ANALOG COMPUTER STUDY OF A BIOLOGICAL TEMPERATURE REGULATOR: CUTANEOUS CIRCULATION

by

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TABLE OF CONTENTS

INTRODUCTION

In the field of biology, homeostasis was described by Cannon in the early twentieth century as the constancy of the internal environment of organisms. In electronics, the theoretical development of automatic control systems gained most of its impetus during the second World War. Then in 1943, Weiner postulated that homeostatic mechanisms were similar in concept to electronic feedback controls. Though biological control systems are much more complex than man-made systems, the similarities of the two, heretofore hidden by the disciplinary language barriers of engineering and biology, are striking.

The dynamics of homeostasis are extremely difficult to describe mathematically. Essential nonlinearities,many inputs and outputs (not all known), parametric feedback loops, lack of generality from species to species and from individual to individual, abnormal functioning under normal conditions, incomplete system isolation, all add to the difficulty of mathematical description. In addition, relevant variables are difficult to maintain, verify, and control.

Nonetheless, the application of control system theory to homeostatic mechanisms can lead to new and significant insights into the mechanisms; conversely, the study of the biological mechanisms might lead to new concepts in control theory (the Schmitt trigger used in switching circuits is a pertinent example). The highly developed details of linear system theory may not apply in a rigorous manner, but the system approach has

much to offer. Man's own designs fall far short of the intricacy and subtlety of biological systems.

In this paper, several representative control systems are described. A specific example, temperature regulation through vasomotor action, is then investigated using the analog computer.

REPRESENTATIVE CONTROL SYSTEMS

The component parts of a control system are shown in Fig. 1.

Coordination of bodily movements requires a complex control system. Nerve endings in the muscles sensitive to movement, called proprioceptors, are used by the brain to facilitate graceful movement and the completion of voluntary action. Two disorders of this biological mechanism correspond to faults of automatic control systems. In one disorder, called intention tremor, attempts at detailed voluntary control of a limb by the afflicted individual result in uncontrolled oscillation of the limb. In the other disorder, called ataxia, the individual's movements overshoot the intended target by large distances. These disorders both result from (1) the lack of reference signals from the muscle proprioceptors to the cortex of the brain, and (2) the disturbances in feedback determination by the cerebellum of the rates of the process, i.e., whether the output is overdamped or underdamped and prone to oscillation.

Endocrine gland action is another system exhibiting many

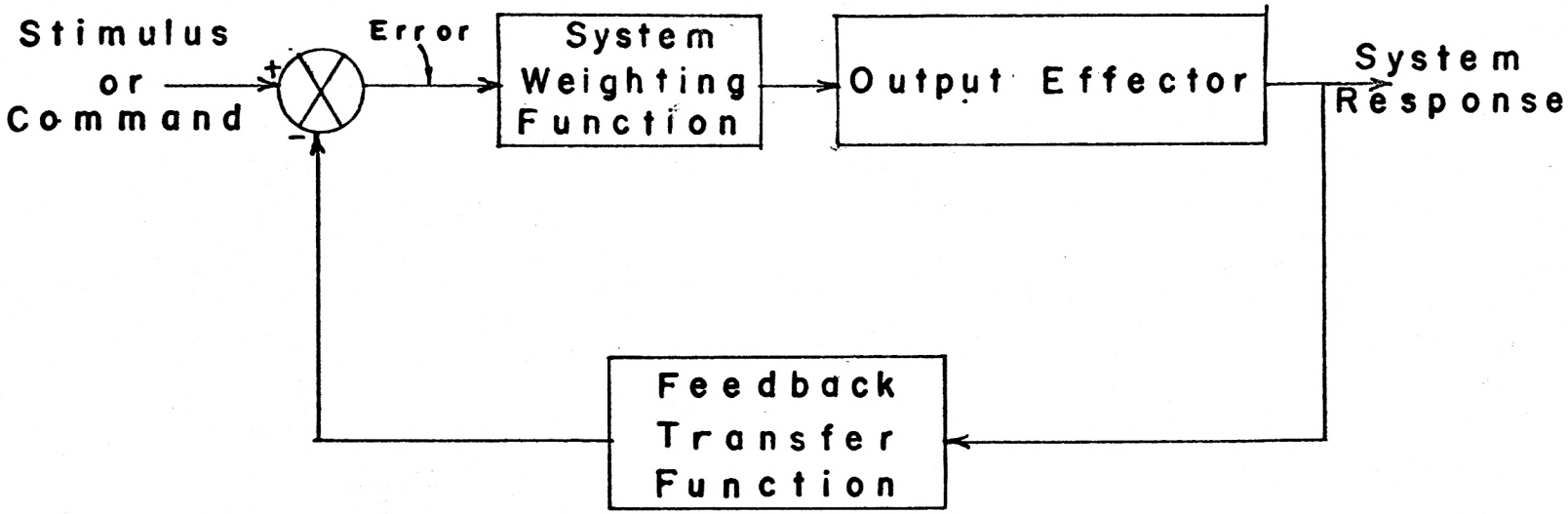

Fig. 1. Feedback control system.

facets of automatic control--too complex in most cases, however, for completely quantitative description. Originally it was thought that the negative feedback concept characterized the main mechanism operating to maintain adequate levels of circulating hormones, but the negative feedback concept has been found to be inadequate to account for other important interrelations brought to light by recent experiments.

As an example, the sensitive and complicated actions of the pituitary gland and hypothalamus (primarily a neural organ) show automatic control mechanisms. On one level, the pituitary releases a hormone into the blood stream called thyrotropin which affects only the thyroid gland. Under thyrotropin stimulation, the thyroid releases another hormone called thyroxin which is essential in the conversion of food to energy. Negative feedback occurs when the pituitary senses the increased circulating level of thyroxin and decreases its output of thyrotropin. On another level, the hypothalamus senses extremes in the concentration of circulating thyroxin. As a result, a neurohormone is released which travels to the adjacent pituitary, stimulating release of thyrotropin and eventually thyroxin, or causing a reduction in thyroxin secreted. Note that when fast action is necessary, the process is neural; for slow action and long periods, the process is hormonal. A block diagram of the mechanism is shown in Fig. 2. Of investigative interest here would be the relative stability of the two levels of control.

Studies of other biological control systems are listed in the references (2, 4, 5, 6, 8, 9, 18, 21).

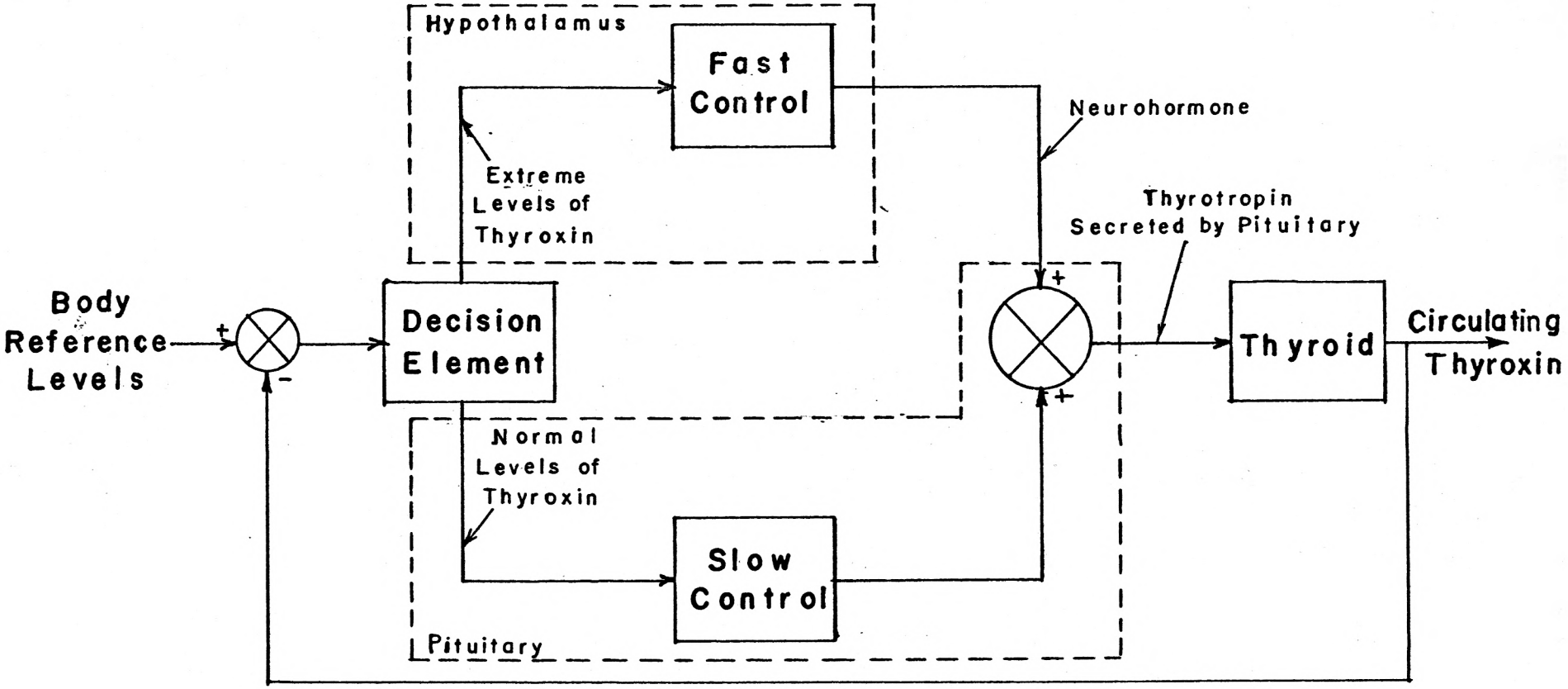

Fig. 2. Multilevel control of circulating thyroxin.

VASOMOTOR REGULATION OF INTERNAL TEMPERATURE

Man may be exposed to heat to 257 degrees Fahrenheit without a significant increase in normal internal body temperature. On the other hand, arctic mammals exposed to cold 30 degrees below zero do not experience any significant fall in internal temperature (4).

Temperature regulation can be described as the maintenance of a body temperature within a prescribed range under varying conditions. It is achieved by metabolic rate control, by muscular activity (as in shivering or active movement of the limbs), sweating, panting, regulation of blood flow to the skin, and by other lesser means. A detailed description of body temperature regulation is thus a difficult procedure. Even the description of a single mechanism is difficult because of the functional interrelationships of all the mechanisms.

In this paper, the temperature control of cutaneous circulation is investigated. Essentially, environmental temperature changes are sensed, the resulting sensations are integrated by the brain, and the necessary changes are made in the tonus of the muscles controlling artery diameter. See Fig. 3. At attempt was made to describe this process by differential equations obtained from a simulation on the analog computer. The validity of the simulation was checked by comparing the actual blood flow volume (more accurately, the volume pulse amplitude) with the computed blood flow volume.

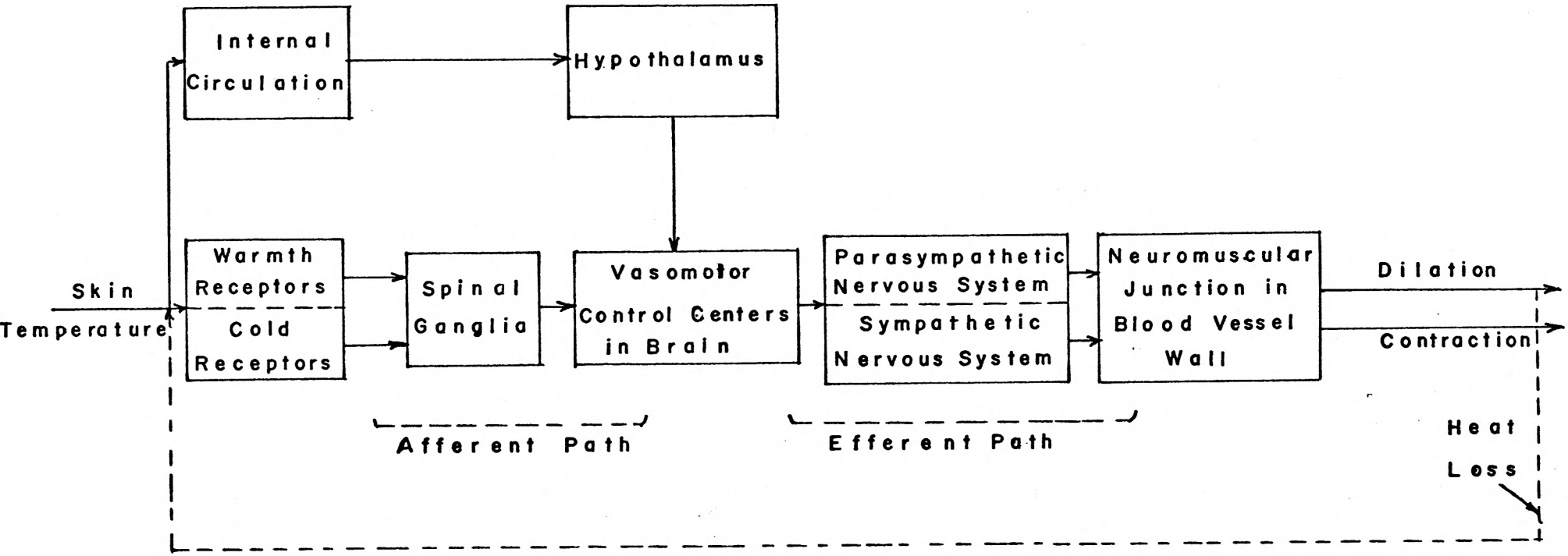

Fig. 3. Block diagram of physiological events in temperature-vasomotor regulation. The analog computer was programmed to simulate these events (the parts played by the hypothalamus and the cold receptors were not considered).

PHYSIOLOGICAL CONSIDERATIONS

The specialized nerve tissues that act as receptors for cold and warmth have been tentatively identified in the skin. The receptors for cold appear to be Krause's end-bulbs, found close to the surface of the skin and in the outermost layers of the blood vessels. The receptors for warmth are Ruffini's end-organs; these lie deeper in the skin where the blood vessels form numerous arterial and venous networks. The depths of these receptors cause a delay in the sensing of applied temperature on the order of one-half second for cold and three-fourth second for warmth.

The basis of sensation is the detection of stimulus levels and level changes. Figure 4 shows the temperature gradients existing at various depths in the skin. The gradient threshold at which stimulation takes place is less for warmth than for cold. Warmth receptors can sense a 0.007-degree Centigrade rise; cold receptors are able to sense a 0.012-degree fall (these figures are given only to indicate the order of magnitude involved). The result is that warmth exaggerates the existing gradient, while cold must overcome the gradient.

The receptors, when stimulated, induce a series of impulses into the signal channels of the central nervous system concerned with thermal sensation. The frequency of the impulses from a single receptor cell is a nonlinear function of the magnitude of the stimulus. See Fig. 5. However, the mean frequency response of a number of cells is linear. The intensity

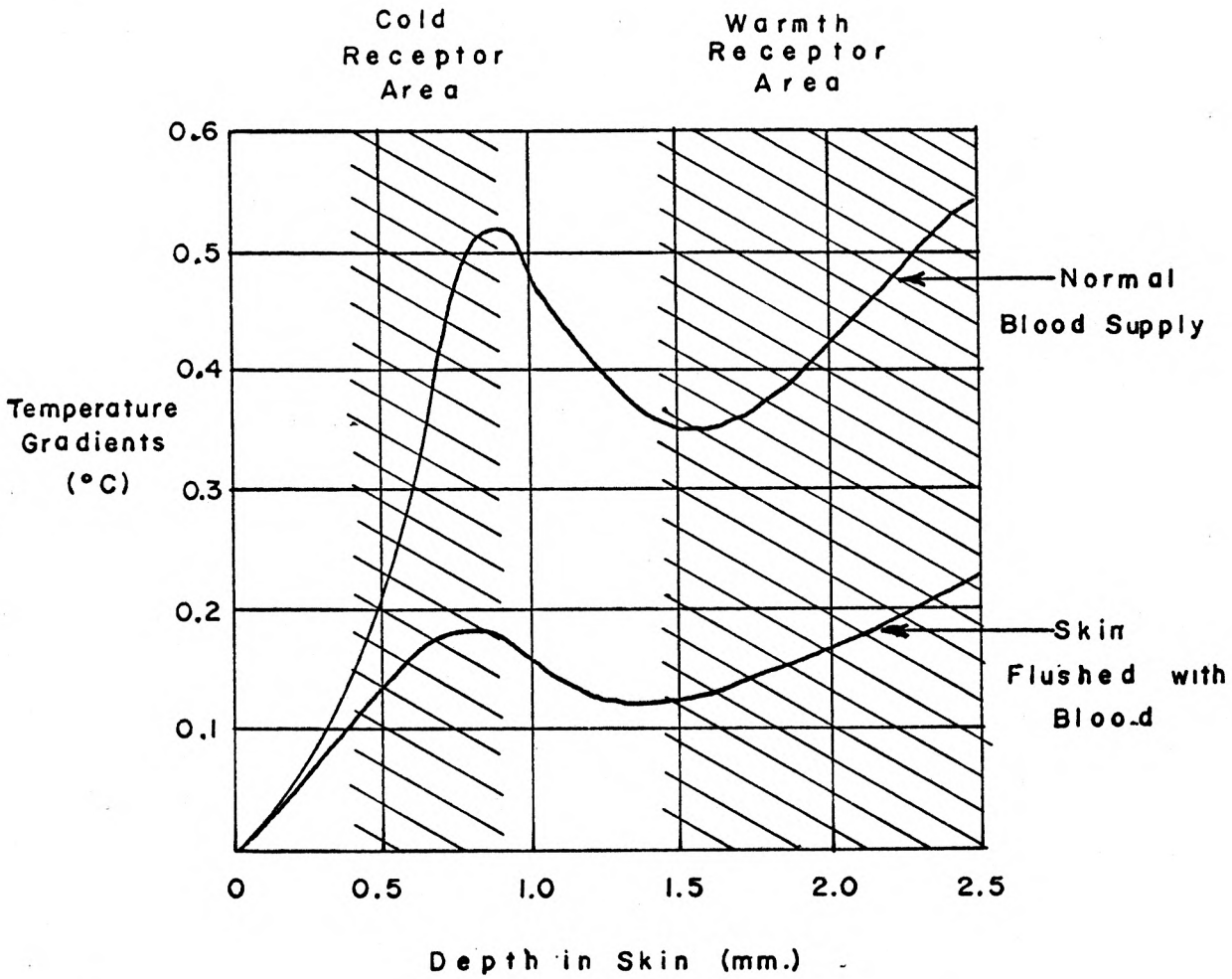

Fig. 4. Temperature gradients between surface temperature and temperature at various depths in the skin. (From Morgan and Eliot (12), p. 240).

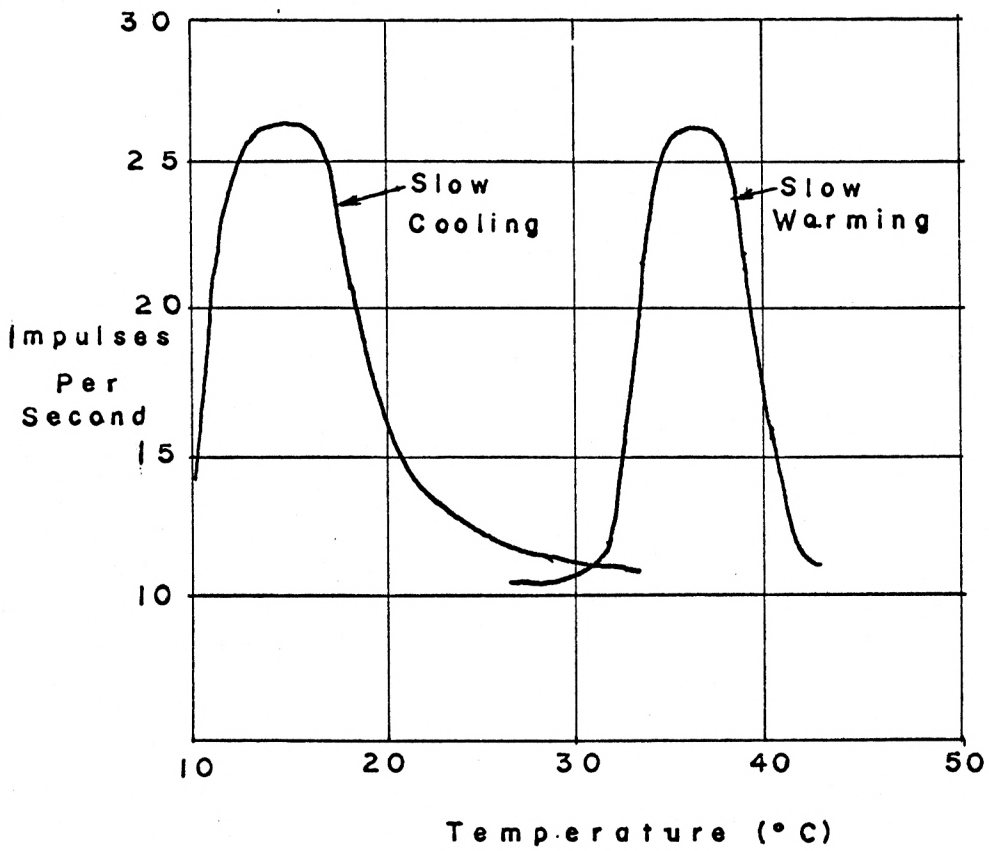

Fig. 5. Frequency of a single thermal receptor response to temperature. (Ibid.)

of the response is determined by the area and number of receptors affected by the stimulus. The amplitude of the impulses remains constant according to the all-or-none law of nerve transmission. After a period of time the frequency of firing decreases to a low constant value. This phenomenon is called adaptation and can be experienced by plunging the hand into hot water; the initial feeling of warmth gradually subsides to a lesser, constant one. Adaptation to warmth is faster than to cold because of the warmth receptors' proximity to the blood vessels. The fact is indicated that a large part of sensory perception is a detection of changes.

Finally, sensory nerves show isolated, spontaneous firings independent of stimulus condition. Possibly extra-sensitive nerve endings--to the point of instability--are responsible.

After traveling through the afferent nerves,[1] the impulses are integrated in the brain with other information from the entire body. Along with skin thermal receptors, there exist receptors in the hypothalamus that sense temperature changes in the cerebral blood supply. The hypothalamus exercises a delicate control over vasomotor regulation of internal temperature, but this aspect of temperature regulation is not to be considered here; even so, neglect of hypothalamus action on skin temperature regulation could result in significant errors. Impulses are sent from the brain through the efferent nerves to

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[1]Afferent nerves are those transmitting signals to the brain or spinal cord; efferent nerves are those transmitting signals from the brain to the motor centers.

the proper neuromuscular junctions in the vessel walls. Many internal organs, including the blood vessels, have walls consisting of layers of smooth muscle cells. Smooth muscle is difficult to study; in fact, experimental evidence of its physiology is very limited. In general, it has a fairly long reaction time and remains in contraction long after stimulation has stopped. Its action is neither smooth nor continuous. See Fig. 6.

A temperature rise eventually causes extension of the muscles in blood vessel walls; a resulting increase in blood flow increases the heat transfer from the internal body to the environment. A temperature fall has an opposite action; more heat is conserved in the internal body by the restriction of blood flowing near the surface. Feedback in this control system takes place when the skin temperature adjusts to the blood flow.

With these physiological considerations in mind, an analog computer simulation of temperature-vasomotor regulation can be constructed.

TEMPERATURE-VASOMOTOR TRANSFER FUNCTION

The dynamic transfer function of a system provides the information for programming the computer. Therefore input-output relations for the entire system are required. Often the very uncertainty of inputs and outputs of biological systems is a limiting factor in systemic studies. The temperature vasomotor-system was chosen because of the availability of these

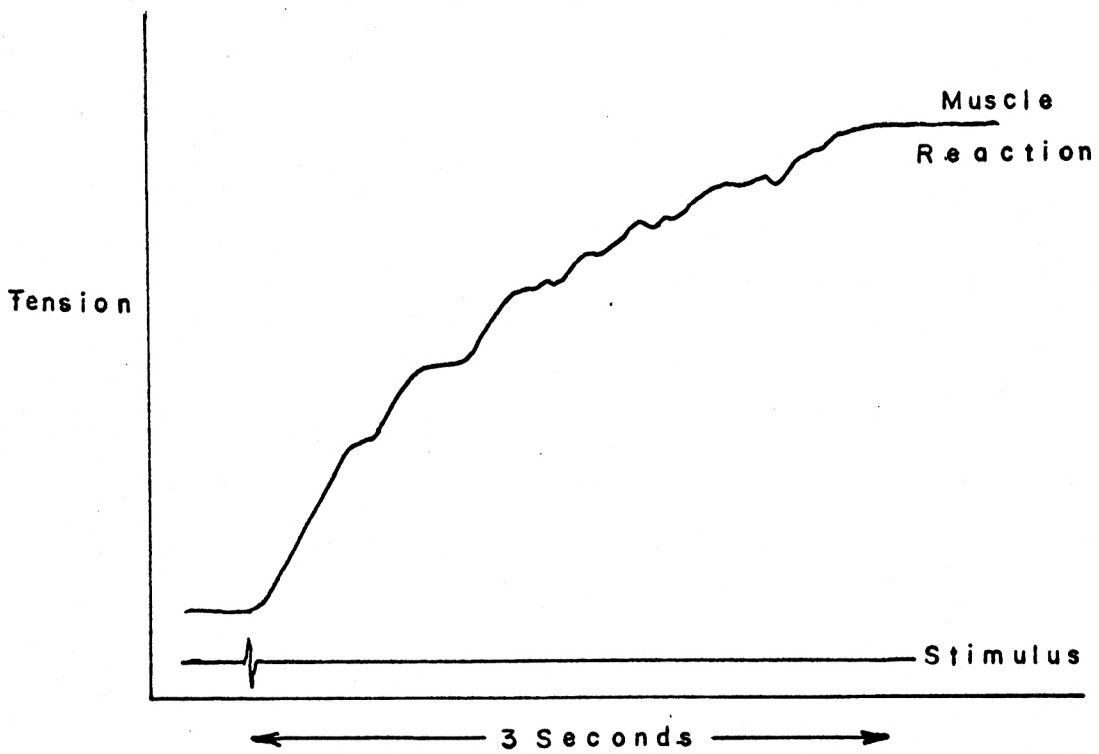


Fig. 6. Reaction of smooth muscle to nerve stimulation. (From Woodbury and Ruch (20), p. 226-227.)

convenient, accessible functions and in the hope that this study would lend insight to more complex, less accessible neural systems. The input was skin temperature and the output was volume blood flow. The corresponding input and output of the computer were voltages proportional to these two functions.

By applying a temperature change approximating a step function to the skin and comparing the computer output with the actual blood flow, the computer program was adjusted to produce a valid blood flow function for a restricted temperature variation.

First, an approximate transfer function, $\frac{B(s)}{T(s)}$, where B(s) is the Laplace transform of blood flow variation with respect to time and T(s) is the transform of temperature variation, was constructed by considering the physiological data for each unit in the system. Secondly, after the computer was programmed and the output compared to actual blood flow, it was decided to approach the problem from another direction by working directly from experimental data.

Since the thermal receptors are located at finite depths in the skin, a short time delay in receptor reaction is expected. In the Laplace transform domain, the time delay operator is

$$e^{-bs} \qquad (1)$$

where b is the length of the delay in seconds.

The thermal receptors respond to rate of change and show adaptation. The transfer function

$$\frac{s}{1 + ks} \qquad (2)$$

represents these two factors. This function, for a step input, has the output shown in Fig. 7. The constant k determines the rate of adaptation. Here, temperature is the input and frequency of firing is the output. Warmth receptors respond to an increasing gradient, i.e.,

$$\frac{\text{Frequency of firing}}{\text{Temperature}} = \frac{s}{1 + ks} \quad \text{for} \quad \frac{dT}{dt} > 0 \qquad (3)$$

$$= 0 \quad \text{for} \quad \frac{dT}{dt} < 0 \qquad (4)$$

Cold receptors respond to a decreasing gradient, within limits.

The receptor cells in turn stimulate neurons of the central nervous system; the stimuli from the entire body are integrated by the brain temperature control centers and sent as an output to the efferent neurons of the sympathetic or parasympathetic systems. The transfer function

$$\frac{s}{1 + hs} \qquad (5)$$

has been indicated as being typical of the integrative action of the brain (5).

The signals impinging on the neuromuscle junctions in the blood vessels from the sympathetic fibers elicit contraction of the smooth muscle; signals from the parasympathetic fibers elicit dilation. The tentative transfer function empirically derived from published data (see Fig. 6) is

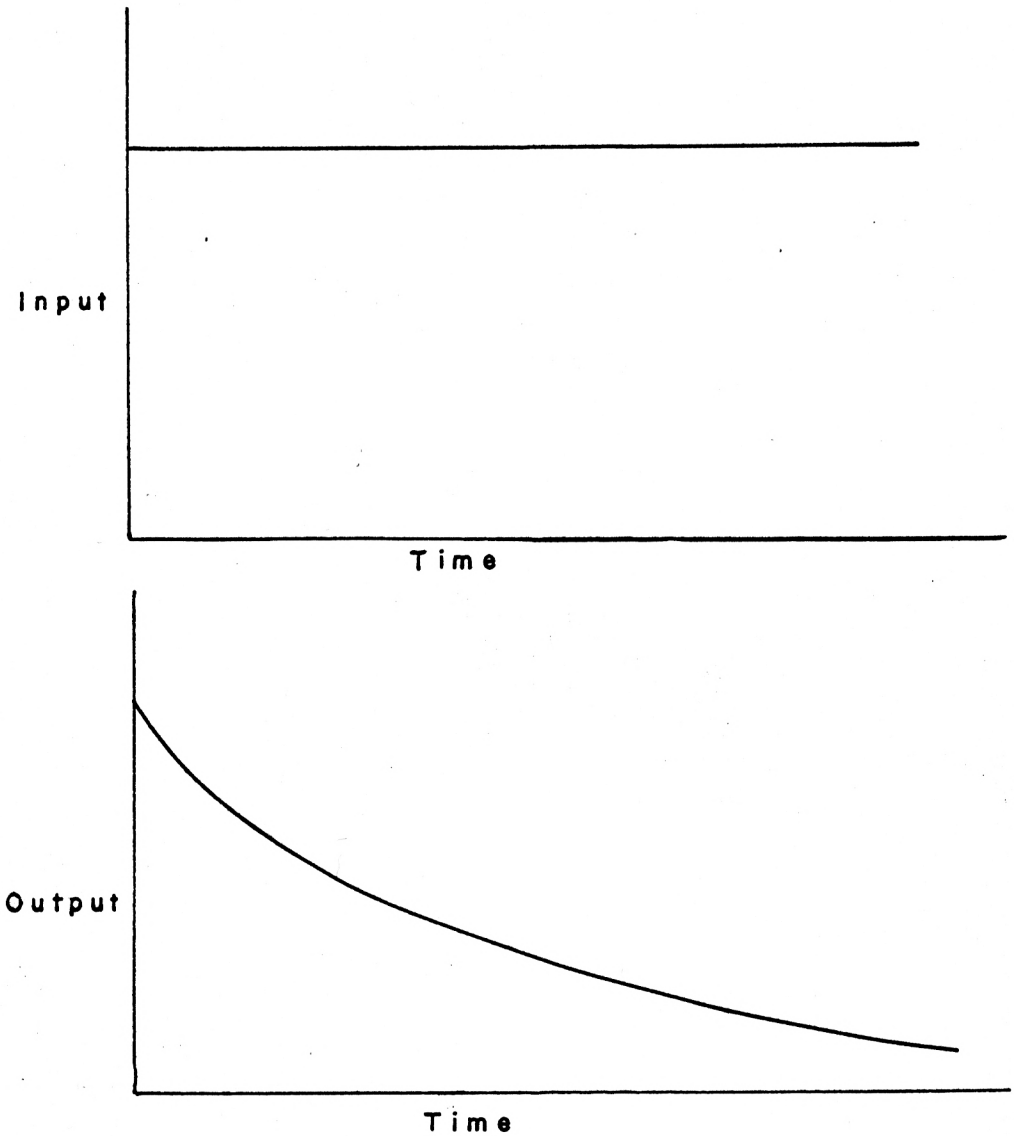


Fig. 7. Output of the temperature receptors with assumed transfer function $\frac{F(s)}{T(s)} = \frac{s}{1 + ks}$ for a step input.

$$\frac{1}{s^2(1 + ms)} \cdot \tag{6}$$

The complete transfer function relating temperature to blood flow is estimated to be

$$\frac{B(s)}{T(s)} = g\, e^{-bs} \left(\frac{s}{1 + hs}\right)\left(\frac{s}{1 + ks}\right)\left(\frac{1}{s^2(1 + ms)}\right) \tag{7}$$

Several idealizations have been made in constructing this transfer function.

1. Within a restricted range, vasomotor action is the principle regulator of heat loss from the skin; other mechanisms become effective outside this range.
2. The regulation varies with the type of heat source.
3. Spontaneous firings and a constant low-frequency firing have been neglected.
4. Though the mean frequency of firing from many cells is linear with respect to temperature, the frequency of firing from a single cell is nonlinear (see Fig. 5).
5. The receptors described above may not be involved in vasomotor action at all but only in thermal sensation.

Considering warmth stimuli only, the differential equation from the above transfer function (Eq. 7) is found to be

$$\delta B(t) + \gamma \frac{dB(t)}{dt} + \alpha \frac{d^2B(t)}{dt^2} + \frac{d^3B(t)}{dt^3} = gT(t - b) \tag{8}$$

where $B(t)$ = blood flow

$\delta = 1/hkm$

$\gamma = (h + k + m)/hkm$

$\alpha = (hk + hm + km)/hkm$

g = constant

$T(t - b)$ = delayed temperature

b = delay time in seconds

This equation, programmed on the computer with $h = 1$, $k = 1$, $b = 1$ second, and $m = 3$, gave the output shown in Fig. 8.[1] The simulated blood flow agreed only roughly with actual blood flow. (Note that blood flow is inversely proportional to the height of the pulses.)

It was then necessary to approach the construction of the computer program from another direction. The new approach was from a systemic viewpoint rather than the previous component viewpoint. The slow temperature variation and the corresponding blood flow shown in Fig. 9 (Visicorder record) indicates a proportional relation between the two. Additional data shown in Fig. 8 (reproduced more concisely as Fig. 10 below) were more revealing. Between t_0 and t_1, a constant temperature resulted in a constant blood flow. At t_1, a suddenly changed temperature $\left(\frac{dT}{dt} > 0\right)$ caused an impulsively larger blood flow. At t_2, another sharp change in temperature $\left(\frac{dT}{dt} < 0\right)$ resulted in an impulsively lesser flow.

These facts indicate that a simulation of a proportional plus derivative control system might be more successful in describing blood flow. A block diagram of this type of control

[1] Figure 8 is omitted; see instead Fig. 10.

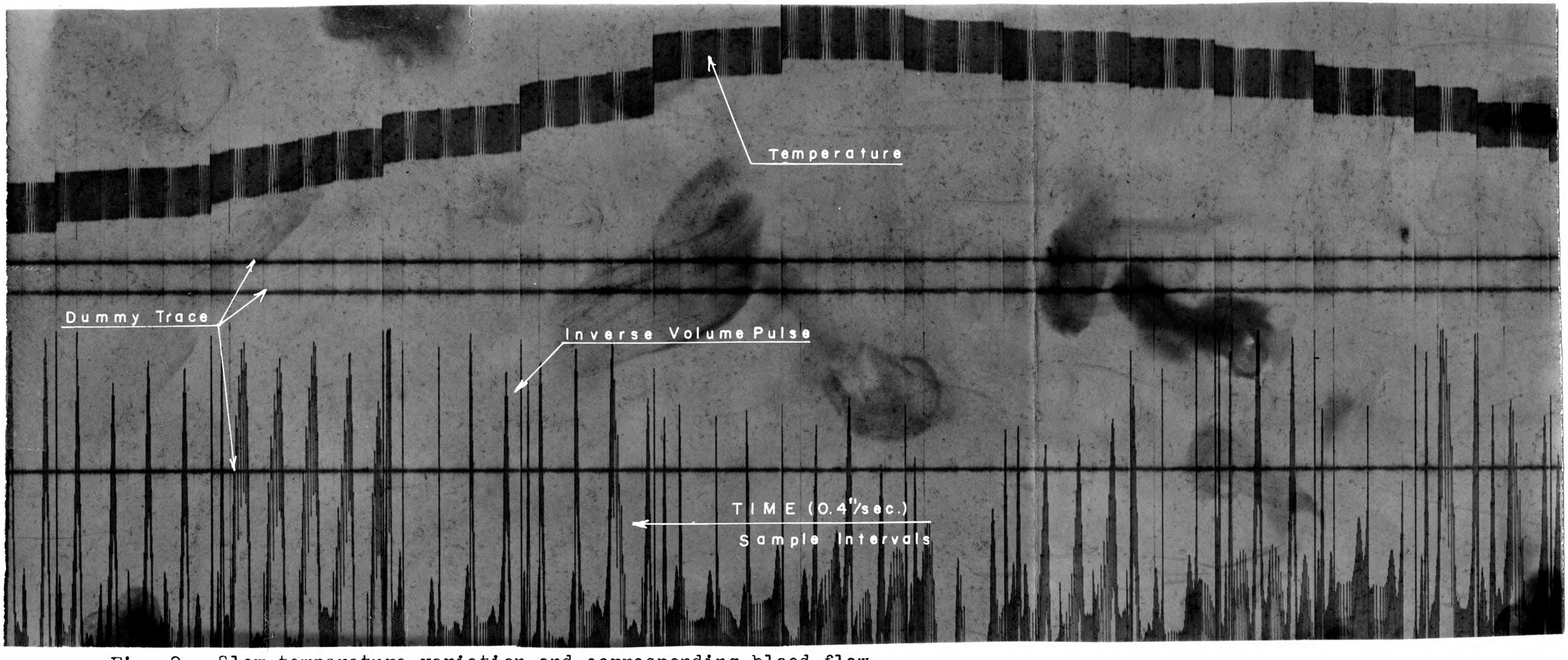


Fig. 9. Slow temperature variation and corresponding blood flow showing a proportional relation between the two.

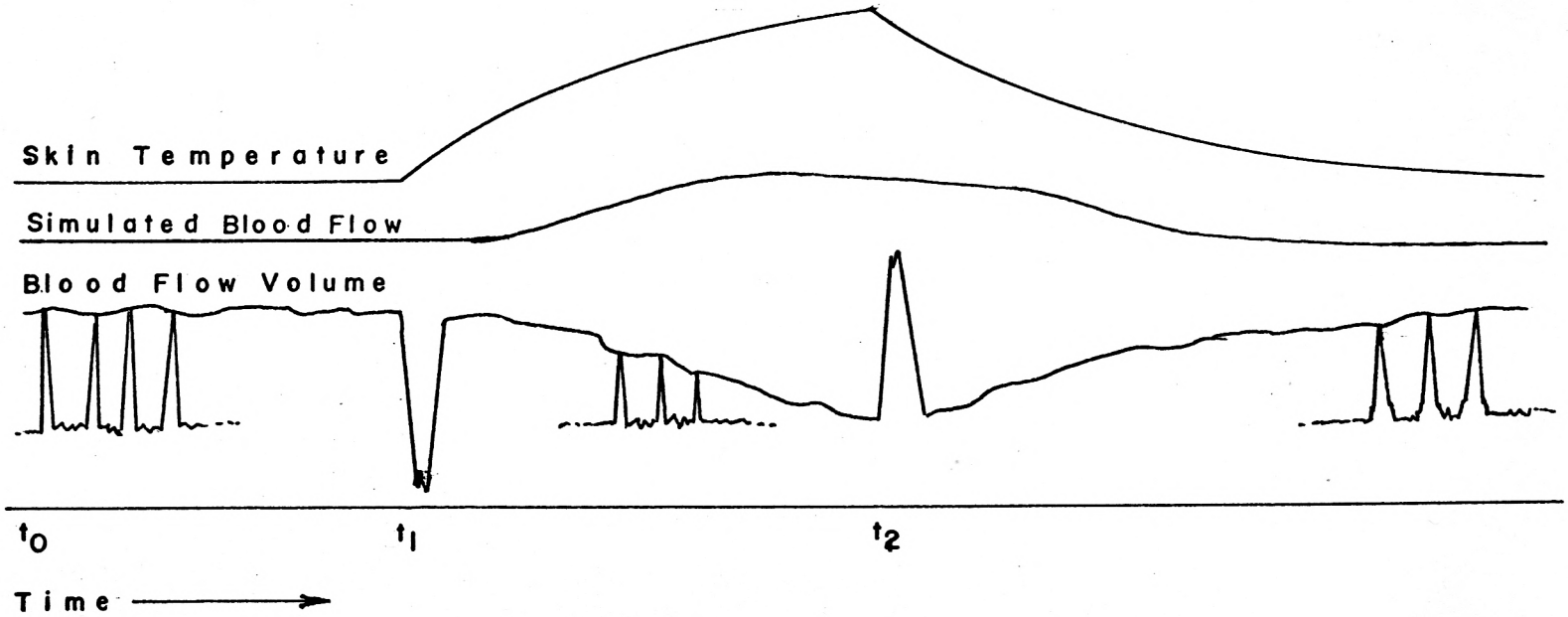


Fig. 10. Simplified version of Fig. 8 (Visicorder record) showing variation of blood flow with temperature. Note that volume of blood flow is inversely proportional to pulse amplitudes shown.

is shown in Fig. 11 and the computer simulation in Fig. 17. The transfer function describing the process is

$$\frac{B(s)}{T(s)} = A + \alpha s \tag{9}$$

and the corresponding differential equation is

$$B(t) = AT(t) + \alpha \frac{dT}{dt} \tag{10}$$

where A is the constant for proportional control and α is the constant of derivative control.

Comparison of the simulation and actual blood flow can be done by referring to Figs. 12 and 13. Figure 12 compares the two blood volumes for a slow temperature rise and fall. In Fig. 13, the effect of sharp temperature changes on simulated and actual blood volume is shown. Neglecting the noise in the recording signals, comparison is good. In this simulation, $\alpha = 1.0$ and $A = 0.915$.

EXPERIMENTAL METHODS

Skin temperature measurement was accomplished with the thermistor bridge shown in Fig. 14. Switch position 1 is used for setting the voltage applied to the bridge at a standard value and is done with the thermistor removed from the circuit. Position 2 is used for measuring the bridge unbalance corresponding to temperature. Another switch position is provided for recording or providing the computer input.

In use, the bridge is balanced at normal skin temperature

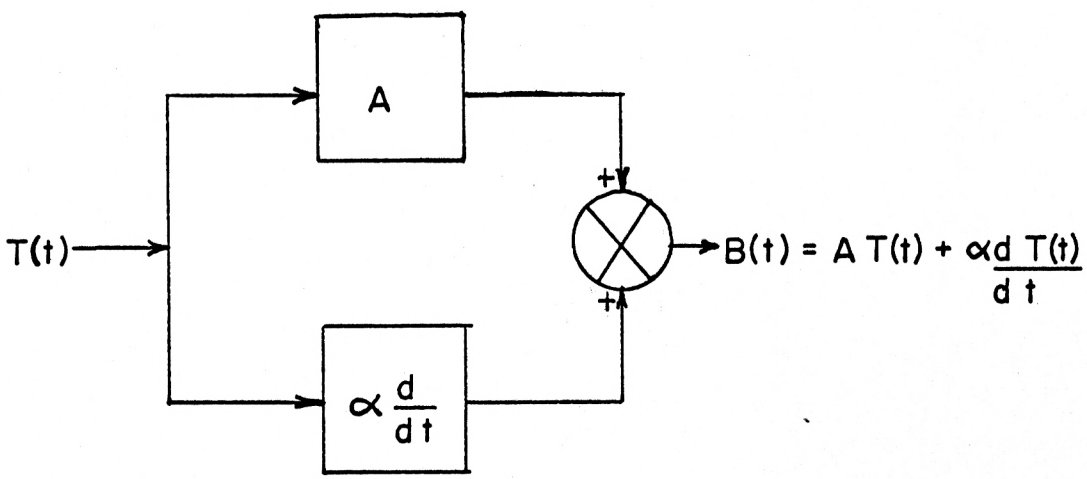


Fig. 11. Block diagram of rate plus proportional control.

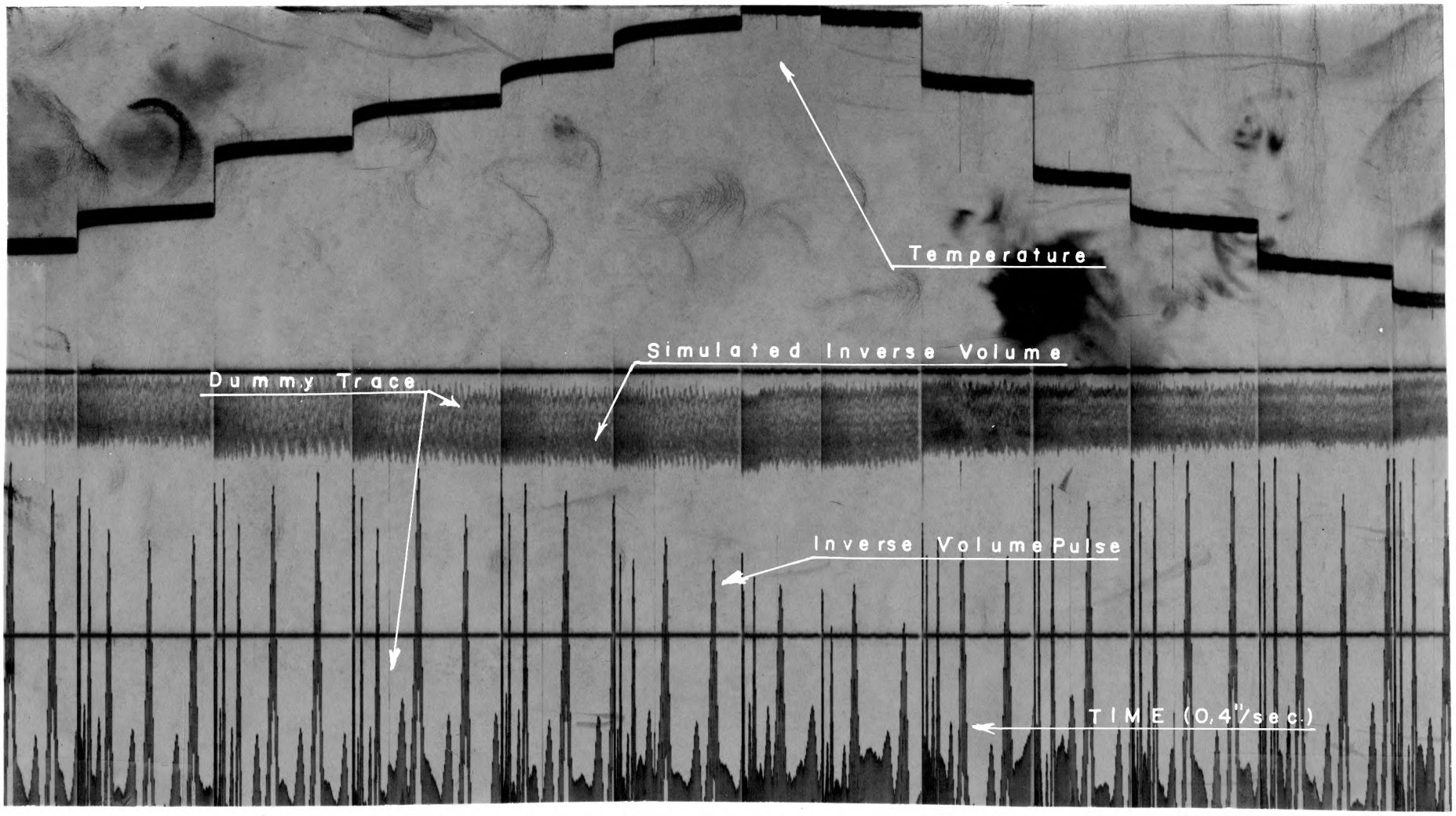


Fig. 12. Comparison of simulated blood volume and actual blood volume for the transfer function $\frac{B(s)}{T(s)} = A + \alpha s$ for slow temperature changes.

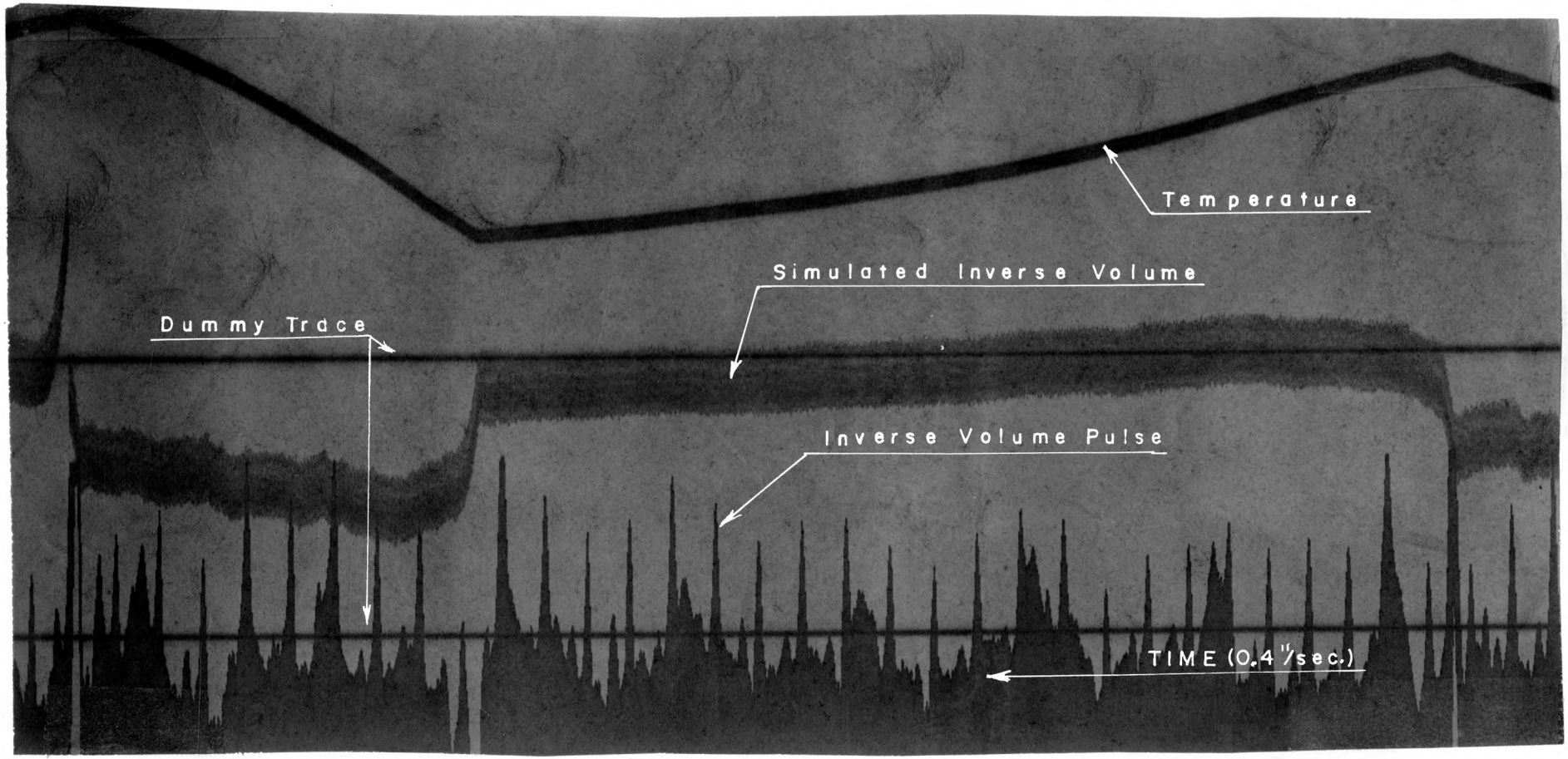


Fig. 13. Comparison of simulated blood volume and actual blood volume for fast temperature changes for the transfer function $\frac{B(s)}{T(s)} = A + \alpha s$.

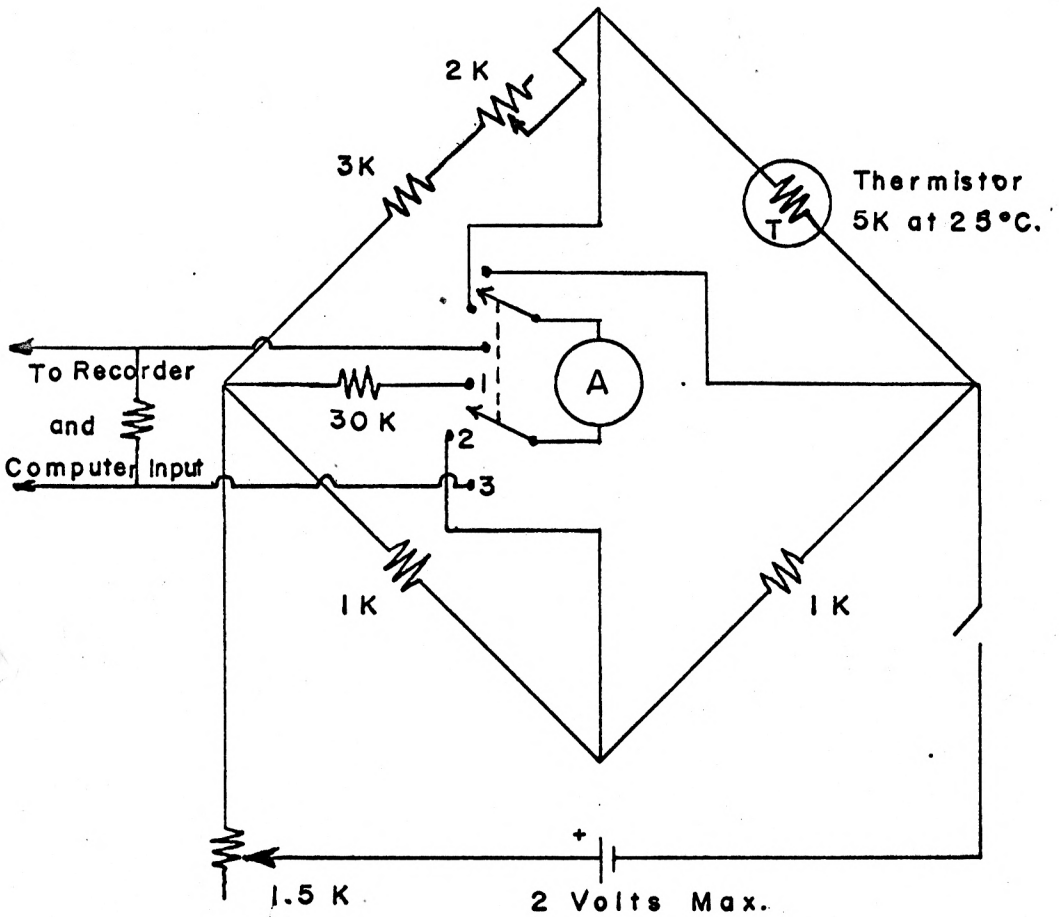


Fig. 14. Temperature-measuring bridge.

Meter: Center-reading microammeter.
Thermistor: Fenwall glass-coated bead; time constant, 2 seconds; dissipation, 0.7 milliwatt maximum for no self heating.

(90 ± 5° F). Other temperatures are read from the meter scale as the amount of bridge unbalance. In the range specified, the bridge unbalance is linear with respect to temperature.

Figure 15 shows the plethysmograph used for measuring blood volume changes. A variation in light intensity striking the photoconductive cell causes a variation in resistance of the cell. Thus the voltage across resistance R varies as the blood volume pulse. The cell used is a Clairex 604 with a peak spectral response at 6900 Angstroms and a resistance at two foot-candles of 30,000 ohms.

Volume blood flow through a tissue is expressed by

$$B = KP$$

where B is the blood flow, K is a constant, and P is the pulse amplitude (11). In the resting state, with normal contraction and dilation of the blood vessels, the pulse amplitude is linear with respect to blood flow volume.

Considerable difficulty was initially encountered in determining the subject and subject area for test purposes. The problem of adequate light transmission through "opaque" tissues suggested the use of a membrane portion of the subject anatomy. A rabbit was chosen as the first subject since the large area of the ear presented a good, translucent membrane in which blood flow was evident. Unfortunately, the instrumentation at this stage of development was inadequate for proper evaluation of results. The signal-to-noise ratio was much too small and considerable filtering failed to improve results significantly. Exciting the rabbit during handling was also an uncontrollable

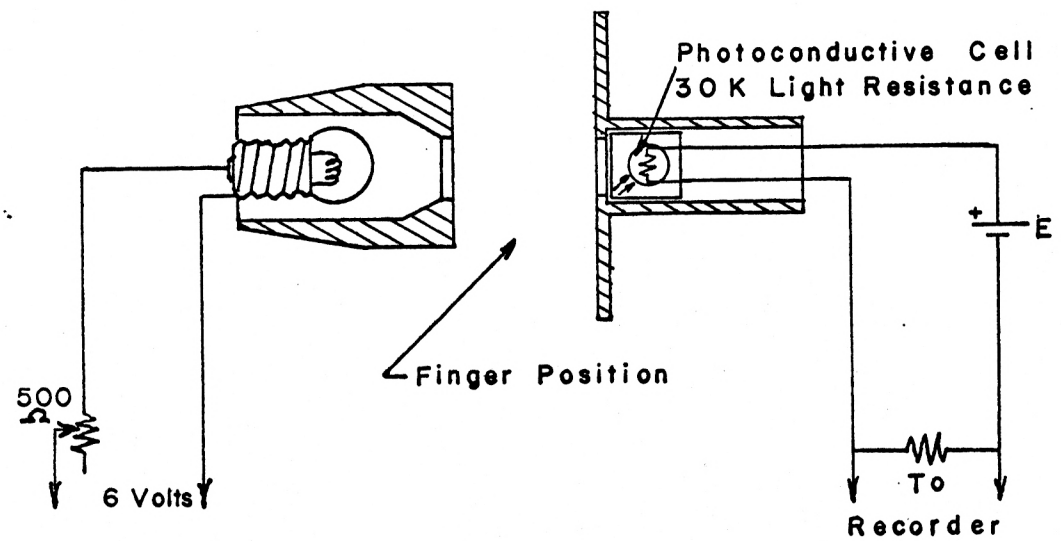


Fig. 15. Photoelectric plethysmograph for blood volume measurement.

factor. Subsequent testing indicated that the human finger tip at the base of the finger nail yielded apparently satisfactory data and was therefore used throughout.

Figure 16 is a block diagram of the experimental arrangement. The details of this arrangement are shown in Fig. 17.

DISCUSSION AND CONCLUSIONS

The first attempt in this experiment at describing the temperature control of vasomotor action through a combination of component transfer functions might be made more accurate if the following were true.

1. Complete factual data were available for each component.
2. The inputs and outputs of each component were known and controllable.
3. Other factors such as hypothalamus and local hormonal actions, and variation of body responses from area-to-area were considered.

The final simulation arrived at for temperature-vasomotor action closely approximates the actual process and agrees with data of other experimenters (6).

In control systems, adding derivative control to proportional control increases the damping factor for fast changes. Therefore it appears as if temperature-vasomotor regulation is a stable process. An attempt to drive the system unstable would be of investigative interest and might give further insight into the details of component action.

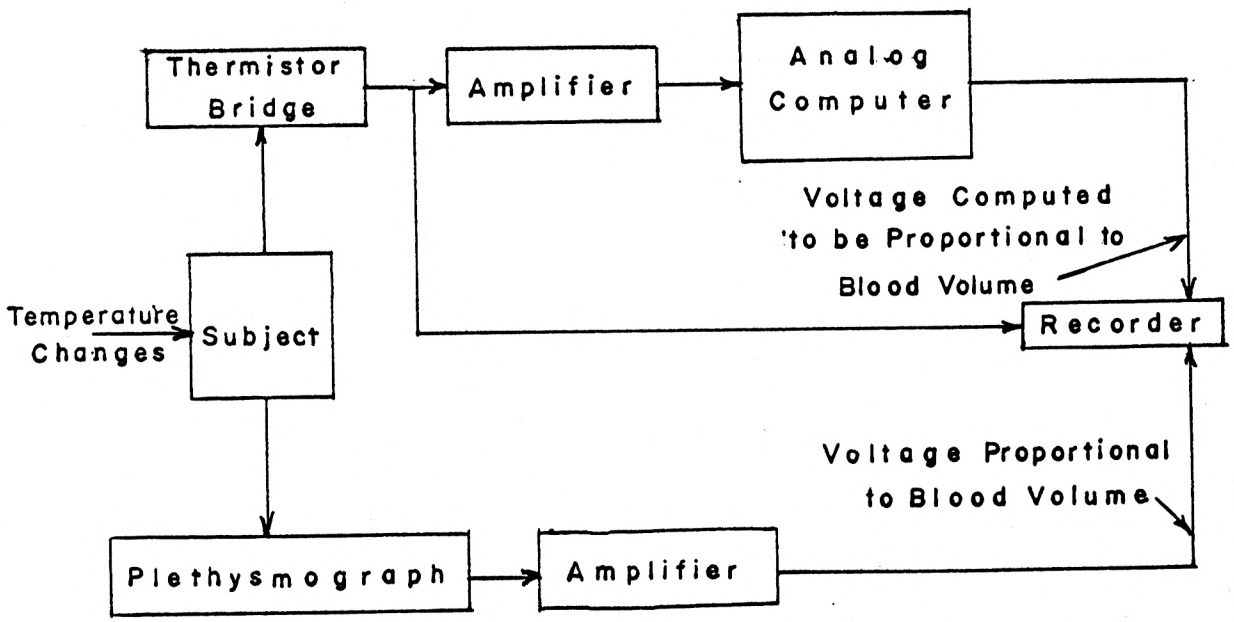
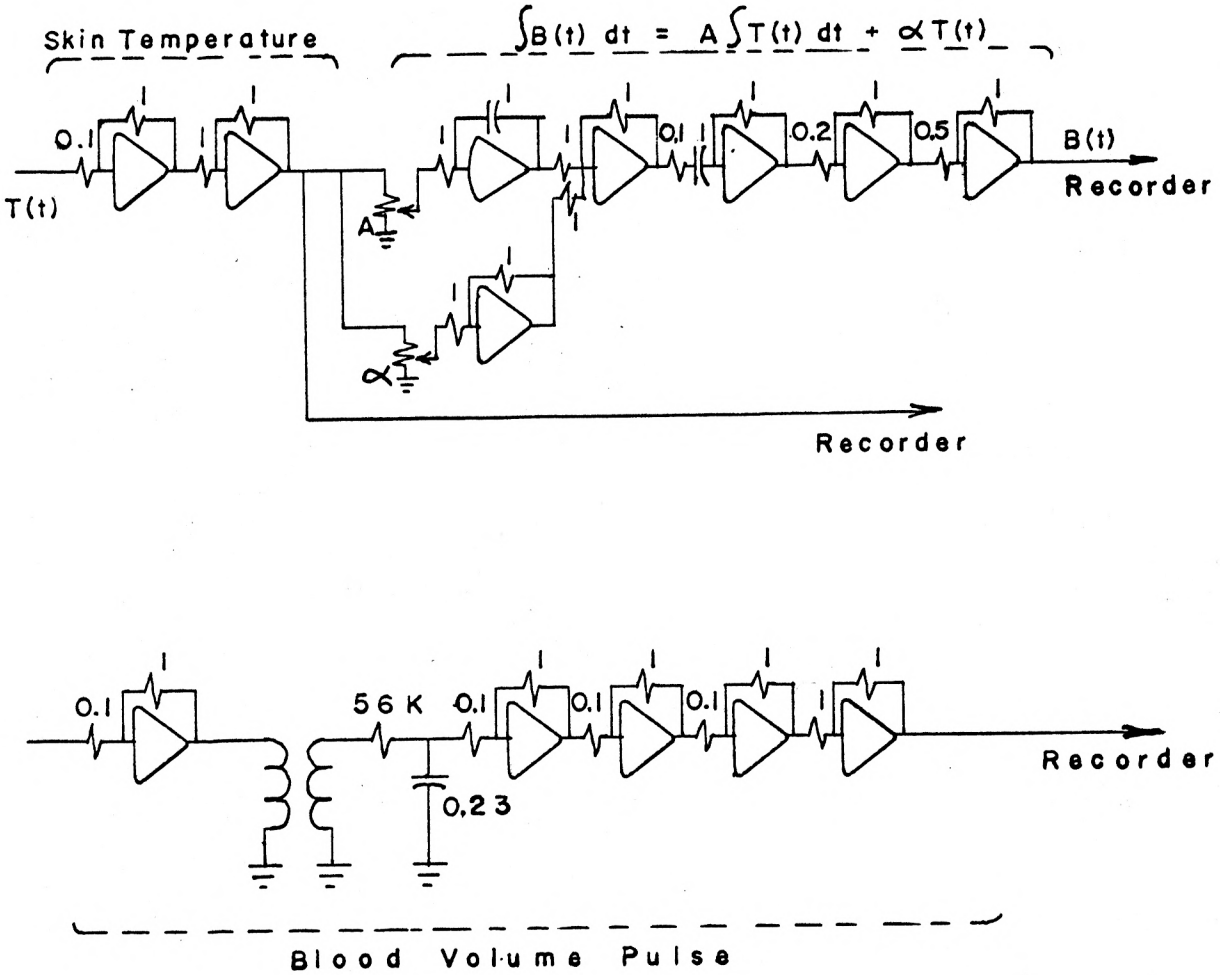


Fig. 16. Block diagram of comparison procedure. The analog computer was developed by the Electrical Engineering staff at Kansas State University.



Capacitances in microfarads, resistances in megohms unless stated otherwise.

Fig. 17. Detailed diagram of experimental arrangement incorporating the computer program.

Further investigation might be made of the complete closed-loop system, where the feedback path is the heat loss as a result of vasomotor action.

Finally, consideration must be given to the fact that though the analog computer simulation constructed may be effective in describing temperature-vasomotor action, it is not necessarily the only simulation; others might be as effective.

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Manhattan, Kansas

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Homeostatic mechanisms in biological organisms have many characteristics of automatic control systems. Two examples are given and a detailed study is made of a third--temperature-vasomotor control as an organism temperature regulator. From this study, a transfer function relating temperature and blood flow volume is constructed. Utilizing the analog computer, the resulting differential equation is programmed and the results are compared with actual blood flow variation in the fingers. A more accurate transfer function is found by approaching the simulation from a direct evaluation of experimental data. This new simulation shows that temperature-vasomotor regulation in the fingers is a form of derivative control plus proportional control. Experimental equipment used includes a photoelectric plethysmograph for blood volume indication and a thermistor bridge for temperature measurement.