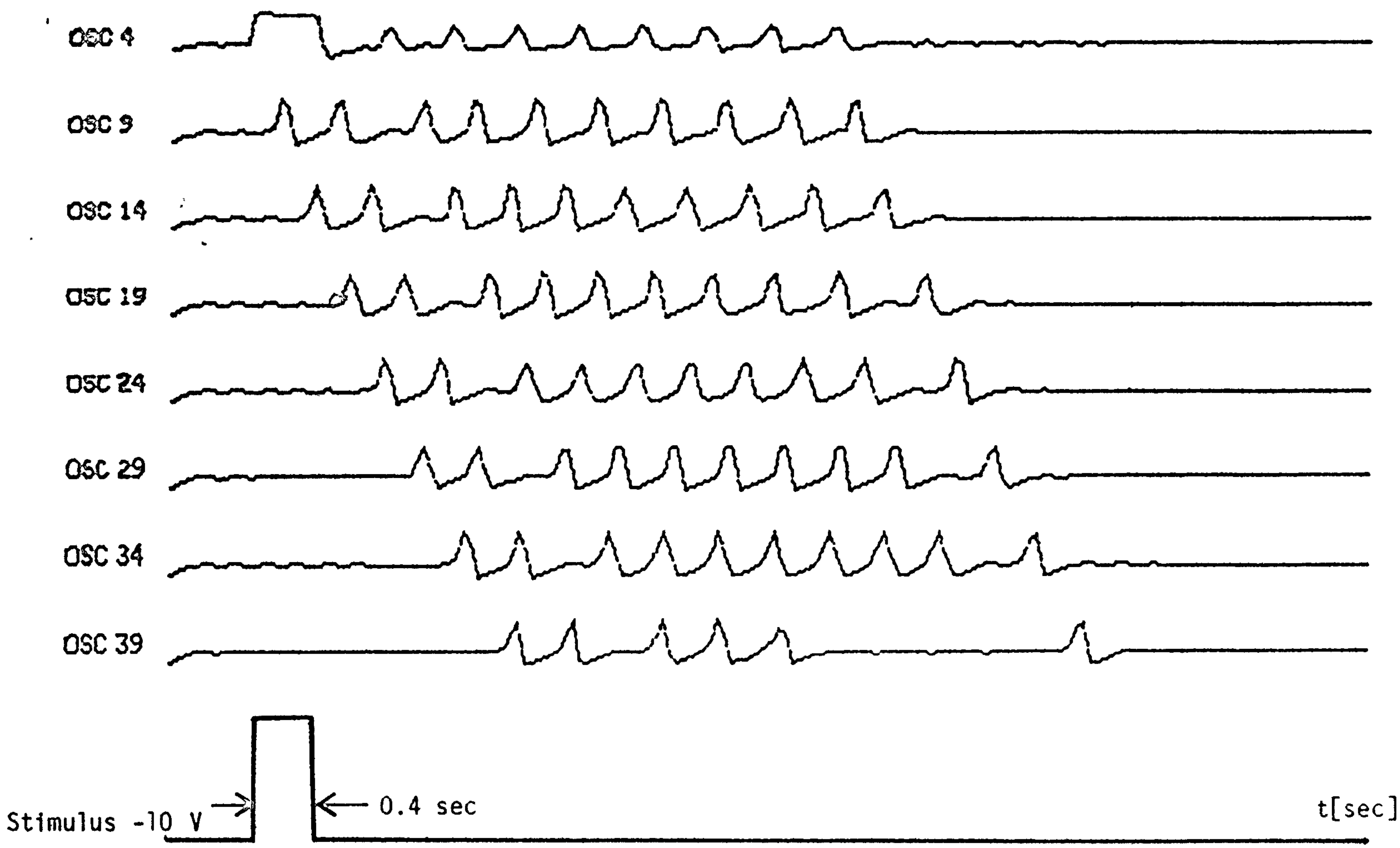

Fig. 4.4a. Distally propagating burst of direct muscle responses obtained with a stimulus of -20 V amplitude and 0.4 sec pulse width applied to oscillator #4.

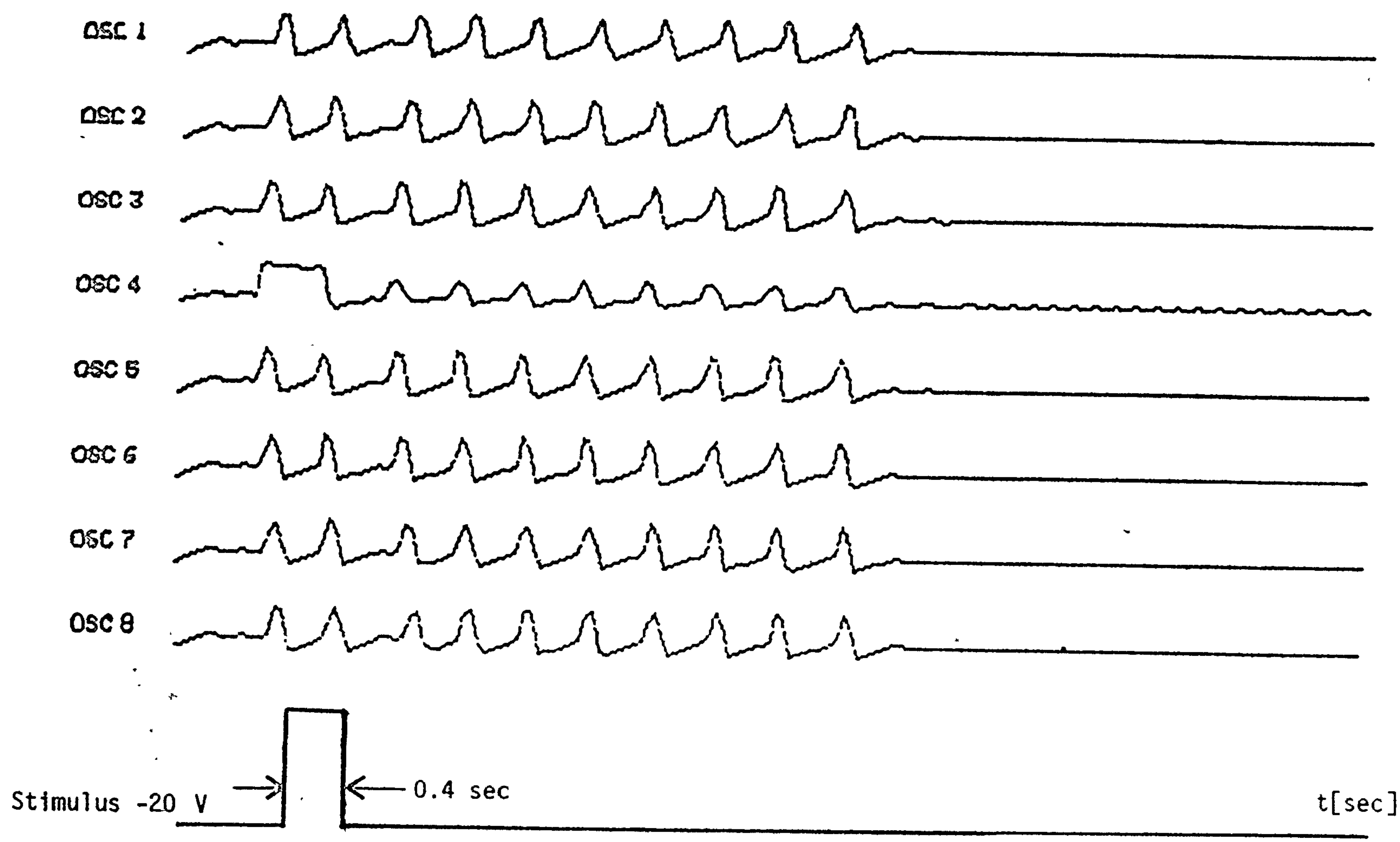

Fig. 4.4b. Direct muscle responses obtained upon the stimulus of -20 V amplitude and 0.4 sec pulse width applied to oscillator #4. Results recorded are those at neighbouring oscillators.

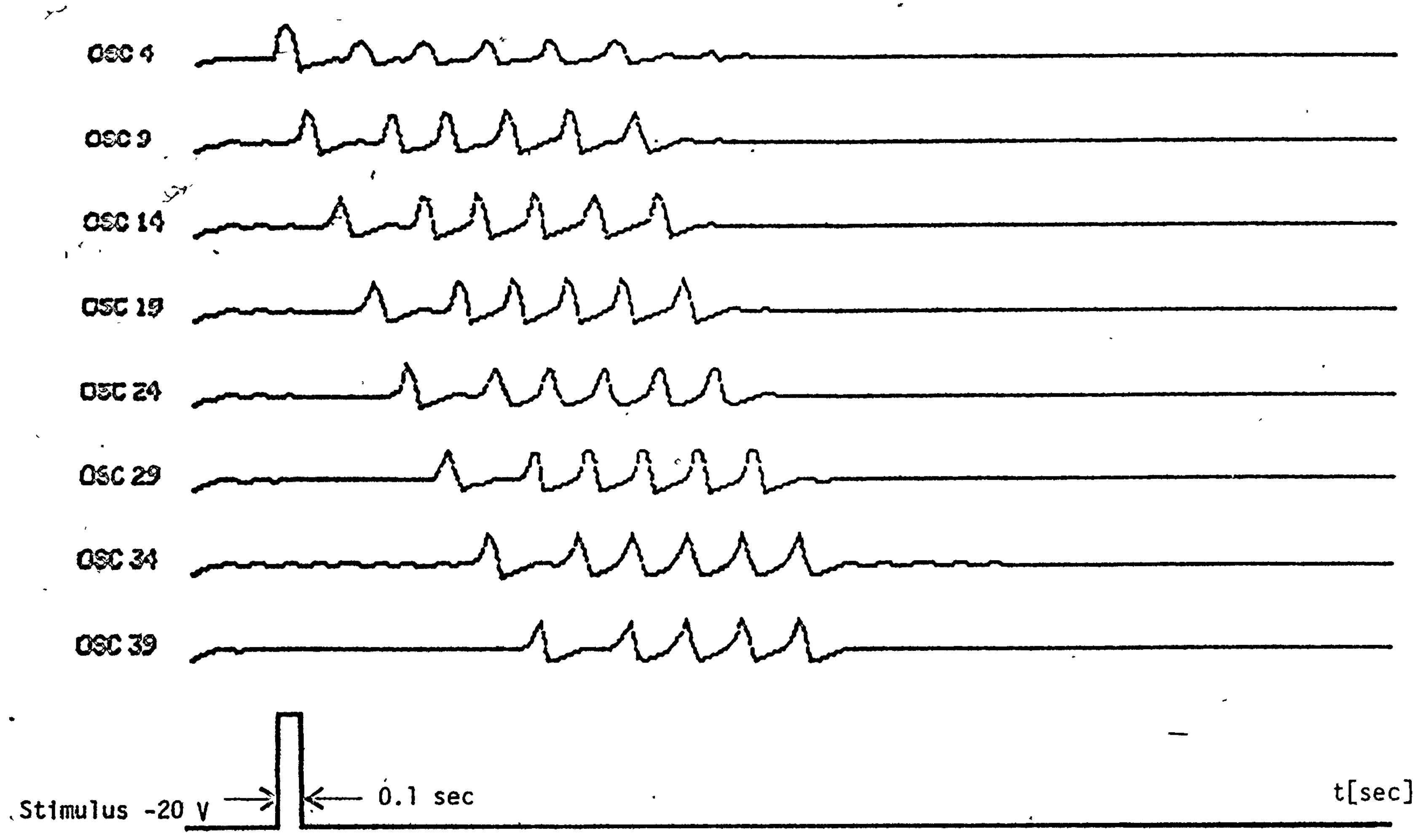

Fig. 4.5a. Distally propagating burst of direct muscle responses obtained with a stimulus of -20 V amplitude and 0.1 sec pulse width applied to oscillator #4.

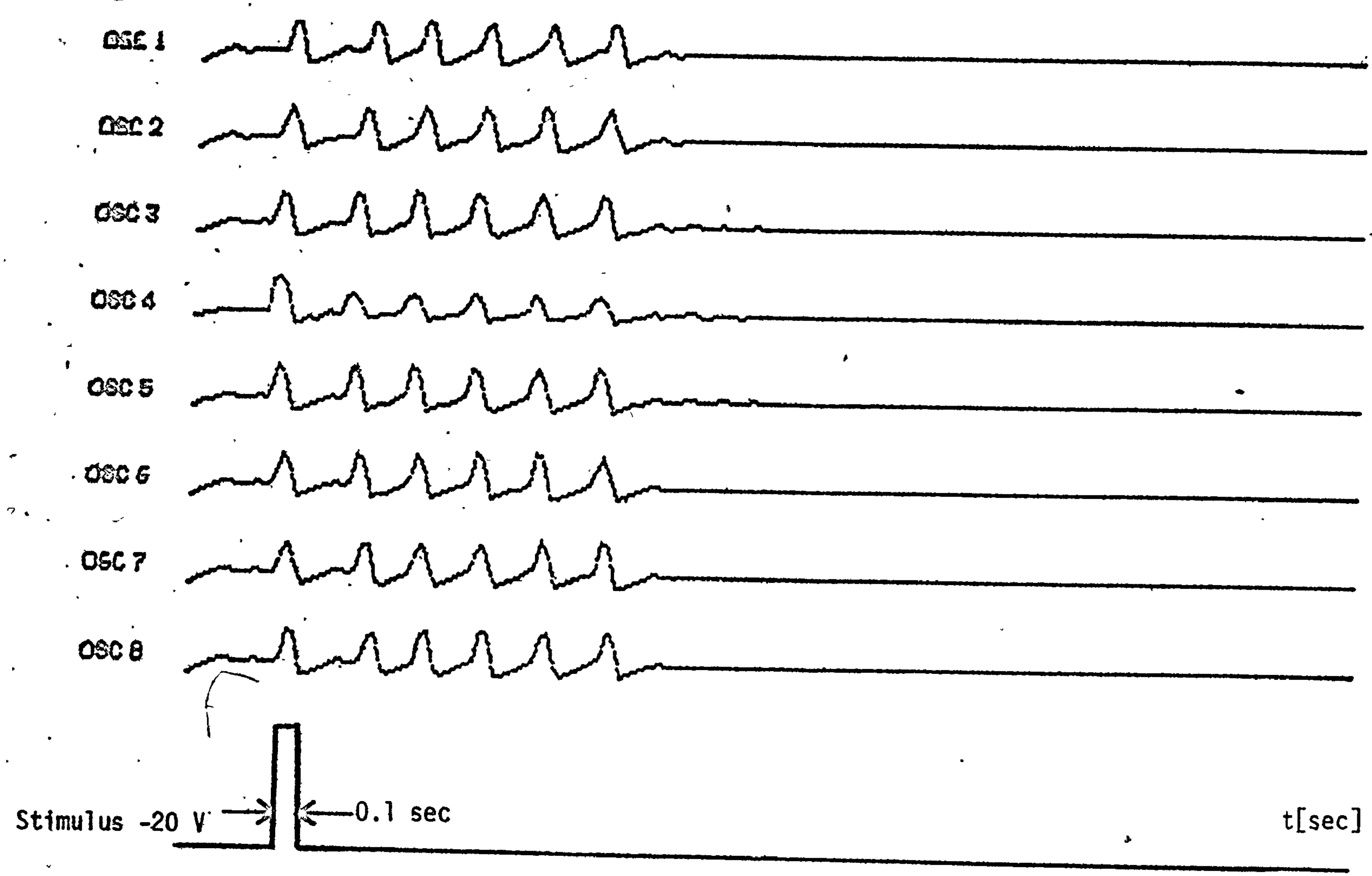

Fig. 4.5b. Direct muscle responses obtained with a stimulus -20 V amplitude and 0.1 sec pulse width applied to oscillator #4.

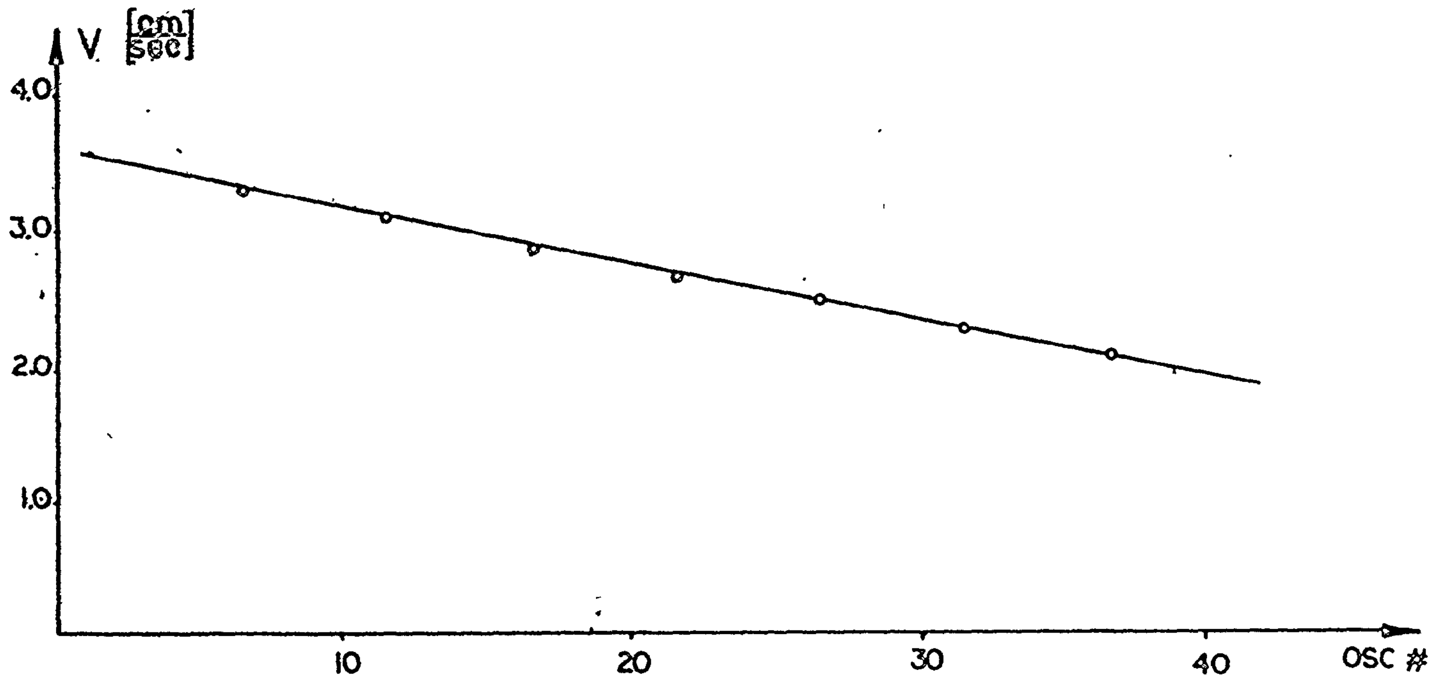

Fig. 4.6. Velocity of propagation of the distally progressing direct muscle responses.

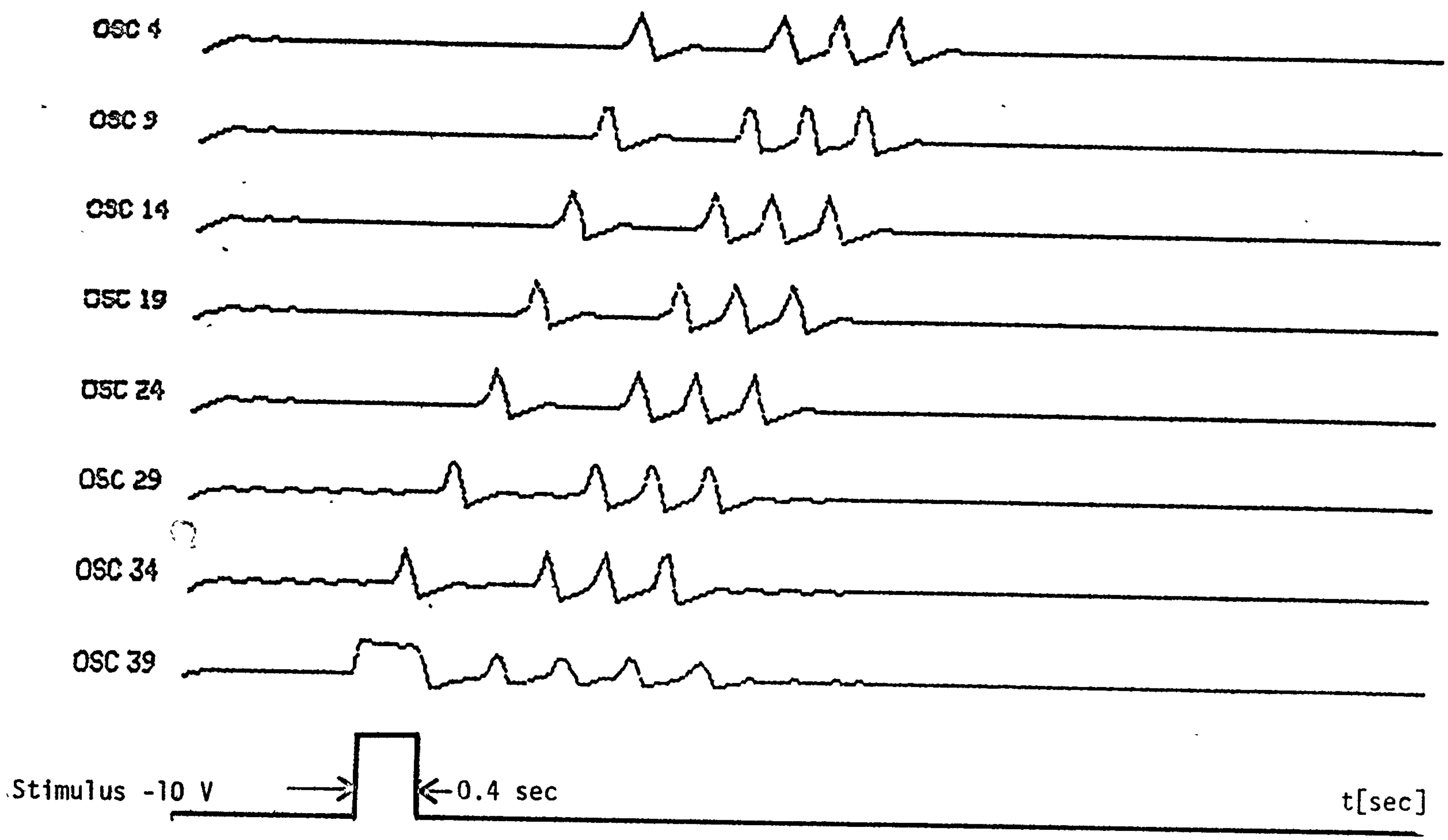

Fig. 4.7a. Proximally propagating burst of direct muscle responses obtained with a stimulus of -10 V amplitude and 0.4 sec pulse width applied to oscillator #39. The responses were recorded throughout the chain of oscillators.

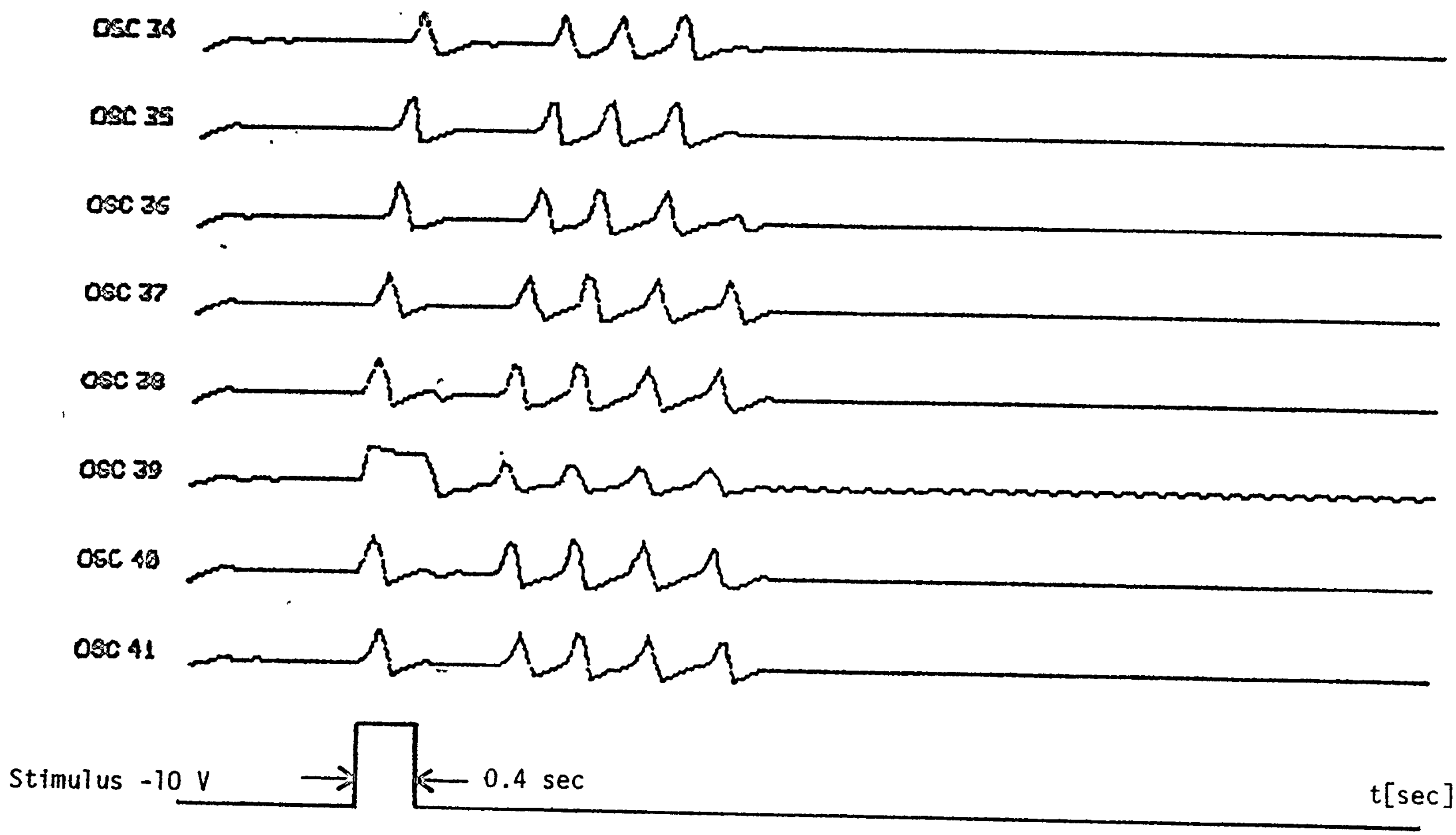

Fig. 4.7b. Direct muscle responses obtained upon the application of a stimulus of -10 V amplitude and the 0.4 sec pulse width to oscillator #39. The results shown are those from the neighbouring oscillators.

generated within the stimulus duration and a burst of four oscillations was generated after stimulus cessation. The number of spikes in a burst was similar to that obtained upon the application of an identical stimulus to oscillator #4 (ref. to fig. 4.3).

Due to computer time limitation (each measurement requires 15 to 50 hours of computer time dependent on the amplitude of the stimulus) the responses to different pulse widths and amplitudes were not obtained in this case. Likewise the bidirectionally propagating responses described next were checked for only one kind of stimulus.

The bidirectionally propagating contractions were simulated by the application of a rectangular stimulus in the middle of the chain. A stimulating pulse of 0.4 sec pulse width and -10 V amplitude when applied to oscillator #21 resulted in bidirectionally propagating oscillations - fig. 4.8a and 4.8b. Two oscillations were generated while the stimulus was present and a burst of four spikes progressing bidrectionally was generated after stimulus cessation. The number of spikes in a burst resembled that generated upon the application of an identical stimulus to oscillator #4 or oscillator #39 (ref. fig. 4.3 and 4.7).

4.3 Responses to Vagal Stimulation and Balloon Distension

The "OFF" and "ON" responses to vagal stimulation and balloon distension described in section 3.3 were simulated in the model by the parallel application of the rectangular stimulating pulse to all oscillators in the chain. The application of the hyperpolarizing pulses to all oscillators for a few seconds followed by simultaneous cessation resulted in "OFF" responses. Three kinds of hyperpolarizing stimuli differing in amplitude and duration were used to check the responses of

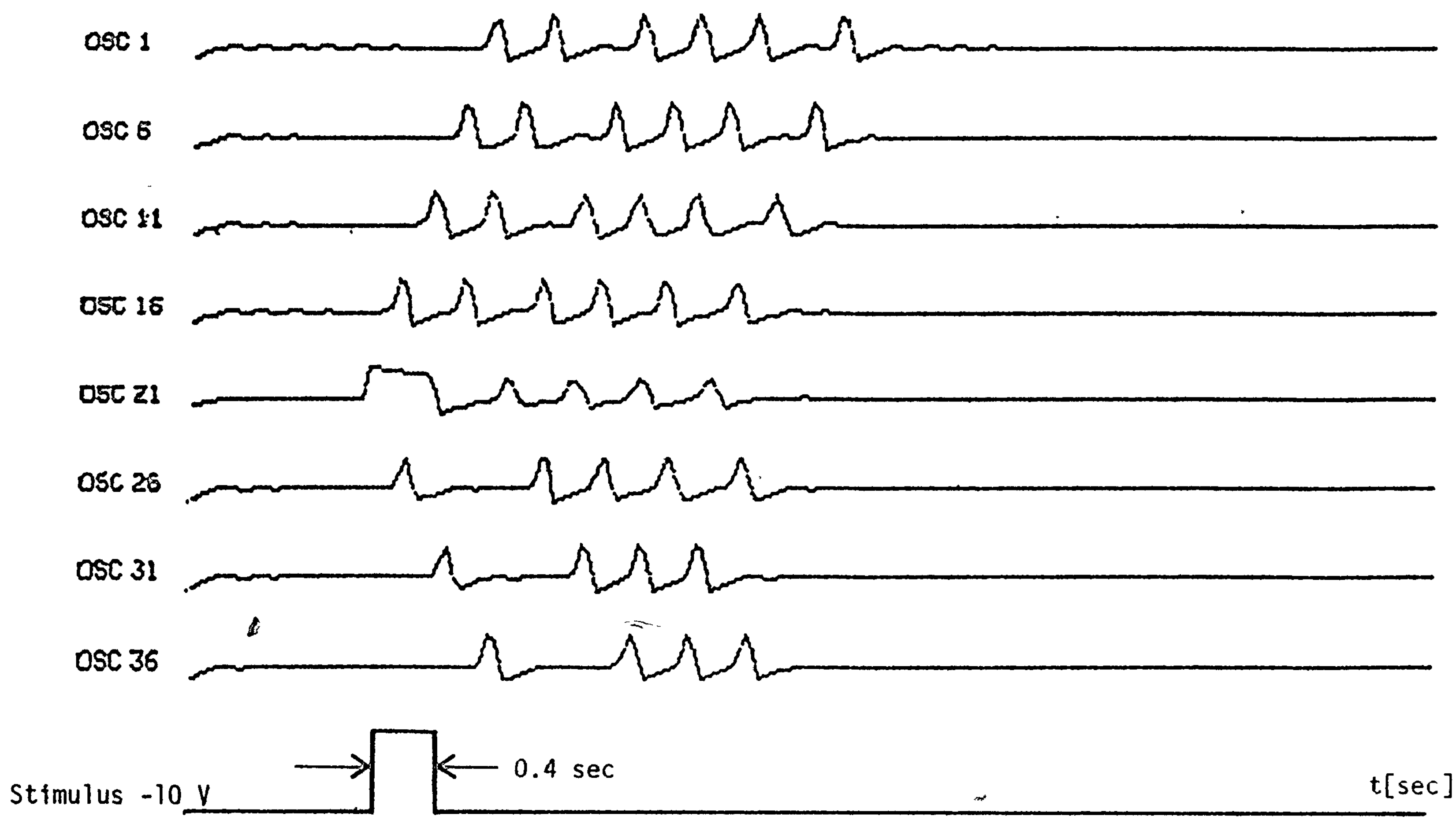

Fig. 4.8a. Bidirectionally propagating burst of direct muscle responses obtained with a stimulus of -10 V amplitude and 0.4 sec pulse width applied to oscillator #21. The responses are recorded throughout the chain of oscillators.

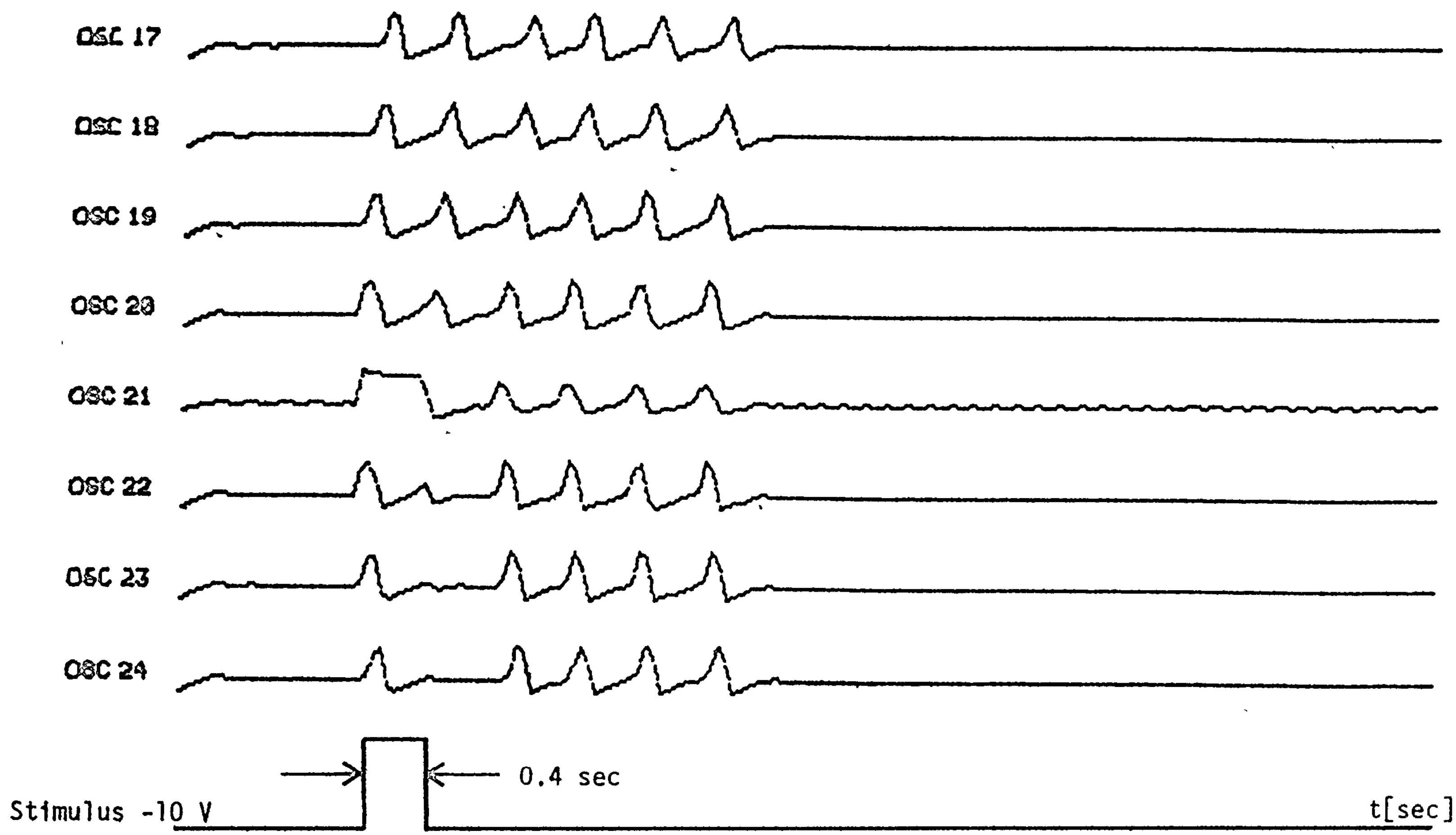

Fig. 4.8b. Direct muscle responses obtained with the application of the stimulus of -10 V amplitude and 0.4 sec pulse width to oscillator #21. The results shown are those from the neighbouring oscillators.

the chain. The stimulating pulse 5 V in amplitude when applied for 3 sec resulted in burst of "OFF" responses. These are represented by several spikes which occurred almost simultaneously throughout the chain. Figures 4.9a,b and c show the results of this stimulation. The decrease in the number of spikes in a burst from the beginning of the chain to the end is due to the difference in location of the stable working point in each oscillator. This decrease does not depend on the duration of the stimulus. For the same amplitude of stimulating pulse when applied for 4 sec - fig. 4.10, the duration of the generated burst of "OFF" responses was identical to that elicited when a stimulus of 5 V was applied for 3 sec (ref. fig. 4.9a,b, and c). A substantial increase in the duration of the burst of "OFF" responses was recorded upon application of the 10 V hyperpolarizing pulse for 3 sec - fig. 4.11a,b and c. In all of preceding cases, the stimulus was applied after 1 sec to show that there is no electrical activity in the absence of an external stimulus as recorded in the esophagus by Helleman et al (11). The velocity of propagation and the frequency of the oscillations were not affected by the amplitude or the duration of the hyperpolarizing pulses.

The "ON" responses were simulated when depolarizing pulses were applied to all oscillators in the chain. Those responses occurred shortly after stimulus onset and persisted throughout the stimulus duration. Three measurements were performed to check if the velocity of propagation of "ON" responses depends upon the amplitude of the depolarizing pulses. In each case a stimulus of different amplitude was applied to all oscillators for 2 sec. For a stimulating pulse with -0.250 V amplitude the "ON" responses occurred almost simultaneously - fig. 4.12.

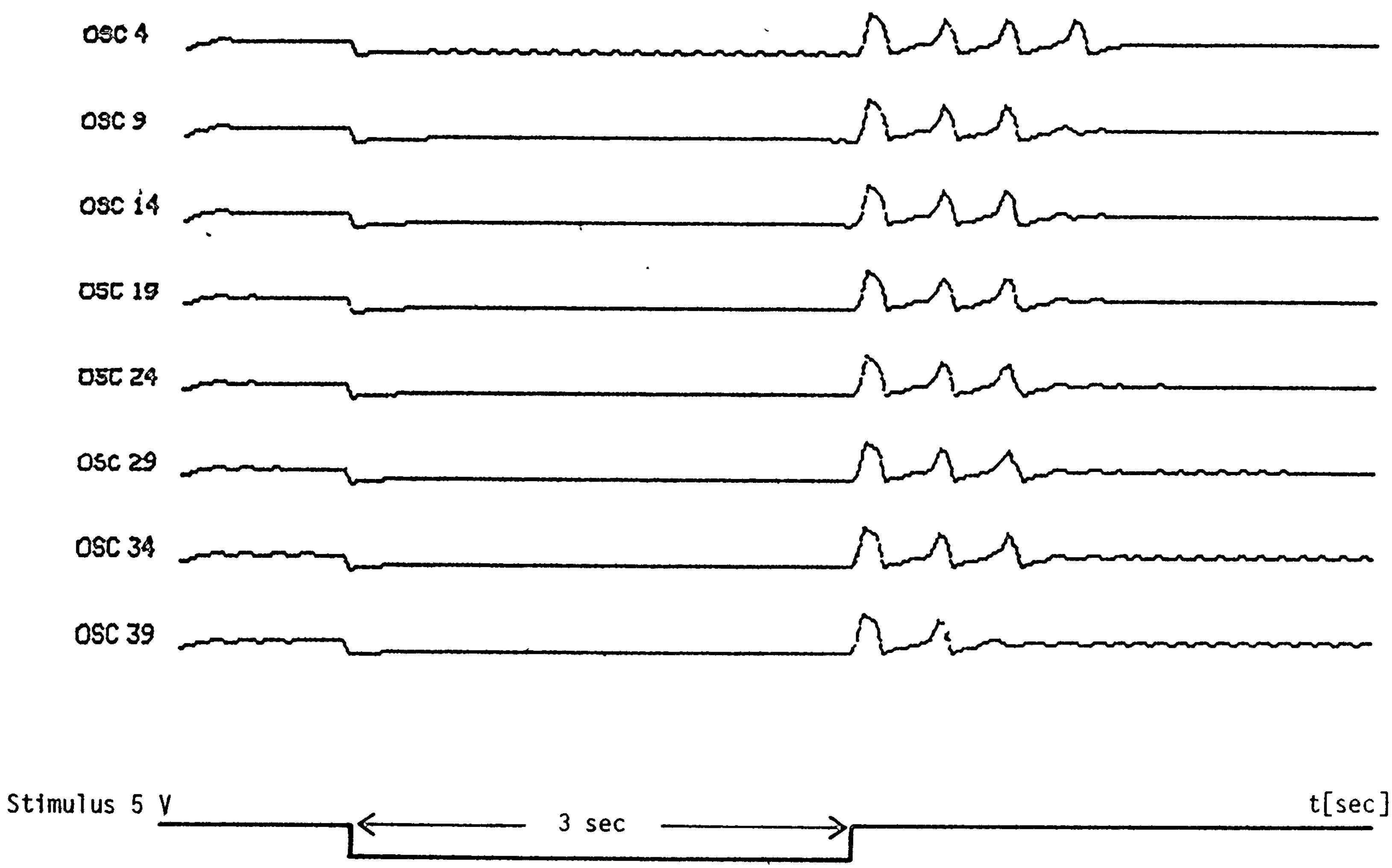

Fig. 4.9a. "OFF" responses recorded throughout the chain of oscillators when a hyporpolarizing pulse of 5 V amplitude was applied to each oscillator for 3 sec.

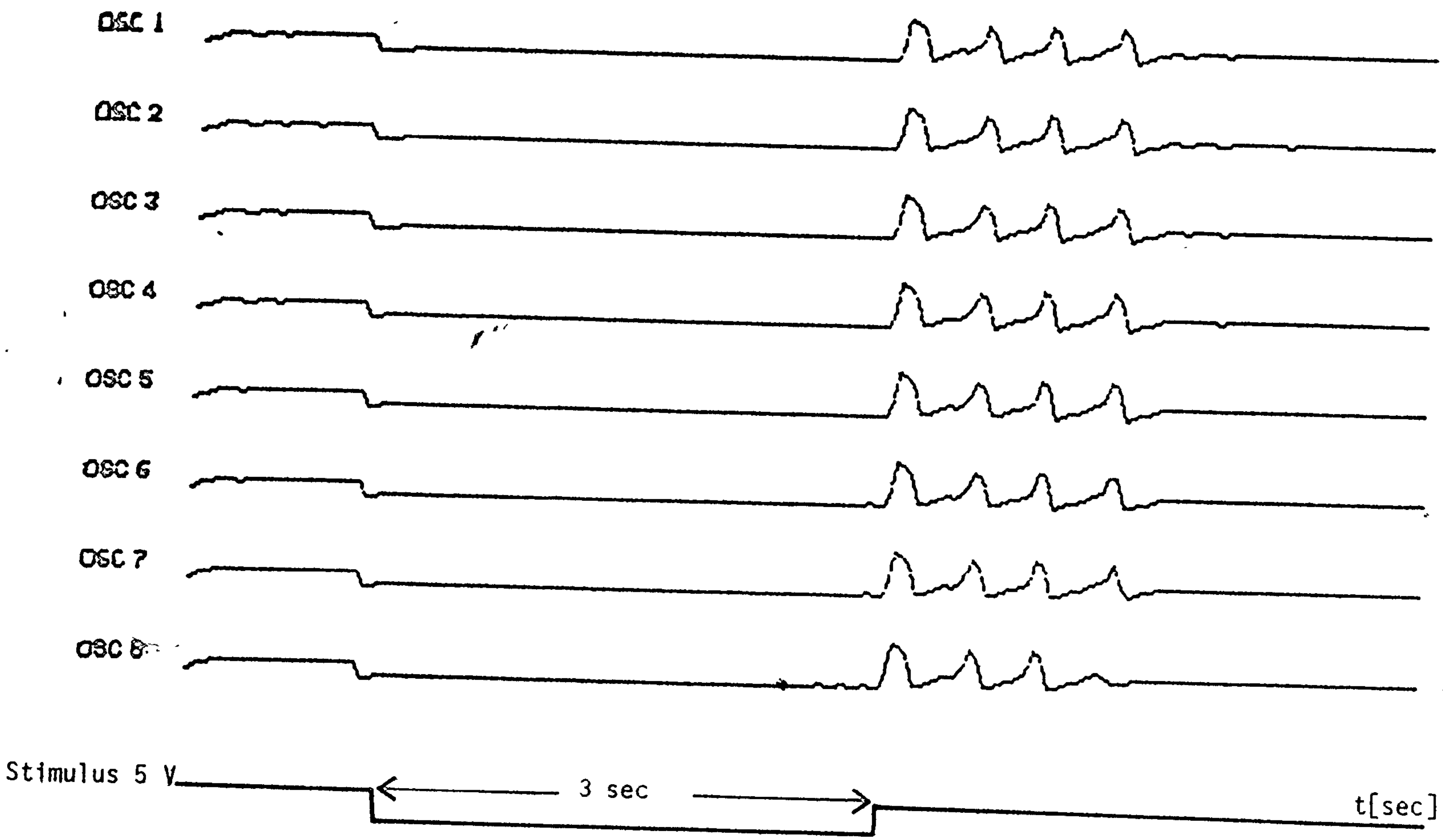

Fig. 4.9b. "OFF" responses elicited upon the application of a hyperpolarizing pulse of 5 V amplitude and 3 sec duration to all oscillators simultaneously. The responses shown are those at the beginning of the chain.

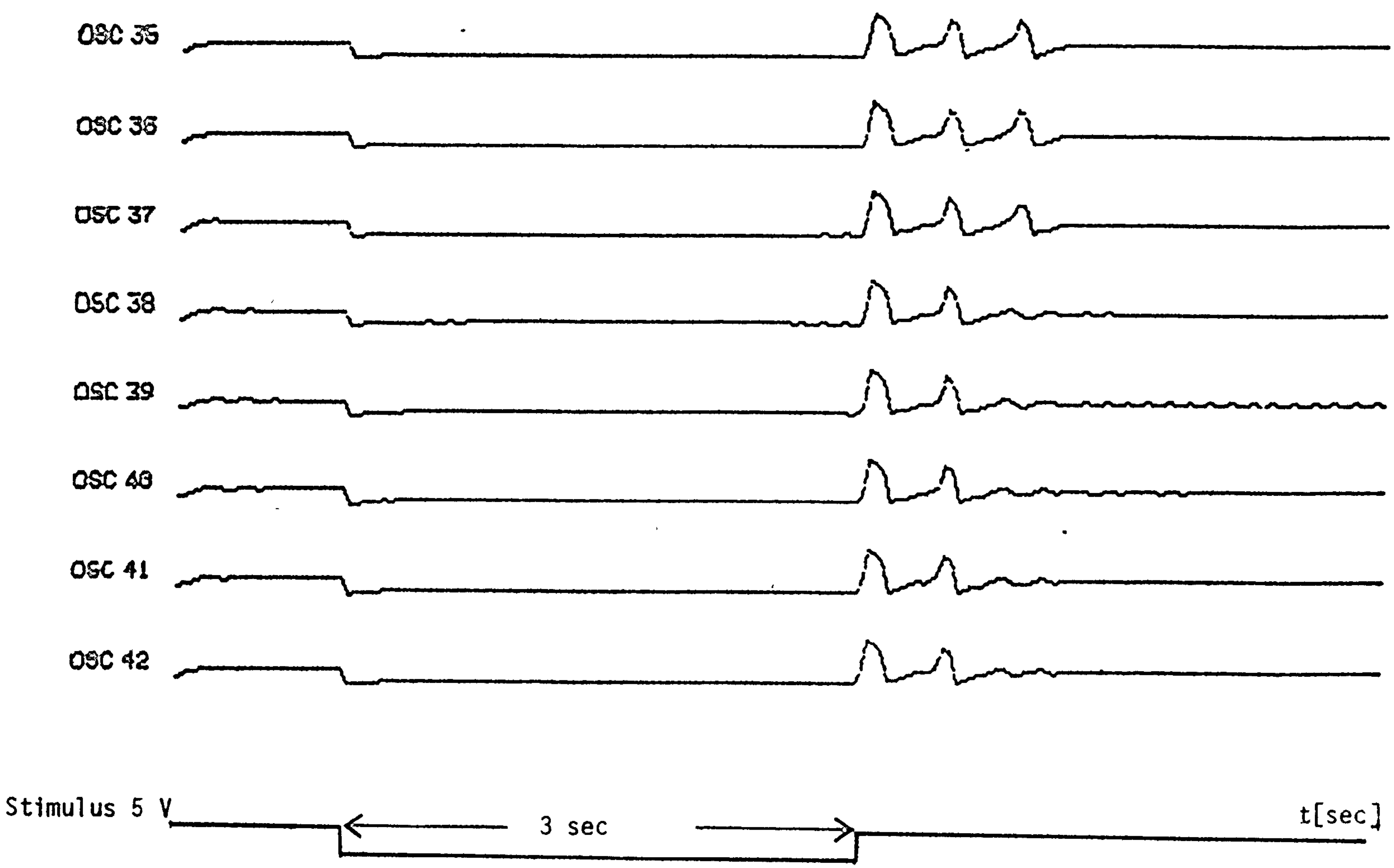

Fig. 4.9c. "OFF" responses elicited upon the application of a hyperpolarizing pulse of 5V amplitude and 3 sec duration to all oscillators simultaneously. The responses shown are those at the end of the chain.

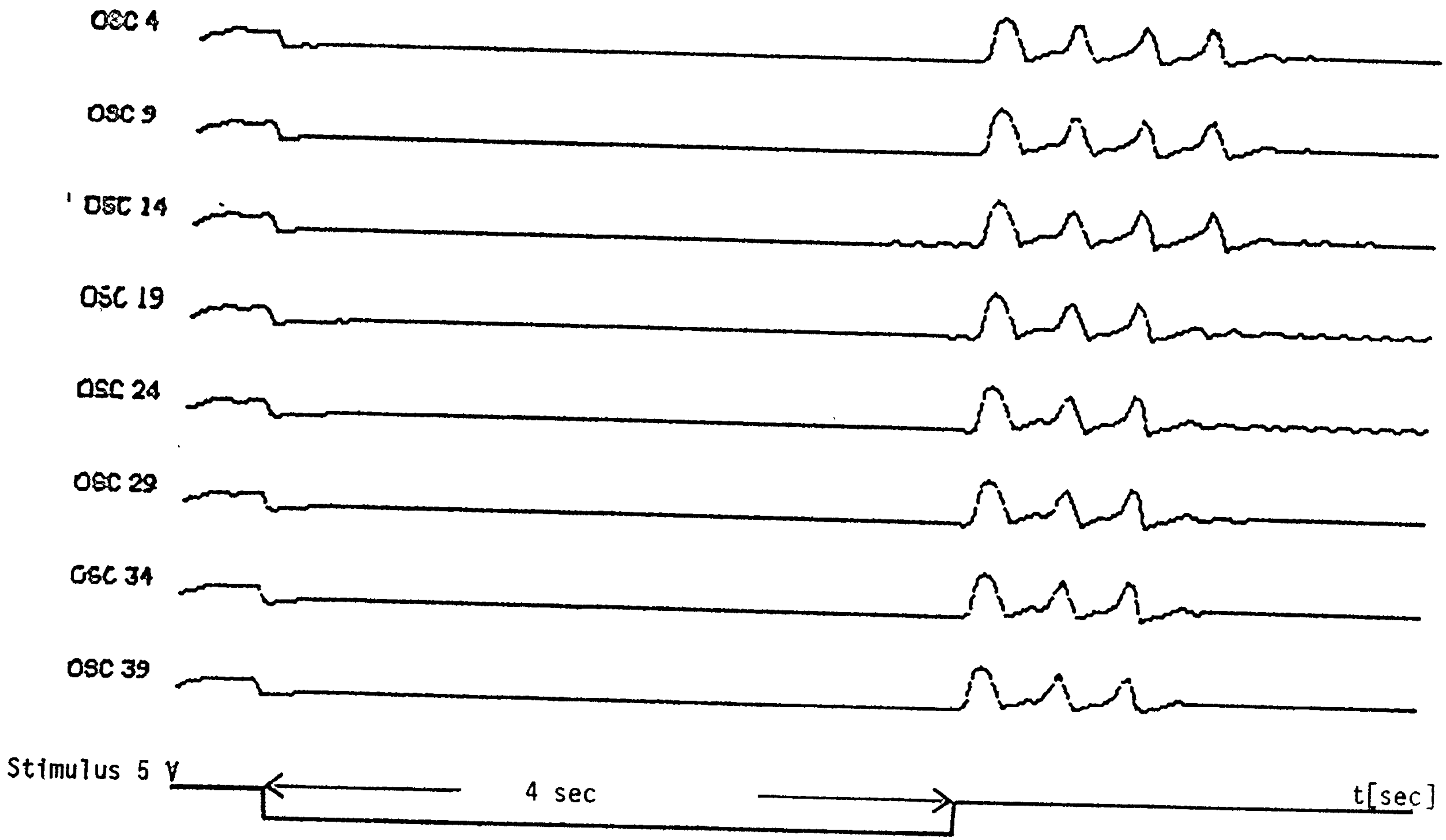

Fig. 4.10. "OFF" responses recorded throughout the chain of oscillators upon the application of a hyperpolarizing pulse of 5 V amplitude and 4 sec duration to all oscillators simultaneously.

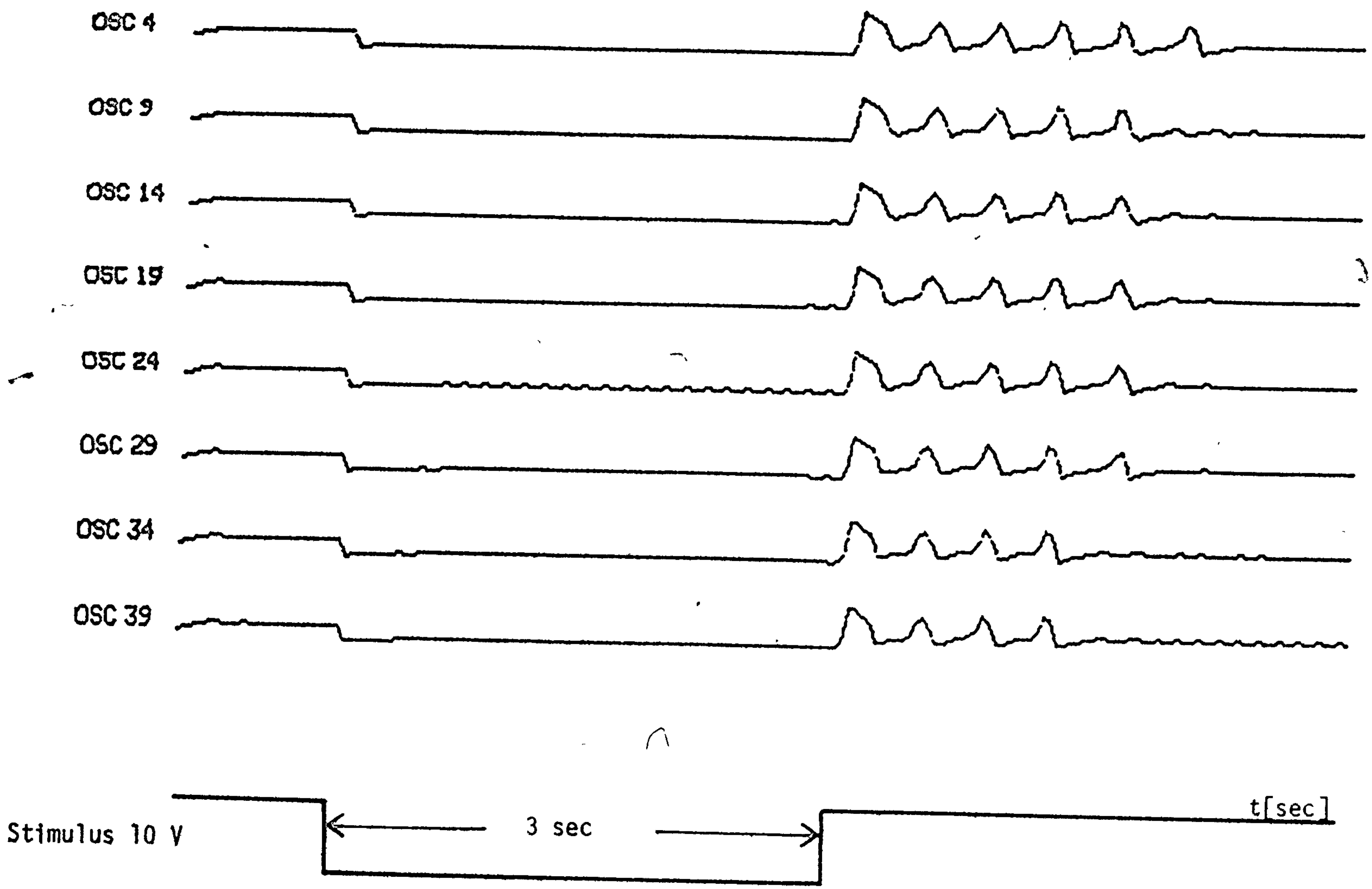

Fig. 4.11a. "OFF" responses elicited upon the application of a hyperpolarizing 10 V pulse for 3 sec to all oscillators simultaneously. The results shown are recorded throughout the chain of oscillators.

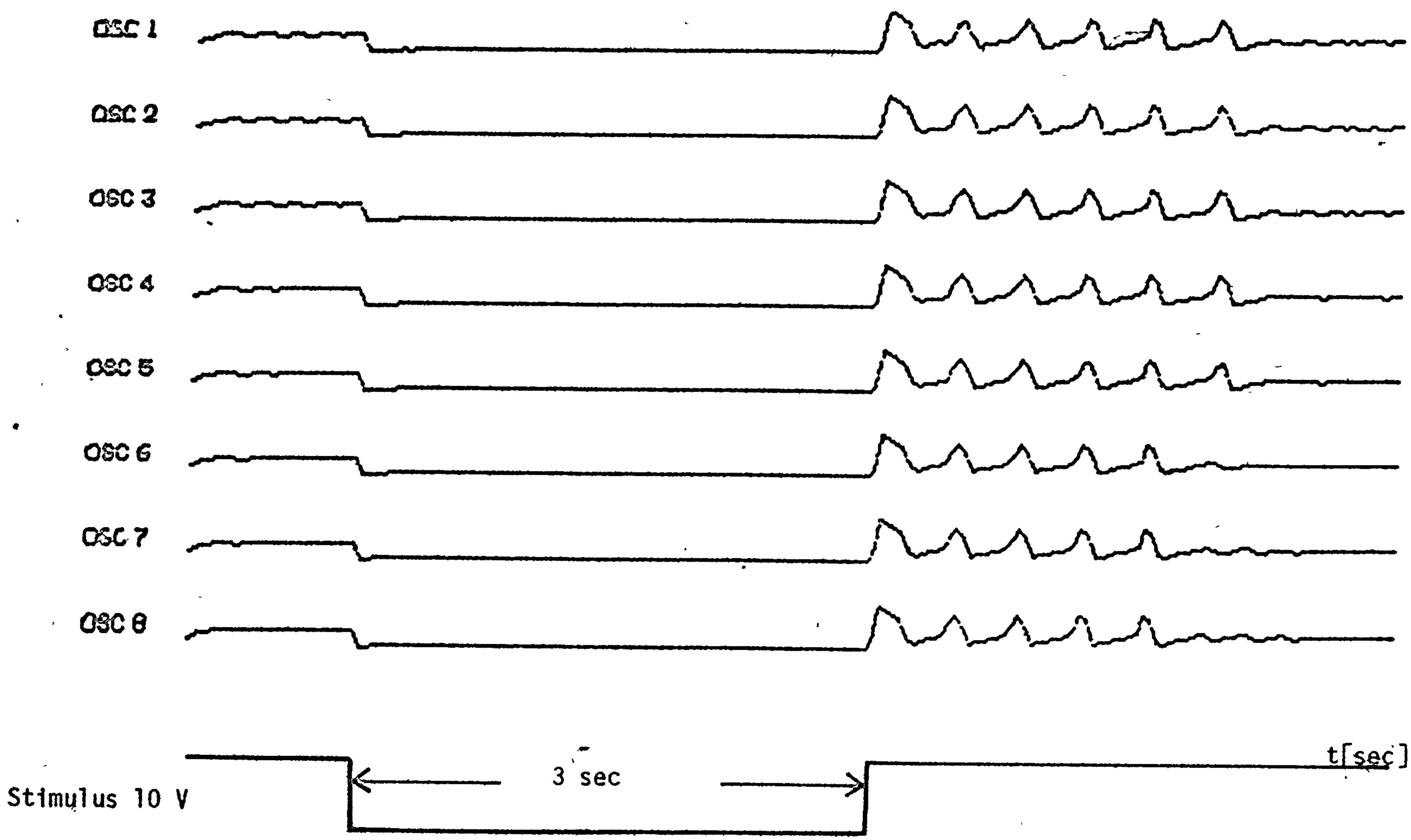

Fig. 4.11b. "OFF" responses elicited upon the application of a hyperpolarizing 10 V pulse for 3 sec to all oscillators. The results recorded are those from the beginning of the chain.

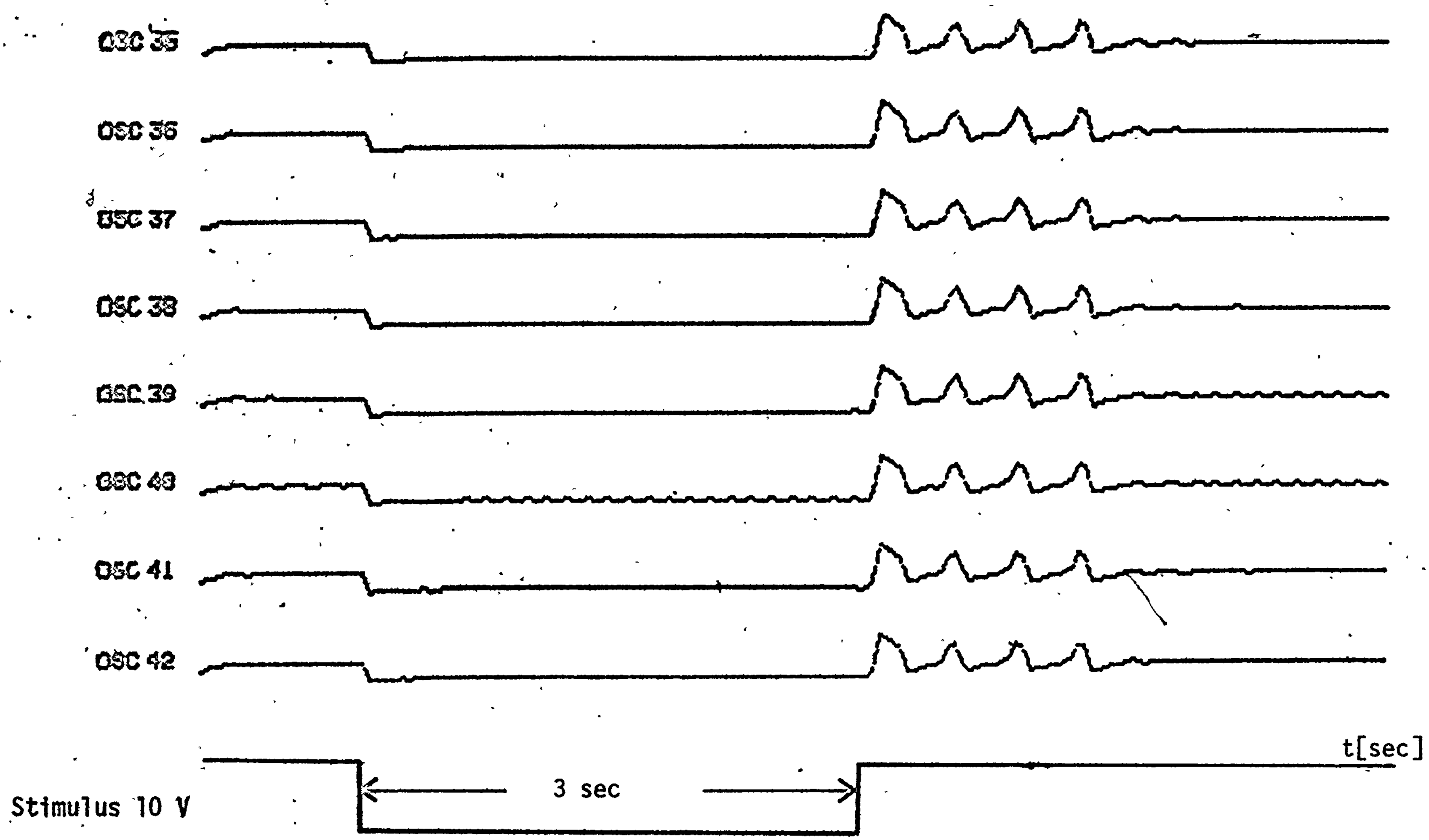

Fig. 4.11c. "OFF" responses elicited upon the application of the hyperpolarizing 10 V pulse for 3 sec to all oscillators. The results shown are those from the end of the chain.

Decreasing the amplitude of the stimulating pulse to -0.125 V and further to -0.100 V caused a small decrease in the velocity of propagation - fig. 4.13 and fig. 4.14.

The esophagus is innervated more in the proximal part than in the distal part. The "ON" responses were also checked when depolarizing pulses of distally decreasing amplitude from -0.125 V at oscillator #1 to -0.05 V at oscillator #42 were applied to all oscillators for 3 sec. The "ON" responses obtained showed a decreasing velocity of propagation throughout the chain - fig. 4.15.

In all of the preceding cases the frequency of generated spikes of "ON" responses was not affected by the amplitude or the duration of applied stimulus.

4.4 Summary

The chain of 42 relaxation oscillators used to model a 5 cm long smooth esophageal muscle simulated all of the characteristics as observed in this part of the gastrointestinal tract on vagal stimulation, balloon distension and direct muscle stimulation.

The ability of the myogenic control system to produce and propagate contractions and its modulation by the neuronal control system was also simulated.

The computer model of the smooth esophageal muscle should be considered as a basis for further studies of electrical events in this part of the gastrointestinal tract.

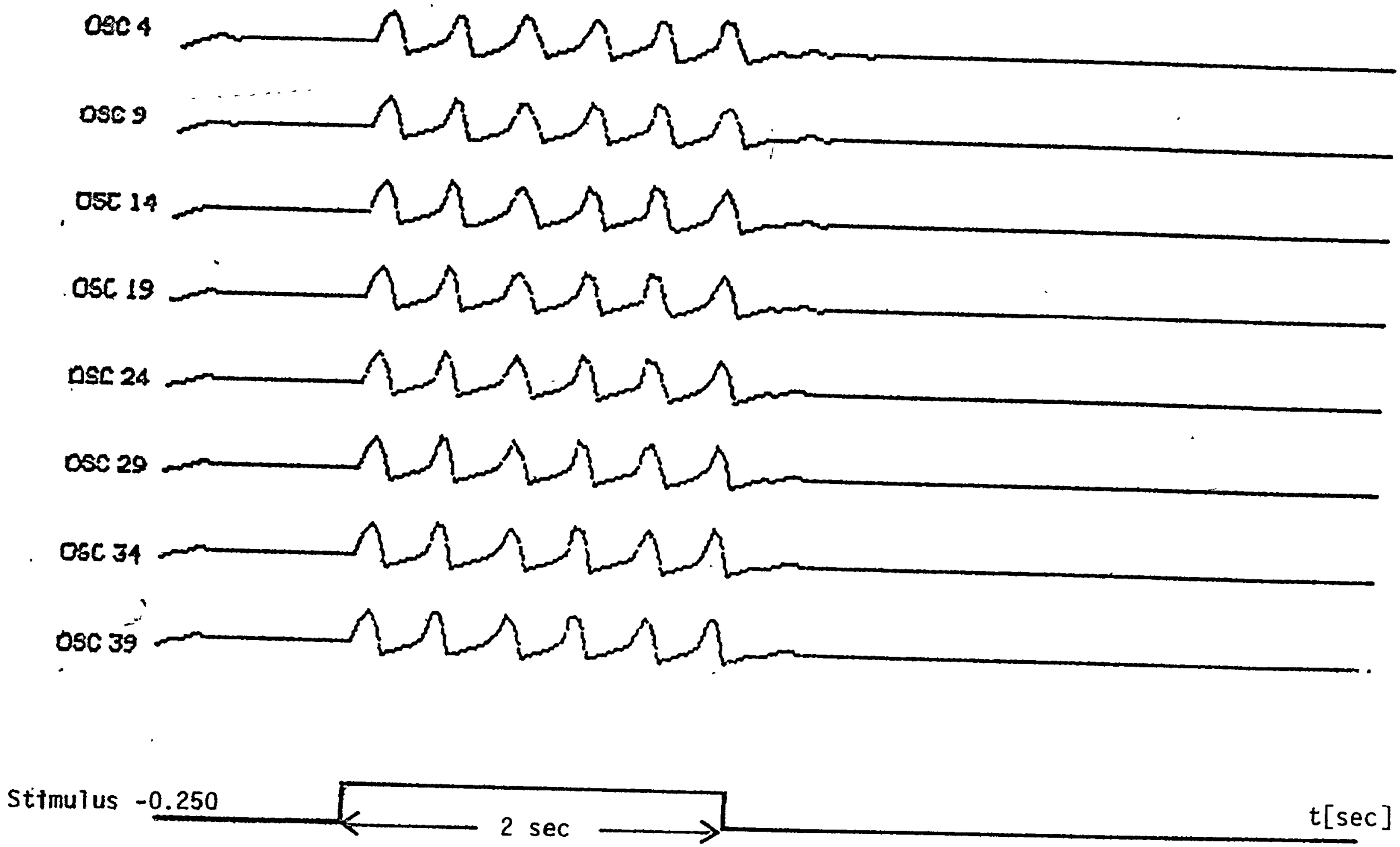

Fig. 4.12 . "ON" responses recorded throughout the chain when the depolarizing pulse of -0.250 amplitude was applied to all oscillators for 2 sec.

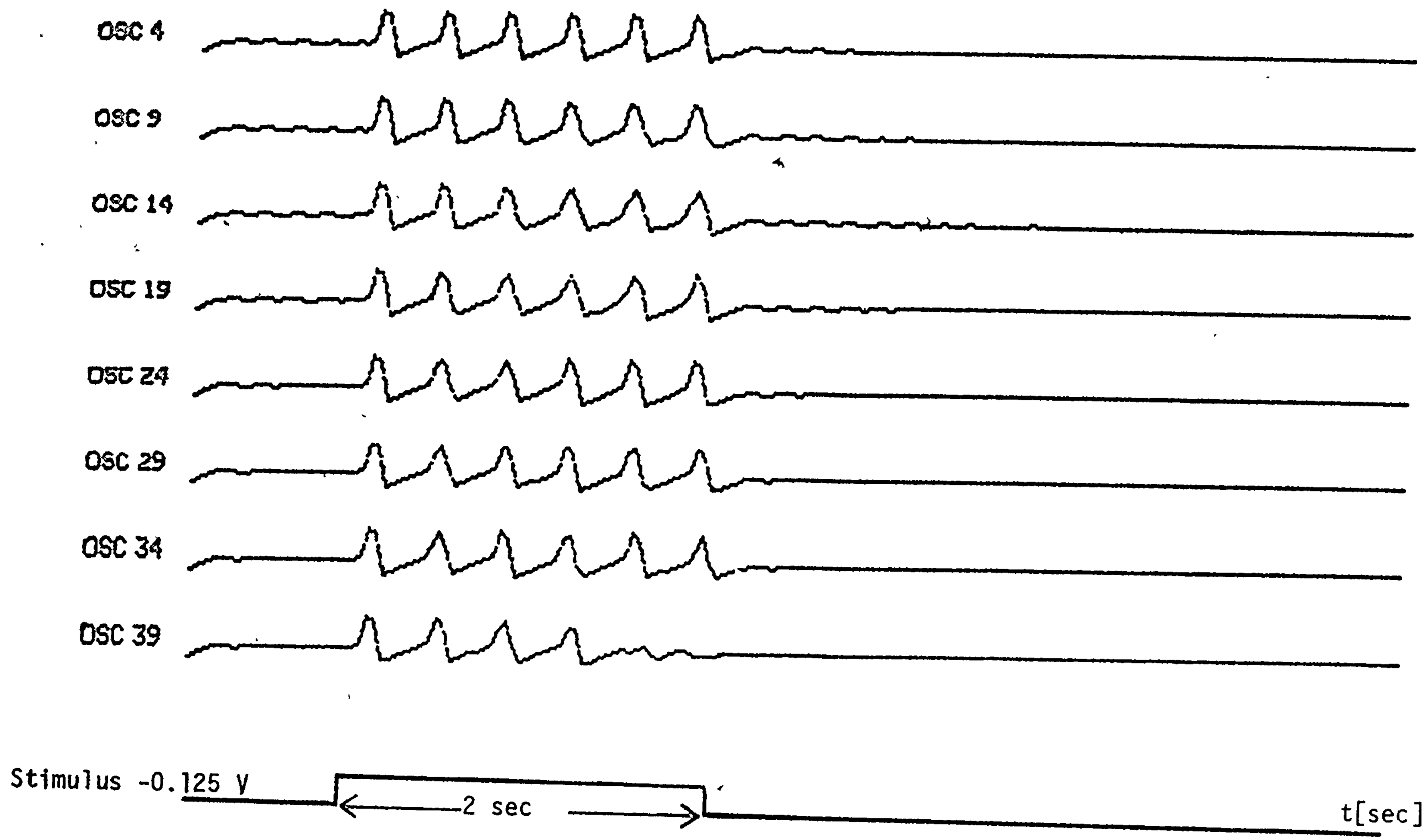

Fig. 4.13. "ON" responses recorded throughout the chain when the depolarizing pulse of -0.125 V amplitude was applied to all oscillators for 2 sec.

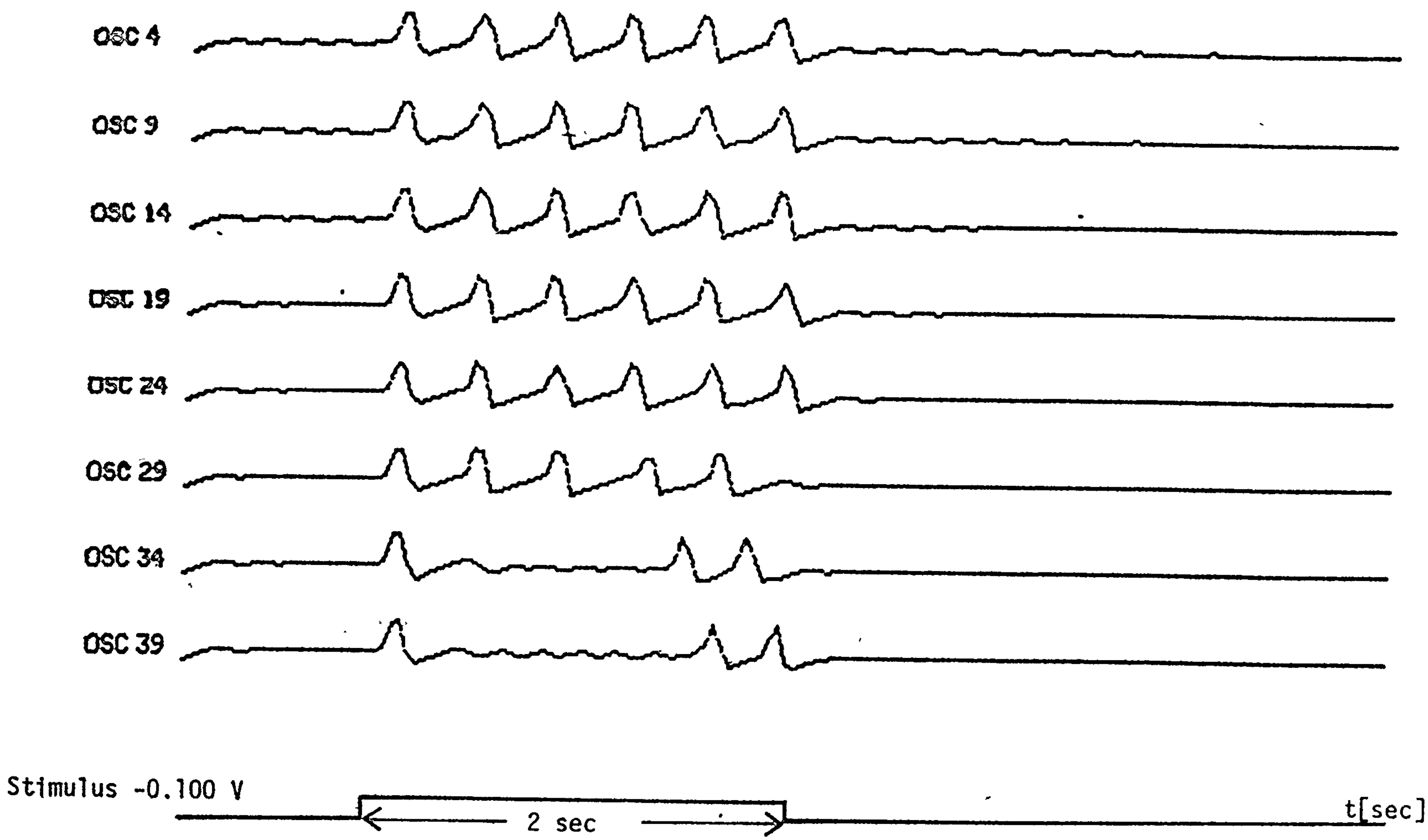

Fig. 4.14. "ON" responses elicited upon the application of the depolarizing pulse of -0.100 V amplitude 2 sec width to all oscillators. Results recorded throughout the chain.

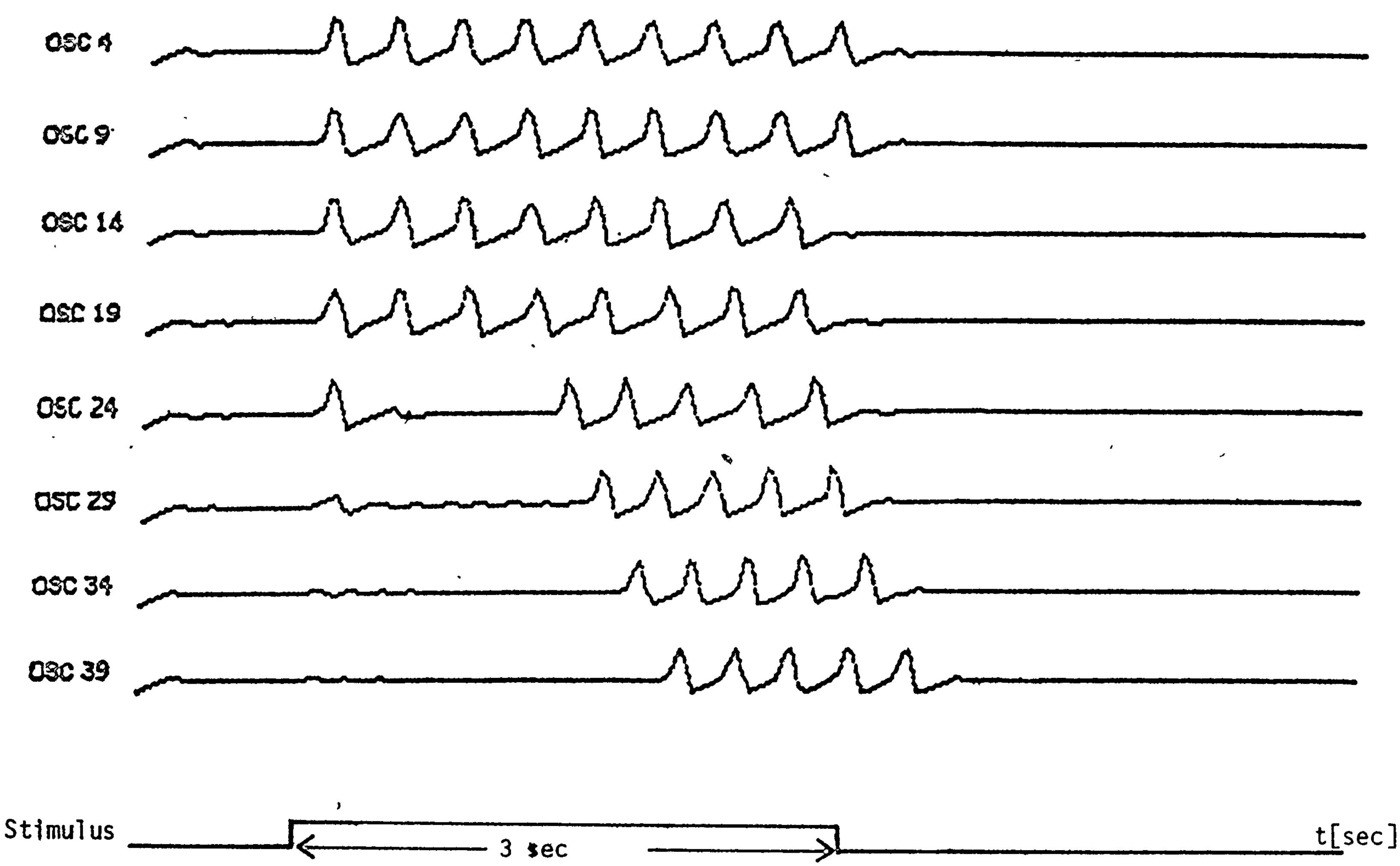

Fig. 4.15 "ON" responses recorded throughout the chain when the depolarizing pulses with decreasing distal amplitude (from -0.125 V at osc. #1 to -0.050 V at osc. #42) were applied for 3 sec to all oscillators.

CHAPTER V

AN ELECTRONIC REPRESENTATION OF THE RELAXATION OSCILLATORS IN THE COMPUTER MODEL OF THE ESOPHAGEAL ELECTRICAL ACTIVITY

5.1 General Information

Nagumo et al (22) have proposed an active transmission line to simulate the nerve axon. A similar transmission line using tunnel diodes is proposed as an electronic representation of the relaxation oscillators used in our computer model of the esophageal electrical activity. The line elements in the electronic simulator may be modelled by the cells each of which represents a single relaxation oscillator in the chain.

The following characteristics of an active line in the transmission of signals made it useful for the representation of the relaxation oscillators in the computer model:

a) bidirectional transmission of signal using the symmetric structure of the line,

b) signals smaller than a threshold value are eliminated during transmission.

5.2 An Electronic Simulation of Relaxation Oscillator

For a network simulation of equations (4.4) and (4.5) we consider the two terminal circuits of fig. 5.1 where TD is a tunnel diode.

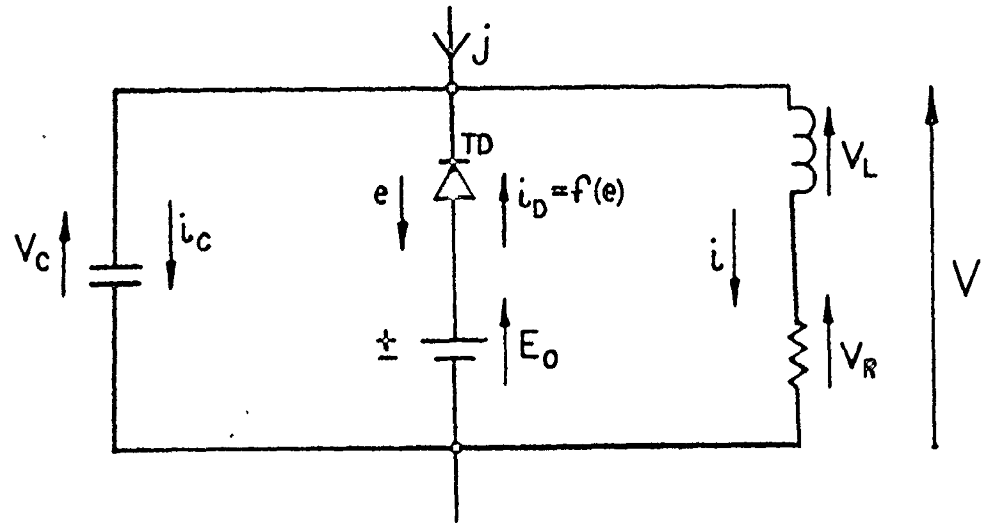

Fig. 5.1. Electronic simulator of the modified Fitzhugh equations.

From Kirchhoff's law we may write:

$$j = i_c + i - f(e)$$

and $$V = V_L + V_R = E_0 - e$$

or $$j = C\,\frac{dv}{d\tau} + i - f(e) \tag{5.1}$$

$$L\,\frac{di}{d\tau} + Ri = V = E_0 - e \tag{5.2}$$

where f(e) is a function which represents the voltage current characteristic of the tunnel diode.

In the mathematical analysis for an electronic simulator of an axon nerve Nagumo et al (22) assumed for simplicity that:

$$f(e) = i_0 - \frac{1}{\rho}\{(e - e_0) - \frac{e - e_0}{3K^2}\} \qquad \text{for } \rho > 0 \text{ and } K > 0$$

Following Nagumo's approach we were able to find the analytical solution to eq. (5.1) and (5.2) (describing the electronic model of the relaxation oscillator) by the introduction of a set of new variables.

The proposed new variables are:

$$\left\{\begin{array}{llll} t = \dfrac{\tau}{\omega\sqrt{LC}}, & u = \dfrac{(E_0 - e_0) - V}{K}, & w = \dfrac{1}{K}(i - i_0), & \\ b = \omega^2 R, & c = \omega\sqrt{\dfrac{L}{C}}, & I = -\dfrac{1}{K} j, & a = \dfrac{[(E_0 - e_0) - Ri_0]\,\omega^2}{K} \end{array}\right\} \quad (5.3)$$

Using the new variables we can represent $\frac{dv}{d\tau}$ from (5.1) and $\frac{di}{d\tau}$ from (5.2) as follows.

$$\frac{dv}{d\tau} = \frac{\frac{dt}{d\tau}}{\frac{du}{dv}}\frac{du}{dt} = \frac{\frac{1}{\omega\sqrt{LC}}}{-\frac{1}{K}}\frac{du}{dt} = \frac{-K}{\omega\sqrt{LC}}\frac{du}{dt}$$

$$\frac{di}{d\tau} = \frac{\frac{dt}{d\tau}}{\frac{dw}{di}}\frac{dw}{dt} = \frac{\frac{1}{\omega\sqrt{LC}}}{\frac{1}{K}}\frac{dw}{dt} = \frac{K}{\omega\sqrt{LC}}\frac{dw}{dt}$$

Introducing variables (5.3) to equation (5.1) we may write

$$-KI = C\left(-\frac{K}{\omega\sqrt{LC}}\right)\frac{du}{dt} + (wK + i_0) - [i_0 - \frac{1}{\rho}\ (e - e_0) - \{\frac{(e-e_0)^3}{3K^2}\}\ ]$$

$$-KI = -\frac{K}{\omega}\sqrt{\frac{C}{L}}\ \frac{du}{dt} + wK + i_0 - i_0 + \frac{1}{\rho}\{(e-e_0) - \frac{(e-e_0)^3}{3K^2}\}$$

$$KI = \frac{K}{\omega}\sqrt{\frac{C}{L}}\ \frac{du}{dt} - wK - \frac{1}{\rho}\ \{(e-e_0) - \frac{(e-e_0)^3}{3K^2}\}$$

but from (5.3)

$$uK = E_o - e_o - V \qquad \text{where} \quad V = E_o - e$$

$$uK = E_o - e_o - E_o + e$$

and so $uK = e - e_o$

therefore

$$KI = \frac{K}{\omega}\sqrt{\frac{C}{L}}\ \frac{du}{dt} - wK - \frac{K}{\rho}\left(u - \frac{u^3}{3}\right) \qquad / K$$

$$I = \frac{1}{\omega}\sqrt{\frac{C}{L}}\ \frac{du}{dt} - w - \frac{1}{\rho}\left(u - \frac{u^3}{3}\right)$$

Since from (5.3) $c = \omega\sqrt{\frac{L}{C}}$ the equation (5.1) can be written as:

$$\frac{du}{dt} = c\left[w + u - \frac{u^3}{3} + I\right] \tag{5.4}$$

Introduction of the new variables specified in (5.3) into equation (5.2) gives the following

$$L\frac{K}{\omega\sqrt{LC}}\ \frac{dw}{dt} + R(wK + i_o) = (E_o - e_o) - uK$$

$$L\frac{K}{\omega\sqrt{LC}}\ \frac{dw}{dt} + RwK + Ri_o = \left(\frac{aK}{\omega^2} + Ri_o\right) - uK \qquad \cdot\omega^2$$

$$\omega K\sqrt{\frac{L}{C}}\ \frac{dw}{dt} + R\omega^2 Kw = aK - uK\omega^2$$

$$\omega\sqrt{\frac{L}{C}}\ \frac{dw}{dt} + R\omega^2 w = a - \omega^2 u$$

$$c\,\frac{dw}{dt} + bw = a - \omega^2 u$$

$$\frac{dw}{dt} = -\frac{1}{c}\left(\omega^2 u - a + bw\right) \tag{5.5}$$

5.3 Conditions For An Electronic Model Simulator

On the basis of the similarity between the equations used to build our computer model (4.4), (4.5) with equations (5.4),(5.5), the conditions for the existence of a single stable point in a phase plane (4.6) and the oscillation cycles on excitation (6.22) can be compared with the proposed new variables (5.3). As a result of above comparisons the necessary requirements for each of the elements in the electronic model are determined.

From equations (4.6) and (6.22)

$$b < \omega^2$$

$$c^2 > b$$

$$k_1 = \frac{a}{b} > \frac{1}{3}$$

From equation (5.3)

$$b = \omega^2 R$$

$$c = \omega\sqrt{\frac{L}{C}}$$

$$a = \frac{[(E_0 - e_0) - Ri_0]\omega^2}{K}$$

Comparing conditions for "b" we have

$$b = \omega^2 R$$

therefore

$$R = \frac{b}{\omega^2} \tag{5.6}$$

The determination of a minimum value of E_0 can be done as follows.

$$a = \frac{[(E_0 - e_0) - R\,i_0]\omega^2}{K}$$

$$\frac{aK}{\omega^2} = (E_0 - e_0) - Ri_0$$

$$\frac{aK}{\omega^2} + Ri_0 = E_0 - e_0$$

$$E_o = \frac{aK}{\omega^2} + Ri_o + e_o \tag{5.7}$$

The conditions for the inductance and the capacitance values needed for electronic model can be determined as follows. We consider $\frac{t}{\tau}$ as a scaling factor, where $\frac{t}{\tau} = \frac{1}{\omega\sqrt{LC}}$.

From (5.3)

$$c^2 = \omega^2 \frac{L}{C}$$

but recognizing the scaling factor

$$C = \frac{\tau^2}{t^2\ \omega^2\ L}$$

$$c^2 = \frac{\omega^2 L}{\frac{\tau^2}{t^2\ \omega^2\ L}} = \frac{t^2\ \omega^2\ L^2\ \omega^2}{\tau^2}$$

$$c = \frac{t\ L\ \omega^2}{\tau}$$

therefore

$$L = \frac{c\ \tau}{t\ \omega^2} \tag{5.8}$$

and

$$C = \frac{\tau^2}{\frac{t^2\ \omega^2\ c\ \tau}{t\ \omega^2}} = \frac{\tau^2\ t\ \omega^2}{t^2\ \omega^2\ c\ \tau}$$

therefore

$$C = \frac{\tau}{t\ c} \tag{5.9}$$

5.4 Finding The Parameters of the Tunnel Diode Required For An Electronic Model

The voltage current characterisitic of the tunnel diode is shown on fig. 5.2.

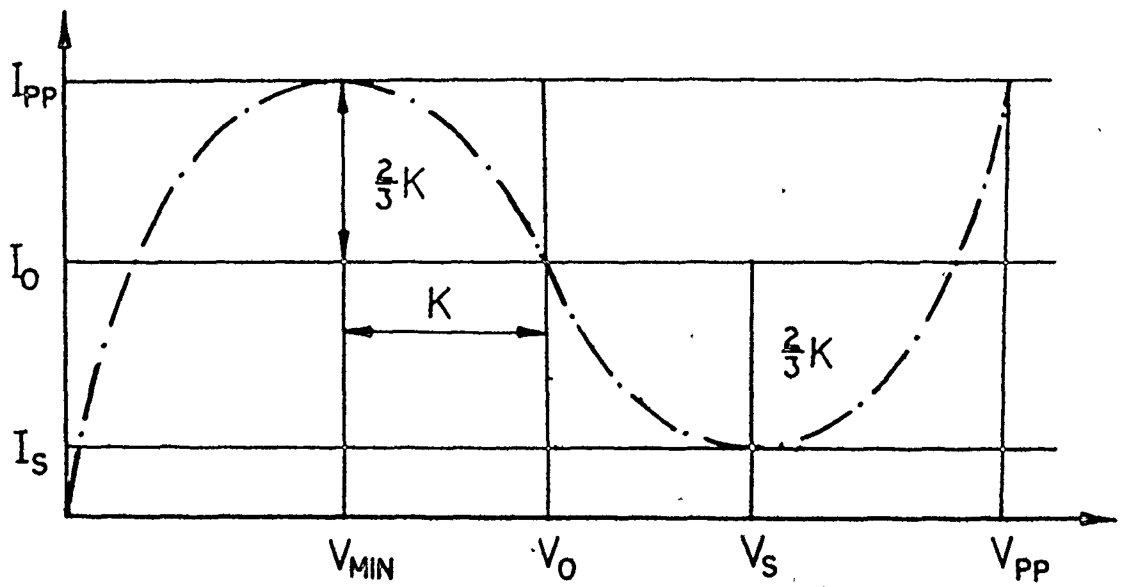

Fig. 5.2. Voltage-current characteristic of the tunnel diode ($V_o = e_o$).

In general

$$V_{MIN} \doteq 0.1 \text{ V}$$

$$V_s \approx 0.3 \text{ V}$$

therefore

$$e_o = V_{MIN} + \frac{V_S - V_{MIN}}{2} = 0.2 \text{ V}$$

but from definition $K = e_o - V_{MIN}$ and so $K = 0.1$ for almost all diodes.

An important factor for the selection of the diode is to find the right value of I_{pp} which is needed for the electronic model. If $I_o = \frac{I_{pp}}{2}$ and $I_o > \frac{2}{3} K$

$$\frac{I_{pp}}{2} > \frac{2}{3} K$$

$$I_{pp} > \frac{4}{3} K$$

Since for most of the diodes K = 0.1

$$I_{pp} > \frac{4}{30}$$

5.5 Example

The parameters for the first relaxation oscillator used in the proposed model (42 bidirectionally coupled oscillators) are:

$$a = 930$$

$$b = 500$$

$$c = 100$$

$$\omega^2 = 1250$$

From the previously determined conditions

$$R < 1$$

since $b = \omega^2 R$

$$R = \frac{b}{\omega^2} = \frac{500}{1250}$$

$$R = 0.4\ \Omega$$

If K = 0.1

$$I_{pp} = \frac{4}{30}$$

$$I_{pp} = 0.13\ \text{A}$$

$$I_o = 0.065\ \text{A}$$

$$E_o = \frac{aK}{\omega^2} + Ri_o + e_o \qquad \text{where } e_o \approx 0.2\ \text{V typical}$$

$$E_o = \frac{930 \times .1}{1250} + (.4 \times .065) + .2$$

$$E_o = 0.3004 \text{ V}$$

$$L = \frac{c}{\omega^2} = \frac{100}{1250} = 0.080$$

$$L = 80 \text{ mH}$$

$$C = \frac{1}{\omega^2 L} = \frac{1}{1250.0.080}$$

$$C = 10 \text{ mF}$$

In conclusion the conditions for the first oscillator are

$$R = 0.4\ \Omega$$

$$C = 10 \text{ mF}$$

$$L = 80 \text{ mH}$$

$$E_o = 0.3004 \text{ V}$$

$$I_{pp} > 0.13 \text{ A}$$

5.6 Summary

An electronic model for each oscillator used in a chain which is described by a set of two first order nonlinear differential equations is proposed. This may be considered as a basis to develop an electronic model of the esophageal electrical activity.

CHAPTER VI

MATHEMATICAL ANALYSIS

6.1 Necessary Conditions For the Existence of a Stable Singular Point "P"

The system equations are:

$$\dot{x} = c[y + x - \frac{x^3}{3} + zz] \tag{6.1}$$

$$\dot{y} = -\frac{1}{c}[\omega^2 x - a + by] \tag{6.2}$$

Fitzhugh (9) has shown that the necessary conditions for the existence of a stable singular point "P" can be calculated as follows.

Set $\dot{x} = 0$, $\dot{y} = 0$ in equation (6.1) and (6.2), then using Taylor series expansion for the function of two variables we have for equation (6.1)

$$f(x,y) = c[y_1 + x_1 - \frac{x_1^3}{3} + zz] + c[(1 - x_1^2)(x - x_1)] + c(y - y_1) - $$

$$- \frac{c\ 2x_1}{2}(x - x_1)^2 - \frac{c2}{6}(x - x_1)^3 + \ldots..$$

Introducing

$$x - x_1 = \xi$$

$$y - y_1 = \eta$$

we have

$$f(x,y) = f(x_1,y_1) + c[(1-x_1^2)\xi] - cx_1\xi^2 - \frac{c}{3}\xi^3 + c\eta$$

$$f(x,y) = f(x_1,y_1) + c[(1-x_1^2)\xi - x_1\xi^2 - \frac{1}{3}\xi^3 + \eta]$$

$$\dot{x} = \dot{x}_1 + ck$$

$$\dot{x} - \dot{x}_1 = ck$$

$$\dot{\xi} = ck$$

$$\dot{\xi} = c[(1 - x_1^2)\xi - \xi^2 x_1 - \frac{\xi^3}{3} + \eta] \qquad (6.3)$$

Using Taylor series for equation (6.2) we have

$$f(x,y) = -\frac{1}{c}(\omega^2 x_1 - a+by_1) - \frac{1}{c}[\omega^2(x-x_1)] - \frac{1}{c}b(y-y_1)$$

$$f(x,y) = f(x_1,y_1) - \frac{1}{c}\omega^2\xi - \frac{1}{c}b\eta$$

$$\dot{y} = \dot{y}_1 - \frac{1}{c}\omega^2\xi - \frac{b}{c}\eta$$

$$\dot{y} - \dot{y}_1 = -\frac{b}{c}\eta - \frac{1}{c}\omega^2\xi$$

$$\dot{\eta} = -\frac{b}{c}\eta - \frac{1}{c}\omega^2\xi \qquad (6.4)$$

We now have a set of equations (6.3), (6.4) of which (6.3) is nonlinear. If we omit the terms of higher than first order from the right hand side we obtain a pair of linear equations which have a singular point at the origin ($\xi = \eta = 0$) - Fitzhugh (9). According to Lyapunoff's theory this point has the same stability properties as the singular point in the non-linear equations - therefore equations (6.3) and (6.4) give the following:

$$\dot{\xi} = c(1 - x_1^2)\xi + \eta c \qquad (6.5)$$

$$\dot{\eta} = -\frac{b}{c}\eta - \frac{\omega^2\xi}{c} \qquad (6.6)$$

Form the matrix of the coefficients of the right hand side of this pair of linear equations we have

$$\begin{bmatrix} \dot{\xi} \\ \dot{\eta} \end{bmatrix} = \begin{bmatrix} c(1 - x_1^2), & c \\ -\frac{\omega^2}{c}, & -\frac{b}{c} \end{bmatrix} - \begin{bmatrix} \xi \\ \eta \end{bmatrix}$$

and so

$$\det(A-\lambda I) = \det\left[\begin{array}{cc} c(1-x_1^2)\ , & c \\ -\frac{\omega^2}{c}\ , & -\frac{b}{c} \end{array}\right] - \left[\begin{array}{cc} 1 & 0 \\ 0 & 1 \end{array}\right]\lambda$$

$$\left|\begin{array}{cc} c(1-x_1^2) - \lambda, & c \\ -\frac{\omega^2}{c}\ , & -\frac{b}{c} - \lambda \end{array}\right| = 0$$

$$[c(1-x_1^2) - \lambda](-\frac{b}{c} - \lambda) + \omega^2 = 0$$

$$\lambda^2 + \lambda[\frac{b}{c} - c(1-x_1^2)] + [\omega^2 - b(1-x_1^2)] = 0$$

or writing in a more compact form we have

$$\lambda^2 + A\lambda + B = 0$$

where $A = \frac{b}{c} - c(1 - x_1^2)$

$$B = \omega^2 - b(1 - x_1^2)$$

The eigenvalues are as follows

$$\lambda_1 = \alpha + j\beta = -\frac{A}{2} + \frac{1}{2}\sqrt{A^2 - 4B} \qquad (6.7)$$

$$\lambda_2 = \alpha - j\beta = -\frac{A}{2} - \frac{1}{2}\sqrt{A^2 - 4B} \qquad (6.8)$$

The general solution for ξ and η can be given in an exponential form as follows:

$$\xi = A_1e^{\lambda_1 t} + B_1e^{\lambda_2 t} = e^{\alpha t}(A_1e^{j\beta t} + B_1e^{-j\beta t}) \qquad (6.9)$$

$$\eta = A_2e^{\lambda_1 t} + B_2e^{\lambda_2 t} = e^{\alpha t}(A_2e^{j\beta t} + B_2e^{-j\beta t}) \qquad (6.10)$$

The solution (6.9) and (6.10) will be stable if for $t \to \infty$, ξ and η approach the constant values implying that α has to be negative, which results in A being positive.

Therefore

$$\frac{b}{c} - c(1 - x_1^2) > 0$$

$$1 - x_1^2 < \frac{b}{c^2} \tag{6.11}$$

In order for the general solution to represent the relaxation oscillator, the imaginary parts of eigenvalues (6.7) and (6.8) have to exist. For a stable point "P" located at $x_1 \simeq 1$ (see fig. 6.1), B >> A, therefore condition B > 0 is sufficient for A ≃ 0, giving the following

$$\omega^2 - b(1 - x_1^2) > 0$$

$$1 - x_1^2 < \frac{\omega^2}{b} \tag{6.12}$$

If $\frac{\omega^2}{b} > 1$ from equation (6.12) we have

$$\omega^2 > b$$

$$b < \omega^2$$

If $\frac{b}{c^2} < 1$, from equation (6.11) we have

$$c^2 > b$$

To derive the conditions on "a" we go back to equation (6.1) and (6.2). Setting $\dot{x} = \dot{y} = 0$ in those equations we have from (6.1)

$$y = -x + \frac{x^3}{3} + zz \tag{6.13}$$

and from (6.2)

$$y = \frac{a - \omega^2 x}{b} \tag{6.14}$$

For zz = 0

$$-x + \frac{x^3}{3} = \frac{a - \omega^2 x}{b}$$

$$-x + \frac{x^3}{3} = \frac{a}{b} - \frac{\omega^2 x}{b}$$

$$\frac{x^3}{3} - \frac{\omega^2 x}{b} - x - \frac{a}{b} = 0$$

$$r = \frac{3}{3} (\frac{\omega^2}{b} - 1)$$

$$q = \frac{1}{2} (-3 \frac{a}{b})$$

For the case $\omega^2 > 0$ we should have $a > 0$ and $b > 0$

$$r^2 + q^3 < 0$$

$$(\frac{\omega^2}{b} - 1)^2 - (\frac{3a}{2b})^3 < 0$$

$$a \geq \frac{2}{3} b \sqrt[3]{(\frac{\omega^2 - 1}{b})^2}$$

In general the location of a singular stable point "P" can be obtained from the conditions

$$b < \omega^2, \qquad c^2 > b , \qquad a \geq \frac{2}{3} b \sqrt[3]{(\frac{\omega^2 - 1}{b})^2} \tag{6.15}$$

6.2 Necessary Conditions for the Stable Point "P" Located Near the Boundary Between Stable and Unstable Region

Equations (6.13) and (6.14) used for the determination of the parameter "a" in stability conditions are represented graphically in fig. 6.1. Introduction of parameters k_1 and k_2 describing the slope of the function $\dot{y} = 0$ allow us to determine parameter "a_{MIN}" which together with parameters "c" and "b" can locate easily the stable singular point "P" close to the boundary of the unstable region.

Equation (6.14) can be written in a form describing a straight

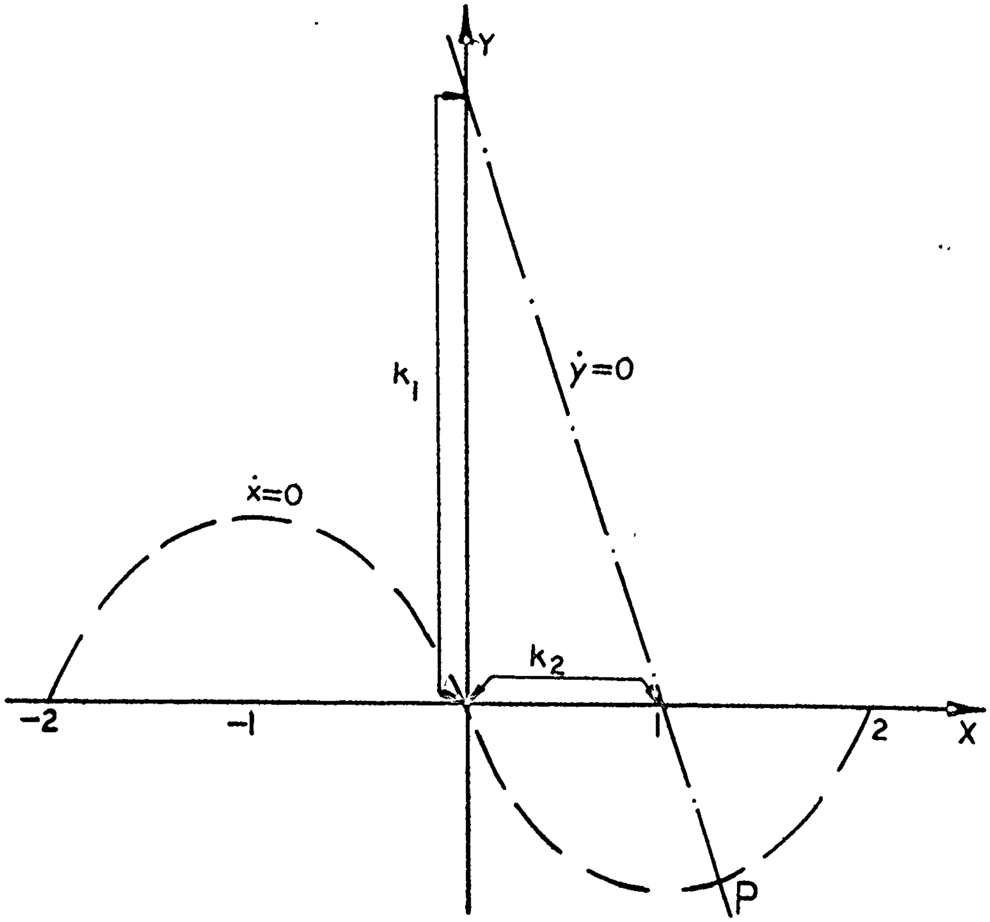

Fig. 6.1 Graphical representation of equations (6.13) and (6.14) ($\dot{x} = \dot{y} = 0$).

line in X, Y plane

$$y = \frac{a}{b} - \left(\frac{\omega^2}{b}\right)x \tag{6.16}$$

Introducing $k_1 = \frac{a}{b}$ and $\frac{\omega^2}{b} = \frac{k_1}{k_2}$ equation (6.16) can be shown as:

$$y = k_1 - \frac{k_1}{k_2}\,x \tag{6.17}$$

For the determination of "a_{MIN}" we go back to equation (6.13). If

zz = 0

$$y = \frac{x^3}{3} - x$$

$$\frac{dy}{dx}{/_{x\,=\,0}} = x^2 - 1$$

$$x^2 = 1$$

$$x = \pm 1$$

For $x = 1$ $\quad y = -\frac{2}{3}$ $\quad$ - min.

$x = -1$ $\quad y = \frac{2}{3}$ $\quad$ - max.

Going back to equation (6.17), for x = 1 we have

$$-\frac{2}{3} = k_1 - \frac{k_1}{k_2}$$

$$k_2 = \frac{1}{1 + \frac{2}{3} k_1}$$

Since from approximation $k_1 = \frac{a}{b}$, $k_2 = \frac{bk_1}{\omega^2}$

$$\frac{bk_1}{\omega^2} = \frac{1}{1 + \frac{2}{3} k_1}$$

$$\frac{a}{\omega^2} = \frac{1}{1 + \frac{2}{3}\frac{b}{a}}$$

$$\frac{a}{\omega^2} = \frac{a}{a + \frac{2}{3} b}$$

$$\omega^2 = a + \frac{2}{3} b$$

$$a = \omega^2 - \frac{2}{3} b$$

Therefore

$$a_{MIN} = \omega^2 - \frac{2}{3} b \tag{6.18}$$

Conditions for "b" and "c" specified in (6.15) and condition for "a_{MIN}" designate the location of the stable point "P" in the first oscillator of our chain

$$a_{MIN} \geq \omega^2 - \frac{2}{3} b \quad , \qquad b < \omega^2 \quad , \qquad c^2 > b \qquad (6.19)$$

The minimum value of k_1 which allows us to get oscillations when the stable point "P" is moved beyond the threshold separtrix can be determined. We write an equation describing a straight line of slope larger than the slope of a function described by equation (6.13) at point x = 0 and crossing a stable point "P" at x = 1 - see fig. 6.2, (the slope of the straight line has to be larger, so that only one unstable point exists during excitation).

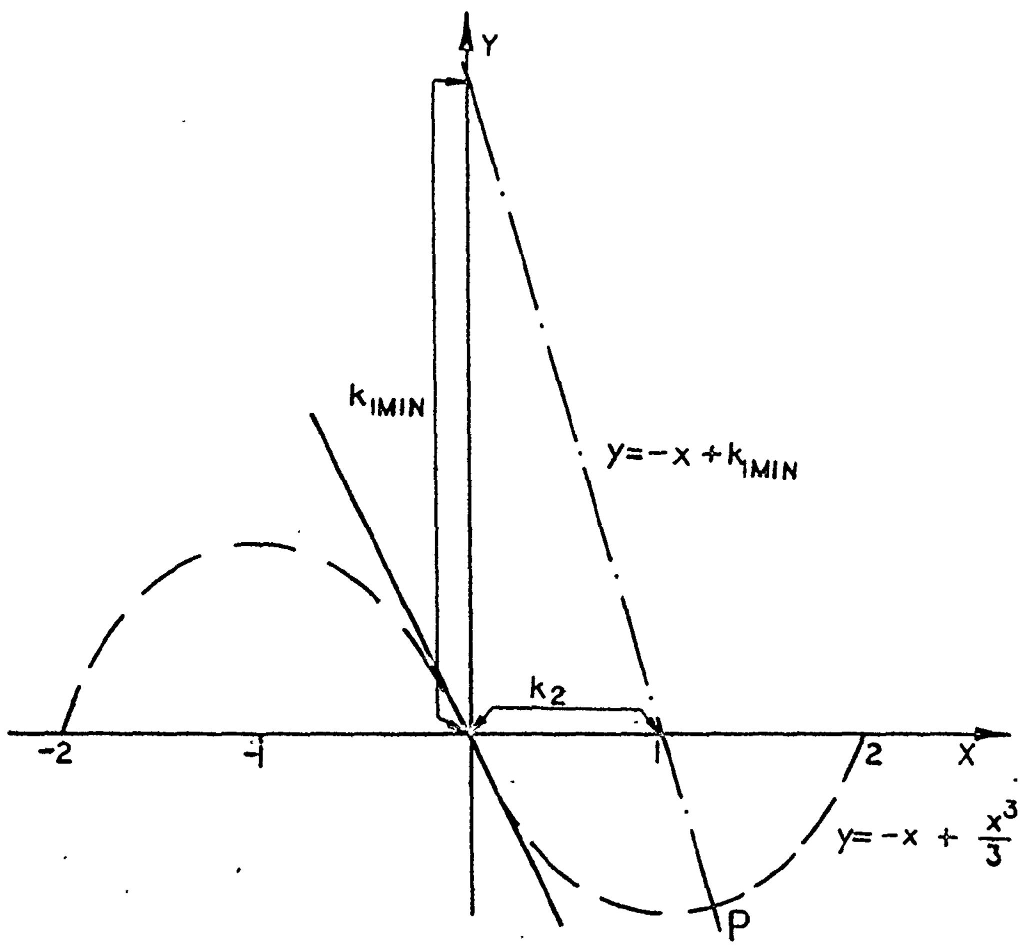

Fig. 6.2. The phase plane used for determination of k_{1MIN}.

The tangent to the function $y = -x + \frac{x^3}{3}$ at $x = 0$ is:

$$\frac{dy}{dx}\Big/_{x=0} = [-1(1 - x^2)]\Big/_{x=0} = -1$$

The equation of an infinite number of straight lines having a slope -1 can be written as

$$y = -x + z \tag{6.20}$$

where z is a coefficient which has to be determined in order to obtain an equation for a line having a slope -1 and going through the stable point "P". From equation (6.13) $y = -x + \frac{x^3}{3}$ for $zz = 0$ the location of stable point "P" is determined as $P(1, -\frac{2}{3})$.

Introducing the coordinates of point "P" into equation (6.20) the coefficient "z" can be determined.

$$-\frac{2}{3} = -1 + z$$

$$z = \frac{1}{3}$$

The general equation of a line having a slope -1 and going through the stable point "P" can be obtained by inserting the value of "z" into equation (6.20)

$$y = -x + \frac{1}{3} \tag{6.21}$$

Comparing equations (6.21) and (6.17) we see that

$$k_{1MIN} = \frac{1}{3} \qquad \text{or} \qquad \frac{a}{b} = \frac{1}{3} \tag{6.22}$$

therefore the minimum value of k_1 which allows oscillations while the stable point "P" is moved beyond threshold has to be $k_1 \geq \frac{1}{3}$.

6.3 Necessary Conditions for a Stimulus "zz"

The conditions for a stimulus "zz" which allows the moving of the stable point "P" beyond the separtrix can be determined as follows. Combining equations (6.13) and (6.14) we get:

$$\frac{x^3}{3} - x - zz = \frac{a}{b} - \frac{\omega^2 x}{b}$$

$$- zz = \frac{a}{b} - \frac{\omega^2 x}{b} + x - \frac{x^3}{3}$$

$$zz = -\left(\frac{a}{b} - \frac{\omega^2 x}{b} + x - \frac{x^3}{3}\right)$$

For $x = 1$

$$zz = -\left(\frac{a}{b} - \frac{\omega^2}{b} + 1 - \frac{1}{3}\right)$$

$$zz = -\left[\left(\frac{a - \omega^2}{b}\right) + \frac{2}{3}\right]$$

$$zz_{MIN} \geq -\left[\left(\frac{a - \omega^2}{b}\right) + \frac{2}{3}\right]$$

For $x = -1$

$$zz = -\left(\frac{a}{b} + \frac{\omega^2}{b} - 1 + \frac{1}{3}\right)$$

$$zz = -\left[\left(\frac{a + \omega^2}{b}\right) - \frac{2}{3}\right]$$

$$zz_{MAX} \leq -\left[\left(\frac{a + \omega^2}{b}\right) - \frac{2}{3}\right]$$

$$-\left[\left(\frac{a - \omega^2}{b}\right) + \frac{2}{3}\right] \leq zz \leq -\left[\left(\frac{a + \omega^2}{b}\right) - \frac{2}{3}\right] \qquad (6.23)$$

6.4 Summary

All the parameters of the oscillators in our model were chosen subject to the above conditions and keeping in mind the desired characteristics. The list of parameters of all oscillators is included in Appendix I.

CHAPTER VII

CONCLUSION

We have proposed a computer model that simulates the smooth muscle esophageal electrical activity. The model confirms Sarna et al's (24) hypothesis that the smooth esophageal muscle behaves like a chain of bidirectionally coupled relaxation oscillators. In the case of the esophagus, when these are depolarized up to the threshold level by a stimulus from an external source or by a neighbouring oscillator they undergo several oscillations. The results obtained show that with a proper choice of parameters the model can simulate all of the characteristics recorded in the esophageal smooth muscle of the opossum.

Our model simulated distally, proximally and bidirectionally propagated contractions recorded upon the direct muscle stimulation. It also simulated "ON" and "OFF" responses recorded in the opossum upon vagal stimulation and balloon distension.

The proposed computer model and the electronic representation of the relaxation oscillators could be used as a basis for further studies of electrical events in the smooth esophageal muscle. They can be used for teaching purposes by simulation of normal or disease conditions. Also, both models can aid in the diagnosis of certain esophageal disorders and eventually they may aid in suggesting treatment through pharmacological and surgical interventions.

No attempt was made at this stage to compare the parameters used in equations to membrane constants of esophageal smooth muscle.

APPENDIX I

LIST OF PARAMETERS USED IN 42 OSCILLATORS MODEL

The parameters of all oscillators used in electrical activity model are listed below:

Osc. 1	a = 930.0	b = 500	c = 100
	ω^2 = 1250	B = .0000	F = .0920
Osc. 2	a = 930.7	b = 500	c = 100
	ω^2 = 1250	B = .0911	F = .0911
Osc. 3	a = 931.4	b = 500	c = 100
	ω^2 = 1250	B = .0902	F = .0902
Osc. 4	a = 932.1	b = 500	c = 100
	ω^2 = 1250	B = .0893	F = .0893
Osc. 5	a = 932.8	b = 500	c = 100
	ω^2 = 1250	B = .0884	F = .0884
Osc. 6	a = 933.5	b = 500	c = 100
	ω^2 = 1250	B = .0875	F = .0875
Osc. 7	a = 934.2	b = 500	c = 100
	ω^2 = 1250	B = .0866	F = .0866

Osc. 8	a = 934.9	b = 500	c = 100
	ω^2 = 1250	B = .0857	F = .0857
Osc. 9	a = 935.6	b = 500	c = 100
	ω^2 = 1250	B = .0848	F = .0848
Osc. 10	a = 936.3	b = 500	c = 100
	ω^2 = 1250	B = .0839	F = .0839
Osc. 11	a = 937.0	b = 500	c = 100
	ω^2 = 1250	B = .0830	F = .0830
Osc. 12	a = 937.7	b = 500	c = 100
	ω^2 = 1250	B = .0821	F = .0821
Osc. 13	a = 938.4	b = 500	c = 100
	ω^2 = 1250	B = .0812	F = .0812
Osc. 14	a = 939.1	b = 500	c = 100
	ω^2 = 1250	B = .0803	F = .0803
Osc. 15	a = 939.8	b = 500	c = 100
	ω^2 = 1250	B = .0794	F = .0794
Osc. 16	a = 940.5	b = 500	c = 100
	ω^2 = 1250	B = .0785	F = .0785
Osc. 17	a = 941.2	b = 500	c = 100
	2		

Osc. 18	a = 941.9	b = 500	c = 100
	ω^2 = 1250	B = .0767	F = .0767
Osc. 19	a = 942.6	b = 500	c = 100
	ω^2 = 1250	B = .0758	F = .0758
Osc. 20	a = 943.3	b = 500	c = 100
	ω^2 = 1250	B = .0749	F = .0749
Osc. 21	a = 944.0	b = 500	c = 100
	ω^2 = 1250	B = .0740	F = .0740
Osc. 22	a = 944.7	b = 500	c = 100
	ω^2 = 1250	B = .0731	F = .0731
Osc. 23	a = 945.4	b = 500	c = 100
	ω^2 = 1250	B = .0722	F = .0722
Osc. 24	a = 946.1	b = 500	c = 100
	ω^2 = 1250	B = .0713	F = .0713
Osc. 25	a = 946.8	b = 500	c = 100
	ω^2 = 1250	B = .0704	F = .0704
Osc. 26	a = 947.5	b = 500	c = 100
	ω^2 = 1250	B = .0695	F = .0695
Osc. 27	a = 948.2	b = 500	c = 100
	ω^2 = 1250	B = .0686	F = .0686

Osc. 28	a = 948.9	b = 500	c = 100
	ω^2 = 1250	B = .0677	F = .0677
Osc. 29	a = 949.6	b = 500	c = 100
	ω^2 = 1250	B = .0668	F = .0668
Osc. 30	a = 950.3	b = 500	c = 100
	ω^2 = 1250	B = .0659	F = .0659
Osc. 31	a = 951.0	b = 500	c = 100
	ω^2 = 1250	B = .0650	F = .0650
Osc. 32	a = 951.7	b = 500	c = 100
	ω^2 = 1250	B = .0641	F = .0641
Osc. 33	a = 952.4	b = 500	c = 100
	ω^2 = 1250	B = .0632	F = .0632
Osc. 34	a = 953.1	b = 500	c = 100
	ω^2 = 1250	B = .0623	F = .0623
Osc. 35	a = 953.8	b = 500	c = 100
	ω^2 = 1250	B = .0614	F = .0614
Osc. 36	a = 954.5	b = 500	c = 100
	ω^2 = 1250	B = .0605	F = .0605

Osc. 37	a = 955.2	b = 500	c = 100
	ω^2 = 1250	B = .0596	F = .0596
Osc. 38	a = 955.9	b = 500	c = 100
	ω^2 = 1250	B = .0587	F = .0587
Osc. 39	a = 956.6	b = 500	c = 100
	ω^2 = 1250	B = .0578	F = .0578
Osc. 40	a = 957.3	b = 500	c = 100
	ω^2 = 1250	B = .0569	F = .0569
Osc. 41	a = 958.0	b = 500	c = 100
	ω^2 = 1250	B = .0560	F = .0560
Osc. 42	a = 958.7	b = 500	c = 100
	ω^2 = 1250	B = .0551	F = .0000

APPENDIX II

AN INTERACTIVE PROGRAM USED TO DEVELOP A COMPUTER MODEL OF THE ESOPHAGEAL ELECTRICAL ACTIVITY

An interactive program for Modeling of Biological Rythms prepared by B. L. Bardakijan (30) was used to develop the computer model of the esophageal electrical activity.

The program consists of a main program "RHYTHM" and several subroutines "OPUS1" to OPUS7" which together form the user-computer dialogue necessary to solve a set of differential equations and to generate a data file B1 of the results.

"RHYTHM" - is a user supplied program required for dimensioning purposes and for interactive simulation of coupled oscillators with parameters specified during user-computer dialogue. Each of the 42 oscillators used in our model can be stimulated by a pre-specified stimulus set at a pre-specified time and of any desired duration.

"OPUS1" - is a subroutine for identification of the words "yes" and "no" used during user-computer dialogue.

"OPUS2" - is a subroutine for run time printing or plotting of the computed time sequences on the line printer or on the screen.

"OPUS3" - is a subroutine for reading or writing model parameters into file PF1, the stimulation parameters into file PF2 or the final conditions into file PF3.

"OPUS4" - is a subroutine for the numerical solution of nonlinear first order differential equations using an automatic step change - Merson differential equation solver.

"OPUS5" - is a user supplied subroutine for prescribing the set of nonlinear differential equations used to describe each oscillator in the proposed model.

The prescribed set of equations is listed below

$$\dot{x}(1) = P(1)\{P(2)x(2) + P(3)x(1) + P(4)[x(1)]^2 + P(5)[x(1)]^3 + P(11)x(1) + P(12)x(3) + SA\}$$

$$\dot{x}(2) = - \frac{1}{P(1)} \{P(7)x(2) + P(8)x(1) + P(9)[x(1)]^2 + P(6)[x(1)]^3 = P(6) + P(10)[x(1)]^3\}$$

where referring to equations (4.4) and (4.5) used in proposed model

$P(1) = c$	$P(2) = 1$	$P(3) = 1$	$P(4) = 0$
$P(5) = -\frac{1}{3}$	$P(6) = a$	$P(7) = b$	$P(8) = \omega^2$
$P(9) = 0$	$P(10) = 0$	$P(11) = C_F$	$P(12) = C_B$

$SA = zz$

"OPUS6" - is a subroutine for stimulating a user specified oscillator by a user specified stimulus at a user specified time.

"OPUS7" - is a subroutine for listing model parameters, initial conditions and stimulation parameters on a line printer or CRT screen.

The results in B1 file can be sorted as required and plotted on a line printer. Two programs - "SLP" and "PLP" were used for sorting and plotting the data as required.

"SLP" - is an interactive program which sorts all data in file B1.

"PLP" - is an interactive program for the plotting of oscillator outputs.

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