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FEEDBACK CONTROL AND THE CONCEPT OF HOMEOSTASIS

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Abstract—The maintenance of life requires a steady-state internal environment that must be held relatively constant within carefully prescribed limits. Feedback control mechanisms that provide this type of restraint work through homeostatic regulators that transmit information through a corresponding syntax that is uniquely their own. The language is coded into electromagnetic information that is of a reference nature (genetic, adaptive or conditioned), sensory (informative) or motor (causative), and which is transmitted as action potentials that have a functional dependence on the error signal and a parametric dependence on the disturbing signal. The analysis of homeostasis within the context of feedback control theory reduces seemingly complex, unrelated sequences of physiologic processes into more readily identifiable sets of common denominators that illucidate some basic principles of biologic function. Appropriate interpretation of these biologic principles may help us move closer to success in our efforts to improve the health, comfort and understanding of man. This is because the specific details of complex physiologic processes may be viewed as simply special cases (or different sets of boundary conditions) of a unified guiding theory.

1. INTRODUCTION

Homeostasis may be defined as the steady-state internal environment that is required for the maintenance of life. The concept of homeostasis includes as well those processes by which physiologic variables are maintained within well-defined and carefully prescribed limits; and inherent to these processes is the corresponding concept of feedback control. This paper offers a generalized approach which can be used to analyze mathematically physiologic function in terms of homeostatic mechanisms. In particular, the approach casts basic aspects of life processes into an overall scheme of feedback control, with the ultimate intent of providing a unified means for formulating the mathematics of such processes in a systematic, rational manner.

A specific distinction of feedback control systems is that they all may be made to fit some canonical pattern, such as that shown in Fig. 1. This scheme is "canonical" in the sense that it provides the simplest possible description of the functional behavior of the system. Each pathway, each signal, each box and each loop may, in fact, contain several pathways (in series or in parallel), several signals, several subsets of interacting boxes and several embedded loops, but the typical schematic configuration shown illustrates the ultimate manifestation of all of these into a basic input/output design.

The reference signal, u_r, is simply a standard to which the system attempts to conform. The feedback signal, u, represents the output variable that is monitored in order to assess the performance of the system relative to u_r (and, perhaps, to *set* the standard, as described later). The signals u and u_r both enter a comparator and the controlling section of the feedback control system. Having an overall linear or nonlinear transfer function, K_2, this part of the system is where decisions are

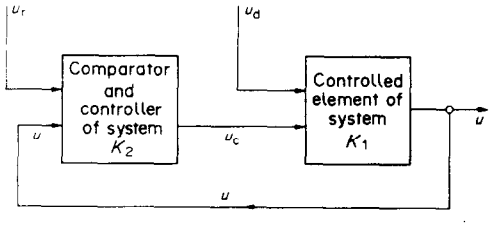

Fig.1.

made, and where appropriate action is taken, depending on whether u is less than, bigger than, or equal to the reference signal, u_r, and on how fast and how consistently u is changing relative to u_r. If $u \neq u_r$ (perhaps due to some disturbance, u_d), then the comparator and controller of the servomechanism issues forth a control signal, u_c, in an attempt to alleviate this situation. The control signal generally contains a component related to the "error signal", $u - u_r$ (proportional control), a component related to the derivative of the error signal, $\frac{d}{dt}(u - u_r)$ (reset control) and a component related to the integral of the error signal, $\int (u - u_r)dt$ (integral control):

$$u_c = K_2'(u - u_r) + K_2'' \frac{d}{dt}(u - u_r) + K_2''' \int (u - u_r)dt. \tag{1}$$

The basic assumption of feedback control theory is that the control signal, u_c, can bring the controlled signal, u, to within an acceptable range of the reference signal, u_r, depending on the value of the disturbing signal, u_d; i.e. there is some envelope of disturbances within which the controller can regulate effectively the controlled elements of the system. Toward this end, the *intensity* of u_c, as given by equation (1)—i.e. the extent to which corrective measures are taken, is in direct proportion to the deviation of the actual output, u, from the desired output, u_r, to the *rate* of such deviation (to prevent the system from over-reacting), and to its consistency (to account for a continuous error signal). Furthermore, if the response is to be stable, then associated with u_c is some characteristic decay time, τ_d, phase angle, ϕ, and overshoot parameter, u_o [1]. Finally, if the disturbance should happen to fall outside of the stable response envelope, then one or more of the controlled systems may become unstable, leading to a breakdown in one or more components of the systems, or to the intervention of some nonlinearity in the system, or to a combination of both.

In a sense, one may think of the control signal as having a *functional* dependence on the error signal, as defined, for example, by equation (1), and a *parametric* dependence on the disturbing signal, to the extent that u_d determines the range of values of u within which the feedback control system will be in stable equilibrium. If u falls outside of this range, then u_c will not be effective in bringing u to within some neighborhood of u_r. The steady-state error of the system will then grow without limit, and it will eventually break down. Alternatively, some nonlinearity may intervene, or, the system may be reset to some new value of u_r to perhaps accommodate a new "window" for u in terms of u_d.

The schematic representation of any feedback control system includes, of course, the controlled element, which is under the influence of both u_c and u_d, and which provides the monitored output signal, u. The latter is related to some linear or nonlinear combination of u_c and u_d through the overall transfer function (or associated gain), K_1 of the controlled element:

$$u = u(u_c, u_d),$$

from which,

$$du = \frac{\partial u}{\partial u_c} du_c + \frac{\partial u}{\partial u_d} du_d = K_1' du_c + K_1'' du_d. \tag{2}$$

With these introductory comments in mind, the text which follows demonstrates how certain fundamental aspects of physiologic function may be made to fit this scheme for the purposes of mathematical formulation, modelling and analysis.

2. REFERENCE SIGNALS IN PHYSIOLOGIC SYSTEMS

The human organism establishes values of u_r for itself based first and foremost on its metabolic and thermoregulatory requirements. These are further fine-tuned to economize on the expenditure of energy that is necessary to meet those requirements [2]. Within this framework, the body sets

for itself reference quantities that constrain its various subsystems to operate within limits that insure stability, competence and safety, while achieving some desired behavioral pattern, some well-defined metabolic goal or some specific task constrained only by the envelope of physiologic performance capabilities. These, we may call "cost functions" or levels of "desired performance" and they are based on millions of years worth of evolutionary experiences that have taught the organism what it needs to know, and *do* to survive.

Indeed, one might think of "reference quantities" as being merely the manifestation of evolution—which teaches us that physiologic systems which operate in the most *fitting* way are those that will ultimately survive. "Fitting" translates into "desired performance", and "desired performance" translates into "reference quantities," u_r. Going one step further, the human organism is capable of coding these reference quantities into genetic material that provides repositories for the information that characterizes a certain species. This allows succeeding generations to inherit all of the standards of performance established through years and years of experience, so that the wheel is not constantly being reinvented.

Biological servomechanisms, or homeostatic feedback control systems do differ, however, in one important way from man-made, engineering-type servomechanisms, in that the desired performance (or reference quantities) to which the system attempts to conform do *not* necessarily remain absolutely constant for all time. Rather, one may think of physiological feedback control systems as having "floating" set-points that "float" in accordance with *changes* (on a moment-to-moment basis) in the metabolic requirements of the organism—or, with a re-prioritization (on an organ-to-organ basis) of the metabolic requirements of certain specific tissues; or, on the state of evolution of the body; or, on any of a number of other factors that may justify a change in u_r. These may include, for example, set-point changes called for by the environment within which the body finds itself, or by the value of the output u, itself, or by the state of health of the organism, or by its desire to achieve some particular pattern of behavior, or by its envelope of capability in the performance of a specific task, or by the associated cost of achieving it, or by certain safety and stability factors, or by many other variables, many of which have perhaps not even been identified as yet.

The significant difference, then, between inanimate and animated systems is that output, u, in physiologic systems tends to be monitored *twice*: once by "higher" control centers (such as the brain) to *establish* the reference signal, u_r, and a second time by comparators and controlling systems to get u to *equal* u_r as closely and as stably as possible. In other words, looking at Fig. 1, biological servomechanisms sense u in accordance with their needs, and then put in the proper reference quantity, u_r, *automatically* to satisfy those needs, which may change as often as on a moment-to-moment basis.

Some of the centers of the brain in humans that are responsible for establishing values for u_r are those that receive sensory information from the special senses (sight, hearing, smell, taste and touch), from exteroceptors that respond to the external environment (cutaneous pain sensors, temperature, balance and equilibrium), and from interoceptors that respond to the internal environment (visceral sensors, baroreceptors, chemoreceptors, proprioceptors, muscle spindles, golgi tendon organs, kinesthetic receptors and so on). These centers of the brain include the subconscious or lower levels (reticular substance of the medulla, pons and mesencephalon; the cerebellum and basal ganglia; and the thalamus and hypothalamus), and the conscious or higher levels that have to do with memory, wakefulness and abstract processes of thought (the somesthetic areas of the cerebral cortex) [3].

Each time a particular sensory signal passes through a sequence of pathways, these pathways become more capable of transmitting the *same* signal the next time it comes through—a process called facilitation, or memory of sensation. One may think of this as "programmed learning", akin to programming a computer to do a specific task. Facilitation ultimately allows the system to *adapt*, in both a long-term and short-term sense, to stay alive. That is to say, facilitation gradually becomes a conditioned reflex, and may even reach the point wherein *no* sensory input is required anymore to elicit a particular response. Taking this one step further, the conditioned reflex soon evolves into a newly defined set point for u. The process of biological adaptation can therefore be modelled mathematically by noting that it is nothing more than the process of changing the set-

points of a living system as necessary (based on experience, "programming" or any of the other parameters listed earlier), to allow it to continue functioning as economically as possible. These set-points, for various subsystems of the body, may also be functions of *each other*, in an integrative sense, to insure that the *whole* organism functions in a synchronized, directed fashion.

As a case in point to illustrate the preceding discussion, consider the physiologic control of red blood cell production (known as "erythropoiesis"). The primary function of red blood cells (erythrocytes) is to transport oxygen to all the cells of the body; a function accomplished by the erythrocyte's carrier molecule, hemoglobin. Red blood cells are produced in bone marrow, their rate of production being controlled by a plasma stimulant called erythropoietin (E), which, in turn, is activated by an "erythropoietic factor" (R), secreted from the kidneys in response to anoxia (low oxygen concentration in the blood). At sea level, where the partial pressure of oxygen in moist alveolar air is about 100–103 mmHg, red blood cell hemoglobin molecules are nearly (97.5%) completely saturated with oxygen as they pass through the lungs, and so the organism's need for oxygen (some 19.6 ml O_2)/100 ml blood) can be met satisfactorily by maintaining the number of cells/mm^3 of whole blood at about 5 million. Since the cells have an average volume (mean corpuscular volume, MCV) of 90 μm^3, 5 million cells/mm^3 of blood occupy some 45% by vol (the so-called hematocrit, H) of the fluid. Since each blood cell contains some 30×10^{-12} g hemoglobin (mean corpuscular hemoglobin, MCH), and since the average individual contains a total blood volume (V_B) of approx. 5 l., at sea level the total need for hemoglobin is around 750 g. This is calculated from the equation

$$\text{total hemoglobin, TH} = \frac{\text{MCH}}{\text{MCV}} \times \frac{\text{H}}{100} \times V_B. \tag{3}$$

In terms of Fig. 1, one may define, for erythropoiesis: u = actual blood hematocrit, at any instant of time; u_r = desired blood hematocrit at sea level (some 45%); u_c = circulating level of plasma erythropoietin, E; K_2 = the kidney; and K_1 = the bone marrow. Disturbing signals, u_d in this case would be normal daily red blood cell destruction rate of about 1% (2–10 million cells/s), or hemorrhaging (blood loss) due to some accident, or perhaps some anemic pathologic condition, or anything else that would cause u to deviate from u_r, giving rise to an error signal, $u - u_r$. The key point, however, is that the *reference signal*, $u_r = 45\%$ does *not* change with u_d at sea level because the disturbance lies *not* in the hematocrit *required* to meet the metabolic needs of the organism, but in the *maintenance* of that hematocrit in the face of upsetting influences. In other words, nothing acts to change any of the variables given in equation (3). Nor do K_2 or K_1 change in response to u_d, and u_c stays generally at some optimum operating level.

Consider now what happens if u_d represents *prolonged anoxia*, generated, for example, by continuous exposure to an environment associated with high altitudes. Acting on the kidney and brain, as well as the bone marrow, this environmental disturbance now creates a situation wherein H = 45% is no longer adequate to satisfy the needs of the organism, i.e. u_r now *becomes* a function of u_d. Responding to the sustained anoxia, the kidney gain, K_2 drives u_c (renal erythropoietic factor) higher, increasing red cell production, while u_r drifts slowly and asymptotically towards a new value that will eventually provide a higher hematocrit to carry sufficient oxygen to all of the cells of the organism. Furthermore, the hypothalamus of the brain, acting through the pituitary gland (anti-diuretic hormone, ADH) and, ultimately, the kidney, again (vasopressin), drives the reference value for total blood volume, V_B, higher, as well. Lastly, MCH is increased slightly—all three of these, MCH, H and V_B, act to increase TH, in accordance with equation (3). In fact, at prolonged exposure to an altitude of 22,500 ft, where arterial oxygen saturation drops to only 50% as air pressure drops from 760 mmHg at sea level to 349 mmHg, MCH increases 1⅔% to about 30.5×10^{-12} g, H increases 44½% to 65% and V_B increases 25% to 6.25 l, leading to an increase in TH of nearly 84%. All of this can be modelled mathematically [e.g. 4–6] because: (a) the functional relationship between alveolar oxygen partial pressure and altitude is known; (b) the functional relationship between alveolar oxygen partial pressure and arterial hemoglobin–oxygen saturation is known; (c) the functional relationship between hemoglobin–oxygen saturation and kidney release of R is known; (d) the functional relationship between plasma erythropoietin con-

centration and R is known; (e) the functional relationship between plasma erythropoietin concentration and bone marrow production of red blood cells is known; and (f) so, too, are known functional relationships between total blood volume and vasopressin concentration, vasopressin concentration and concentration of ADH, and concentration of ADH vs hypothalamic activity.

The important point to be emphasized is that these changes in u_r are long-term adaptations to sustained values of u_d that significantly affect the *needs* of the organism. In the situation depicted above, for example, virtually no effect is observed for some 2–3 weeks following continuous exposure to a high-altitude environment. About half the effects begin to be manifest after about a month, and it takes several months before the effects become fully developed. Then, interestingly, over a further period of time, the E levels in plasma, *drop* back to their normal sea-level values, but the bone marrow *continues* to manufacture red blood cells at the *new* (higher-altitude) H value. That is to say, the kidney gain, K_2, drops back to its sea-level value, while the bone marrow gain, K_1, goes up, and stays at its high-altitude value—so the stimulus is no longer necessary to elicit the response! (stimulus being E). Going still further, over an extended period of time, all of these changes generate a new coding in genetic material, such that subsequent generations of high-altitude natives automatically possess greater quantities of hemoglobin, more efficient hemoglobin–oxygen dissociation curve characteristics, greatly expanded pulmonary capillary systems, larger hearts (especially the right side that feeds the pulmonary circulation) and a higher ratio of ventilatory capacity to body mass (increased chest size coupled with a somewhat decreased body size).

Physiologic examples of floating set-points and adaptation are numerous, and the literature on adaptive control systems is vast [6–12]. For instance, the re-setting of body core temperature in the case of fever is viewed as an attempt on the part of the body to fight off infection by creating an adverse environment for the invading organism. The manufacture of insulin is known to have a drifting set-point which goes awry in the case of diabetes; the human vestibular system and various joint receptors are known to have remarkable (sometimes detrimental) capacities for adaptation; and the list goes on and on.

The concepts of programmed learning, facilitation, conditioned reflexes and adaptation may also be factors in developing one's self-image and attitudes towards life. Thus, for example, programmed (conditioned) negativism, which begins very early in life with such words as, "no" or "do not", or "don't touch", or "you can't" or "you must not", or "that's stupid", and so on, very quickly establishes self-image, self-belief or self-esteem set-points that *expect* defeat, and, therefore, "will" it to happen whether an individual realizes it, or not. There is an underlying truth in the concept that our bodies can be programmed by constant reinforcement of certain attitudes and perceptions. Brain-washing is a perfect example of this. But in a less-dramatic, though everyday sense, we are constantly being brain-washed to think the worst, expect the worst, hope for the best (almost *against* hope) but plan for disasters. Those disasters are almost sure to come because we *virtually plan* (i.e. *set* u_r) it that way! Expect the worst, and you will *get* the worst! This is programming, conditioning and establishing negative emotional set-points (feelings) that are sure to generate corresponding behavioral patterns and actions.

But all is not lost. If one accepts the idea of programmed learning, then one can also accept the corollary of "de-programming" which can *change* the set-points with *positive* reinforcement, rather than negative. At any stage in life, one can effectively "erase" the old disk, and program in a new one using the *same* principles of repetition, conditioning and adaptation. The new science of biofeedback may offer a means for doing this, as may some other new approaches termed, "self-talk", or "transcendental meditation," or "the relaxation response", or "dyanetics", or "autohypnosis" and so on. These are based on some of the ideas presented below concerning feedback signals, u.

3. FEEDBACK SIGNALS IN PHYSIOLOGIC SYSTEMS

Thinking in terms of information transport in feedback control systems, one may view reference signals as being coded temporarily into conditioned or adaptive responses, and permanently into genetic repositories. Similarly, one may view feedback signals, u, as being coded into electromagnetic sensory information that may be termed, "body language" (not to be confused with the more common physical implication of such terminology). Sensory information is generated by specialized transducers that monitor the controlled elements of physiologic systems, or the internal and external

Table 1. Some examples of the different dialects associated with sensory body language

1)	Electroencephalosyntax (Brain Waves)	11)	Proprioceptive-syntax (Posture & Locomotion)
2)	Electroretinosyntax (Sight, Vision)	12)	Electrothermal Syntax (Heat, Temperature)
3)	Electroaudiosyntax (Sound, Audition)	13)	Electrochemosyntax (Biochemical Reactions)
4)	Electrosalivosyntax (Taste, Gustation)	14)	Electro-kinesthetic-syntax (Joint Position & Orientation)
5)	Electrotactilesyntax (Touch, Tactual)	15)	Muscle Spindle Electrosyntax (Stretch)
6)	Electrobarosyntax (Pressure)	16)	Golgi Tendon Organ Syntax (Force Perception)
7)	Electro-olfactosyntax (Smell, Olfaction)	17)	Visceral Sensorisyntax (Stretch Perception)
8)	Electrovestibulosyntax (Balance & Equilibrium)	18)	Somesthetic Syntax (Consciously Perceived Sensations)
9)	Electrocochleosyntax (Hearing and Balance)	19)	Extero-and-Intero-Syntax
10)	Electroaxono-syntax (Action Potential)	20)	Electronystagmosyntax (Eyeball Movements)

environments of the body, or both. The "body language" generated is simply based on biological signals that are transmitted as action potentials, such signals providing a communications network that continuously tells the organism what its current condition is, so that this condition may be compared to the desired goal and appropriate action taken accordingly. Sensory body language may actually include several "dialects", or even consist of many *different* languages, as is illustrated in Table 1.

Indeed, body language—feedback control signals—may be the key to understanding the very basis of physiologic function. We know, for example, that heart muscle tissue "obeys" commands issued from its "pacing" control center, which is the sino-atrial (SA) node. The SA-node "speaks" in the language of electrocardiosyntax, and the heart muscle, understanding this language, responds. And the effectiveness of the results obtained by electrocardiosyntax is monitored in its transduced form—which is blood pressure—by baroreceptors placed at strategic sites (such as the carotid artery and the aorta) in the vascular system. These baroreceptors send feedback signals (electro-barosyntax, see Table 1) to higher control centers in the brain, where comparisons are made between "actual" blood pressure (u) and "desired" blood pressure (u_r). This is the language of the baroreceptor reflex arc that ultimately attempts to regulate blood pressure.

Going one step further, we also know that the human eye does not see—the brain does; and the human ear does not hear—the brain does; and the human nose does not smell—the brain does! Indeed, all of our "special" senses are merely transducers that convert one form of energy (e.g. light or sound) into electrochemical energy. The latter is transmitted via respective nerve pathways to appropriate centers in the brain, where the incoming "language" or syntax is decoded and translated into a corresponding image, or sound, or taste, or smell, or feeling, or whatever.

Imagine, now, that *we* could "speak" electroretinosyntax, or, more specifically, that we could design and build a transducer that has precisely the same input/output characteristics as the human optical transducer. Then, assuming we could properly interface such a device with the optic nerve to form a continuous pathway to the brain, our man-made "eye" would be capable of speaking to the visual centers of the brain in a language they are designed to understand. As far as these centers are concerned, then, they would be "seeing" just as if the *natural* eye were transmitting the signals instead of the *synthetic* one. The same argument could be presented for the development of an artificial ear, or for the development of an artificial limb that is operated by the same α-motoneurons that operated the corresponding natural limb, or for the inclusion of sensory feedback information in artificial limbs—or, for the development of *any* prosthetic device that is to be used to replace a part of the human body. If only we understood the proper body *language* that is native to the part we are replacing, then we could, indeed, replace the exact *function* of the part, as well as its *structure*.

The above reasoning is not as abstract as it may sound at first. Biological signals, from an engineering point of view, are remarkably reproducible (see the excellent works of Plonsey [13], Bendat and Piersol [14] and Coulon [15]. This means that electromagnetic recordings of

physiological action potentials can be subjected to sophisticated techniques of biological signal analysis in order to "decode" (hence, gain the ability to reproduce) the feedback language of the human feedback control systems. Once understood, these languages can become integral software to the microprocessor hardware of man-made devices, thus moving us closer to being able to communicate with the organism. All that is left, then, is to develop techniques for interfacing synthetic devices with physiologic tissue, and the process is complete. When that day finally arrives—and it is not all that far away when viewed in terms of modern-day technological accomplishments (see, for example, Sayers [16])—what an exciting time it will be!

One area in which the decoding of biological signals has been very successful is the development of upper-extremity myoelectric prosthetic devices [17]. Another relates to the piezoelectric functional properties of bone tissue, and the corresponding treatment of bone ailments through electromagnetic induction [18]. Progress towards being able to attach synthetic nerves to physiologic ones is proceeding along the lines of using metal (Na, K, Ca) monolayers-coated sutures to bind the living with the artificial [19]. Hardly a day goes by that one does not hear or read about major technological breakthroughs that bridge the gap between science fiction and reality. But in the interest of space, it is best to move on.

Before doing so, however, one more important point should be made, and that has to do with the role of *biofeedback* in control systems theory. The idea in biofeedback is that internal physiologic control processes are transducted to produce input signals to the body's various senses [2]. A subject learns to interpret the meaning of this information in terms of a corresponding physiologic state of affairs (a "feeling", if you will). He or she is then trained to respond *consciously* in a way that produces a desired alteration of this state of affairs, thus allowing the subject to "willfully regulate" his or her internal environment. Enormous success has been reported in using biofeedback to relieve pain, to regulate muscle spindle behavior, to control the circulation, to maintain body temperature, to relieve migraine headache syndromes, to control metabolism and even to provide effective therapy in a wide variety of psychological disorders. One cannot deny its potential for increasing our "will" power by making us aware of what it "feels" like when such control is manifest—and, by bringing to consciousness such feelings, giving us the ability to affect control over bodily processes that heretofore have traditionally been considered to be uncontrollable at the conscious level. Which brings us to the subject of comparator and controlling sections of biological feedback control systems or servomechanisms.

4. CONTROL SIGNALS IN PHYSIOLOGIC SYSTEMS

Comparator and controlling systems of biological servomechanisms are called homeostatic regulators. Recall that homeostasis is the process through which variables critical to life, and others not so critical, are maintained with prescribed limits, where, as reasoned earlier, these limits may be based on anatomical limitations, on the laws of physics, on associated "cost functions," and so on.

Thus, a homeostatic regulator will first *compare* the achieved performance, u, of a physiologic subsystem with the desired performance, u_r, of that system and, within certain constraints, *decide* upon and *execute* the best course of action in order to bring the two into correspondence. Of course, if $u = u_r$ (i.e. the error signal, $u - u_r = 0$), then everything is fine and nothing happens. But rarely, if ever, is this the case, for we live in an environment that is constantly challenging the equilibrium of our physiologic systems; and if the environment is not doing it, we do it ourselves by the very life styles that we lead. Therefore, the more likely situation is one in which homeostatic regulators are continually making corrections (homeokinetics is a descriptive term that has been coined to describe this) in order to bring u to within an acceptable range of u_r, when the equilibrium of the system is upset by some disturbance, u_d.

When $u \neq u_r$, then the homeostatic regulator issues forth a control signal [the intensity of which is a function of the error signal, $u - u_r$, as in equation (1)], in an attempt to alleviate this situation. Again, the guiding principle here is that u_c can affect the controlled system to bring u to within an acceptable range of u_r, depending on the value of u_d. That is to say, one can surmise that there is some normal "envelope" of u_d within which homeostatic regulators can function effectively to keep the various subsystems of the human body in states of stable equilibrium. Should the disturbing

signals fall outside of this envelope, then one or more of these systems may become unstable and fail. In real life, instabilities of a feedback control system—i.e. those situations when there is no longer an associated decay time for u_c, with a corresponding stable overshoot and phase relationship—manifest themselves in the breakdown of one or more components of the system, or the intervention of some nonlinearity (K not constant), or a combination of both. Thus, one might look for such malfunctions in physiologic subsystems that become unstable, and, these malfunctions may become manifest in what we have come to call *disease*, or *pathology*, or *allergic reactions*, or other forms of substandard physiologic performance.

One theory of disease, then, is that it represents an inability of the body to cope with or handle disturbances that fall outside of the operating ranges of its homeostatic regulators—or that insult these regulators too frequently in space and time—and to which the system cannot adapt quickly enough to prevent damage. Furthermore, such regulator operating ranges may not have fixed limits. Rather, they may depend on an individual's lifestyle, emotional state, age, physical condition, diet and environmental factors such as climate. Moreover, the operating range of any one homeostatic regulator may be a function of the operating range of other regulators in the body, since they undoubtedly influence one another as they all act in harmony to maintain stable equilibrium.

Control signals, while having a *functional* dependence on the error signal, as illustrated by equation (1), may also have a *parametric* dependence on the disturbing signal. In other words, u_d may determine the range of values of u within which the feedback control system will be in stable equilibrium, as already discussed. If u falls outside of this range, then the steady-state error of the system will grow essentially without limit, and it will eventually break down (or get "sick"). Alternatively, the system may attempt to *adapt* (evolve) to change u_r in order to accommodate a new "window" for u in terms of u_d. In that case, one could write:

$$u_c = u_c(u_r, u) = u_c(u_r(u_d), u) \tag{4}$$

and proceed to treat the control signal as a *functional* whose value (or range of values) depends on the relationship between u_r and u_d. It may even be possible to show that there is some optimization scheme wherein, of all the allowable functions that can relate u_r to u_d, the ones upon which physiologic function is based are chosen such that a minimum amount of control, u_c, is required to maintain a homeostatic state of affairs.

Some current thinking suggests that our body's immune system functions according to the above hypotheses [20]. That is to say, the system does well as long as it receives insults spaced far enough apart in time and in space, but it breaks down otherwise if the insults are superimposed too close together. These, then, "tip the scales" in favor of physiologic malfunctions that may range in severity from a simple allergic attack to dreaded diseases such as cancer. Given enough time, however, or helped along by successful immunotherapy, the system may adapt or evolve to change its reference signals (u_r), its transfer functions (K) or its control signals (u_c) to accommodate persistent values of disturbances (u_d) that affect system outputs (u). It is important to note that such accommodation may ultimately be manifest by changes in K, as discussed earlier in the example of adaptation to a high-altitude environment, and the ultimate effects on the kidney and on bone marrow.

Controlling signals may *also* be coded into various types of "body language", which is now classified as motor signals, rather than feedback sensory signals. It is known, for example, that there is a language that seems to govern healing. Send the proper piezoelectric signal (electro-osteosyntax) to the osteoblasts in the region of a bone fracture and they "understand" to start manufacturing new bone tissue [18]. In fact, such signals are responsible for the servomechanisms that allow bone to function at an optimum stress level in a process called *functional adaptation*. Moreover, "injury potentials" have been measured at the site of damaged physiologic tissue, and these electromagnetic signals have been shown to stimulate the growth of *new* tissue in the injured area (e.g. the growth of a new finger from a joint at which an existing finger has been severed). It is known further that various of the body's immune reactions are related to electrochemical potentials that establish the stereospecificity of lymphocytes. The list goes on and on, to include, for example, some of the dialects illustrated in Table 2.

The point is that there is a sophisticated communications network in the body whereby

Table 2. Some examples of the different dialects associated with motor body language

1) Electrocardiosyntax (Heart Muscle)	7) Electro-Osteo Syntax (Functional Adaptation)
2) Electromyosyntax (Striated Skeletal Muscle)	8) Electromagnetic Induction Of Cell Proliferation (Injury Potentials)
3) Post-Ganglionic Electro-axonic-syntax of the Autonomic Nervous System	9) Electromagnetic Induction Of DNA and RNA Synthesis
4) Electro-Gastrosyntax (Smooth Muscles, including Peristaltic movements of the Gastrointestinal Tract, and the Gastro-Colic Reflex)	10) Electromagnetic Induction Of Lymphocyte Activity (Immune System)
5) Electrotropism Syntax	11) Electromagnetic Motor Stimulation (Autonomic) of the Endocrine Glands of Secretion
6) Electro-Oculosyntax (Motor function of the Muscles of the Eyes)	12) Electromagnetic Speech Synthesis
	13) Electroarteriolar Syntax (Control of Smooth Muscle In Arterioles)

homeostatic regulators can "speak" (motor control) to their constituents. Again, if we could somehow learn to understand (de-code [14, 15]) and speak (reproduce in synthetic form) this "body language" of metabolic processes that control life, then we would be brought one step closer to being able to *intervene* in these processes when they malfunction. Thus, by appropriate intervention—perhaps electromagnetically, perhaps electrochemically, perhaps pharmaceutically,..., or whatever—we could control disease, affect cures for many (if not all) pathologic conditions, replace ailing or malfunctioning body parts, and even learn how to improve upon and exceed the present limitations imposed on human performance. But, since this discussion remains speculative at this point in time, it is best to move on again to address controlled elements in physiologic systems.

5. CONTROLLED ELEMENTS IN PHYSIOLOGIC SYSTEMS

In physiologic terms, very little is known about the inter-relationships and functional dependencies that exist between the disturbing signals, u_d, the control signals, u_c, and the feedback signals, u, that constitute the input/output characteristics of the controlled elements in physiologic systems. Indeed, if more was known, then the practice of medicine would be more *preventive* (or "proactive") than *symptomatic*, retrospective and *ex post facto* (or "reactive"). That is to say, a greater knowledge of the parametric dependence of u_c on u_d [c.f. equation (4)] in terms of ultimate values of u for which homeostatic regulators become unstable, would allow us to *anticipate* and intervene where necessary to prevent breakdowns. Anticipation implies functional dependence on derivatives of $u_r(u_d)$, u_d and u, as well as on the instantaneous values of these variables. The medical community is not generally trained to be sensitive to *rates-of-change*, as opposed to *amounts-of-change*, and so the health care delivery system tends to be out-of-phase with real-time physiologic events.

To wit: much of the practice of medicine today treats *symptoms* (after-the-fact), not *causes* (before-the-fact). It tends to be reactive, not proactive. In fact, when a treatment does affect a cure, or provide relief to the patient, the chances are very likely that the physician may not even have diagnosed the condition exactly, or at all, for that matter. He or she is intent first, and foremost, on alleviating what it is that is happening to the patient, and the treatment of the symptoms of discomfort is prescribed accordingly.

Fortunately, because one type of treatment may be equally effective in managing several disorders which present similar symptoms, it is of less immediate concern to the physician to establish *exactly* what is wrong with the individual—unless the first line of defense fails to produce satisfactory results. Then, and only then, does it become necessary to probe deeper. This is not to put down medical practitioners (they are basically supplying what the public wants), or to imply that they are not concerned with an accurate diagnosis. But short of charging the patient a small fortune for diagnostic tests (some of which may cause considerable discomfort or be exposing the patient to some risk and danger), and spending a great deal of time interviewing, examining, contemplating

and evaluating, the physician first makes an "educated guess" as to what the problem is, based on a more superficial assessment of the patient's symptoms.

Again, fortunately for the physician, statistics are also on his or her side, for they reveal that, in as many as 70–80% of all cases, an educated guess is good enough. This is due primarily to the fact that most ailments tend to disappear on their own, given enough time, even if they go untreated, and, in some instances, *in spite* of the prescribed treatment. So, in a sense, the medical practitioner is "buying time" in his or her first volley against the symptoms of a physical ailment, expecting that the body will heal itself anyway. Where the guess, or first approximation in mathematical terms, does not solve the problem, the medical team goes through several more iterations in an effort to help the patient. In about 10–20% of all cases, this second iteration works if the condition is treatable. At other times, it does not and subsequent iterations are necessary. Sometimes, even given the proper diagnosis, nothing further can be done for the patient anyway. *Always*, there is a great deal of trial and error involved—and a little bit of luck! So much of medicine is still an art, not a science.

On the other hand, if we had a greater understanding of cause-and-effect relationships, based, for example, on theories such as are postulated in this paper, then we could formulate clinical *warning signals*, u_{warning}, or u_w, which would alert us of impending malfunctions or breakdowns:

$$u_w = f\left(u_d, \frac{du_d}{dt}, \frac{d^2u_d}{dt^2}, \ldots, u_r, \frac{du_r}{dt}, \ldots, u_c, K_1, K_2, u, \ldots\right); \tag{5}$$

where, essentially, the warning signals take into account the response characteristics of the respective homeostatic regulators, the ability of the organism to adapt, the envelope of normal physiologic function and the actual state of the system, all viewed with respect to the characteristics of the disturbance.

In principle, the above is not necessarily an altogether new concept. Indeed, medicine has tried for many years to define "correlates" and warning symptoms for many pathologic conditions. But only recently have attempts been made to establish such listings based on a systems control theory of physiologic function. This is where mathematical modelling and engineering concepts have made such great contributions to the health-care delivery system, and where these disciplines promise to make even more headway as they continue to use the scientific method to define, quantify and inter-relate biological control processes.

6. TRANSFER FUNCTIONS IN PHYSIOLOGIC SYSTEMS

Among other things, the transfer function (and associated gain) of a feedback control system is a measure of the *sensitivity* of that system to a disturbance. For a supersensitive system, for example, very slight fluctuations of u_d may produce wild undulations in u—even though the overall system is fundamentally stable. A perfect physiologic example of this is the famous "knee jerk", wherein a mere tap of the quadriceps tendon that inserts just below the knee cap results in a rather dramatic contraction of the quadriceps musculature, causing a sudden extension ("jerk") of the knee.

On the other hand, for a relatively insensitive system, u_d might have to change by orders of magnitude, and persist for a very long period of time, to affect even a slight change in u. A physiologic example of the latter is the functional adaptation mechanism in the skeletal system, wherein bone tissue can alter its cross-sectional area to reduce overall stress in response to a long-term and persistent increase in external loading. Such an increase needs to be rather extensive before any permanent, readily measureable change in cross-sectional area is manifest, and the change progresses rather slowly in rather small increments. So, too, does that associated with bone marrow responses to hypoxia, as discussed earlier.

The sensitivity of the controlled element of a feedback control system can be adjusted by putting a "bias" on the feedback sensor that monitors u, effectively changing K_2; or, by altering the response of the controlled system to u_d, effectively changing K_1. This may occur in the short-term sense by pre-loading the monitoring transducers, and, in the long-term sense by mechanisms associated with adaptation, conditioning and evolution. In the short-term sense, one can cite γ-nerve innervation

of the spindles of striated skeletal muscles as a physiologic example of "biasing" [7]. That is to say, muscle spindles are basically strain-gage-type stretch transducers that convert changes in muscle length into a proportional excitation signal that stimulates α-motoneuron activity—causing the corresponding muscle to contract (as in the "knee jerk" example used earlier). γ-Nerve stimulation of the spindle receptors effectively puts a pre-stretch on these transducers, making them highly sensitive to any additional deformation or disturbance. This, in fact, is how the knee jerk actually works, i.e. the spindle receptors of the quadriceps musculature are so highly biased that the *slightest* additional stretch of the tendons (e.g. by a light tap below the knee where they insert into the shank of the lower leg) produces a total contraction of the muscle, and a consequent jerk at the knee joint. In terms of Fig. 1, this myotactic reflex arc, as it is known, can be modelled mathematically by letting:

$u_r = f_t$ = threshold firing frequency of an α-motoneuron;
$u = f_{Ia}$ = actual firing frequency of the muscle spindle Ia sensory fibers;
$u_c = f_\alpha$ = actual firing frequency of the α-motoneuron fibers;
u_d = a combination of f_γ (the firing frequency of the biasing γ-motoneurons, actively sensitizing the muscle spindles to stretch), plus ξ, a passive stretch-disturbance applied to the muscle spindle;
K_2 = the transfer function of the α-motoneuron, which is the comparator and controller of the system;
K_1 = the transfer function of the motor unit controlled by the corresponding muscle spindle being stimulated, which is the controlled element of the system.

Then

$$u = u(u_d, u_c) = u(f_\gamma, \xi, f_\alpha) = f_{Ia}$$

and

$$df_{Ia} = K_\gamma df_\gamma + K_\xi d\xi - K_\alpha df_\alpha, \tag{6}$$

where, $K_1 = K_1(K_\gamma$, temperature, and other physiologic variables).

Specific details describing the mathematical treatment of the above schematic representation are given in Ref. [7], along with other examples relevant to many of the points made in this paper.

Alteration of the gains and transfer functions of elements in a feedback control loop is what is meant by saying that some nonlinearity may intervene in determining the response of the system. Through proper research, one can actually establish functional relationships that define changes in u which are produced by changes in K or in the sensitivity of the controlled element. Many of these have already been identified and labelled *response functions* for homeostatic regulators [4, 7, 9–12, 21]. Unfortunately, *most* response functions remain basically unknown for the majority of homeostatic regulators, but it is hoped that publications such as this will stimulate research based on this line of reasoning. Toward that end, the following summary and concluding remarks may prove useful.

7. SUMMARY AND CONCLUDING REMARKS

This paper has put forth the premise that physiologic function is carefully controlled by homeostatic regulators, and that such regulators may have a corresponding syntax, or language that is uniquely their own. The language is coded into electromagnetic information that is transmitted through the medium of action potentials. These are digitized bits of data that are sensory (informative) or motor (causative), depending upon whether they are being transmitted to (afferent) or from (efferent) the central nervous system.

The systems approach to physiologic function has received a great deal of attention by other investigators, most notable among these being Apter [8], Clynes [22], Milsum [9, 21], Milhorn [10], Brown and Gann [11] and Huffaker [12]. The uniqueness of this approach is that it reduces

seemingly complex, unrelated sequences of physiologic processes into more readily identifiable sets of common denominators that illucidate some basic principles of biologic function. Appropriate interpretation of these biologic principles can be expected to move us closer to success in our efforts to improve the health, comfort and understanding of man. Indeed, the ideas formulated herein—addressing the spectrum of physiologic issues ranging from adaptation to pathologic processes, from optimization to biological signal analysis, from genetics to psychological conditioning or from normal metabolism to allergic reactions—are done so with the ultimate intent of stimulating new creative approaches to the mathematical analysis of physiologic function. Such approaches should proceed from the point of view that *all* such function basically fits an underlying pattern. The details then become simply special cases (or different sets of boundary conditions) of a unified guiding theory.

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