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A LITERATURE SURVEY OF BIOCONTROL SYSTEMS

by

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ABSTRACT

Review of the various aspects of Biological Control Systems and their relation to feedback theory is presented in this report. To systematize the study of Biocontrol Systems the material is classified into the following topics: 1) General Human Dynamics; 2) Neuromuscular Systems; 3) Eye Dynamics; 4) Biological Regulator Systems; 5) Biological Process Control; 6) Central Nervous Systems and Brain.

Each of the above topics is summarily discussed and each is separately documented with the pertinent literature and research activities. In the conclusion of the report, the connection between the recent theoretical work in feedback control and the problems of biocontrol systems is duscussed. It is hoped that with this survey a new burst of research activities on the part of control scientists, in the challenging field of biocontrol systems, will be materialized.

TABLE OF CONTENTS

Introduction

It is well known that the human organism represents a very complicated and sophisticated feedback system. Such a control system in the human body arises in a variety of functions such as regulation of body temperature, sugar level in the blood, carbon dioxide in the tissues, etc., [3, 4, 5]. Cannon [4] described as homeostasis the function of the organism to regulate and to keep an "internal environment" constant.

The mathematical study [1-9] of Biological Control Systems (which for brevity we designate as Biocontrol Systems in this report) is still in its early stages and not yet thoroughly investigated. Although most of Biocontrol Systems are inherently nonlinear and time varying, most of the methods proposed are linear and represent a crude approximation of the actual systems. Moreover, recent studies both by other authors and by the writers have established that the precise representation of certain Biocontrol Systems is discrete (or of sampled-data form). This represents a major step in the understanding of Biocontrol Systems by the precise simulation of its actual behavior.

A thorough mathematical study of Biocontrol Systems is very important for the following two reasons. First, through such a study a better understanding of the various physiological processes can be achieved. The influence of this on medical treatment of human organs could be greatly enhanced. Secondly, by studying the actual adaptive and intricate action of the Biocontrol Systems, the control engineer could benefit tremendously in the actual design of feedback control systems. [10, 11, 12, 14].

Most of the present work in Biocontrol Systems is being studied by physiologists, and very few control engineers have been concerned with this subject (except in the case of human dynamics). The purpose in writing this report is to review the up-to-date literature and to indicate the possible areas of interest. This is hoped to be achieved by classifying the different groups of physiological systems and to represent a classified bibliography for each category which includes only the important characteristic work. The classification has been done according to the biological function of different systems. Probably the classification would be better according to the kind of control systems which are present but this is not possible in the present stage of development of this field.

Several books have been listed as a general reference.[1-9]. Some of these books [1, 3, 5] have been written for physiologists, however, their study by systems engineers is rather useful and should not be overlooked. Furthermore, a list of journals in which the control engineer would find important material in his studies of Biocontrol Systems is also included at the end of the bibliography.

It is hoped that this survey would serve the dual purpose of stimulating the control engineers' interest in Biocontrol Systems, and in indicating to the physiologists the vast system theory that can be used for more profound understanding of the biological processes in the human organism.

1. General Human Dynamics [1.01-1.08]

Among the early applications of Control Theory to biological systems is the study of the human operator transfer function when functioning as a part of a control system such as in fire control and tracking systems.

The first study of this subject was performed by Tustin [1.08] in England in 1947 whereby frequency techniques were employed. Using the same techniques, the human operator in a tracking system has been extensively studied in the U. S. by McRuer and Kendall [1. 04, 1. 05] . In view of the strong evidence that the human operator acts in a discontinuous or discrete form, Bekey [1. 01] recently proposed a sampling model of the human operator. His analysis is again based on the frequency response, and the sampled-data representation yields more satisfactory results. This study represents the first major attempt to analyze such systems in discrete form. For illustrative purposes the system studied by Bekey is shown in Fig. 1. The hold circuit indicated can be of different forms.

The most interesting results of the above studies indicates that the human operator transfer function depends largely on the dynamics of the other elements of the control loop. This is due to the fact that the human operator acts in a form that stabilizes and optimizes the complete system.

The general form of the human operator transfer function which was found under the assumption of continuous model is [1. 05]

$$\frac{Ke^{-s\tau}(T_1s+1)}{(T_2s+1)(T_3s+1)}$$

where the values K, τ, T_1, T_2, and T_3 are largely dependent on the control system dynamics.

Although this method of study of the human operator as a whole is of significant practical application, it is, however, necessarily limited, because results obtained in certain control systems cannot be generalized. A better approach to the problem of the human operator is to obtain the transfer functions of the small components (i. e. , the arm, eye, ears) and then synthesize from them the general transfer function. This approach will be discussed in the following sections.

2. Neuromuscular Systems[2.01-2.06]

The term neuromuscular systems means the part of the human organism responsible for movement and posture. For engineering interest the movements of different parts of the body are of importance. The study of such movements has been considered [2.03] and useful results have been achieved. As pointed out in the preceding section, the larger the system under study the less valuable are the results for generalization. Hence, the study of the restricted system, i.e., of the movement of a limb around a joint has been attempted. This movement is accomplished by the cooperation of two muscles (flexor-extensor) which are stimulated from the central nervous systems. In each muscle there are position pick-ups (Spindle γ -afferents and Golgi organs) which feed back information into the central nervous system. Both the physical system and its equivalent block are shown in a simplified form in Fig. 2 (a, b). It should be noted that paths I and II in (a) always carry opposite signals. A detailed study of such a system for the knee joint has been performed by Adolph [2.01]. The system diagram is much more complicated than in Fig. 1b. In this study, the response of the different parts of the system were experimentally obtained and Bode-diagram for the transfer function of these parts was obtained.

The analysis using the Nyquist diagram showed that the system is stable under the conditions of physically realizable neurophysiological components. The sensitivity of the system was also studied using statistical methods.

Another pertinent study in this area was performed by Stark [2.04, 2.05] whereby he considered the hand control system. The block diagram of this system is shown in Fig. 3 where we notice that it is of multiloop type. Experimental work done by Stark showed that the Bode-diagram of the system of Fig. 3 exhibits two peaks (Fig. 4) which is analogous to Bekey's experimental frequency responses. It should be noted that the second peak occurs at about 3 cps. This frequency behavior is indicative of the discrete behavior of such systems.

Smith [2.03], in a related study, had considered the movement of the forearm. In the experimental work performed it was found that the human control is of the bang-bang form which indicates that the natural behavior of biocontrol systems is optimal.

A general characteristic of the hand-control systems studies was the fact that part of the experimental loop included the visual system. For example, Stark's experiment consisted of a setup of two braces, one driven by the input signal and the other by the hand. The subject has to keep them in coincidence. In such an experiment it is difficult to separate the delay of the muscle mechanism from the delay due to the eye. A possible improvement would be the use of sound signals. In this case, the subject will have to keep a mechanism "silent" so the results will be independent of the visual system dynamics. Comparing results obtained by both methods (optical and sound) one can possibly identify more closely the hand dynamics.

3. Eye Dynamics[3.01-3.20]

The eye is the biological mechanism which has been studied in more detail because of its importance in the performance of the human operator in a control system and because of the ease of performing experimental work for checking the analytical studies [3.13, 3.14]. One interesting property of the eye is the adaptivity to light intensity which is obtained through two mechanisms. The first is the variation of the diameter of the pupil (pupillary reflex) and the other is the change of the photochemical sensitivity of the nerve receptors on the retina. The first covers a range of 25 to 1 and is of quick action (1 to 2 secs) and the second is of wider range but slower action (several minutes). More detail of this mechanism can be found in two papers, one by Jones [3.07] and another by Stark [3.14]. One interesting fact of this study which can be used in design is the idea of "double adaptation" of a control system.

Extensive study of the pupillary reflex has been performed by Stark in several papers.[+] This study was performed by using elementary concepts of control theory (Nyquist Diagram). By special and simple arrangement an open loop transfer function was possible to obtain. Using the usual values of the physiological parameters the system was found to be stable. However, by increasing the gain (experimentally) oscillations (variation of the pupil diameter) were noticed and their frequency was in good agreement with the analytical results.

The transfer function of the pupillary reflex obtained by Stark [3.14] is the following:

$$G(s) = \frac{0.16\, e^{-0.18s}}{(1+s)^3}$$

The above represents the transfer function between the pupil area and the optic nerve impulse. Despite the pure delay, the feedback system is stable because of the low gain.

Another interesting subject is the study of the disjunctive and conjugate eye movements. This subject has been studied experimentally by Westheimer and Rashbass [3.09, 3.10]. The same researchers

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[+] However, all the work has been summarized in one paper [3.14]. The same material can also be found in [3.13].

also studied the saccadic and smooth eye movements [3.11, 3.17, 3.18, 3.19]. Westheimer and Campbell have also studied the accommodation response of the eye (i.e., focusing the lens of the eye) [3.01-3.04]. In these studies it is noticed that the Bode-diagrams of the different systems exhibit a peak in high frequency as in Fig. 4. This is indication that these mechanisms work through the sampling process and the sampled-data theory could be more appropriate for the study of such systems.

In a recent work, Young [3.20] studied both the saccadic (fixation of the eye on a target) and the pursuit (following the target) eye movements by using a sampled-data model and the z-transform theory, which will be of much use for future work in this area.

For illustrative purposes the flow diagram of the model devised by Young is shown in Fig. 5.

4. Biological Regulatory Systems[4.01-4.08]

The term biological regulation means the regulation of certain life long processes of the organism, for example, the beating of the heart, the blood pressure and others.

Work on the respiratory heart rate reflex (i.e., the change of the heart rhythm during inspiration or expiration) was performed by Clynes [4.01, 4.02]. An interesting feature of this study is the unidirectional rate sensitivity of this system. Also the differential equation of the pacemaker oscillator is of much analytical interest. Based on this analytical study, Clynes has constructed the analog of the heart whose output under various inputs was in a good agreement with the output of the heart under the same inputs..

For illustrative purposes the model proposed by Clynes is shown in Fig. 6.

The regulation of the blood measure was studied by Warner [4. 06] through the aid of electonic equipment. The arterial pressure of a dog was translated to the nerve through a frequency modulator. In this manner an artificial "fall" of blood pressure was produced in the information supplied to the nerve and the results were carefully studied.

5. Biological Process Control[5. 01-5. 16]

From a physiological point of view this is probably the most interesting control problem because it concerns some of the most important operations in a living organism (role of hormones, etc.). Regulation of the sugar in the blood is another form of such systems. The upset of the latter regulation causes diabetes. The experimental study of such systems causes a major difficulty because most of the system variables are not always accessible to measurements.

Clynes in one paper discusses the dynamic analysis of the thyroid function through the iodine metabolism [5. 03]. In another paper [5. 04], he concerns himself with the regulation of the sugar level in the blood. Work on the iodine metabolism has been performed also by Fukuda and Sugita [5. 05] .

Among the first applications of control theory to a physiological problem was the study of Grodins and others [5. 11] in 1954 on the regulation of carbon dioxide (CO_2) in the body. The controlled subsystems are the ventilation in the lungs and the CO_2 which is produced in the tissues because of catabolism. The two subsystems are linked through the blood. The controller was the concentration of CO_2 in the body which acts on the ventilation. It should be noted that the more CO_2 is produced in the body the more intensive becomes the ventillation in the lungs. Hence, more oxygen enters the blood which results in the decrease of CO_2 in the tissues. Good agreement between the experimental and analytical results were achieved.

A study of the endocrine systems has been made by Danzinger and Elmergreen in a series of papers [5.06, 5.07, 5.08]. In the more recent paper of theirs, they generalize their studies by the use of piecewise linear models and define conditions for stability or oscillations (a common phenomena in biological systems, as in the menstrual cycle, studied also analytically by Rapport [5.14]) through the use of Routh criterion. Since the parameters of models were not determined, their results were not checked experimentally. However, their study is quite valuable even in the qualitative stage. It should be noted that in certain cases [5.06] even qualitative results are valuable for medical reasons (treatment of a certain mental disorder by prescribing to the patient the appropriate hormone). In this paper [5.06] the study of the system has also been done through phase-plane techniques.

Other interesting work along these lines is the simulation of the biochemical reactions of the respiration in analog and digital computers in RAND [5.09] and Goldman's study of a model for the blood glucose control system [5].

6. Central Nervous Systems and Brain [6.01-6.08]

These systems have been studied in connection with the understanding of the thinking processes and its applications to computers. This area is often referred to as "Cybernetics." It is being extensively studied in the Soviet Union and many papers are presently appearing in their literature.

From control system's point of view, some work is being done in this area. For instance, the stability properties of the nerve membrane have been studied through Nyquist diagrams [6.01]. An interesting feature of the nerves is that information is transmitted through pulse-frequency modulation (another application of discrete system theory).

The mathematical study of these systems have been performed by Jones and his collaborators [6. 07].

Using the phase-plane techniques, Nelson [6. 08] in a recent paper (in French) was able to analyze the neuron models. The models represent mainly qualitative characteristics which are in agreement with experimental results.

N. Rashevsky in his book [7, Vol. 1, part II and Vol. 2, part I] has presented a detailed study of the mathematical models of the nervous systems. Although this work does not present application of control theory, it indicates a thorough background for general study of most biological systems

Conclusions and Areas of Future Research:

In this brief survey of Biocontrol Systems it is indicated that this areais still in its early stage of development. Most of the research area was performed by physiologist while control or system engineers had made only sporadic contributions. It is felt that the latest tools available in system theory could be of much help in further understanding of biological processes, thus bringing more sophistication to the analysis methods of biocontrol systems. One of the major problems arising from these studies lies in the area of identification and characterization. It is in this field that most of the contributions to Biocontrol lies. The control engineer to be able to do further research in this area, needs to obtain a certain knowledge of physiological systems. This is important not only to understand biological processes better but also to be able to read the literature and to communicate with physiologists and others.

It is hoped that although this survey is necessarily brief and the contents were arbitrarily categorized, the contribution toward focusing the control engineer's attention to this area would outweigh these disadvantages to a certain degree.

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IRE Trans. on Human Factors in Electronics
IRE Trans. on Biomedical Electronics
A. K. of Science U. S. S. R. Doklady Biological Science (in English Translation)
Sechenov Physiology, Journal of U. S. S. R., (translation in English)
Bulletin of Ex. Biology and Medicine (Russian translation into English)
Kybernetik (German)
Biophysics (Russian translation in English)
Cybernetica (in French)

FIGURE CAPTIONS

Fig. 1	Human Operator Sampled-Data Model.
Fig. 2a	Limp Joint
Fig. 2b	Limp Joint Model.
Fig. 3	Model of Hand Control System.
Fig. 4	Bode Diagram Characteristic of Various Control Systems of the Human Organism.
Fig. 5	Flow Diagram of a Model for the Pursuit and the Saccadic Eye Movement.
Fig. 6	Block Diagram of Heart Rate Reflex Proposed by Clyne.

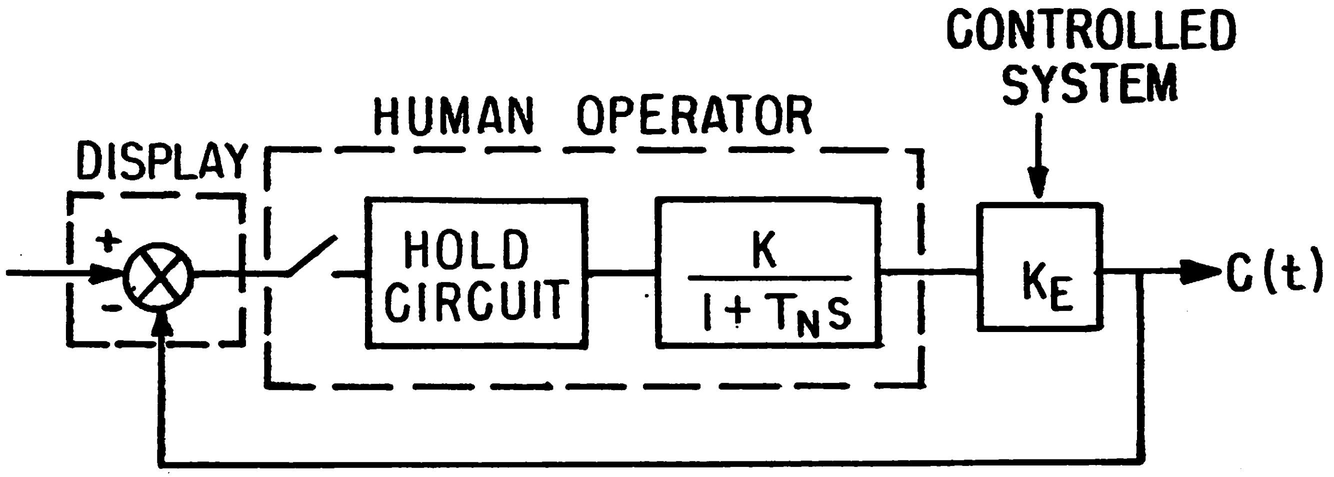
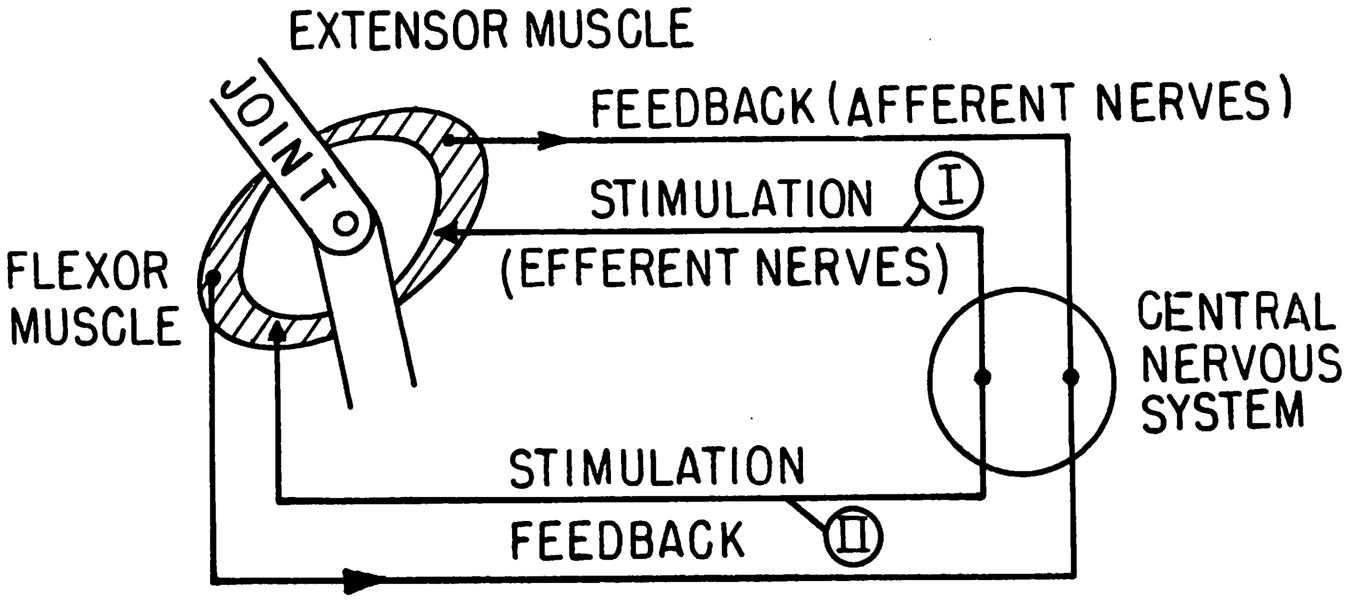
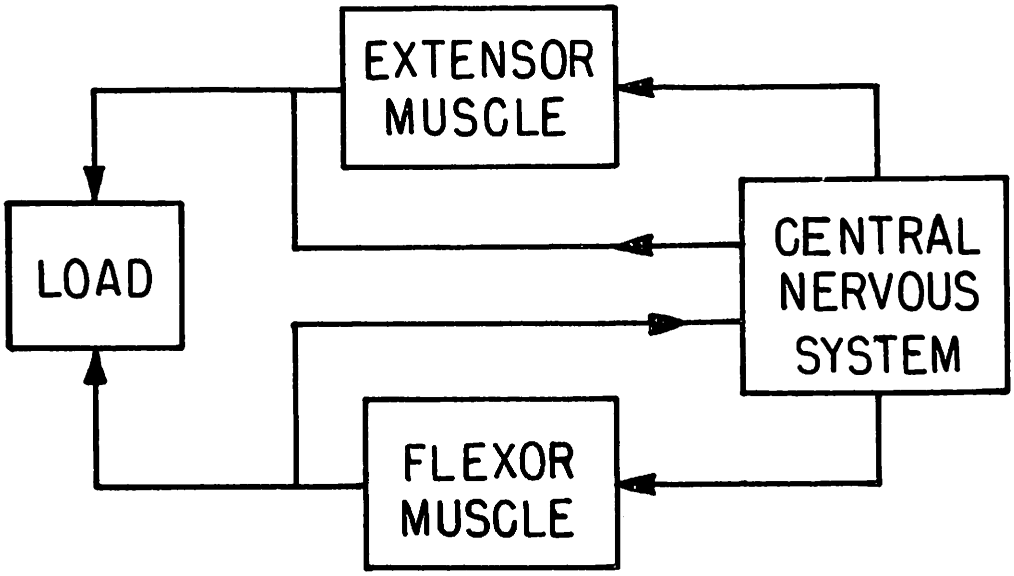

CONTROLLED SYSTEM
HUMAN OPERATOR
DISPLAY
+
-
HOLD CIRCUIT
$\frac{K}{1+T_N s}$
K_E
C(t)

FIG. 1



EXTENSOR MUSCLE
JOINT
FEEDBACK (AFFERENT NERVES)
STIMULATION
①
(EFFERENT NERVES)
FLEXOR MUSCLE
CENTRAL NERVOUS SYSTEM
STIMULATION
FEEDBACK
②

FIG. 2a



EXTENSOR MUSCLE
LOAD
CENTRAL NERVOUS SYSTEM
FLEXOR MUSCLE

FIG. 2b

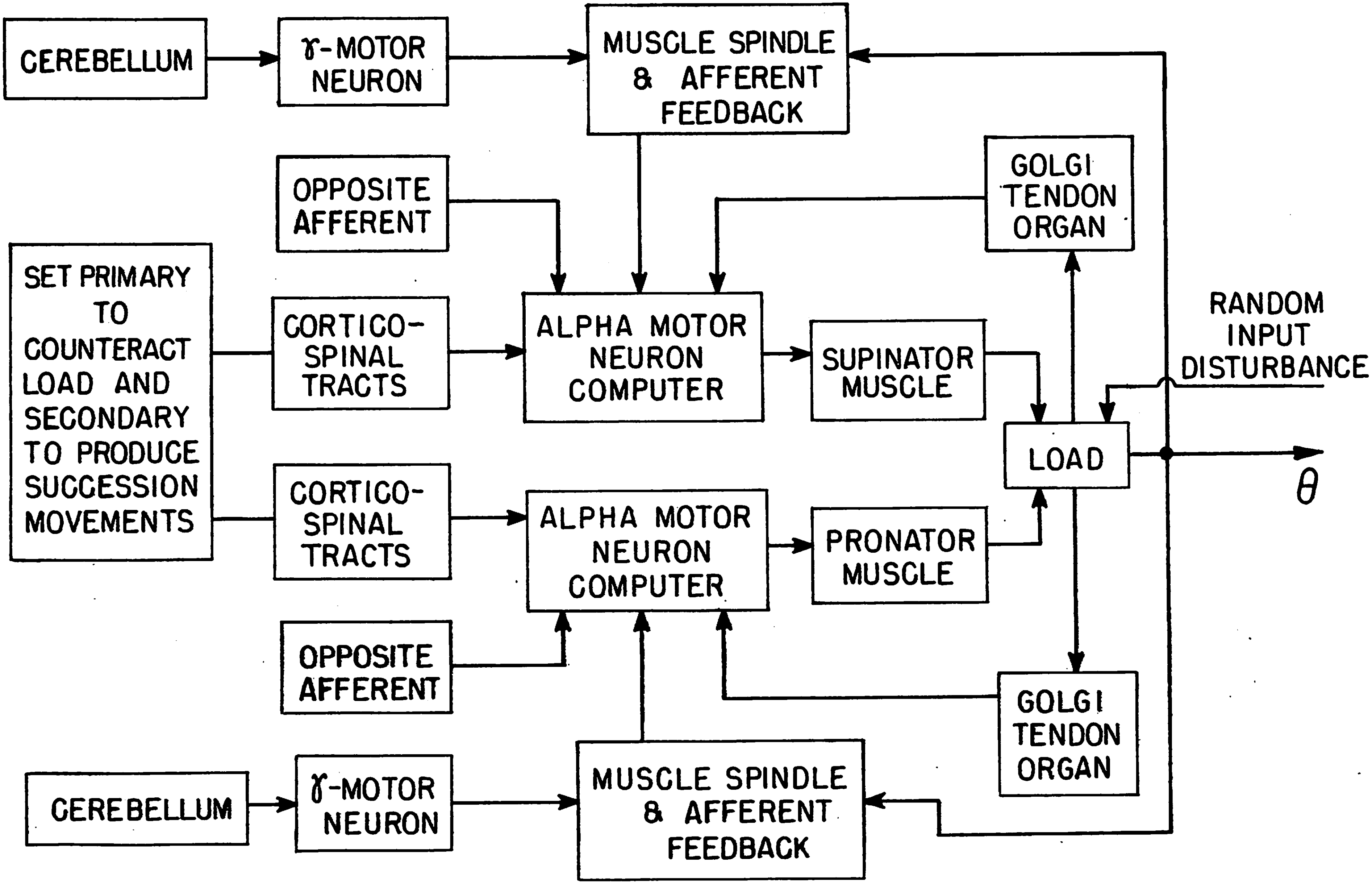

CEREBELLUM
γ-MOTOR NEURON
MUSCLE SPINDLE & AFFERENT FEEDBACK
OPPOSITE AFFERENT
GOLGI TENDON ORGAN
SET PRIMARY TO COUNTERACT LOAD AND SECONDARY TO PRODUCE SUCCESSION MOVEMENTS
CORTICO-SPINAL TRACTS
ALPHA MOTOR NEURON COMPUTER
SUPINATOR MUSCLE
RANDOM INPUT DISTURBANCE
LOAD
θ
CORTICO-SPINAL TRACTS
ALPHA MOTOR NEURON COMPUTER
PRONATOR MUSCLE
OPPOSITE AFFERENT
GOLGI TENDON ORGAN
CEREBELLUM
γ-MOTOR NEURON
MUSCLE SPINDLE & AFFERENT FEEDBACK

FIG. 3

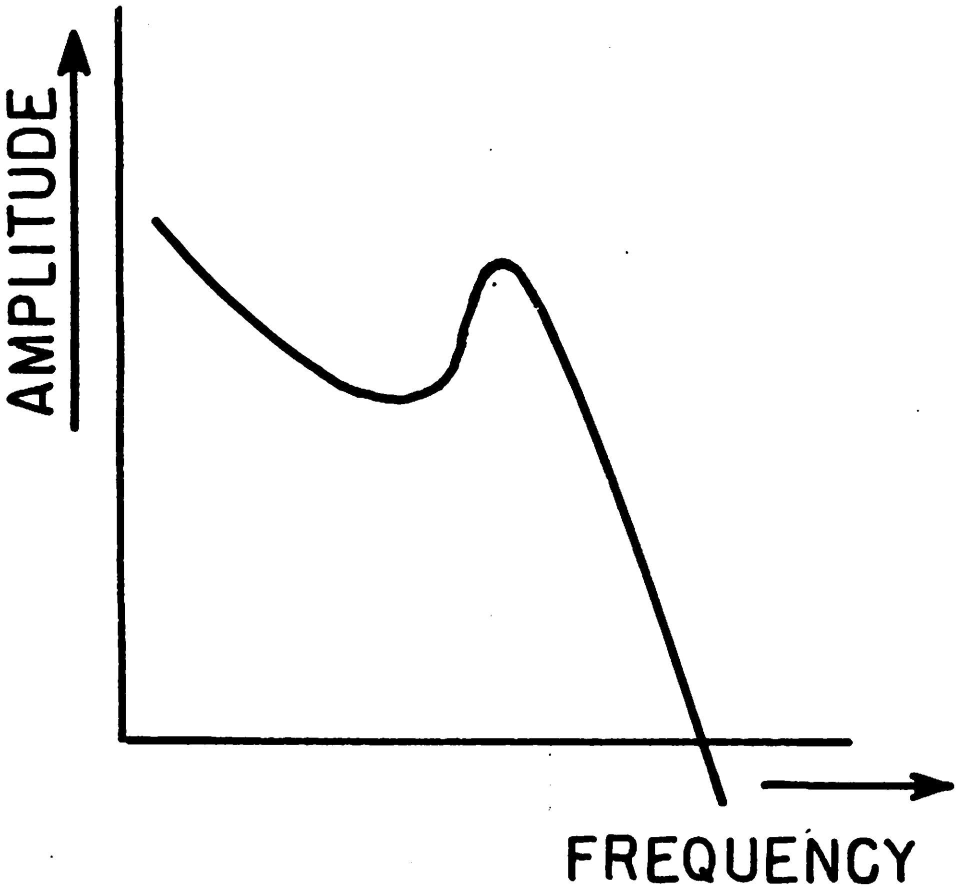


FIG. 4

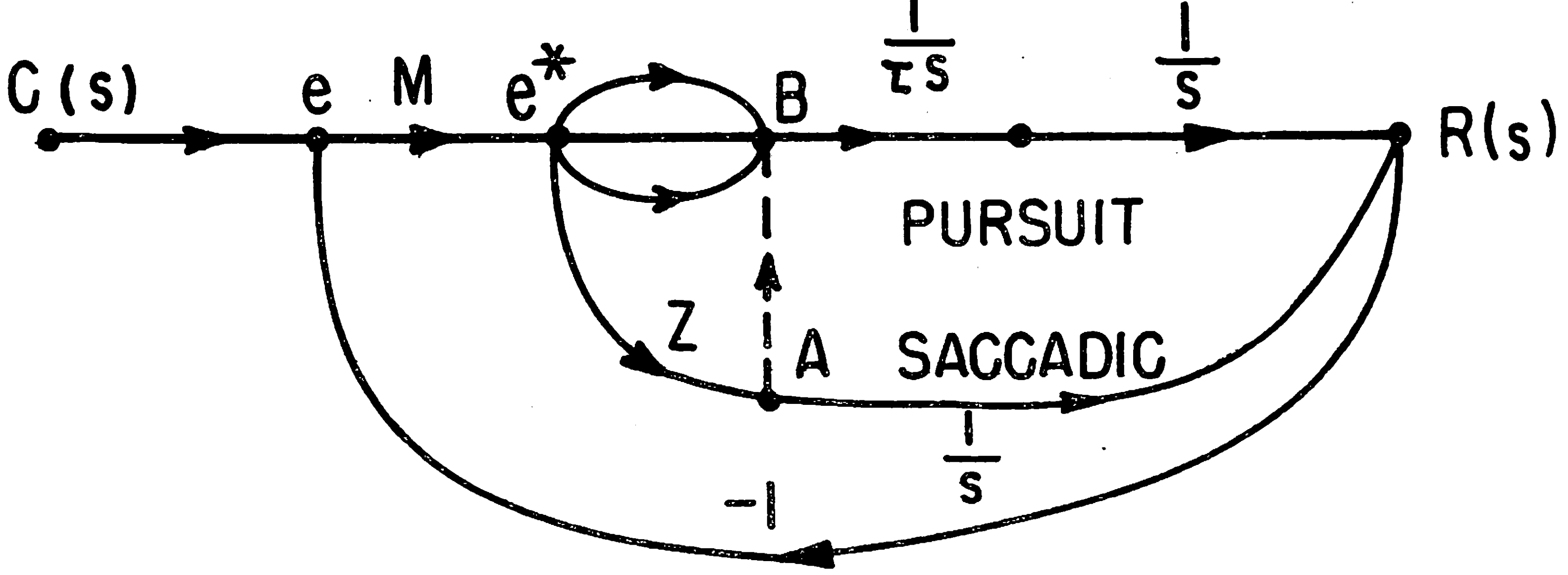


FIG. 5

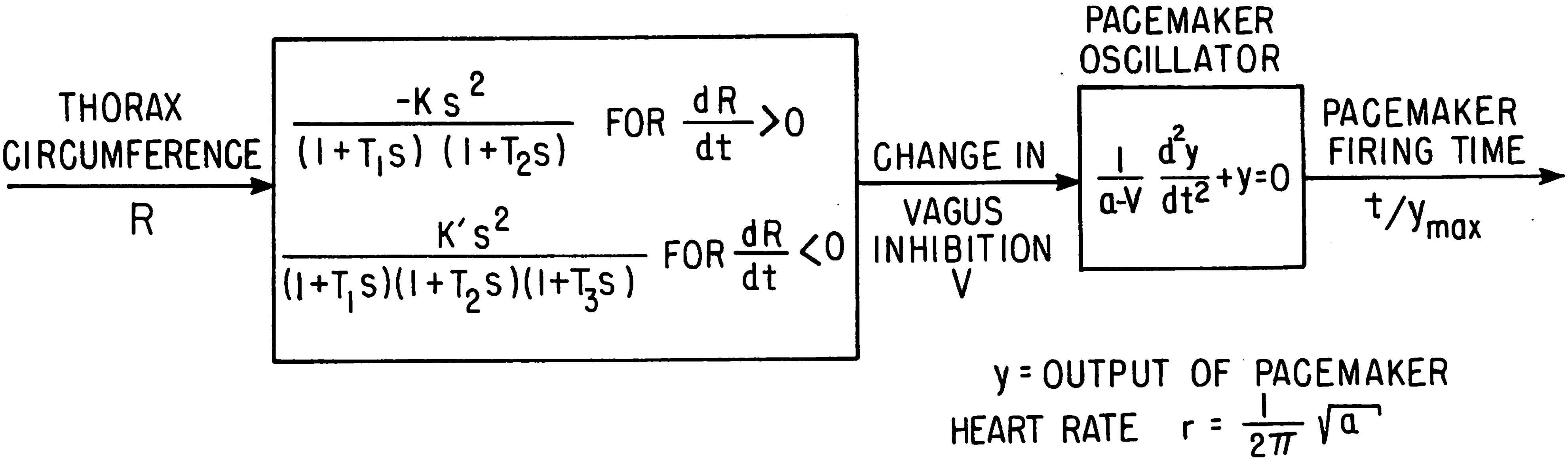

THORAX CIRCUMFERENCE
R
$\frac{-Ks^2}{(1+T_1s)(1+T_2s)}$ FOR $\frac{dR}{dt}>0$
$\frac{K's^2}{(1+T_1s)(1+T_2s)(1+T_3s)}$ FOR $\frac{dR}{dt}<0$
CHANGE IN VAGUS INHIBITION
V
PACEMAKER OSCILLATOR
$\frac{1}{a-V}\frac{d^2y}{dt^2}+y=0$
PACEMAKER FIRING TIME
t/y_{max}
y = OUTPUT OF PACEMAKER
HEART RATE $r = \frac{1}{2\pi}\sqrt{a}$

FIG. 6