

The Dynamic Response of the Baroreceptor Reflex Loop in the Rabbit ;  
Estimated Using a Statistical Signal Approach

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by

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## Abstract

The principal objective of the research was to determine whether the dynamic response of the baroreceptor control loop could be evaluated in terms of a system description which was consistent with the physiology.

A series of rabbit experiments were designed and carried out which allowed the baroreceptor control loop to be driven by a wideband Pseudo-random binary sequence stimulus. The PRBS was applied to the cardiac depressor nerve, and ECG, respiration and arterial blood pressure were measured as the system's output signals. Signal processing techniques were developed to produce the stimulus, and also to convert the raw data into estimates of the system response. The latter were based upon frequency domain cross-correlation of the data. The system response estimates were in turn used to specify possible transfer functions for the baroreceptor control loop.

System analysis showed that the responses from the three parts of the system could be modelled by the same control elements, and therefore by the same basic physiological mechanisms. The system was found to be first-order, but the presence of lag compensation increased this to second order. The premise that the system could be treated as linear over specified stimulus ranges was upheld. The response across the entire stimulus range was, however, nonlinear. This work confirms the result found by other researchers that arterial blood pressure is primarily controlled by circulatory resistance at low stimulus frequencies, and by heart rate at high frequencies. Block diagrams were developed which allowed the expression of the derived transfer function in physiological terms.

From the results it would appear that that the cross-correlation approach to frequency response estimation is particularly appropriate for investigating the dynamics of physiological systems because it allows the system to be studied in its closed loop state; in this context, it represents a powerful tool in obtaining a complete description of the physiological system.

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## Introduction

This thesis aims to explore the frequency response of the baroreceptor reflex loop in the rabbit. The aortic baroreceptor reflex loop is defined as the interconnecting physiological pathways leading from the aortic baroreceptors via the cardiac depressor nerves to the medullary control areas, which in turn elicit autonomic responses which alter arterial blood pressure. A fine degree of blood pressure control is thus achieved.

This work covers three main areas :-

- i) Data collection. The cardiac depressor nerve was stimulated by a Pseudo-random binary sequence and the closed loop response measured in terms of variation in heart rate, blood pressure and respiration
- ii) Data manipulation. The experimental results were electronically and digitally manipulated in both time and frequency domains to produce estimates of the system frequency response
- iii) Data analysis. The estimates were used in the construction of a mathematical model which adequately described the experimental results.

The study can essentially be viewed as an exercise in analysis and simulation of a complex biological control system. In engineering systems the problems faced by control theorists tend to be synthetic; they are given a set of parameters which the system to be constructed must fit. In biology the problem becomes analytical;

the system is ready-made and its components must be deciphered. The biologist faces further obstacles in his analysis since any attempt at external interference or to open loops may result in instability and irreparable damage. For this reason application of systems analysis techniques to biology has been restricted to those systems which are most readily accessible, namely sensory and motor control. These systems often have the advantage of showing some degree of linearity, a feature which most homeostatic systems do not share.

The main criteria for deciding which methods of analysis should be employed in the investigation of this system were that they should therefore either

- a) be non-invasive
- b) employ techniques proven not to drive the system outside its natural range, should invasive techniques prove unavoidable.

It is intended to demonstrate the way in which this premise has been used in the exploration of the frequency response of the baroreceptor control loop. Fundamental to the study is an understanding of the physiology of the cardiovascular system. The first chapter therefore gives an overview of the physiology, while laying the foundations for this particular study. Chapter 3 summarises the grounds for introducing control engineering techniques into biological research, and reviews work which has already taken this approach. Chapters 2 and 4 supply details of experiments carried out personally. Chapters 5 and 6 present a detailed analysis of the experimental results using frequency response methods. The implications of these findings with respect to understanding the physiological system are considered.

## Chapter 1

## Overview of cardiovascular physiology.

## 1.1 Introduction

The primary aim of the cardiovascular system is to ensure that all the organs of the body receive an adequate supply of blood. The word "adequate" highlights the difficulties which the system faces; an adequate supply must depend on the amount of work which an organ is doing at any particular time. Since blood volume is a fixed quantity, delivering an amount of blood to one organ which is sufficient to meet its needs may well mean depriving another. The system must therefore have some idea of its own priorities.

Figure 1 presents a picture of the proportions of blood normally taken by each of the major components of the Cardiovascular (C.V.) system. Although the diagram is necessarily simplified, it gives some idea of the way in which many parts of the body must act together in order to achieve the conglomerate effect which is termed cardiovascular control. In the course of this study, it will be seen that the cardiovascular system is a complex feedback system, which influences many processes through its controller elements.

The complexity of the C.V. system is not surprising when one considers the multiplicity of functions which blood transport performs, and their vital importance to the homeostasis of the organism. Each peripheral tissue of the body controls its own blood flow, and all of this blood must return via the venous system to the heart to be pumped round the system once more. This means that the heart must be able to adapt itself, sometimes instantaneously, to

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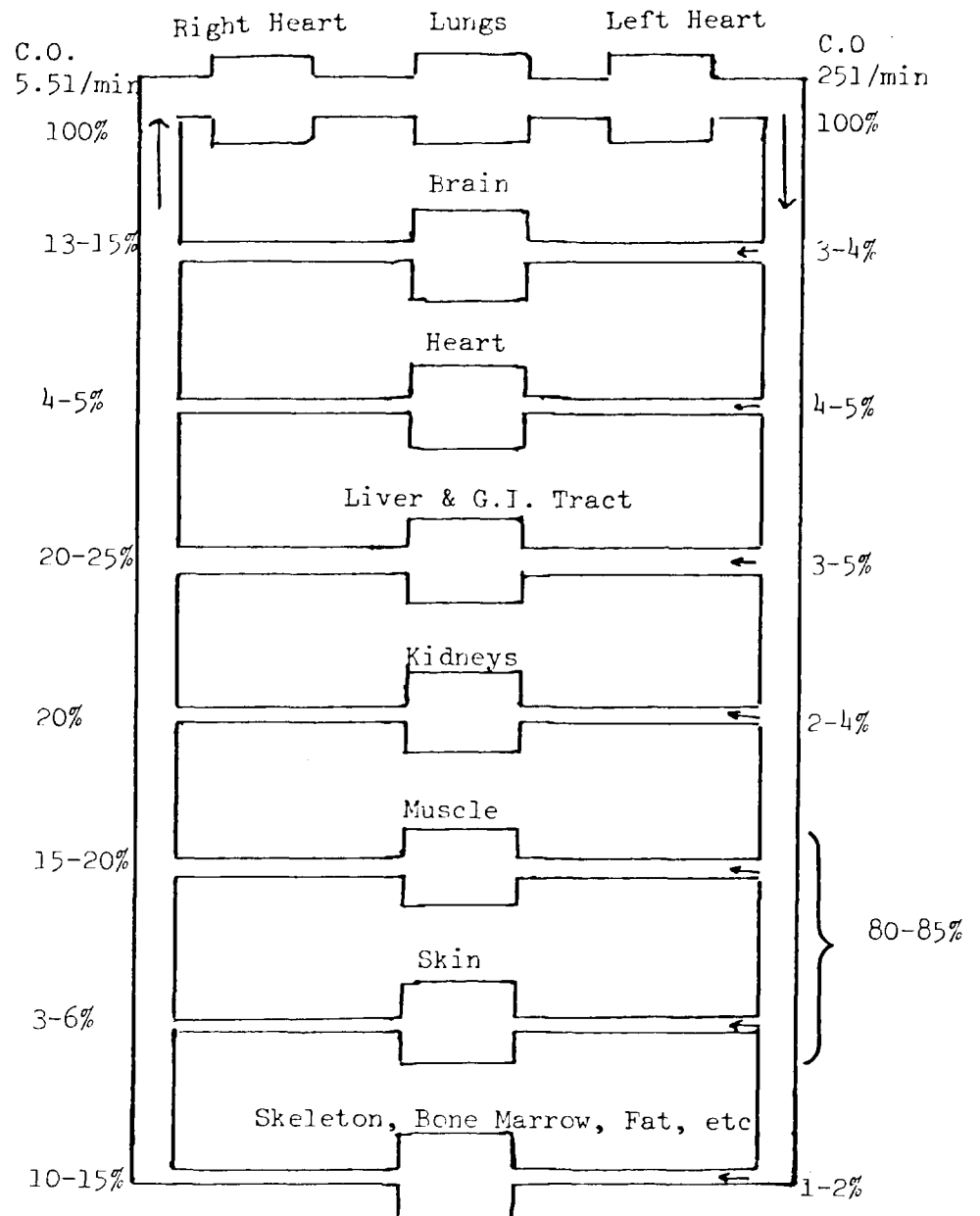


Figure 1. Diagram illustrating the flow distribution among the vascular circuits in man during rest and heavy exercise. From Falkow and Neil, 1971.

cope with demands from the circulation varying as widely as 2.3 to 25 litres a minute. The system therefore contains mechanisms for short term and emergency action, as well as for long term adaptive control: these mechanisms are often both anatomically and physiologically independent (Guyton et al, 1974).

Broadly, long term control is the maintenance of systemic blood flow at a set level during the normal life of the animal. Its concerns are blood fluid level, the age and lifestyle of the animal, and coping with chronic circulatory disorders which may develop.

Short term control of blood flow refers to the adaptations which must be made to cope with changes in posture, excitement or other external factors which influence the circulation on a temporary basis. These adaptations therefore act to minimise the variation in blood flow around the set level. It must, of course, be noted that all factors acting to control blood flow in the short term will affect long term control to some degree, either directly or indirectly (Guyton et al, 1974).

Short term control is the major concern of this thesis, since it is mediated primarily through the action of the baroreceptor reflex loop.

## 1.2 Short term blood flow regulation

Short term blood flow regulation refers to changes which have an effect on the circulation during the space of seconds rather than minutes or hours. Blood flow is usually measured in litres per minute ejected by the heart, and is termed cardiac output. Because the C.V. system is a closed loop, cardiac output is equal to venous return.

The C.V. system has three main methods of quickly achieving flow regulation:-

- a) Heart rate can be altered, to change the amount of blood which enters the arteries per unit time.
- b) The amount of blood ejected per heart beat, known as the stroke volume, can be altered.
- c) The diameter of the blood vessels can be changed to vary the resistances, known as the Total Peripheral Resistance, TPR, which these vessels give to blood flow.

Changing any of these factors results in a change in arterial blood pressure. Arterial blood pressure is directly related to both Cardiac Output and TPR, where

$$\begin{aligned}\text{Cardiac Output} &= \text{Stroke volume} \times \text{Heart Rate} \\ &= \text{Blood Velocity} \times \text{Vessel Cross-sectional} \\ &\quad \text{Area.}\end{aligned}$$

(from Starling, 1968).

The effector pathways for control are largely neural, involving the autonomic nervous system, since vascular changes require a

longer time course to take effect (Guyton et al, 1974).

The ways in which short term control is achieved are discussed in the remainder of this section. Although the various mechanisms are physically separate and act upon different cardiovascular parameters, it is important to bear in mind that they normally work in concert. Once the individual parts of the reflex have been described, their respective roles in generating the total baroreceptor response are considered in section 1.3.

#### 1.2.1 Baroreceptors and the afferent pathway.

As shown in the previous section, changes in blood distribution are immediately reflected in a change in arterial blood pressure. Conversely, the ability of an organ to achieve an alteration in its blood supply depends upon the maintenance of an arterial pressure head to drive the blood through the vascular network. Blood pressure is therefore a cardiovascular parameter which is inevitably and constantly influenced by circulatory changes, but which must also be monitored continuously to ensure against the depletion of the pressure head on the one hand, and starvation of the organs on the other. The sensors of short term blood flow control are therefore pressure receptors.

The cardiac control areas of the medulla (covered in detail in subsequent sections) receive inputs from stretch receptors situated in many parts of the arterial system, via the vagus. The function of these receptors is to continuously relay the state of arterial blood pressure to the decision-making areas of the central nervous system.

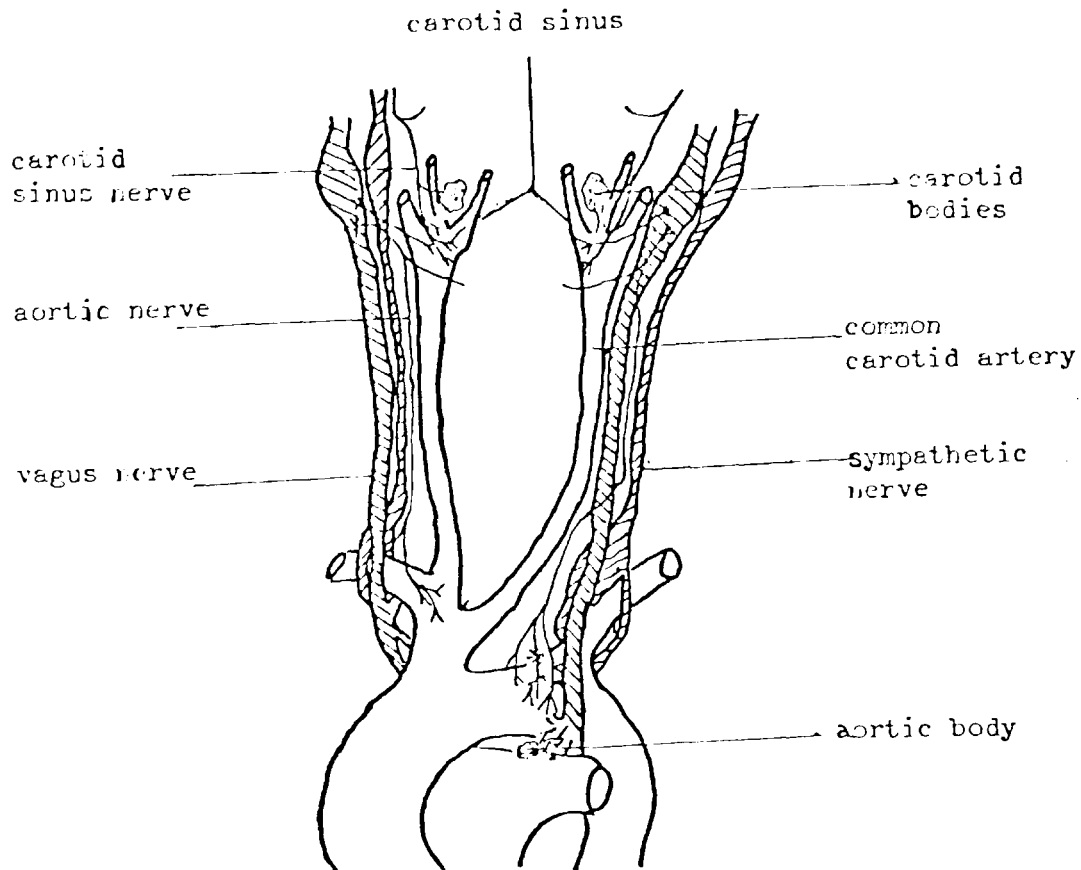


Figure 2. Location of the carotid and aortic baroreceptors (from Starling and Lovatt Evans, 1968).

Receptors are the cells which comprise the body's sensory organs. They signal the presence of a particular physical stimulus, such as heat, light, or as in this case, pressure. By comparing the evidence from sufficient numbers of receptors located throughout the body, the brain is able to interpret the condition of its environment.

The most important groups of receptors are situated in the aortic arch and carotid sinus bifurcation, as shown in Figure 2. The role which these receptors play has long been understood. For example, Cowley, Liard and Guyton (1973) studied dogs in which the baroreceptors were either intact or denervated, for a period of 24 hours. While mean arterial blood pressure was found to be similar in the two cases, the denervated dog was unable to cope with instantaneous changes in pressure. Figure 3 illustrates this most dramatically. The conclusion was that the baroreceptors were responsible for smoothing out the effects of these variations, while having little influence on the overall pressure level: that is, they were the mechanism of short term C.V. control.

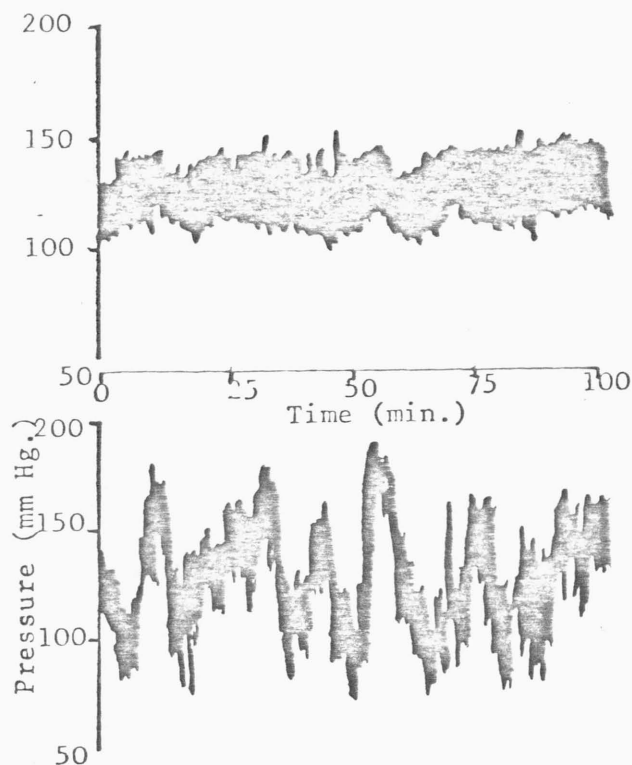


Figure 3. Arterial blood pressure trace from normal (top trace) and baroreceptor denervated (bottom trace) dogs. (from Cowley, Liard and Guyton, 1973).

Receptors are very special cells in that they are almost continuations of the nerve fibre endings to which each is attached. Irrespective of the type of physical stimulus to which it is sensitive, a receptor responds by generating impulses in the afferent nerve fibre. The mode of action of nerve fibres is discussed in detail in section 4.2.

Figure 4 shows the discharge pattern of an isolated fibre in the nerve leading from the aortic arch baroreceptors, the cardiac depressor nerve. Katona et al (1968) demonstrated that although individual fibres had different thresholds of response, each fibre maintained an almost identical pattern of firing in response to each pressure cycle. The reason why the nerve response consists of a series of impulses is considered in section 4.2, when the construction of a neural stimulus is discussed. The rate at which the nerve discharges is in this case directly proportional to the degree of stretch applied. Irisawa and Ninomiya (1967) found from studies on cats and rabbits that nerve discharge took place mainly during systole, when the arteries were maximally distended. Diastolic impulses were only found when the pressure was abnormally elevated. In general, baroreceptors respond best to pulsatile pressure changes.

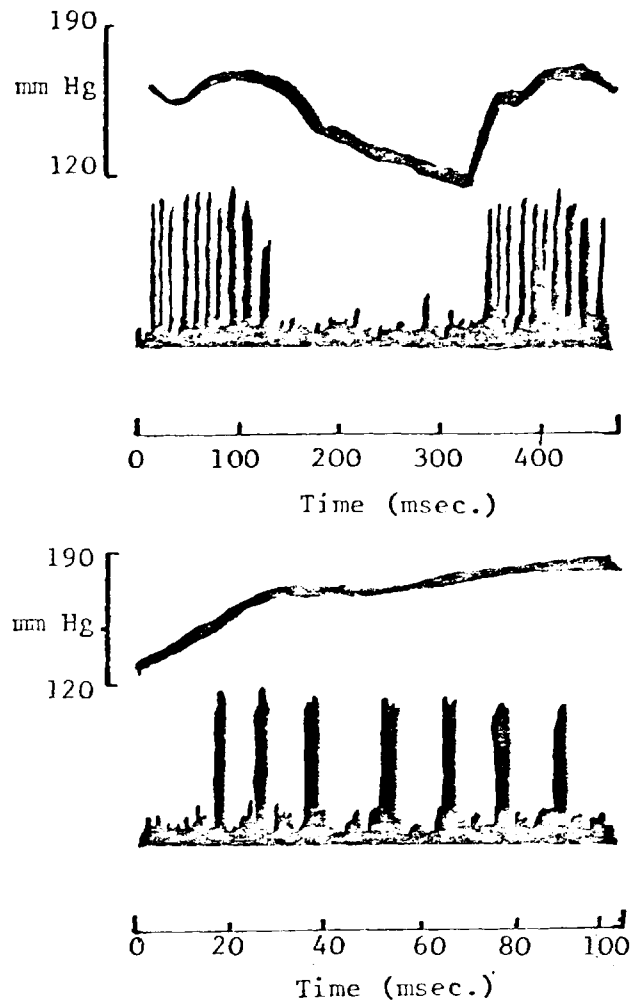


Figure 4. Response of an isolated baroreceptor nerve fibre to blood pressure (35 cycles superimposed). Upper trace shows the whole blood pressure cycle. Lower trace is the beginning of the cycle expanded 5 times (from Katona et al, 1968).

The carotid baroreceptors are vascularly situated some 10 - 20 cm further away from the heart than those of the aortic arch. Consequently, the pressure wave reaches the carotid receptors 20 -

40 msec later. This is reflected in a time lag between the positions of maximum discharge of the nerves leading from the two sets of receptors (Irisawa and Ninomiya, 1967). This information could be used by the brain to calculate blood velocity.

The two sets of receptors seem to carry out very different functions. Those of the aortic arch have been found to be largely silent at normal levels of mean arterial pressure, but sensitive at much higher pressure levels (in excess of 260 mm Hg.) than those of the carotid sinus (Conrad, Pelletier, Clement and Shepherd, 1972). Fig. 5 shows a typical baroreceptor response curve for both sets of receptors in the dog, and it can be seen that in the carotid sinus the greatest rate of change of impulses per second is found over the range occupied by normal blood pressure, i.e. 80 - 100 mm Hg., whereas the aortic arch receptors are at their most sensitive between 150 and 200mm Hg.

From this evidence, it might be assumed that loss of the carotid receptors would be extremely damaging to the normal animal. Evidence to the contrary has come from Ito and Scher, 1979, who showed that blood pressure was regulated almost normally in carotid denervated dogs. Removal of aortic baroreceptors, however, led to hypertension and uncontrolled pressure changes. These contradictory results might be due to differences in surgical procedure and stimuli (Coleridge and Coleridge, 1980).

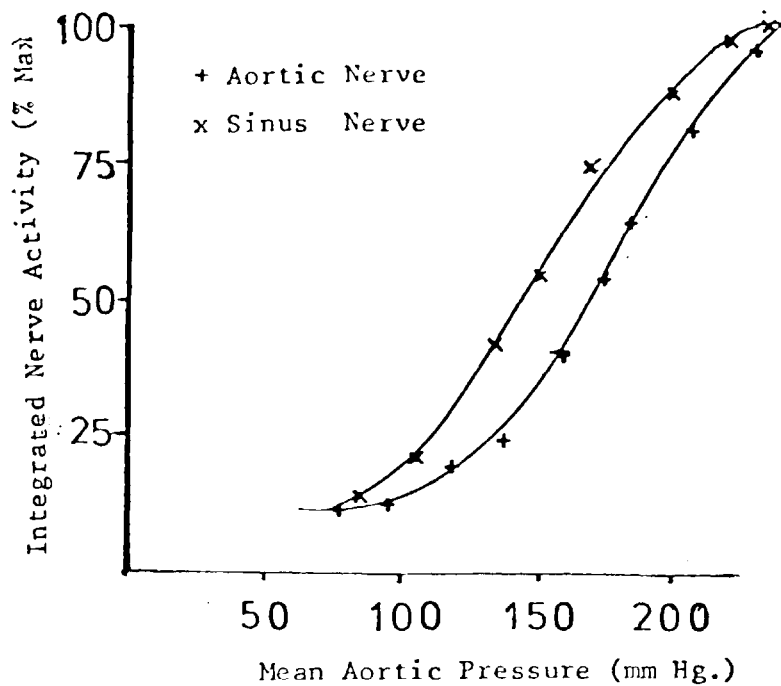


Figure 5. Response of carotid and aortic baroreceptors in the dog to arterial blood pressure changes (Conrad, Pelletier and Shepherd, 1972).

The baroreceptor reflex loop is not a suitable vehicle of long term control. It does not control mean pressure, only variations around it. The baroreceptors also show adaptation, in that if an elevated or lowered blood pressure is artificially maintained, the rate of firing of the baroreceptors will return to normal after 1 - 2 days (Cowley, Liard and Guyton, 1973).

#### 1.2.2 The efferent pathways

Having identified the sensory part of the baroreceptor loop, the paths through which corrective action may be taken are now

considered. These involve the autonomic efferents from the cardiac control areas, for which two main areas of control exist.

a) Cardiac control.

The way in which the autonomic nervous system controls the heart, and therefore blood flow, is a complex and important issue. It will therefore be considered separately here, before going on to study the other methods by which blood flow is regulated.

The heart is richly innervated with autonomic fibres: parasympathetic nerves supply mainly the sino-atrial (S.A.) and atriculo-ventricular (A.V.) nodes and the atria, with very few branches to the ventricles, while sympathetic nerves are more evenly distributed to all parts of the circulation.

Parasympathetic stimulation leads to the release of the chemical transmitter Acetyl Choline which lowers S.A. and A.V. nodal excitability, leading to decreased S.A. nodal rhythm and slower transmission of the cardiac impulse to the ventricles. Sympathetic stimulation has the opposite effect of increasing the excitability of the S.A. and A.V. nodes so that heart rate increases and cardiac transmission time decreases. Stimulation can also increase the force with which both the atria and ventricles contract. The sympathetic transmitter is Noradrenalin. This interaction is represented in block diagram form in Figure 6. The components not yet discussed will be covered in detail in the rest of this chapter as part of the total loop function. The significance of the block elements in control engineering terms is explained in chapter 3.

For many years it was believed that the two sets of nerves

acted in direct opposition to each other, to speed up or slow down the heart as required. The view that sympathetic and parasympathetic cardiac effector nerves are simply mutually antagonistic (Rushmer, 1959) is no longer widely held. Scher and Young (1970) found that vagal stimulation dominates. Unmodulated human heart rate is in excess of 100 beats a minute, so constant vagal tone is needed to reduce this to the normal rate of 70 beats a minute. Strong sympathetic stimulation can be suppressed by weaker vagal stimulation, and adding sympathetic tone to existing vagal tone need not cause any increase in heart rate.

In fact, Rosenblueth and Simeone (1934) found that the reduction in heart rate caused by vagal stimulation in cats became even greater when the basal heart rate was increased through sympathetic stimulation. If a non-adrenergic heart stimulant was used, this effect did not occur. This vagal dominance is termed "accentuated antagonism". Under certain conditions, this effect can be taken to extremes, the parasympathetic division being shown to speed up the heart and the sympathetic to slow it down (Levy, 1971).

Autonomic efferents to the heart originate in the pontomedullary and spinal circulatory centres (Korner, Shaw, West and Oliver, 1972). The upper and lateral portion of the medullary area is spontaneously active and control vasoconstriction and increase of heart rate via the sympathetics. This is generally termed the pressor area. The medial and lower portion can inhibit this facilitatory area, and comprises the depressor area. There is no vasodilator function, but heart rate can be controlled via the vagus.

These areas, often termed the cardiovascular centre, are under

the control of higher centres, notably those concerned with emotive responses, such as the hypothalamus and septum. Experiments have shown that the threshold and gain of the baroreceptor - midbrain loop were identical in pontine and sham-operated rabbits when the vagus alone was considered. The sympathetic pathways operated at a lower threshold and higher gain in the pontine rabbits, showing that these nerves are normally restrained by the suprabulbar centres (Korner, Shaw, West and Oliver, 1972). The pontine rabbit therefore coped with large changes in arterial blood pressure by significantly increasing the activity in the relevant autonomic branch. In the sham-operated rabbit, reciprocal and nearly equal autonomic interaction achieved the same effect.

b) Sympathetic vasoconstrictor fibres.

The control of blood pressure mediated by the baroreceptors of the aortic arch may be achieved by varying heart rate as described in section 1.2.2 (a). Equally, and under normal conditions perhaps more, important is the variation in blood flow which results from changing the diameter of the arterial vessels. Sympathetic fibres project to most of the arterial vasculature and hold the vessels in a constant state of tension. The fibres are driven by the tonic activity in the medullary pressor area (Adrian, Bronk and Phillips, 1932). Inhibition of the pressor area causes the level of sympathetic stimulation to decrease and vessel diameter to increase, thereby making it easier for blood to pass round the circulation. This is described as a lowering of the Total Peripheral Resistance (TPR). Arterial pressure falls as a consequence (see Figure 6).

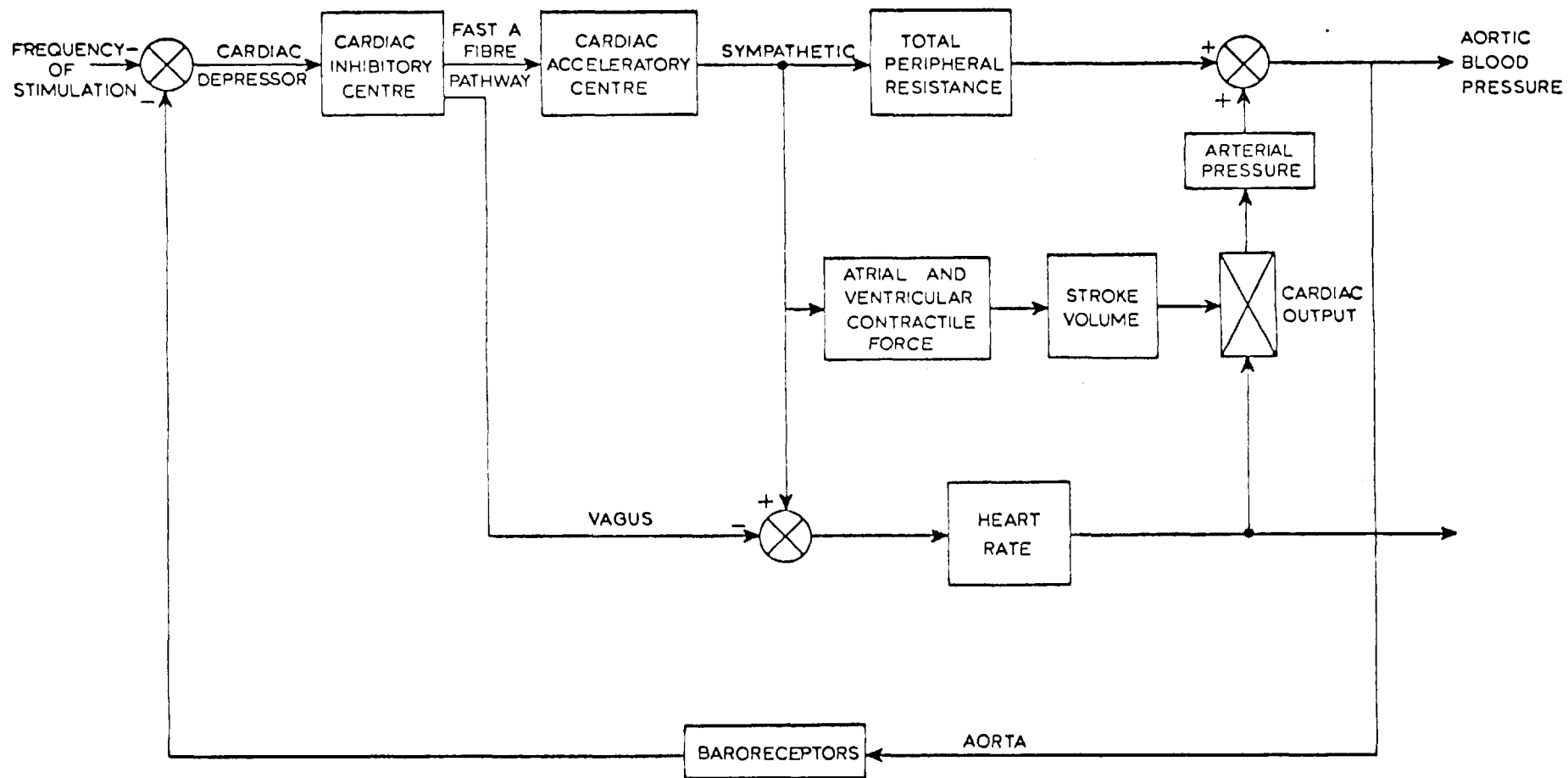


Figure 6. Block diagram representation of the major physiological structures of the baroreceptor control loop.

### 1.2.3 Non-neural control.

The heart itself is inherently capable of coping with varying loads to a certain degree. Under normal circumstances the major factor determining cardiac output is the rate of venous return, and provided that this stays the same, stroke volume keeps a constant value. According to the Frank-Starling law, the more the heart is filled in diastole, the greater the stroke volume will be, up to the limit of the heart. This is achieved in part by heterometric regulation, i.e. as muscle tone is stretched more, it contracts more vigorously (Vick, 1963). Heart rate is also increased by 20 - 70% as a result of stretching the S.A. nodal tissue (Pathak, 1973).

### 1.3 The baroreceptor control loop.

Having studied the various methods of blood flow regulation, it is necessary at this point to see how they fit together as components of the baroreceptor control loop. As with all topics in cardiovascular physiology, simplifications must be made in order to gain initial understanding. Figure 6 described the baroreceptor loop in block diagram form, and many of its components have already been considered. To appreciate the total action of the loop, its normal operative pathways will be traced, starting from the baroreceptors themselves.

The baroreceptors under consideration are located in the wall of the aortic arch and respond to deformation of that wall. The other major sites at which baroreceptors are located are the carotid sinus and pulmonary artery. In the rabbit, the aortic arch receptors dominate those of the carotid sinus (Ito and Scher, 1979), and are linked to the depressor centre of the medulla via the cardiac depressor nerve. This nerve runs parallel to and separate from (in this animal) the vagus.

Under normal conditions the nerve discharges on the rising edge of each blood pressure pulse. There is some tonic activity at normal pressures, so that a change in blood pressure is directly reflected by the firing rate of the nerve. Like any other sensory nerve, the cardiac depressor operates on the principle of recruitment. As stimulus intensity increases, so fibres of slower and slower conduction velocities are recruited, until the whole nerve is active. Fast fibres are sheathed or myelinated, preventing dissipation of the impulse as it travels along the nerve, and aiding the nerves' excitability.

The nerve consists of three fibre groups, fast myelinated A fibres ( $> 30$  m/sec.), slow A fibres ( $< 30$  m/sec.) and smaller unmyelinated C fibres, conducting at 2.5 m/sec or less (Kardon, Peterson and Bishop, 1973). Individual fibres within a group also have differing thresholds. Low stimulus intensity activates the fastest A fibres. Further increase in depressor stimulation recruits the slower A fibres, then the C fibres. Only when all fibres within a group have been recruited does frequency of stimulation become important (Angell-James, 1971). Thus, experiments in which the depressor nerve is stimulated are more likely to reflect the true action of the system if whole, rather than single, fibre stimulation is used (Katona, 1968, Salgado Kreiger, 1970).

The percentage and type of fibres active at normal pressures (mean pressure = 80 mm Hg.) is a matter for contention. Estimates range from one or two fast A fibres (Conrad et al., 1972), to 90% of all A fibres and 25% of C fibres (Thoren and Jones, 1977). C fibres are said to have thresholds 30 - 50 mm Hg. higher than A fibres, but saturate much sooner. This is because their rate of firing is proportionately greater in response to a given pressure increase (Brown, Saum and Yasui, 1978), although the firing rate itself is lower for C fibres (Thoren and Jones, 1977).

The effect of fast A fibre stimulation is to cause the depressor centre to inhibit the pressor centre without exciting the depressor centre itself. These fibres cause no reflex bradycardia; blood flow appears to be reduced entirely via the inhibition of the sympathetic vasoconstrictor fibres (Kardon, 1973). Further, Kumada and Nakajima (1972) found that while the depressor area received

input from by both A and C fibres, no anatomical or physiological connection could be found between the C fibres and the pressor area. Thus, the C fibres act almost entirely by changing vagal influence on heart rate (Kardon, Peterson and Bishop, 1975).

Bearing in mind that the C fibres are not activated below arterial pressures of 110 mm Hg. (Aars, 1980), when the whole nerve is stimulated maximally, the C fibres do most of the work in controlling blood pressure (Douglas, Richie and Schaumann, 1956). Kardon et al. (1973), found not surprisingly that the same was true for heart rate. Figure 7 gives a comparison of responses to stimulation of both types of fibre in the rabbit.

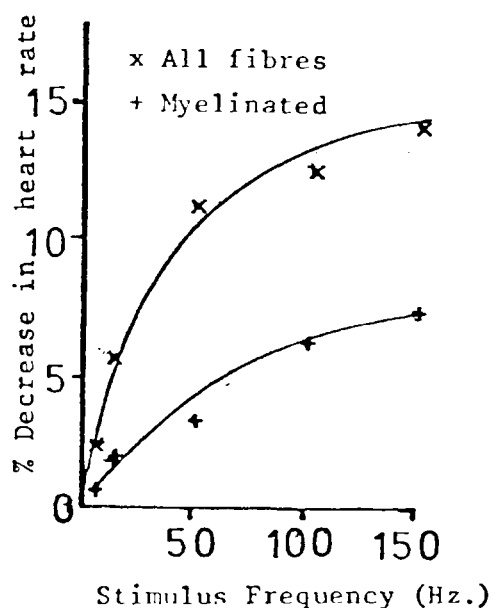


Figure 7. Comparison of slow A and C fibres in the rabbit's aortic nerve (Kardon, Peterson and Bishop, 1973).

Katona et al.(1970), identified a species difference in the

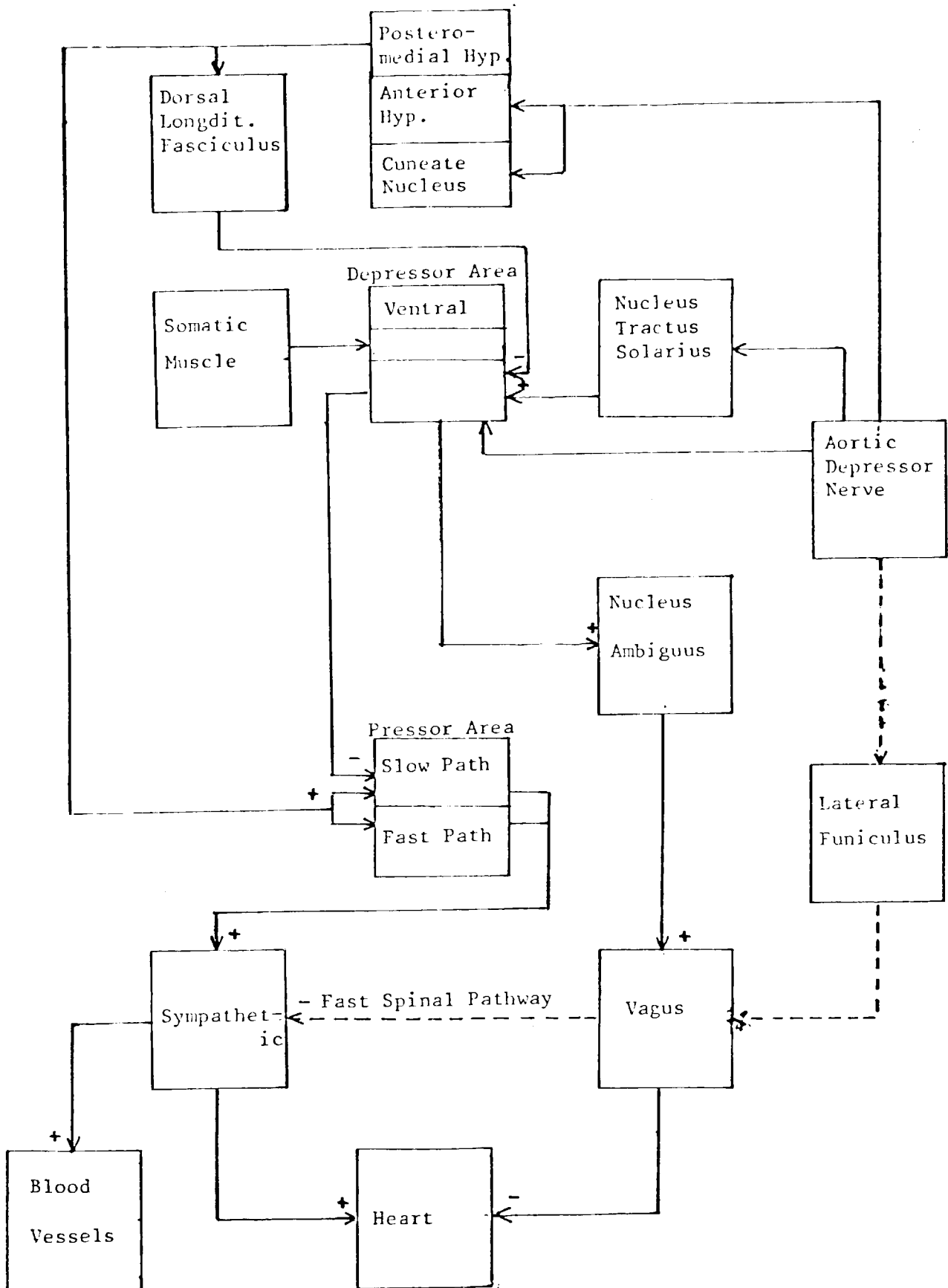


Figure 8. Block diagram representation of the main neural pathways and sub-cortical areas involved in the regulation of blood flow.

amount of vagally induced bradycardia obtained, with cats showing very little vagal response at all. They did, however find that under many conditions there was a linear relationship between vagal firing and heart rate. It was harder to identify a similar relationship between baroreceptor nerve and vagal activity. Sharp bursts of firing in the former appeared widened and smoothed in the vagus, and vagal activity often continued for a few seconds after the baroreceptor activity had ceased.

The cause of the non-linearity had to be the neural structures linking the afferent and efferent pathways. Figure 8 diagrammatically shows the linking between the major medullary and spinal areas involved; the picture summarizes the knowledge available to date in a rapidly expanding field of research. The depressor and pressor areas are anatomically laid out in Figure 9. Activation of the hypothalamic areas can effectively block the vagal component of the baroreflex, while the sympathetic part continues (Oberg, 1976). Even if only one of the main baroreceptor areas is stimulated, a maximal depressor response may be obtained which is not enhanced by stimulating another area (Oberg, 1976). This indicates some antagonistic convergence of all baroreceptor afferents in the medulla.

This idea of convergent occlusion has been investigated recently (Chen, and Chen, Chai, Tung and Chen, both 1979) to try to explain an observed interaction between either the Bainbridge or the Bezold-Jarisch reflex and the baroreceptor response. Both reflexes attenuate the baroreflex effects on heart rate and blood pressure, even though the reflexes are trying to bring about completely opposite changes. In both cases, the strength of the reflex depends

inversely upon the prevailing amount of baroreceptor activity. This points strongly to all three reflexes sharing common afferent pathways, the anatomy of which has not yet been defined.

The conclusion must be drawn that the baroreceptor loop is a system capable of a fine degree of control.

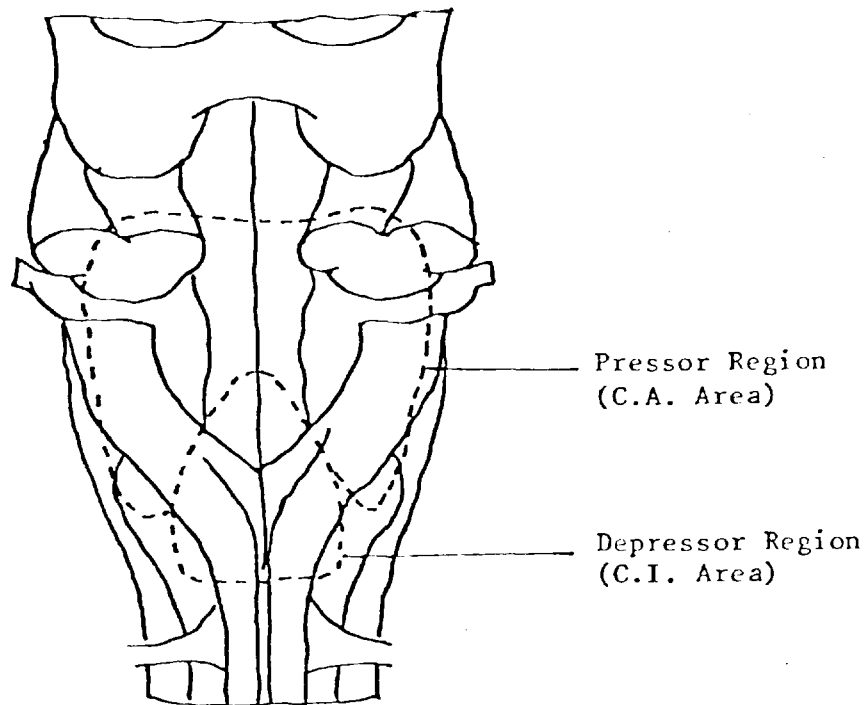


Figure 9. Pressor and depressor regions of the cat's medulla (Gebber, 1980).

If the depressor nerve is artificially subjected to continuous stimulation, the cardiac control centres will interpret this as a rise in blood pressure which is never compensated for. As discussed above, the initial response of the system to depressor stimulation is a decrease in TPR (Kardon et al., 1975). That is, if the stimulus is not too severe (only fast A fibres are excited), the sympathetic branches to the heart need not be inhibited to cause a reduction of

cardiac output, and hence of arterial blood pressure, through bradycardia. Rather, lowering of TPR means a direct change in arterial blood pressure. If the arterial dilation persists, stroke volume and therefore cardiac output will eventually be affected, due to reduced venous return.

Interestingly, relaxation of the aortic walls themselves in response to this sympathetic inhibition acts to reduce the activity in the baroreceptors (Oberg, 1976). This is thought to be the mechanism whereby the baroreceptors are observed to reset themselves in the face of sustained changes in systemic blood pressure (Salgado and Kreiger, 1978). Resetting can thus be seen to be mainly a function of the A fibres (Jones and Thoren, 1977).

Once the fast A fibres have been recruited, further increase in stimulus intensity brings in the slow A fibres. As well as affecting vasoconstriction, these fibres cause reflex bradycardia. Kardon et al., 1975, were able to isolate the bradycardia as being sympathetically mediated, since it had the long time course associated with the largely unmyelinated sympathetic efferents.

Increasing stimulus intensity to maximum successively recruits the C fibres, which act directly by stimulating the vagal efferents to reduce heart rate. The finding of Douglas, Richie and Schaumann, 1956, that the C fibres provoke the greatest part of blood pressure control when the whole nerve is active, points to blood pressure being mainly reduced through falling heart rate, rather than by changing TPR, at high pressures (Kardon et al., 1975). Furthermore, this effect is more pronounced in aortic than in carotid receptors (Eckberg, Fletcher and Braunwald, 1972). Schmidt, Kumada and Sagawa (1971) added weight to this argument when the

found that TPR only played a significant part in the baroreflex at mean pressures of 100 - 150 mm Hg. That is, pressures above the normal range were dealt with primarily through slowing of the heart rate.

Whether or not changes in stroke volume assist the baroreceptor reflex is a matter of contention. Stroke volume is determined largely by venous return through the Frank-Starling law. Some researchers claim that in addition to arterial vasoconstriction, the reflex initiates changes in the venous capacitance vessels (Shoukas and Sagawa, 1963). They found that a reflex change in venous contractility causing an increase in venous pressure of 1.6mm Hg., could bring about increased cardiac output of up to 30%.

#### 1.4 Long term cardiovascular control.

For the sake of completeness, it is worth considering the mechanisms of long term blood flow regulation at this point. This is particularly valid in the light of recent work which purports to show reflexes in contradiction to the baroreceptor loop function, but which in reality are probably mediators of long, not short term, control.

The body's long term blood flow regulation depends on three factors :-

- a) Fluid intake to the body
- b) Fluid loss by the kidneys
- c) Fluid loss by non-renal tissues (Guyton et al, 1974).

The physiological means of controlling these factors fall into five main groups.

##### a) Sympathetic pathways.

When all parts of the system are functioning normally, cardiac output is determined by venous return, which is in turn almost entirely controlled by the degree of dilation of the blood vessels in the tissues. The sympathetic vasoconstrictor function is thus an important factor in controlling the long term homeostasis of the system.

##### b) Parasympathetic pathways.

The parasympathetic system has the complementary role of controlling vasodilation, by stimulating various glands to release the enzyme bradykinin into the bloodstream. Dilation of the

afferent arterioles in the kidneys in particular, plus reflex signalling from the vasomotor center to the hypothalamus to reduce the secretion of Anti-diuretic hormone (ADH ), leads to rapid loss of fluid into urine ( Vick, 1963).

c) Pulmonary receptors.

The pulmonary artery also contains stretch receptors similar in function to the baroreceptors. These are thought to be more sensitive to low pressures, below the range of the baroreceptors. They help further in controlling changes resulting from fluctuations in blood volume.

d) Atrial receptors.

The Bainbridge reflex is a method of heart rate control which acts as an emergency procedure to relieve the damming of blood in the venous system, and often acts in opposition to the baroreceptor reflex. Changes in the arterial blood pressure load against which the heart is pumping have almost no effect on the amount of blood pumped out of the heart per minute. Arterial blood pressure must be in the order of 200 mm Hg. before this situation changes. The most important factor in determining the amount of blood pumped by the heart is the pressure developed in the Right Atrium. If this pressure rises too quickly, stretch receptors in the atria send messages via the vagus to the medullary control centres. Sympathetic facilitation then brings about increased heart rate and force of contraction to cope with the increased inflow to the heart ( Guyton, 1976).

In such a situation, sympathetic reflex innervation becomes very important. Normal sympathetic tone increases ventricular

contraction by 20% above the basal rate, and has the power to increase it by as much as 100%. The parasympathetic branches to the atria and ventricles do not have such a powerful reciprocal effect. They can reduce the force of contraction by a maximum of 30%.

Atrial receptors are not thought to play a significant role in overall cardiac control (Oberg, 1976). Recent studies have shown that stimulation of the atrial receptors causes vasodilation of the renal capillaries, and this effect may well be more important than the Bainbridge reflex under normal conditions. The atrial receptor fibres are thought to project to hypothalamic areas and inhibit Anti-diuretic hormone (ADH) secretion, thereby causing renal vasodilation (Oberg, 1976).

e) Ventricular receptors.

Stimulation of the non-medullated fibres from the ventricular stretch receptors causes bradycardia and vasodilation due to sympathetic inhibition. This is known as the Bezold-Jarisch reflex, and its effect is the complete opposite to the Bainbridge reflex. Again, it is thought that renal fluid volume is the prime control function of this reflex (Oberg, 1976).

### 1.5 Summary

The subject of this thesis is the estimation of a possible transfer function for the baroreceptor reflex loop in the rabbit, which controls short term variation of blood flow.

The baroreceptors of the carotid sinus and aortic arch are the primary sensors for the control loop. The receptors of the aortic arch are studied in this work since they dominate those of the carotid sinus in the rabbit (Ito & Scher, 1979). The aortic baroreceptors provide sensory input to the medullary cardiac control areas via the cardiac depressor nerve.

The medullary control areas respond to baroreceptor input through the autonomic nervous system. Stimulation of the fast vagal pathway to the heart causes bradycardia, while sympathetic stimulation brings about tachycardia and constriction of the peripheral vessels. At normal pressures, control is achieved mainly by altering TPR via the sympathetic nerves. At higher pressures, the control loop response is almost entirely due to changing heart rate.

## Chapter 2

## Pilot Experiments.

## 2.1 Introduction.

In this chapter a pilot series of experiments will be described which was designed as a preparation for the more comprehensive tests described in Chapter 4.

As already stated, the prime considerations were (i) that the surgical techniques employed should involve minimal disturbance of the total system, and (ii) that the perturbations applied to the system should not drive it beyond its linear range. The objectives of the pilot study were to establish:

- a) a sound experimental and surgical protocol
- b) the degree of linearity of the baroreceptor control system.

The pilot experiments utilised constant frequency stimulation of the cardiac depressor nerve. Consequently, the results generated were unsuitable for Frequency Response calculation, for reasons explained in Chapter 3. However, much of the experimental protocol was designed with system identification in mind, in preparation for the experiments described in Chapter 4.

An explanation of the protocol is given in the next two sections (2.2 and 2.3). The final sections of the chapter (2.4 and 2.5) cover in detail the methods used in the analysis of the experimental data.

## 2.2 Experimental Protocol.

### 2.2.1 System input and output signals.

Existing studies of the aortic baroreceptor reflex loop fall into two primary groups, those using aortic wall disturbance to stimulate the baroreceptors, and those which utilise cardiac depressor nerve stimulation. The aortic wall disturbance approach presents two major problems. Firstly, locating the aorta involves major physiological disruption as a result of opening the thoracic cavity, which is the main reason why few studies have been carried out using the aortic arch (Douglas and Schaumann, 1956, Kardon et al., all refs., and references in the rest of this chapter), compared with the wealth of information relating to carotid sinus stimulation. Secondly, the application of a test signal by varying blood pressure is mechanically difficult to achieve, making the use of complex test signals largely impracticable. The use of sophisticated analysis methods therefore may be invalidated due to the paucity of information provided by the data.

In this study, therefore, neural intervention was chosen as the point of entry to the system. Rabbits were used as the experimental animal since the cardiac depressor nerve exists as a separate entity, rather than as part of the vagus. The nerve also comprises baroreceptor rather than chemoreceptor fibres almost exclusively (Gernandt, 1946). Because of this, the rabbit is one of the standard, and certainly one of the most convenient, animals to use in work involving the cardiac depressor nerve (references to other workers are given in succeeding chapters).

In the pilot study, constant frequency stimulation of the

depressor nerve was used. Such studies are plentiful in the literature (e.g. Oberg, 1976). The ability to compare results with established workers was seen as a considerable advantage, allowing the validation of the surgical preparation and experimental equipment being used. The appropriate stimulus frequencies were obtained from Douglas and Schaumann (1956) and Kardon, Peterson and Bishop (1974). The former found that the cat's aortic nerve was responsive up to 250 Hz. with the maximum depressor response obtained at about 100 Hz.. Their results are summarised in Fig. 10. Kardon et al. found that the aortic nerves of the rabbit were most sensitive at about 50 to 80 Hz., and depressor responses continued in excess of 150 Hz. Work done by Bloor (1963), studying the pressures at which peak aortic nerve discharge frequencies were obtained in rabbits, gave confirmation that at normal pressures (110 mm Hg.), the aortic nerve fibres naturally discharge at about 80 Hz.. It was therefore decided to use stimulus frequencies in the range 20 to 100 Hz., in increments of 10 Hz, working with whole fibre preparations.

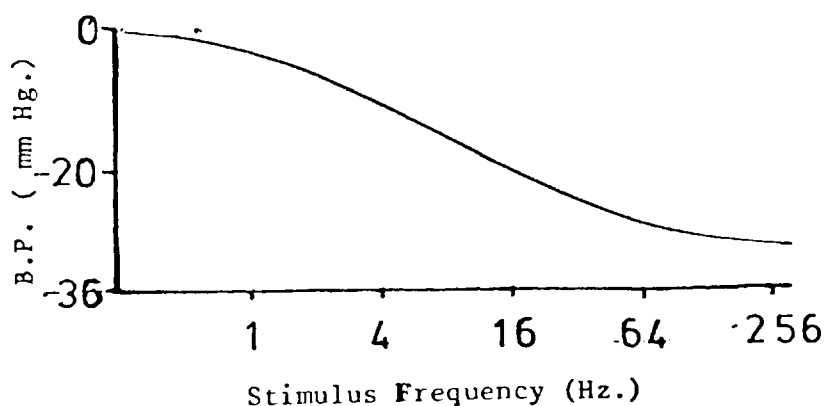


Figure 10. Maximum depressor response of cat's arterial blood pressure due to aortic nerve stimulation. Douglas and Schaumann, 1956.

It has already been shown (section 1.3) that the baroreceptor control loop does not operate in a linear manner; in the present case we are interested in establishing whether the curves of Figures 7 and 10 are approximately linear when considered over small ranges. If so, the magnitude of the linear range must be established. Stimulus-response testing under linear conditions is a necessary prerequisite for Frequency Response testing, as laid out in Chapter 3. The 10Hz. frequency increment between tests was chosen because Kardon et al (1973) found that this was the minimum increment which gave a detectable change in response. Since the available literature yielded no possible value for the settling time of the baroreceptor control system in response to a step input, 30 sec. was chosen as the stimulus time. In the event, this proved to be somewhat short when high frequency stimulation was considered (see section 2.5).

The best approach to whole fibre stimulation was to use stimuli of sufficient intensity that all fibres would be activated. Submaximal stimulation inevitably yields results which vary between experiments and make quantitative analysis impossible. It was not feasible to study the output from individual fibres, much less to make observations on the active fibre population during each test. A stimulus intensity of 5v and pulse width of 0.2msec. (Kardon, Peterson and Bishop, 1973, 1974, 1975) was considered to be sufficient in this particular set-up to activate all the fibres, since tests had shown no difference in results obtained at higher voltages.

Although a protocol incorporating submaximal stimulation may have provided a useful insight into the comparative roles of the two

autonomic divisions, it was felt that the purpose of the study was to establish whether the baroreceptor loop dynamics could be characterised by frequency response estimation. Hence, it was considered important to initially limit the control variables involved. Once proven, the technique could be modified for use in more complex situations.

System identification requires comparison of the signal used to drive the system with the system's response(s) to that signal, as will be discussed more fully in the next chapter. The system responses in this case are those elicited by stimulation of the cardiac depressor nerve, primarily changes in heart rate and TPR. The animal's E.C.G. was therefore recorded during the experiments for subsequent conversion into a heart rate signal.

Attempting to measure TPR directly would have made the experiment very complex. A more practical indication of changing TPR could be found by measuring arterial blood pressure. If the stimulation of the depressor nerve caused only heart rate changes, then the heart rate and blood pressure signals should yield identical information. However, if changes in TPR resulted instead (or as well) as changes in heart rate, the two measured signals should reflect this in differing response times, gains, and so on.

Respiration was also measured since it was considered interesting that in the spontaneously ventilating animal, respiration often exhibits a depressor response. This may be due to interaction (either deliberate or simply as a result of neural proximity) at the medullary level, perhaps in the Nucleus Tractus Solarius (Hilton and Spyer, 1980). Since the depressor nerve contains no chemoreceptor fibres, a direct pathway to the

respiratory centres is unlikely, though it cannot be ruled out. It is difficult to visualize what advantage a deliberate limitation of respiratory intake would bring to the baroreceptor loop.

It has long been known that neural connections exist in the reverse direction, i.e. under normal conditions sympathetic vasoconstrictor activity is modulated by respiration, without the involvement of the vagus (Adrian, Bronk and Phillips, 1932). Interesting work has been done by Gebber and Barman (1977) which suggests how these observations might combine anatomically. These authors propose two oscillators which independently control respiratory frequency and sympathetic tone. If the two oscillators are close in frequency, then one can be seen to drive the other, i.e. they exhibit mutual entrainment.

Heart rate, blood pressure and respiration therefore provide measurement of the major physiological variables affected by stimulation of the cardiac depressor nerve. Although a relationship would be expected between heart rate and blood pressure under most conditions, it is possible to visualise a situation in which the three outputs exhibit independent responses. The data would therefore reflect what may be considered to be three individual systems which, in the extreme, would operate independently in response to the same input signal (see fig 26).

### 2.2.2 Anaesthesia.

Having chosen neural stimulation as the best experimental approach, it was necessary to determine which anaesthetic agent was most appropriate. The primary concern was, of course, the wellbeing of the animal during the experiment. However, anaesthetic agents by

their very nature exert influences over the central nervous system which alter the normal physiological state of the animal. Indeed, one of the main disadvantages of invasive experimentation is that the influence of anaesthesia on the results is difficult to gauge accurately.

Anaesthesia by definition depresses the higher autonomic centres. Korner, Shaw, West and Oliver (1972) have compared the results of many studies of the baroreceptor loop in anaesthetized and conscious animals, the latter having undergone brain lesioning. They found that the anaesthetized animal generally resembled the unanaesthetized pontine animal. That is, anaesthesia was similar in effect to removal of the suprabulbar centres which control sympathetic reflexes (see section 1.2.1). The result was that the sympathetic excitation of the heart was activated at a lower threshold and with increased gain in these animals. Korner et al (1972) concluded that the absence of these suprabulbar influences explains the discrepancy between their own work and that of Glick and Brunwald (1965).

Use of an anaesthetic agent does not seem to alter the type of blood pressure response obtained with depressor nerve stimulation. Some care was taken to establish this fact while the surgical techniques were being perfected. Papers by Neil, Redwood and Schweitzer (1948) reinforce this point. A recent paper by Cox and Bagshaw (1979) showed that several agents commonly used in baroreceptor experiments cause a reduction in the expected response. The conclusions from this work and from tests carried out personally may be summarised as follows.

#### Halothane

relaxes vascular smooth muscle, thereby hindering attempts to experimentally cause blood pressure to rise.

#### Pentobarbital

also has an effect on the reactivity of the vasculature. Donald and Shepherd (1980) claim that the medullated fibres in the depressor nerve of the dog also generally become less responsive .

#### Chloralose and Ether

were not seriously considered since there was a high incidence of respiratory difficulties due to excessive mucous production in animals treated with these agents.

#### Nembutal

while keeping heart rate near normal, gave rise to an unstable state of anaesthesia unless the animal was "topped up" as often as every 20 minutes.

#### Urethane

was chosen on the grounds of safety since no evidence was found which positively suggested that one particular agent would yield better results. Its application induced a very stable state of anaesthesia; the initial dose only needed to be supplemented every 1 - 2 hours. Furthermore the animal's respiration, colour and heart rate remained good, if a little high, during the tests.

### 2.2.3 Surgical Preparation.

The experimental preparation was based on information obtained from other workers (Kardon, Peterson and Bishop, 1973 and 1975; Angell-James, personal communication). The aim was to establish a protocol which yielded accurate and consistent results, and which allowed the cardiovascular system to function in a near normal manner. The depressor nerve in the rabbit is separate from the vagus and therefore more accessible. Also, rabbits are large enough to make it feasible to work on these relatively small nerves without resorting to a microscope. Rabbits will also withstand several hours of experimentation under anaesthetic. Figure 11 shows the main anatomical features exposed by the surgery. Male rabbits weighing between 2.0 and 2.5 Kg. were used.

The animal was anaesthetised using Urethane (7 ml./Kg.). When a level of anaesthesia in which corneal or deep joint reflexes were absent was reached, a midline incision was made from the jaw to the sternum. Superficial fatty tissue was removed to expose the Jugular vein on one side, which was cannulated to allow further application of anaesthetic and saline as necessary. The animal was maintained at this level of anaesthesia throughout the experiment.

The pectoralis muscle was cut and the sterno-hyoid muscle was tied and removed to expose the thyroid and trachea. The latter was cleared of any appending tissue and cannulated to allow recording of respiration via a thermal transducer.

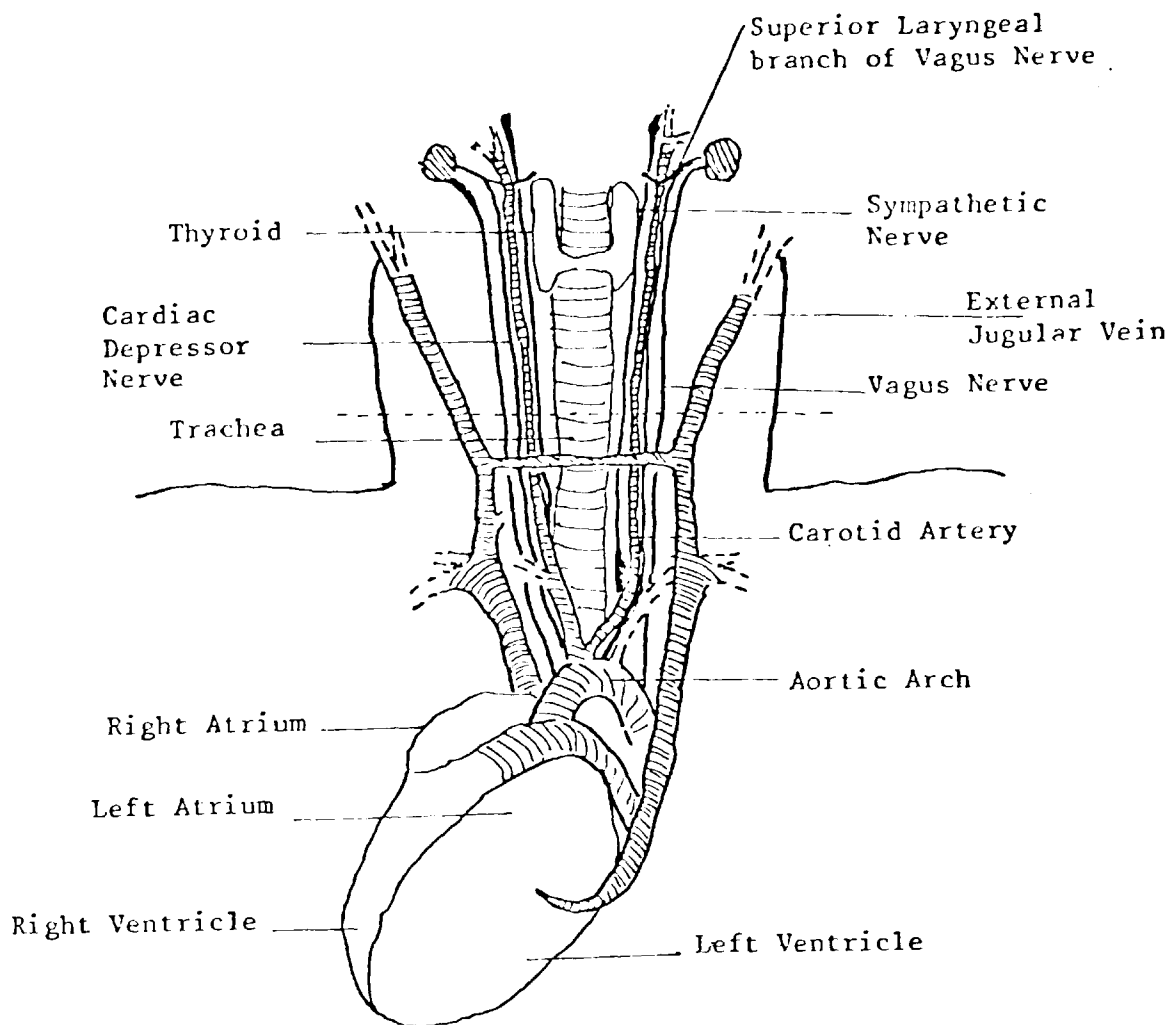


Figure 11. Anatomical features of the surgery. Dotted line indicates the extent of the exposed areas.

The sterno-thyroid and omo-hyoid muscle blocks were carefully removed from either side of the trachea to expose the carotid artery and its three associated nerves. These nerves, the vagus, sympathetic and cardiac depressor, were identified and freed for about three centimetres of their length using glass hooks and silk thread. The area was bathed repeatedly with Krebs-Henselite

solution at 37 C. to keep the exposed nerves alive. The cardiac depressor was distinguished from the sympathetic and vagus by its size and location. It is approximately half the diameter of the sympathetic and one quarter that of the vagus, and is looped by the superior laryngeal nerve at the level of the thyroid. Since Irisawa and Ninomiya (1967) found the responsiveness of the right and left depressor nerves to be identical, either one was used.

The contralateral carotid artery was then cannulated and the cannula fed toward the aorta as far as possible (up to 3 inches) to measure central arterial blood pressure. The cannula was flushed at regular intervals with heparinised saline to prevent clotting of blood at its tip.

The skin flaps around the exposed area were sewn to a metal ring to form a pool. The depressor nerve was rested on bipolar platinum electrodes and the pool filled with liquid paraffin at body temperature.

Needle electrodes were inserted subcutaneously for the purpose of recording the ECG.

The physiological data were recorded on a P.I. eight channel AM/FM tape recorder. The experimental set-up is shown in Figure 12.

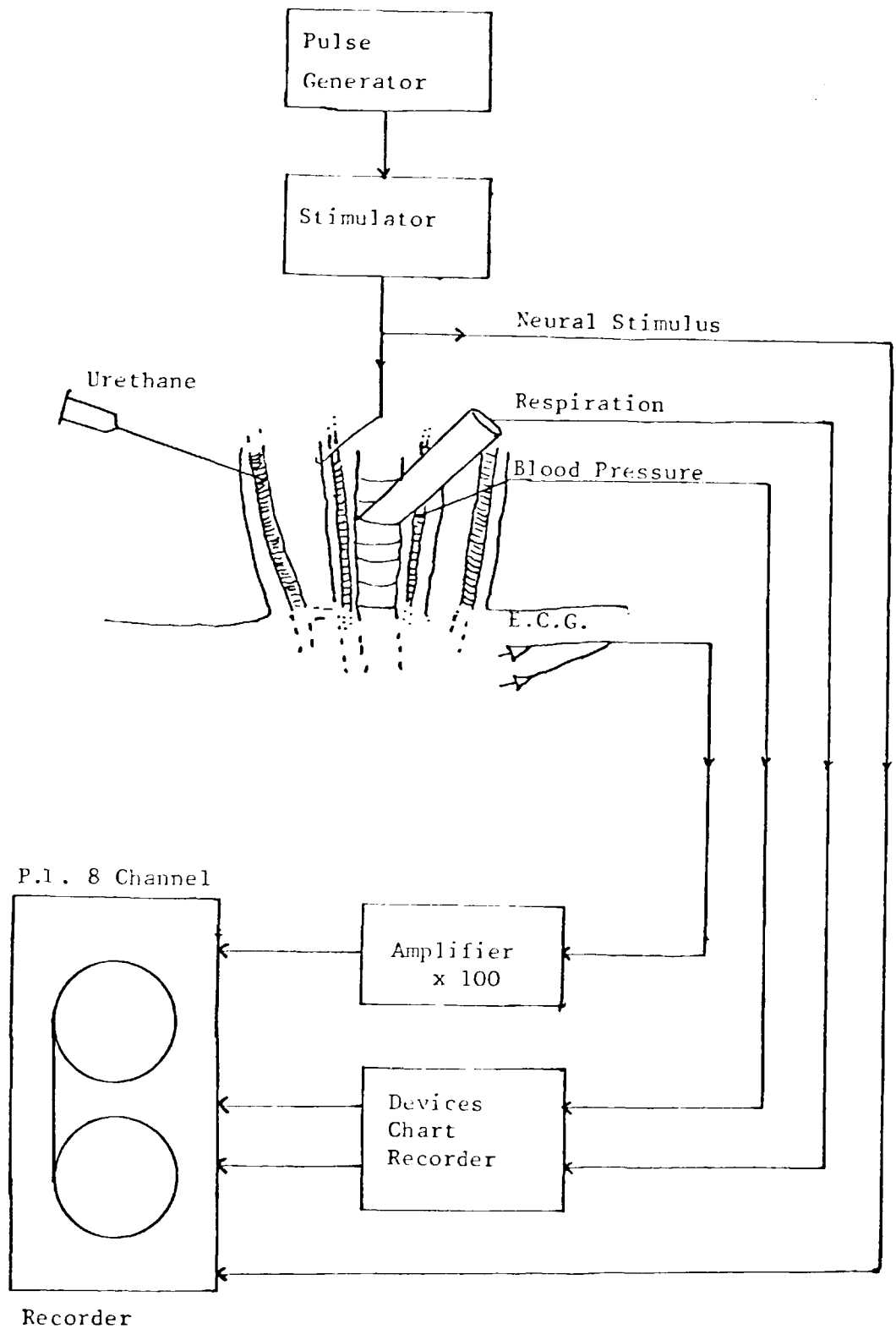


Figure 12. Diagram illustrating the experimental set-up used in stimulating the cardiac depressor nerve in the rabbit and recording ECG, respiration and arterial blood pressure.

### 2.3 Application of the stimulus and recording the physiological data.

Once these preparations were made, the nerve was stimulated using constant frequency pulse trains of 0.2 msec. pulse width, and 5v intensity. The frequencies used were 20 - 100 Hz., in steps of 10 Hz. Each signal was applied for 30 seconds. Two or three minutes recovery time was allowed between tests. As stated in section 2.2.1, these values were chosen to provide the best opportunity to evaluate the linear range of the baroreceptor control loop.

Four channels of data were recorded on tape:

- a) Neural stimulus
- b) ECG
- c) B.P.
- d) Respiration

Channel b) was amplified 100 times before being recorded (see Figure 12) since the surface E.C.G. is only 1-2mV peak to peak. Channels c) and d) were amplified as a result of feeding them through a Devices two channel chart recorder prior to storing them on tape.

Obtaining a continuous visual record of signals (c) and (d) during the experiment was especially important since sudden variation in their regular pattern gave early warning that the animal was experiencing some physiological imbalance. In addition, the characteristic exponential drop in blood pressure which accompanies stimulation of the depressor nerve (see Figs. 15 - 23) provided the simplest proof that the neural preparation was still

intact. It is of paramount importance in neural tests to ensure that exposed nerves do not dry out. This can happen in minutes to a nerve as small as the cardiac depressor. Once the nerve starts to dry out, it is no longer capable of efficient conduction, and further testing is rendered invalid.

At the end of the experiment , the animal was killed by injection of excess Urethane.

## 2.4 Preparing the data for analysis

### 2.4.1 Digitization of the data.

The first stage in the analysis was to convert the continuous experimental data into digital form, suitable for computer use. It was advantageous to keep the chosen sampling rate as low as possible so that subsequent calculations performed upon the data involved the minimum number of points. As the data arrays tended to be very large, computer time and memory were at a premium.

The results of the tests showed that for the present purposes the highest significant frequency for blood pressure, respiration and E.C.G. was their repetition rate, i.e. 4 to 5 Hz. for both blood pressure and E.C.G., and 1 to 3 Hz. for respiration in rabbits. Bearing in mind that the time-dependent feature of interest in these signals was the variation of repetition rate due to extraneous stimuli, the frequency components of interest therefore lay well below 4 to 5 Hz. By Nyquist's criterion,

$$\text{minimum sampling rate} = \text{maximum frequency} \times 2.$$

so that a sampling rate of 10.0 Hz. would have been sufficient to include all systems information.

The neural stimulus had a repetition width of 1 msec. and a maximum repetition frequency of 100 Hz. A sampling rate of 1 KHz. would therefore have been preferable, but since this signal was used only as a marker, i.e. to determine the data points corresponding to the start and end of stimulation the error induced by filtering was negligably small.

Initially the raw ECG and neural stimulus information were

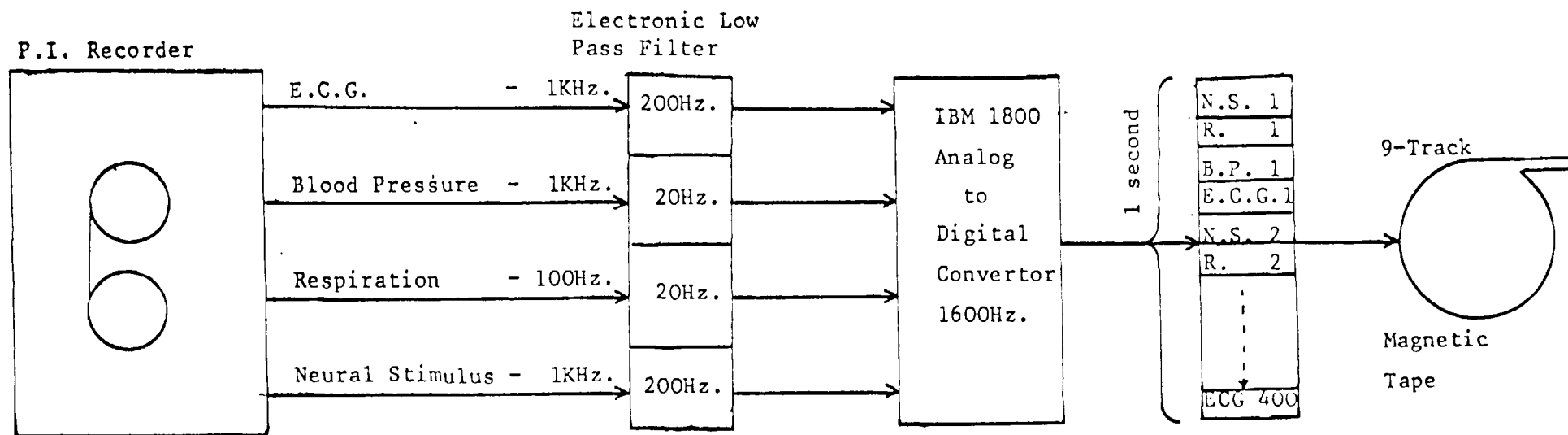


Figure 13. Diagram illustrating the process of converting the experimental data from continuous to digital form.

electrically low pass filtered to 200Hz. from their recording frequency of 1KHz. The blood pressure and respiratory signals were low pass filtered to 20Hz. The sampling rate used for the digitisation was therefore

$$\text{lowest common frequency} \times 2 = 400\text{Hz./channel},$$

and the overall digitisation rate was

$$\text{frequency per channel} \times \text{no. of channels} = 1600 \text{ Hz.}$$

The analog to digital conversion was performed on the IBM 1800 in the Engineering in Medicine Laboratory at Imperial College, and the result written to 9 track magnetic tape. The tapes were then transferred to the CDC 6600 at Imperial College, on which all subsequent stages of analysis were performed. The digitisation was normally carried out at ten times normal speed, hence tape speed, digitisation rate and filter cutoff frequencies were also increased by a factor of 10. Figure 13 illustrates the analog to digital conversion process.

#### 2.4.2 Formation of the heart rate signal

Before the results of the above tests could be interpreted, the E.C.G. data had to be converted to a form which illustrated changes in rate more clearly.

In investigating the changes which occur in the baroreceptor loop as a result of neural stimulation, we were not interested in studying the ECG itself; the characteristic shape of the QRS complex remained virtually unchanged throughout. Rather, the timing of successive beats was the crucial factor, since this is what the baroreceptors reflexly control.

Appendix A(i) shows the programming algorithm used in forming a

continuous heart rate signal from the recorded ECG. Rompelman, Coenen and Kitney (1977) described this signal as the "instantaneous heart rate", being the series of reciprocals of R-R interval duration plotted as a function of time.

As shown in Fig. 14, in the first instance an irregularly spaced event series was formed which represented the time of occurrence of each R wave. This series was then interpolated to form a continuous, regularly sampled signal to allow further numerical manipulation. Interpolation was required only to create regularly spaced data, not to increase the information content of the signal which was still, at 400 Hz., considerably over-sampled. It was therefore found in practice that more complex methods of polynomial interpolation (e.g. Runge-Kutta, sinc function) did not yield results which were significantly different from those of the method finally chosen; i.e. stepwise building of a continuous signal. The advantage of interval information rather than the ECG is that the sampling rate need only be the same as the mean heart rate in order to completely describe the signal (Rompelman, Coenen and Kitney, 1977). Once this signal was constructed, the sampling rate of all three signals being used for analysis (heart rate, blood pressure and respiration) was decreased to 40Hz. This choice of sampling rate was based upon the signal with the highest frequency bandwidth (blood pressure). The low pass filtering was achieved by forming from each signal a new sequence which contained every tenth data point from the old array.

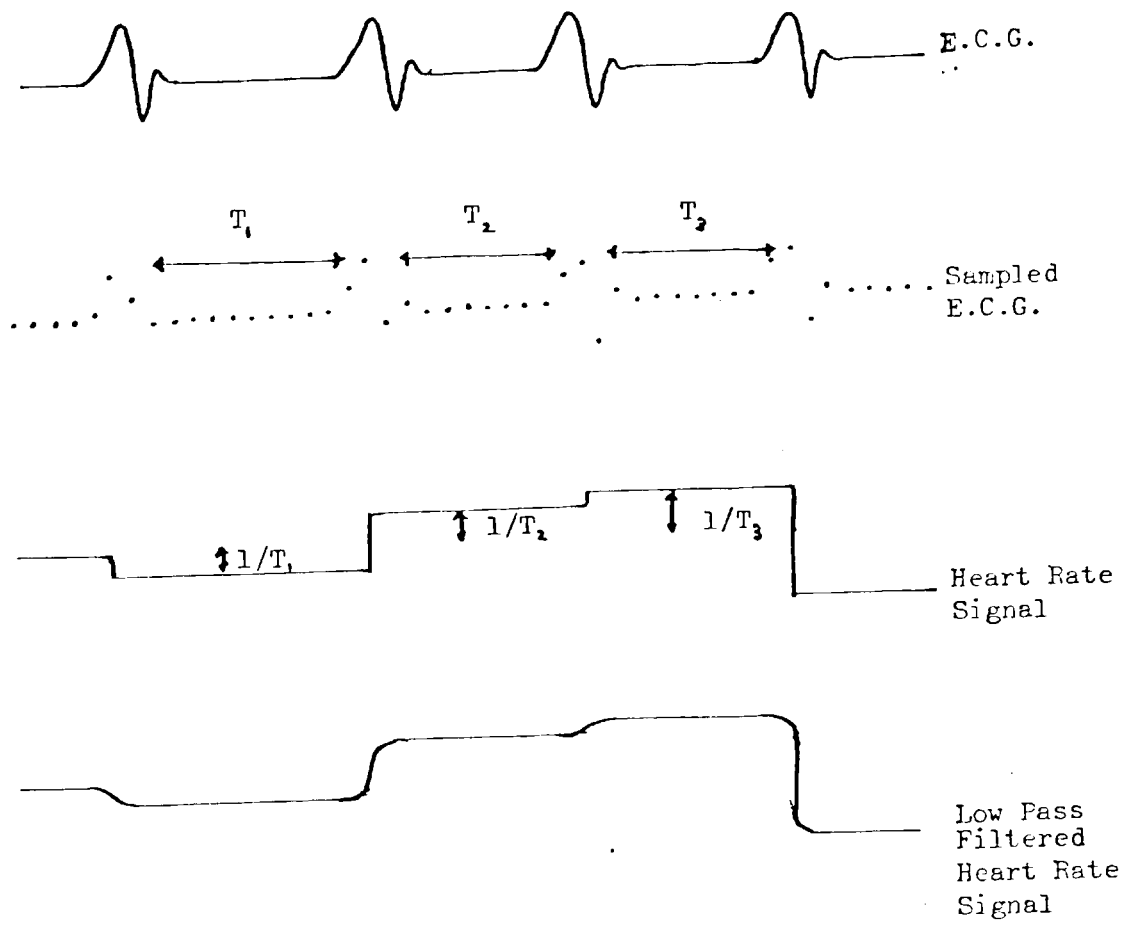


Figure 14. Constructing the heart rate signal from the E.C.G.

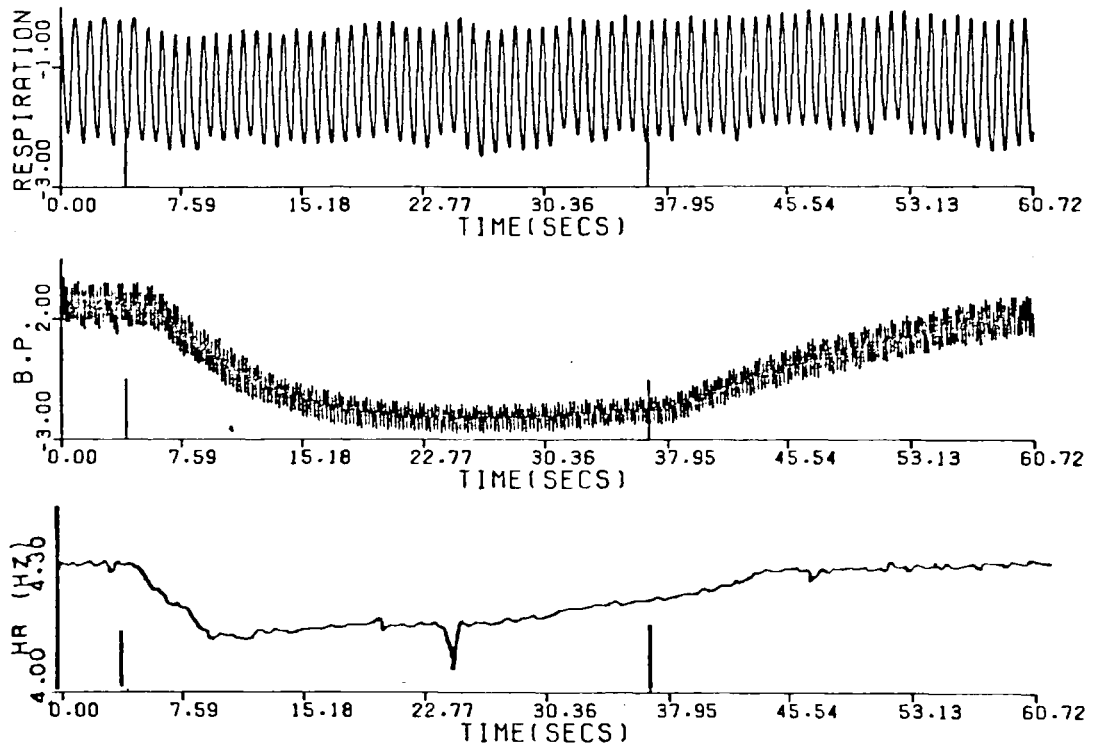


Figure 15. Results of experiment demonstrating the effect of constant frequency stimulation of the cardiac depressor nerve in the rabbit upon respiration, arterial blood pressure and heart rate. Frequency of stimulation - 20Hz.

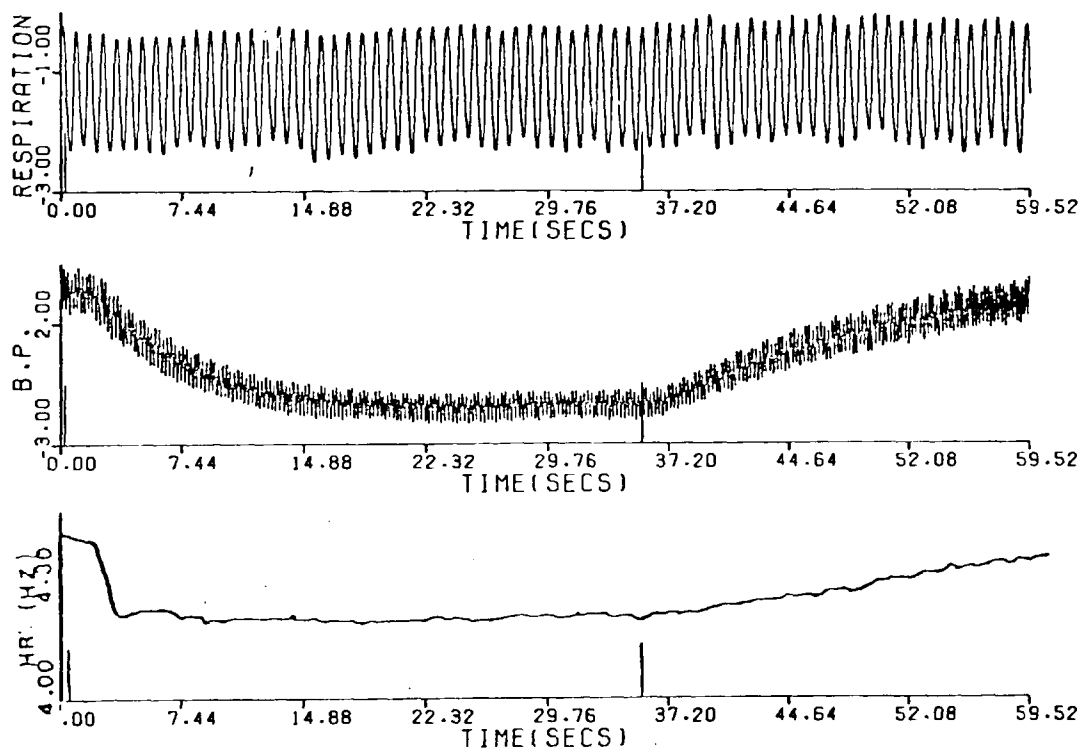


Figure 16. Results of experiment demonstrating the effect of constant frequency stimulation of the cardiac depressor nerve in the rabbit upon respiration, arterial blood pressure and heart rate. Frequency of stimulation - 30Hz.

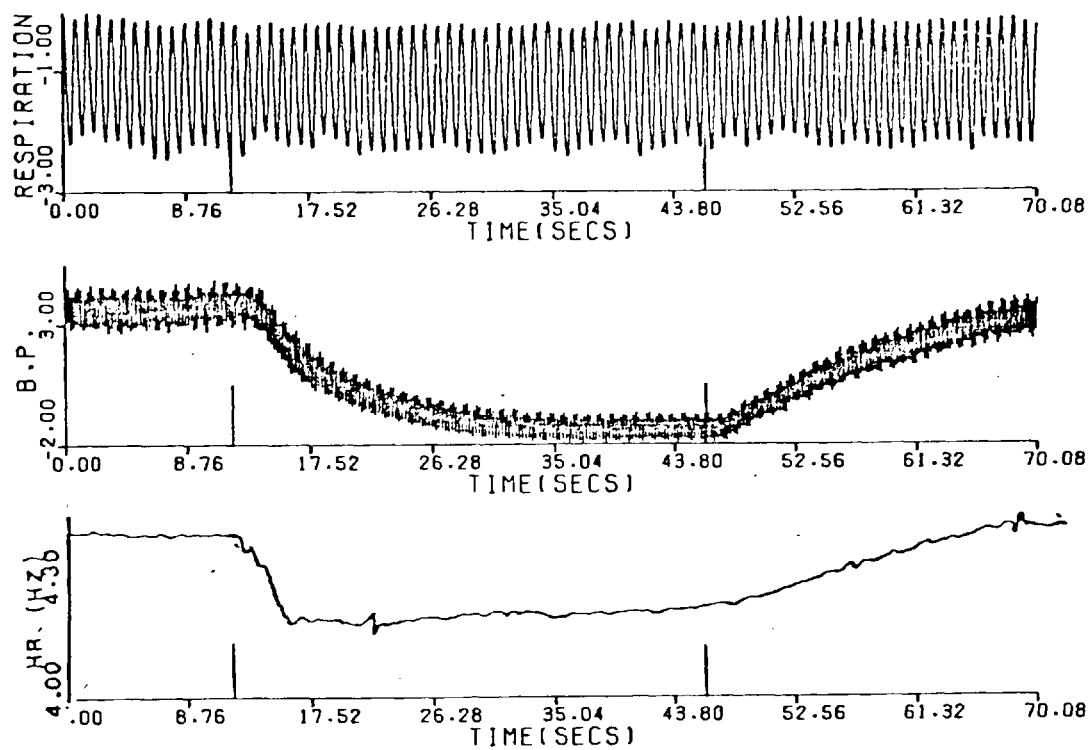


Figure 17. Results of experiment demonstrating the effect of constant frequency stimulation of the cardiac depressor nerve in the rabbit upon respiration, arterial blood pressure and heart rate. Frequency of stimulation - 40Hz.

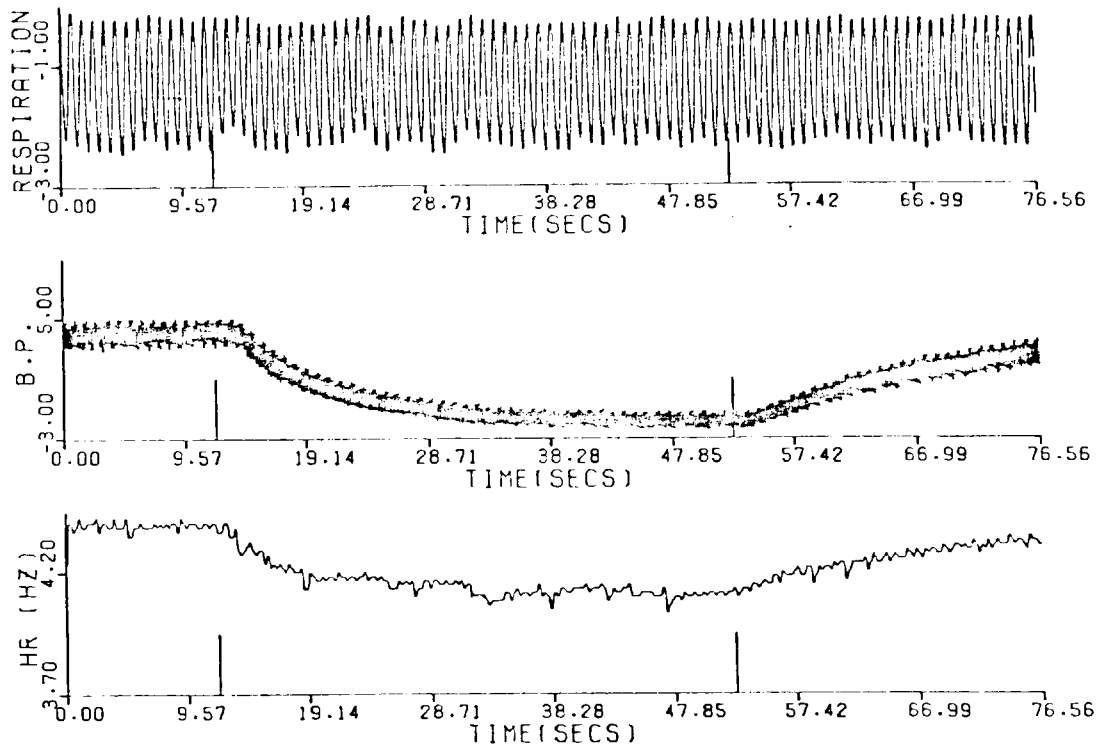


Figure 18. Results of experiment demonstrating the effect of constant frequency stimulation of the cardiac depressor nerve in the rabbit upon respiration, arterial blood pressure and heart rate. Frequency of stimulation - 50Hz.

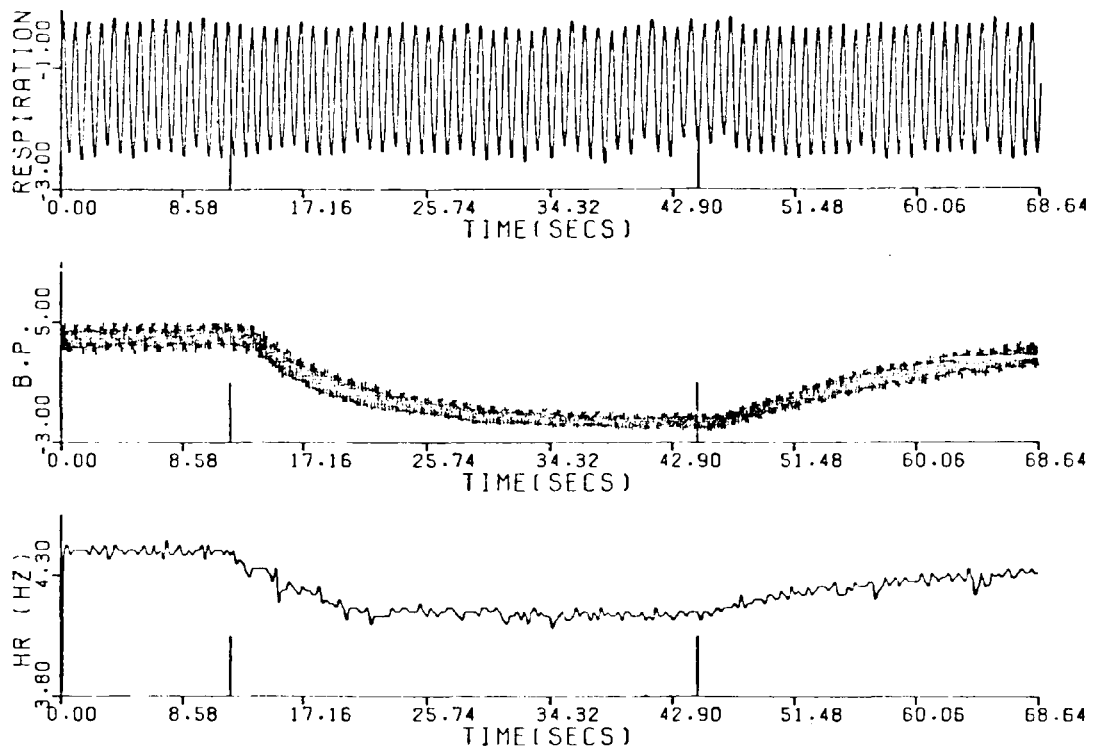


Figure 19. Results of experiment demonstrating the effect of constant frequency stimulation of the cardiac depressor nerve in the rabbit upon respiration, arterial blood pressure and heart rate. Frequency of stimulation - 60Hz.

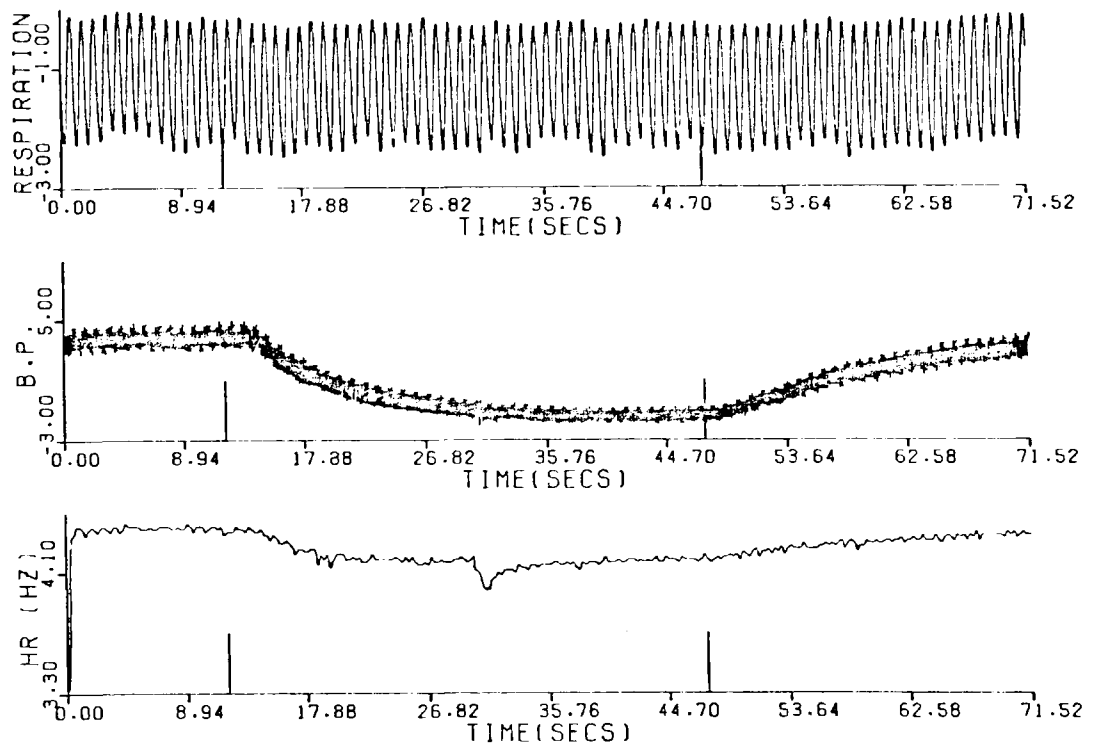


Figure 20. Results of experiment demonstrating the effect of constant frequency stimulation of the cardiac depressor nerve in the rabbit upon respiration, arterial blood pressure and heart rate. Frequency of stimulation - 70Hz.

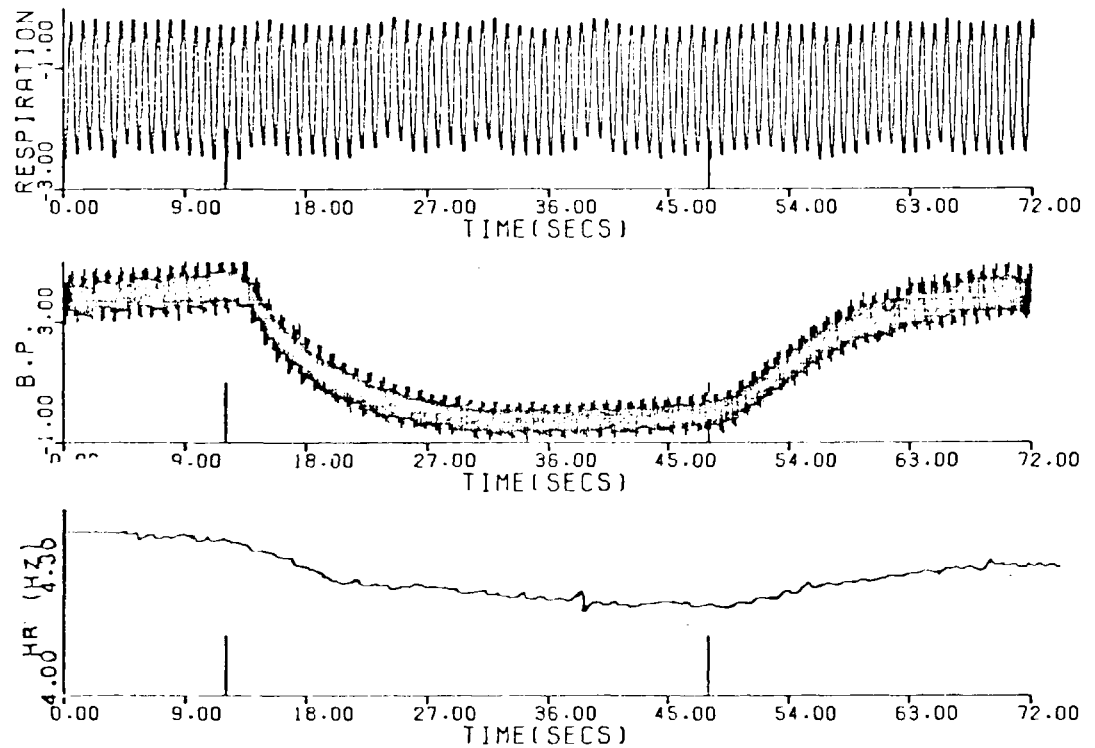


Figure 21. Results of experiment demonstrating the effect of constant frequency stimulation of the cardiac depressor nerve in the rabbit upon respiration, arterial blood pressure and heart rate. Frequency of stimulation - 80Hz.

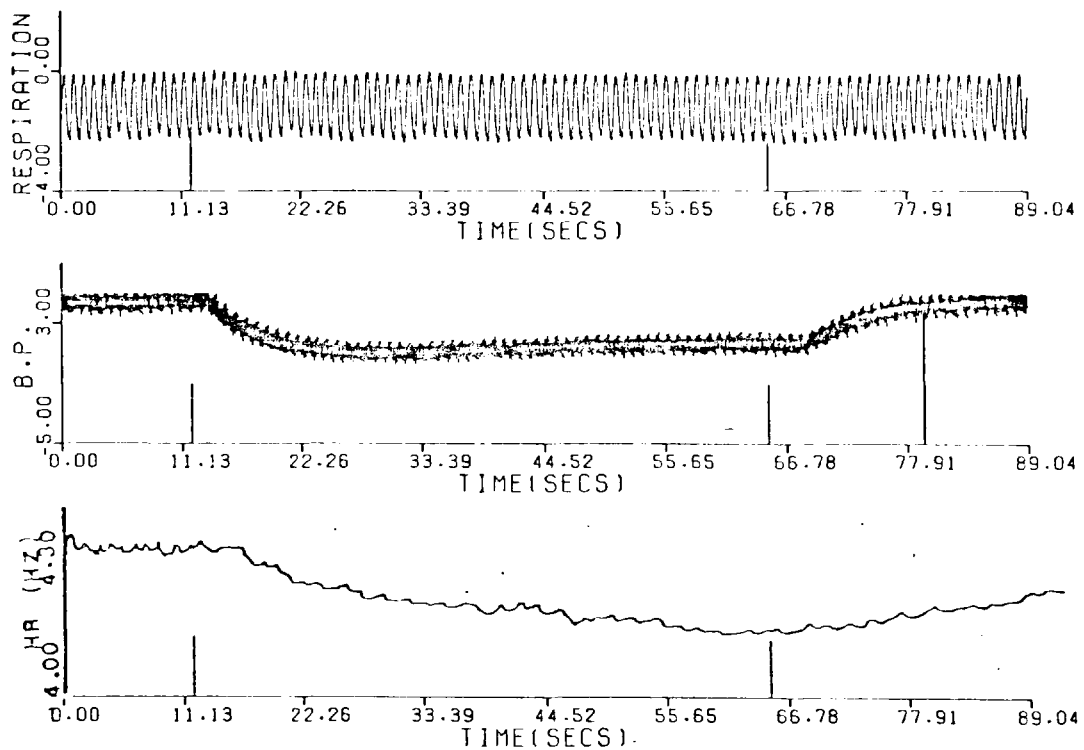


Figure 22. Results of experiment demonstrating the effect of constant frequency stimulation of the cardiac depressor nerve in the rabbit upon respiration, arterial blood pressure and heart rate. Frequency of stimulation - 90Hz.

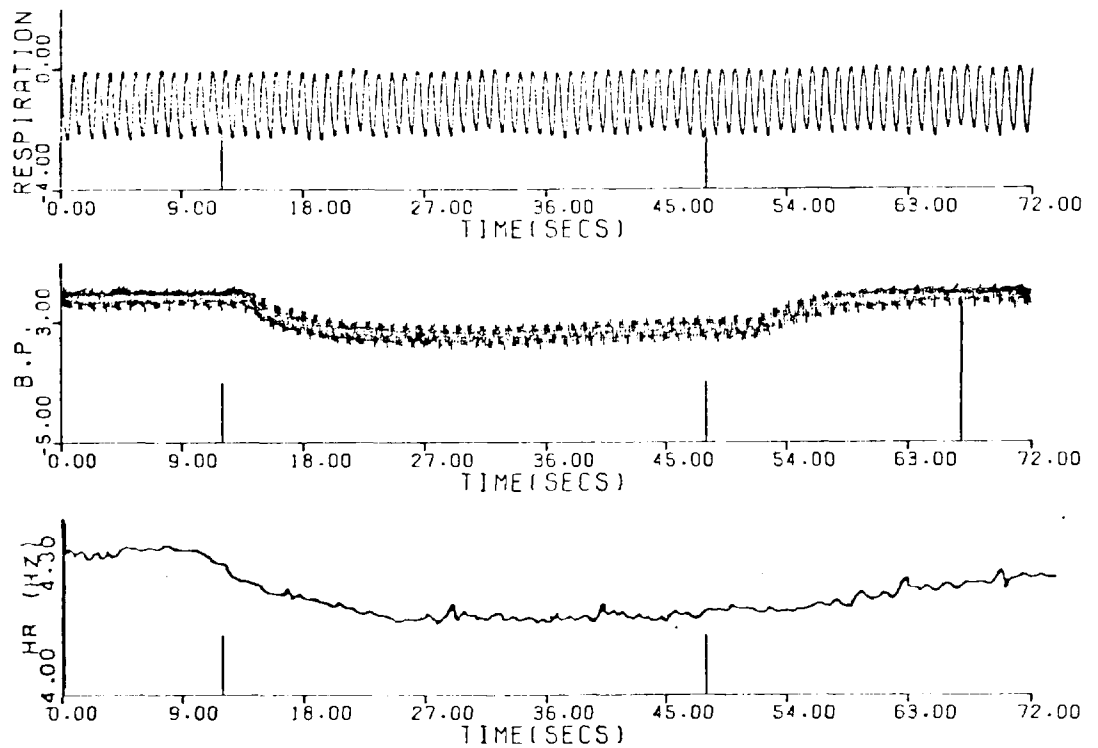


Figure 23. Results of experiment demonstrating the effect of constant frequency stimulation of the cardiac depressor nerve in the rabbit upon respiration, arterial blood pressure and heart rate. Frequency of stimulation - 100Hz.

## 2.5 Results of stimulating the depressor nerve with constant frequencies.

Figures 15 to 23 illustrate the results obtained from the preliminary tests using constant frequency stimulation of the depressor nerve for a period of 30 sec. and 5v intensity. As previously stated, the stimulus frequencies used were 20 to 100Hz., in increments of 10Hz. For each stimulus frequency, it was found that heart rate reached a minimum, then rose again momentarily during the first one or two seconds of stimulus, while blood pressure was still decreasing. The most likely cause was contradictory information from the numerous other receptors in the circulation about the true level of the arterial blood pressure (Kardon, Peterson and Bishop, 1973). The fact that this information did not manage to completely negate the effect of the stimulus was an indication of the dominance of the aortic arch baroreceptors in the cardiovascular system of the rabbit (Ito and Scher, 1979).

In this instance, heart rate and TPR were obviously both involved in the response. The reversal in heart rate but not blood pressure indicated the presence of fast vagal influences affecting heart rate, while the unmyelinated sympathetic vasoconstrictors affecting TPR worked over a much longer time course and were the primary cause of blood pressure change (see section 1.3). A second important reason why the TPR response is slow in relation to heart rate changes is the relatively long time constant of peripheral smooth muscle. This is supported by the work of Grodins (1963) who suggested that arteriolar smooth muscle acts as a first-order lag with a time constant of the order of 5 to 10 sec. The momentary reversal of heart rate became less marked as stimulus frequency

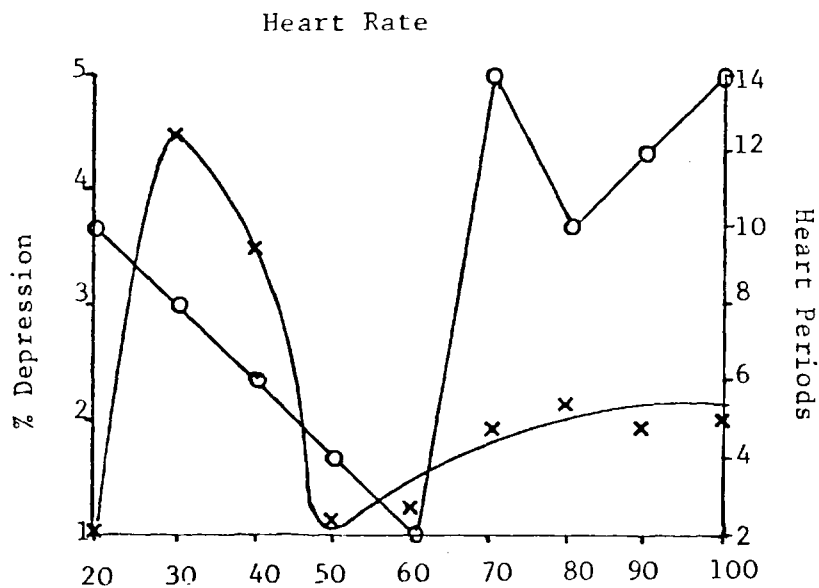
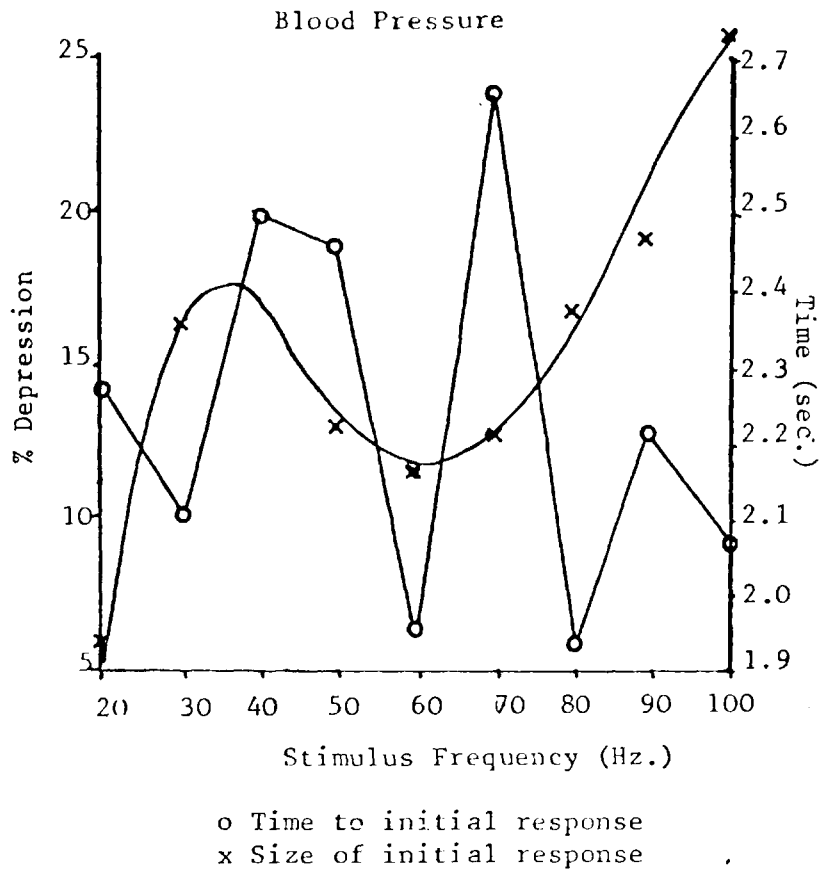


Figure 24. Diagram summarising the results of applying constant frequency stimuli to the cardiac depressor nerve in the rabbit. x indicates size of initial response in terms of % depression from pre-stimulus values: o illustrates the time at which this response occurred, relative to onset of stimulation.

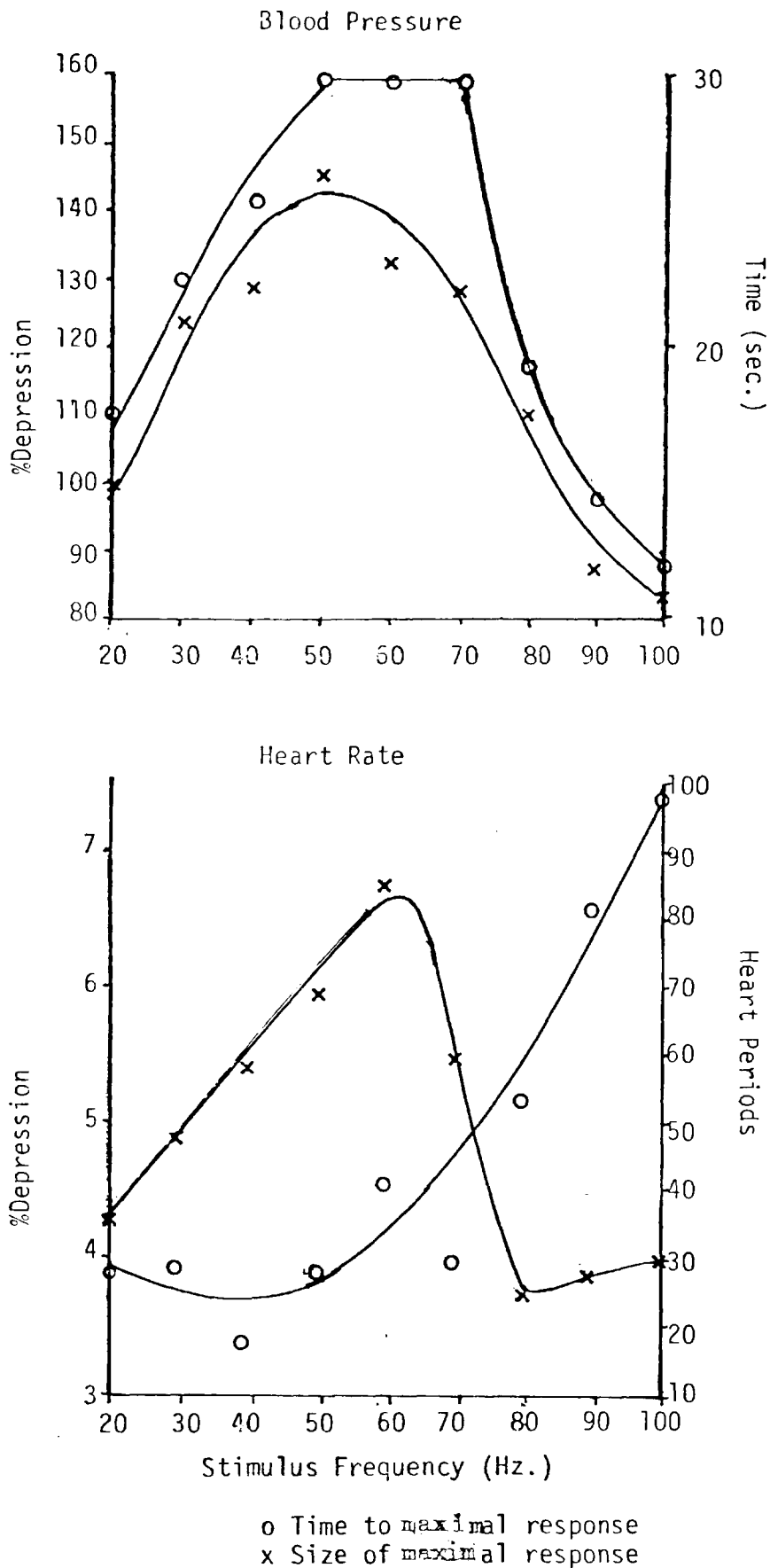


Figure 25. Diagram summarising the results of applying constant frequency stimuli to the cardiac depressor nerve in the rabbit. x indicates the size of the maximum response obtained in terms of % depression from pre-stimulus values: o indicates the time at which this response occurred.

increased, probably due to input from the depressor nerve overwhelming that from other receptors.

Figure 24 illustrates the initial response of the system to stimulation, and shows that both heart rate and blood pressure follow a similar pattern as stimulus frequency increases. The assumption that stimulus frequency is sufficient to mobilise both autonomic pathways is again validated: heart rate appears to be the dominant mechanism above 30Hz., when blood pressure response times become random while those of heart rate continue to fall linearly. The fastest responses occurred over the range 50 to 60Hz., which is in accordance with the work of Kardon, Peterson and Bishop (1973), and Douglas and Schaumann (1956).

Blood pressure declined in an exponential rather than linear manner during the application of the stimulus. The most likely reason for this is that, even if sympathetic stimulation decreased linearly, the peripheral vessels themselves would find it progressively harder to expand against their own elastic forces. It was unlikely that any reflex relaxation of the aorta causing reduced natural baroreceptor firing would have much influence on slowing down the fall in blood pressure under these circumstances.

Maximal response in terms of both heart rate and blood pressure (see Figure 25) lay between 50 and 70 Hz., although they did not reach a minimum level simultaneously. Heart rate stabilised within 10 to 15 sec. at the lower frequencies, increasing to 30 sec. at 100Hz. Blood pressure took longer than 30 sec. to reach a steady level over the most sensitive range, and varied in accordance with the size of the response. This underlined the fact that heart rate was largely vagally controlled, whereas blood pressure had a large

component which was mediated by the slow sympathetic vasoconstrictor fibres. Heart rate was also shown to be the most important line of response, especially at higher frequencies.

Reductions in heart rate and blood pressure were maintained in spite of the fact that the carotid sinus system was intact. This agrees with the work of Kardon, Peterson and Bishop (1973) who showed that the buffering effect of this system was negligible when strong aortic nerve stimulation was used. On the other hand, these workers showed that the contralateral aortic nerve did buffer the response.

Respiration was measured in the pilot experiments since a strong correspondence is often found between the blood pressure and respiratory responses, probably due to interaction at a central level. However, in this instance no similarities could be visually distinguished.

The results of these tests appear to confirm the view proposed in section 2.2.1, that the baroreceptor control loop can be considered to contain two separate types of response, heart rate and TPR. A possible influence of the baroreceptor regulator over the pattern of breathing should also be considered. The results of the pilot study showed that to some extent that the system may be treated as linear over small stimulus ranges (10-20Hz.). The experimental protocol was thus validated.

The next area for consideration was therefore how best to utilise control engineering methods to elucidate the interactions within the baroreceptor loop.

## 2.6 Summary

A series of pilot experiments was carried out using the cardiac depressor nerve as the point of stimulation of the baroreceptor loop in the rabbit. The experiments used whole fibre constant frequency stimulation of the nerve at frequencies between 20 and 100 Hz. All physiological pathways involved were left intact in order to study the total response of the system under as near normal conditions as possible.

Recordings were taken during the experiment of the neural stimulus, E.C.G., arterial blood pressure and respiration.

These data were digitized for computer use, and the E.C.G. signal was then converted into continuous heart rate information.

Examination of the results obtained showed a good likeness to those of other workers. Even at stimulus voltages sufficient to excite all fibre groups, increasing stimulus intensity produced a non-linear family of responses. TPR appeared to be a significant control mechanism during low frequency stimulation. Heart rate contributed strongly over the entire frequency range, and was probably entirely responsible for the high frequency responses. The system could, however, be considered to be linear over small stimulus ranges (10-20Hz.).

## Chapter 3

Identification techniques for the analysis of the baroreceptor control loop.

### 3.1 Introduction.

Most of the information relating to the baroreceptor control loop has been obtained from experiments in which a single input to the cardiovascular system is varied while as many other inputs as possible are kept constant, or eliminated. Such information is fundamental to the analysis of the circulatory system, but is still not sufficient to account for the way in which the system regulates in situations which elicit a response from the system as a whole rather than from isolated components. A detailed understanding of the normal mode of operation of the cardiovascular system therefore demands an appreciation of the way in which these multiple resources are co-ordinated into a total cardiovascular response.

### 3.2 General identification of the control system.

In this section the structure of the control system will be discussed in relation to Figure 26. This figure is a block diagram which illustrates the major components of the baroreceptor loop, and illustrates why the blood pressure regulatory system is usually referred to as a feedback system. The baroreceptors are a type of transducer, in that their function is to convert one form of signal to another. The input to the receptors is the pattern of distention of the aortic wall which mirror changes in blood pressure. The output is electrical impulses which control the rate and level of neural firing.

The cardiac depressor nerve discharge provides negative feedback (afferent information) to the central regulatory areas. On the basis of this afferent information, the discrepancy between actual and required blood flow is calculated. The central regulatory areas are therefore shown as a comparator in the block diagram. The forward loop (efferent pathway) thus comprises the autonomic effector nerves which directly modify levels of blood pressure and heart rate.

For completeness the pathways describing the interaction with the carotid sinus loop are included in lumped form. The proposed pathway of influence over the respiratory system is also shown. Nevertheless, Figure 26 is a gross simplification of the physiology and is intended only to illustrate the general structure of the afferent and efferent pathways.

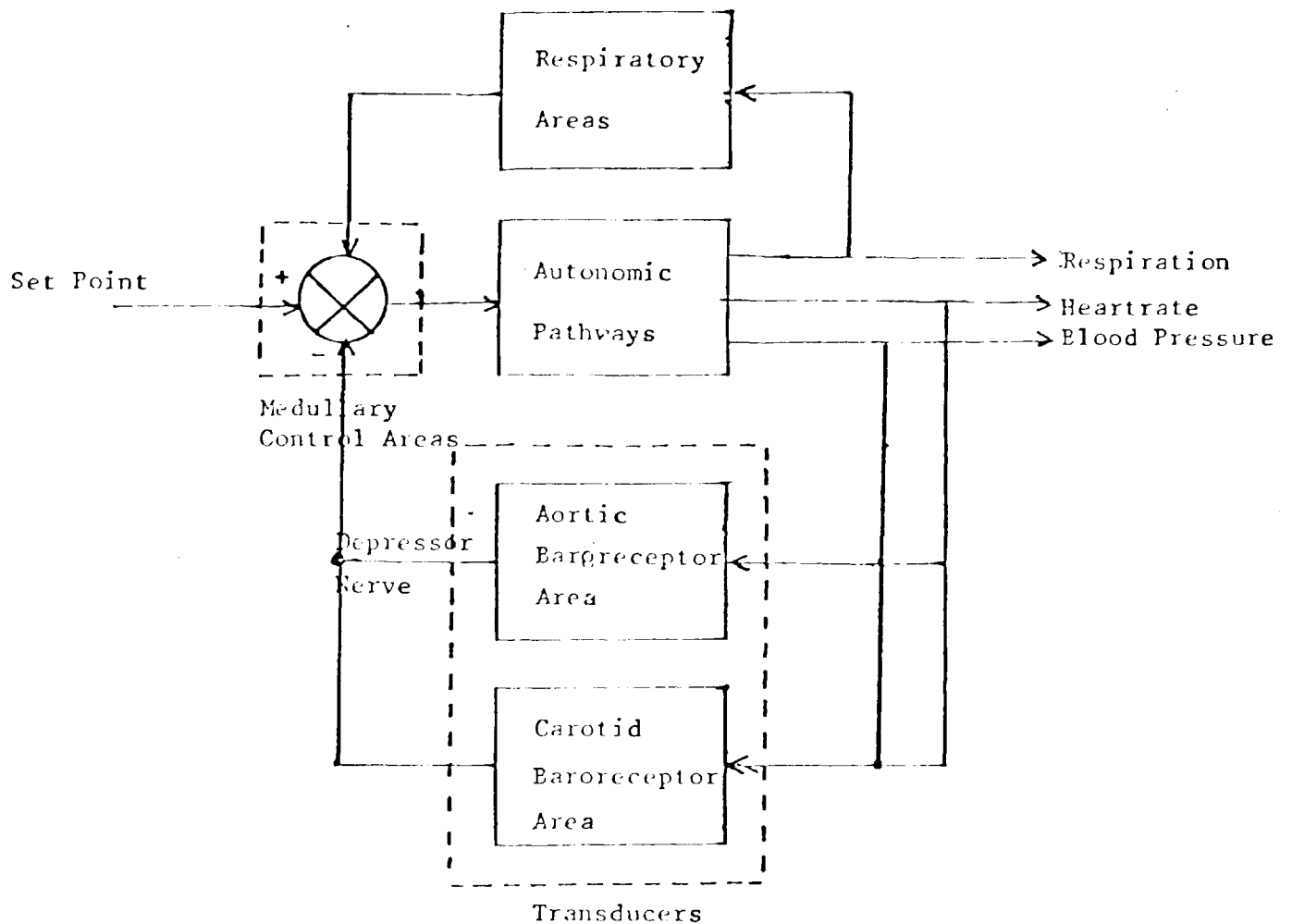


Figure 26. Block diagram representation of the baroreceptor control loop.

In recent years, many researchers have realised the usefulness of studying biological systems from the standpoint of control engineering. The outstanding advantage of the approach is the ability to quantify the system under conditions in which traditional methods would fail. Such quantification, even if crude or incomplete, acts as a base model for further systems testing. A

dynamic process is therefore established which hopefully results in a model which satisfies the real world. A significant constraint upon the study of many biological processes has traditionally been the fact that most processes do not act alone, but are part of the total homeostatic mechanism. To study an individual process therefore meant occluding much of the total information flow. This approach is not always satisfactory since it is limited by the information lost. Control engineering methodology allows the study of individual processes in situ, thereby increasing the information content of the data while retaining the facility to distinguish between the processes involved.

As a precursor to whole system identification, many of the components of the baroreceptor control loop have been studied individually. For example Kardon, Peterson and Bishop (1974) have investigated changes in heart rate as a result of cardiac depressor stimulation. Penaz (1962) has tested the cardiac response to vagal stimulation. Warner and Cox (1961) and numerous other workers took the process a stage further and built mathematical models of autonomic interaction in controlling changes in heart rate. The overall conclusion of this work is that although the components do not function linearly, they can be treated as linear over small ranges.

Most of the above work was based on stimulus-response situations in which classical stimulus functions such as pulse trains, sinusoids or step inputs were used. Such signals are not the optimal choice for biological systems testing, as will be shown in section 3.5.

Some workers have gone further in the application of control

theory techniques to the elucidation of the baroreceptor loop. For example, Levison, Octo Barnett and Jackson (1965) used sinusoidal variation of carotid sinus pressure to create Bode diagrams of the system. Their approach was not a non-linear analysis, as it made use of methods of linear system analysis by treating the baroreceptor response as linear at the frequency of the sinusoidal stimulus. A consequence of their choice of test signal was that they risked a loss of information through narrow rather than wideband system testing.

Grodins (1963) also made use of sinusoidal forcing of carotid sinus pressure in estimating the frequency response of the baroreceptor loop. He formed Bode and Nyquist diagrams for the vagotomised dog, and proposed a mathematical model to describe the situation in which bradycardia is not the dominant response.

Hatakeyama (1967) conducted system analysis of the blood pressure control loop. He carried out step response testing of both the carotid sinus and aortic baroreceptor loops. From the transient response obtained he found that both loops corresponded to first order proportional feedback systems, the carotid sinus having a time constant of 5 seconds and a latency of 2 seconds, and the aortic depressor a somewhat longer time constant of 4 to 15 seconds. In both cases, the system exhibited non-linearity in that the value of the time constant increased with frequency of stimulus. The Transfer Function for both loops was of the form

$$G = \frac{Ke^{-sL}}{(1 + Ts)}$$

being a first-order lag element plus time delay. In forced response analysis he found that the system was extremely stable due to its

wide gain and phase margins.

The results obtained by both workers are examined more fully in Chapter 5 in connection with the results obtained from the present study.

The evidence discussed in this and in the previous chapters shows that the baroreceptor control system exhibits both servo and regulatory functions. The system is dedicated to following a set point which is defined by higher centres. The system also has the capacity to compensate for external disturbances which are applied to the system. In biological terms, such behaviour is encompassed by the concept of homeostasis, that is, that all biological processes are dedicated to maintaining an unchanging internal environment.

Korner (1971) developed this idea by describing neural cardiovascular control as a system dedicated to controlling a single output variable, arterial blood pressure. This view is analogous to that described by Figure 26. If arterial blood pressure diverges from a set point, autonomic pathways are activated to restore homeostasis.

Homeostasis is effected at a central level via the cardiac control centres. They compensate for disturbance through the concerted mobilization of the physiological structures discussed so far. The baroreceptor reflex loop is part of this effector mechanism and as such its gain and reference point dynamically reflect the status of the rest of the total control mechanism. The problem in hand is whether such a volatile control mechanism can be characterised *in situ*.

### 3.3 Linear methods for system identification.

In the elucidation of control systems it is common practice to analyse the system in its open loop form. Hence, in trying to understand the nature of a biological control system, it is surgically and conceptually simpler to open the control loop and thereby eliminate, or alternatively obtain more effective control over, some of the control variables. Open loop analysis accounts for the majority of the work discussed. The assumption is made that opening the loop does not change the nature of the system. While this may be true for man made control systems, the elements of biological systems are often highly interdependent, so that the behaviour of the open loop may not be a true reflection of that of the intact system (Hatakeyama, 1967).

As stated previously, the objective of the work was to explore the dynamics of the control loop over its normal range of operation. There are several ways of obtaining a summary of the information which characterises a closed loop system. One of these ways is the construction of the impulse response .

A black box system  $H$  is subjected to an input comprising an impulse of infinite height and negligible width. Such an impulse, a Dirac pulse, represents the in-phase summation of equal parts of all frequencies to infinity. The output from the system therefore directly reflects the frequencies to which the system is responsive, and any phase changes induced by the system. The output function is called the impulse response of that system, and is used to identify the components of the black box (Cooper and McGillem, 1967).

The impulse response of a system may be calculated from any

input function, provided that the system is linear. The input function can be represented as a series of regularly spaced impulses (having observed Nyquist's criterion), in the way that all real signals are presented to a digital computer. The superposition theorem then states that the summation of the response to each individual impulse gives the total impulse response of the system.

It is often more useful to hold the system response in terms of the Fourier Transform (F.T.) of the impulse response, the frequency response. It is appropriate to digress somewhat at this point, in order to define the terminology used to describe Fourier components in the succeeding pages.

Any periodic signal may be represented in terms of its Fourier series i.e.

$$x(t) = A_0 + \sum_{n=1}^{\infty} A_n \cos(n\omega t) + \sum_{n=1}^{\infty} B_n \sin(n\omega t)$$

where  $\omega = 2\pi/T$  and  $T$  is the period of the signal. The sum of sine and cosine waveforms of various amplitudes form an orthogonal series. This equation may be rewritten as

$$x(t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} F(\omega) \exp(j\omega t) d\omega$$

(Inverse Fourier Transform of  $F(\omega)$ )

since

$$\cos x = (e^{jx} + e^{-jx})/2$$

$$\text{and } \sin x = -j(e^{jx} - e^{-jx})/2$$

Similarly,

$$F(\omega) = \int_{-\infty}^{\infty} x(t) \exp(-j\omega t) dt.$$

(Fourier Transform of  $x(t)$ )

The two functions  $x(t)$  and  $F(\omega)$  are called the Fourier Transform pair.

Rearranging this equation, we get

$$F(\omega) = \frac{(A(\omega) - B(\omega))}{2} \quad \text{when } n > 0$$

and  $F(\omega) = \frac{(A(\omega) + B(\omega))}{2} \quad \text{when } n < 0$

The spectrum therefore has both real and imaginary parts. It covers negative as well as positive frequencies, as shown in Figure 27 (b), which considers the spectral properties of a Cosine wave.

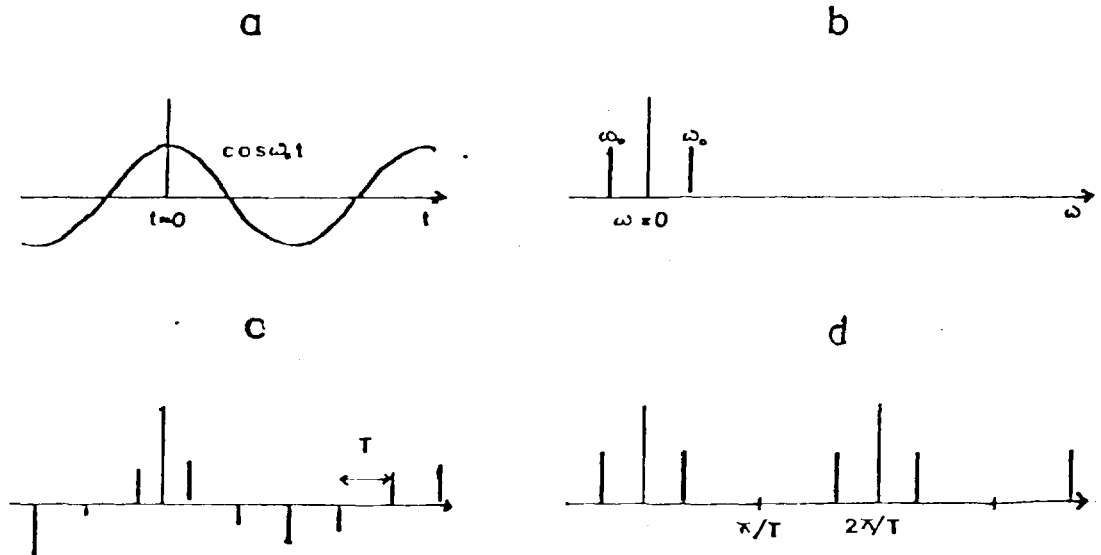


Figure 27. Diagram illustrating continuous (a) and sampled (c) representations of a Cosine waveform. The spectrum of the sampled waveform repeats indefinitely at intervals in  $\omega$  of  $2\pi/T$ .

When, as is normally the case, a digital computer is used in calculating the Fourier coefficients, the signal  $x(t)$  is not continuous, but sampled at regular time intervals. Digitisation is equivalent to multiplying each sample value by a Dirac pulse (Figure 27 (c)). The resulting spectrum therefore reflects not only the original signal but also the periodicity of the pulse train imposed upon it. This causes the original spectrum to be repeated at intervals equal to the sampling frequency (Figure 27 (d)).

Clearly, from Figure 27 (d) it is unnecessary to calculate

harmonics outside the range  $w = 0$  to  $w = \Pi/T$ , since all the signal information is contained within this range. The frequency  $\Pi/T$  is termed the Nyquist frequency, as mentioned in section 2.4.1. The F.F.T. algorithm used in this study returned harmonics only over this range, termed the one-sided spectrum.

The Fourier series then becomes

$$x(qh) = A_0 + \sum_{n=1}^{N/2} A_n \cos(2\pi nq/N) + \sum_{n=1}^{(N/2)-1} B_n \sin(2\pi nq/N)$$

where  $h$  is the sampling interval,  $n$  is harmonic number and  $q$  is the sample number. The output of the F.F.T. algorithm is the real and imaginary parts of  $F(w)$  (Stuart, 1961), such that

$$a(w) = A(w) = \frac{2}{N} \sum_{q=1}^N x(qh) \cos(2\pi qn/N)$$

$$n = 1, 2, \dots, N/2-1$$

$$b(w) = -B(w) = \frac{-2}{N} \sum_{q=1}^N x(qh) \sin(2\pi qn/N)$$

$$n = 1, 2, \dots, N/2-1$$

Each Fourier component returned by the F.F.T. may therefore be expressed as

$$X_n = a_n + jb_n$$

Figure 28 shows the relationship between the impulse response and its F.F.T., the frequency response. Equation 1 in the diagram is the convolution integral of  $H(t)$  and  $X(t)$ . Although it is possible to solve the equation for  $H(t)$ , the numerical process is tedious. It is computationally and conceptually easier to take the discrete F.T. of  $X(t)$  and  $Y(t)$ , and solve equation 2 instead. The equation is simplified by considering the real and imaginary parts of the spectra involved, so that if

$$X(f) = a(f) + jb(f)$$

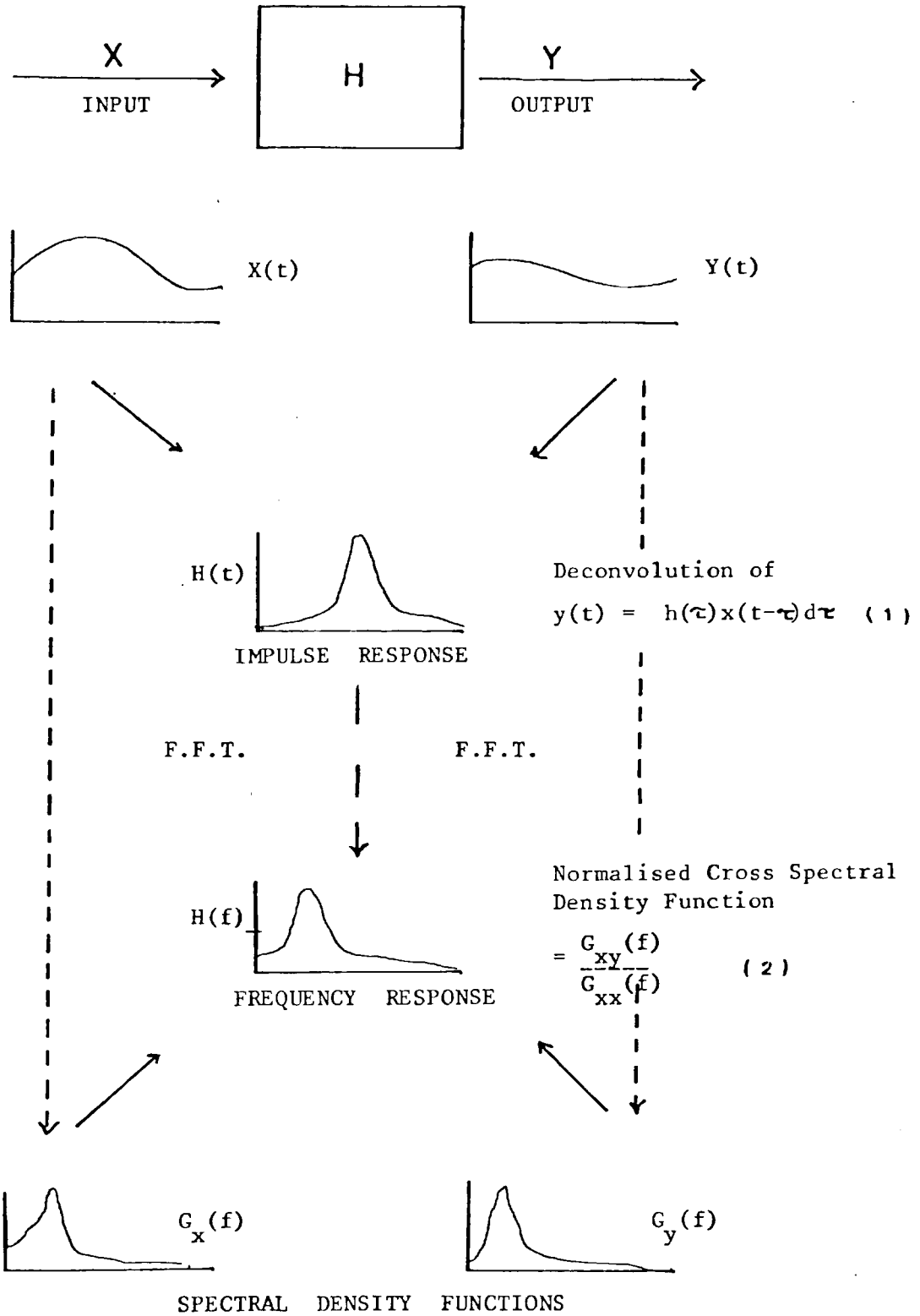


Figure 28. Diagram illustrating the relationship between the frequency response and the impulse response of a system  $H$ .

$$\text{and } Y(f) = c(f) + jd(f)$$

$$H(f) = \frac{Y(f)}{X(f)} = \frac{c(f) + jd(f)}{a(f) + jb(f)} = \frac{(c(f) + jd(f))(a(f) - jb(f))}{(a(f) + jb(f))(a(f) - jb(f))}$$

multiplying top and bottom by the

complex conjugate of  $X(f)$ ,

$$= \frac{(a(f)c(f) + b(f)d(f)) + j(a(f)d(f) - b(f)c(f))}{a(f)^2 + b(f)^2}$$

$$\text{which is } = \frac{\text{Cross spectrum of } X(f) \text{ and } Y(f)}{\text{Power spectrum of } X(f)}$$

$$= \frac{G_{xy}(f)}{G_{xx}(f)}$$

where  $G(f)$  is the one-sided power spectral density function.

The frequency response or impulse response may be calculated by studying the system's intrinsic input and output signals. In many cases, however, the input signal cannot be recorded with sufficient accuracy to make this method viable. If a stronger signal, uncorrelated with the input signal, is used to drive the system while it is still operating, then the response can be calculated as before. Supposing that the input to the system consisted of a natural ( $r(t)$ ) and a driving component  $u(t)$ , that is

$$X(t) = r(t) + u(t)$$

$$\text{and } Y(t) = Y_r(t) + Y_u(t) \text{ is the system output .}$$

Similarly the cross-spectrum relative to the test signal is :

$$\begin{aligned} G_{uy}(f) &= G_{uyr}(f) + G_{uyu}(f) \\ &= G_{uyu}(f) \end{aligned}$$

since  $r(t)$  and  $u(t)$  are uncorrelated. This allows the measurement

of the system response without interrupting its normal operation, provided that the autocorrelation function (being the time domain equivalent of the power spectrum) of the test signal and the total output in response to this signal, are known. That is,

$$H(f) = G_{uy}(f) / G_{uu}(f)$$

for  $G_{uu}(f)$  not equal to zero.

(Davies, 1972).

The steps involved in calculating these functions are discussed in the rest of this chapter. In the "real world" this involves the application of a test signal appropriate to the system and collection of the response. This method is suitable for testing the dynamic response of systems which are thought to be at least predictable, if not linear. Since the method is based on correlation of input and output signals, it is not suitable for analysis of data containing significant amounts of non-additive noise. Again, since the method involves averaging many records to reduce variability (see section 5.2), the system must obviously be time invariant.

There is no guarantee that any biological control system conforms to these requirements. However, research carried out by other workers in this area (see Chapter 1) and the pilot experiments of Chapter 2 lead to the belief that the system is sufficiently linear if treated over small ranges to be conducive to this form of testing. In addition, the technique of frequency response analysis is so powerful but simple compared with other system identification methods that it is worth exploring its usefulness as a tool for understanding biological systems.

### 3.4 Choice of the test signal.

As discussed in section 3.2, the baroreceptor control loop is being treated as a single input, multiple output system which is linear when studied in small steps over its total dynamic range. Any applied perturbation must be prevented from over-driving the system to avoid introducing non-linear effects into the output.

The choice of input signal is therefore of fundamental importance. For the reasons stated in the previous section, the ideal test function is a Dirac pulse. In practice, any impulse of sufficient amplitude to approximate a Dirac pulse would certainly drive the system outside its normal range.

Similarly, white noise, having a flat frequency spectrum and random phase, is a useful test signal in theory only. Like Dirac functions, true white noise is difficult to generate and would have to be band-limited for any practical application.

In testing biological systems where the signal to noise ratio is likely to be poor, it is advantageous to choose a waveform which can be reproduced routinely so that averaging techniques may be used to clarify results. For this reason, sine function testing is often employed. A sine wave of each frequency of interest is applied to the system in turn. The disadvantage here is one of time. Most biological systems change their response to a given stimulus over a period of time, due to adaptation, fatigue or the influence of other systems. When a system as complex as cardiovascular control is being studied, the chances of external events influencing the results become very large. In addition, application of sine waves

at specific frequencies will yield fragmented results compared with wideband stimuli, so that there is a danger that areas of the frequency response may be inadequately covered.

Furthermore, Hyndman, Kitney and Sayers (1971) have shown that stimulating the cardiovascular system using simple periodic signals can have unexpected results. Many biological systems exhibit spontaneous oscillation as part of their homeostatic mechanism. Blood pressure is thought to be such a system, having a frequency of oscillation of 0.1 Hz.. Kitney (1975) showed that the system exhibits the phenomenon of frequency selective entrainment, a characteristic of nonlinear oscillatory systems. If a periodic signal is applied to the system, the intrinsic oscillation may lock on to the stimulus if the frequency is not far from that of the self component. Thus, far from exploring the dynamics of blood pressure control, a sine stimulus may serve only to draw the system away from its normal state.

Referring back to the previous section the test signal must also be uncorrelated with any waveform which normally enters the system. The optimum choice of test signal was therefore one which was

- a) wideband but tailored to the expected frequency characteristic of the system
- b) periodic for averaging purposes, but non-oscillatory
- c) spectrally flat, or at least predictable over the frequency range in question
- d) uncorrelated with the natural system inputs.

### 3.5 The Pseudo Random Binary Sequence

The use of random signals in system identification is derived from the theoretical suitability of white noise as a disturbance function. By definition, white noise contains constant power per unit bandwidth over all frequencies, that is, its power spectral density plot is flat.

Referring to Figure 28, the equation

$$H(f) = G_{xy}(f) / G_{xx}(f)$$

then reduces to

$$H(f) = G_{xy}(f) / A \quad \text{where } A \text{ is a constant.}$$

That is, for white noise, the impulse response is directly proportional to the cross-correlation function (being the time domain equivalent of the cross-spectrum) of input and output signals.

Since the signal power is spread over such a large frequency range, application of such a disturbance will not affect the normal operation of the system. A considerable advantage may therefore be gained over the more usual methods of sine and step response testing, since the system can be investigated while it is still operating normally.

Another advantage is that since the I. R. is derived through cross-correlation, any noise present in the measurements will not degrade the estimate, provided that the noise is uncorrelated with the input signal.

A major disadvantage of the white noise method is that although theoretically the signal comprises all frequencies, to achieve a flat spectrum in practice requires the signal to be applied over infinite time. In practice, any random signal may be treated as white noise if its bandwidth is considerably greater than that of the system being tested. The autocorrelation function of white noise is a Dirac pulse, that is, the signal does not repeat itself at any point between plus and minus infinity. A way of circumventing the long stimulus time problem would be to produce a signal which had such an impulse autocorrelation function, but which repeated itself every  $T$  seconds. Provided that  $T$  is longer than the impulse response in question, the signal may still be treated as white noise and the condition

$$H(f) = G_{xy}(f)$$

still holds (Davies, 1972). A practical method of constraining white noise in this way is the Pseudo Random Binary Sequence. Figure 29 illustrates the main characteristics of such a signal, compared with white noise. The signal is close enough to the ideal to be a viable alternative. There are several methods of constructing binary sequences which may be termed random.

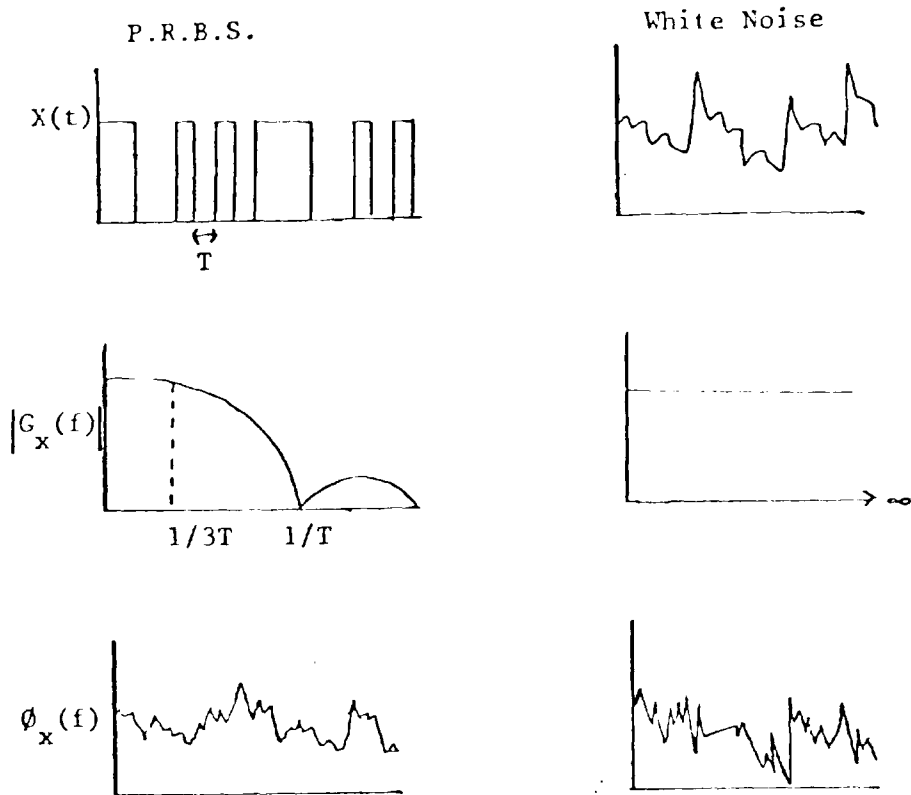


Figure 29. Time and frequency characteristics of the P.R.B.S. compared with those of white noise.

The P.R.B.S. chosen for this study was generated by a combination of bits in a shift register being exclusively OR'ed and the result fed back into the register. The length of the shift register determines the number of states the P.R.B.S. takes before it repeats, that is, an  $N$  bit register produces a sequence  $2^N$  states long. The amplitude spectrum is of the form

$$(\sin x / x)^2 \quad \text{where } x = \omega t / 2$$

and  $t$  is the clock width

The first zero occurs at  $x = \pi$ , that is, at  $1 / t$  Hz.. The 3dB point occurs where

$$\begin{aligned} (\sin x / x)^2 &= 0.707, \\ \text{i.e. } x &= .98 \\ \text{and } F &= 1 / 3 t \end{aligned}$$

In practice the P.R.B.S. can be considered truly random over frequencies up to the 3dB point, the power spectrum being almost flat up to this point. It is of fundamental importance therefore that the system to be tested does not contain significant power at frequencies in excess of the 3dB point of the P.R.B.S. used to drive it. The effective bandwidth of a P.R.B.S. is therefore given in terms of the reciprocal of its repetition period at the lower end, and its 3dB point at the upper.

It is thus possible to tailor a P.R.B.S. specific to the requirements of the system under test. P.R.B.S. testing has been used successfully by Ponte and Purves (1974) in estimating the frequency response of the baroreceptors themselves.

It was necessary to have some estimate of the responsive range of the baroreceptor loop before testing could commence. Hyndman, Kitney and Sayers (1971) found that in humans the maximum frequency of oscillation of the loop was 2-3 Hz.. In rabbits, where the pathways involved are shorter, this frequency was likely to be about 4 Hz.. A preliminary series of tests showed that for sufficient spectral resolution as well as inclusion of all important components, a P.R.B.S. range of 0.01 to 3.3 Hz was ideal. A

P.R.B.S. which had a length of 100 sec. before it repeated, and and changed state every 0.1 sec. was therefore required. The next longest sequence which could be constructed was (see Fig. 30) 1024 states, meaning that the 3dB point was at

$$10.24 / 3 = 3.41 \text{ Hz.}$$

| no. of stages<br>in register, n | no. of clocks<br>per sequence<br>$N = 2^n - 1$ | stages joined<br>for feedback |
|---------------------------------|------------------------------------------------|-------------------------------|
| 2                               | 3                                              | 1 & 2                         |
| 3                               | 7                                              | 2 & 3                         |
| 4                               | 15                                             | 3 & 4                         |
| 5                               | 31                                             | 3 & 5                         |
| 6                               | 63                                             | 5 & 6                         |
| 7                               | 127                                            | 4 & 7                         |
| 8                               | 255                                            | 2, 3, 5 & 8                   |
| 9                               | 511                                            | 5 & 9                         |
| 10                              | 1023                                           | 7 & 10                        |
| 11                              | 2047                                           | 9 & 11                        |

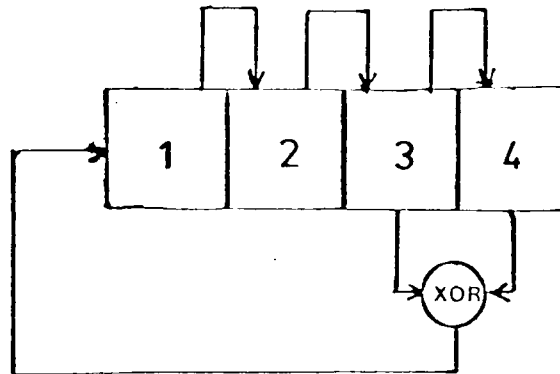


Figure 30. Relationship between length of shift register and number of P.R.B.S. states (Paterson, 1961).

There are many advantages to the use of pseudo random signal testing for the baroreceptor loop. Firstly, the method was developed for the in-line testing of process control systems, and therefore made in situ testing possible without having to restrict the influence of other related systems. This made a closer understanding of the way in which the system operates normally a viable target. Secondly, the fact that the test signal could be applied concurrent with any existing neural activity meant that the system could be studied without resorting to opening the feedback loop.

### 3.6 Summary

The baroreceptor control loop is an example of a servo and regulatory control system, and must also be considered as part of the total homeostatic mechanism. The assumption that opening biological loops does not change the nature of the system is challenged. One purpose of this work is therefore to find out whether it is possible to characterise the system with all pathways intact.

Frequency and Impulse response estimation was chosen as the method of characterisation of the steady state response. The method may only be used for linear systems, or as in this case, systems which are linear over defined ranges. The method employs the correlation of system output to a known input.

A PRBS was chosen as the system input. The reasons for this choice were the flat wideband spectrum of the PRBS, and its ease of generation and replication. The ideal bandwidth for the PRBS in this case was calculated to be 0.01 to 3.4 Hz, which yielded a sequence length of 1024 clock states.

## Chapter 4

## Pseudo random stimulation of the baroreceptor loop

## 4.1 Introduction

The PRBS has been identified as the optimum stimulus for testing the frequency response of the baroreceptor loop, since:

- a) a PRBS can be constructed to stimulate the system within its linear range
- b) its wideband properties increase the information content of the collected data and thus decrease stimulus time
- c) it is relatively straightforward to convert the PRBS to a form suitable for neural stimulation, as discussed below.

This chapter covers the use of a PRBS in determining the frequency response of the system, under three main headings:

- 1) A detailed consideration of the way in which a PRBS can be manipulated to render it a suitable neural stimulus. This requires an understanding of the way in which nerves conduct information (sections 4.2 and 4.3).
- 2) The experimental protocol for applying the PRBS to the depressor nerve (section 4.4).
- 3) A step by step account of the treatment of the experimental data in producing estimates of their spectral components (section 4.5).

#### 4.2 The information carrying capability of a nerve.

An important function of the nervous system is to relay information from one point in the body to another. A unit of information is transferred along a nerve as a wave of electrical current, a process which, once started, is actively maintained by means of ionic exchange across the nerve membrane (see Fig. 31 ). Any particular point on a nerve resides in one of two states; polarized (resting) or depolarized (transmitting). Since depolarization of a nerve membrane is an "all or nothing " event, every unit of information which traverses a nerve is the same as every other. These properties are common to all nerves; the properties specific to the nerves of the baroreceptor control loop (fibre type, firing rate, etc) were discussed in Chapter 1.

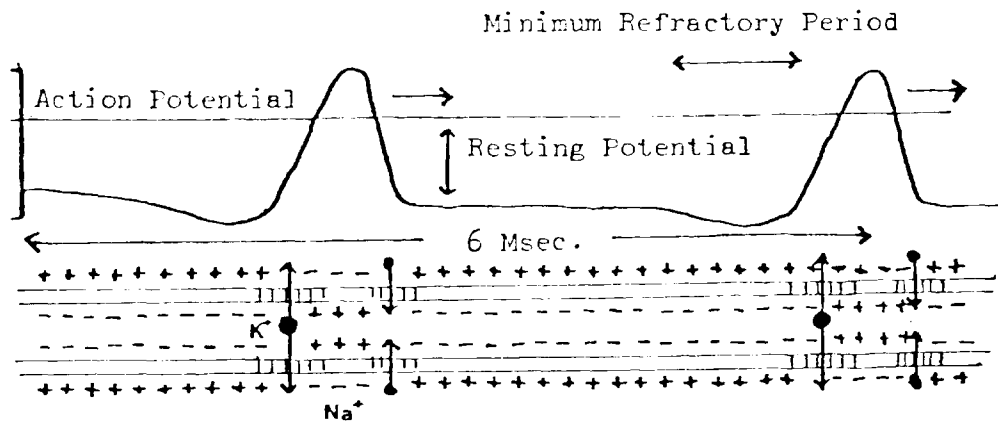


Figure 31. Depolarization of a nerve membrane. From Stevens, 1979.

Receptors are the structures which convert information contained in continuous signals such as pressure or temperature, into a form which may be neurally transmitted. The process involved approximates to Pulse Frequency Modulation (PFM), a method of digital representation of continuous signals, which is explained fully in the next section. The receptor acts as the modulator, converting changes in amplitude of the input signal to changes in the spacing of a basal pulse sequence. The next section explains this process in detail. The approximation is incomplete since receptors themselves are nonlinear (Ponte and Purves, 1974). The nerve is also a nonlinear structure, since it is limited by its threshold of response and by its refractory period. The latter is the length of time which must elapse before a membrane which has just discharged is capable of depolarizing once more.

Penaz (1962) successfully used PFM of sine waves to investigate the Vagus. Stein (1967) and Lee (1969) have also utilised PFM in attempting to model the information carrying capability of the nervous system. This is particularly significant, since it showed that processes akin to PFM actually constitute the schema of neural information transmission. In his work Penaz presented the view that within certain pre-defined limits, the nervous system converted the information content of continuous physiological variables into PFM form. This view is supported by this work. On this basis, the experimental excitation of the nervous system was achieved by converting the test signal to its PFM equivalent.

### 4.3 Integral Pulse Frequency Modulation.

All methods of Pulse Frequency Modulation act by outputting pulses at intervals depending on the integral of the continuous input signal. Jones (1961) showed that the most appropriate schema was Integral Pulse Frequency Modulation, partly because other methods of modulation required components which were biologically unlikely. As its name implies, Integral Pulse Frequency Modulation does not make use of regular sampling of the input signal to produce the output pulse train, as in pulse position modulation, but of an integrator charging to threshold which then discharges and outputs a pulse. In physiological terms, the integrator resembles the "relaxation oscillator" elements attributed to most sensory organs.

#### 4.3.1 Generation of an IPFM signal

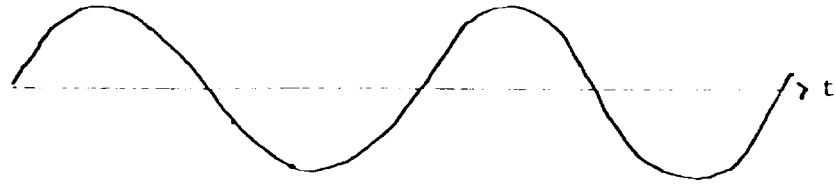
The system (according to Bayly, 1968) is illustrated in Figure 32. With no input, the output of the model comprises a pulse train of frequency  $f$  which results from the constant level input  $M(t)$ . This is modulated by the incoming signal  $N(t)$  such that a pulse is generated when

$$(M(t) + N(t)) dt = r$$

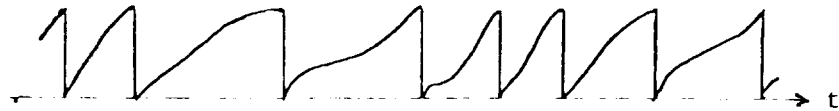
where  $r$  is the threshold of the integrator. It must be noted that  $r$  is not implicitly a constant, but merely assumes constant value while the spacing between pulses varies with changing  $N(t)$ , i.e. if the spacing was held constant,  $r$  would be forced to vary with  $N(t)$  and a Pulse Amplitude Modulated signal would result.

If a sinusoidal modulating signal is assumed, as shown by Bayly (1968) the output pulse train can be described by the Fourier series

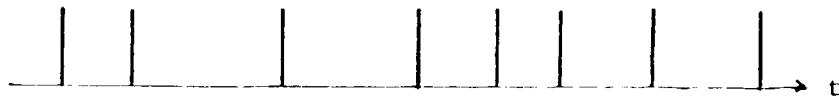
a) Input  $N(t) = N \cos (2 f_N t + \theta)$



b) Charging Function  $c(t, \infty)$



c) Pulse Train  $p(t, \infty)$



d) Integral Pulse Frequency Modulator

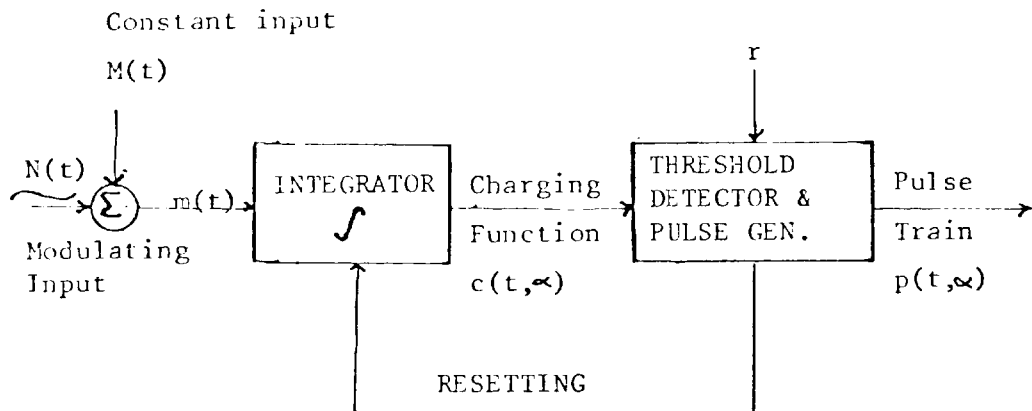


Figure 32. Diagram illustrating pulse frequency modulation of a cosine wave. ( from Bayly, 1968).

$$\begin{aligned}
p(t, \alpha) = & Aaf_M + \frac{AaN(t)}{r} \frac{\sin(naf_N)}{naf_N} \cos(2\pi f_N t - naf_N + \theta) \\
& + 2Aaf_M \sum_{k=1}^{\infty} \sum_{n=0}^{\infty} J_n\left(\frac{kN(t)}{rf_N}\right) \frac{\sin(na(kf_M + nf_N))}{nakf_M} \\
& \times \cos(2\pi(kf_M + nf_N)t - n(kf_M + nf_N)a \\
& + 2\pi kf_M \alpha + n\theta - \frac{kN(t)}{rf_N} \sin(\theta - 2\pi f_N \alpha))
\end{aligned}$$

which demonstrates several useful facts. The equation implies that when  $N(t) = 0$  the unmodulated pulse repetition rate is  $f_M = M/r$ .  $f_N$  is the frequency of the modulating signal,  $A$  and  $a$  are pulse amplitude and width respectively, and  $J$  is a Bessel function of the first kind and order  $n$ . The value  $\alpha$  corresponds to the time difference between  $t$  and the time of occurrence of the previous pulse. The output functions are expressed in terms of  $t$  and  $\alpha$  to indicate that the modulating and modulated inputs cannot be completely defined in terms of the output pulse train unless the position of the last pulse the starting time is known. Similarly,  $\theta$  is the angle of the sine wave at time  $t$ .

The first term of the equation is the d.c. component. The second term relates to the frequency of the modulating signal. The third and successive terms contain double integration of factors involving  $f_M$  and  $f_N$ , with the result that the carrier signal gives rise not to a simple double sideband at  $f_M - f_N$  and  $f_M + f_N$  but to sidebands spreading out to  $\pm\infty$  at  $f_N + f_M$ ,  $f_N + 2f_M$ , etc. This means that recovery of the signal  $N(t)$  by low pass filtering may be distorted to a greater or lesser degree due to the spread of the

sidebands. Distortion is kept to a minimum if the variation in position of the pulse due to modulation is small compared with the distance between pulses. The frequency spectrum of  $p(t, \infty)$  is shown in figure 33.

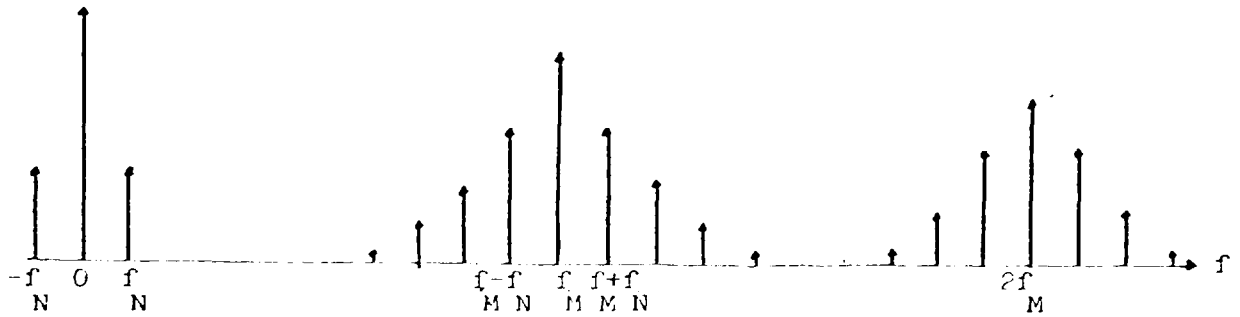


Figure 33. Spectrum of frequency modulated pulse train  $p(t, \infty)$  (from Bayly, 1968).

The IPFM system is limited, therefore, by two factors. The first is that the modulating signal must be considerably lower in frequency than the carrier signal. When  $f_M$  and  $f_N$  are of comparable size, overlapping occurs which makes it impossible to separate the signals completely.

The second factor is the relative amplitudes of the two signals. Summing the carrier signal to the modulating input,  $N(t)$ , is equivalent to applying a d.c. shift to it. The type of IPFM discussed here is termed single sided since the pulse train produced has pulses only in the positive direction. The system cannot cope with a negative charging function, so care must be taken that the amplitude of  $N(t)$  is never so large compared with  $M(t)$  that the summation yields an overall negative d.c. shift.

The optimum values for  $M(t)$  and  $r$  for a particular value of  $N(t)$  can be calculated as follows. According to Lee (1969), the criterion for synthesis of an IPFM system when  $N(t)$  contains more than one frequency is

$$\frac{w_0 X_0}{w_{\max}} > L + k \quad (1)$$

where

$w_{\max}$  = maximum significant frequency of  $N(t)$

$w_0 = 2\pi/r$

$X$  = amplitude of  $M(t)$

$k = w / w_{\max}$  where

$w_c$  = cutoff frequency of demodulating lpf.

$L$  is a positive number related to the noise component due to sideband spread such that

$$L \approx \frac{w_0 D + 2}{w_{\max}}$$

where  $D$  is the maximum amplitude of  $N(t)$ .

Thus  $w_0$  and  $X_0$  should be selected such that the number of pulses per period of the maximum significant frequency contained in the message signal  $N(t)$  is greater than  $L + k$ . When setting up an IPFM system the maximum possible variation in amplitude and frequency of  $N(t)$  must therefore be known before deciding the optimum values of  $r$  and the amplitude of  $M(t)$ .

#### 4.3.2 Recovery of the modulating signal

The exact recovery of  $N(t)$  from  $p(t, \alpha)$  would involve the use of an ideal low pass filter, i.e. one having a sharp cutoff frequency (see Figure 34). However, implementing such a filter in the

frequency domain would result in "ringing" in the corresponding time domain signal. This effect is reduced if the rectangular filter is multiplied by a half cosine taper, so that the cutoff is no longer quite as sharp.

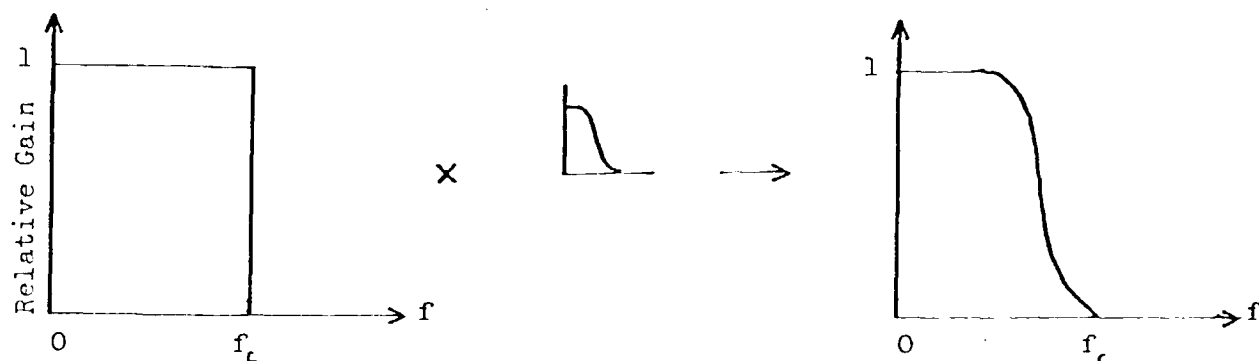


Figure 34. Ideal frequency domain filter and result of multiplication with half cosine taper.

Equivalently, the filtering can be undertaken in the time domain by convoluting the signal with a  $\sin x/x$  function where  $x=2\pi ft$ .

(see Figure 35). The zero crossovers occur at intervals of  $1/f$ , where  $f$  is the cutoff frequency of the filter. Errors due to aliasing are avoided if  $T$ , the sample period of the demodulated signal, is less than or equal to  $1/2f$ , by Nyquist's criterion. In the ideal case, the sidelobes of the  $\sin x/x$  function stretch out to  $\pm\infty$ . In practical terms, ten sidelobes either side is sufficient, in which case the frequency spectrum of the function very similar to the frequency domain filter of Fig. 34.

Since convolution is computationally tedious, and is moreover subject to "start up" and "shut down" errors which may be serious if the data length is short compared with the filter, it is usually

more satisfactory to use the frequency domain filter of Figure 31. Time domain digital filtering is usually only attempted if the signal to be filtered cannot be FFT'd, for example if it is irregularly sampled.

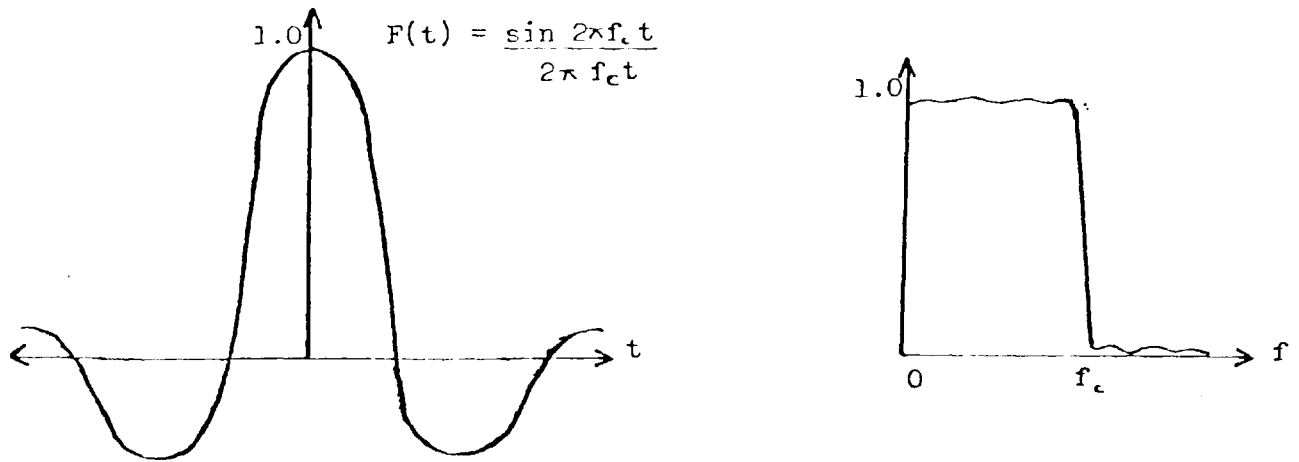


Figure 35.  $\sin x/x$  time domain filter and corresponding frequency spectrum.

#### 4.4 Pulse Frequency Modulation of the P.R.B.S.

PFM requires integration of the input signal and it is therefore unlikely that an accurate result could be obtained easily by programming a digital computer for PFM of anything more complex than a sine wave. When considering the form of the PRBS, however, it was clear that modulation of a two-state signal was a much simpler proposition. If an IPFM system is considered which has a constant input of 80 units per second, and the threshold  $r$  has a value of 1, an output pulse train of 80Hz. will be produced when no modulating input is present.

The inclusion of a PRBS, having an amplitude of either +10 or -10, as the modulating input, causes the integrator to reach threshold 1.125 times faster during the positive phase of the PRBS, and 0.875 times faster during the negative phase. The effect is that the output pulse train flip-flops between 90 and 70Hz. When the PRBS changes level, pulses are produced which lie between the two frequency limits, as shown in figure 36. Since the PRBS is always predictable, the PFM'd signal can be created easily using real-time programming.

Appendix A2 shows the program used to produce the PRBS on the IBM 1800 computer. The PRBS was transferred onto FM magnetic tape via the analog outputs of the IBM 1800 .

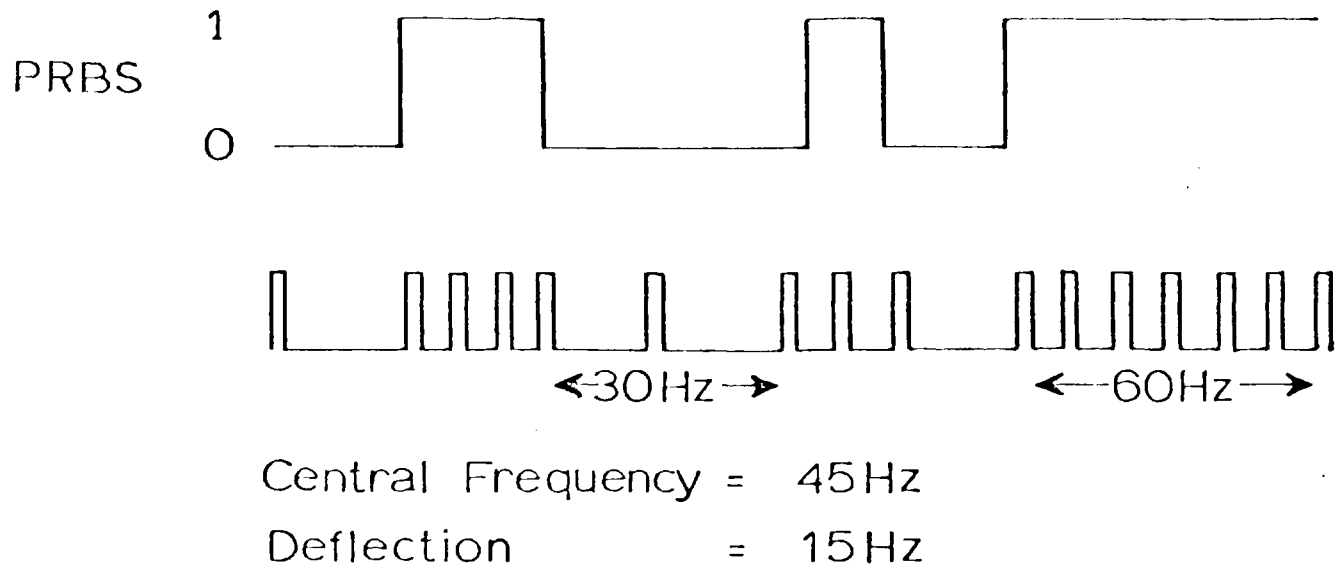


Figure 36. Construction of a Pulse Frequency Modulated P.R.B.S.

Careful choice of values for the constant and modulating input amplitudes allowed the investigation of a large section of the dynamic range of the baroreceptor loop. The frequency limits of the PRBS were set at -10 to +10Hz. These values were chosen as a result of the preliminary study (see section 1.3.3), and also from the work of Kardon, Peterson and Bishop (1973) who found that the responsive frequency range to stimulation of the depressor nerve was 5 to 150 Hz, with an ability to detect changes of about 10 Hz. at the optimum stimulus frequency of 50 Hz. Douglas and Schaumann (1955) obtained similar figures when observing cat's buffer nerves, and also showed that a bandwidth of 20Hz. was unlikely to elicit nonlinear responses from the system.

The constant input values for  $M(t)$ , upon which the PRBS was superimposed, were chosen to be 30, 50, 70 and 90Hz. These values were verified using the methods outlined in previous section. The most appropriate way of testing whether values for the constant and modulating inputs are compatible is to calculate  $w_c$ , the cutoff

frequency of the filter which could separate the PFM'd signals. Clearly, as long as  $w_c > w_{max}$  separation is possible. Table 2 shows the relationship between  $M(t)$  and  $w_c$  for a PRBS of actual bandwidth 0.01 - 3.41Hz., and a PFM bandwidth of -10 to +10Hz. The limiting case for PFM occurs when either

$$\begin{aligned} & \text{a) } w_{max} > w_c, \quad \text{i.e. } M(t) < 11.63 \\ \text{or } & \text{b) } M(t) - N(t) < 0, \quad \text{i.e. } M(t) < 10 \end{aligned}$$

Table 2. Relationship between constant input and  $w_c$  for a given modulating input.

| $M(t)$ | $w_c$    |
|--------|----------|
| 90     | 2859.8Hz |
| 70     | 370.265  |
| 50     | 244.572  |
| 30     | 118.879  |
| 10     | -6.813   |

As expected, low pass filtering of a P.R.B.S. modulated in this way restored the original P.R.B.S., as shown in Figure 37. The noise on the spectral density plots of the Pulse Frequency Modulated sequences was due to overlap between the primary frequency range and the secondary sidebands. The plots of the autocorrelation function show that this was of little consequence, and that the Pulse Frequency Modulated PRBS still retained its original random characteristics.

Each test signal was constructed as 22 complete repetitions of the P.R.B.S.. Information gathered as a result of the first and last of these repetitions was discarded. This procedure was used

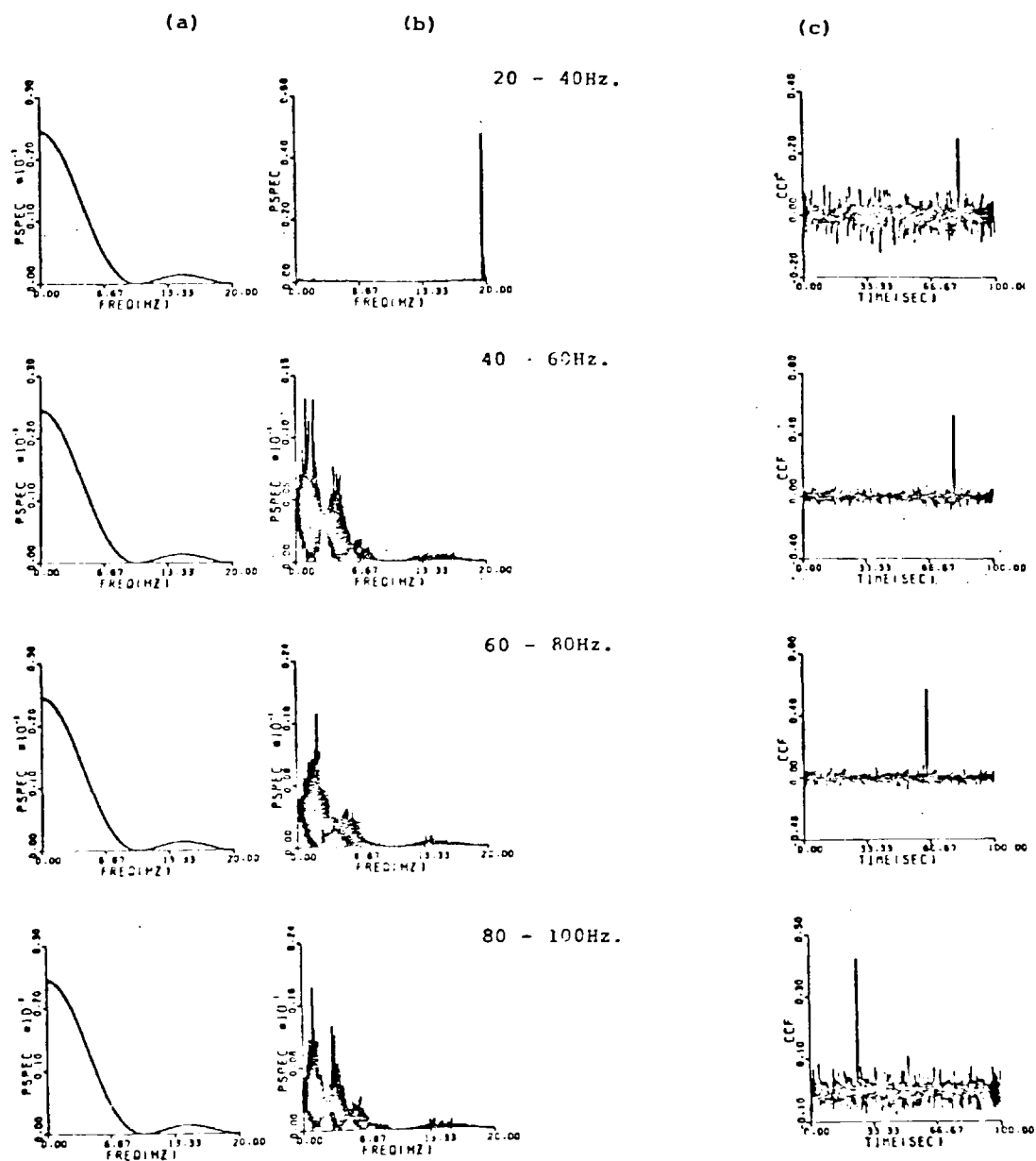


Figure 3 Z Diagram illustrating the spectral properties of Pulse Frequency Modulated PRBS's. Graphs (a) represent the power spectra of a PRBS of bandwidth 3.41-10.0Hz. Graphs (b) are the power spectra of the PRBS modulated at the frequency band indicated. Graphs (c) show the cross correlation function between the time domain equivalents of (a) and (b) in each case.

for two reasons:

1) the data from repetition 1 contained the 20sec. or so required for the system to settle down following the onset of stimulation. Inclusion of this information would distort the development of the average steady state response.

2) the analysis methods used are based on the premise that the signals involved extend over the range - to +  $\infty$ . In the context of the experiments the main consequence of the this is that since the PRBS repeats exactly, the premise is true for repetitions 2 to 21, but invalid for repetitions 1 and 22. Because of start up and shut down transients, repetitions 1 and 22 are nonstationary.

#### 4.5 Experimental Protocol.

The surgical protocol was identical to that described in Chapter 2. In the pilot experiments, the neural stimulus was a regular series of impulses formed by setting the internal clock of the pulse generator unit to the required interval (see Figure 12).

In the present series of experiments, the Pulse Frequency Modulated PRBS, pre-recorded on tape, was played back from a RACAL STORE4 recorder and fed into the pulse generator. This signal was used to drive the internal clock of the pulse generator. The output of the generator was tailored to the correct pulse amplitude and width for the stimulation electrodes.

Each of the 4 PRBS signals used took

$$22 \times 100 / 60 = 36 \text{ min. } 40 \text{ sec.}$$

to apply (refer to section 3.6 for details). A recovery time of 15 minutes was allowed between tests.

The total duration of the data collection phase of the experiment was therefore in the order of 4 hours. This was considered to be acceptable since the neural preparation remained responsive. From a systems point of view, it has been shown that, after an initial settling down period of 15 minutes, baroreceptor stimulation gives stable responses for up to 6 hours before adaptation becomes significant (Salgado & Kreiger, 1978).

#### 4.6 Preliminary data analysis.

##### 4.6.1 Preparation of the data.

The initial objective in the analysis of the experimental data was to calculate the frequency response of the system from the input test signal and each of the three system outputs. As before the bulk of the analysis was carried out in the frequency domain since the numerical manipulations involved are simpler and more economical of computer time. Another important reason for using frequency domain analysis was that similarities are often easier to perceive between spectra than between time domain plots.

Each experimental record consisted, as before, of 4 channels of information :

- A Neural Stimulus
- B E.C.G.
- C Arterial Blood Pressure
- D Respiration

These 4 channels covered the same time span, comprising

- a) ~ 30 sec. pre-stimulus
- b) 36.6 min. neural stimulation
- c) ~ 1 min. post-stimulus recovery.

The information from channel A was not used in calculating the frequency response. The recorded stimulus signal would have needed to be sampled at a minimum of 1KHz. to ensure that each pulse was represented This would have meant an array size of

$$1000 \times 36.66 \times 60 = 2,200,000 \text{ data points}$$

would have to be held in core and manipulated. This was beyond the

scope of even the excellent computer facilities available.

It will become clear from the next section that the frequency spectrum of one PRBS repetition was all that was needed for subsequent calculations, and this was constructed using the software which generated the test signals. Consequently, the only way in which the information from channel A was used was as an indicator of the instant in time at which stimulation commenced and terminated, relative to the start of the record. These timings were obtained visually from the ADC records (400Hz/channel). The error involved was of the order of 0.01% over the entire stimulus period.

As in the analysis of the pilot experiments, once the signals were digitized the H.R. signal was formed, all signals digitally filtered and the sampling rate reduced to 1/10th of its previous value.

A more significant source of error was the impracticability of setting the ADC unit to the exact frequency required. Since the stimulus period was known to be exactly 2200 seconds, and it was vital that this integrity be maintained, it was more accurate to proceed with a calculated sampling rate,  $f$ , where

$$f = \frac{X - Y}{2200} \quad (\text{Hz.})$$

and  $X$  = data point corresponding to start of stimulation

$Y$  = data point corresponding to end of stimulation.

The derived sampling rate was typically in the order of 39 to 41 Hz.

#### 4.6.2 Formation of the frequency spectra.

Figure 38 illustrates the processes involved in calculating the

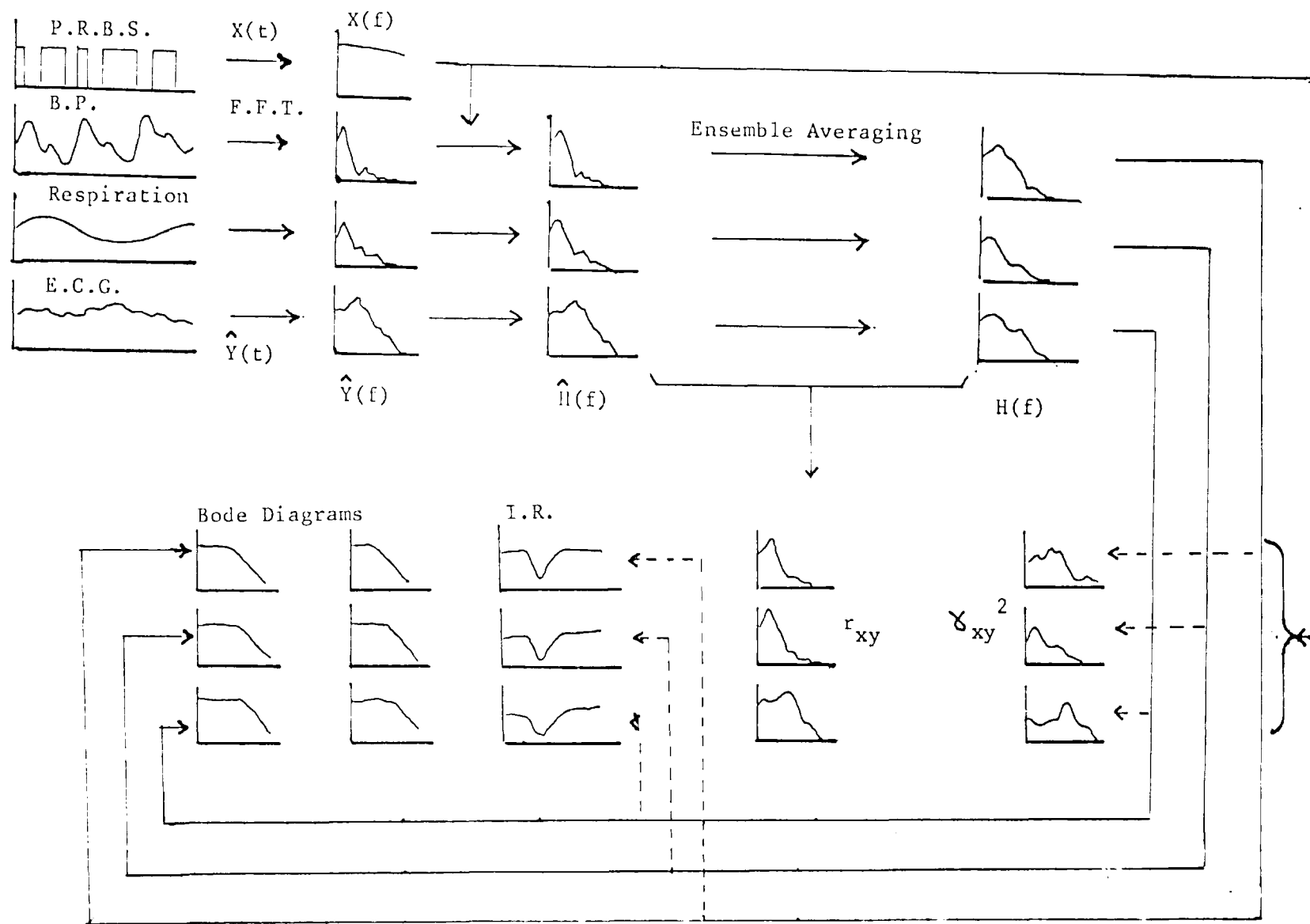


Figure 38. Diagram illustrating the processing sequence of the experimental data.

frequency response. The first step was to convert all the data from the time to the frequency domain, by means of Fast Fourier Transformation.

Section 3.6 explained that the calculated length of a PRBS is fundamental to its unique properties as a test signal. Each set of experimental data consisted of responses to 22 uninterrupted repetitions of a PRBS of 100 sec. duration. Under ideal conditions, since the data is always the same, the response to each of the 22 repetitions would be identical. Indeed, in the ideal world only one repetition would be sufficient to estimate the frequency response. In fact, applying the same stimulus many times gave the opportunity to average the responses obtained, thereby reducing variation due to noise and enhancing the frequency response estimate. The data was therefore analysed in blocks of

$100 \times \text{sampling rate} = 4000 \text{ data points (approximately).}$

The amount of computer time required made it impracticable to use anything other than a Fast Fourier Transformation to convert arrays of this size to the frequency domain.

The FFT algorithm requires that the number of data points input to it be a power of two. Padding or truncating the PRBS to accomodate this would yield a distorted transform (Sheppard, 1976), since the sequence would no longer reflect the random method in which it was generated. This also applies, of course, to the responses to PRBS stimulation.

Chirp-Z transformation, however, allows fast Fourier estimation of the discrete Fourier transform (DFT) of a waveform of any length. The method (Rabiner, Schafer and Rader, 1969) involves convolution of the waveform with a Chirp function having a length

which is a power of two, and which is longer than the waveform.

Transformation of the data records therefore yielded the real and imaginary parts of the frequency spectra, having a maximum frequency of

sampling frequency / 2 which in this case was 20 Hz.

and a frequency resolution of

$$1 / T = 0.01 \text{ Hz.}$$

The Chirp-Z algorithm was supplied as part of the laboratory's user-written library for the CDC 6500; Figure 39 illustrates the form in which data is returned by it.

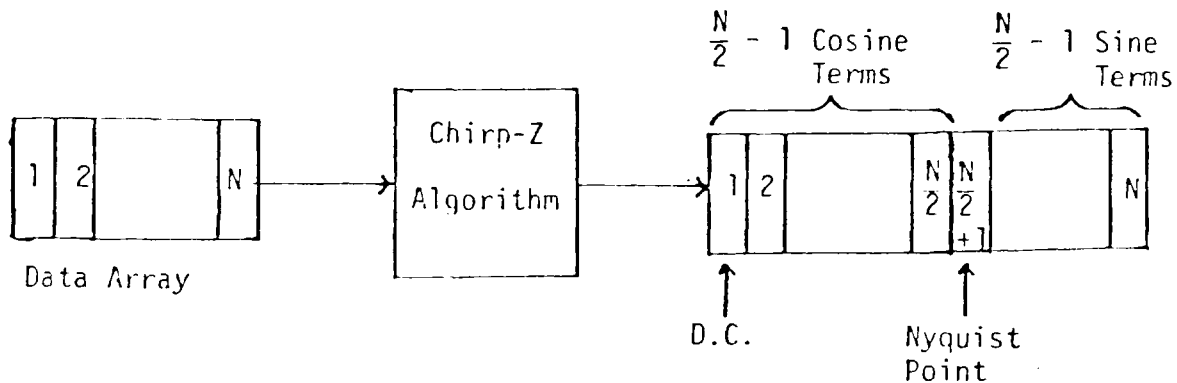


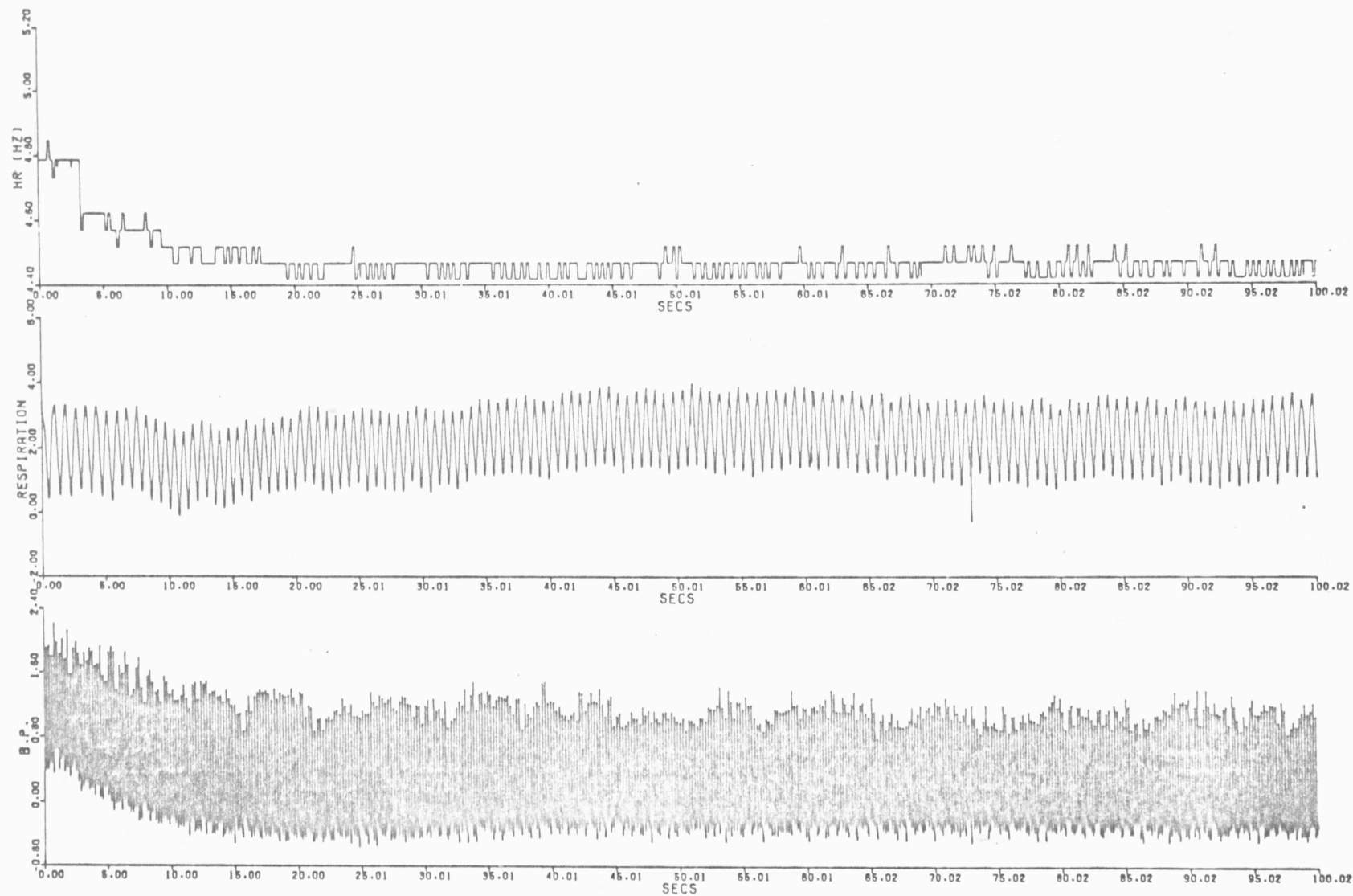
Figure 39. Form of the Chirp-Z algorithm.

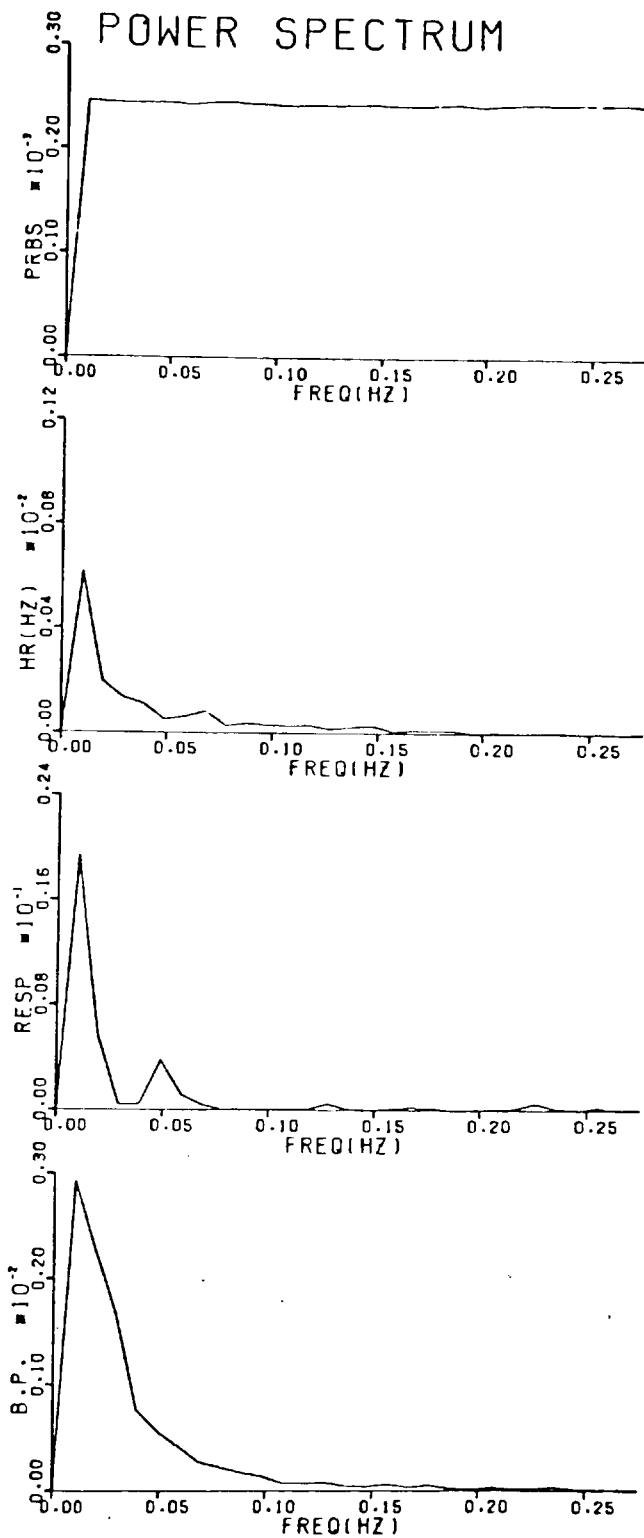
Figures 40 to 61 show the time series plots for the outputs from one experiment, using the 80 - 100Hz. stimulus level. Pre-stimulus and post stimulus records are included for completeness. Alongside each time plot is its corresponding power spectral density function formed from one-sided spectra as

$$P_n = a_n^2 + j b_n^2, \quad n = 1, (N/2 - 1)$$

where  $a$  and  $j b$  represent the real and imaginary components of

Figure 40a





## FREQUENCY RESPONSE

Figure 40b.

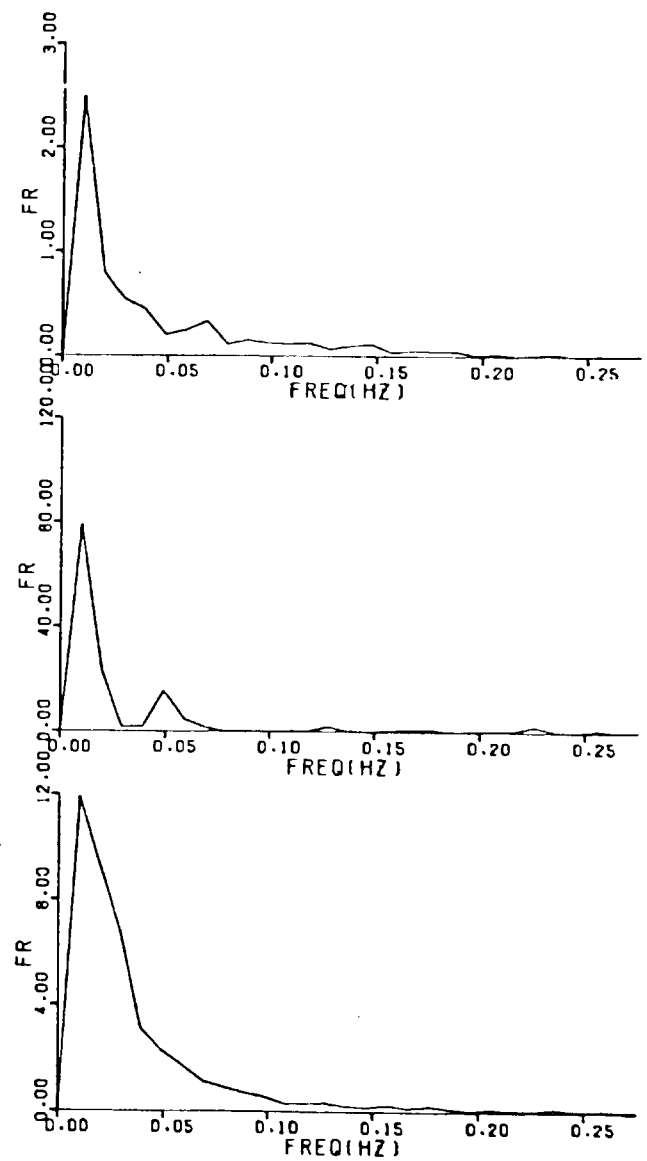
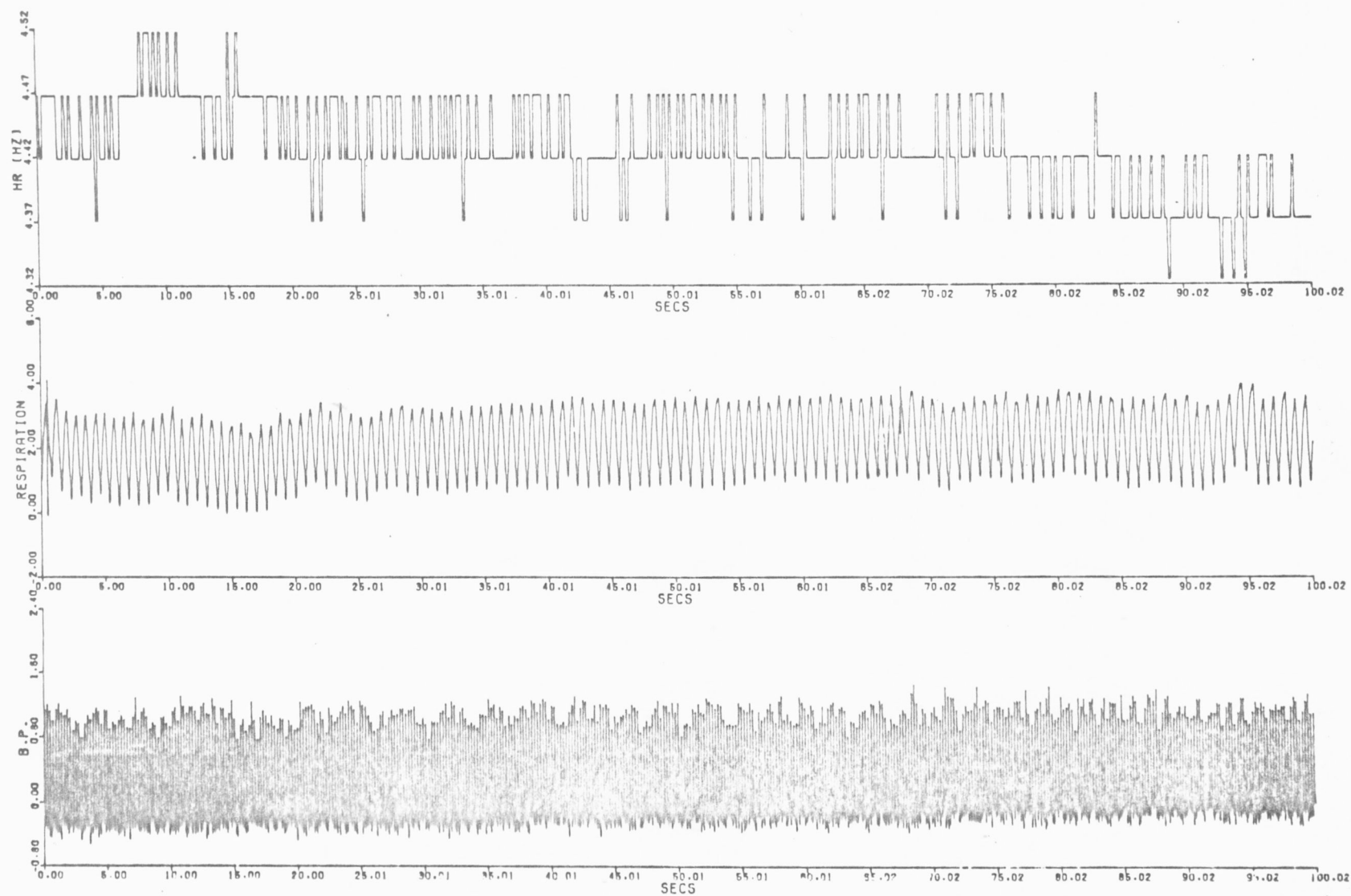
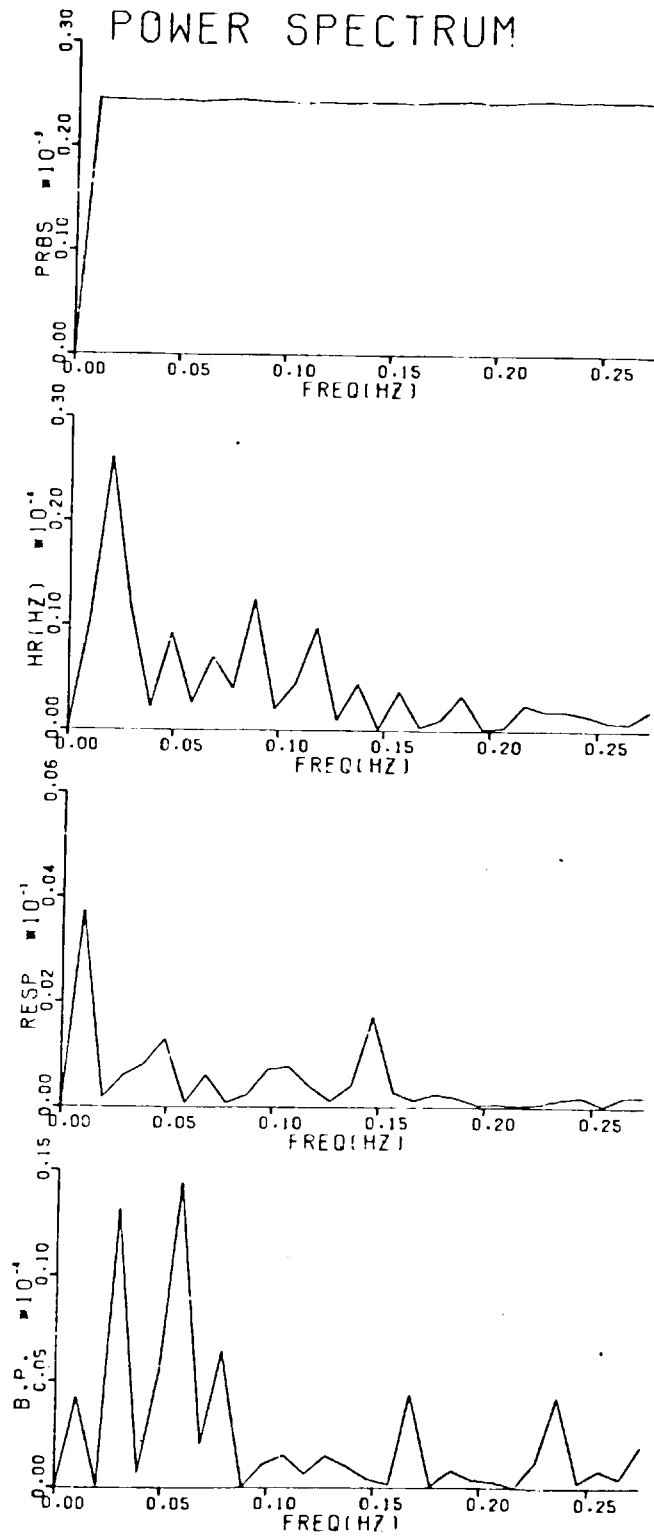


Figure 41a





## FREQUENCY RESPONSE

Figure 41b.

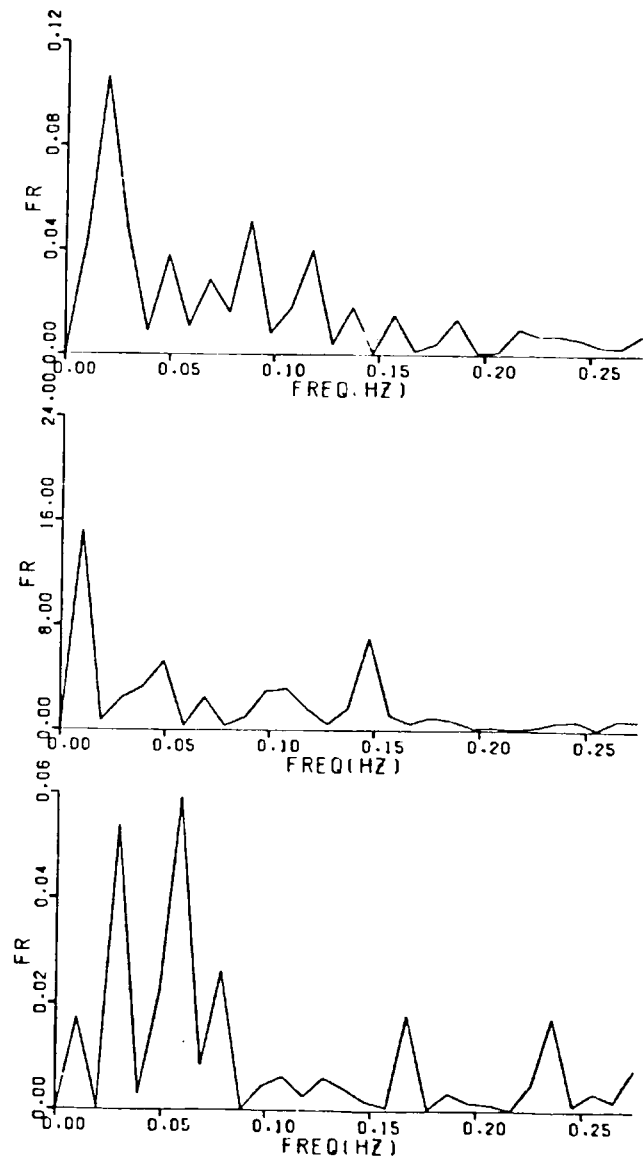
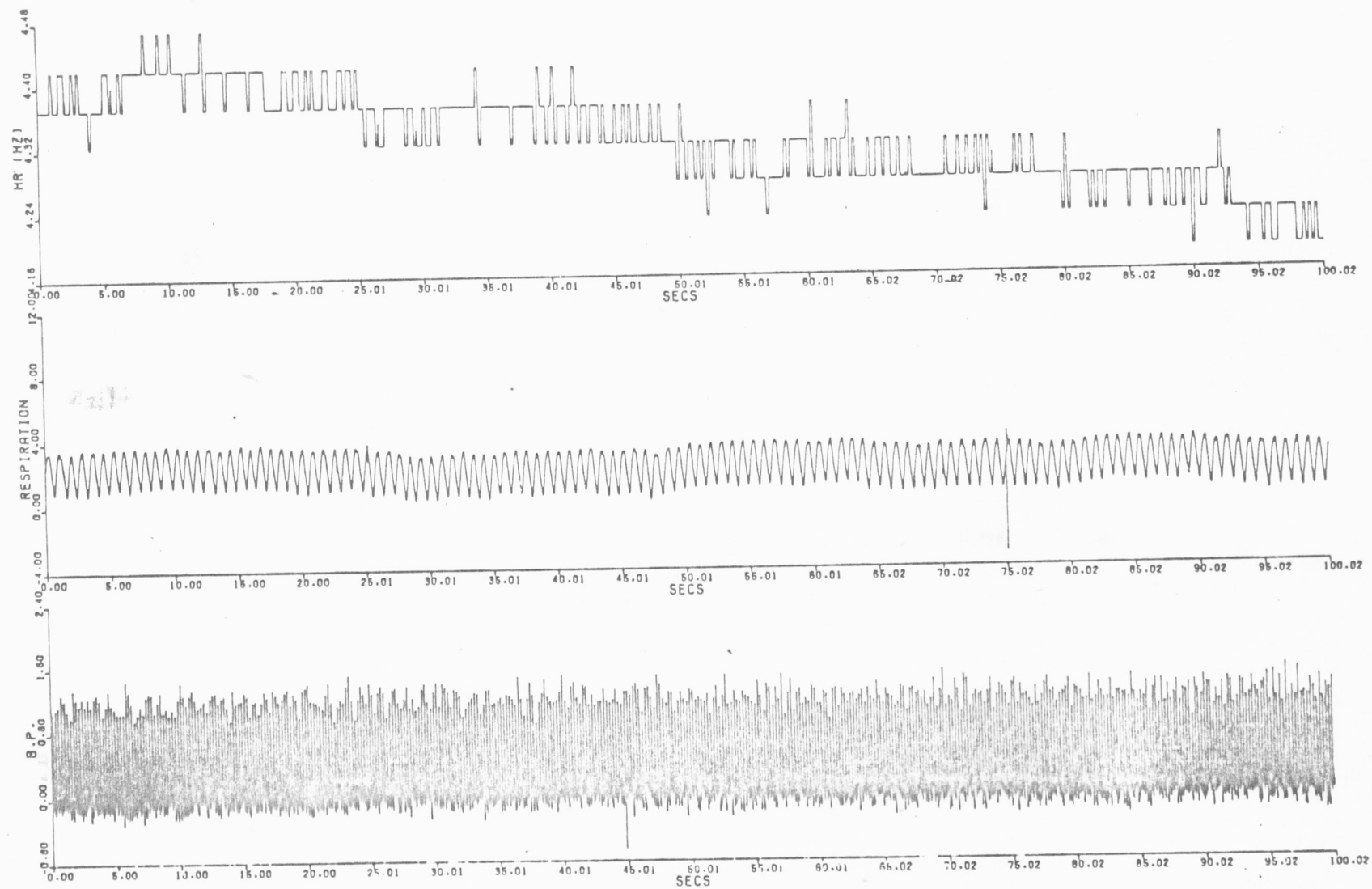
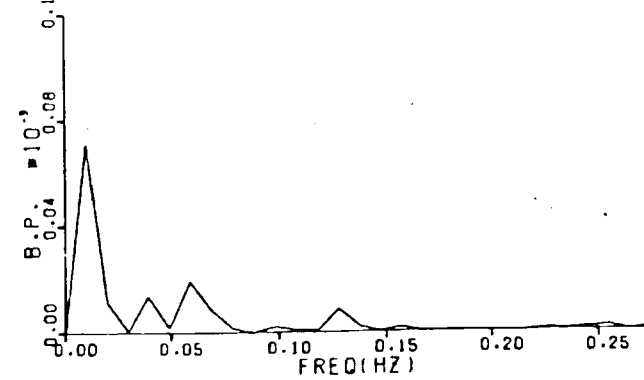
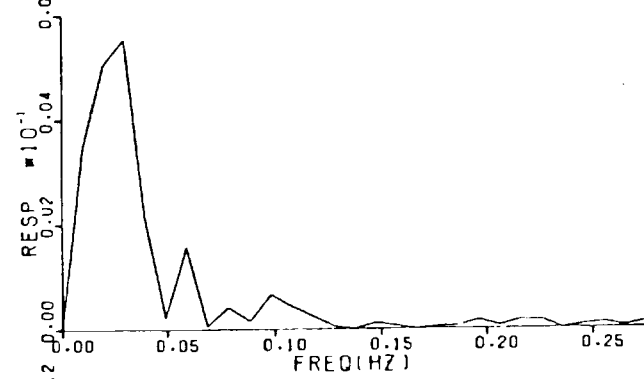
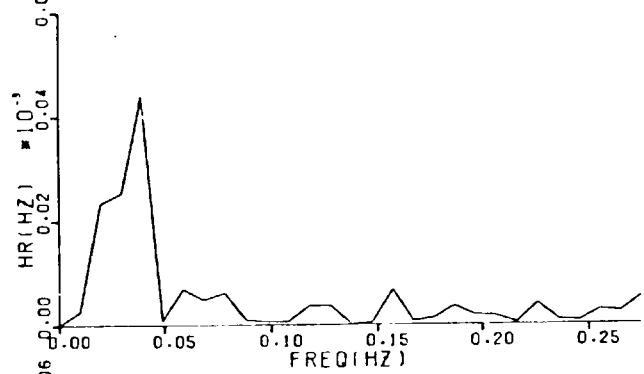
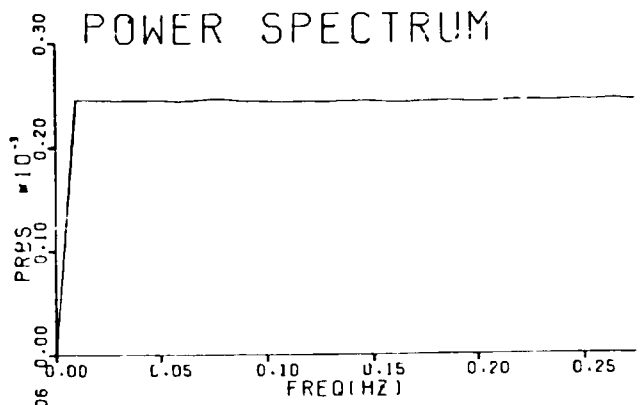


Figure 42a





### FREQUENCY RESPONSE

Figure 42b.

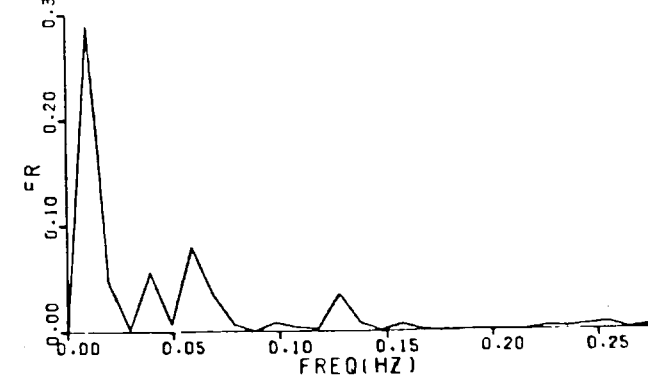
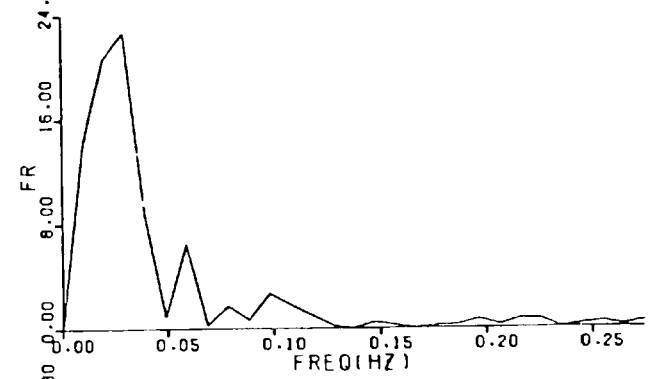
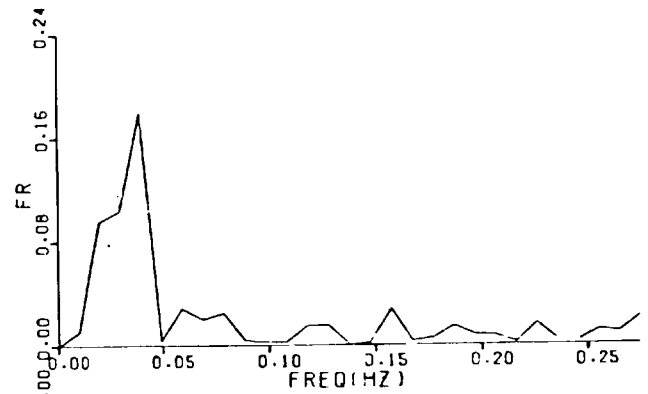
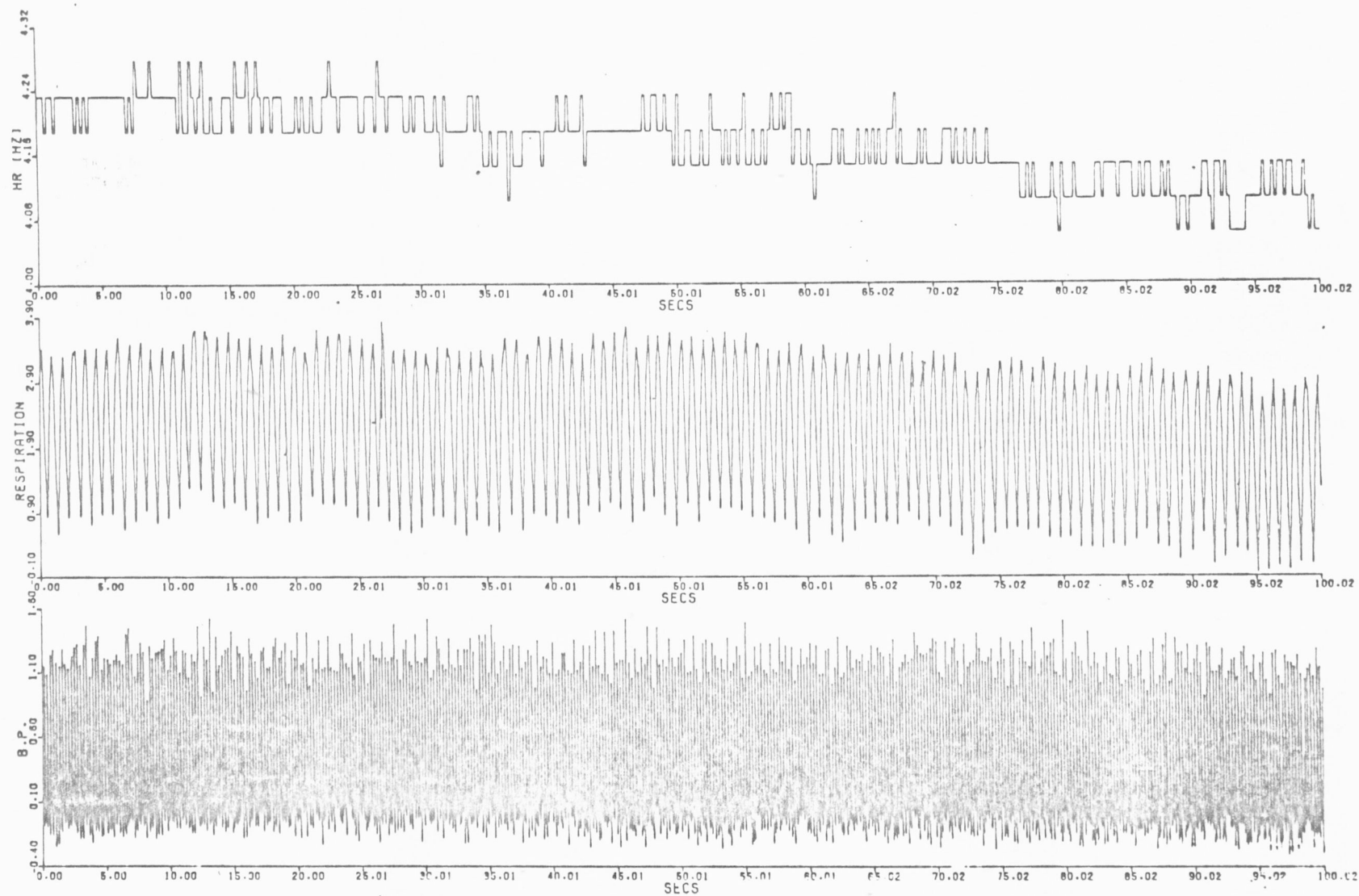
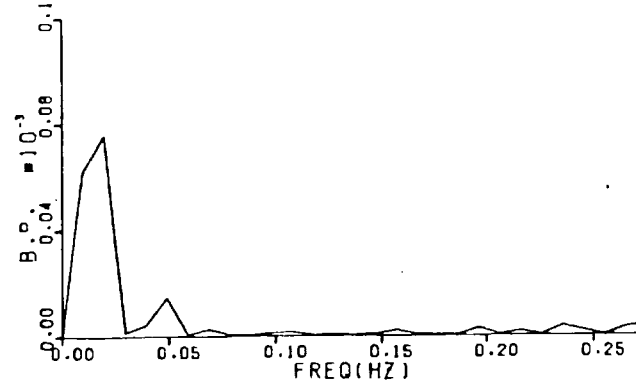
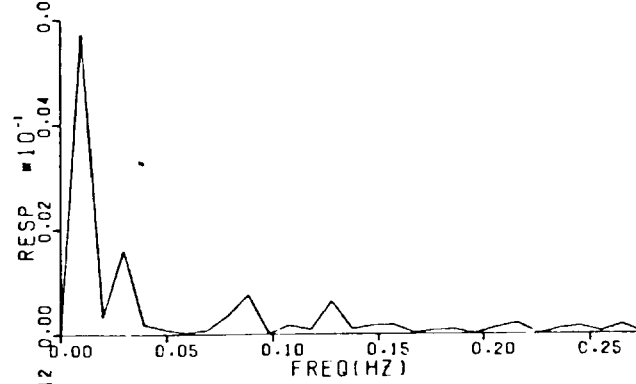
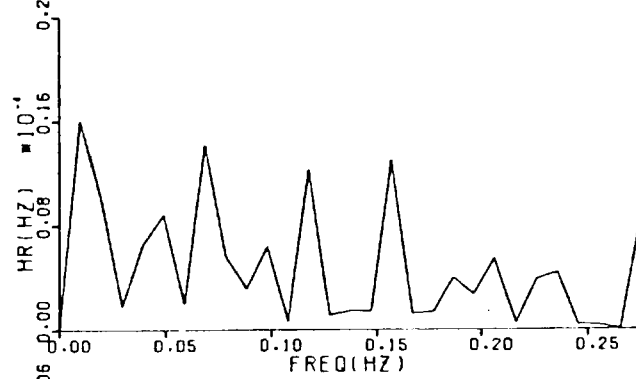
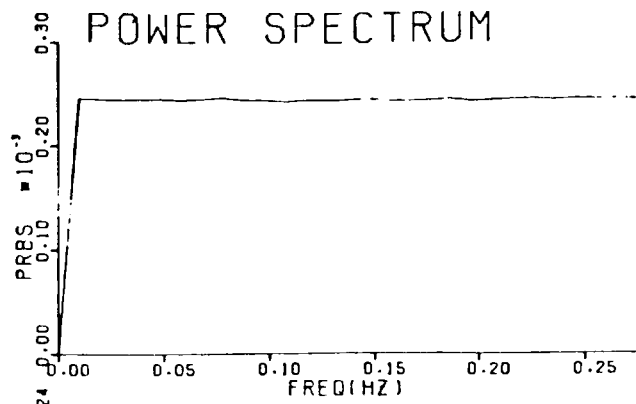


Figure 43a





### FREQUENCY RESPONSE

Figure 43b.

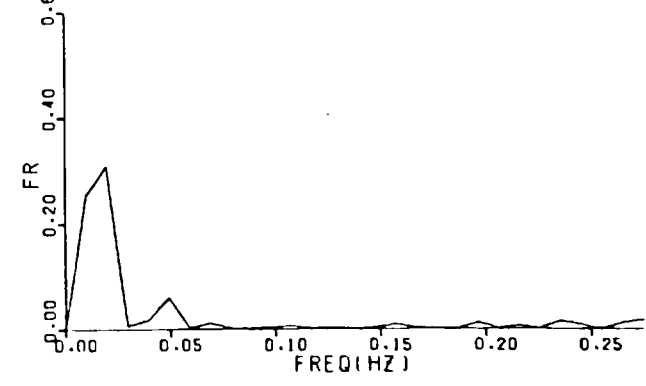
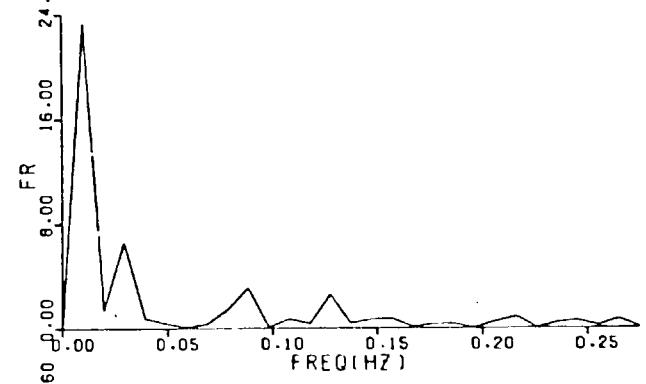
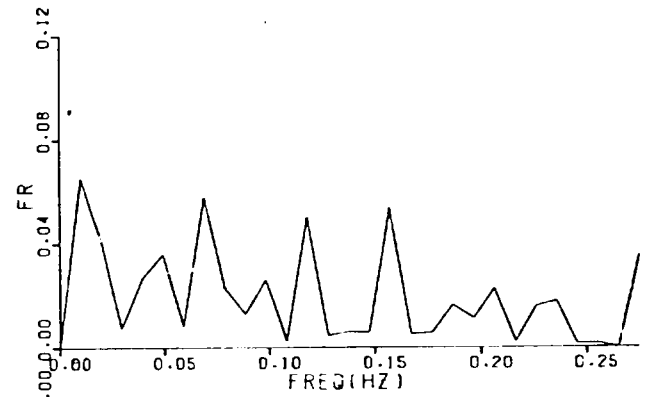
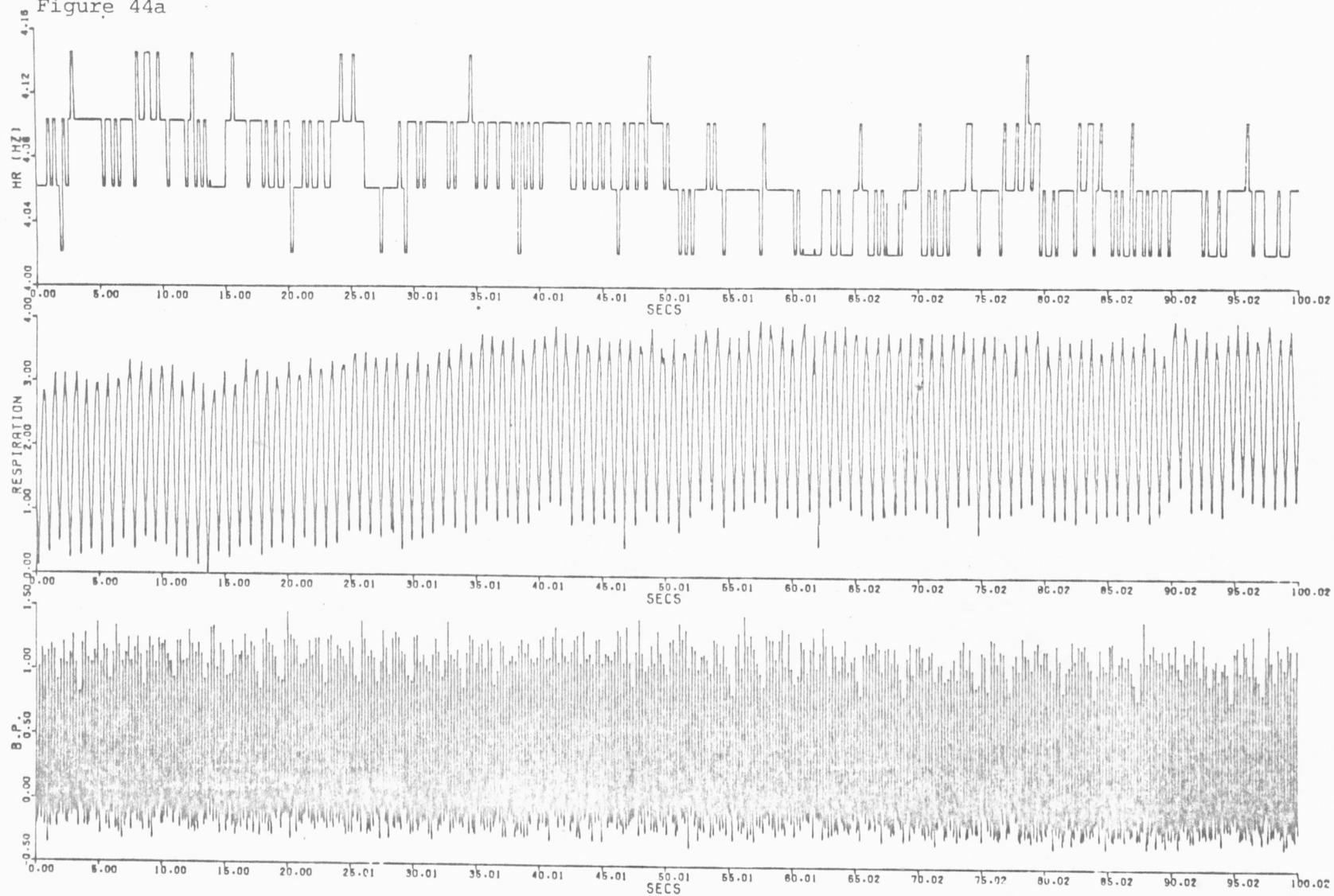
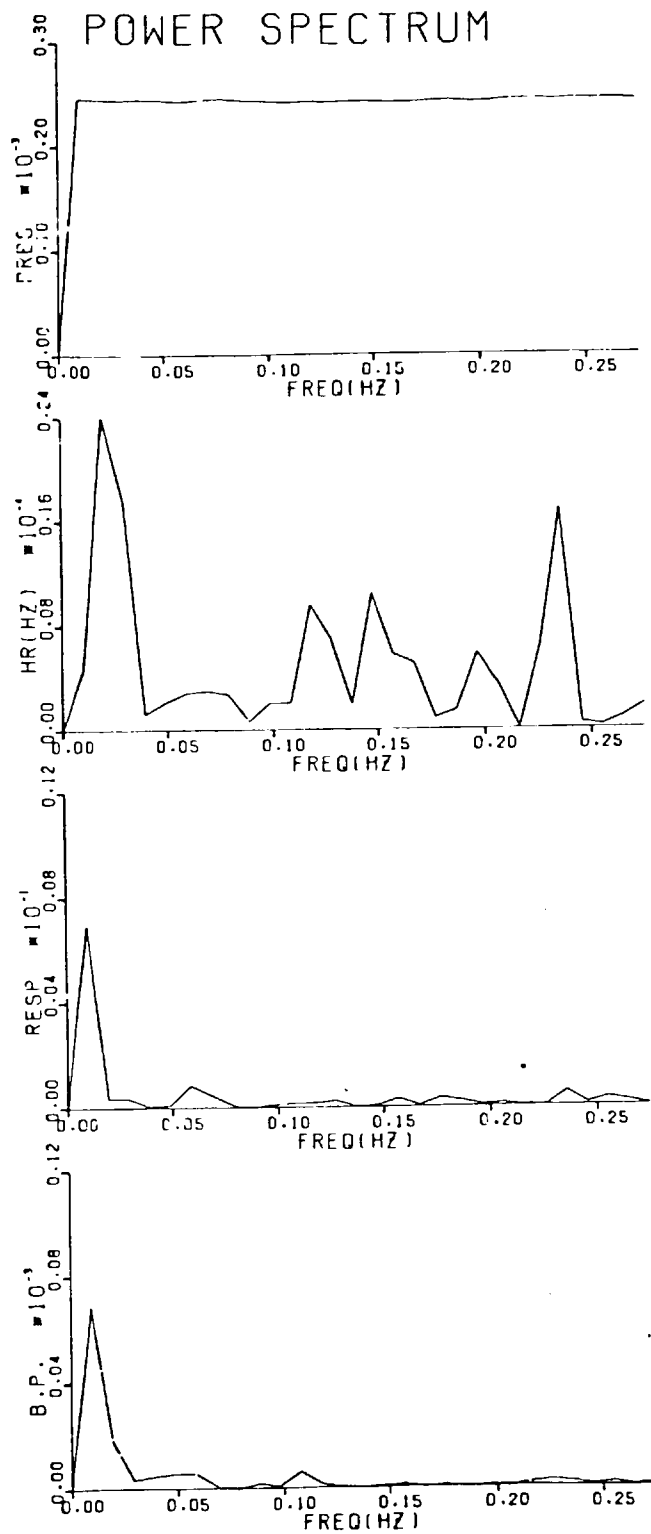


Figure 44a





## FREQUENCY RESPONSE

Figure 44b.

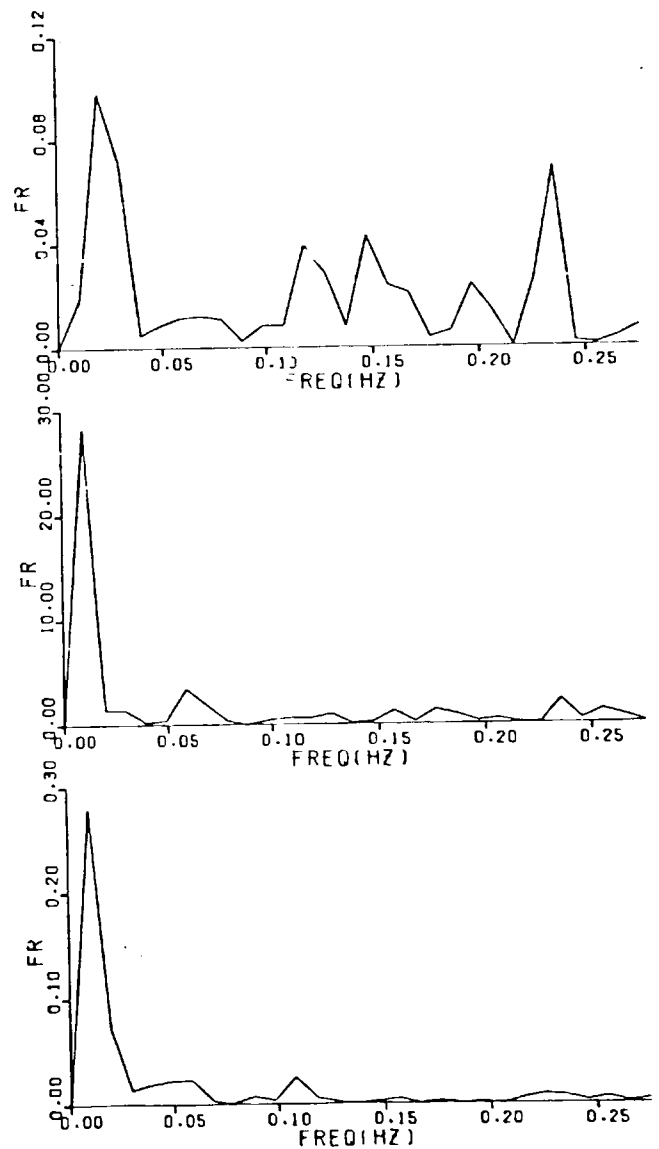
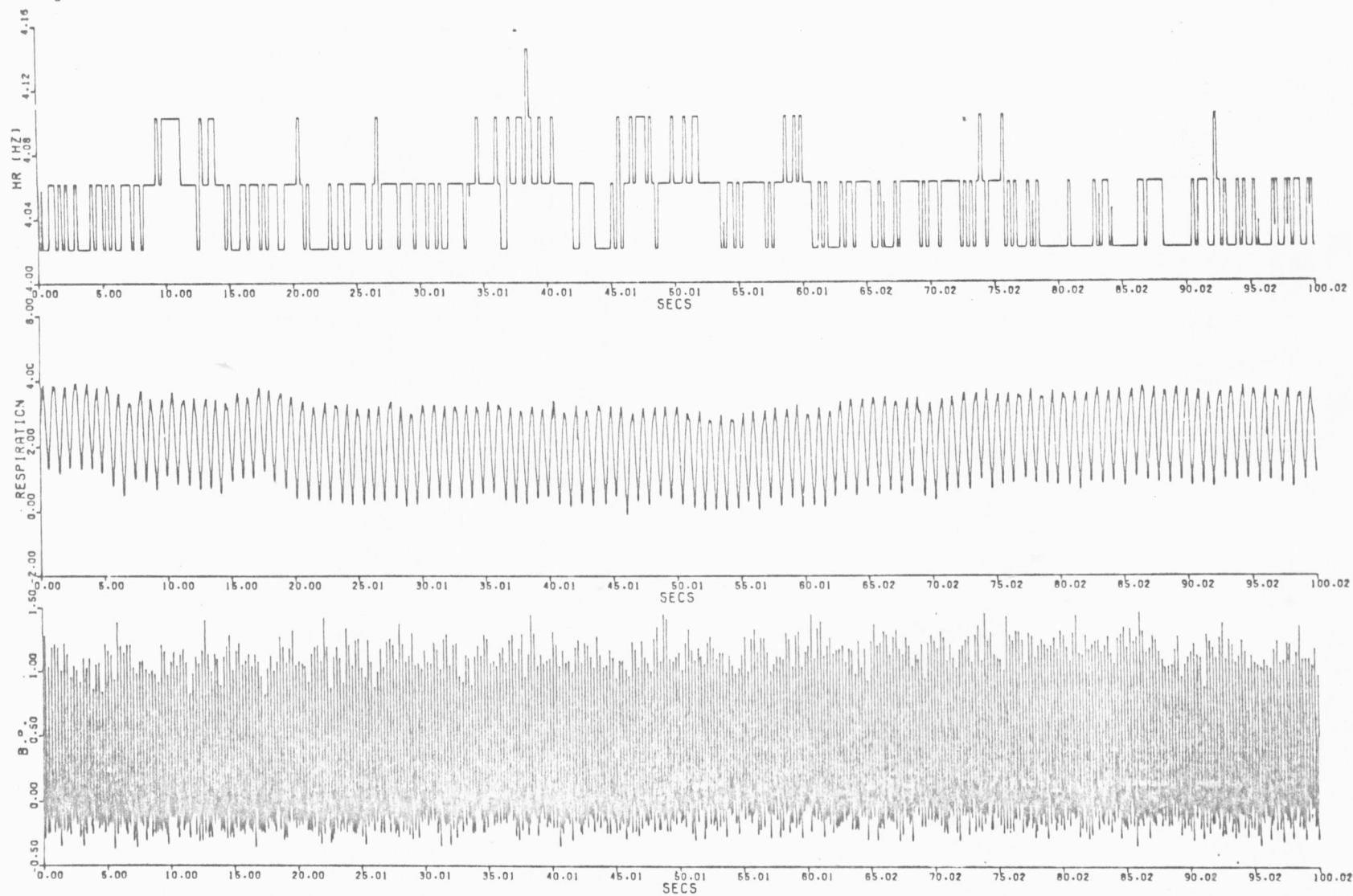
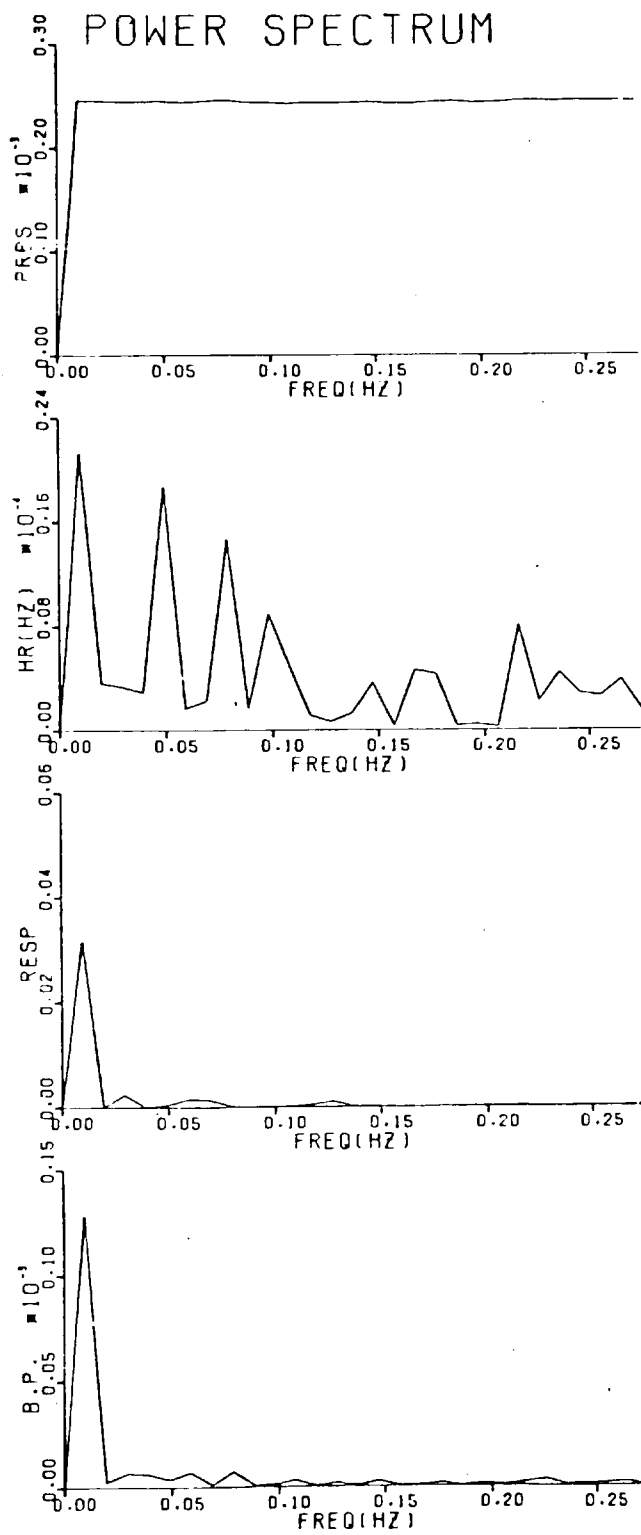


Figure 45a





### FREQUENCY RESPONSE

Figure 45b.

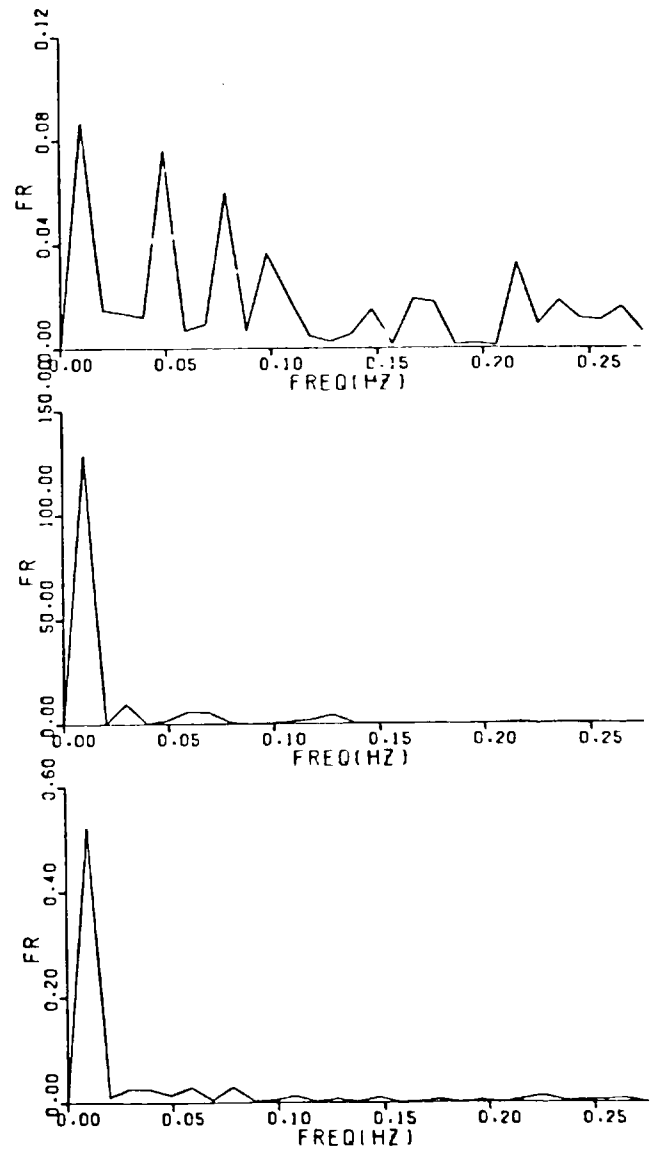
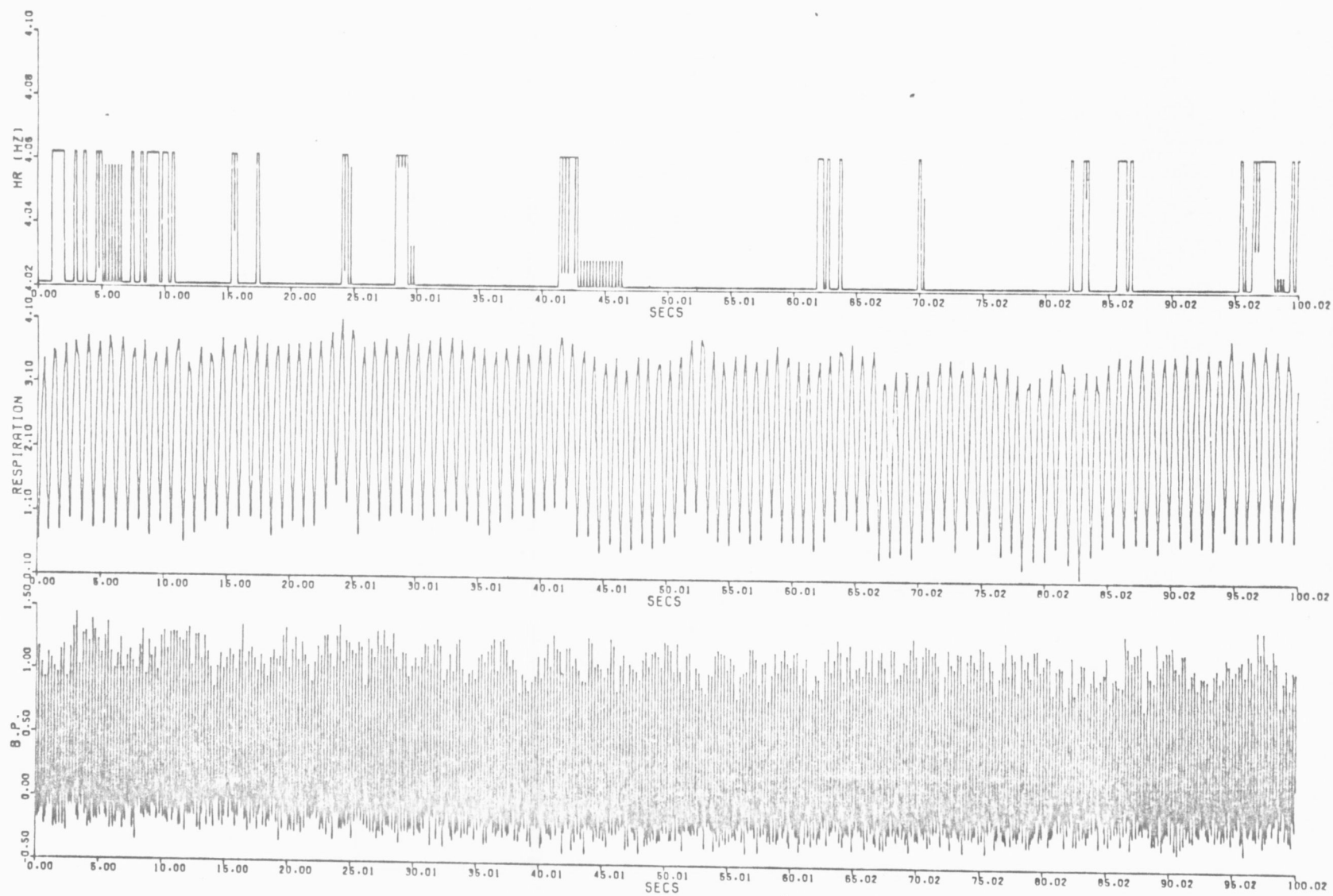
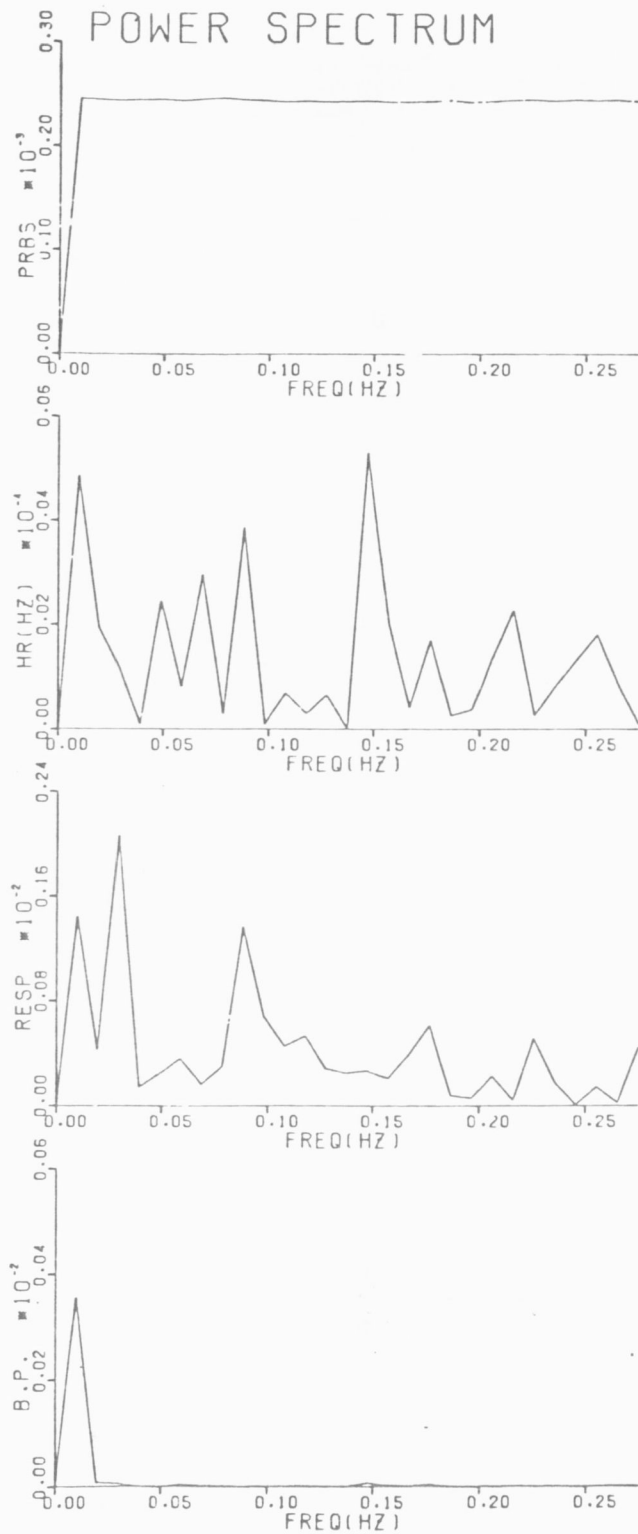


Figure 46a





## FREQUENCY RESPONSE

Figure 46b.

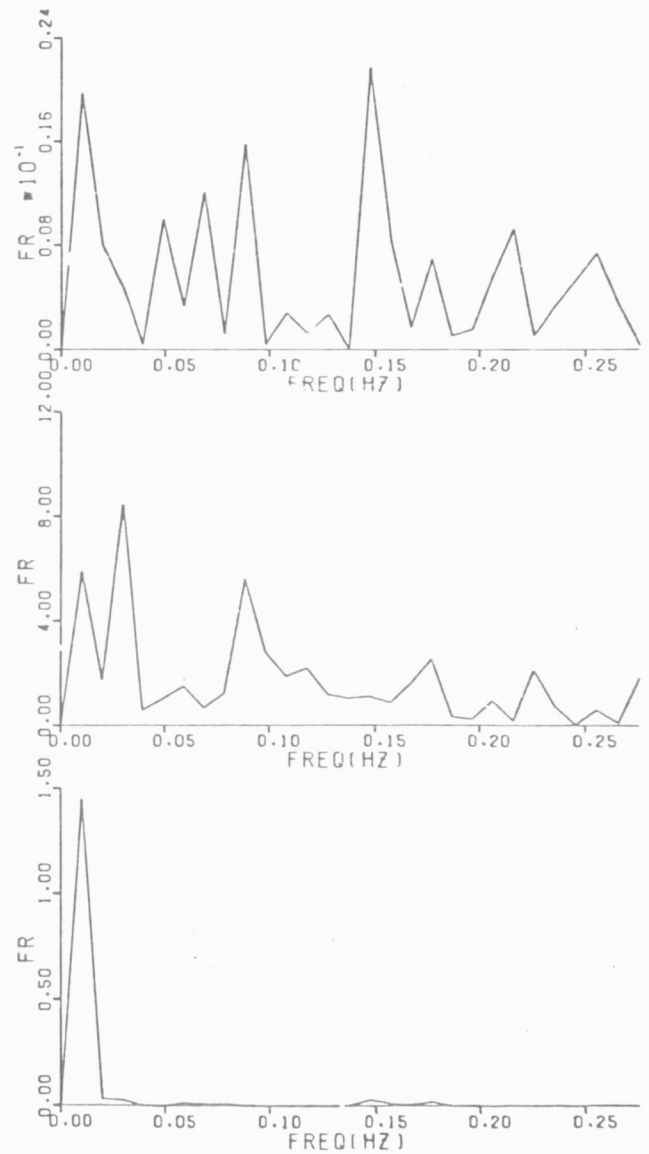
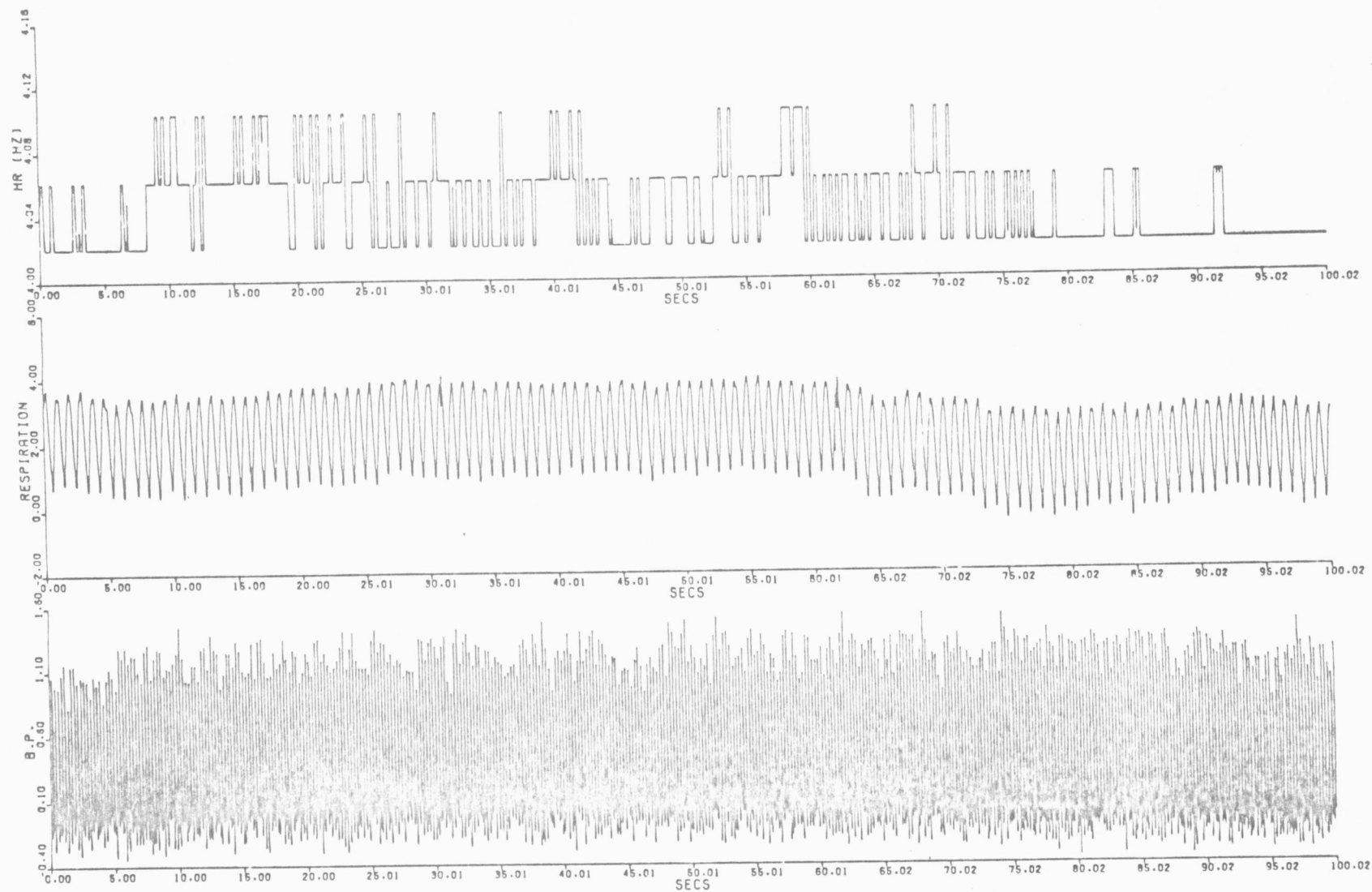
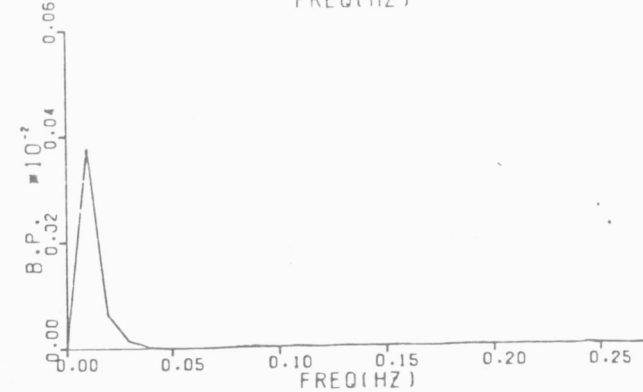
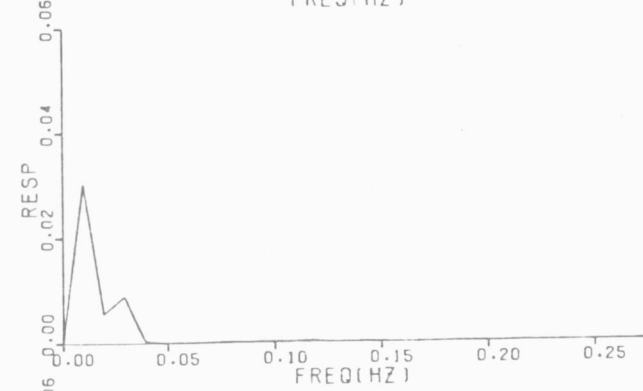
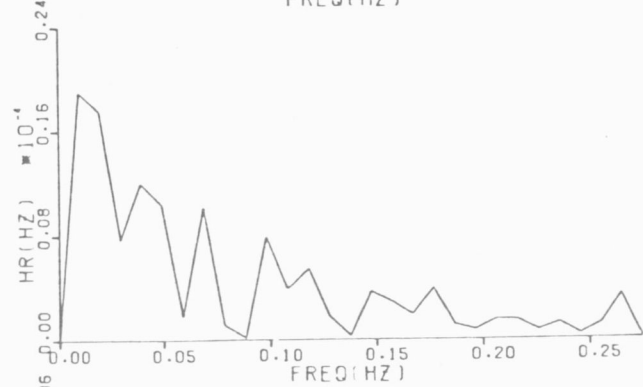
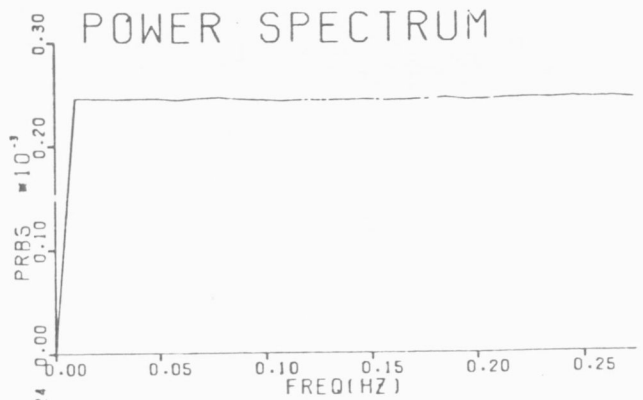


Figure 47a





### FREQUENCY RESPONSE

Figure 47b.

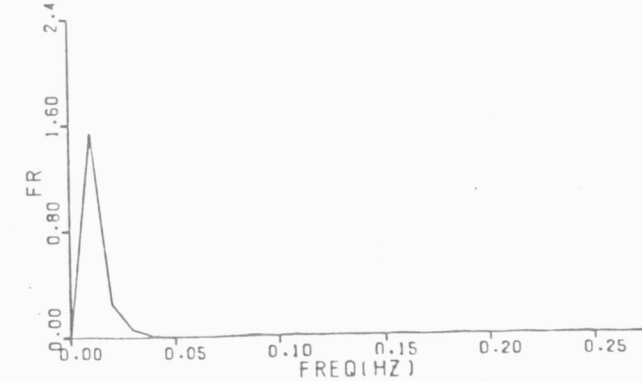
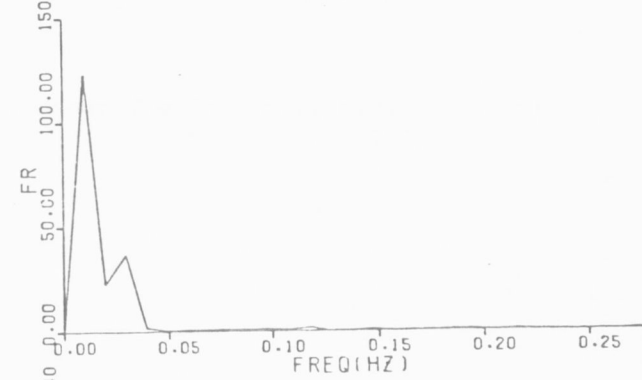
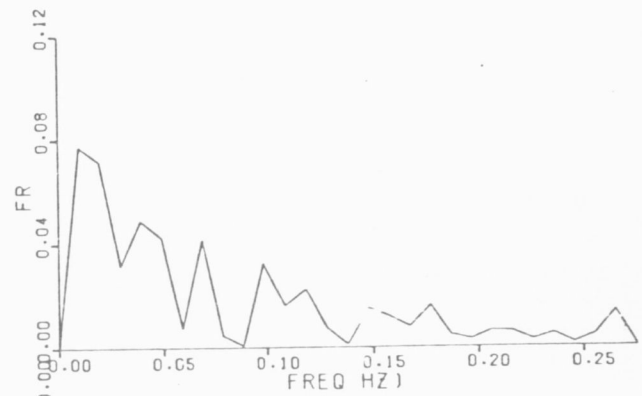
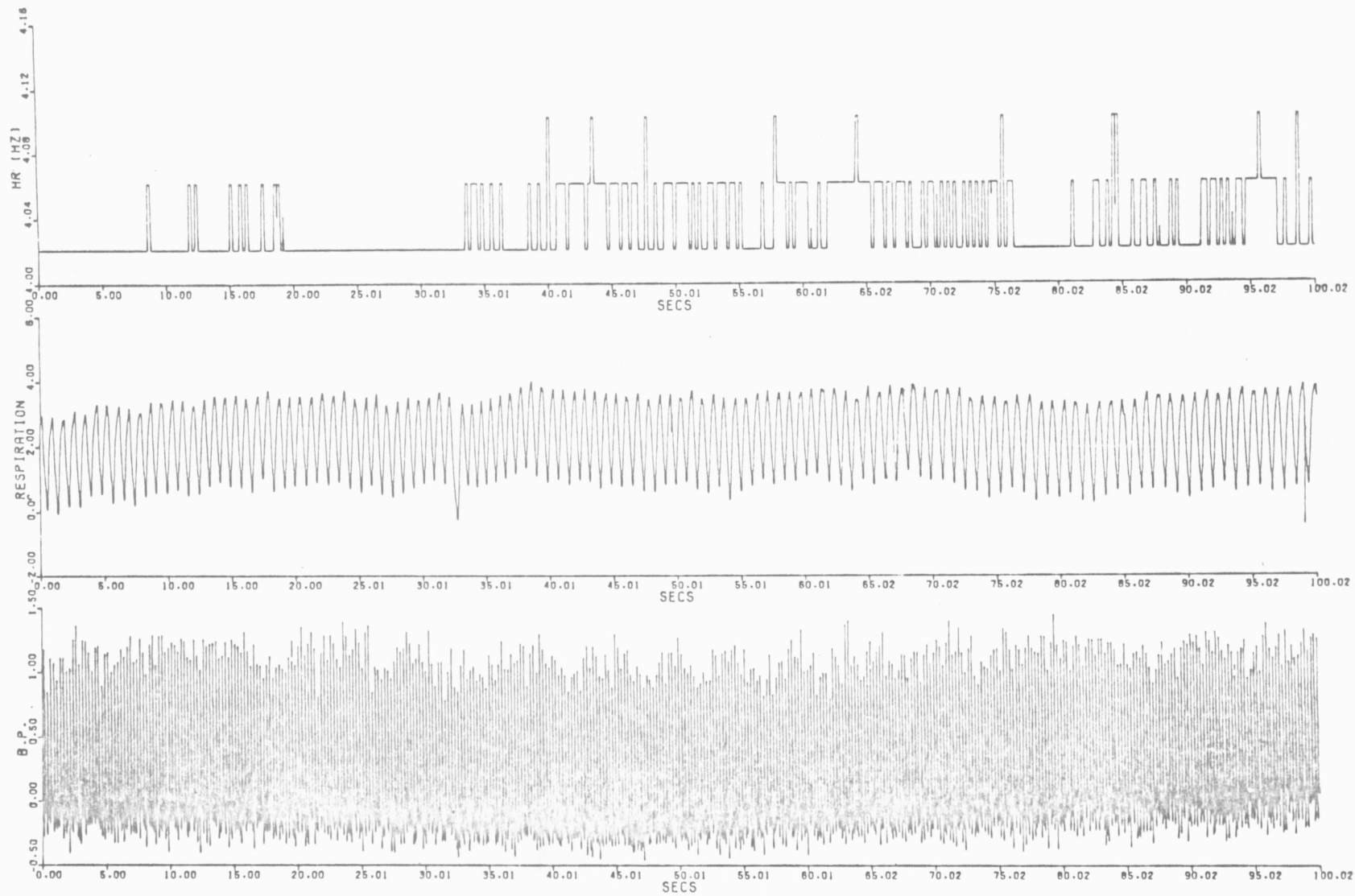
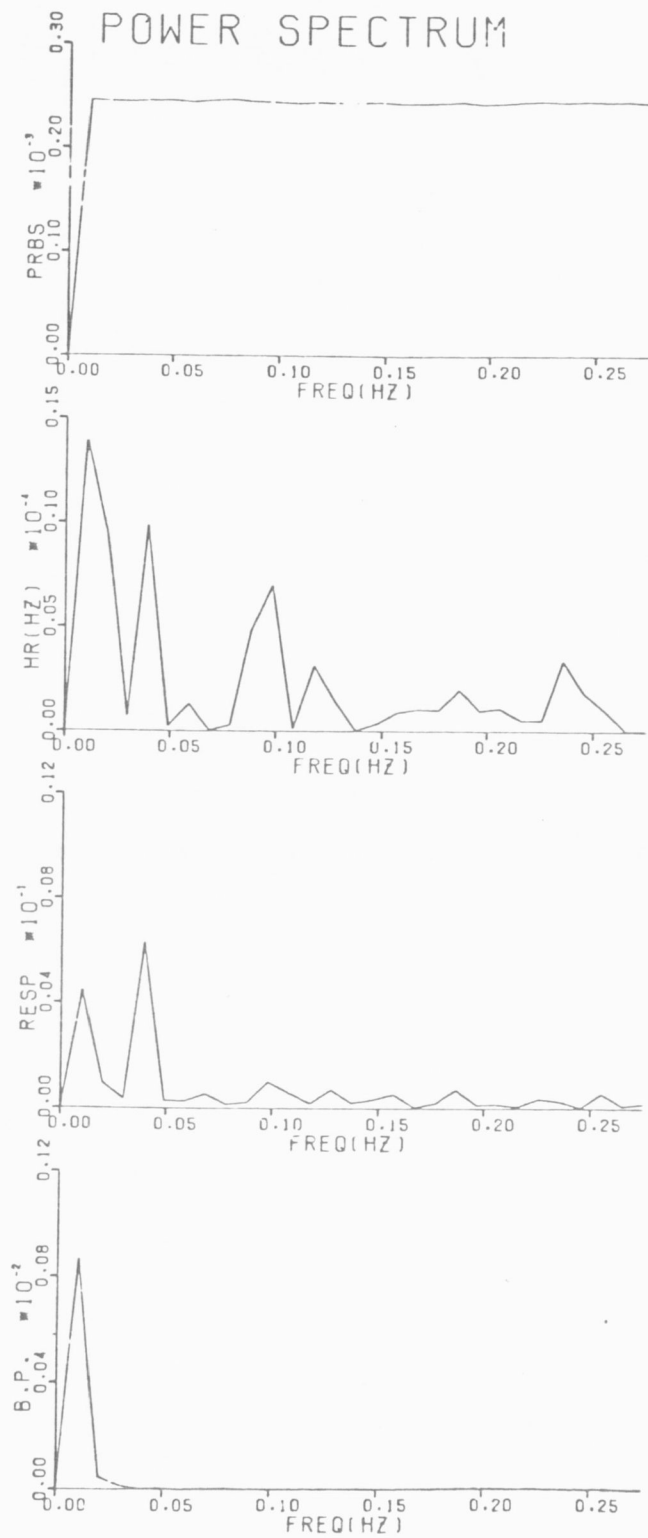


Figure 48a





## FREQUENCY RESPONSE

Figure 48b.

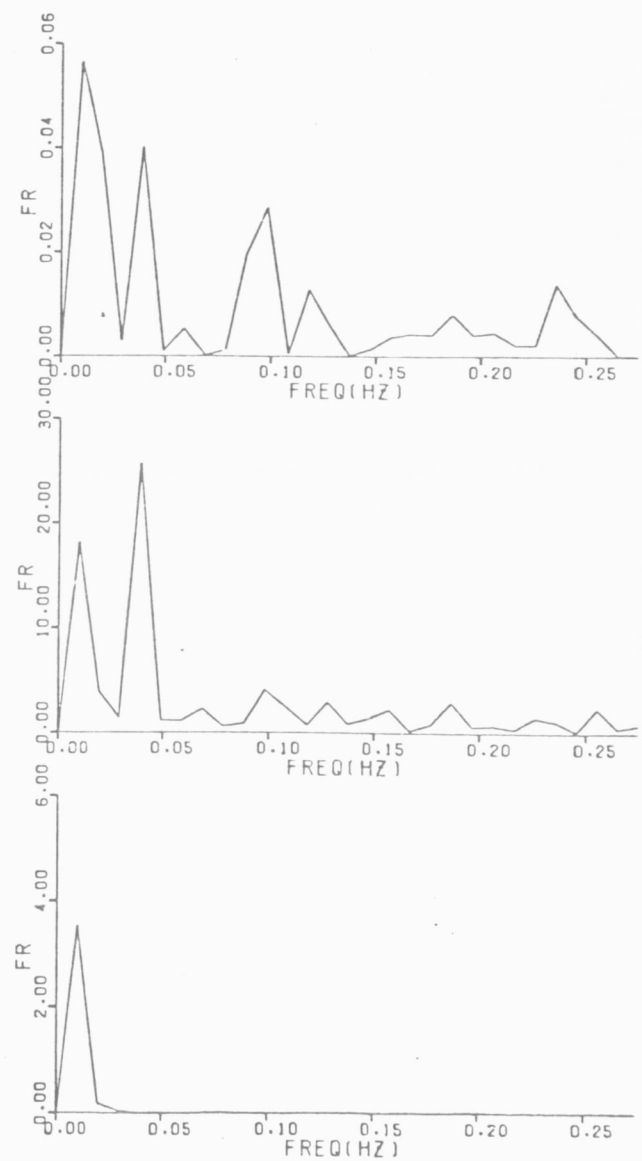
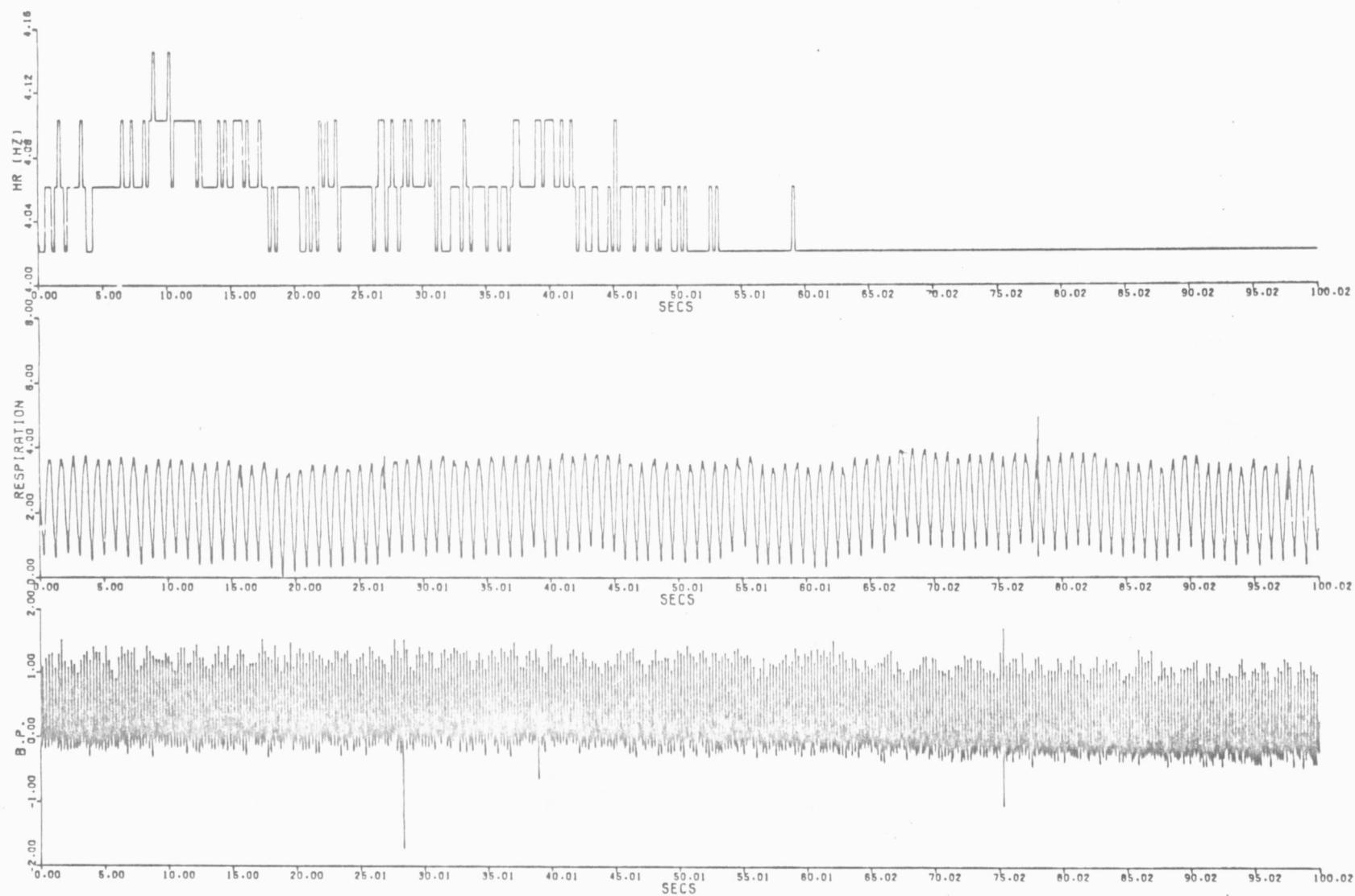
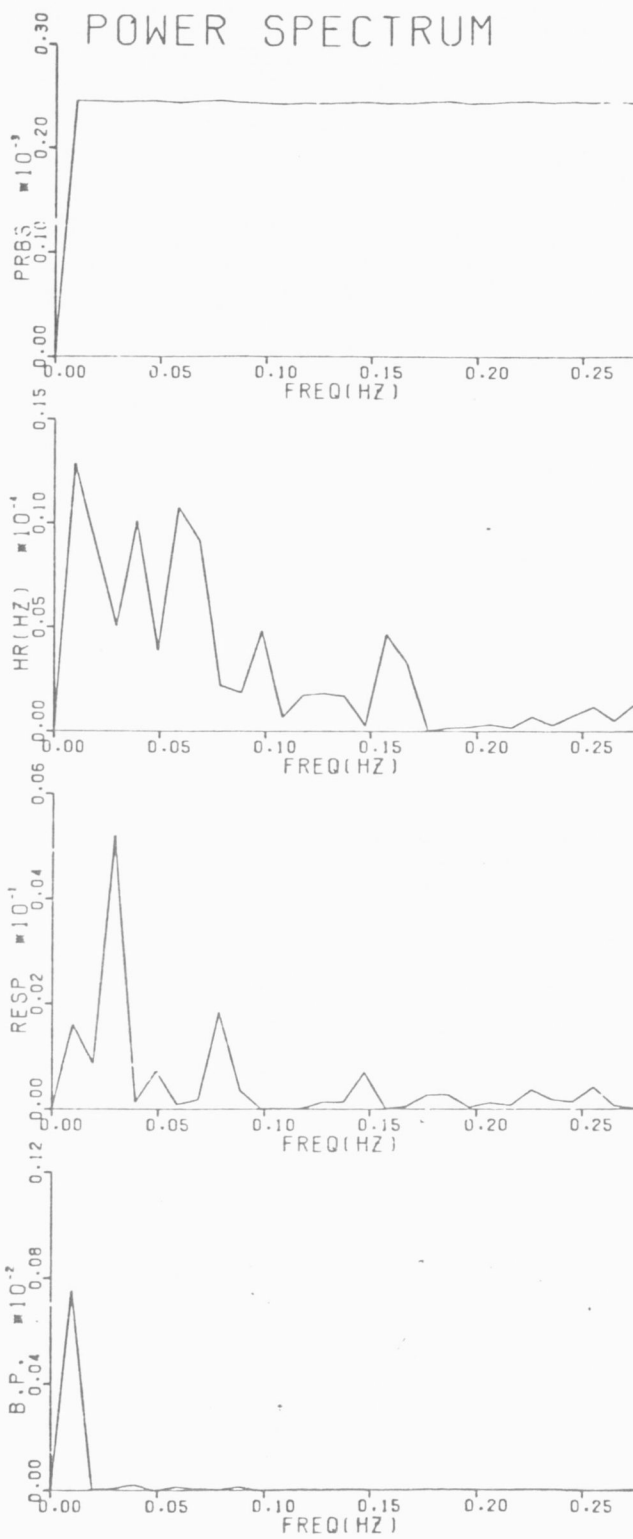


Figure 49a





## FREQUENCY RESPONSE

Figure 49b.

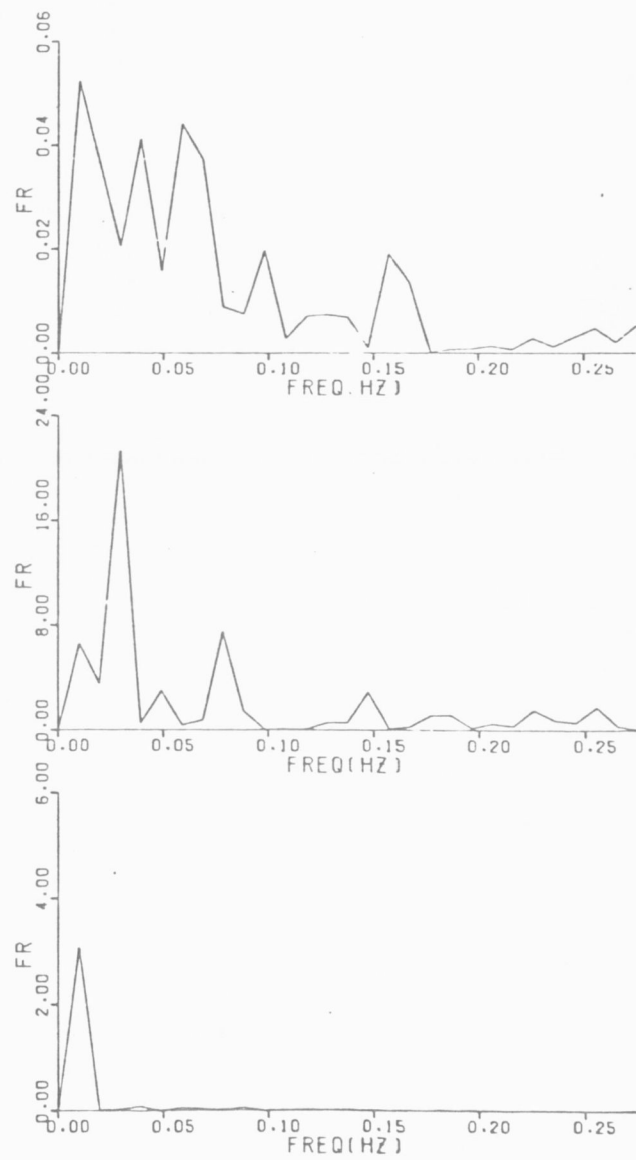
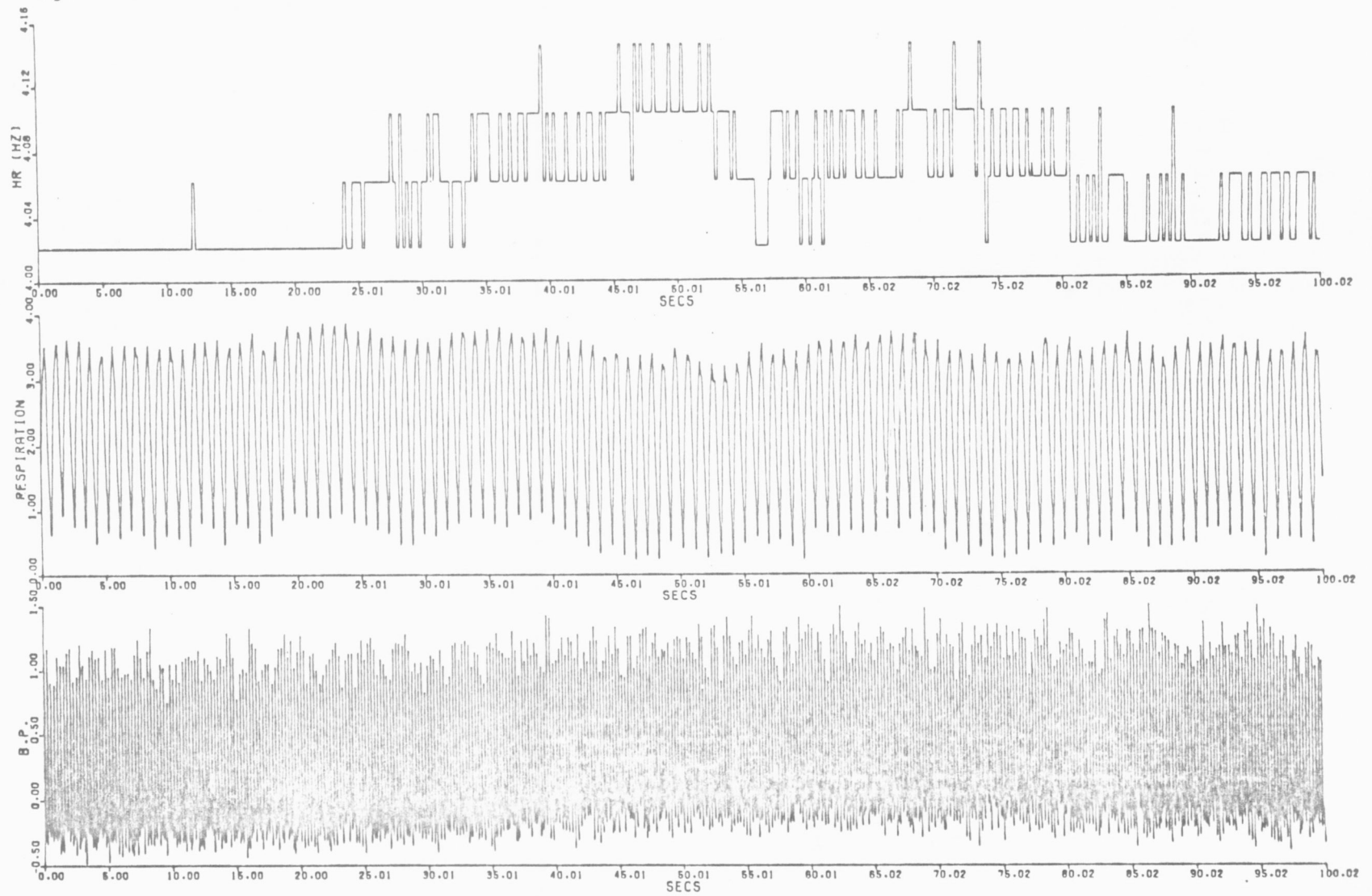
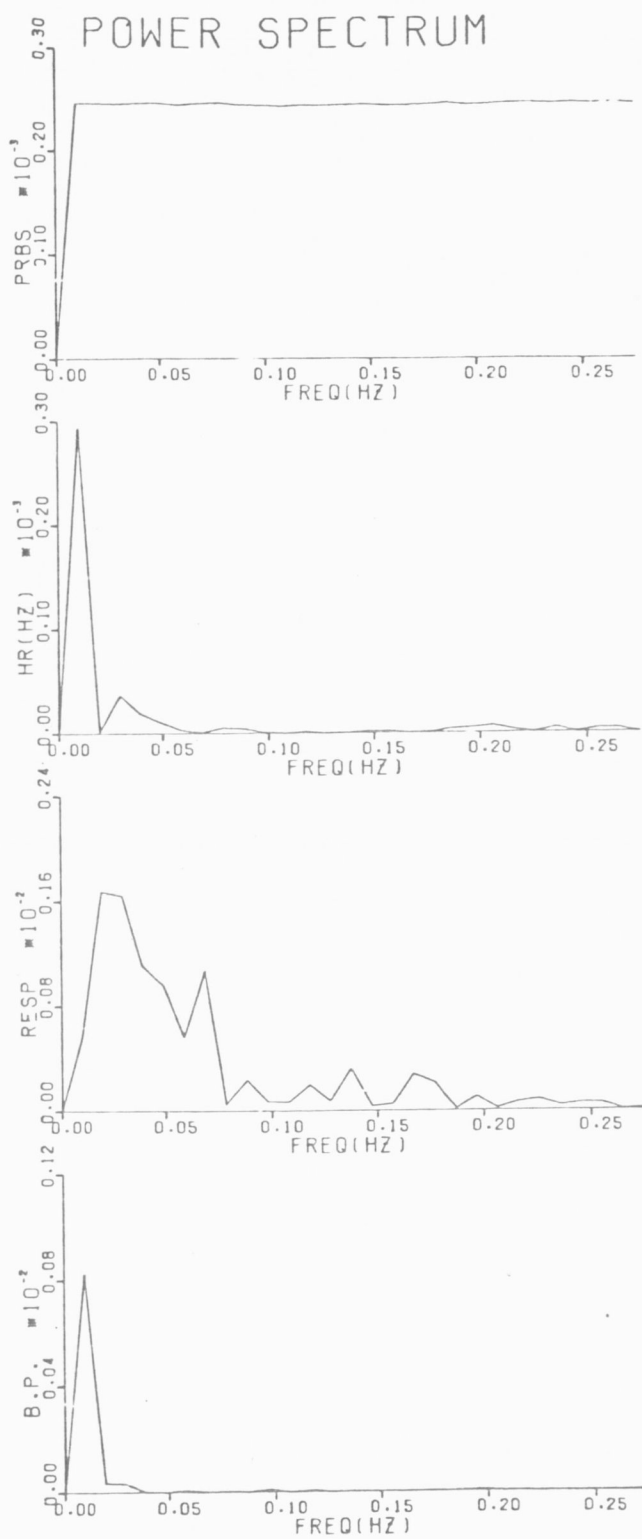


Figure 50a





### FREQUENCY RESPONSE

Figure 50b.

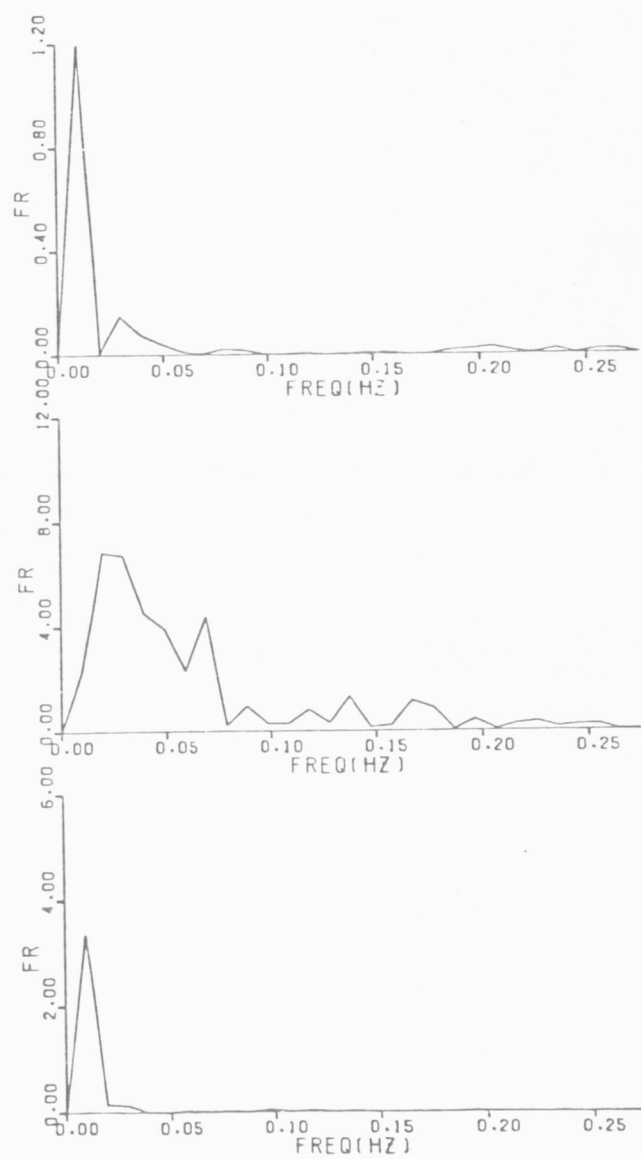
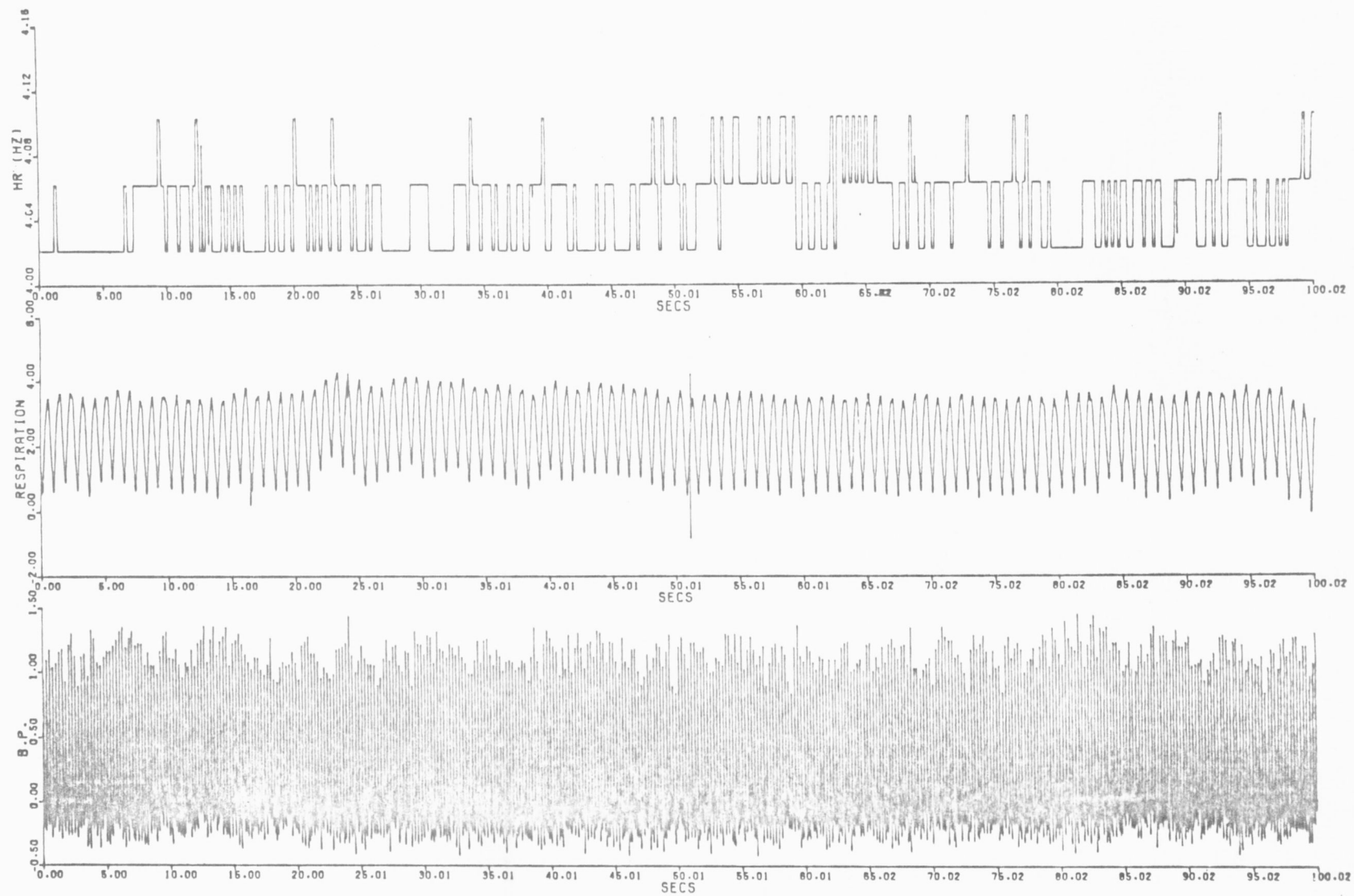
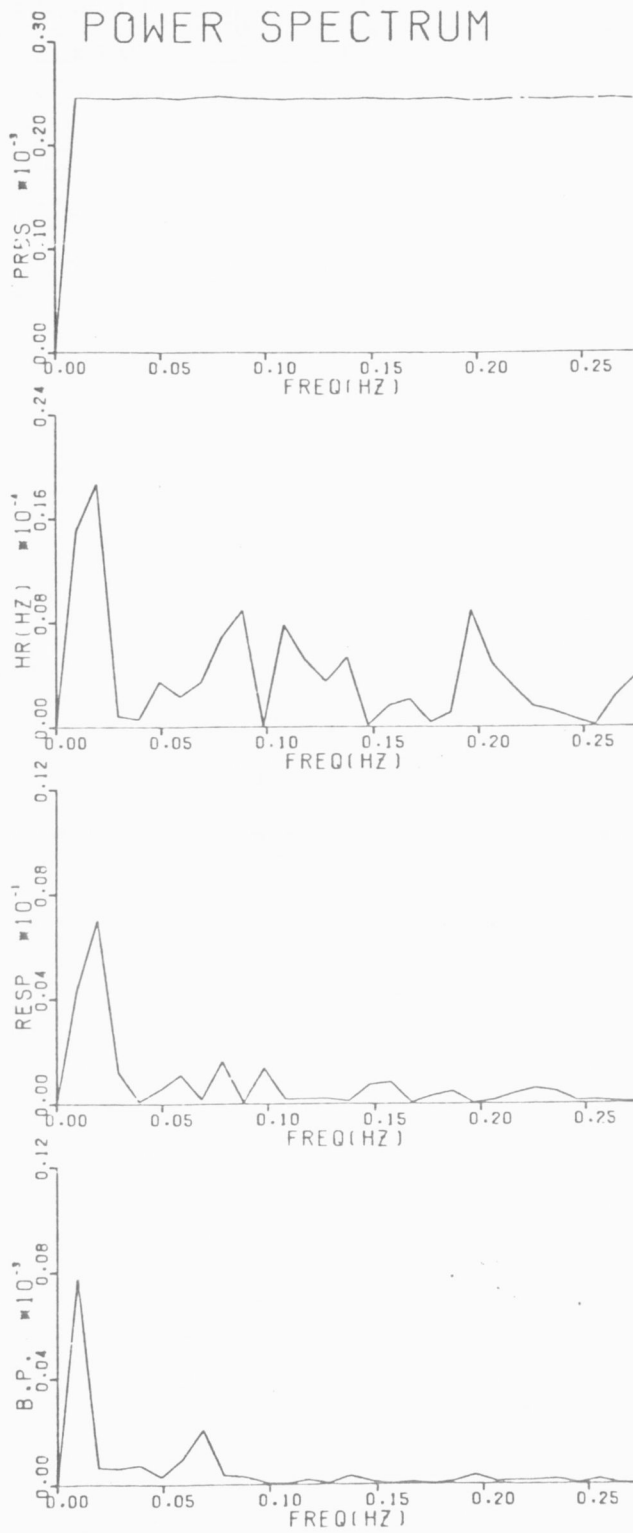


Figure 51a





## FREQUENCY RESPONSE

Figure 51b.

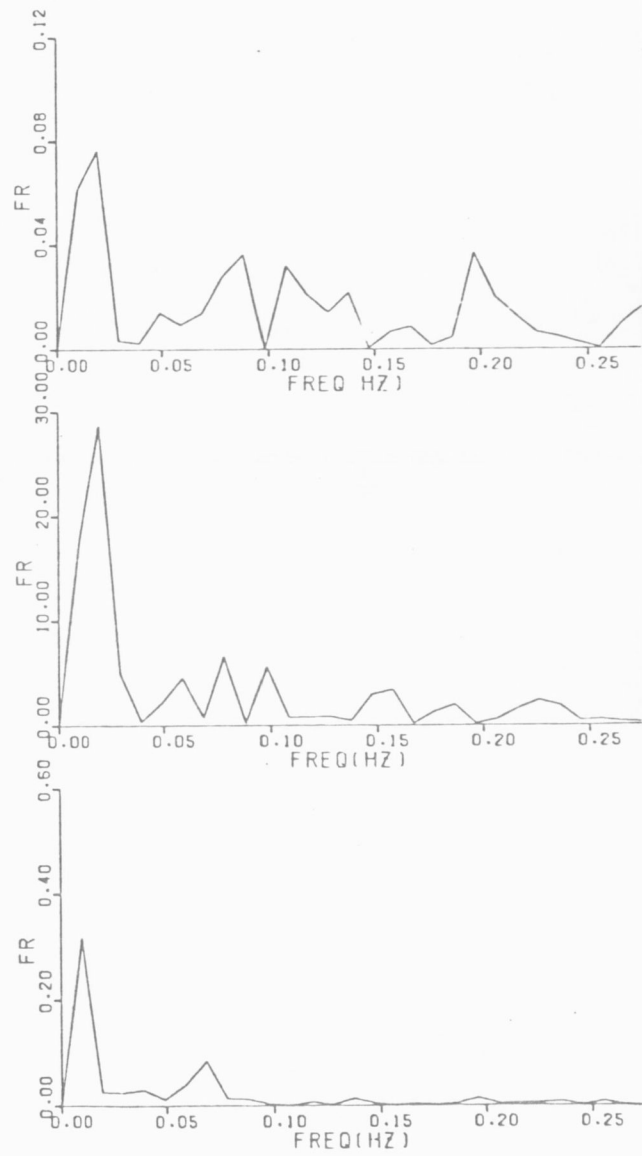
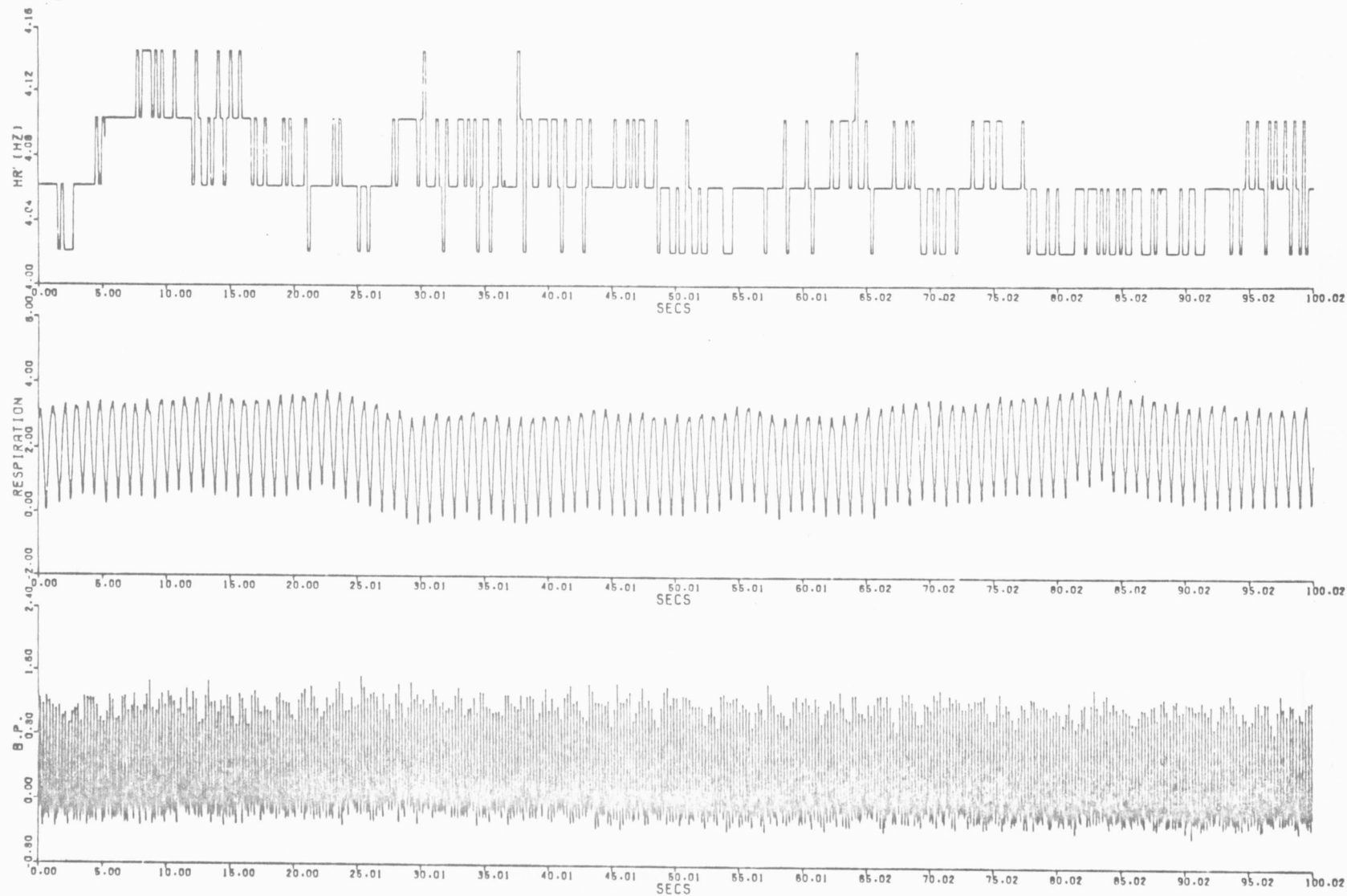
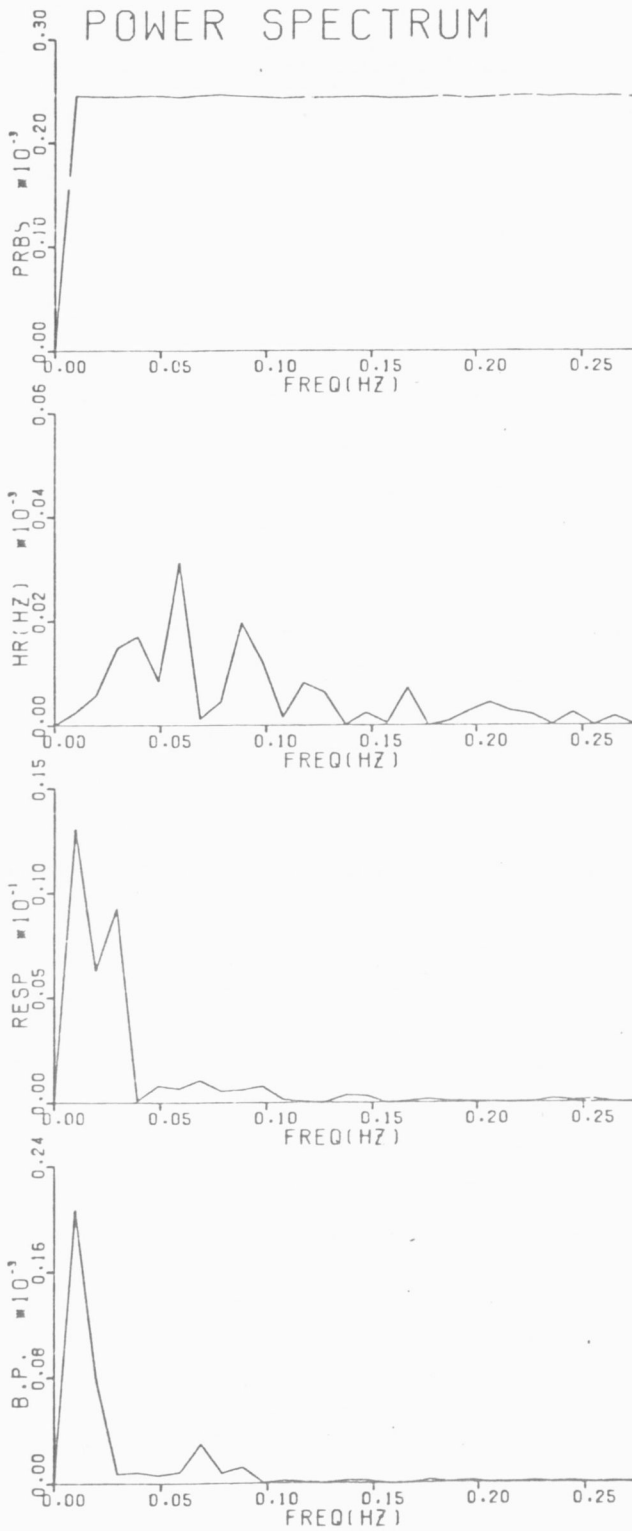


Figure 52a





### FREQUENCY RESPONSE

Figure 52b.

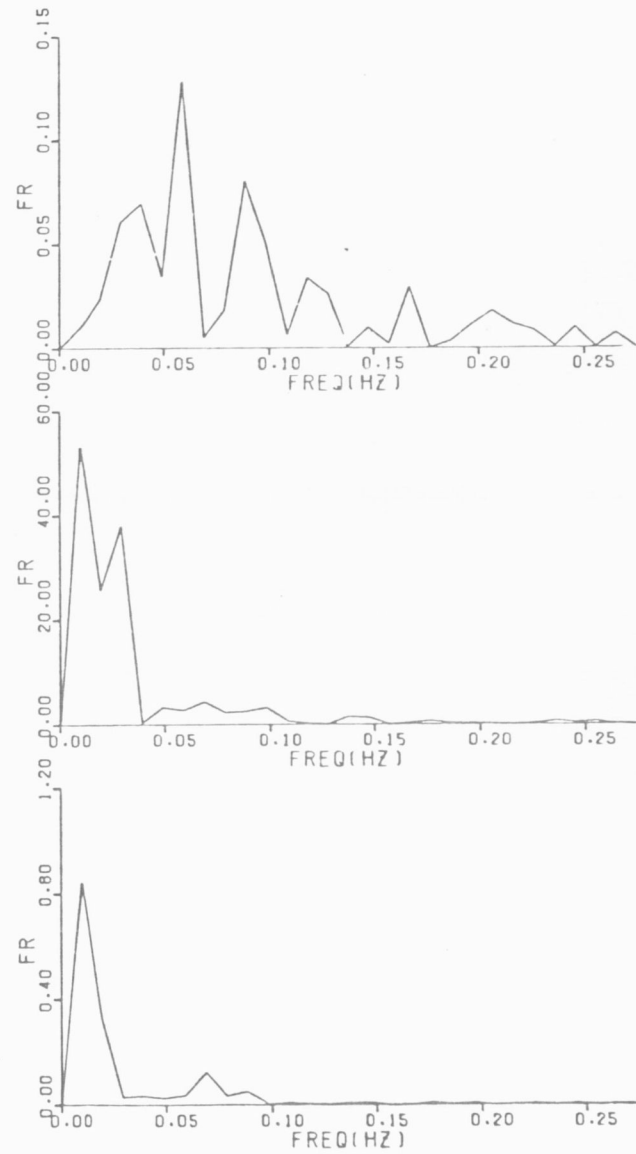
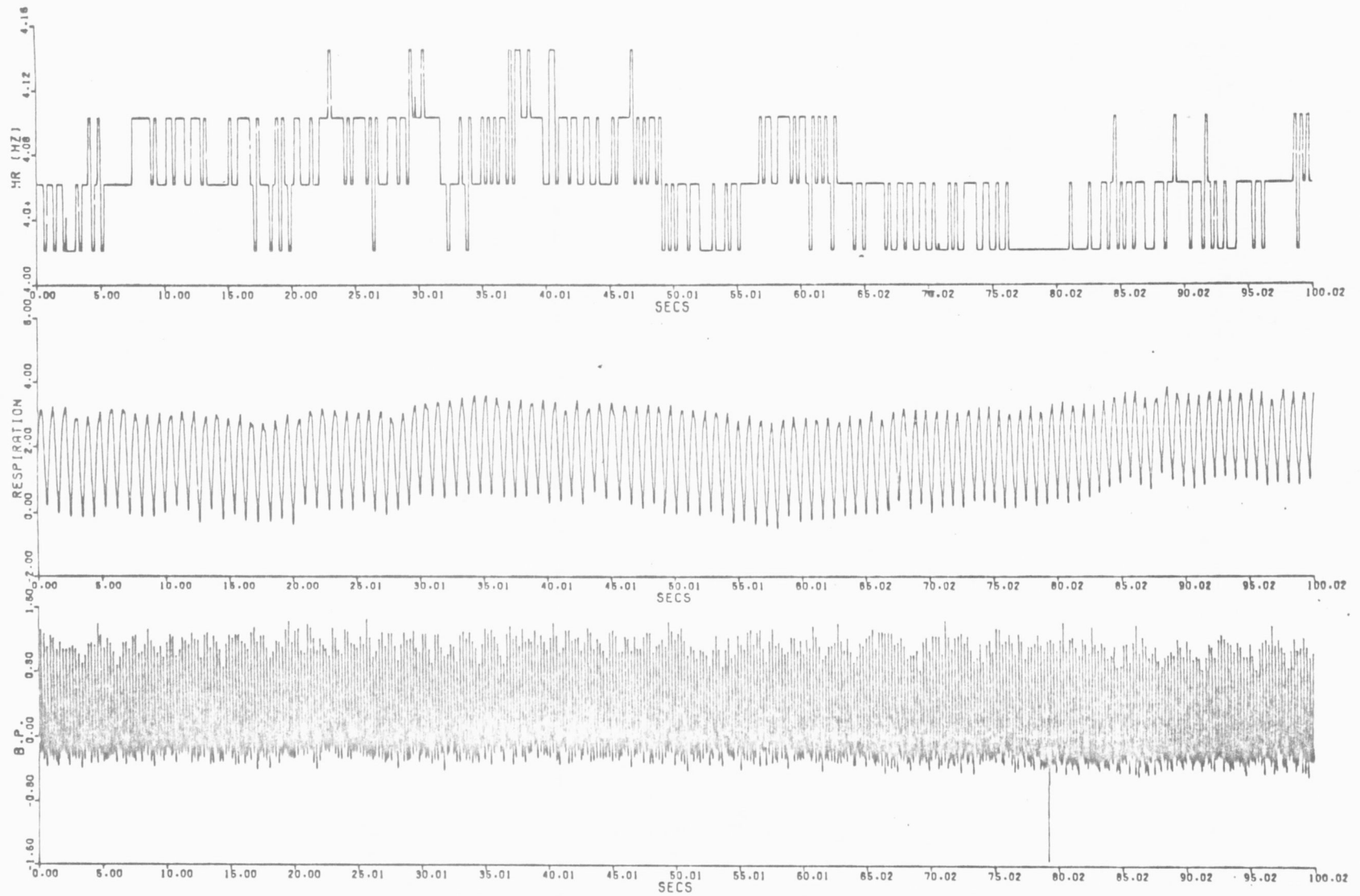
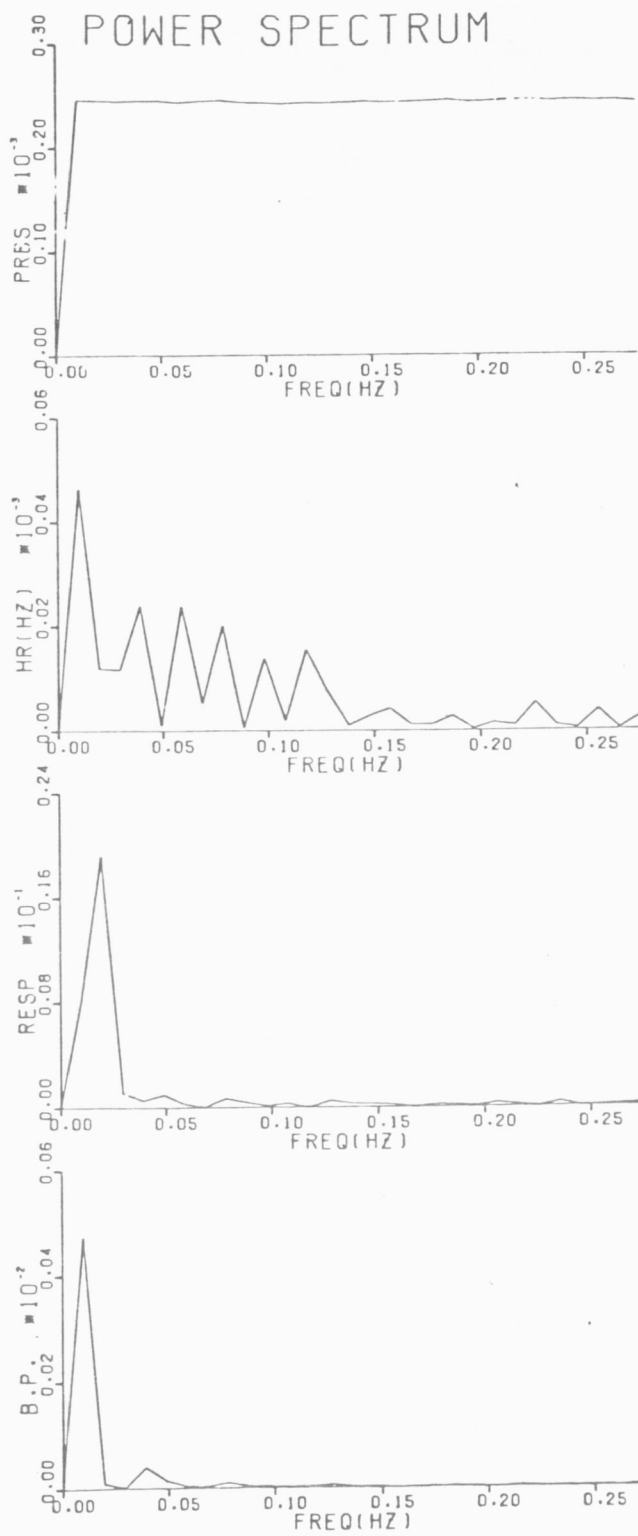


Figure 53a





### FREQUENCY RESPONSE

Figure 53b.

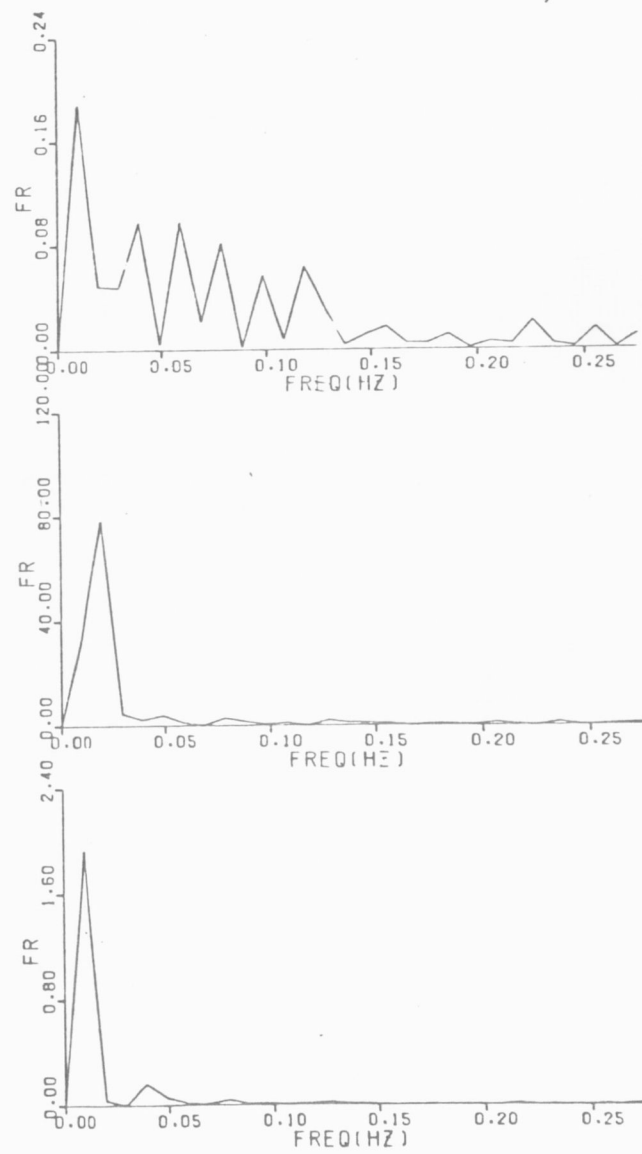
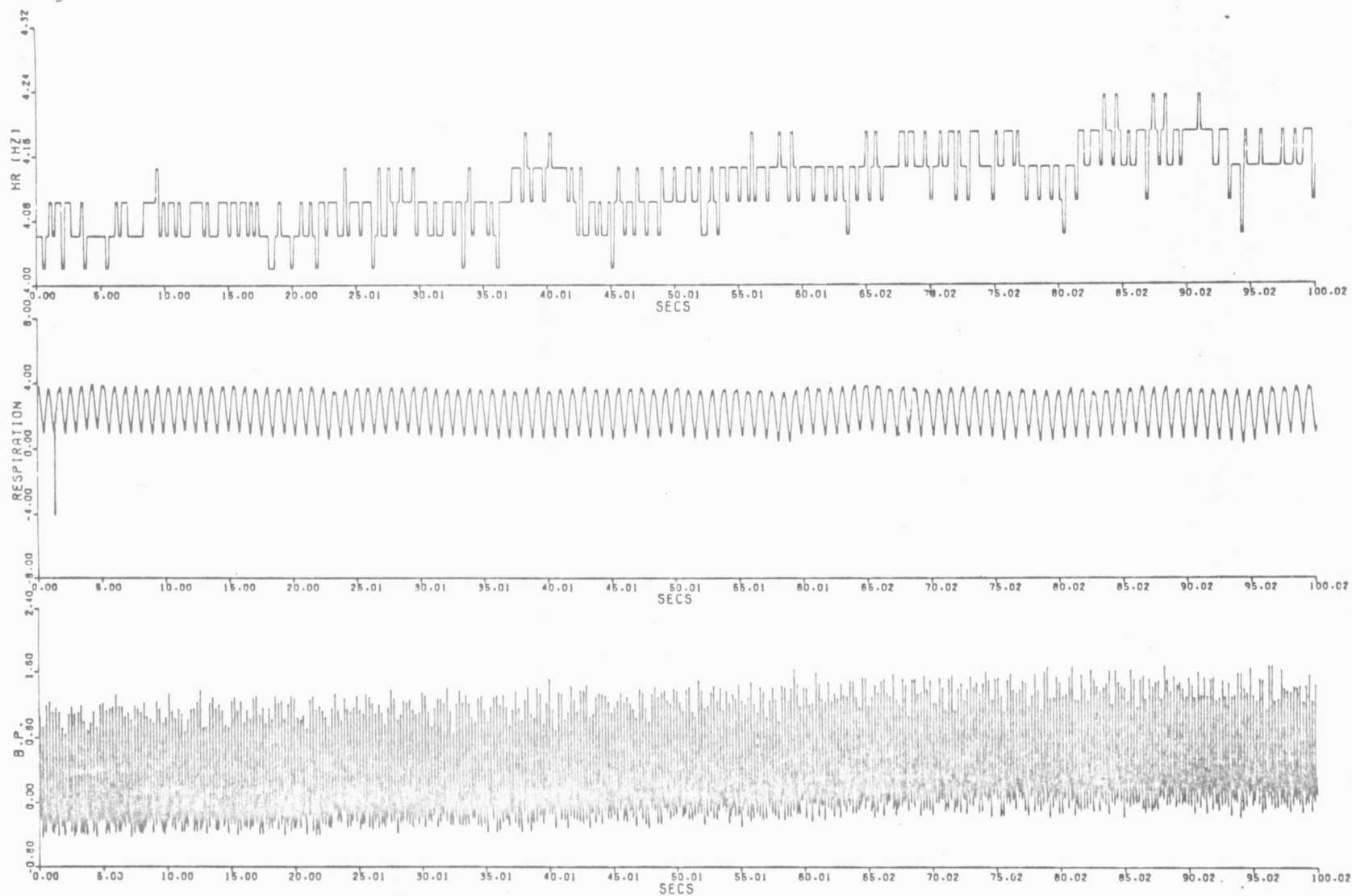
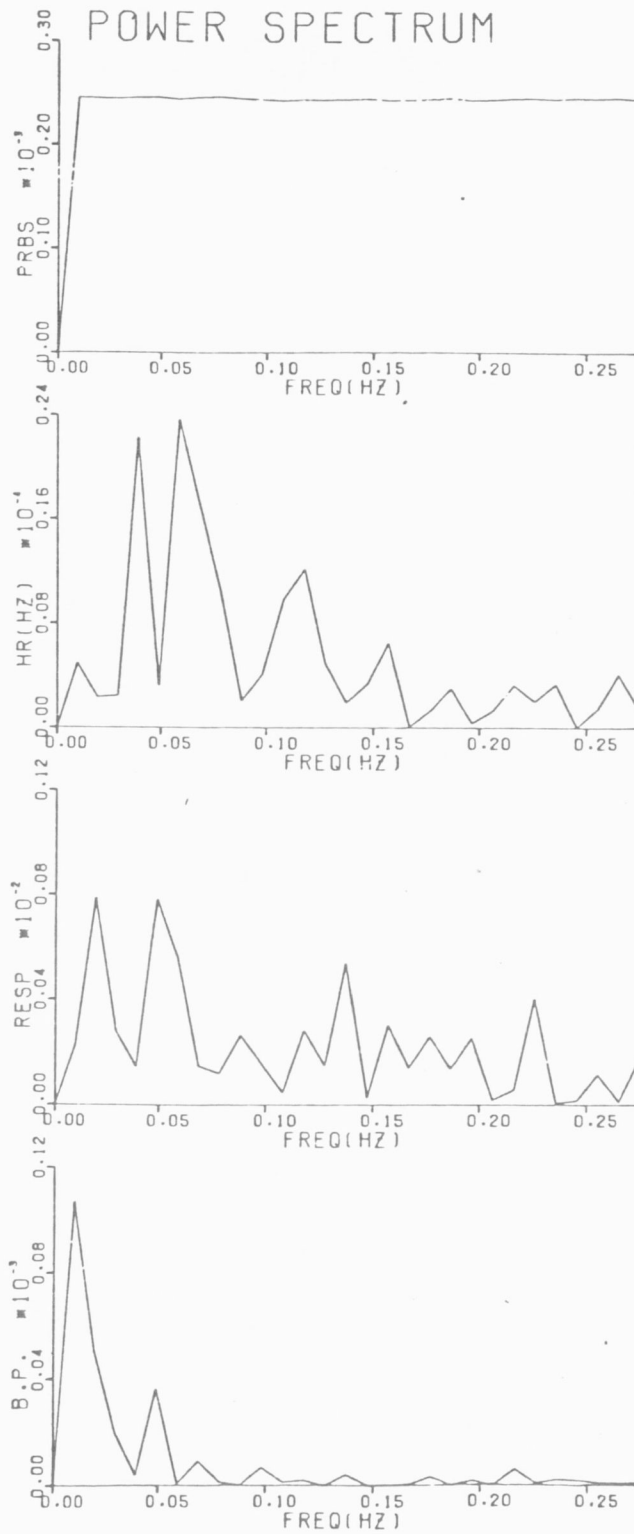


Figure 54a





## FREQUENCY RESPONSE

Figure 54b.

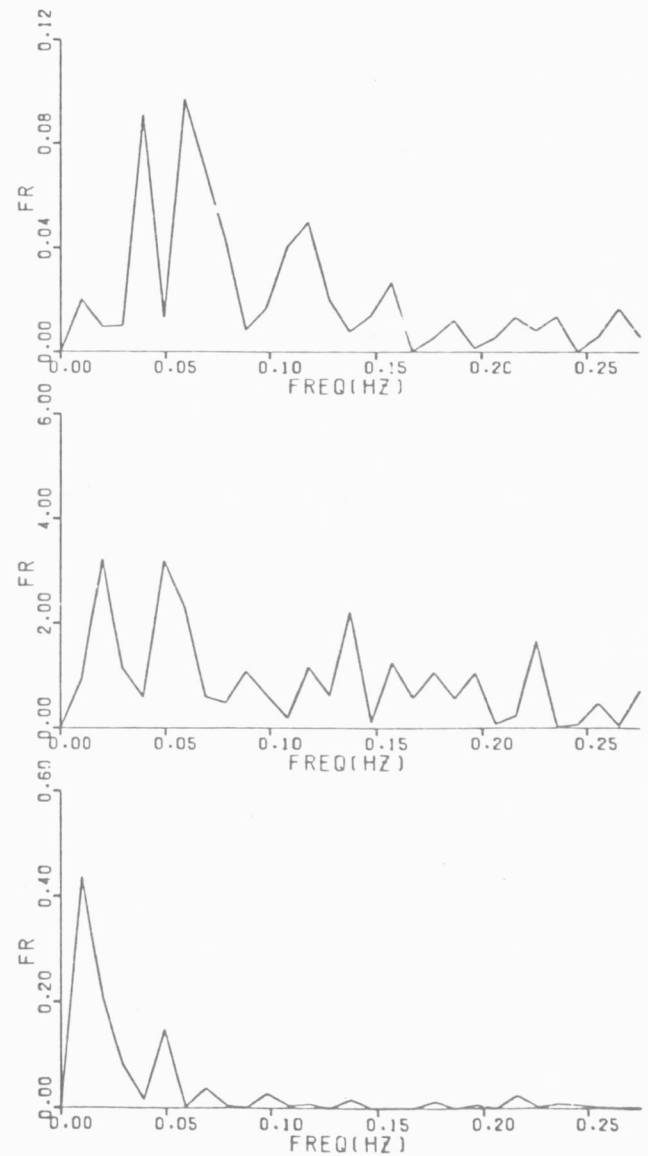
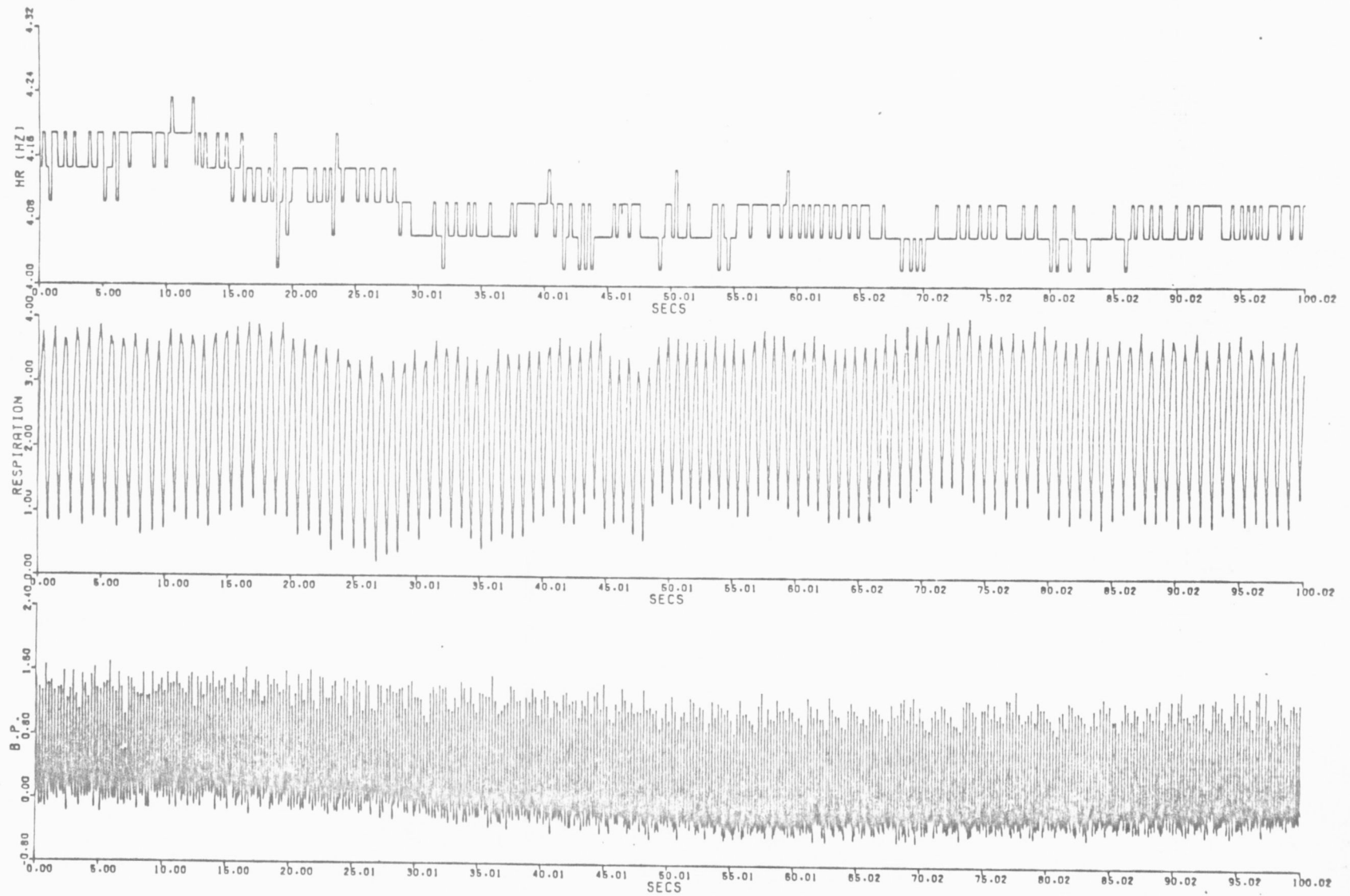
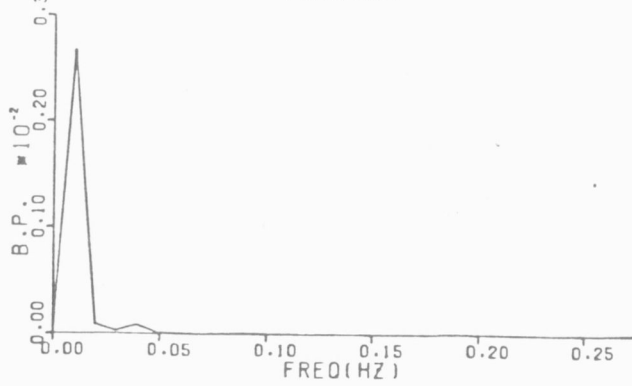
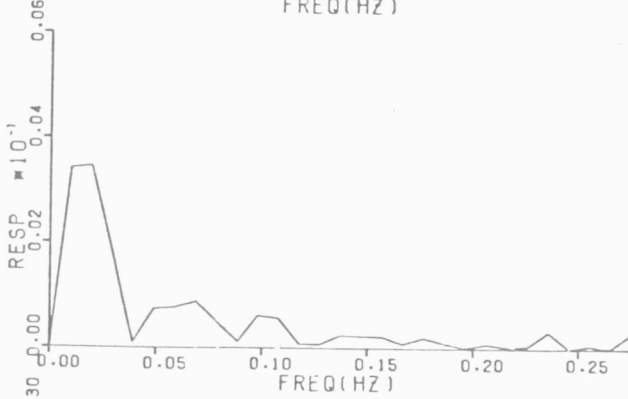
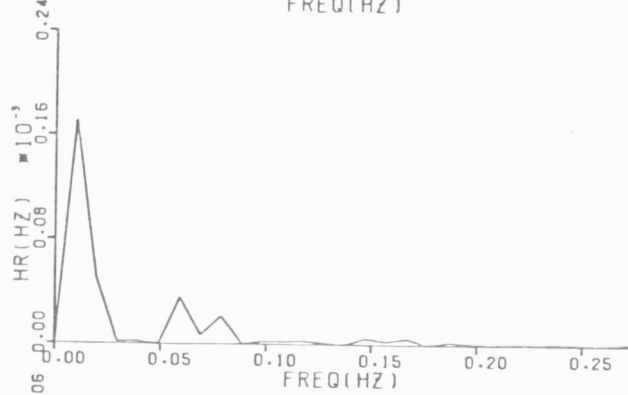
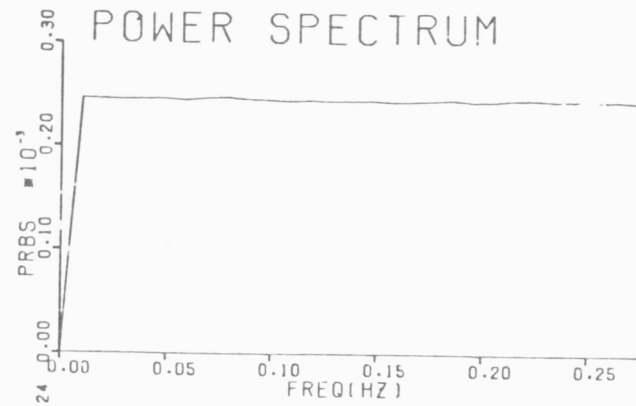


Figure 55a





### FREQUENCY RESPONSE

Figure 55b.

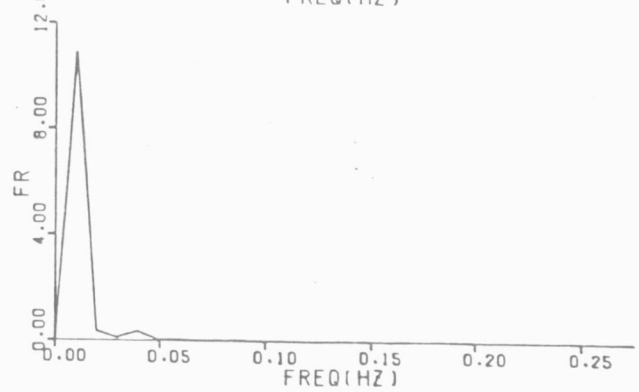
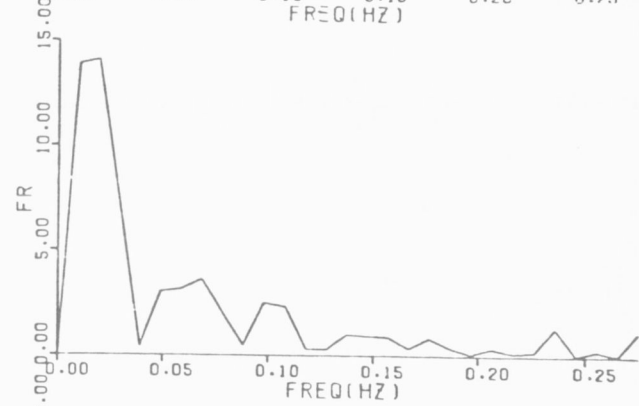
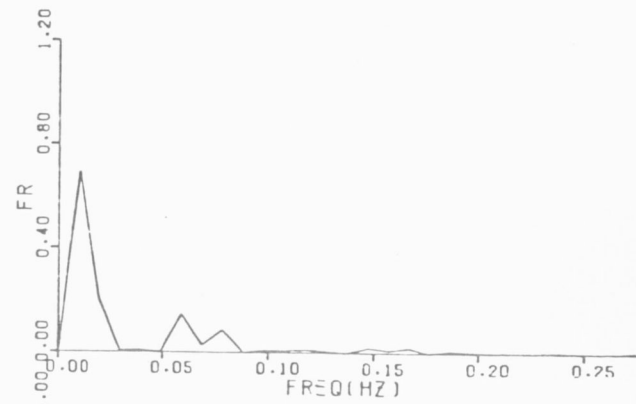
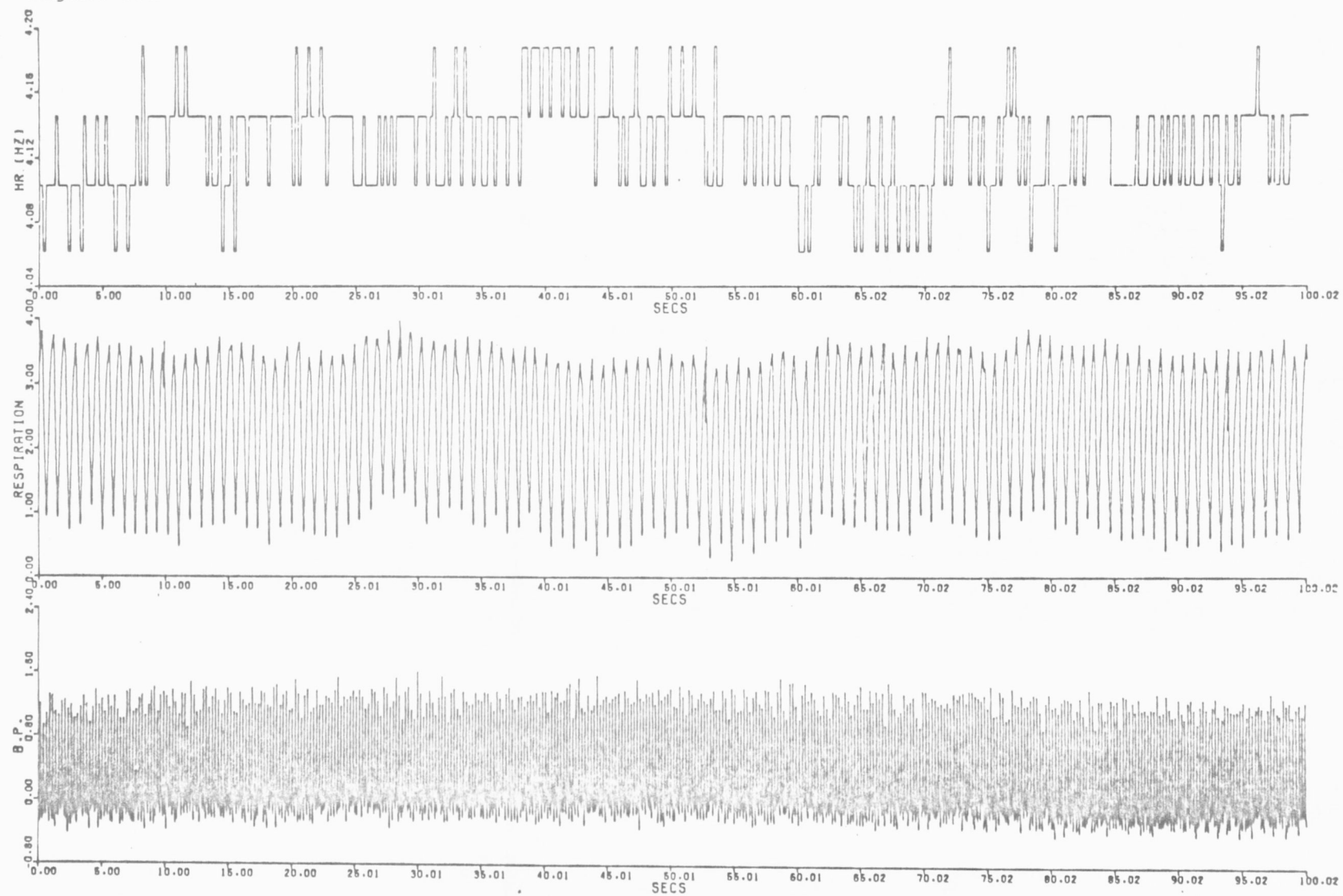
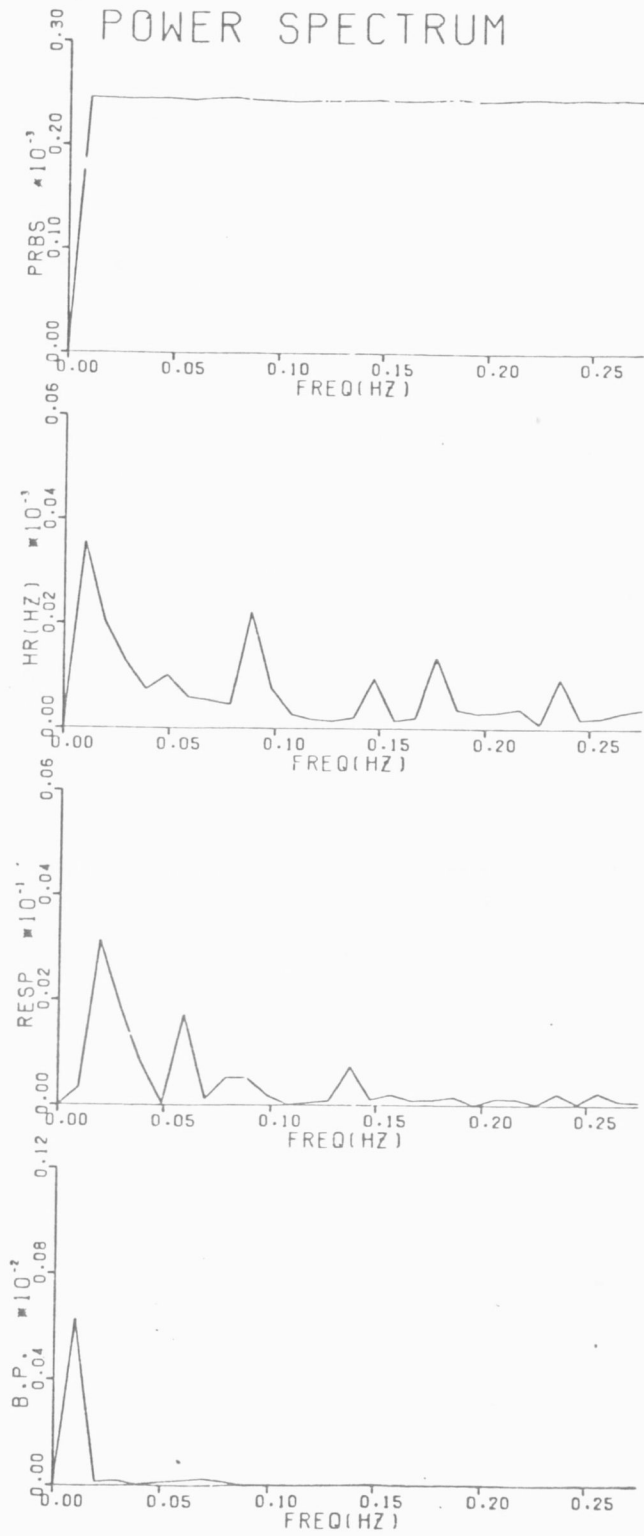


Figure 56a





### FREQUENCY RESPONSE

Figure 56b.

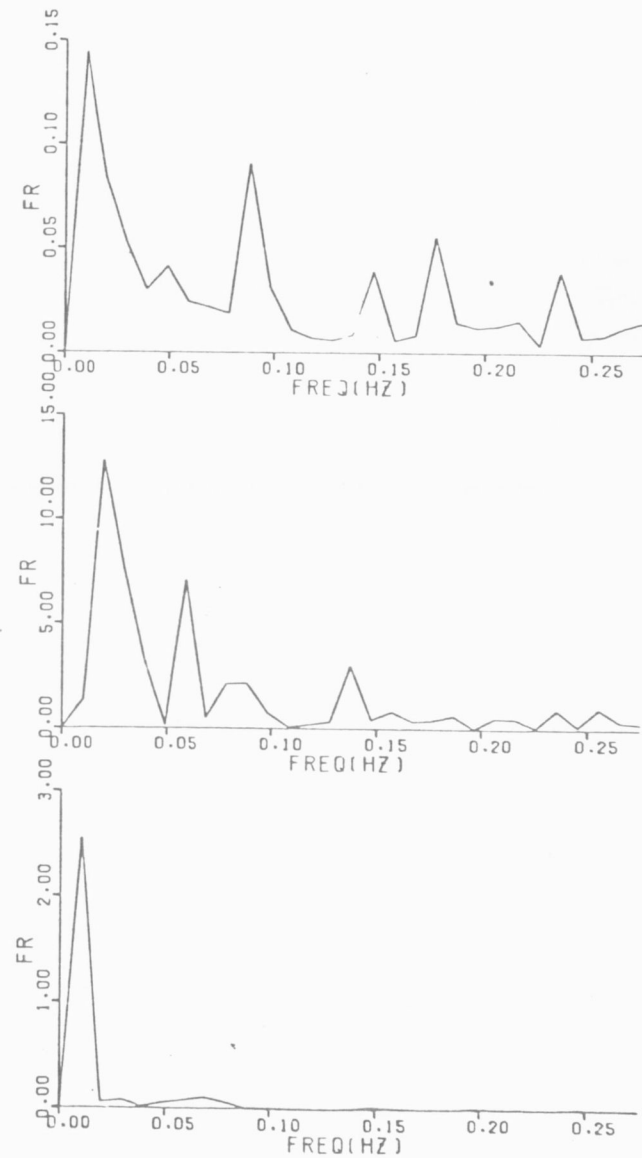
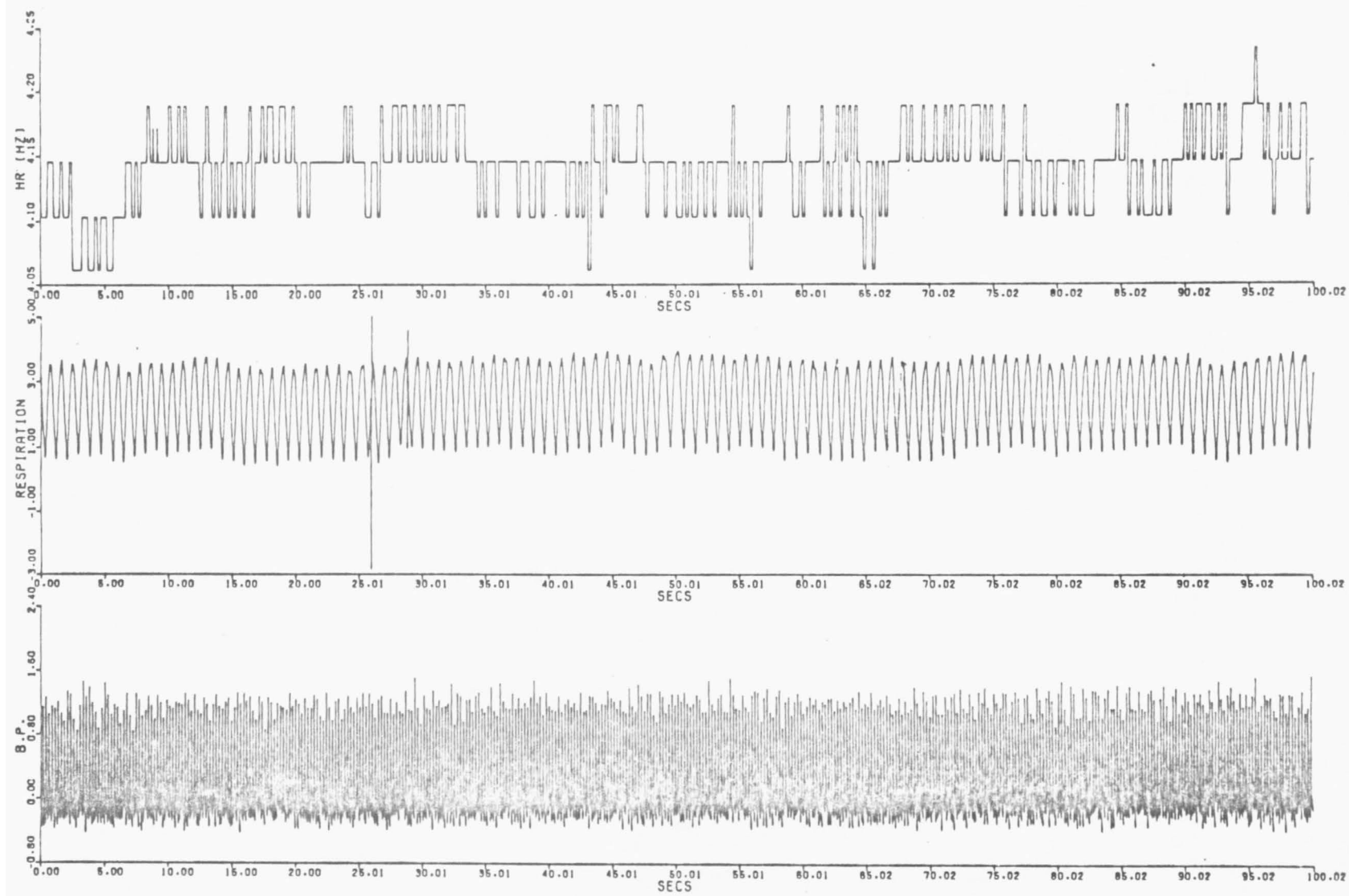
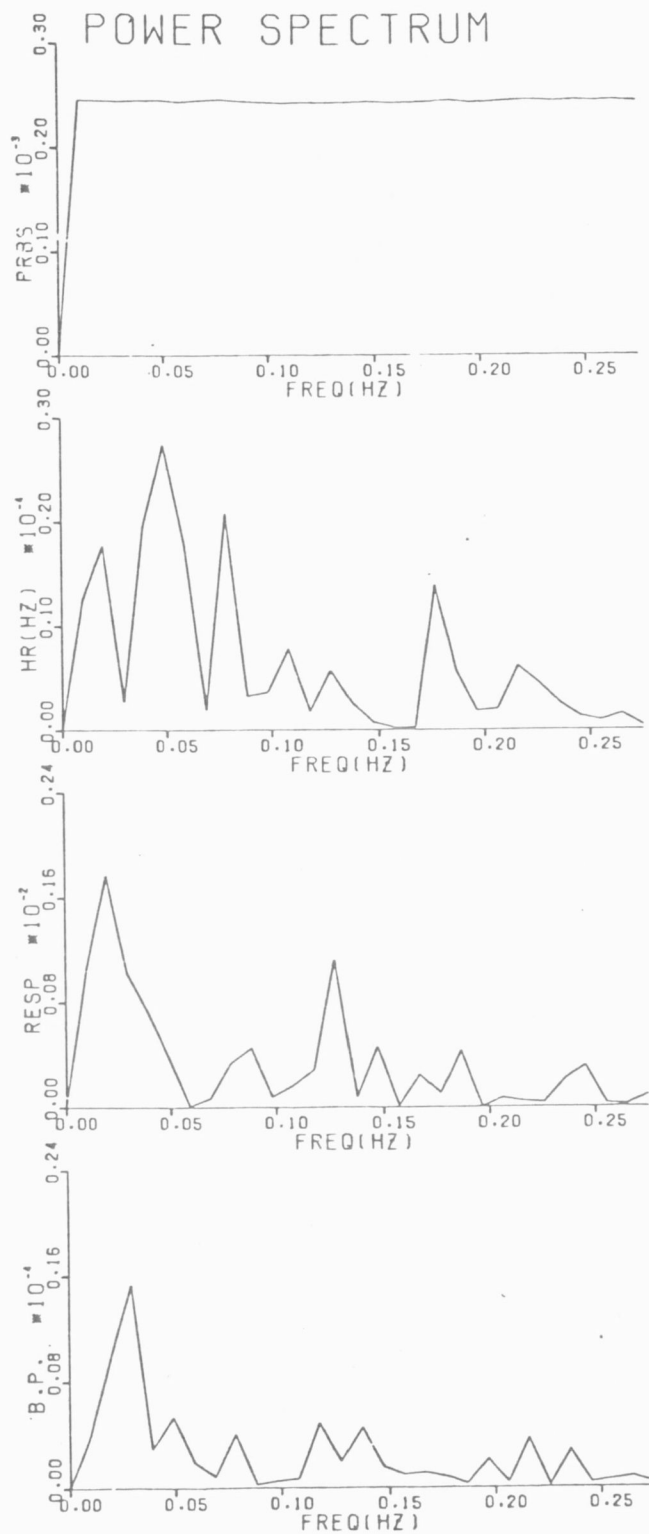


Figure 57a





### FREQUENCY RESPONSE

Figure 57b.

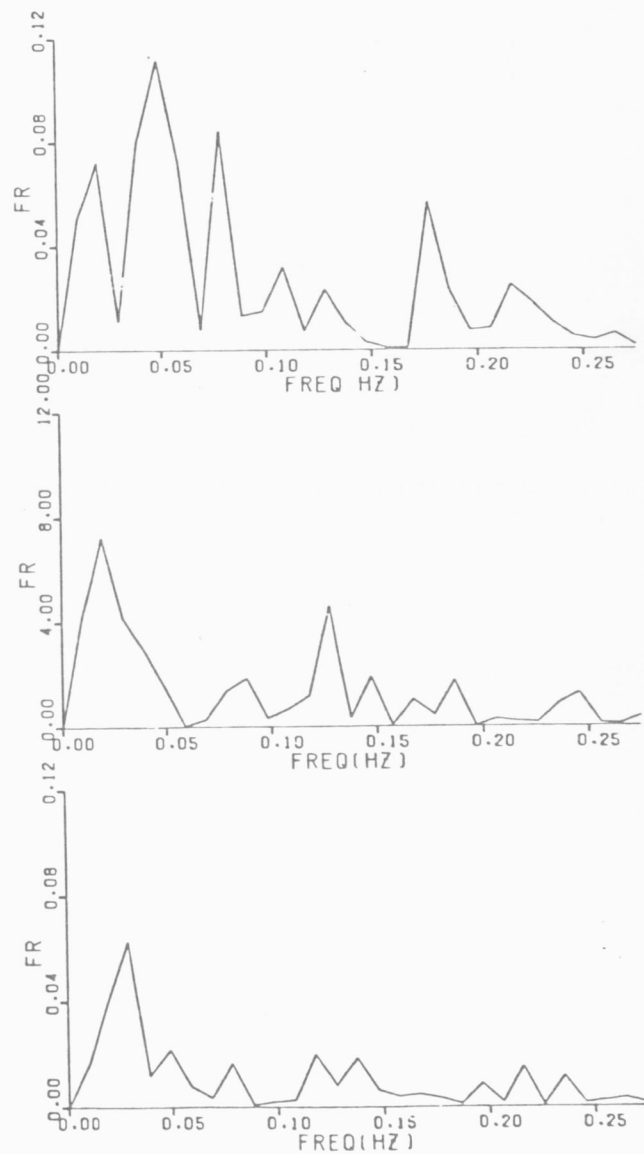
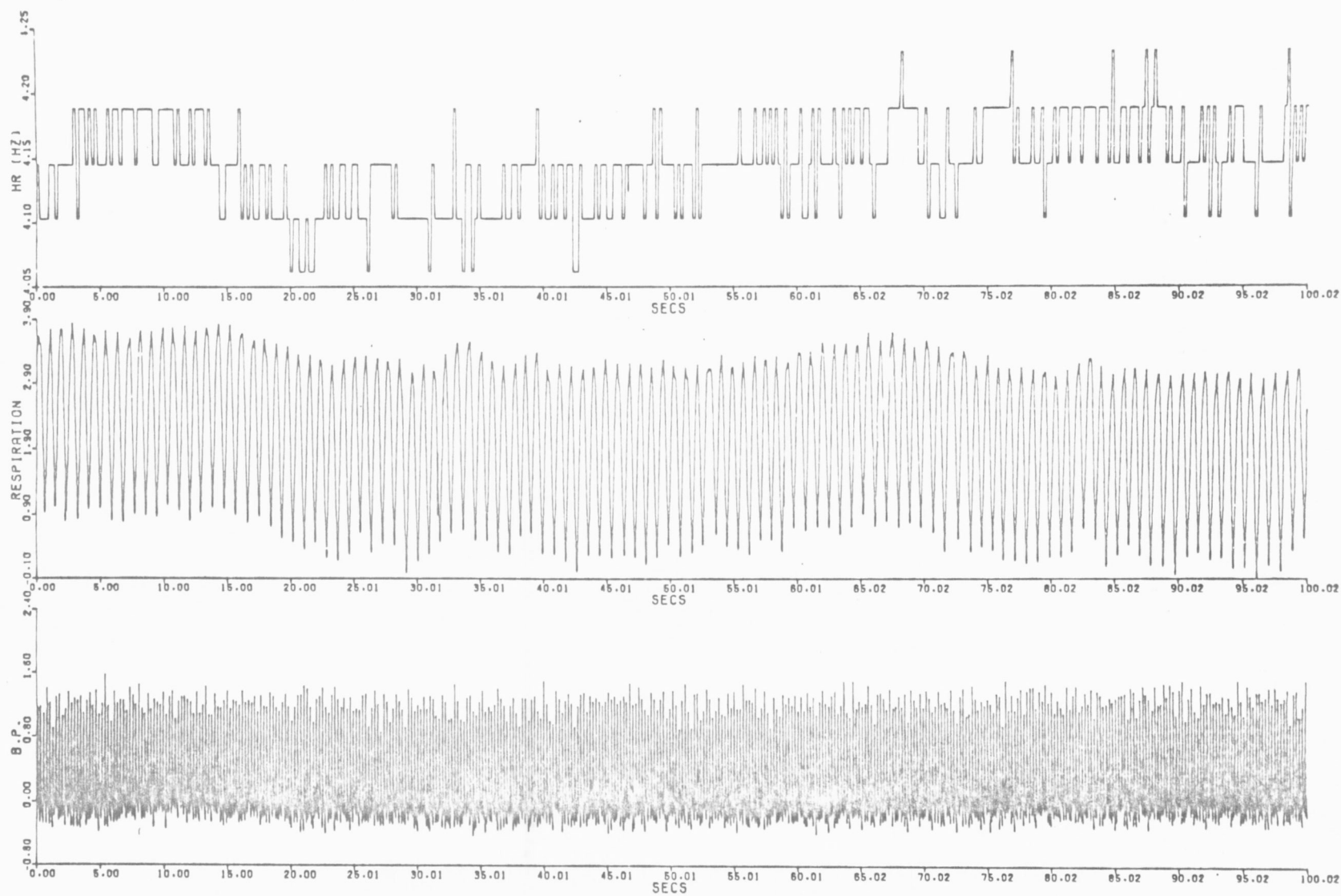
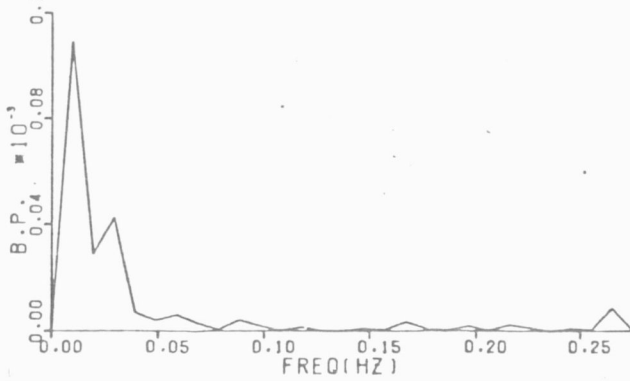
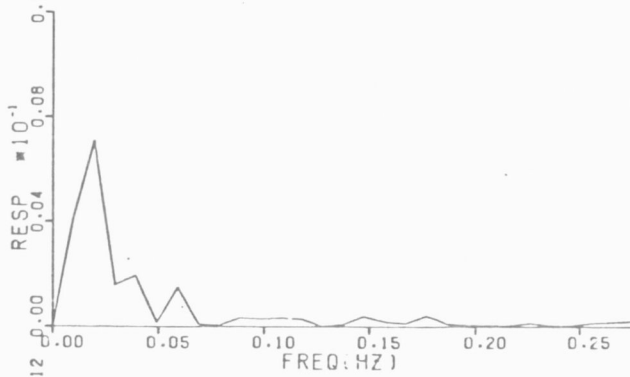
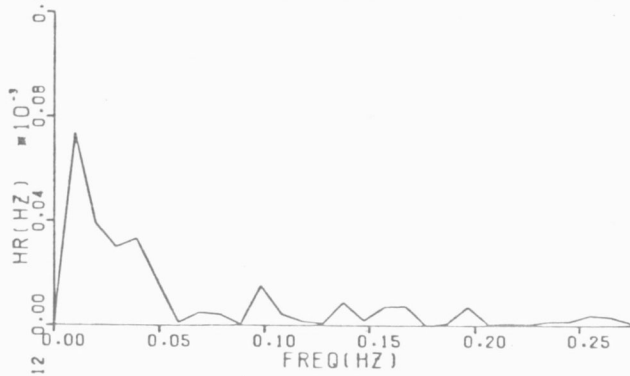
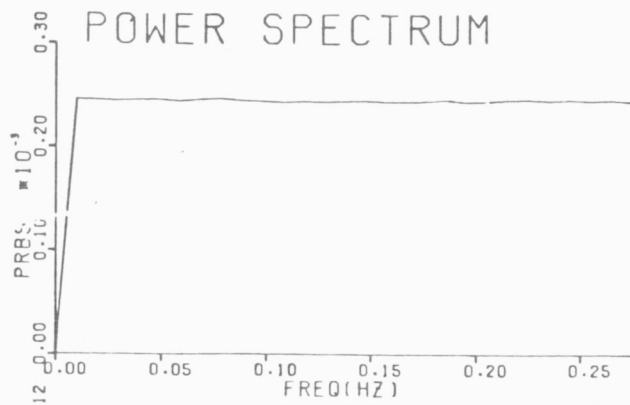


Figure 58a





## FREQUENCY RESPONSE

Figure 58b.

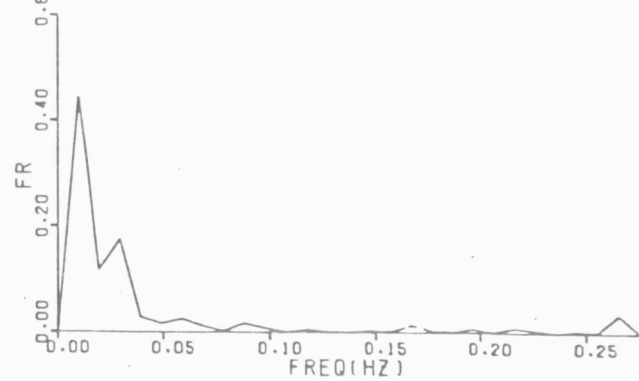
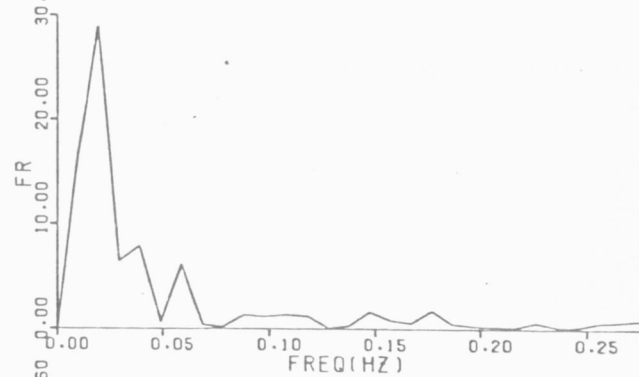
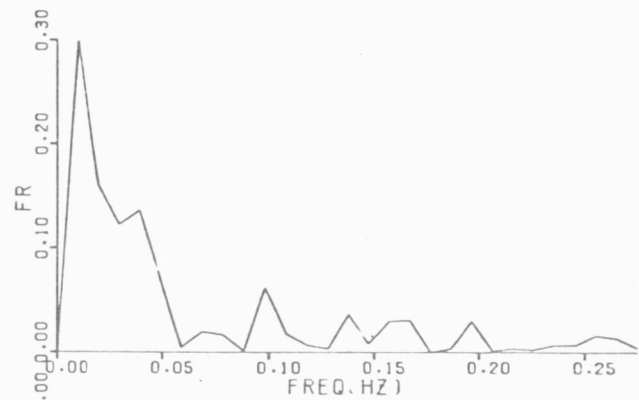
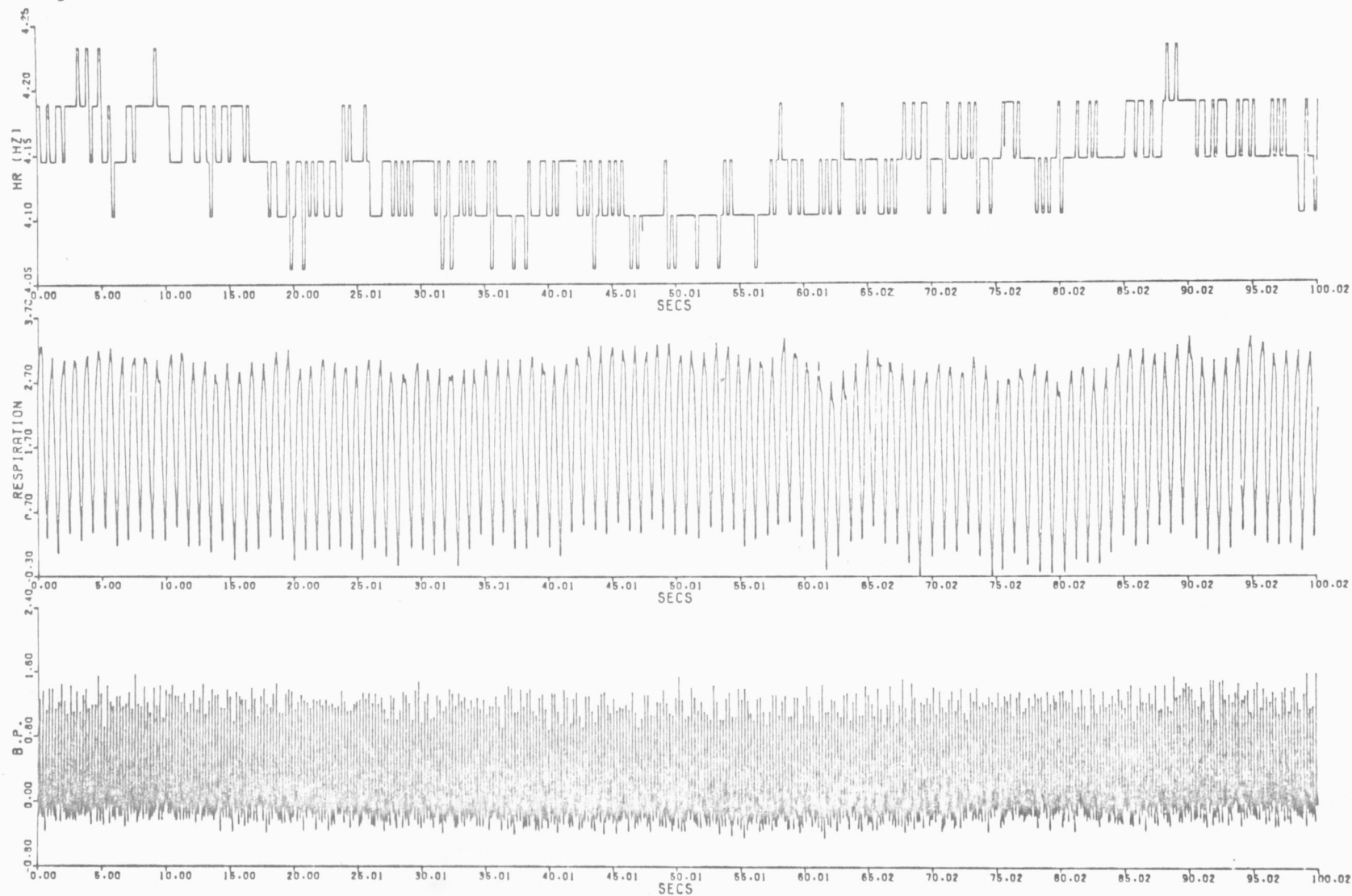
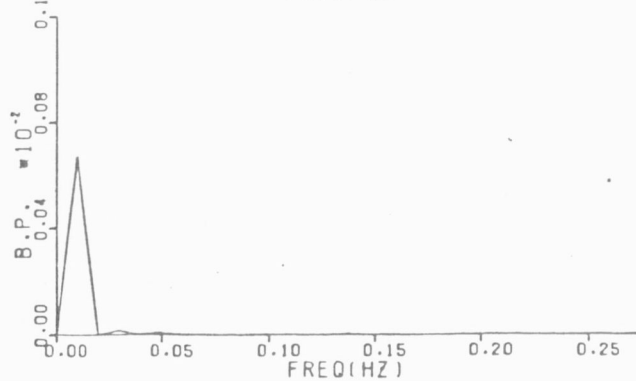
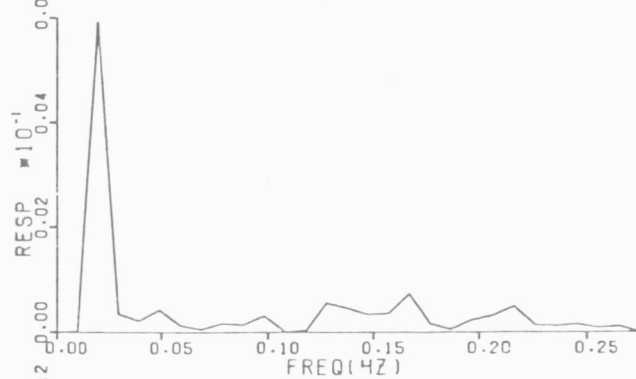
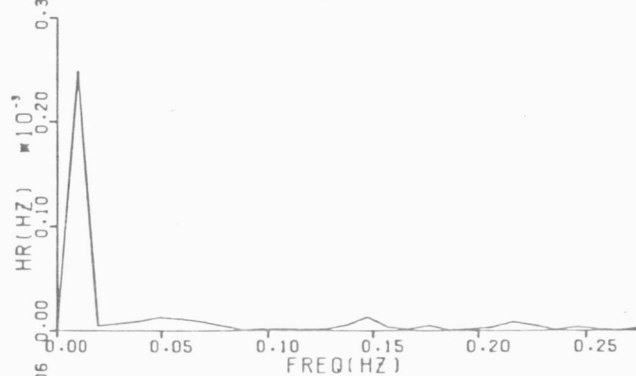
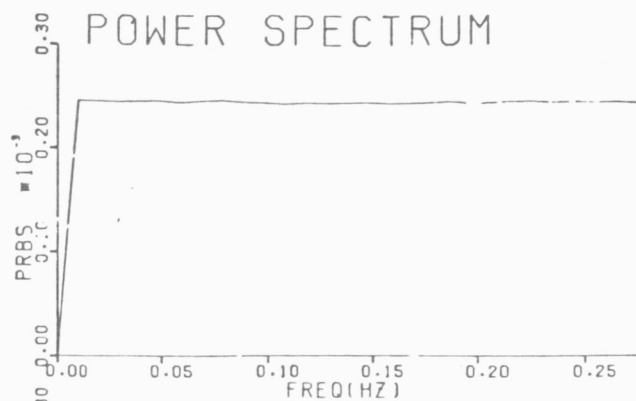


Figure 59a





### FREQUENCY RESPONSE

Figure 59b.

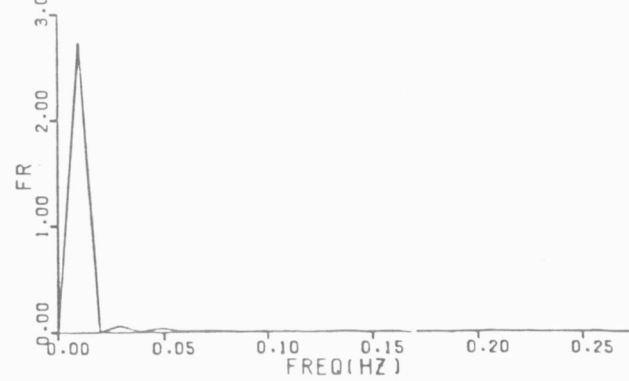
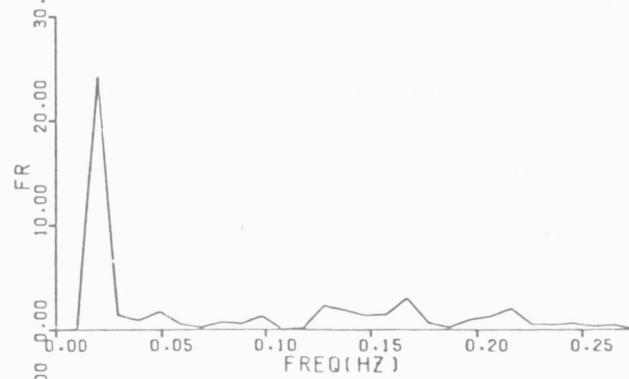
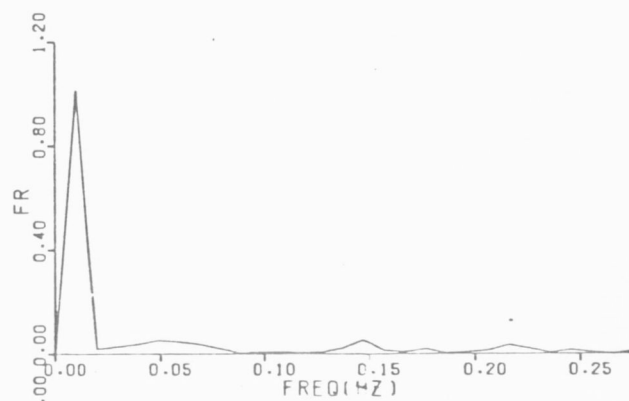
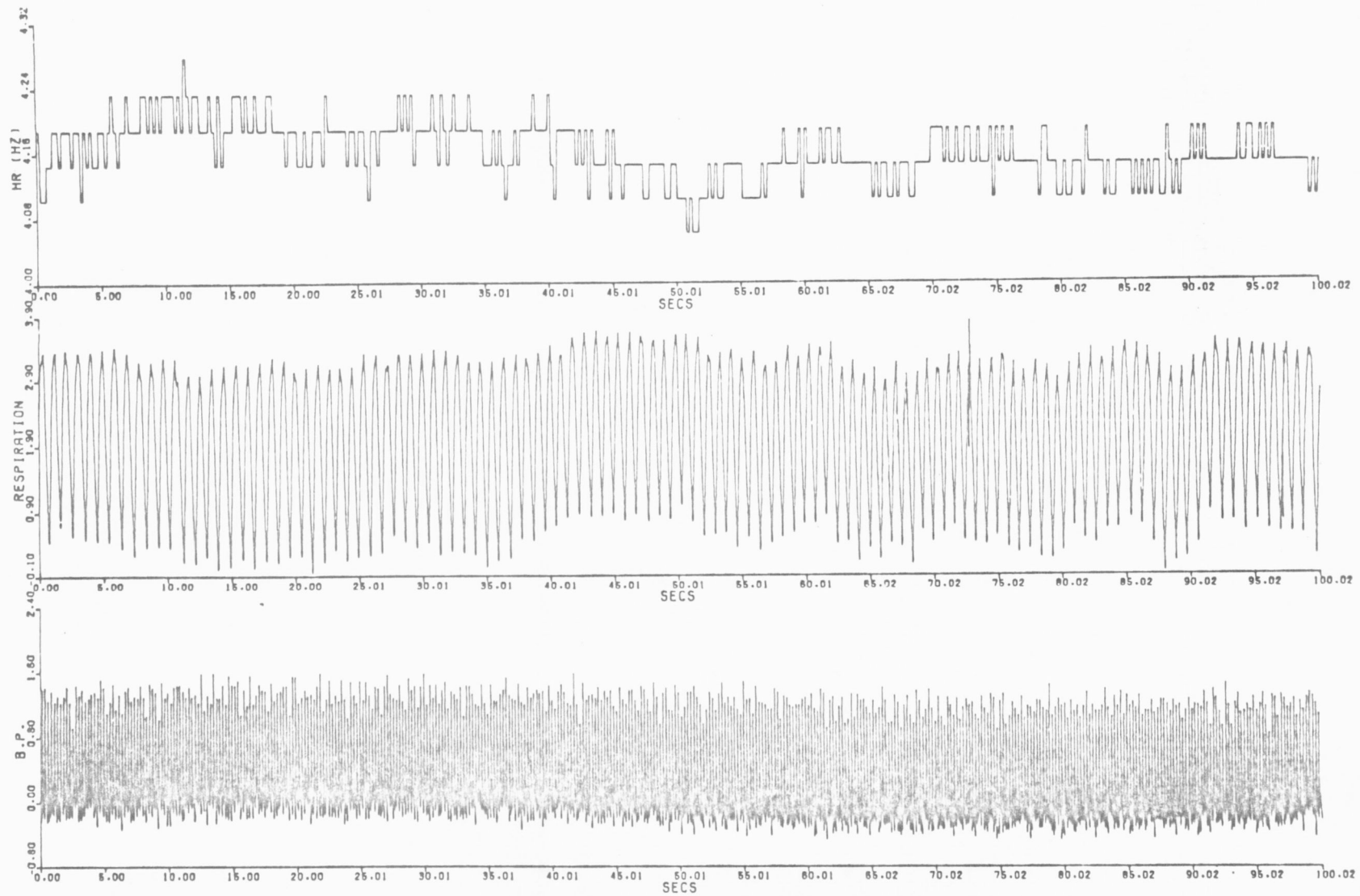
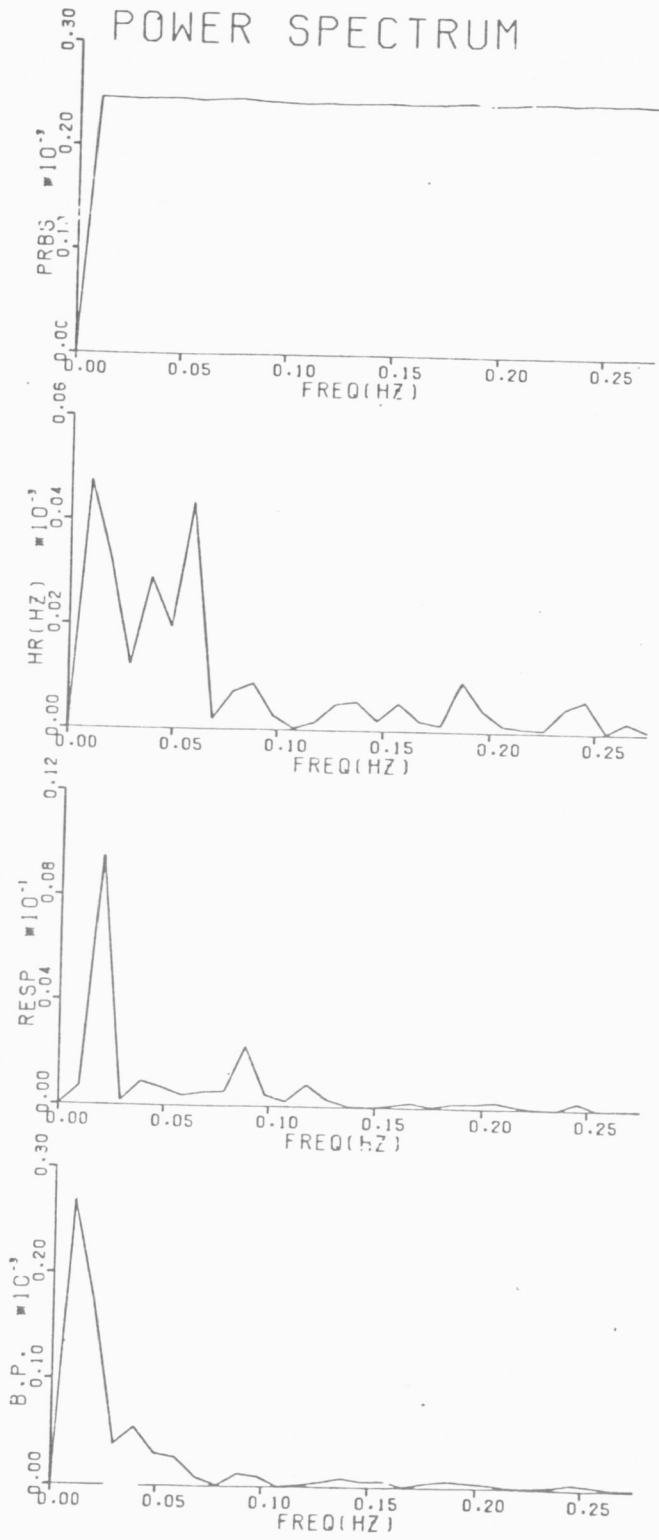


Figure 60a





FREQUENCY RESPONSE

Figure 60b.

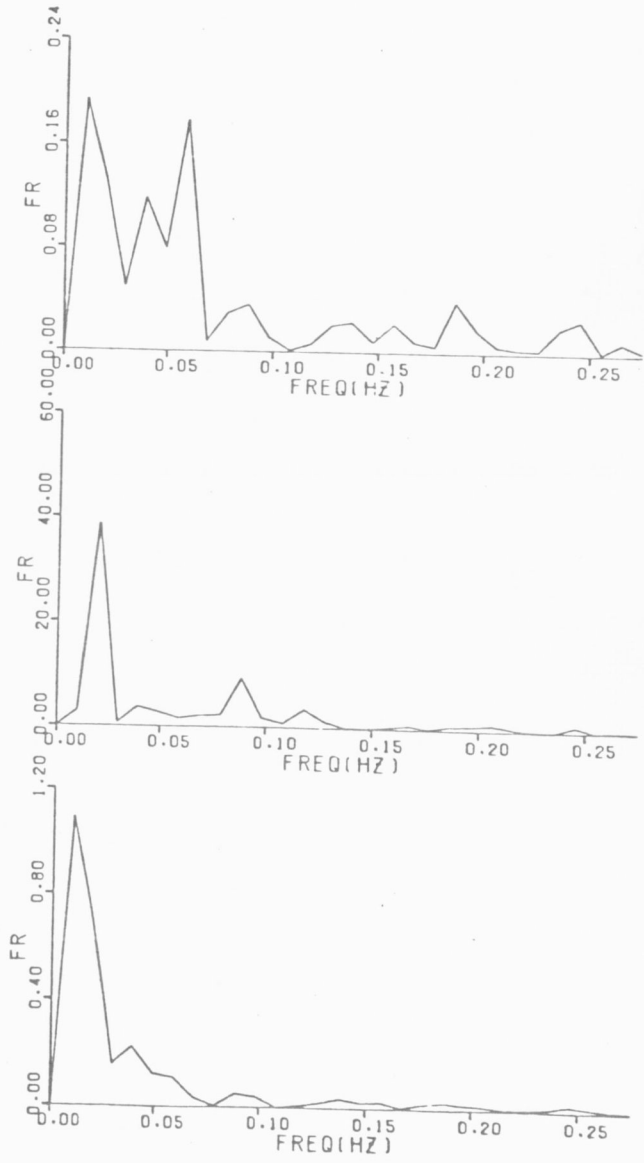
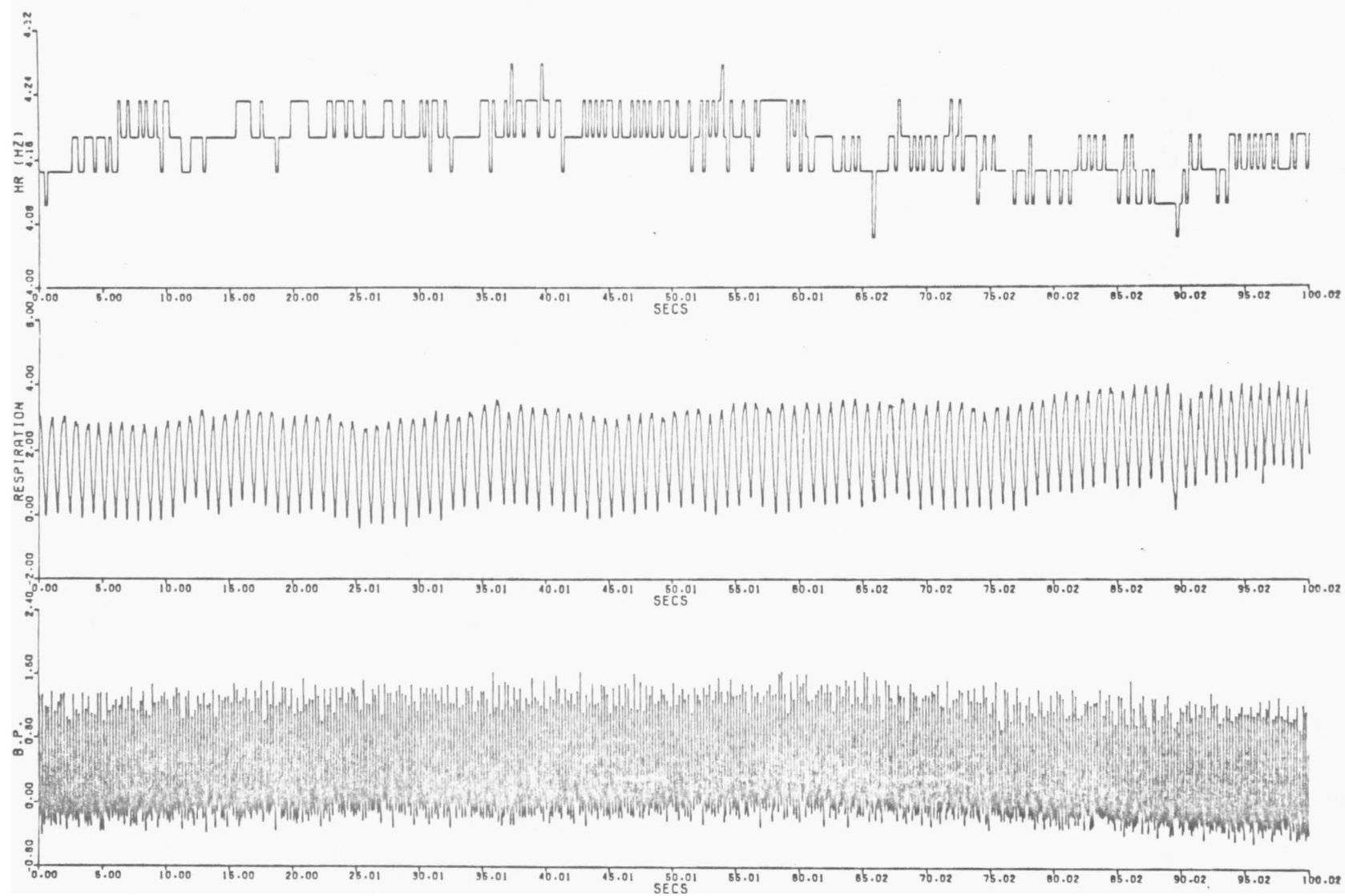
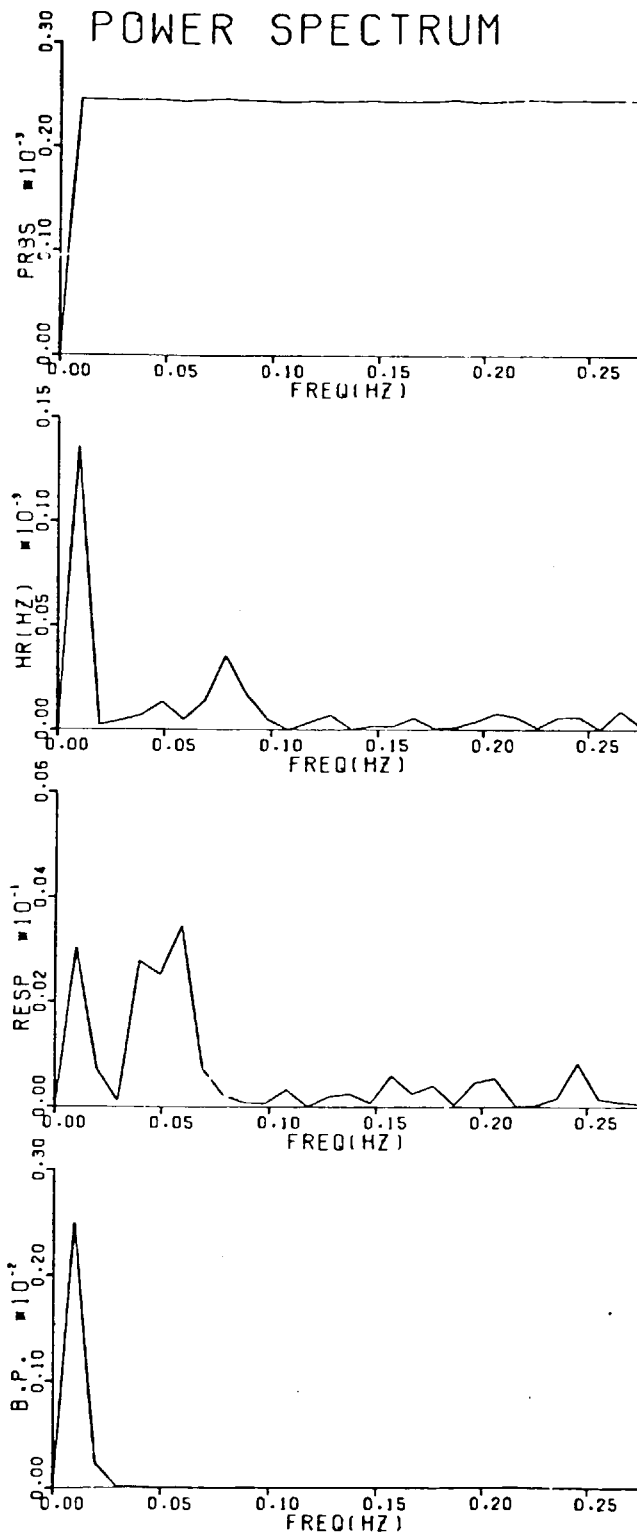


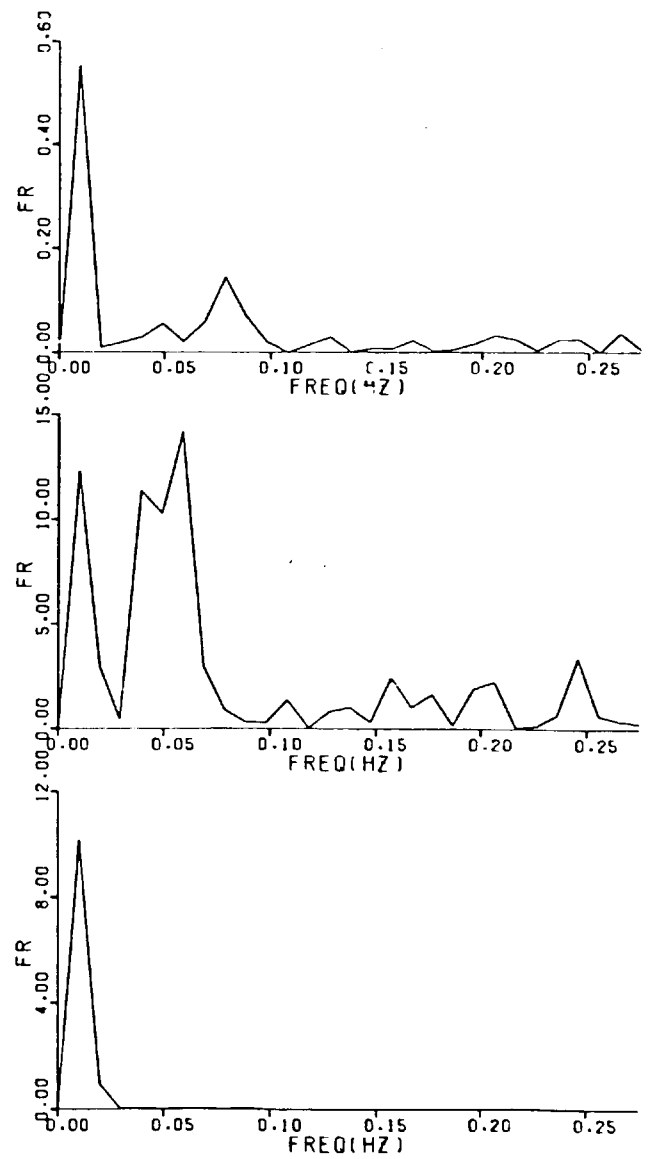
Figure 61a





# FREQUENCY RESPONSE

Figure 61b.



the transformed data.

For clarity, all illustrations of the stages involved in processing the data (Figures 40 to 68) refer to the same experiment.

It was found that most of the spectral activity for the H.R. and B.P. signals took place below 0.3Hz., a figure which is supported by the work of Hatakeyama (1967) and Kitney (1979). The significant components for respiration are even more closely grouped at the low frequency end of the spectrum.

The spectral density plots of Figures 40 to 61 represent only half the information conveyed by the F.F.T. Section 3.3 represented the Fourier Series as

$$f(t) = A_0 + \sum_{n=1}^{\infty} A_n \cos(n\omega t) + B_n \sin(n\omega t)$$

This can be re-expressed as

$$f(t) = C_0 + \sum_{n=1}^{\infty} C_n \cos(n\omega t + \theta_n)$$

where

$$C_n = \sqrt{A_n^2 + B_n^2} \quad (\text{amplitude spectrum})$$

and therefore

$$P_n = A_n^2 + B_n^2 \quad (\text{power spectrum})$$

The rest of the Fourier information is therefore contained in the phases,  $\theta$ , defined as

$$\theta_n = -\text{Atan}(B_n / A_n).$$

Figure 62 clarifies these equations by demonstrating their trigonometric relationship.

The phase information derived from the F.F.T. can be used without modification only if the original signal was centred around zero time. If the signal was displaced from zero time, the phases returned by the F.F.T. have an increased value, such that

$$\theta_{nt_1} = \theta_{nt_0} + (360nt_1)/T$$

where n is harmonic number,

T is the period of the signal,

and  $t_1$  is the time shift from zero.

The result is that a slope is imposed upon the original phases (Sutton, 1976).

The range of possible phases returned by the F.F.T. are limited to values between  $\pm 180$  degrees. If the slope due to shifting reaches either limit, the next harmonic value will be represented by a "fold" in the phase spectrum. Thus, an actual phase decrease from  $-150^\circ$  to  $-200^\circ$  will result in returned values of  $-150^\circ$  and  $+160^\circ$ .

In the present case, as with most biological data the signals being transformed are complex, and signal power is not distributed simply. It was not therefore possible to establish "zero time" (i.e. power equally distributed about zero) prior to transformation. The resulting phase information contained many slopes (and consequently many folds) corresponding to different features of the signal being displaced from zero time.

To restore the true phase information, it was necessary to retrace the steps taken in forming the phases. This was done by a programming algorithm (Jennings, 1981) which performed the following procedure:

- 1) F.F.T. phases were unfolded on the basis of minimum shift between harmonics, yielding values not constrained between  $\pm 180^\circ$
- 2) A regression line was fitted to the unfolded data, and removed.

3) Steps 1 and 2 were repeated until all phases lay between  $+180^\circ$ .

Figure 63 gives examples of the data before and after the algorithm was used. Better results were obtained if only the high power portion of the phase spectrum was unfolded. This prevented components due to noise biasing the regression line. Formation of the frequency spectra in this way formed the basis for all subsequent data manipulation leading to a definition of the control system. A quantitative investigation of the harmonics which comprise the frequency response for each part of the system is the subject of the first part of the next chapter. The succeeding sections show how the frequency response estimates were used in system identification.

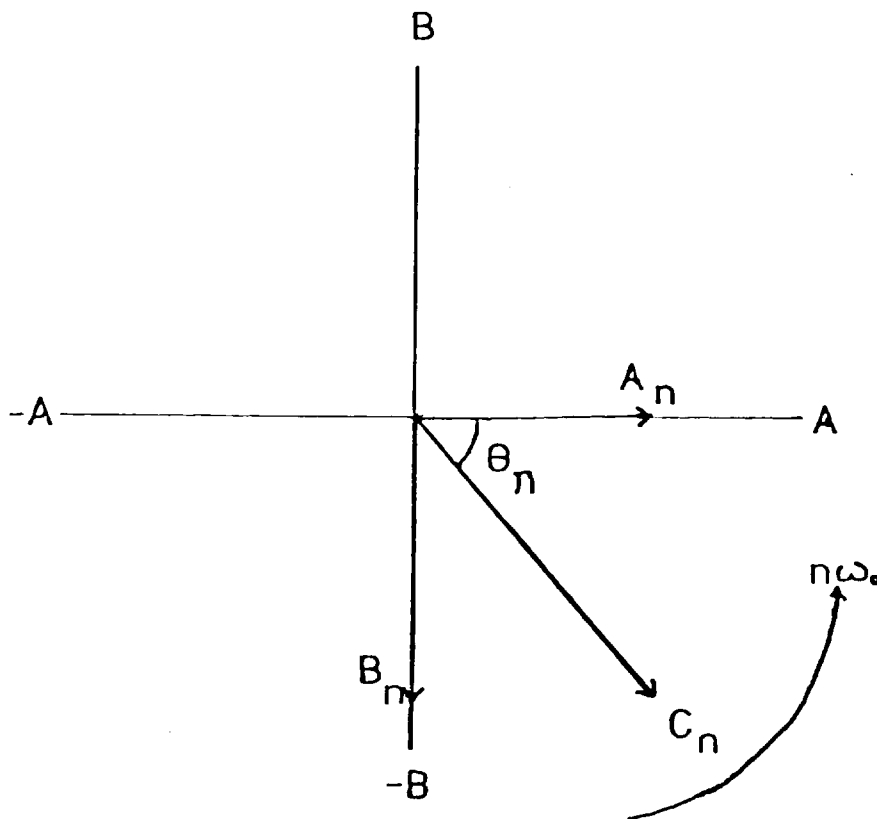


Figure 62. Vector diagram illustrating the trigonometric relationship between real and imaginary numbers.

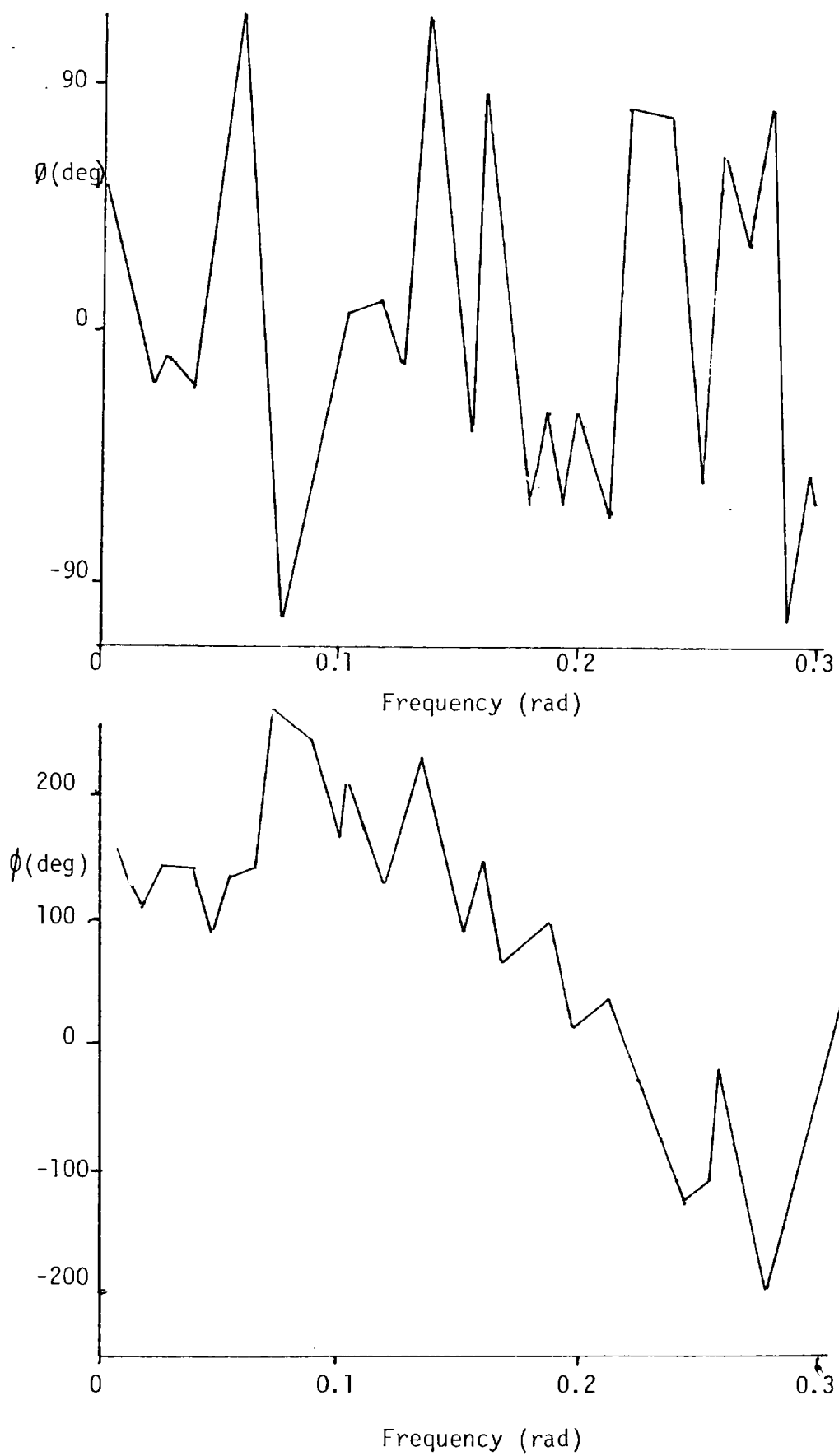


Figure 63. Diagram illustrating the difference between phase values before and after unwrapping.

#### 4.7 Summary

A series of experiments was carried out which resembled the pilot study except that the cardiac depressor stimulus was the PBRS defined in Chapter 3. In order to render the PBRS a suitable neural stimulus, it was Pulse Frequency Modulated to yield a signal which deviated by  $\pm 10$  Hz about a central frequency of 30, 50, 70 or 90 Hz. Each P.R.B.S. used for the experiments consisted of continuous identical sequences.

As before, the data collected from the experiments was digitized and the Heart Rate signal formed. Since subsequent analysis involved signal averaging, the data was treated in blocks corresponding to one PRBS repetition. Each block was Chirp-Z transformed to convert it to its frequency domain representation. A phase unwrapping algorithm was employed to remove the folds introduced by Fast Fourier Transformation.

## Chapter 5

Investigation of the frequency response of the baroreceptor loop.

### 5.1 Introduction.

As stated in section 3.3, the frequency response of a system characterises its steady state response. Moreover, the frequency response may be used to interpret system stability. The data collection experiments were carried out with the physiological pathways unbroken to improve the quality of the data. The quantity evaluated in this chapter is therefore the closed loop frequency response. The entire baroreceptor feedback loop was treated as a black box system, with an input of depressor nerve excitation and outputs of heart rate, blood pressure and respiration. Figure 26 illustrates the viewpoint taken.

Before frequency response estimation could be carried out (section 5.4), it was necessary to verify that the output data collected was

a) due to the P.R.B.S. input

and b) sufficiently stationary for the estimation to be valid

The methods whereby the validity of the data was established are the subject of the succeeding two sections.

Having obtained the system frequency response, the information was used to explore the system's characteristics in terms of its transfer function. This in turn was used as a model of the physiological system. The development of the transfer function and assessment of its usefulness as a tool for modelling the

baroreceptor loop is the subject of the remaining section of this chapter (5.4.2).

## 5.2 Coherence function estimation.

Before using any method of system identification which relies on input-output relationships, it is necessary to establish how closely the experimental input driving function relates to the derived system response.

This relationship is quantified by the Ordinary Coherence function, defined as

$$\hat{\gamma}_{xy}^2(f) = \frac{|G_{xy}(f)|^2}{G_x(f) \cdot G_y(f)}$$

where  $G_x$ ,  $G_y$  are the one-sided spectral density functions and  $G_{xy}$  is the one-sided cross-spectral density. The coherence function therefore expresses the portion of the output which is linearly related to the input at each frequency.

The coherence function has a value of 1 when the system under test is a constant parameter linear system having a single input and output (Bendat and Piersol, 1971). If values of between 0 and 1 are obtained, it is considered that

- a) the system is nonlinear
- b) the measurements of input and output functions contain noise
- c) the output is only partially due to the input

Clearly in the present situation, all the three conditions are likely to be true, so that a value of  $\hat{\gamma}_{xy}^2 = 1$  was not anticipated.

Further, Bendat and Piersol showed that if the coherence function is calculated on the basis of a spectral estimate,

$$\hat{y}_{xy}^2 = \frac{\hat{G}_{xy} \cdot \hat{G}_{xy}}{\hat{G}_x \cdot \hat{G}_y} = \frac{X(f) \cdot Y(f) \cdot X(f) \cdot Y(f)}{X(f) \cdot X(f) \cdot Y(f) \cdot Y(f)} = 1$$

where  $\hat{\phantom{x}}$  represents estimated values of the functions. This initially surprising result is a consequence of the fact that each spectral density estimate,  $\hat{G}_x(f)$ , is related to the true power spectrum  $G_x(f)$  by

$$\frac{\hat{G}_x(f)}{G_x(f)} = \frac{\chi_2^2}{2}$$

where  $\chi_2^2$  is chi-square with 2 degrees of freedom. This has the further consequence that the normalized standard error associated with the estimate is

$$\epsilon_r = \frac{\sigma\{\hat{G}_x(f)\}}{G_x(f)} = \frac{\sqrt{2n}}{n} = \frac{\sqrt{2 \times 2}}{2} = 1$$

where  $n$  = degrees of freedom.

That is, the standard deviation of the estimate is as large as the estimate itself.

Clearly, the situation is improved by increasing the number of degrees of freedom of the estimate. This can be done either

a) by ensemble averaging many estimates of  $\hat{G}_x(f)$ ,

where  $n = 2 \times \text{no. of estimates in average}$

b) by frequency smoothing  $\hat{G}_x(f)$ , where  $n = 2B_c t$  and

$B_c$  is the bandwidth of the smoothing window used.

The coherence function is usually estimated from the equation

$$y_{xy}^2 = \frac{(\sum (a_n c_n + b_n d_n))^2 + (\sum (a_n d_n - b_n c_n))^2}{\sum (a_n^2 + b_n^2) \cdot \sum (c_n^2 + d_n^2)}$$

where  $a_n$  and  $b_n$  are the real and imaginary components of  $X(f)$  and  $c_n$  and  $d_n$  are the real and imaginary components of  $Y(f)$ . The summation sign represents either spectral averaging or smoothing.

In the present study, smoothing of the data was kept to a minimum. Since the spectral density plots for the output signals had shown that the signal power was concentrated in the first few harmonics, there was a danger that excessive spectral smoothing would distort the spread of power, due to "start-up" effects of weighted average filters. Rather, ensemble averaging was used as much as possible.

The confidence limits for the present case, where  $n=40$ , are shown in Table 3.

|             | 0.2  | 0.4  | 0.6  | 0.8  |
|-------------|------|------|------|------|
| Lower limit | 0.02 | 0.15 | 0.36 | 0.65 |
| Upper limit | 0.42 | 0.6  | 0.75 | 0.88 |

Table 3. Upper and lower 95% confidence limits for the ordinary coherence function having 40 degrees of freedom.

It is considered that coherence values below 0.4 should probably be regarded as showing no significant coherence.

The coherence values for the experimental data are shown in Figure 64. Heart rate shows the best coherence values, and can probably be considered to show good correspondence between input and output over the entire frequency range considered. Blood pressure also contains significant coherence values across the whole frequency range, but these are rather more widely spaced than in heart rate. Respiration shows the poorest coherence function, it being debatable whether it contains any significant values.

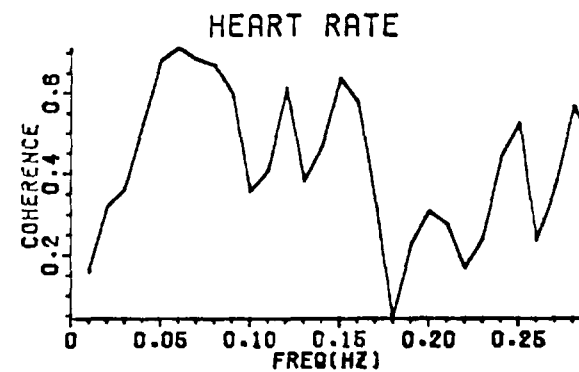
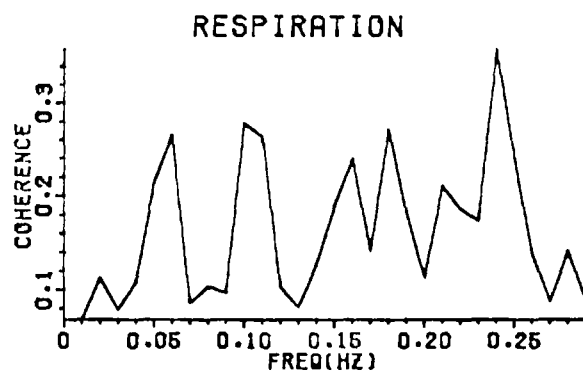
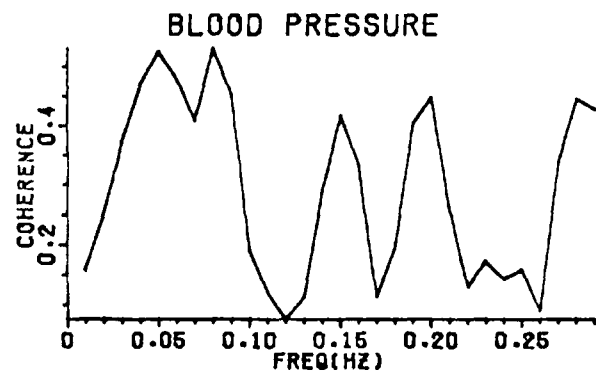
The conclusion must therefore be either that the experimental data does not correspond well to the stimulus, or that the coherence

Figure 64.

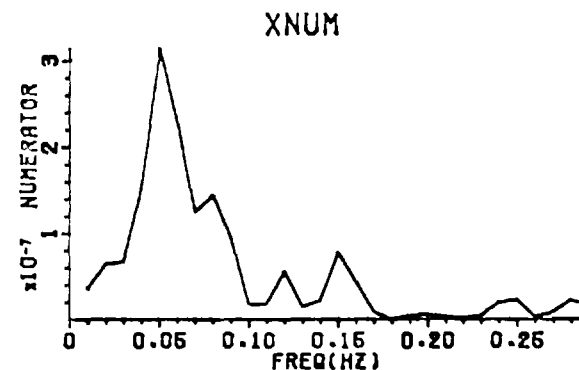
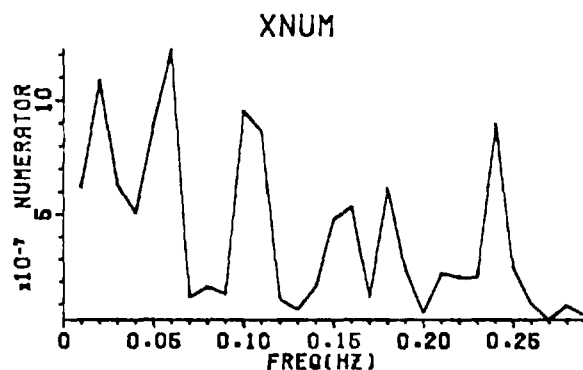
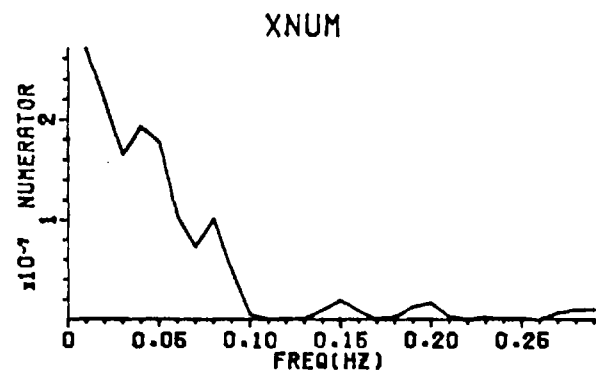
# COHERENCE FUNCTIONS

20 - 40Hz. test.

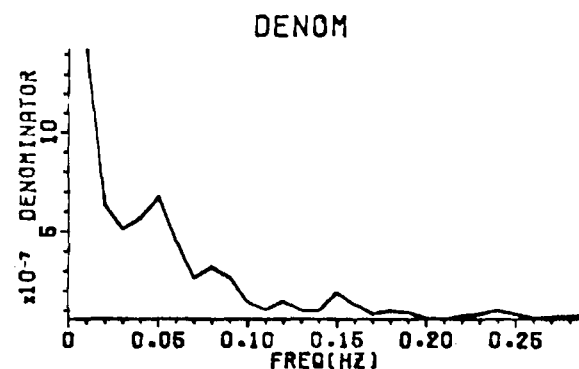
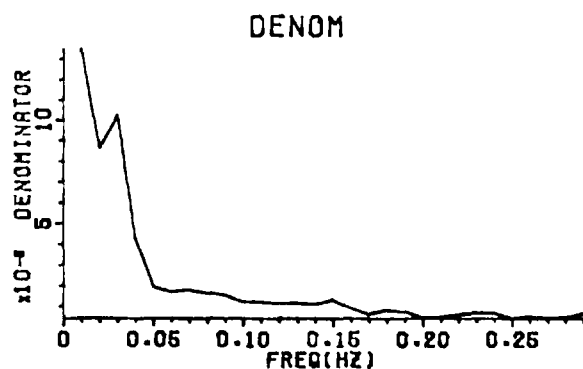
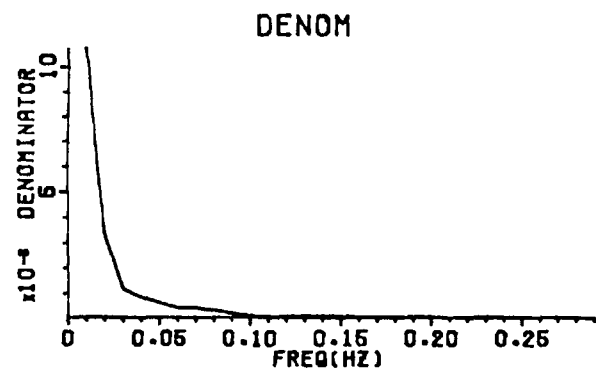
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Numerators of the coherence function



Denominators of the coherence function



function estimation is not appropriate in the present case. Since the spectra were subject to a certain amount of non-stationarity, as shown in the next section, one consequence was certainly that the coherence functions were somewhat poorer than would have been obtained if repeated smoothing of the same record had been used in calculating the functions. Coherence estimation is therefore not entirely appropriate unless high resolution frequency spectra are available.

The form of the input signal may also render the calculation of the coherence function invalid in this case. The PRBS is not only identical for every data estimate, so that ensemble averaging will not increase its degrees of freedom, but is also spectrally flat, so that smoothing would also give no increase in degrees of freedom. The validity of calculating the coherence function in this case is therefore questioned.

### 5.3 Formation of the frequency response

Section 3.4 showed that the frequency response is defined as

$$H(f) = \frac{G_{yy}(f)}{G_{xx}(f)}$$

Once again, it was necessary to use ensemble averaging of the spectra involved to obtain a value for  $H(f)$ , the frequency response, for which the standard deviation was small (see previous section).

The input P.R.B.S. is a deterministic signal being the same for all observations of  $\hat{Y}(f)$ , so that in this instance

$$\hat{X}(f) = \hat{X}(f)$$

Consequently, this meant that it made no difference either to the amplitude or phase of  $H(f)$  whether  $\hat{Y}(f)$  or  $\hat{H}(f)$  was used in the ensemble average.  $H(f)$  here symbolises the average frequency response.

The output estimates,  $\hat{Y}(f)$ , necessarily contained a certain amount of noise which, if uncorrelated with  $Y(f)$ , was reduced by the averaging process. Since  $H(f)$  was to be used in system identification, a necessary first step was to establish which harmonic components of  $\hat{H}(f)$  contributed most significantly to  $H(f)$ . Uncorrelated noise generally occupied higher frequency bands than the system response, so that investigation of the contribution of each component to the correlation coefficient of  $\hat{H}(f)$  and  $H(f)$  gave some insight into the dividing line between the high frequency end of the system response and the low frequency noise components. The presence of noise which may be correlated with the system response could not be ruled out. Since such noise would occupy the same harmonic ranges as those of interest, the correlation coefficient estimate would be smaller than if no such noise was present. Thus,

comparison of each estimate of  $\hat{H}(f)$  with  $H(f)$  was used to pinpoint any non-stationarities which existed in the system.

The cross correlation coefficient is defined as

$$r_{xy} = \frac{\sum_{n=1}^{n=N} G_{xy}(n)}{G_x(n) \cdot G_y(n)}$$

The correlation coefficient  $r_{xy}$  varies between +1 and -1, a value of +1 indicating complete correlation between the two signals.

In the present case,  $\hat{H}(f)$  and  $H(f)$  were used in the correlation, yielding 20 estimates of  $r_{xy}$  for each experiment. The values for  $r_{xy}$  for the three parts of the system covered the following ranges for the experiment illustrated when calculated over 30 harmonics :-

| System         | Maximum $r_{xy}$ | minimum $r_{xy}$ |
|----------------|------------------|------------------|
| Blood Pressure | 0.953            | 0.757            |
| respiration    | 0.9099           | 0.812            |
| Heart Rate     | 0.938            | 0.7855           |

The averaged maximum and minimum correlation coefficients over all the experimental data are given in Table 4. The contribution of each harmonic to the value of  $r_{xy}$  for that record was expressed as a percentage of the total. The results for all 20 records were found to have the greatest visual clarity when expressed as a three dimensional graph, as shown in Figures 65 to 67.

Of the three sections considered, the blood pressure response exhibited the narrowest bandwidth; the power distribution in  $H(f)$  is contributed almost entirely by the first five or six harmonics, with the first and second components contributing 60% or more of the total power.

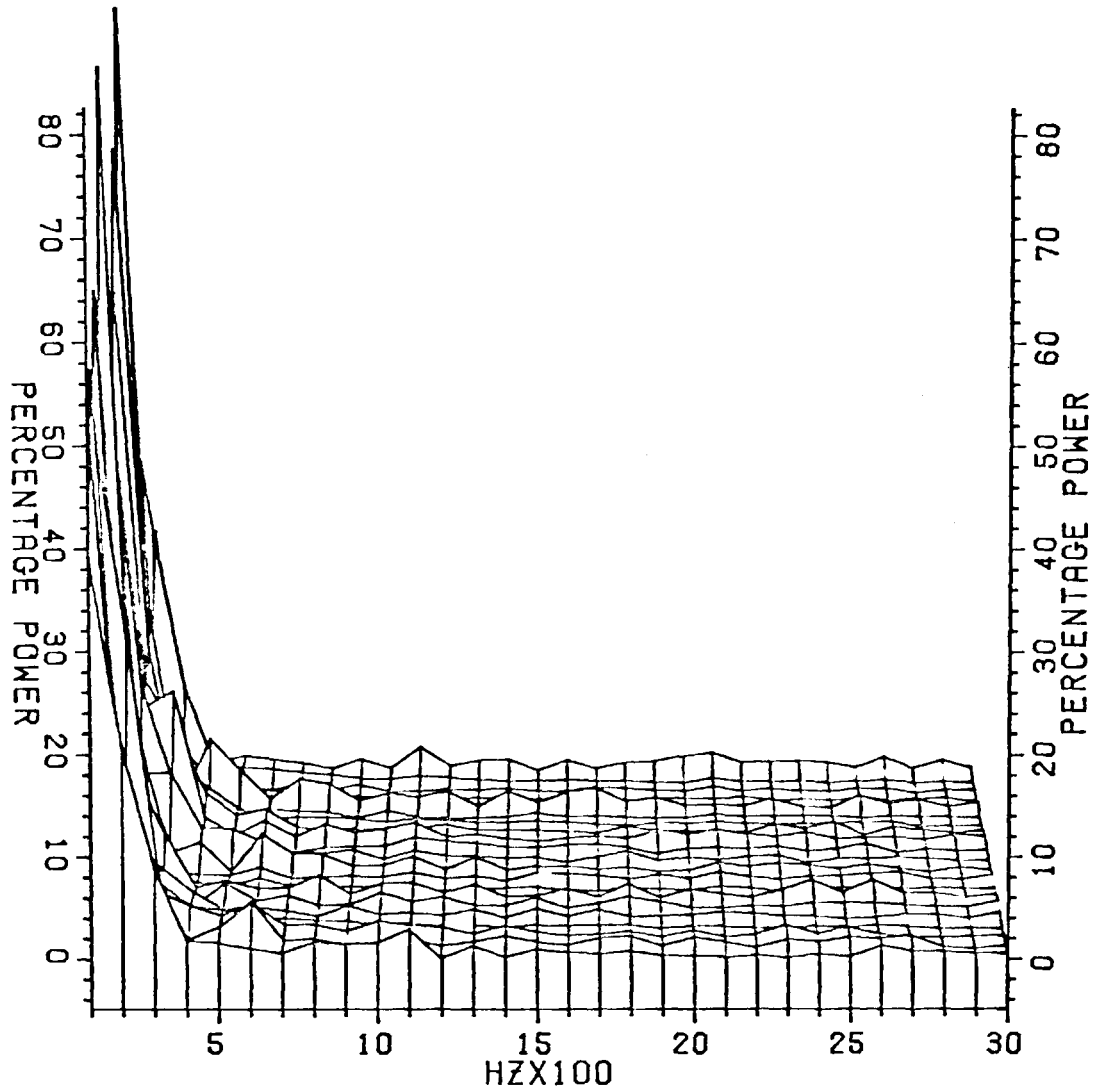


Figure 65. Three dimensional representation of the correlation coefficient for each harmonic between each blood pressure frequency response estimate and the ensemble average of 20 estimates. 20 - 40Hz. test.

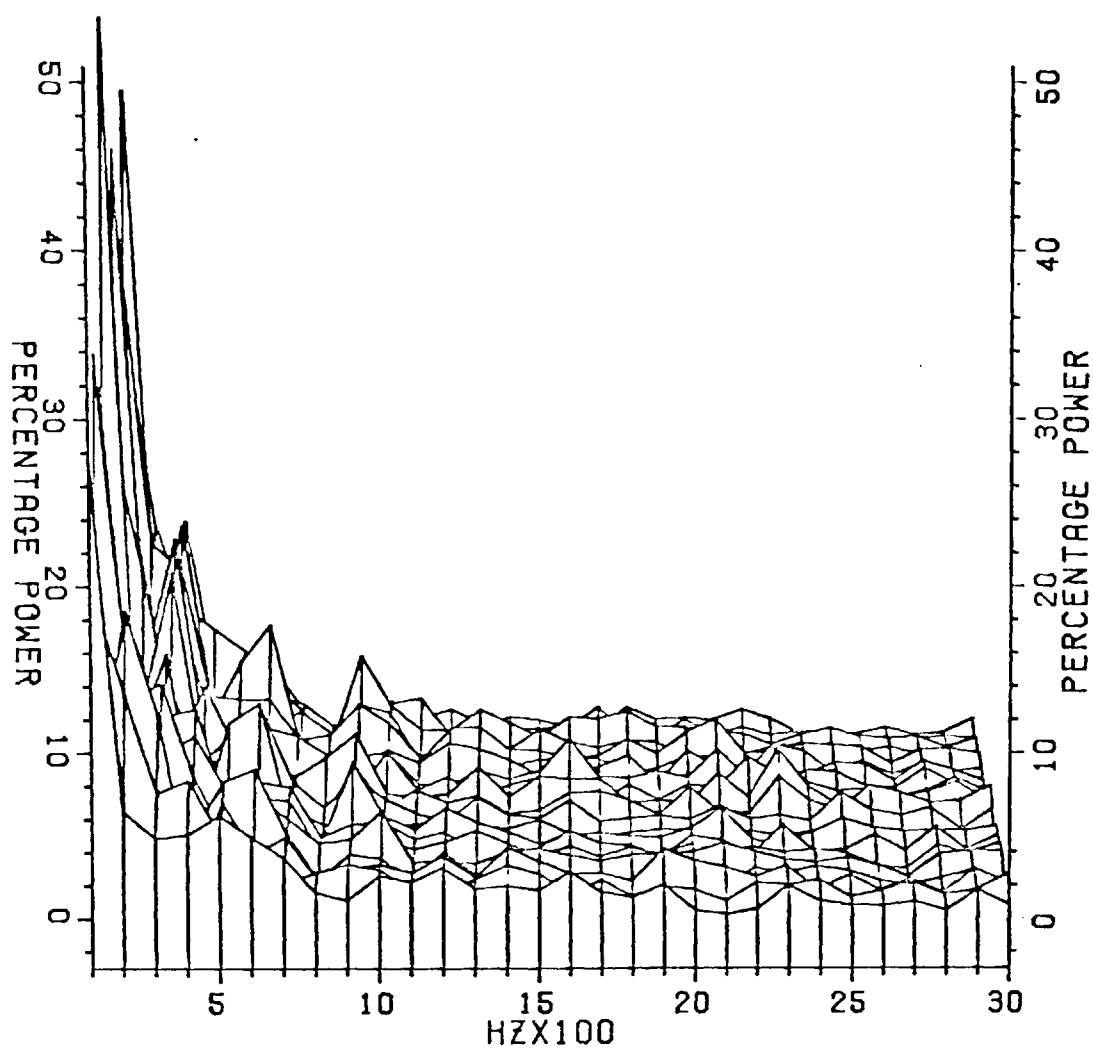


Figure 66. Three dimensional representation of the correlation coefficient for each harmonic between each respiration frequency response estimate and the ensemble average of 20 estimates. 20 - 40Hz. test.

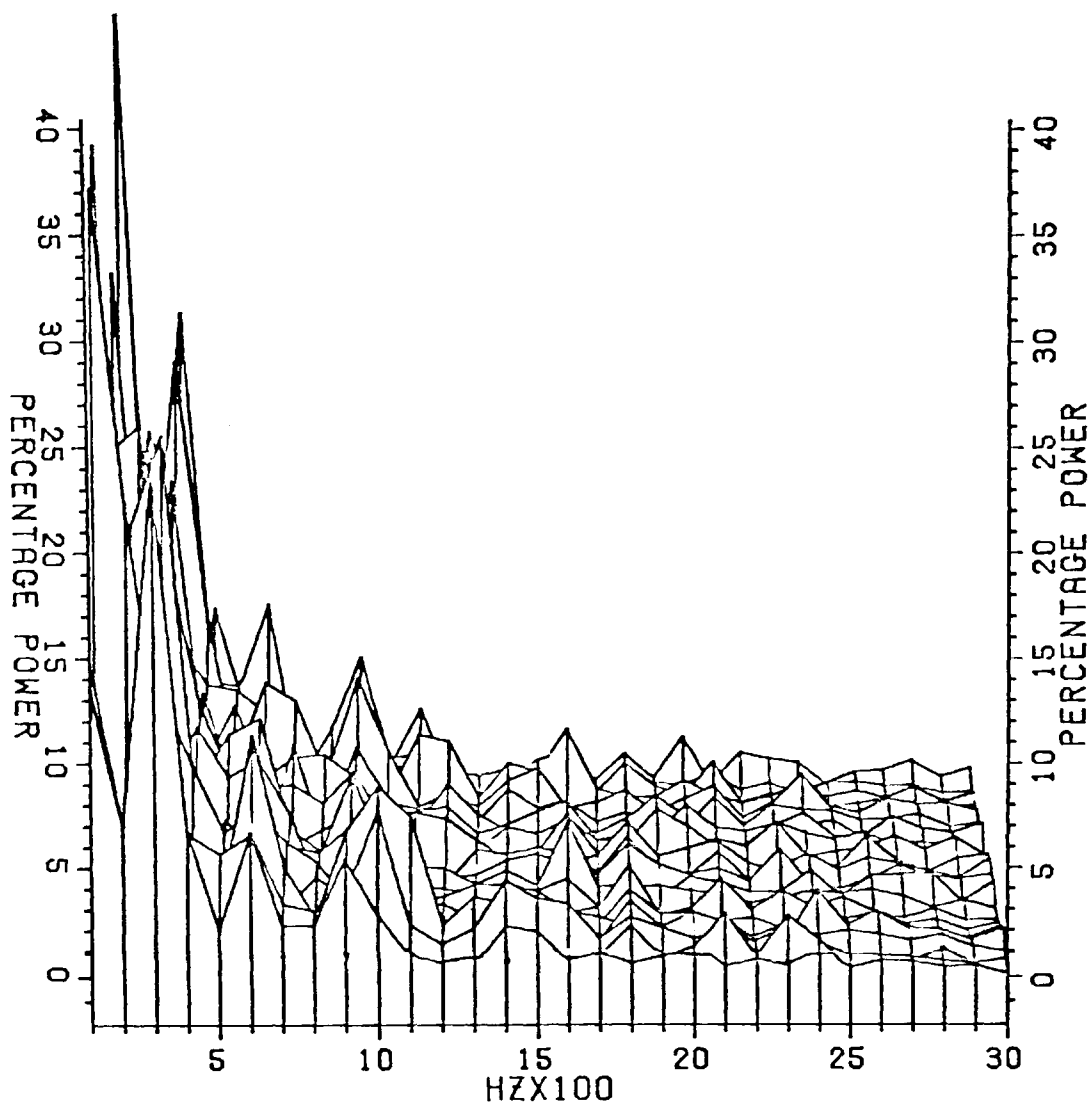


Figure 67. Three dimensional representation of the correlation coefficient for each harmonic between each heart rate frequency response estimate and the ensemble average of 20 estimates. 20 - 40Hz. test.

|                | 20 - 40Hz.    | 40 - 60Hz.    | 60 - 80Hz.    | 80 - 100Hz.   |
|----------------|---------------|---------------|---------------|---------------|
| Blood Pressure | 0.972 - 0.67  | 0.967 - 0.732 | 0.965 - 0.695 | 0.974 - 0.682 |
| Respiration    | 0.951 - 0.753 | 0.964 - 0.814 | 0.943 - 0.81  | 0.94 - 0.831  |
| Heart Rate     | 0.956 - 0.793 | 0.964 - 0.797 | 0.942 - 0.769 | 0.947 - 0.79  |

Table 4. Averaged maximum and minimum correlation coefficient values for each stimulus range.

Heart rate and respiration were more widely spread, with a much more even spread of power over the first five or six harmonics. The respiration response contains significant frequencies up to 0.15Hz, while the heart rate response shows a spread of power which covers twenty to twenty-five components.

All parts of the system exhibited a certain amount of non-stationarity, but not enough to significantly affect the values obtained for the correlation coefficient. Table 4 showed that in all cases the correlation between estimates was very high. The values obtained for blood pressure were slightly lower than those for heart rate and respiration in each stimulus range. Stimulus level did not appear to affect the values obtained. The overall conclusion was therefore that the data was sufficiently stationary to allow the ensemble average to be a representative estimate of the system response for each experiment.

#### 5.4 Determination of the system characteristics.

In this section the characterisation of the system is considered and transfer functions developed. The transfer function yields information about the type and order of the system. The stability and operational frequency range of the system may also be calculated. In the present case, the linearity of the system can be assessed since responses were obtained at several different input levels. Section 5.4.1 takes the control engineering approach, while section 5.4.2 presents the physiological arguments. For reference in the next sections, the proposed block diagram for the baroreceptor control loop is repeated here (Figure 68).

##### 5.4.1 Bode and impulse response analysis.

An appropriate way of expressing the frequency response curves was in Bode diagram form. Each frequency response function is represented as a pair of graphs, plotting the amplitude ( in decibels) and phase ( in degrees) of the frequency response against the logarithm of frequency in radians. The Bode amplitude ratio is defined as the ratio of system output amplitude to input amplitude at a given frequency, divided by the ratio of the amplitudes at zero frequency. This dimensionless representation of Bode amplitude is the standard when input and output signals do not have the same dimensions (Harriott, 1967). Figure 69 shows an example of Bode diagrams for the three parts of the system, together with the corresponding impulse responses, being the inverse F.T. of the frequency response.

The most striking feature of the Bode and impulse response diagrams for the three parts of the system is their similarity to

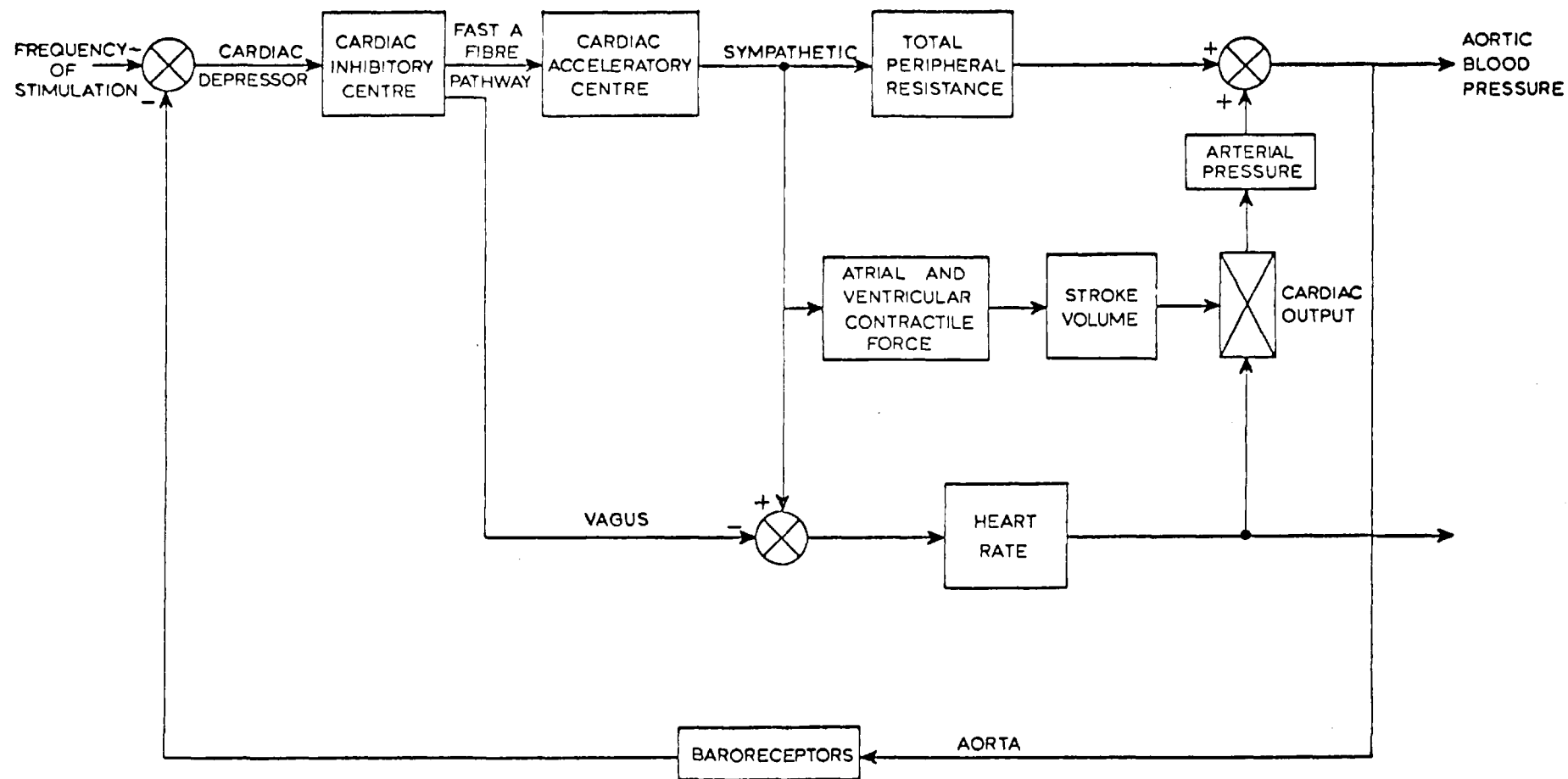
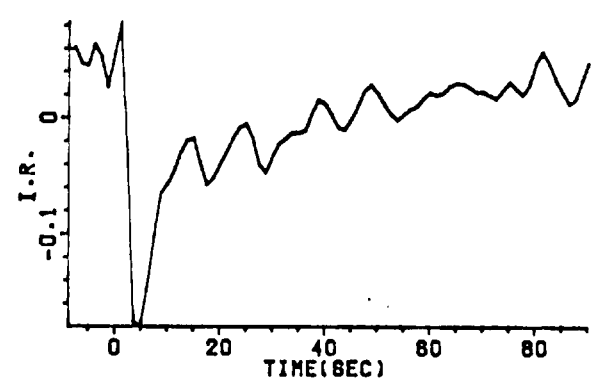
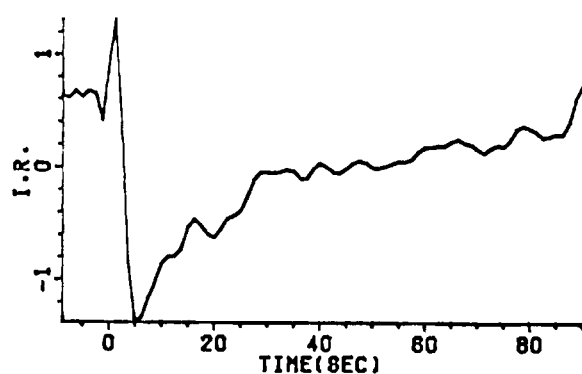
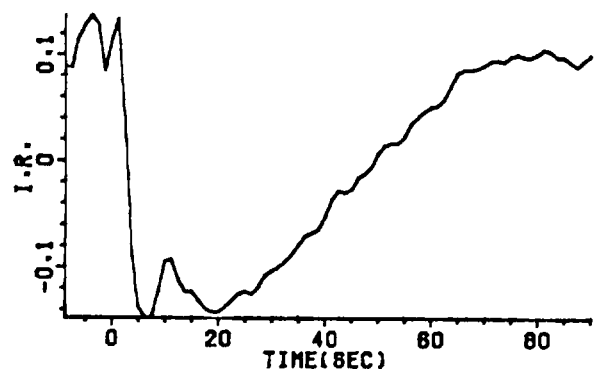
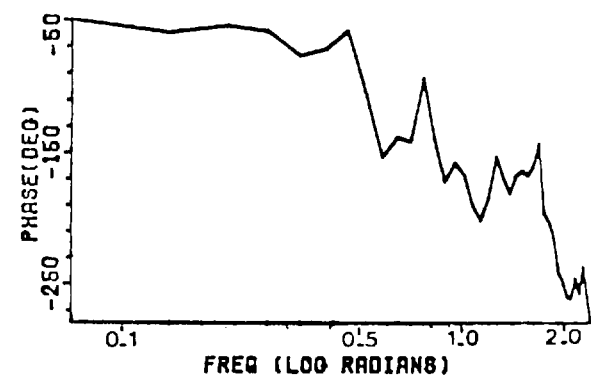
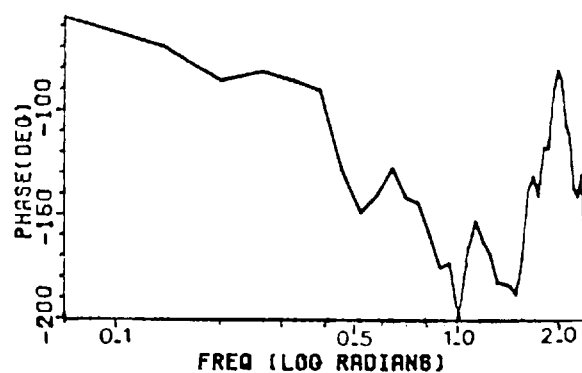
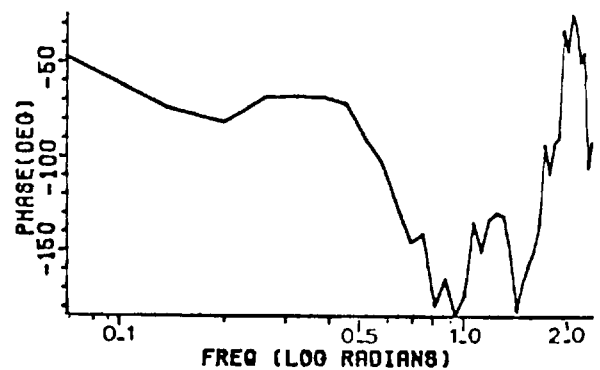
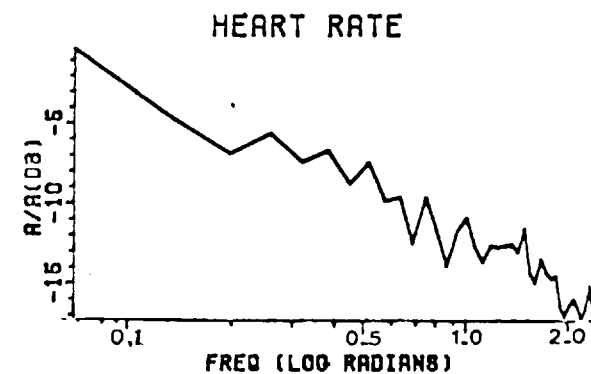
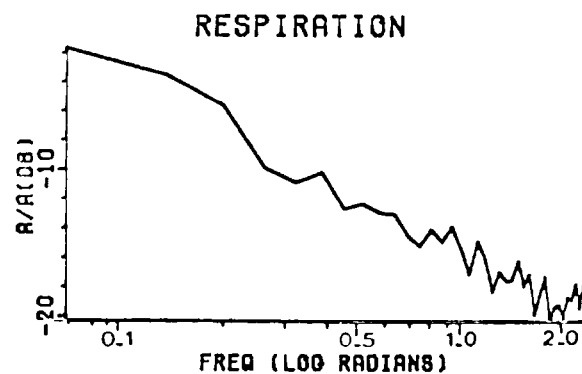
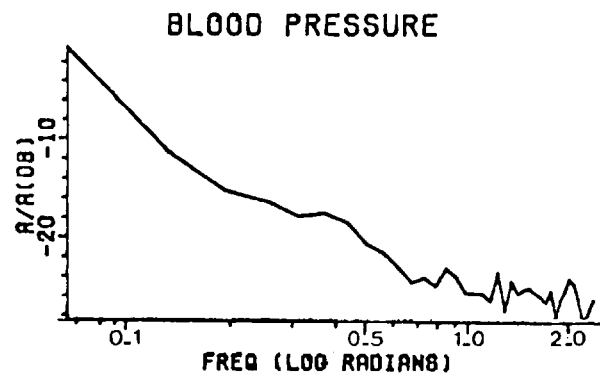


Figure 68. Block diagram representation of the major components of the baroreceptor loop.

Figure 69.

## BODE PLOTS AND IMPULSE RESPONSES

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20 - 40Hz.

each other. At frequencies above 0.2 to 0.3rad/sec all three diagrams exhibit the characteristics of a first-order lag. That is, the amplitude plot has a slope of -6dB/octave. This feature is illustrated in Figure 70, which shows the Bode amplitude plot for heart rate to which a lag element of corner frequency 0.5rad/sec. has been fitted.

The low frequency end of all of the Bode diagrams describes an element comprising one pole and one zero; the pole has a longer time constant than the zero, causing the initial downward ramp to level out between 0.1 and 0.2rad/sec. A common example of such an element is a proportional plus integral (P.I.) controller. Figure 71 again shows the heart rate Bode amplitude, together with a P.I. element having a reset corner at 0.2rad/sec. Although the slope of the blood pressure plot is somewhat steeper than that of heart rate and respiration, the reset corner value is approximately the same for all three.

In the blood pressure and respiration responses, the contribution of harmonics above 1rad/sec. are considered to be due to noise. The heart rate response probably extends up to 2rad/sec. This conclusion is confirmed by the correlation coefficients calculated in the previous section.

As a first approximation, the system may therefore be considered to be due to a combination of these two elements. In order to improve the interpretation, the information supplied by the Bode diagrams must be considered in the context of system input and output points. Figure 72 restates the experimental protocol in control terms. A negative load,  $L$ , was applied to the system by stimulating the cardiac depressor nerve, and the system outputs of

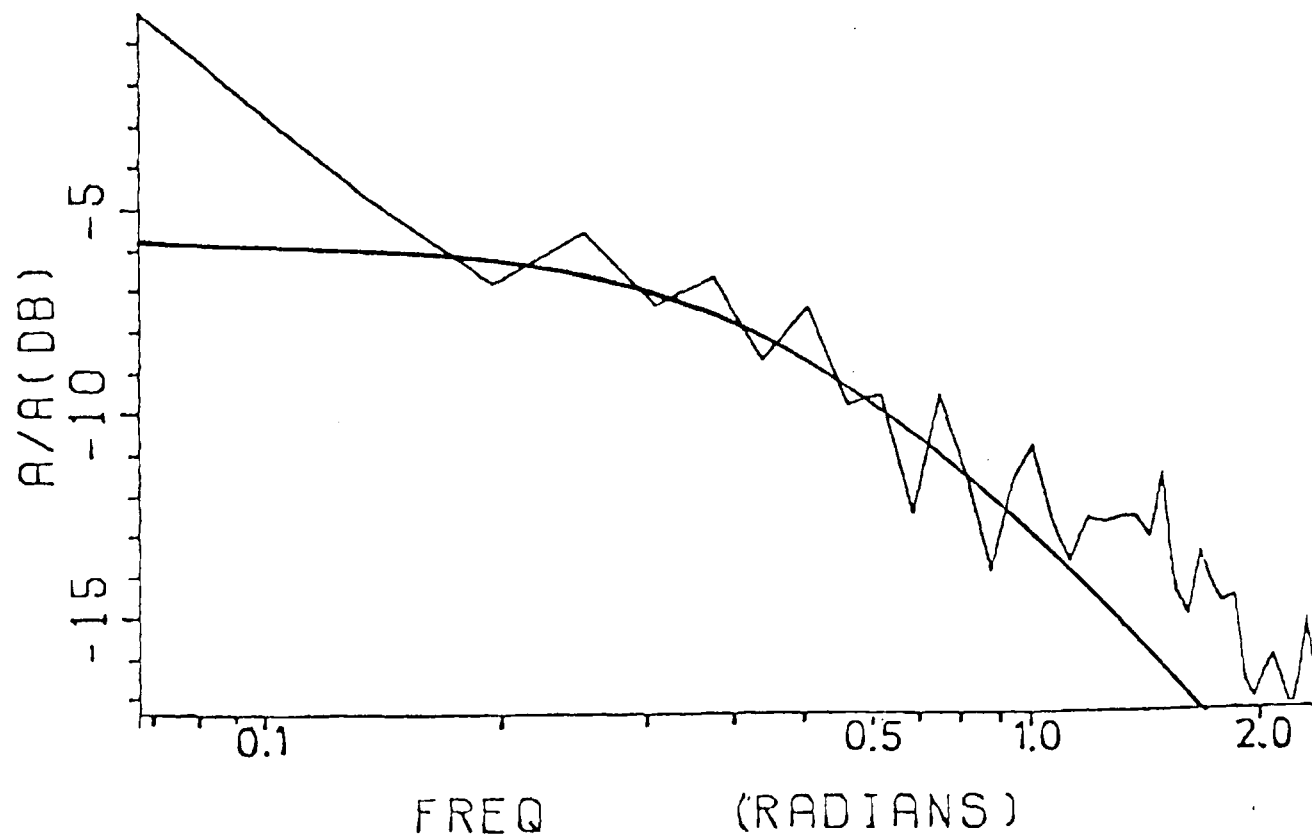


Figure 70. Heart rate Bode amplitude, together with the frequency response of a first-order lag of corner frequency 0.5rad./sec.

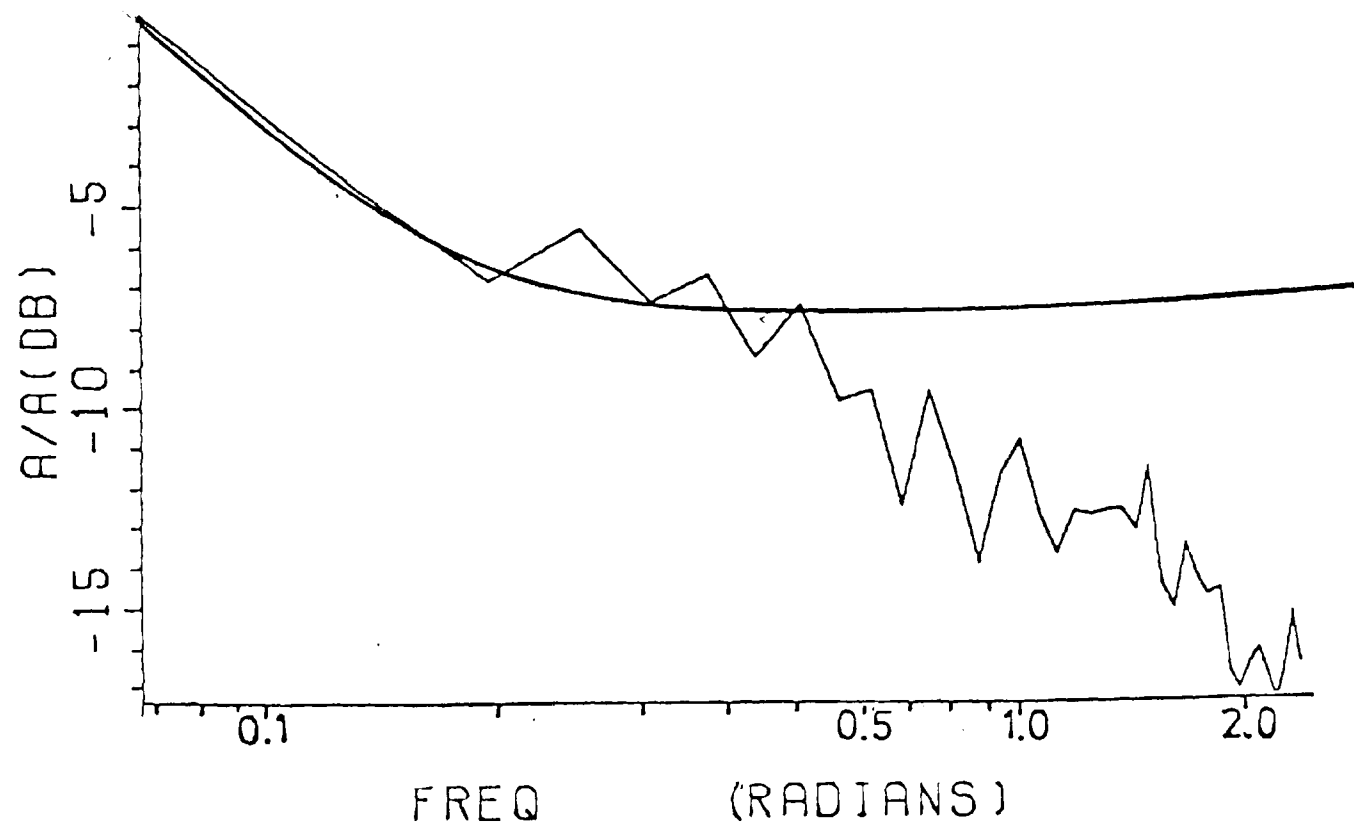


Figure 71. Heart rate Bode amplitude, together with the frequency response of a P.I. element of corner frequency 0.2rad/sec.

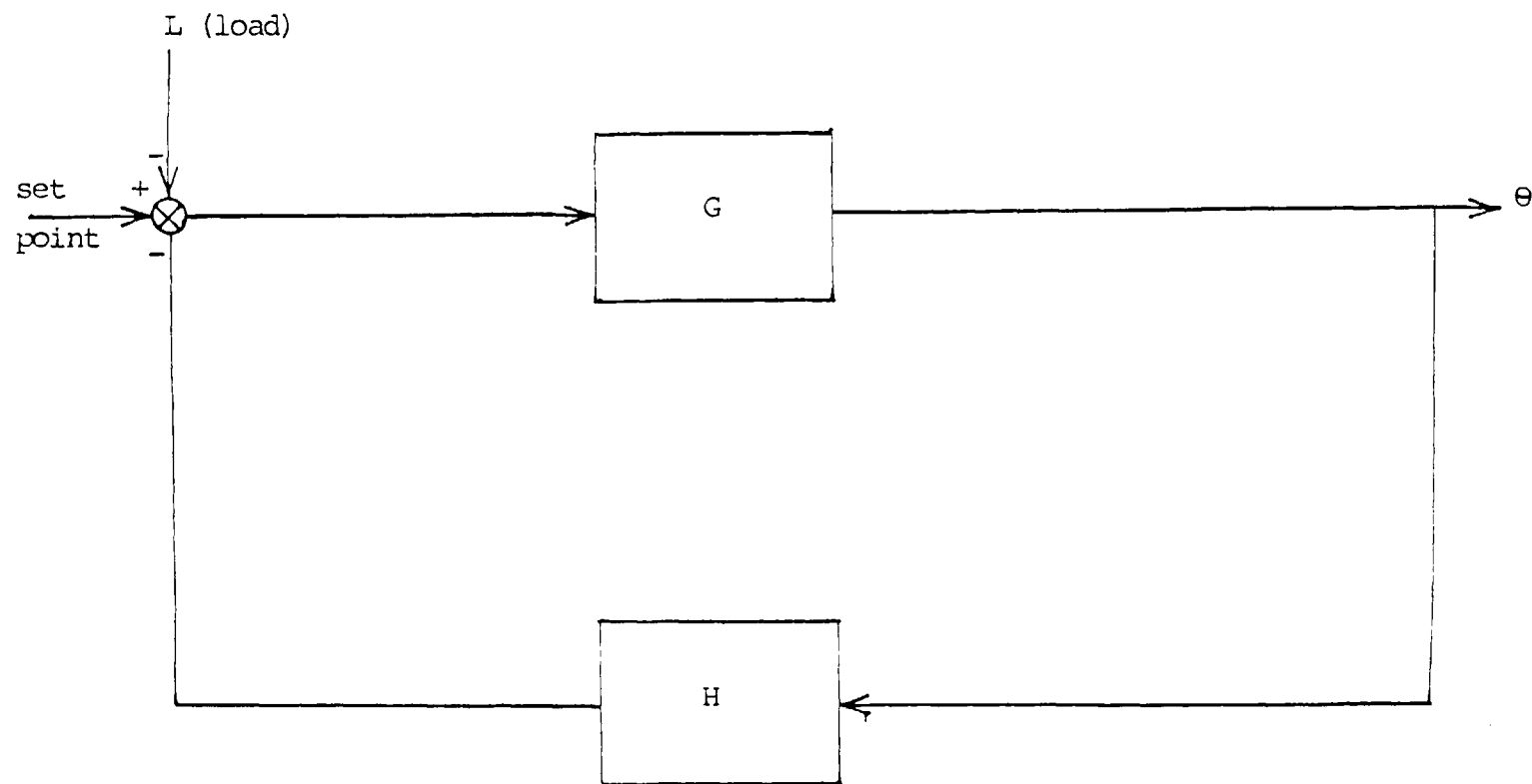


Figure 72. Simplified block diagram representing the stimulus - response pathways of the experiment in control terms.

heart rate, blood pressure and respiration were measured. For each case, the Bode information therefore represents

$$\theta = - \frac{G}{1+GH}$$

That is, each Bode diagram is a representation of the closed loop transfer function for that part of the system, since no part of the loop was opened during the experiments. For simplicity, the system was initially considered to have unity feedback, i.e.  $H=1$ .

The closed loop transfer function of a control element behaves differently from its open loop form. Figures 73 and 74 illustrate the open and closed loop functions of a lag and a P.I. element respectively. It can be seen that the closed loop lag function is identical to the open loop function, except that the corner frequency is exactly doubled for the same time constant value.

The closed loop P.I. element also has twice the open loop corner frequency, but its slope is also reduced to 2dB/octave. Figure 74 shows that the slope can be altered by changing the proportional gain, the maximum slope being -6dB/octave. In its closed loop form, the transfer function of the P.I. element takes the form of a limited action controller or lag compensator. In Laplace terms this is represented by

$$G(j\omega) = \frac{1+j\omega T}{1+j\omega T_A} \quad \text{where } T_A > T$$

where  $T_A$  and  $T$  are the time constants for the two corner frequencies. The downward dip in the phase plot is typical of this type of element.

Combinations of the two proposed elements were studied in order

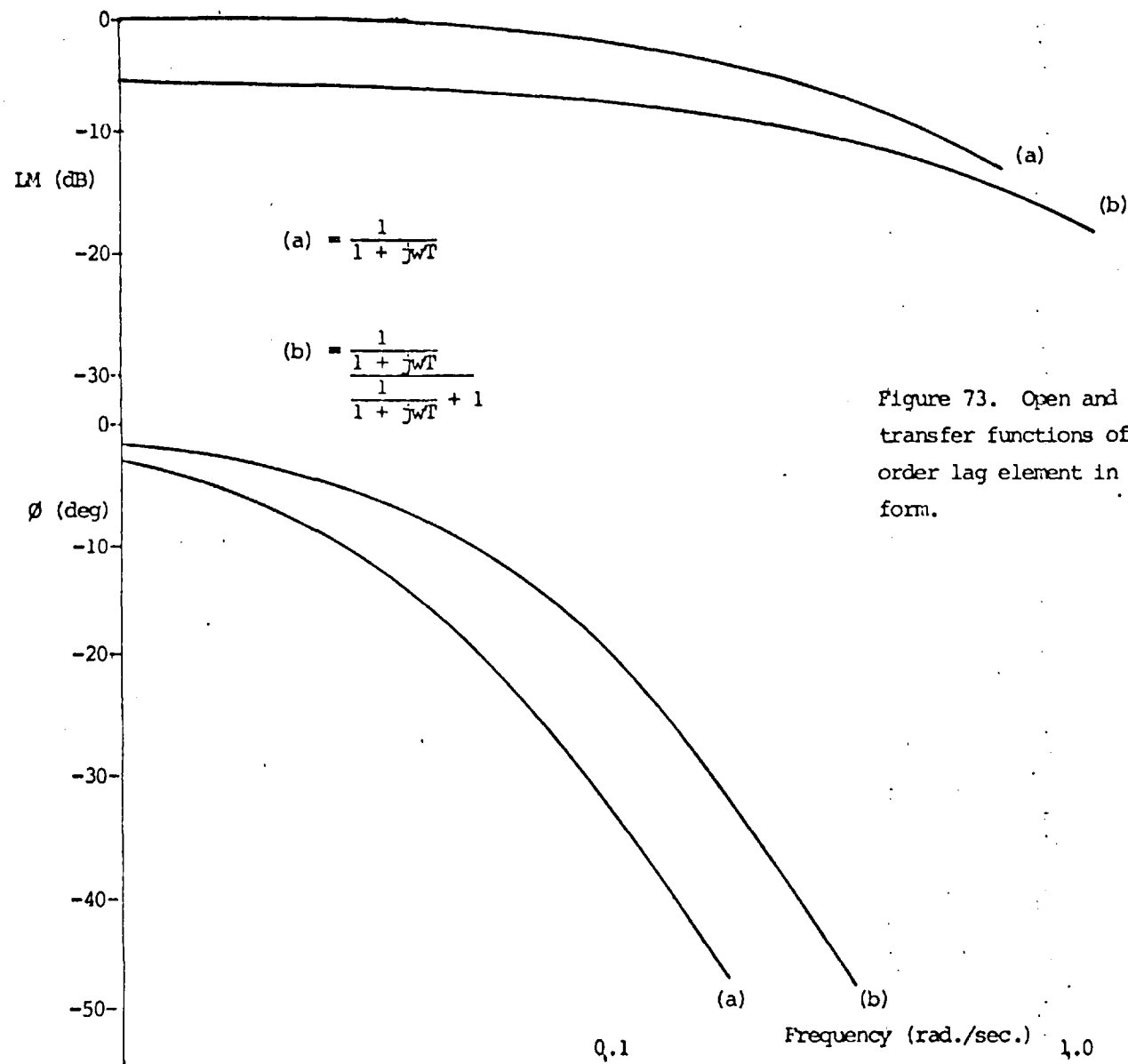


Figure 73. Open and closed loop transfer functions of a first-order lag element in Bode diagram form.

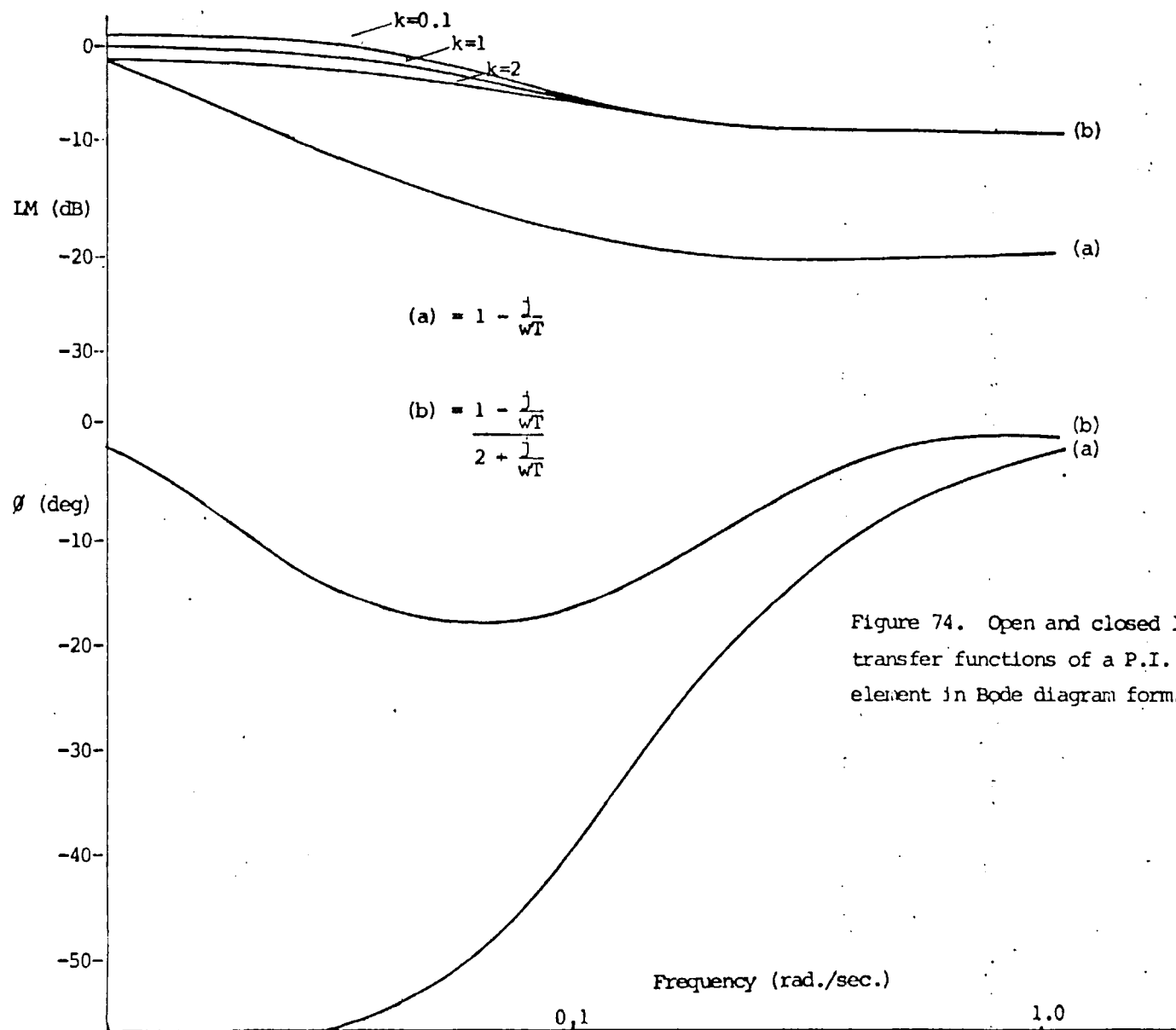


Figure 74. Open and closed loop transfer functions of a P.I. element in Bode diagram form.

to establish a transfer function which yielded an adequate model of the experimental frequency and impulse responses. The best match overall was found by considering the elements to be in series, rather than in parallel or in some combination of the two. Any parallel combination of the elements depressed the low frequency amplitudes so that the P.I. slope was only 1 to 3dB/octave, instead of the desired 6dB/octave found in the experimental data. As will be seen, parallel combination also held problems when the impulse responses were considered.

Series combination of the P.I. and lag elements gives the following closed loop transfer function:

$$\text{If } G_1(j\omega) = K - (jk/\omega T) \quad \text{and } G_2(j\omega) = 1/(1+j\omega T_l)$$

$$\begin{aligned} G(j\omega) &= \frac{G_1(j\omega) G_2(j\omega)}{1 + G_1(j\omega) G_2(j\omega)} \\ &= \frac{\{K - (jK/\omega T)\} \times \{1/(1+j\omega T_l)\}}{\{(K - (jK/\omega T)) \times (1/(1+j\omega T_l))\} + 1} \\ &= \frac{K - (jK/\omega T)}{K - (jK/\omega T) + 1 + j\omega T_l} \end{aligned}$$

where  $T$  and  $T_l$  are the time constants of the P.I. and lag elements respectively, and  $K$  is the proportional gain.

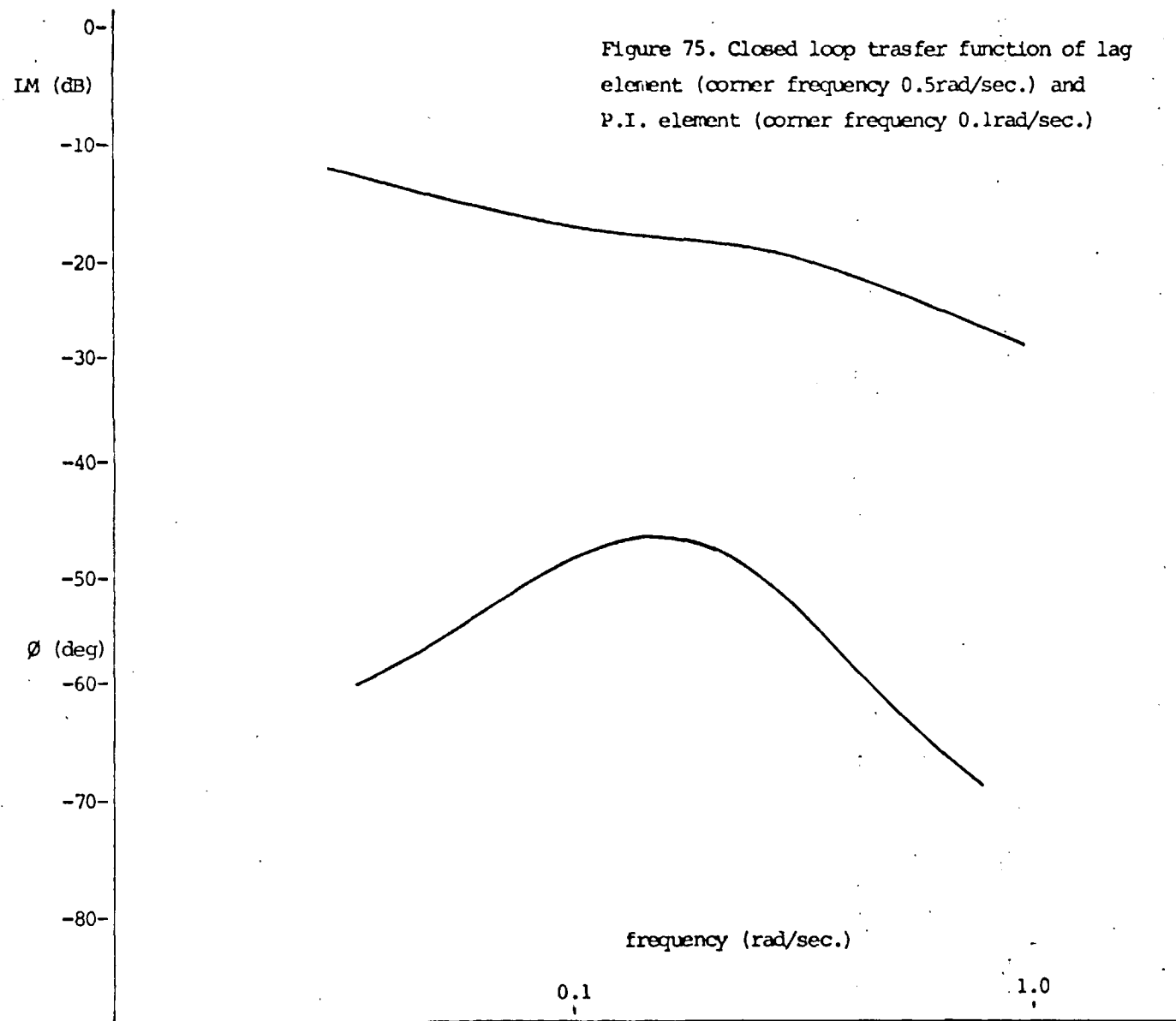
The Bode amplitude and phase may then be calculated as

$$LM(\omega) = 10 \log \left[ \frac{K^2 + (K/\omega T)^2}{(K+1)^2 + (\omega T_l - (K/\omega T))^2} \right]$$

and

$$\phi(\omega) = \text{ATAN}(-1/\omega T) - \text{ATAN}\{(\omega T_l - (K/\omega T))/(K+1)\}$$

Figure 75 illustrates the form of the Bode diagrams for the



values  $K=0.1$ ,  $T=10$  and  $T_i=1.75$ . When combined in this way, the lag element shows a corner frequency in the expected position, while the P.I. element continues to take up a value of  $w=2/T$ . It was not possible to reproduce the dip in the phase plot found in the transfer function of the P.I. element alone (Fig. 74), even by decreasing the P.I. element time constant.

Figure 76 shows the result of plotting the derived transfer function against the experimental data of Figure 69. Since the elements are considered to be in series, any time delays around the loop are therefore additive. Time delays have constant gain and a phase angle of  $-wT_D$  where  $T_D$  is the delay in seconds. In order to match the experimental results, a total loop delay of 1.6 sec. was estimated. For heart rate,  $K$  was set to 0.1 since the required slope was only 4 to 5dB/octave. Respiration and blood pressure required a value of  $K=0.05$  to boost the P.I. slope to 6dB/octave. In all cases, the  $T$  and  $T_i$  values were 10 and 1.75 respectively. On the whole, the fit between actual and derived data was good; the discrepancies lay in the first one or two harmonics in each case.

There are two main ways in which the model appears to differ from the experimental results. Firstly, the slope of the Bode amplitude for blood pressure appears to be greater than 6dB/octave, which is the maximum slope obtainable from a P.I. element. However, if the first harmonic is discounted, a good 6dB/octave fit is obtained. Over all the results obtained, 82% of blood pressure plots showed an initial slope of 6dB/octave. In this case therefore the discrepancy is probably attributable to spreading of power from the d.c. component to the first harmonic.

Secondly, in all three cases the phase plots exhibit the dip

Figure 76.

## BODE PLOTS AND IMPULSE RESPONSES

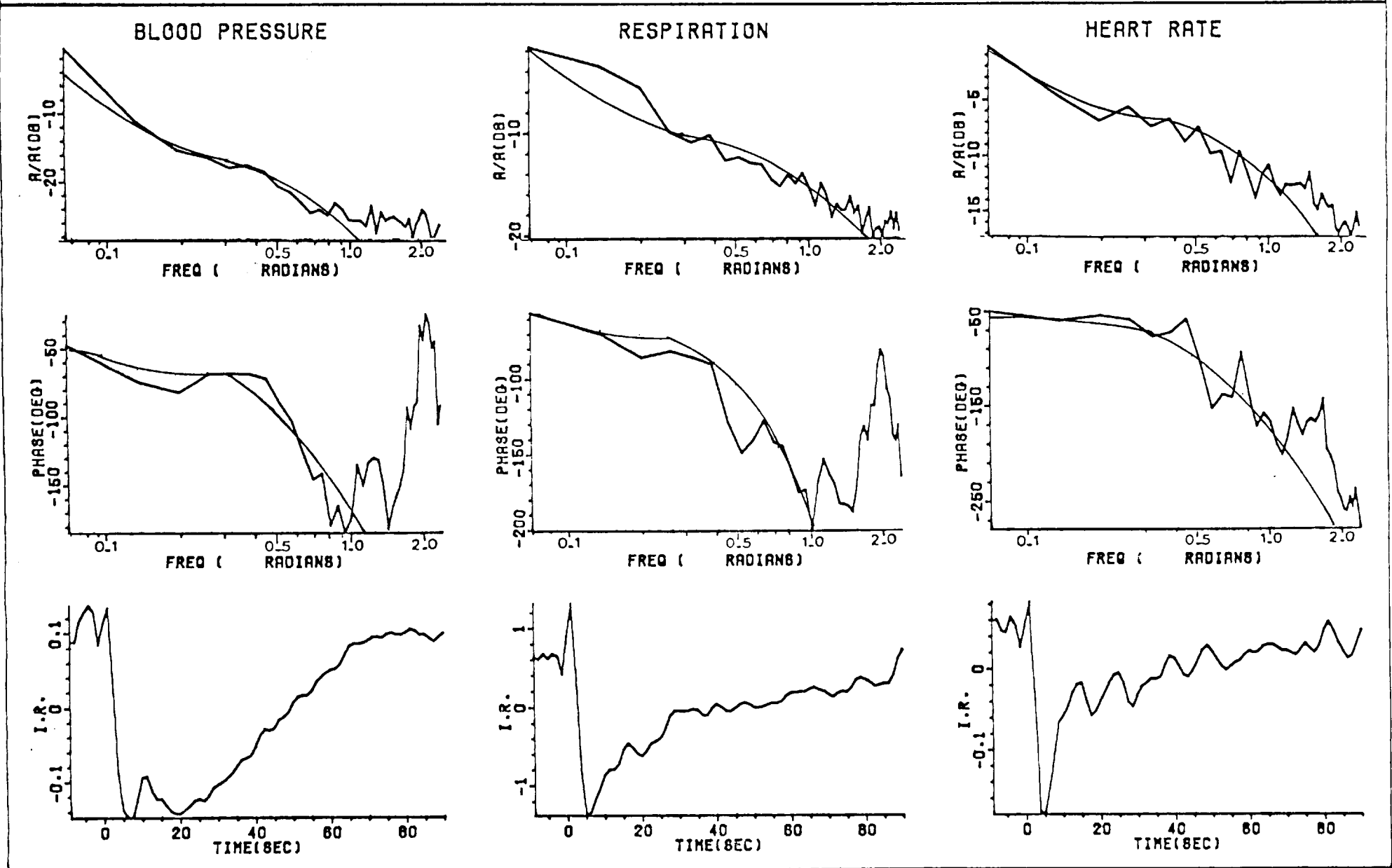
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Illustration of the fit between the Bode diagrams for actual data and for the model.

found in Figure 74. It was not possible to reproduce the initial downturn in phase plots for the model. Even substituting  $G(j\omega) = (1+j\omega T)/(1+j\omega T_A)$  for  $G(j\omega) = K - (jK/\omega T)$  in the loop transfer function did not help, since the minimum phase angle occurred at or below the first harmonic. The most likely explanation for the discrepancy is that the system is more complex than the model: it is possible that the P.I. element influences the total system by other pathways as well as serial combination, yielding a low-gain additive term which resembles Fig. 74. Alternatively, it has been shown (Jennings, 1981) that the first and second harmonics of Fourier transformed data are frequently inaccurate, largely as a result of smoothing methods employed prior to Fourier transformation of finite data.

It is useful to consider the information presented by the impulse response diagrams in association with that from the Bode plots. The impulse response diagrams for the three functions indicate that the same basic elements are responsible for all 3 responses. The common characteristics are a very fast initial negative response, followed by fast partial recovery and slower complete recovery.

It should be noted that the theoretical impulse referred to here is an impulse change in firing rate of the aortic depressor nerve. Since the impulse is applied to the feedback path (see fig 72), the response (measured from the forward loop) is the response to a negative impulse.

The impulse response diagrams are circular over the repetition period of the PRBS, since to all intents and purposes the PRBS was repeating indefinitely while the response data was collected. The

impulse responses were plotted with the data point corresponding to zero time displaced by 10 seconds, to allow an appreciation of the system state immediately prior to the zero time point. In all three cases the system response appears to start before zero time. This is often a consequence of the correlation analysis methods used here and may indicate the presence of a feedback path internal to the system (Harris, 1966). The circularity of the impulse response can in this instance make it hard to distinguish a point at which heart rate response achieved a return to its pre-disturbance level. The last few seconds of the response merge with the pre-zero commencement of the response. It is probable that at 20-40 Hz stimulation, 100 sec was not long enough for heart rate to recover fully.

The impulse response of the model can be derived from the Bode diagrams using the formula

$$f(t) = 10^{*(LM(w)/20)} \times \cos(wt - (\phi(w)\pi/180))$$

for inverse Fourier transformation. This method was found to be more successful than Laplace transformation in obtaining graphical representations of the model's impulse response. This was largely because Laplace transformation using the standard tables assumes continuous data. Inverse Fourier transformation of the model's frequency response was more likely to show the same biases as the real data, which was also Fourier transformed.

Figure 77 illustrates the derived impulse response using the parameters for heart rate (also shown). The fit is good enough to add weight to the model's accuracy. The model's impulse response accounts for some of the pre-zero oscillation found in the experimental data as being artefacts of the transformation.

In order to develop a satisfactory solution for blood pressure as well, it was useful to consider the components of the loop impulse response. The loop transfer function in Laplace terms is

$$G(s) = \frac{KTs + K}{2KTs + K + TT_1s^2}$$

using the Laplace form of the P.I. transfer function (Harriott, 1967). Laplace transformation of the loop transfer function yields a time function of the form

$$F(s) = \frac{s+a}{(s+b)(s+c)}$$

$$f(t) = \{1/(c-b)\} \{(a-b)e^{-bt} - (a-c)e^{-ct}\}$$

where  $a$  is proportional to  $1/T$  and  $b$  and  $c$  are dependent upon the difference between  $T_1$  and  $T$ .

The model's impulse response is thus the result of the addition of two exponentials, one of which has a considerably longer time constant than the other. For example, for the case where  $T_1=1.75$  and  $T=10$ ,  $a$  becomes 0.1,  $b$  is 1.09 and  $c$  is 0.052. That is, the Laplace transform is based upon the summation of two first-order lags, having corner frequencies of 1.09 and 0.052rad/sec. When the results of Fourier transformation of a finite number of harmonics is taken into account, a result very close to that shown in Figure 77 is obtained.

The blood pressure impulse response takes a somewhat different form from the heart rate response, the dominant feature being a slow, almost sine function recovery pattern. This feature can be modelled by band-limiting the two exponentials which form the heart

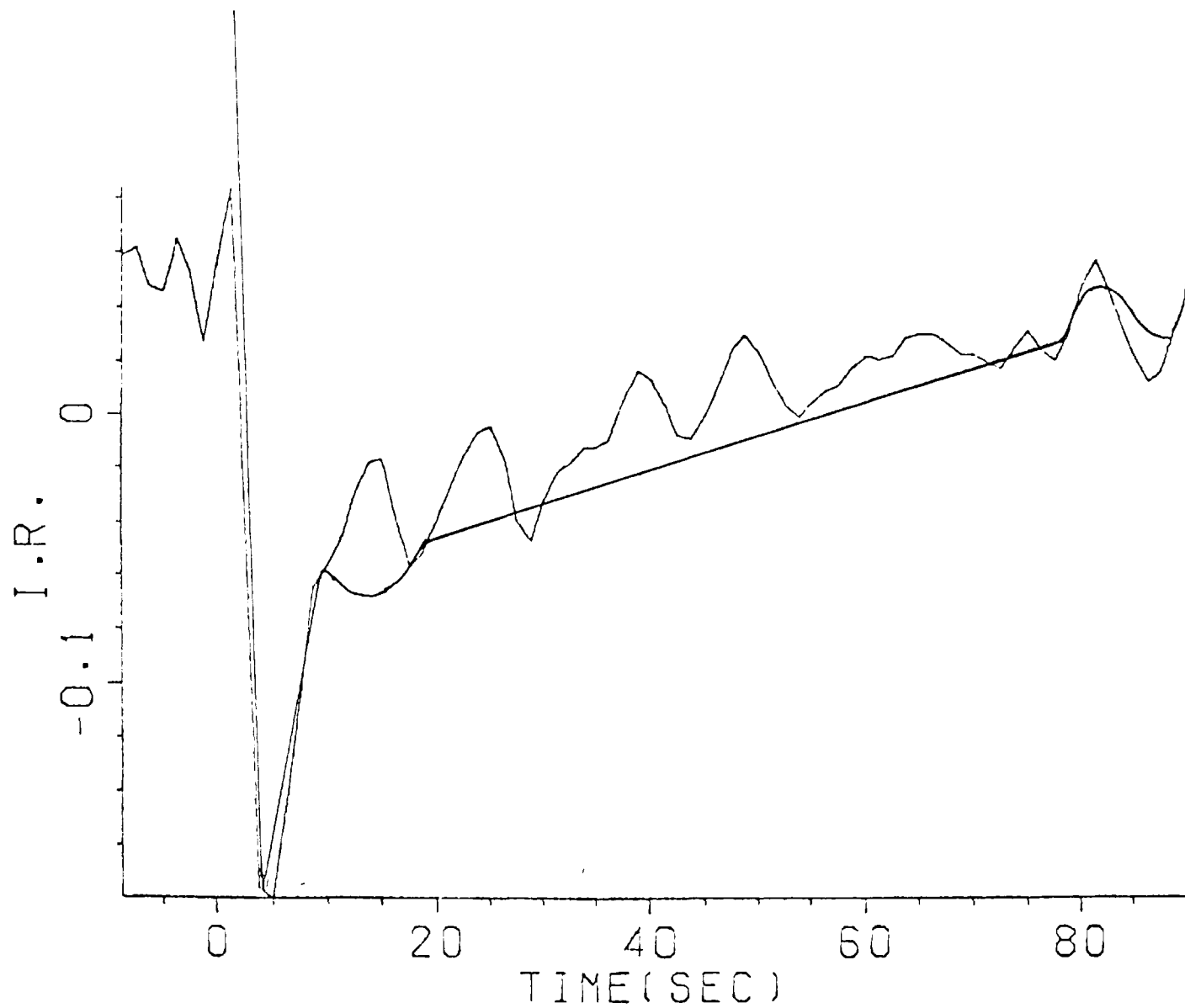


Figure 77. Impulse response of heart rate together with the impulse response of the model. The latter was calculated as the inverse Fourier Transform of the closed loop lag plus P.I. frequency response.

rate response. Figure 78 shows a negative exponential decay, calculated as  $e^{-x}$  where  $x = 2\pi/c$ . The same exponential, band limited to four harmonics, is also shown.

In the present case, the two exponentials which constitute the impulse response have time constants which depend upon the corresponding time constants of the series-linked P.I. and lag elements. Thus, any filtering applied to one element will affect both elements, and therefore both exponentials.

Some evidence that a filtering operation is taking place comes from the Bode diagrams. Taken as a whole, the 20-40Hz. blood pressure results almost invariably maintain a steeper P.I. slope than heart rate. This effect could be due to some degree of attenuation being applied to the higher frequency blood pressure components. At the 1rad/sec. point, the blood pressure Bode amplitude was typically -20 to -25dB, while heart rate usually remained at -10 to -15dB. Figure 79 presents the Bode amplitude diagrams for blood pressure and heart rate for other 20-40Hz tests, to illustrate this point. The presence of some filtering action could also explain the spreading of power at the low frequency end of the blood pressure responses, which sometimes showed a slightly higher reset corner frequency than heart rate. The presence of some filtering action is also confirmed by the correlation coefficients calculated in the previous section. It was found that the blood pressure signal generally held all its power in the first 10-15 harmonics, with the first 3-4 harmonics contributing over 60% of the power. Heart rate and respiration were more widely spread, the first 10-15 harmonics contributing 60% of the power.

The blood pressure response cannot be modelled completely in

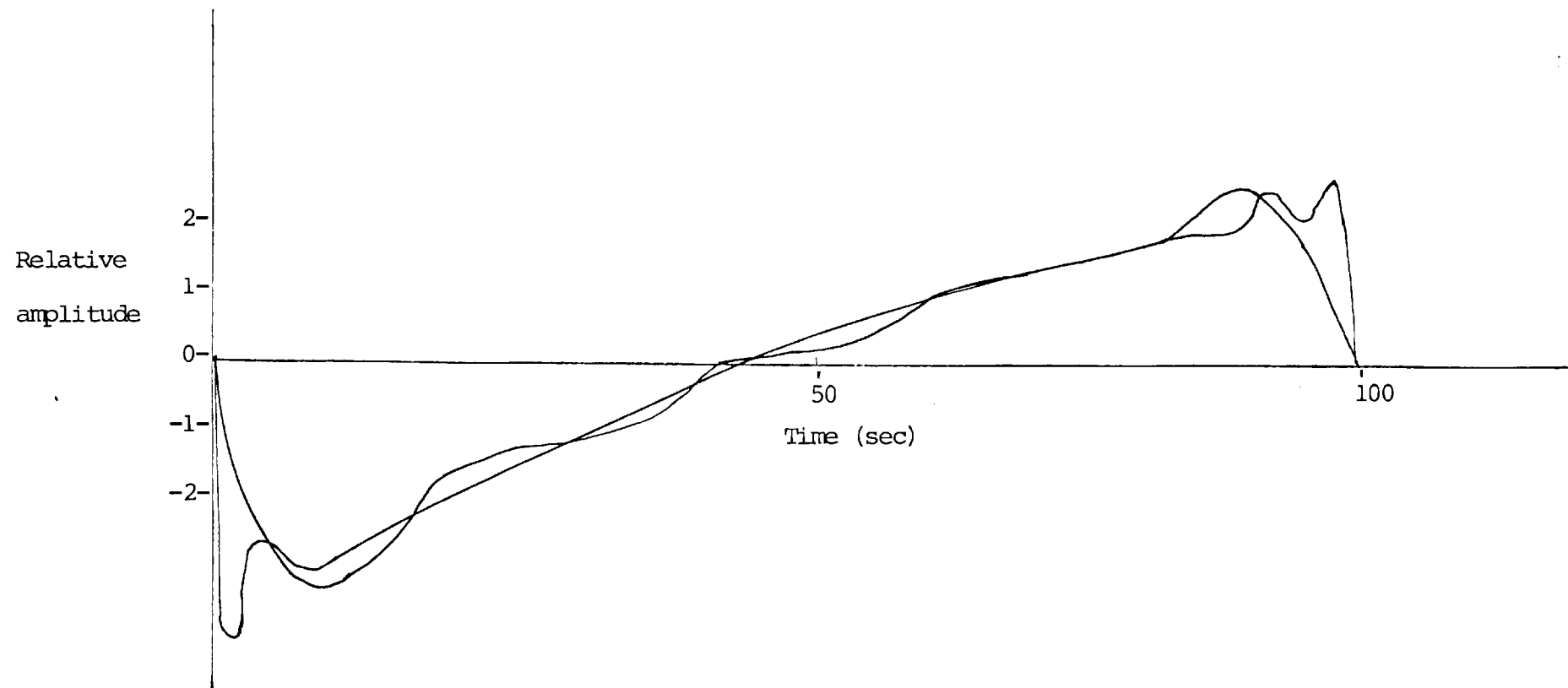


Figure 78. Diagram illustrating the impulse response of a first order lag of corner frequency  $0.052\text{rad/sec.}$ , and the same lag band-limited to 4 harmonics.

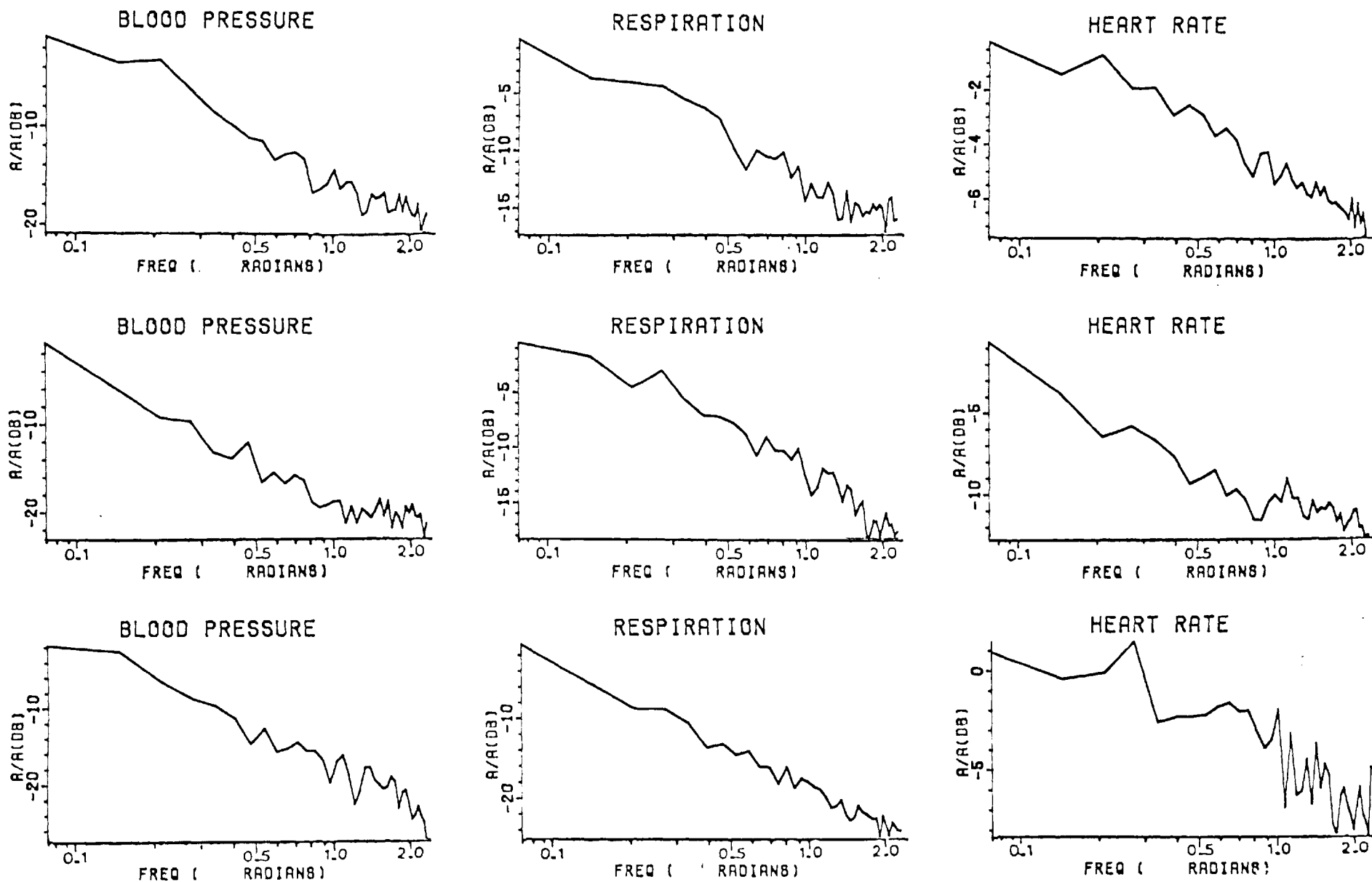


Figure 79. Examples of other 20 - 40Hz. Bode amplitude diagrams illustrating the wider decibel range found in blood pressure than in the other two responses. This is evidence of attenuation of the blood pressure response.

terms of a filtered version of the heart rate response, since the fast initial blood pressure response is still not accounted for. The best explanation for the fast response must be that the heart rate information reaches the point of blood pressure measurement before the filtered information. The delay between the two is about 5 seconds. Since this result has implications which are strongly related to the physiology, it is discussed in greater depth in the next section.

The proposed model for the blood pressure response underlines the desirability of considering the impulse response information alongside the frequency responses, since information presented clearly in one is sometimes not as obvious in the other.

Figure 80 shows the addition of the band-limited exponential of Figure 78 to another having a time constant twenty times faster. This is added to the heart rate impulse response, with a delay of 5 seconds. The result is a good match for the blood pressure response (also shown).

The respiration impulse response is interesting since it appears to resemble blood pressure more closely for the first 30 seconds of the response, then reverts to the ramp-like response pattern of heart rate. Since the Bode plots for respiration do not appear to differ appreciably from those of the other two responses, it is possible that under the present conditions respiration acts as a passive element. As such it reflects whichever part of the system is dominant at the point at which respiration connects with the baroreceptor control loop.

Consideration of the system impulse response in Laplace terms

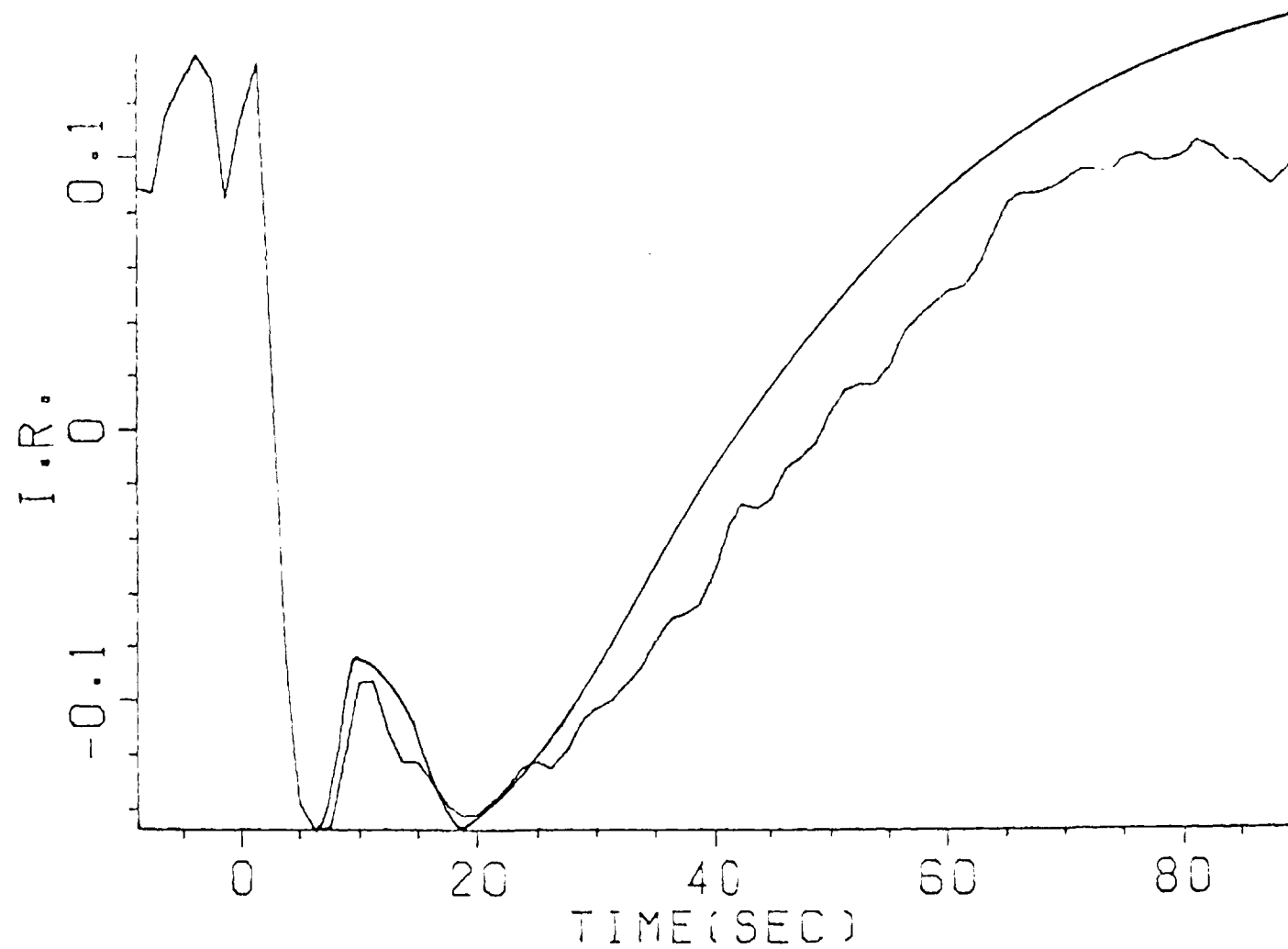


Figure 80. Impulse response of blood pressure, together with the impulse response for the model. The latter consists of the heart rate impulse response, added to a band-limited version of this response, delayed by approx. 5sec.

also adds weight to the premise that the model is based upon serial combination of the system elements. Parallel combination leads to a time function which consists of the summation of a decaying and a rising exponential. Their time constants are such that the decaying exponential reverses the rising one, as shown in Figure 81. Integration does not therefore result.

Rather than develop a physiological model on the basis of one graph, it is appropriate at this stage to see how these findings fit in with the rest of the data collected.

Figure 82 shows the Bode and impulse response diagrams for a PRBS stimulus of 80-100 Hz. This time, both heart rate and blood pressure exhibit the same time response; fast initial response and slow return to normal, not stabilizing within the 100 sec. Respiration once again shows a mixed response, with a slowing of the reset curve after the 30 sec. point.

The Bode diagrams for heart rate and blood pressure are also very similar, being consistent with that of a P.I. controller plus first order lag as before.

Figure 83 illustrates the response to a PRBS stimulus of 40-60 Hz. Here heart rate exhibits essentially the same response as before. Blood pressure and respiration are now similar, and both show a "corner" in the impulse response of 38-40 seconds.

The next figure (Fig.84), illustrating the response to a PRBS of frequency range 60-80 Hz., tells essentially the same story for blood pressure and heart rate as in the 40-60 Hz response. Blood pressure has shorter reset time but again exhibits the transition from faster to slower response at 38-40 sec in the impulse response.

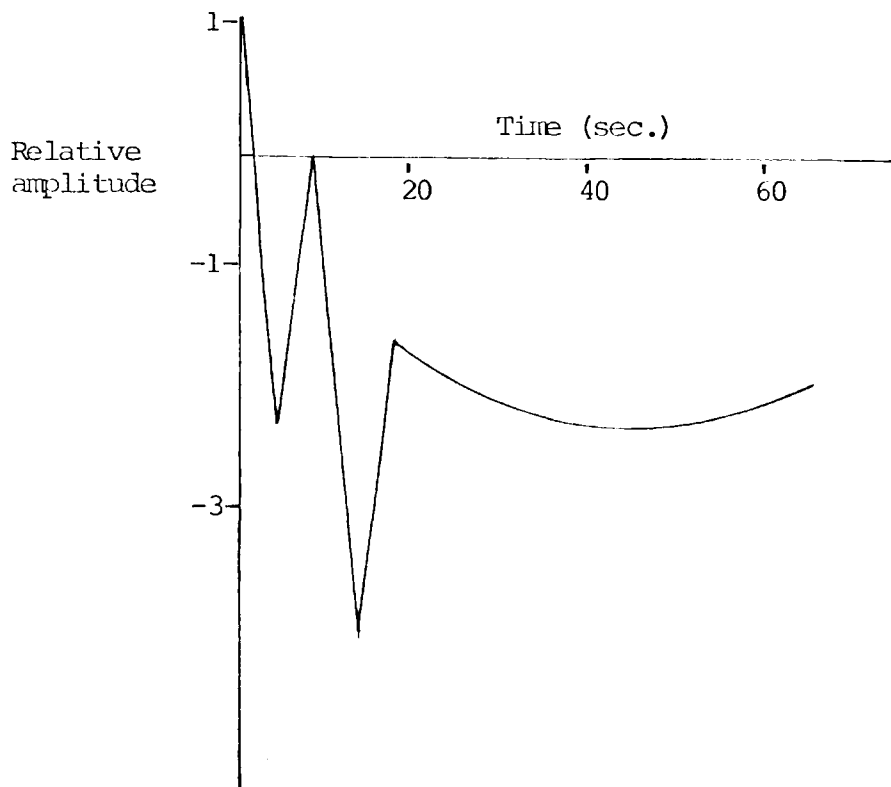


Figure 81. Diagram illustrating the impulse response of parallel combination of the lag and P.I. elements. Opposing exponentials mean that integration is not achieved.

Figure 82.

## BODE PLOTS AND IMPULSE RESPONSES

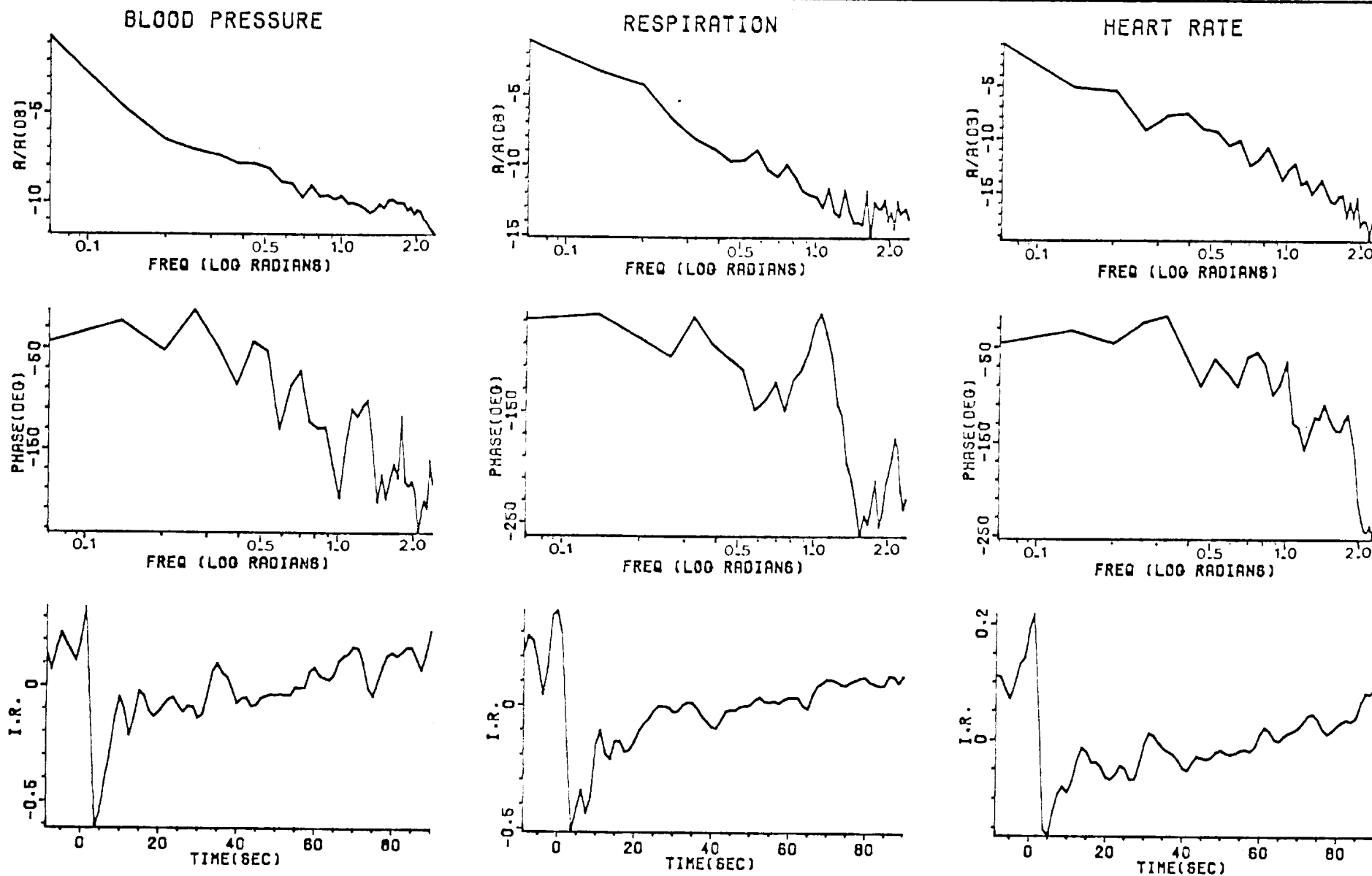
9 OCT 81  
80 - 100Hz.

Figure 83.

# BODE PLOTS AND IMPULSE RESPONSES

40 - 60Hz. <sup>9</sup> OCT 81

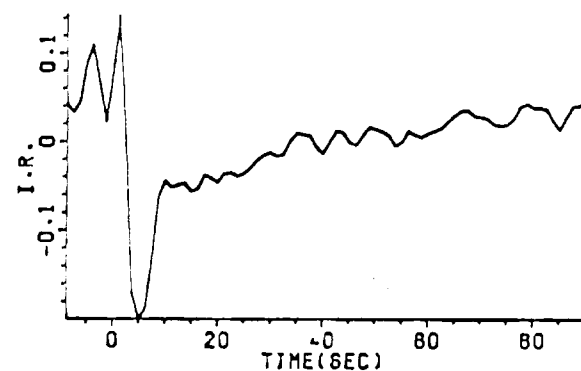
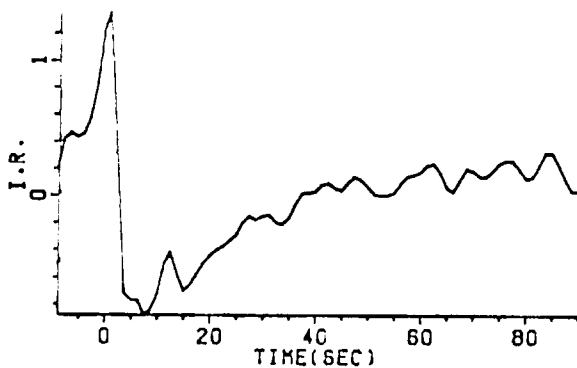
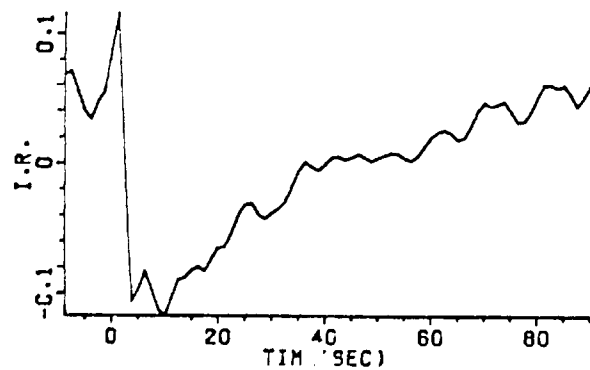
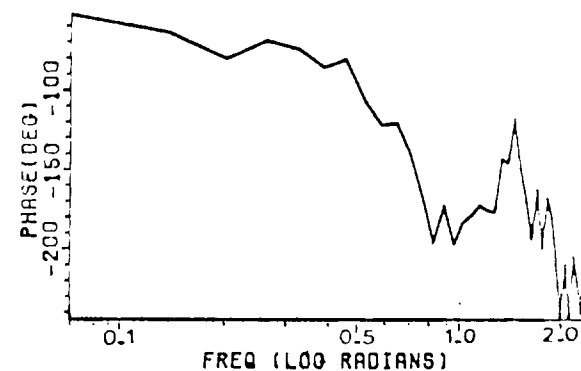
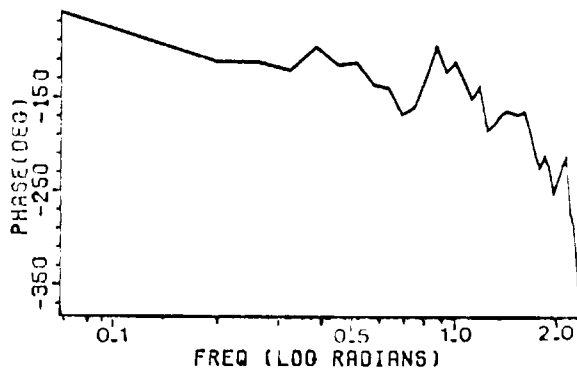
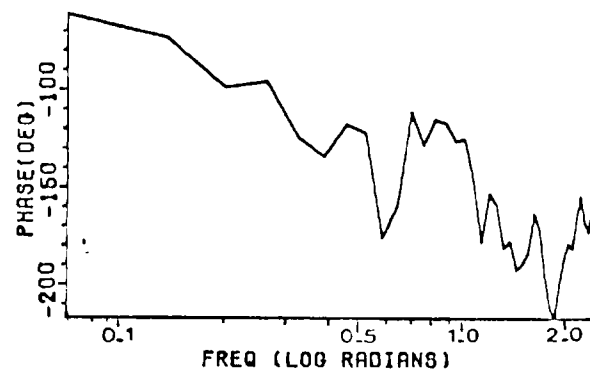
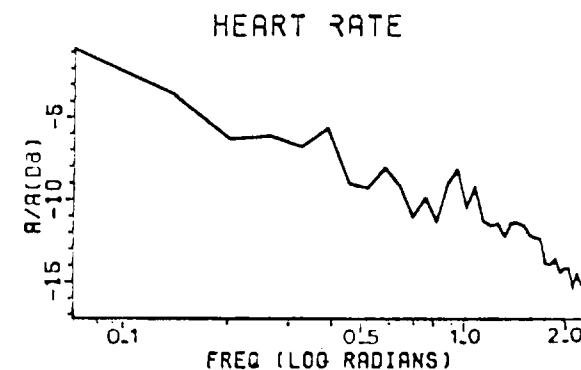
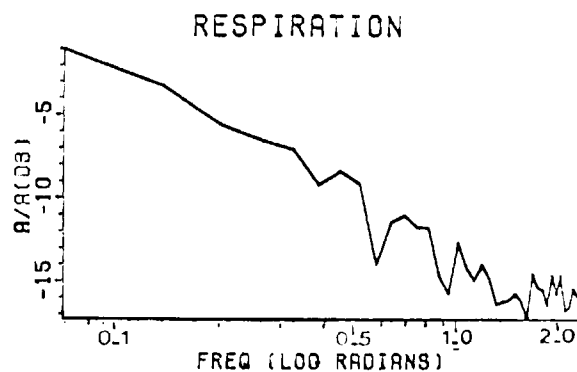
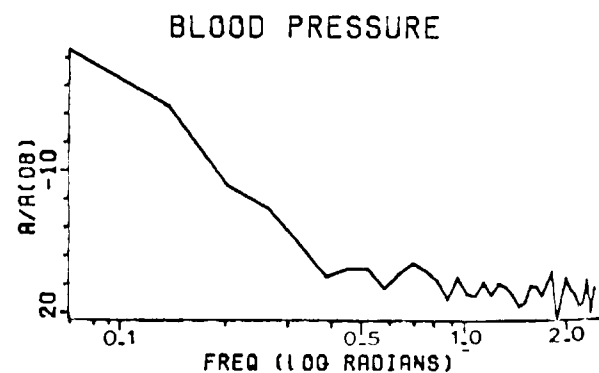
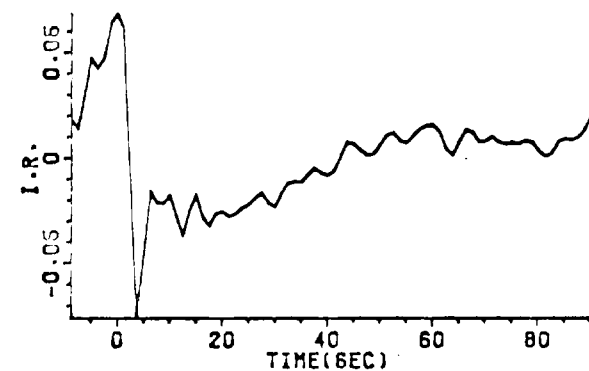
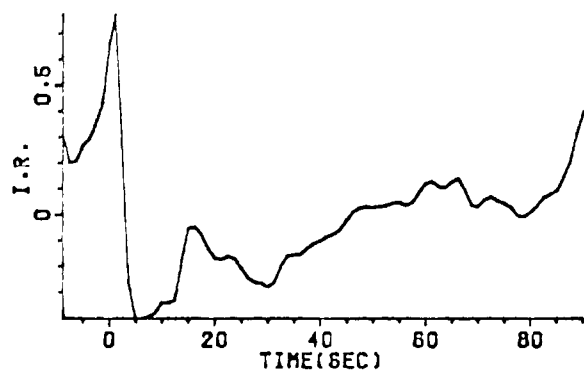
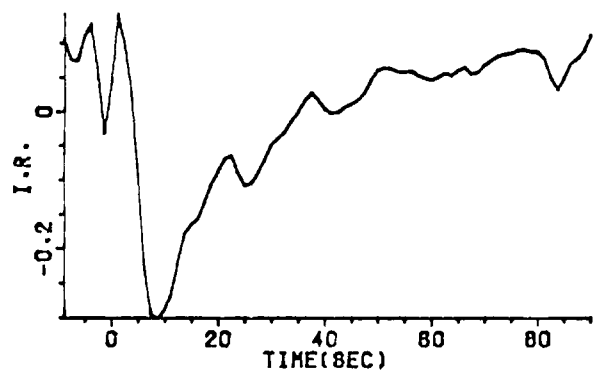
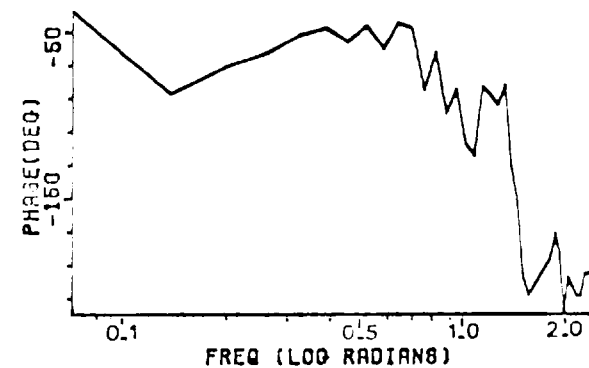
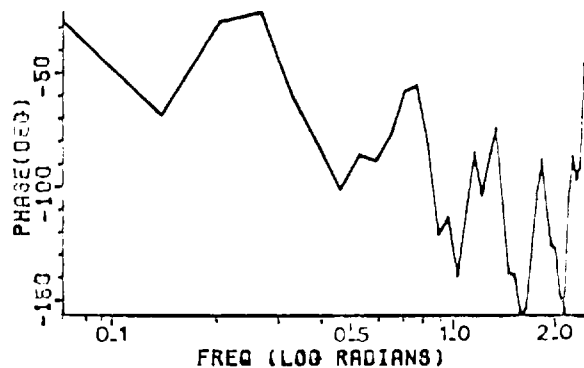
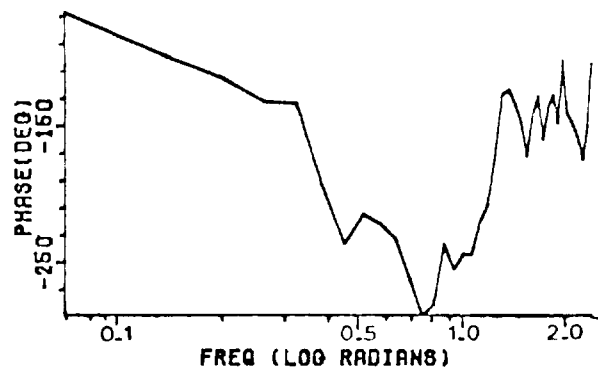
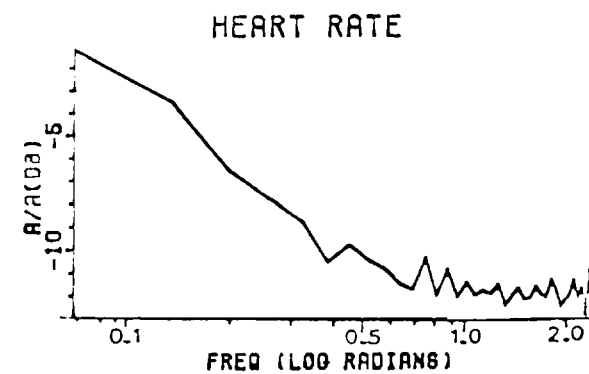
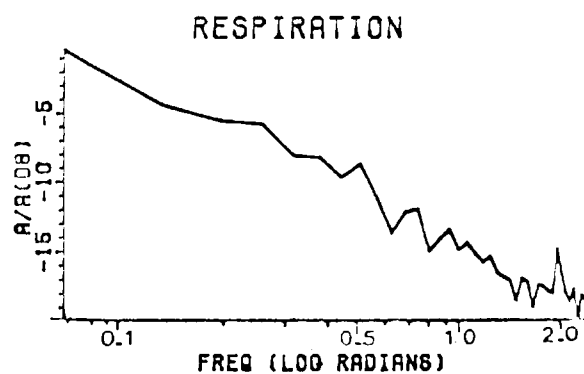
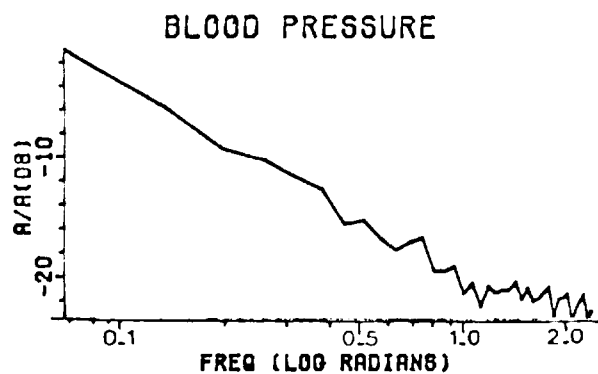


Figure 84.

# BODE PLOTS AND IMPULSE RESPONSES

60 - 80Hz. 9 OCT 81



The respiration response in this instance is very much closer to heart rate than that of blood pressure.

There are several points which can be drawn from this information:

- 1) The first-order lag and P.I. elements are common to all 3 responses and do not vary with increasing frequency.
- 2) The heart rate response shows the same characteristics over the entire frequency range.
- 3) The blood pressure response shows characteristics which differ from heart rate at low frequencies but become increasingly similar to heart rate as stimulus frequency increases.
- 4) The respiration response is similar to blood pressure at low frequencies but closer to heart rate at high frequencies.

#### 5.4.2 Physiological explanation of the the system responses.

Having looked at the system responses from a purely theoretical point of view, it is necessary to see how far the above conclusions are compatible with what is known about the physiological system. A few points should be borne in mind during the interpretation:

- 1) The system responses represent the effect of applying a stimulus in the form of an impulse to the cardiac depressor nerve.
- 2) The neural stimulus was of sufficient intensity to activate all fibre groups in the depressor nerve.
- 3) Blood pressure was measured in close proximity to the heart and thus should reflect either cardiac output

or TPR, whichever is dominant.

First it is useful to reconsider the known physiological layout of the control system as presented in fig 68 in a manner more appropriate to control analysis. Figure 85 redefines the control loop in a way which coincides with the viewpoint taken in figure 72.

The function of a feedback system is to compute the difference between the setpoint and the feedback signal. The difference is the error signal, and is used as the input to the control system elements. It follows that the role of feedback comparator can be assigned to the depressor area, since it receives the feedback input from the cardiac depressor and compares this with the desired blood pressure level as dictated by higher centres.

The concept of suppression of the pressor centre by the depressor centre now becomes much clearer. If, for example, a set point of 200 mm Hg has been specified, but the cardiac depressor relays the information that the current level is only 150 mm Hg, the depressor area generates an error signal of +50 mm Hg. The pressor area therefore increases its output signal until the error is reduced to zero. Similarly, a negative error signal will cause the pressor area to reduce its output. The pressor area therefore acts in direct relation to the error signal.

It is more appropriate to say that the depressor area acts to suppress vagal activity. Again, if a positive error is generated indicating that circulatory pressure is too low, the vagus is caused to decrease its level of firing. Similarly, a negative error causes an increase in firing. An extra element with a transfer function of -1 has therefore been inserted in the vagal path of fig 85.

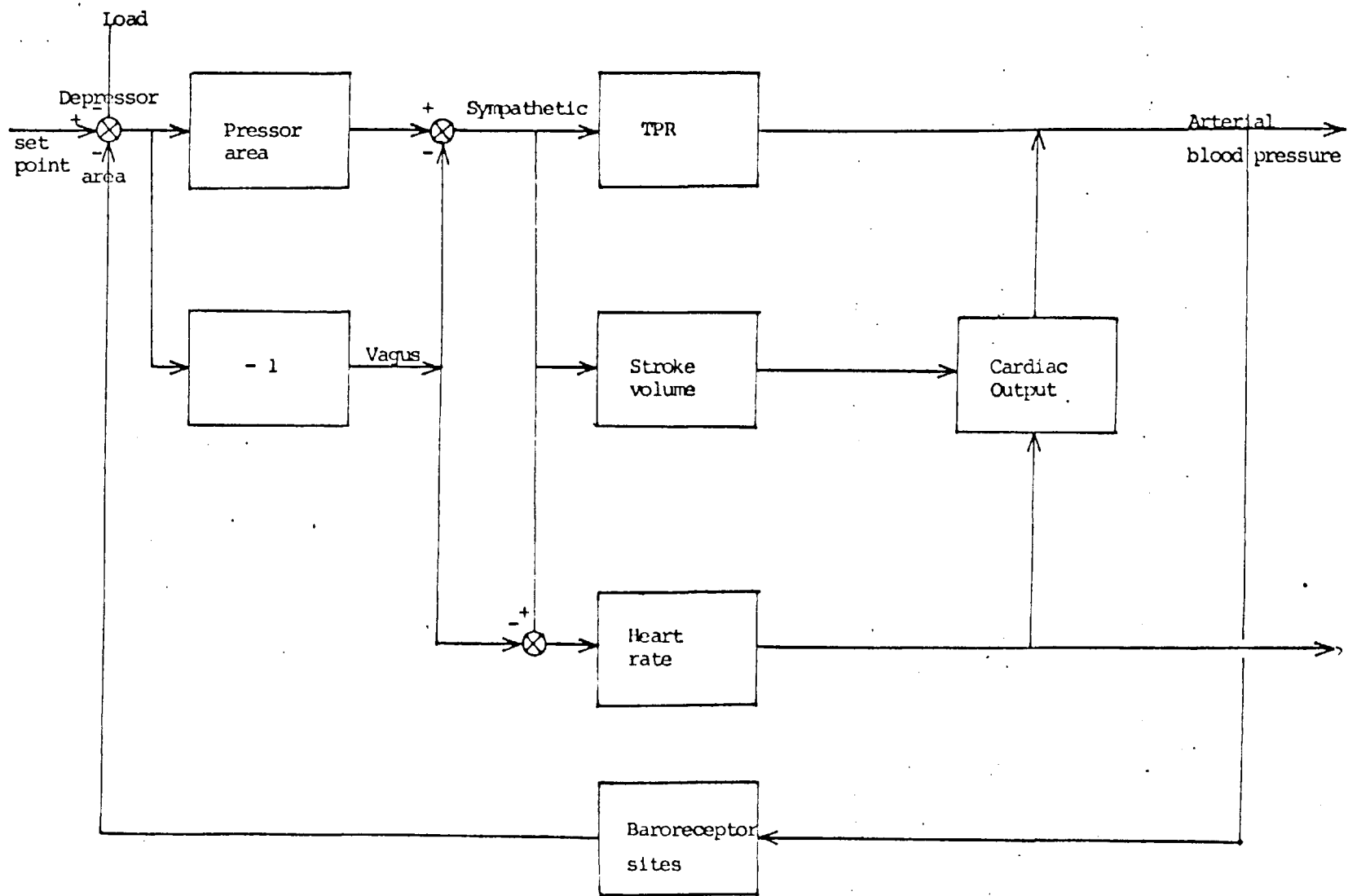


Figure 85. Restatement of the block diagram of the baroreceptor control loop.

However, due to the transmitter used, stronger vagal firing has the end effect of reducing heart rate or TPR. Overall, therefore the two autonomic pathways add in control terms, and vagal/sympathetic interaction may be represented as the addition of two parallel pathways. There are several ways in which the model described in the previous section can be made to fit the physical control system of fig 83. Ultimately, the only way to decide which option has the best chance of being right is to weigh each against the results of other workers.

Remembering that the model calls for the series combination of a lag and a P.I. element there are certain factors which are common to all interpretations. Firstly, because of its short time constant, it is likely that the first-order lag represents the total neural lag around the system. That is, it incorporates the transfer functions of the pressor and pressor areas, together with the lags introduced by the nerves themselves. That neural networks may be modelled by first-order lags has been amply demonstrated by other workers. For example, Penaz(1962) found that the vagus itself acted as a first-order lag with corner frequency of about 1 rad/sec. Since the corner frequency will decrease with the length of the pathway, the present finding of 0.5-0.55 rad/sec for the total loop is not unreasonable. Similarly, Hatakeyama (1967) quoted a somewhat variable 0.25-0.06 rad/sec as the corner frequency for the total loop lag, but this still ties in with the present results. The fact that lag element was absolutely invariant for all tests adds weight to the idea that it corresponds to the physical rather than the physiological, system.

Secondly, it was suggested that the low frequency blood

pressure responses were subject to some kind low pass filtering which did not appear at higher frequencies. From the results of the pilot experiments of Chapter 2, it was expected that blood pressure and heart rate would act differently at such low frequencies. At these frequencies, the maintenance of blood flow has been shown to be controlled primarily by the alteration of vascular resistance ; that is, by changing TPR rather than heart rate. It follows that the filtering effect is connected to TPR, and therefore is likely to represent the transfer function of the vessels themselves. It is easy to visualize the elastic vascular vessels as being more efficient at transmitting lower frequency information.

Support for this idea can be found in the literature. Rosenbaum and Race(1968) calculated the frequency response of the peripheral arterial vessels using sinusoidal stimulation of the sympathetic nerve. They estimated the transfer function to be a first- or second order lag with corner frequency 0.11 rad/sec, plus dead time of 0.5 sec (see Figure 86). Information from the Bode diagram in the last section (Figure 69) suggest rather that the transfer functions of the vessels resemble that of a lag compensator, with  $1/T_A < 0.06$  rad/sec and  $1/T$  slightly greater than the reset corner of the P.I. element. Thus, frequencies up to  $1/T$  would be magnified, relative to the rest. Rosenbaum and Race's results would include some lag component due to the sympathetic itself, which could account for the second order amplitude slope, but first order phases. Grodins(1963) found that arterial muscle acted as a lag element with corner frequency 0.1-0.2 rad/sec which reinforces the idea that the frequency band attributed to the filter element is appropriate to vascular structure. Furthermore, the presence of this lag-compensator element could account for the dip

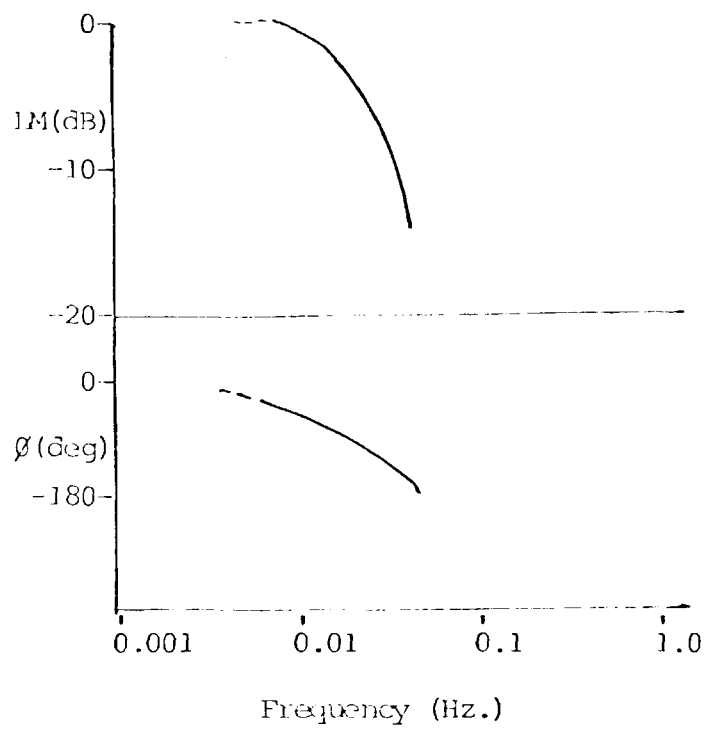


Figure 86. Bode amplitude and phase plots of the response of peripheral resistance vessels to stimulation of the sympathetic nerve. From Rosenbaum and Race, 1968 .

in the phase diagrams discussed in the previous section.

The main problem outstanding, therefore is accounting for the action of the parallel autonomic pathways in terms of a model which contains only serial elements. It is proposed that only part of the model not yet accounted for, the P.I. element, represents the transfer function of the autonomic action. There are basically three ways in which the model may be fitted to the physiology:

The simplest way, shown in figure 87, is also the most improbable. In this scheme, the serial pathway is achieved by using only the vagus or the sympathetic as a representation of the P.I. action. Although the solution works from a control point of view, physiologically it is difficult to visualise. Since the pressor area (and thus the sympathetic) cannot act without the depressor area being activated, the vagus is the only pathway that is capable of doing all the work. This ties in with the finding of Douglas, Richie and Schaumann (1956) that when the depressor nerve is maximally stimulated (as in this case), the vagus is the main effector pathway. The response of blood pressure at low frequencies then becomes a stumbling block. Since the activity of sympathetic vasoconstrictors is indicated, parallel pathways must again be in operation. This is probably true even if the fast vagal-sympathetic link shown in Figure 85 is the pathway for vasoconstriction in this case.

The strongest argument against a system such as that shown in figure 87 is that it does not explain the complexity of the baroreceptor effector system. Any useful model must necessarily provide some justification for the existence of two central control areas and two effector pathways. The most likely reason for

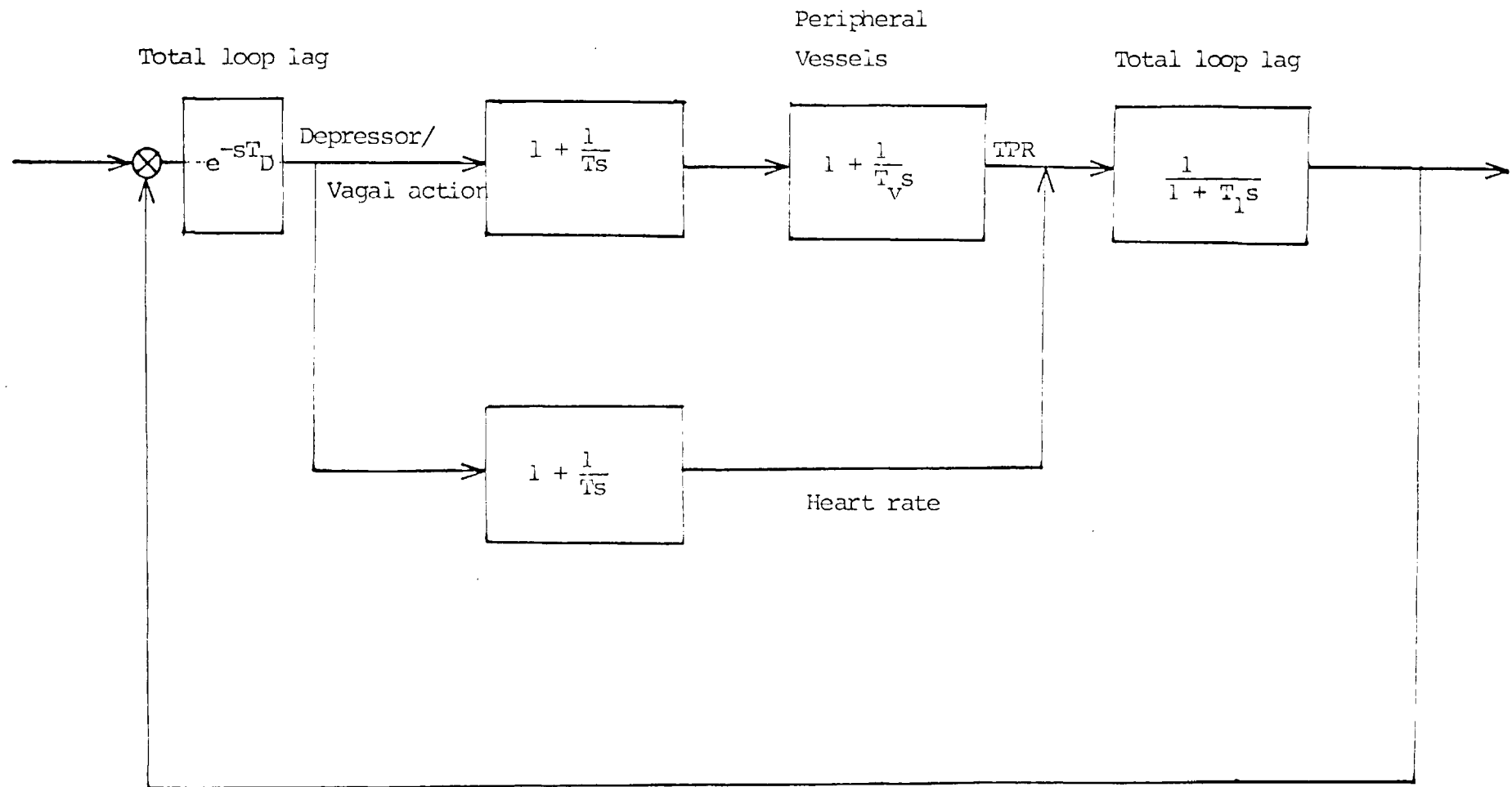


Figure 87. Block diagram representation of the model's transfer function in terms of the physiology of the baroreceptor loop. Vagal action only constitutes the response path.

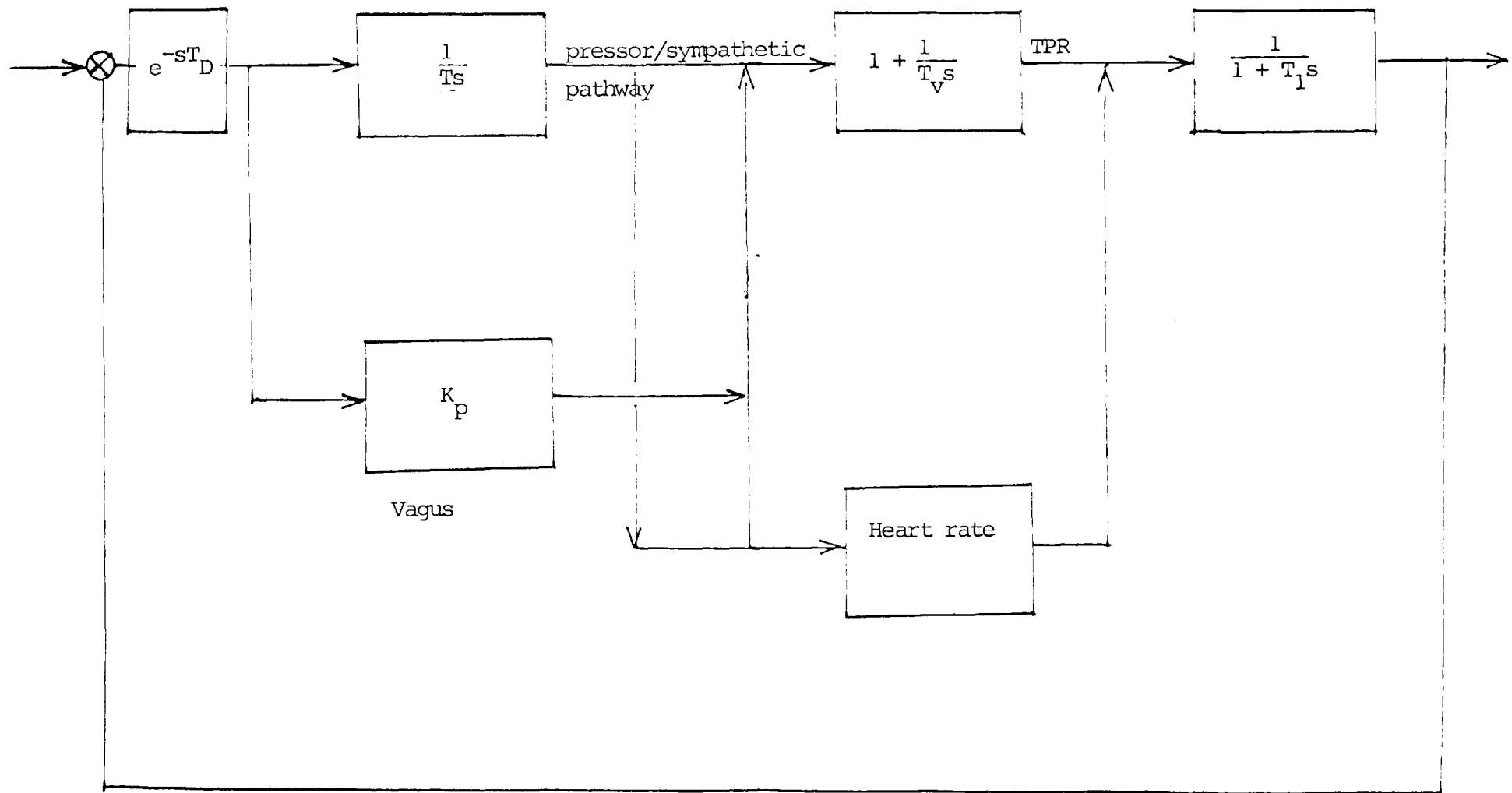


Figure 88. Block diagram representation of the transfer function of the model in terms of the physiology of the baroreceptor loop. The vagus represents the proportional element, while the sympathetic models an integrator element.

maintaining these otherwise redundant components is that their presence improves the system response. If their interaction results in proportional plus integral action, then their existence is immediately justified. Hatakeyama's (1967) suggestion that the baroreceptor loop can be modelled by a first-order lag cannot provide a complete solution to the problem since an offset would always exist. This offset is eliminated by the inclusion of integral control. Certainly, no offset can be seen in study of the physiological data.

One way of equating P.I. control to sympathetic/parasympathetic action is shown in Figure 88. The P.I. transfer function is treated as a summation of its proportional and integral parts, represented by the vagus and the pressor area-sympathetic link respectively. The vagus is in fact a good candidate for a proportional element, since its corner frequency of about 1 rad/sec. (Penaz, 1962) is twice the value of the corner frequency of the total loop lag. This means that the vagal frequency response is effectively flat over the frequency range of interest.

The Bode diagrams for an integrator are shown in Figure 89. The amplitude curve has a constant -6dB/octave slope, and the phases maintain a constant -90 level. Support for the idea that the sympathetic nerve could act as part of an integrator element again comes from Rosenbaum and Race (1968). The Bode diagrams which they obtained for sympathetic vasoconstrictor stimulation and measurement of systemic arterial pressure (Figure 82) show that when the transfer function of the vessels themselves is taken into account, the amplitude response may also incorporate the requisite -6dB/octave slope over the frequency range considered (0.01 to

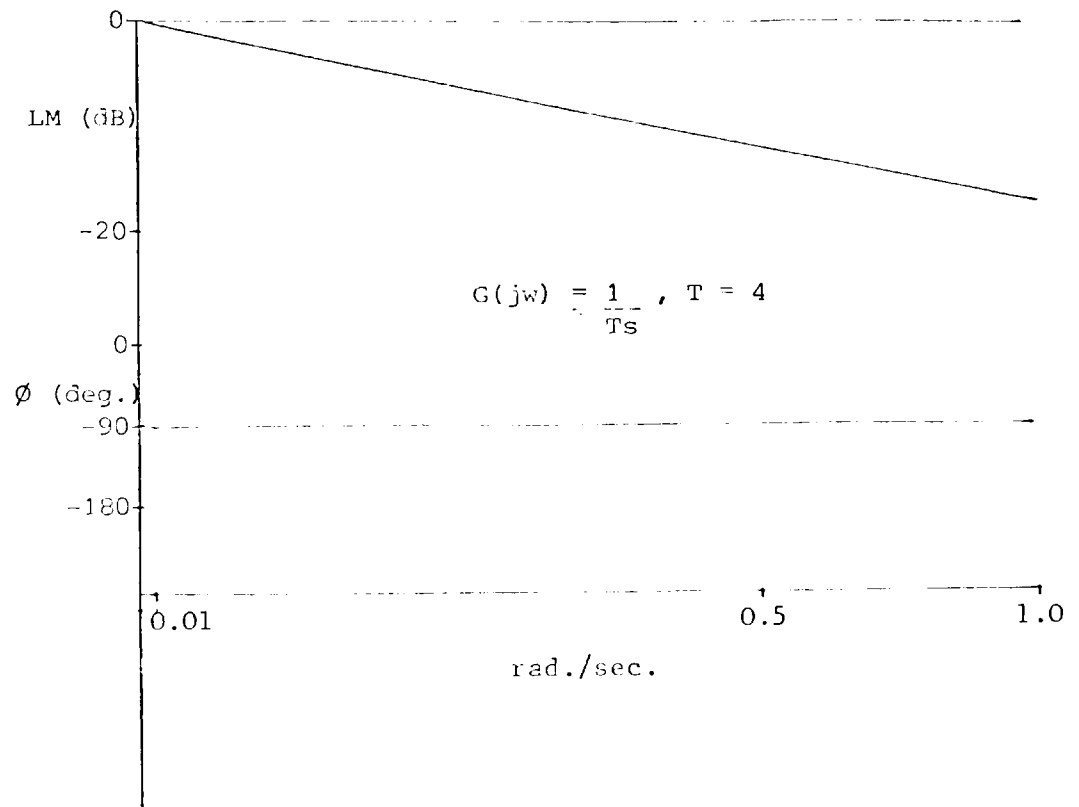


Figure 89. Frequency response of an integrator element.

0.303Hz.). The ideal proof would obviously be frequency responses obtained from stimulation of the depressor nerve and recording of sympathetic input to the heart or to the peripheral vessels. No evidence of such a study could be found from the literature.

The final scheme, and potentially the most useful one, for matching the model to the physiology is shown in Figure 90. Here, the P.I. transfer function is treated in its alternate form as a lag compensator. It is possible to simplify the transfer function of the lag compensator into two lag elements, so that

$$\frac{T_s+1}{T_A s+1} = \left[ \frac{1}{T_A (s+(1/T_A))} + \frac{T}{T_A} \left[ 1 - \frac{1}{T_A (s+(1/T_A))} \right] \right]$$

where  $T_A > T$ . This combination of a rising and a smaller negative rising exponential has an open loop time response of the characteristic integral ramp. The attractiveness of this scheme is that it is very easy to visualise the autonomic nerves acting together in this way. A step input applied to the depressor nerve would cause an exponential drop in sympathetic firing, plus a corresponding exponential rise in vagal action. In addition, the exponential rise is larger than the negative rise element, which is consistent with the physiological dominance of the vagus over the sympathetic. Another advantage of this scheme is that it does not require the presence of any components which are physiologically difficult to visualise. It has already been shown that nervous pathways approximate to first-order lag elements; in the present case their combination produces a good facsimile of the more complex P.I. controller.

The advantage of P.I. action over purely proportional control

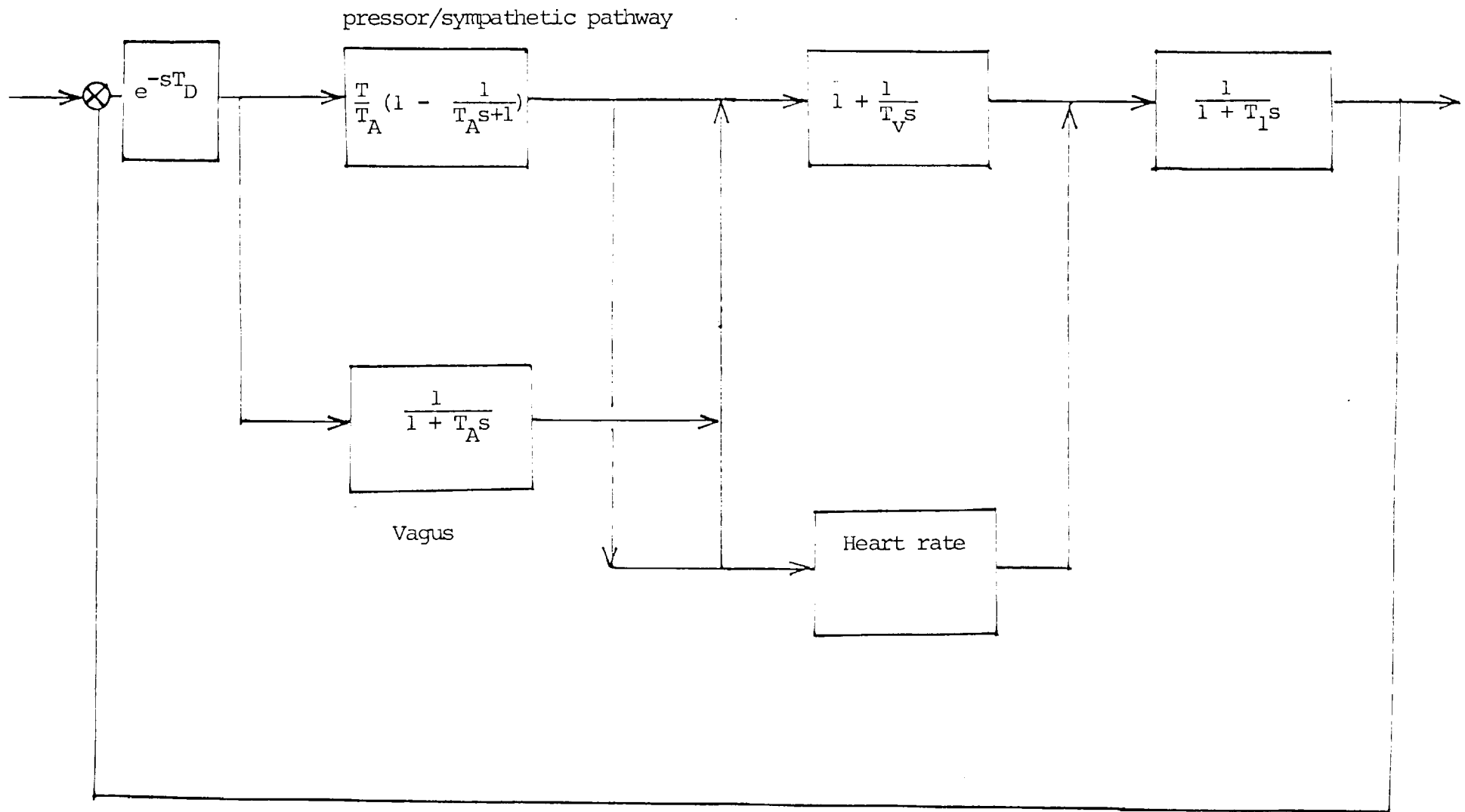


Figure 90. Block diagram representation of the transfer function of the model in terms of the physiology of the baroreceptor loop. The vagus represents a lag element, while the sympathetic is a negative lag.

is that the error is always reduced to zero. That is, the response lines out at the set point with no offset. The time taken to line out depends upon the reset time. Short reset time is obviously desirable, but moving the reset corner too far to the right decreases the critical frequency of the underlying system lag(s) and thus makes the control system response sluggish (Harriott, 1964). In man-made systems a compromise is made and the reset time is often set equal to the ultimate period for the process with just proportional control. Under these conditions,  $w_c T = 2\pi$ . A tolerable system is one where the response lines out within 3-4 reset periods. In the present case, line-out occurs within this time.

The final topic to be considered is that of respiration. The reason for studying respiration was to clarify the point of interaction between the respiratory system and the baroreceptor control loop. Research carried out by other workers (see Chapter 2) showed that the interaction could occur either at a central level, by spillover from the cardiac control centres to the adjoining respiratory control centre, or at a circulatory level, via the arterial chemoreceptors. In the present case, it was found that respiration followed the response of blood pressure at low stimulus frequencies and heart rate at higher frequencies. Since the difference between the blood pressure and heart rate responses has been shown to occur at a circulatory rather than at a central level, the same must be true for respiration. In the anaesthetised animal, therefore, it is concluded that the chemoreceptors of the carotid sinus cause the passive modulation of respiration. The pathways which effect this modulation do not appear to have a transfer function which can be isolated from that of the

baroreceptor loop.

Respiration begins to follow heart rate at a lower stimulus frequency than the measured blood pressure response does. It follows that arterial blood pressure was measured at a distance from the heart which was greater than the distance between the heart and the carotid sinus.

It has been shown that as PRBS intensity increased, the heart rate response remained essentially the same, while that of blood pressure followed the heart rate response more and more closely. It has already been shown (section 2.4) that TPR becomes less influential in controlling blood flow as stimulus intensity increases. Heart rate was shown to dominate TPR above the 50-60 Hz stimulus level. This agrees well with the present results, since the 40-60 Hz response diagram (Fig. 83) shows a blood pressure response which initially follows the faster-changing TPR, but switches to the slower heart rate slope after about 35 sec. The 60-80 Hz response (Fig 84) also shows this effect. The 80-100Hz response (Fig 82) was sufficiently strong for heart rate to overshadow the effect of TPR on blood pressure, and the response appears to be entirely due to heart rate.

A final problem to be solved is that most of the Bode diagrams show phase information which exceeds  $-90$  degrees at the high-frequency end. At first sight, this is incompatible with the frequency response of a first-order lag. The answer is that both the blood pressure and heart rate responses contain time delays. Blood pressure has a delay of 2-4.5sec. (Scher and Young) or 0.2-2 sec. (Rosenbaum and Race). A further 0.2 sec. is attributed to the vagal system (Penaz, 1962). The heart rate response also

contains these delays, as well as some dead time due to venous musculature. Dead time has no effect upon the Bode amplitude ratios, but leads to a phase shift which is proportional to frequency, so that

$$\phi = -\omega T_D \text{ radians (Shilling, 1963)}$$

where  $T_D$  is dead time. Scher and Young noted that estimation and removal of the dead time yielded a frequency response with phases not exceeding 90 degrees. They took a value of 2.5sec for the dead time in cats and dogs. In the present case, the maximum phase shifts obtained are rather less than those found by Scher and Young. A delay of about 1.5sec was sufficient to realign the phases in all cases. As pointed out in the previous section, the only satisfactory way to explain the blood pressure response at stimulus frequencies where TPR was the dominant response was as a combination of the responses due to heart rate and TPR. The latter was thought to be delayed about 5sec. relative to the former, which is consistent with the results of Scher & Young. The blood pressure response was measured close to the heart, and therefore reflects the summation of the parallel TPR and heart rate pathways shown in Figure 84. The time delay shown by the frequency response will be given by the relationship

$$\frac{e^{-st_1}}{e} + \frac{e^{-st_2}}{e}$$

where  $t_1$  and  $t_2$  are the delays of heart rate and TPR. The resulting total time delay lies between the two values. It is therefore considered that the value found for the total loop delay is consistent with that found by other workers.

Levison et al also found that the frequency response which they obtained for the carotid sinus system contained phase values in excess of -90 degrees. They attributed these values to the presence

of a second-order system having no dead time. Second-order characteristics (-12dB/Octave attenuation and -180 degrees/Octave phase shift) were never observed in the present case. In addition, it is unlikely that a physiological control system would have no delay time at all.

### 5.5 Summary

The stationarity of the experimental data was considered by calculation of the coherence function. While some results were acceptable, on the whole it was argued that coherence estimation was not entirely valid in this instance, due to the nature of the data. Values were also calculated for the correlation coefficient between each of the twenty estimates of the frequency response for each experiment, and their ensemble average. The correlation was found to be high, allowing the assumption that the ensemble average was a good representation of the true frequency response of the system.

It is proposed that the baroreceptor control loop can be described by the following control elements:

- 1) A first order lag of corner frequency  $0.5 \text{ rad./sec.}$ , representing the total of all lags around the loop. These lags are thought to represent the transfer functions of the physical pathways
- 2) A P.I. or lag compensator element of corner frequency  $0.01 \text{ rad./sec.}$  which represents the parallel interaction of the medullary control areas and the autonomic nerves
- 3) A total time delay of about  $1.5 \text{ sec.}$ , which is largely attributable to the peripheral resistance vessels
- 4) A filter element which applies only to blood pressure, and which is thought to represent the transfer function of the peripheral vessels

The system is basically first-order, but the presence of the P.I.

action increases this to second order. No significant transfer function could be distinguished which applied to either heart rate, respiration, or to the feedback loop. The system behaved linearly within each stimulus range, but blood pressure exhibited some changes in form when the entire experimental range was considered.

## Chapter 6

## Conclusions.

The primary aim of the project was the estimation of the closed loop frequency and impulse responses of the baroreceptor control loop. This was considered to be an essential step in gaining a more detailed understanding of the baroreceptor system, continuing from open loop studies carried out by other workers. The results of the experimental studies tend to confirm that the primary aim has been achieved, and have established the viability of the analysis methods.

This research is considered to be the first analysis of the baroreceptor control loop in which wideband test signals have been used, and where the closed loop has been studied. Furthermore, the animal experimentation took into account the single input - multiple output nature of the baroreceptor control loop.

Data analysis was undertaken by frequency domain estimation of the system frequency response by cross-correlation of system input and output. This approach is considered to have many advantages. Firstly, it was conceptually and computationally simple compared with time-domain system identification of polynomial approximation. Secondly, the long response time (100sec.) of the baroreceptor control loop favoured frequency domain analysis. Time domain algorithms commonly offer the ability either to work only on short data lengths, or to use longer data and suffer excessive computer processing time. Thirdly, the method allowed the direct formation of the frequency and impulse responses without the additional complexities of Laplace transformation.

Because few comparable studies have been conducted previously, very little information is available from the literature about the nature of the response, and the various time constants which might be relevant. For example, little information could be obtained as to whether the system was sufficiently linear to lend any consistency to the results. The experimental design was therefore based to a certain extent upon trial and error, and with hindsight some modifications would have enhanced the results. A significant improvement in the experimental results could be achieved by doubling the PRBS period. It was not expected that the lowest harmonics would prove so important and thus the present data represents the proportional plus integral (P.I.) element with only 4-5 harmonics. A longer base frequency would have clarified the system more, for example by confirming the presence of a corner frequency below 0.01Hz., and thus whether P.I. or lag compensation was the most appropriate model.

Similarly, there are various studies which could be carried out which would supplement the present work. A major problem was that no reference could be found in the literature to a study of the frequency response of the sympathetic nerve, without the inclusion of the peripheral vessels. Such a study would show whether the sympathetic acts as an integrator, or whether it resembles a first order lag of time constant comparable to the vagus. Similarly, a study of the frequency response of the peripheral vessels themselves would be useful in determining whether they act as a filter to the autonomic information.

With these exceptions, the results presented in this thesis are seen as a significant clarification of the dynamics of the

baroreceptor control loop. The methods of control engineering have again proven to be valuable tools in the investigation of biological systems.

## Appendix A

## Programming algorithms

## 1) Program for real-time generation of PFM'd PRBS

```

00400 DIMENSION ISET(11),IX(9050)
00110 COMMON IT(2)
00120 M4=-4
00130 LM=22
00140 IP=0
00150 XL=20.
00160C***** SPECIFY UPPER AND LOWER FREQUENCIES *****
00170 IP1=IFIX(8000./XL)
00180 IP2=IFIX(8000./(XL+20.))
00190C***** INITIALIZE TO SHIFT REGISTER *****
00200 DO 5 J=1,10
00210 5 JSET(J)=1
00220C***** SPECIFY CLOCK INTERVAL *****
00230 IC=IFIX(8000./10.23)
00240 TS=0
00250 TA=0
00260 K=0
00270C*CALCULATE SHIFT REGISTER OUTPUT *****
00280 DO 50 KK=1,1023
00290 JSET=IEOR(ISET(7),ISET(10))
00300C***** MOVE ALL STAGES DOWN ONE *****
00310 DO 35 I=1,9
00320 KZ=10-I+1
00330 35 ISET(KZ)=ISET(KZ-1)
00340 ISET(1)=JSET
00350 TS=TS+FLOAT(IC)
00360 IPP=IP
00370C***** FIND OUT IF UPPER OR LOWER RATE REQUIRED ***
00380 IF(JSET)10,10,20
00390 10 IP=IP1
00400 GO TO 12
00410 20 IP=IP2
00420 12 IF(KK-1)30,70,30
00430 30 IF(ISPAR)70,70,40
00440C***** IF CROSSOVER FROM ONE LEVEL TO THE OTHER, WORK OUT
00450C***** APPROPRIATE PULSE INTERVAL *****
00460 40 ITIME=IFIX(FLOAT(IP)*(FLOAT(ISPAR)/FLOAT(IPP)))+ISPAR
00470 GO TO 47
00480 60 K=K+1
00490 IX(K)=ITIME
00500 70 ITIME=IP
00510 47 TA=TA+FLOAT(ITIME)
00520 IF((TS-TA)-FLOAT(IP))65,60,60
00530C***** KEEP TRACK OF TIME LEFT IN THIS CLOCK *****
00540 65 ISPAR=IFIX(TS-TA)
00550 K=K+1
00560 IX(K)=ITIME
00570 50 CONTINUE

```

```

00580 CALL TIME(0,I1)
00590C**** OUTPUT PULSE TRAIN TO ANALOG OUTPUTS ****
00600 CALL AODON(3277,0)
00610 CALL AODON(0,0)
00620 DO 200 L=1,LM
00630 DO 100 J=1,K
00640 85 I2=IT(M4)
00650 IF((I2-I1)-(IX(J)))85,90,92
00660 90 I1-I2
00670 GO TO 96
00680 92 I1=I2-((I2-I1)-IX(J))
00690 96 CALL AODON(3277,0)
00700 CALL AODON(0,0)
00710 100 CONTINUE
00720 200 CONTINUE
00730 CALL EXIT
00740 END

```

## 2) Program to convert ECG to heart rate signal

```

00100 PROGRAM ECGCONV(TAPE6=INPUT,TAPE7=OUTPUT)
00110 DIMENSION X(1000),Y(1000)
00120C***** PROGRAM TO CONVERT ECG TO HEART RATE
00130 SR=400.
00140C***** SAMPLING RATE *****
00150 READ(6,*)(X(I),I=1,1000)
00160C***** READ ECG *****
00170 DO 100 I=2,999
00180 IF(X(I).LE.(X(I-1).OR.X(I).LE.X(I+1)))GO TO 100
00190C***** OTHERWISE, ITS AN R WAVE PEAK *****
00200 HZ=SR/(I-NPREV)
00210C***** WORK OUT DISTANCE FROM LAST PEAK ***
00220 DO 20 J=(NPREV+1),I
00230 20 Y(J)=HZ
00240 NPREV=I
00250 100 CONTINUE
00260C***** FILL R-R INTERVAL WITH HZ VALUE ***
00270 Y(1)=Y(2)
00280 Y(1000)=Y(999)
00290 CALL SMOOTH(Y,X,1000)
00300 CALL SMOOTH(Y,X,1000)
00310 WRITE(7,*)(Y(I),I=1,1000)
00320 STOP
00330 END
00340 SUBROUTINE SMOOTH(PRAY,X,NP4)
00350C***** TRIANGULAR FILTERING *****
00360 DIMENSION PRAY(150),X(150)
00370 DO 10 I=2,(NP4-1)
00380 10 X(I)=(PRAY(I-1)+PRAY(I+1))*0.25+PRAY(I)*0.5
00390 X(1)=(PRAY(2)+PRAY(NP4))*0.25+PRAY(1)*0.5
00400 X(NP4)=(PRAY(1)+PRAY(NP4-1))*0.25+PRAY(NP4)*0.5
00410 DO 20 I=1,NP4
00420 20 PRAY(I)=X(I)
00430 RETURN
00440 END

```

## 3) Program for half-cosine tapering

```
00100 SUBROUTINE HALFCOS(XR,NL)
00110 DIMENSION XR(1)
00120***** HALFCOSINE TAPER FOR CHIRP-Z ARRAY ****
00130***** (HALF REAL, HALF IMAGINARY TERMS) ****
00140 PI=4*ATAN(1.)
00150 NZ=NL/2
00160***** STARTING DATA POINT OF TAPER *****
00170 NM=NZ-5
00180 DO 5 I=1,5
00190 FACT=0.5*(1.+COS((I-1)*PI/4.))
00200 XR(NM+I)=XR(NM+I)*FACT
00210 5 XR(NM+I+NZ)=XR(NM+I+NZ)*FACT
00220 RETURN
00230 END
```

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