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Regulation and Control in Biological Systems

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1. OSCILLATORS IN THE BIOLOGICAL SYSTEM

The experimental survey of a complex biological system like the human discloses a large number of autonomous oscillators continuously operating in the system. A partial frequency spectrum in man would consist of primary neural frequencies in the range of 5 to 50 cps, a muscle motor unit frequency at about 10 cps, heart beat about 1 cps, breathing rate about 1 cycle per 4 seconds, several eating cycles per day, circadian rhythms of 1 cycle per day, sex urge approximately 1 cycle per few days and menstruation about 1 cycle per 30 days. To these may be added cycles, demonstrated within the past few years, in ventilation rate, local skin temperature, and metabolism of approximately 100 seconds, 400 seconds, 30 minutes, and 3 hours. The first appears to be an engine cycle, primarily in skeletal muscles, in which the major heat production takes place. The 400 second cycle appears to represent a vasomotor action which partitions blood flow among the major systemic circulations. The 30 minute cycle may be a gas exchange cycle, likely representing a total body carbon dioxide equilibrium, and the 3 hour cycle is probably an overall thermal balance. A 3 day cycle has been found in body weight. It has been tentatively identified as a water balance cycle.

It has become increasingly apparent that the many oscillators in the biological system are not incidental characteristics of the system, but represent the working components of the system. In summation, they are the biological system. In accordance with this view, it is proposed that homeostasis, Cannon's organizing biological concept of a complex regulation characteristic of the system, is obtained as a result of shifting the stability of these intrinsic non-linear oscillators. The oscillators are likely modulated or shifted in operating point by electrical and chemical signals. In our view such action is an illustration of dynamic regulation. It is possible that the biological system is not able to operate in any other way. In fact, it is likely that the same type of instability mediation is the foundation for all automatic control theory. However, the more general thesis is beyond the scope of discussion in this paper.

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2. THE POWER PLANT

To illustrate the mechanisms of homeostasis, a number of biological systems will be discussed. A first case in point is that of heat production in mammals, which is of interest as part of the system of human thermoregulation. Local skin temperatures, ventilation rate, and oxygen consumption rate all show sustained limit cycle oscillations with a prominent component near 100 seconds. We have postulated that this is a heat engine cycle; that the engine consists essentially of skeletal muscles; that the level of operation of local muscle engines is regulated by an oxygen choke which limits the oxygen supply and thus the rate of local oxidation; that regulation of oxygen rate is achieved in a 100 second cycle of capillary red blood cell flow, mediated by the vasodilatory effect of adrenaline. That adrenaline is the hormone mediator of the cycle is suggested by its calorigenic action, its vasodilatory effect primarily in skeletal muscles, its effect of increasing muscle activity, and a time of action for transient effects in a range between one and two minutes.

The mechanism of the adrenaline action is not known. One possibility is that there is an oscillating adrenaline blood level which is centrally produced. This may interact at the level of the microcirculation to effectively control the opening and closing of capillaries or capillary networks to the flow of blood or blood cells. Another possibility is that there is a constant level of adrenaline in the blood which acts to produce a locally determined cycle by interaction with the local metabolic chemical chain in small sections of the microcirculation. Changes in the mean adrenaline blood level could produce changes in the amplitude of the heat production cycle without significantly affecting the frequency.

3. DISTRIBUTION CYCLES IN THE CIRCULATION

There are other processes which are also regulated directly or indirectly through the cardiovascular system. Thus, one can expect to find coupling among the various systems, and it becomes difficult to sort out the independent oscillators. For example, a fundamental regulating process appears to be an oscillator ring of blood flow to the various major circulations to the skin, kidney, heart, brain, skeletal muscles, etc., which operates with about a 400 second cycle. This grosser blood flow cycle appears to be under the control of the hypothalamus, and may involve the temperature sensitivity of specific regions in the hypothalamus. One line of evidence to support this suggestion is data on hypothalamic temperature (Benzinger) which shows such cycle time. The ring oscillator sequencing is not sharply deterministic, and it may involve additional signal elements, such as specific hormones, from the various circulations. For example, the renin-angiotensin pair of hormones is reported as acting in the kidney at this time scale (Page) to change the blood pressure characteristics of the system. A more direct connection to the hypothalamus is likely vasopressin which also affects blood pressure as well as urine flow and is reported to act in this time domain. Furthermore, vasopressin is elaborated in the pituitary and appears to be under direct hypothalamic control. It is possible that vasopressin is a general chemical mediator of the 400 second cycle, and that the requirements of a particular organ like the kidney are reported centrally by a separate hormone signal like the renin-angiotensin pair. This might then require a local signalling hormone for each circulation—all acting in the domain of a seven minute time scale. In general, the actual function of this major vasomotor blood flow cycle is to control the gross resistance of each of the individual circulations. One must hypothesize a somewhat different resistance control for the 400 second cycle than for the 100 second cycle. Illustratively, it would be simplifying if the red blood cell flow were locally mediated, electrically, for the 100 second cycle, and the total blood flow centrally mediated, possibly through arteriolar sphincters, for the 400 second cycle. Major experimental exploration is required to clarify these points. Such work is under way.

At a higher frequency, of the order of a number of cycles per second, there appears to be an axial jitter in the number of blood cells per unit time passing a given point in a capillary. It is probable that this jitter is electrically determined by interaction with the walls of the system. Thus, the most fundamental involvement of the cardiovascular system in body functions already indicates the degree of possible oscillator complexity in the body.

An interesting regulated constituent of the blood carrier is the blood sugar. It has been shown (Anderson) that blood glucose in the non-absorptive state oscillates in a 30 second cycle, and that injection of glucagon-free insulin greatly increases the amplitude of the current cycle, with a more gradual removal of sugar from the blood at longer time of two and seven minutes. We have suggested that the 30 second cycle is a centrally produced concentration pulse, and that gradual removal is then effected peripherally in the 100 and 400 second blood flow cycles. This cycle in which mean blood sugar concentration is maintained by stability shifts of an oscillatory process is the first evidence for dynamic regulation of a chemical concentration in the blood. It is probable that the other blood constituents maintained at regulated levels also exhibit oscillating concentrations and that the homeostatic mechanisms are to be found in the mechanisms of these oscillators.

4. CENTRAL PACING OF CYCLIC PROCESSES

Breathing at the rate of 1 cycle per 4 seconds is commonly discussed in terms of control by a carbon dioxide trigger at a respiratory center, possibly with a spring return from a stretch receptor in the lungs. This does not adequately consider an observation of Adrian's which demonstrated respiratory rhythms in an isolated brain stem. Breathing, the heart pacemaker, muscle microvibration, nervous system rhythms, viewed in concert, suggest that a standard operating scheme in a biological system may consist of a low level, but strongly persistent, relaxation oscillator, acting as a pacer (i.e., sometimes as a pace maker and sometimes as a pace follower) which allows a number of other specific triggers to advance or retard the frequency. The necessity for such mechanisms is suggested by the considerable stochastic component that rides as a quavering on the extensive biology frequency spectrum.

At the present time, there is no adequate explanation for the rhythms associated with the nervous system, although there is a considerable body of experimental knowledge on the various rhythmic components in neural frequencies. Typical responses are found in brain wave rhythms with the characteristic of becoming regular and dominant (with a near dominant 10 cps alpha rhythm) in quiescent or familiar situations, and weak and irregular in novel situations. In muscle motor units, there is a near 10 cps 'tonus' vibration which appears in all skeletal muscle. Involvement of the muscles in heavier activity would seem to be built up from this low level signal. (A similar response in the microcirculation, believed to be connected with this one, has already been mentioned. Thus the diverse properties of becoming regular after activity or being regular before activity are both associated with the nervous system and other cyclic processes. One can only surmise that the pervasive high frequencies are representative of a fundamental neural oscillator design frequency, like 60 cps household current, that is structurally repeated throughout the nervous system. In the past, in biology, an explanation for such cycles has been sought in the form of reverberating networks in the nervous system. However, the problem is really no closer to solution.

5. FOLLOWER CHARACTERISTICS OF THE MAIN METABOLIC PROCESS

Having proposed an oxygen choke with an escapement as a determinant for the thermodynamic engine cycle, it is necessary to visualize longer time scale follower characteristics for other products in the chemically reacting streams that are involved in metabolism. For example, there is a growing literature on the control of ventilation rate (Gray, Grodins, Defares, Goodman, Guyton) in the period of minutes. However, the large storage capacitance for carbon dioxide in the system, provided by the blood in an active mode, probably leads to a longer range 30-minute balance cycle for carbon dioxide. An approximate 3-hour cycle agrees with the thermal resistance-capacitance time constant for the system and probably represents the overall thermodynamic balance.

6. PRESSURE REGULATION IN THE CIRCULATION

The superposition of cyclic regulatory processes is complex. This can be illustrated in the case of blood pressure, which is apparently regulated by the action of a pressure sensor, an oxygen sensor, other distributed pressure sensors in the arterial system, resistance changes in the microcirculation, and long time changes associated with the kidney circulation and its hormonal regulators. These are the chemical-mechanical elements involved. There are also a number of nervous system concomitants. The blood pressure is directly determined by heart rate, stroke volume, and the resistance in the microcirculation. An interesting feature of biological regulation is here shown. These three direct coupled mechanisms operate in different time domains to shift the means of the various oscillator mechanisms. Thus the stroke volume response appears to control the blood pressure change from beat to beat. The baroreceptor response appears to control the mean blood pressure level over a 3 to 10 seconds range. The chemoreceptor seems to affect blood pressure in the 5 to 15 seconds range. The microcirculation resistance affects the system in the 100 seconds domain; the hypothalamus in the 400 seconds domain; and kidney hormones in ranges near 100 seconds and 400 seconds. Longer range effects from the same hormones are also found in blood pressure. (For example, the baroreceptor action can be overridden by angiotensin). The segregation of effects into various time domains by relaxation oscillators seems to avoid a problem of system instability. However, the fact that one variable, in this case a hormone, can be effective in more than one time scale poses a problem. A general, plausible hypothesis is that the hormone can be trapped chemically in a bound state. Its first effect lies in a fast time scale in which a free excess is absorbed; then a longer time effect is produced when the bound form is released at a slower time scale. In this manner, one hormone may act to control more than one rate governing reaction. This, of course, is quite speculative.

7. LONG PERIOD REGULATION CYCLES

A large body of literature exists with regard to circadian, approximately 24 hour, rhythms (Halberg). It is conceivable that these rhythms, where they really exist, are associated with an extreme sensitivity of the biological system to light-dark variation. Such a determinate response to the weak input signal become plausible when one considers that much of the human brain is occupied with processing optic, more generally electromagnetic, signals. The circadian rhythm, acting as a driven timing signal and a zeitgeber, probably illustrates another prime characteristic of the biological system, namely time fracturing. Limit cycles in the system tend to form when there is a coalescence of a real physical time constant for some process and some internal physical-chemical regulating mechanism that fits the time scale. Thus the system develops a spectrum of limit cycle fractures of time or frequency that covers the required functions. Any required regulating function, while it may vary in frequency to some extent, is generally regularized or synchronized by a primary process into a fairly regular limit cycle. The use of electrical mediation to fit the time scale is not excluded. As an illustration, a vague outline of the brain is conceivable in which the oscillator action is mapped at various specialized centers so that some regularization of oscillator function does take place centrally. The band of high frequency brain rhythms (5 to 50 cps) are probably illustrative of the use of such a spectrum, although it may be more clearly evident for muscle function, including microvibrations. Considerable data exists in which cross-coupling by electrical means between one faster signal and a slower signal is quite obvious. Typical examples are the heart beat and ventilation cycles, which appear in other system responses. It is difficult at present to evaluate the significance of cross-coupled effects which appear in processes operating at widely different time domains.

Slower cycles may be effected by the mediation of hormones acting in longer range absorptive modes. For example, there is no satisfactory mechanism that accounts for the eating cycle, although the relaxation oscillator involvement of blood sugar is most persistently considered. One can only guess that some subtle hormonal cycle is involved. The fact that the cycle can be easily shifted or that it wobbles is not unique. All of the 'hunger' responses of the system—oxygen, water, food, sleep, sex—show this characteristic. One can normally defer individual 'feedings' with practically no noticeable effect. On the other hand, in groups of perhaps 5 to 10, there is regularization of the rhythm. (For example, if one talks, one misses individual breaths, while the 5 to 7 breath running average is much more regular. In extremes, it is possible to omit 'eating' for perhaps 30 to 50 cycles, but only with severe physiological involvement. Thus one can hold his breath for 20 breaths, or not drink for 3 days, or not eat for 10 days, or not sleep for 5 days, or avoid sex for a few months, but the body becomes heavily involved in an effort to provide the regularization). It is also clear that the wobble is at least partially voluntary, although much less than one might casually suspect. Human behavior in the mass will show a 'twinkling' performance, namely, that the average of a group will show a characteristic mean behavior for the species under the existing ambient conditions, with probably cyclic behavior exhibited by the individuals, and a random 'twinkling' surrounding the numbers of individuals who are instantaneously involved. In the long run, human behavior probably satisfies an ergodic hypothesis, in that the individual's course in time and the group course at any one time in its distributed spatial environment, essentially agree. This suggests another characteristic of regulation and control in biological systems, perhaps best described as orbital synchrony. A 'free body' biological system travels through its milieu and falls into synchronized orbits for limited periods of time before snapping out of orbit and again engaging in free motion. Such motion is characteristic of free electrons in metallic conduction, and so the concept is not completely novel. The internal schema, both developmental and behavioral, are thus included in a general synchronization scheme.

The individual eating cycle apparently cannot be presently explained on a hormonal basis. The problem becomes even more interesting and puzzling over longer periods of time. It becomes the question of what governs longer time weight level. It is obvious that the gross course of weight in lifetime is a gain in weight to a saturation level, a nominal first order reaction with a time constant of perhaps 10 years. However, the regulation of the saturation level is not clear. It is clear that the saturation level is not a rest state, but a sustained mass balance between input energy rate and energy expenditure rate. For example, a change in average weight of five pounds in twenty years represents a mean regulation to a precision of about three calories per day (at 3500 calories per pound) out of a daily consumption of about 2000 calories. It is not likely that weight is governed as an 'instantaneous' quasistatic regulation. In fact if a person is weighed daily as he operates in a normal mode, one finds a fairly uniform daily metabolic input, a fairly uniform daily activity pattern, but a cyclic weight variation of approximately a few pounds per three days, (i.e., of the order of a significant portion of the entire weight intake of food). Since the energy balance is assured at much shorter time scales, (i.e., three to five hour), it would appear that the weight variation must be due to a hormonally mediated water cycle. This appears especially clear in some obese people or some females near their menstrual period, who show much larger weight variation cycles of comparable cyclicality, apparently directly tied to water balance. Another characteristic is that water retention, upon change in diet or activity pattern, can show extended delays, almost approaching deadtimes, of as much as 10 to 20 days before release takes place. Commonly, a regulating mechanism has been sought for direct hormonal control of the mean metabolic level, with thyroid being the most plausible choice, though never satisfactorily proved. One can administer thyroid and obtain an increase in metabolism, but the demonstration that it is the main factor of metabolism is a much more difficult problem. In fact, it is likely that the primary action of thyroid is to regulate the basic oxidation reaction (i.e., the enzymatic reaction). If one injects thyroid, a time lag of several days is noted before the maximum effect on metabolism is reached. It is hardly expected that a hormone with a time constant of several days has its primary effect on a system with an action time of the order of seconds or minutes. It is more plausible to us that the thyroid acts more directly on the three day water balance cycle and that the effect on metabolism is a secondary one.

A hypothetical account for weight regulation is the following: One or more hormones, likely thyroid at a longer time scale, and ADH at a short time scale, are involved to regulate the basic water oscillator cycle in the body, and food intake is essentially proportioned to the water cycle. The detailed balance is determined by a behaviorally determined level of activity, (which includes the psychological conflicts of development) and a food intake which is physiologically determined by the water oscillator. The body then grows to a point at which its energy expenditure for a given activity level will be equal to the energy intake. For the same activity level, a heavier body requires a heavier metabolic intake and conversely. While this might seem startling applied to a large mammalian system, it would not be surprising in a single celled animal. Size, essentially water content, is primarily regulated, and food is proportioned to water.

8. HORMONAL DYNAMICS—CHEMICAL REGULATION

The discussion of thyroid and metabolism leads to another vantage point for the biological system. An adequate decoding of the hormonal system is not possible today. However, a physically valid approach is to code the hormones into a spectrum of their major times of action and then correlate this with major system oscillators. For example, we have re-interpreted the current biologically popular concept of binding sites as a mechanism by which hormone kinetics of a non-linear nature can take place. Generally, two mechanisms are discussed for hormone action:

1. The hormones react in a rate-determining step with an enzyme of a bio-chemical chain with the result that production of the chain is affected. This is the older concept of hormone-enzyme interaction within the cell.
2. The hormones react with structural or other barriers to material transport in and out of cells and modify the barrier to promote or inhibit transport, thereby increasing or decreasing availability of raw materials for reaction with resulting increase or decrease in net production. This concept originated with cell membrane permeability and has now extended to permeability within cells and perhaps to membranes around the cells, as in the kidney and bones.

It is clear that either of such types of interaction, occurring at some rapid locally determined time scale, is sufficient to produce phenomenological transport coefficients on the macroscopic field scale. Thus one might expect hormones to mediate biological field properties by as many types of transport characteristics as we are physically familiar with. This would have to include such properties as linear coupling coefficients (e.g., linear dependance on concentration or other potentials), degradation of energy (analogous to the dissipation function in hydrodynamics), non-linear thresholds, non-linear freezing out of degrees of freedom, and non-linear limit cycles. Thus, the physical approach to the hormones proposed is the correlation of their phenomenological action with their phenomenological time scales. This correlation enhances the possibility of associating meaningful bio-chemical chains. One can proceed along a path of discussion that is independent of molecular biology, a process similar to the one of classical physics avoiding molecular physics, except at the statistical mechanical interface.

Some illustrations are appropriate. We have assigned a major heat production control action to adrenaline at the 100 second time scale. This neglects another, much faster, time scale of adrenaline involvement in other tissues. It appears clear that vasopressin is involved in a somewhat rapid time scale affecting blood pressure. It appears that insulin may be associated with two different time scales; a high frequency 30 second involvement with blood sugar, and a longer involvement in the range of hours. ACTH is probably involved in a range of minutes (Urquhart) in overall central chemical regulation. This may likely be under direct nervous control through the hypothalamus to pituitary link. A current keynote in endocrinology (Harris), more generally, is that the pituitary is the master hormone regulating gland of the system, and that the hypothalamus-pituitary link is the main electrical to hormonal connection. Thyroid involvement seems to be in the domain of days. Growth and sex hormones seem to be involved in similar or even longer periods. In the action of the sex hormones one can see the typical nature of a relaxation oscillator process at the base of the non-linear limit cycle operation in which the timing phase is quite clearly determined by a growth rate.

9. SOME CONFLICTS AND CONFUSIONS IN THE CHEMICAL REGULATION

One must be cautious in oversimplifying the same conflicts and confusions in the chemical regulation assignment of effects to the hormones in the biological spectrum. This can be illustrated with adrenaline. A 30 minute cycle was found in ventilation rate and heat flux. It appears that this period may be associated with a carbon dioxide release process. A primary slow lactic acid diffusion, or a slow carbon dioxide diffusion, may provide a possible timing phase. It is alternately possible that the timing phase may result from slow liberation of adrenaline previously absorbed from the blood at various binding sites. Thus, the concept of binding sites can suggest a mechanism for an extended delay action of hormones (such as may also be the case with thyroid.) It is worrisome, however, that a hormone injected directly into the blood can take extended times, such as days, to produce its maximum physiological effect. If hormones are immediately absorbed on blood consituents or binding sites in the organs and then metered out slowly, a long action period can be produced.

Actually, this mechanism may be similar to the common storage processes that an animal utilizes. Food is taken in larger amounts than immediately needed. The first food action is probably in the order of minutes. The excess is stored in various storage depots of the body; for example, carbohydrate in the liver, and fat in special storage cells. The stored materials, after suitable conversion, are then metered to demanding tissues in a much slower time scale. This is indicated as much slower limit cycle oscillations of the mean supply and mean metabolic action. (The only major substance essential to metabolism, for which there is little or no storage, is oxygen. This has been one of the determining factors leading to the proposed hypothesis that choking of oxygen is the effective regulator of muscle action and heat production).

In the case of food and water storage it would appear reasonable that such storage has been developed to partially free the animal from a constant dependence on the environment for required raw materials. It is not likely that the same requirement has led to storage and delayed action for hormones. Rather, the biological system uses the storage technique which is common in the system, to achieve time delays for regulation and control activities, (i.e., these are active process capacitances, rather than passive capacitances).

A second worrisome phenomenon is illustrated in the angiotension effect in the kidney. Its time of effect is of the order of 7 minutes (Page) making it competitive with the action proposed for the hypothalamus in controlling the systemic blood circulations. This effect leaves one with the problem of competition and possible instability within a prime operating domain. It is not clear to us, although attractive, that a ring oscillator among the various systemic circulations is the consequence of a variety of such instabilities that seek to regularize the actions of individual hormones, seeking target organs, in a competitive time domain. The system certainly can respond quite satisfactorily to any excessive demand put on a particular systemic circulation. (If one eats, or swims in cold water, or is involved with heavy kidney loads, the system performs quite well. It is not quite so clear what happens when conflicting large demands are put on several systems simultaneously).

10. HIERARCHIAL CONTROL AS POSSIBLE SOLUTION

It is perhaps to guard against such possible confusion in periods of great stress that the sympathetic system is brought into play. It appears that there are at least two main general states of the body. In the non-stress situation, the normal operation of internal organs, the motor units, and the nervous system is conducted in an idling state routine. In the stress situation the sympathetic-adrenaline system comes into play. Internal organs not needed for locomotion and other muscular activity are operated at a depressed level, while the muscles are alerted to a capability for great activity by increased blood flow, increased heart rate, and increases in protective and recovery mechanisms. Thus, the response to conflicting demands in this case, appears as an upgrading of the availability of a whole bank of systems potentially required, and downgrading of the availability of a whole bank of systems useless for the required state. It is entirely conceivable that an electrical to hormonal link is required. It is considered far from coincidental that one is found from the hypothalamus to the pituitary at the same time scale as the hypothalamic effect, and that the pituitary *is* a "master regulator".

It is not clear, however, how the regulation is achieved. One may surmise, at this point, that the 7 minute time scale is an extremely busy one for the hormones. Thus, regulating and control action of the electrical and hormonal systems comes into vague focus. One surmises that there may be two frequency bands; one, a major electrical spectrum in the 5–50 cps range, and a second slower, broader range for the hormones from 10 cps to 50 years. The high frequency range in hormones is most likely electro-chemical. However, it is most likely that hormones, as chemical mediators, do not initiate their macroscopic action in less than the seconds range. This is evident from the general requirement that the hormones are produced in one part of the animal for action in another part far removed from the first. Thus, a minimum time lag for hormone transport action is the order of tens of seconds, possibly 15 to 25 seconds, as circulation time of the blood, (i.e., as humoral agents). This period is further extended when production of one hormone requires the stimulating effect of a tropic hormone, such as ACTH and the adreno-cortical hormones, or thyrotropin and the thyroid hormones. If coupling occurs, which is probable, such as between the trophic and effected hormone, then time constants may be further changed. For example, it has been demonstrated that thyrotropin stimulates the production of thyroid hormone, while thyroid hormone in the blood inhibits the formation of thyrotropin in slow cyclic fashion (Elmergreen and Danziger). A similar coupling mechanism has been proposed by use for the interaction of insulin from the pancreas with carbohydrate from the liver. It is not likely, within current endocrinological descriptions, that any circulating hormone can produce effects faster than circulation time unless there is neural activated release locally from binding sites, or in local action (such as may be evidenced by the catecholamines).

Thus in summary a general hierarchial control scheme for the homeotherm may be the following. The electrical system primarily appears to produce a high frequency signalling range. Successive chemical (hormone) operators superimpose levels of regulation at increasing long periods to shift the operating levels of the faster oscillators. For example, there is a high frequency microvibration in muscle fibers—most probably determined by nervous signal. The motor units can be discharged directly by high frequency nervous signals, or the system prepared for more prolonged action within the same high frequency time domain, electrically, by actuation of the microcirculation (i.e., resetting of local resistance patterns). The adrenaline-oxygen choke process coordinates this high frequency stochastic muscle action into an engine cycle in a range around 100 seconds. The highest autonomic (automatic) level in the central nervous system then controls the division of the systemic blood supplies. The idling metabolic rate is probably effected at the time scale of days by thyroid hormones, although this action may be secondary to its relation to a water balance cycle. Intermediate time scales involving metabolism between a scale of minutes and days is confused and overladen by the more voluntary portions of daily rhythms of eating, working, and resting.

Follower action is required for the consequences of metabolism. The main metabolic byproduct, carbon dioxide, may be involved in an autonomic nervous system rhythm; as a servo follower at the 4 seconds breathing rhythm scale; and in a gas equilibrium regulation cycle at 30 minutes. The long time scale may be a consequence of the considerable gas capacitance of the system. Although under considerable exploration, the mechanism for these actions are not satisfactorily explained dynamically. Similarly, there are difficult hierarchial problems involved in the regulation of water level, electrolytes, and waste materials. In fact, in this regard, the kidney has been described as the master chemical regulator of the body (Smith). At still longer time scales, growth hormones and aging mechanisms further modify the metabolic regulation over still longer periods. In fact it has been suggested that the hormonal system can continue to function without deterioration as long as the gonadal system is normal.

It should be noted that much of the regulation and control, at least in the slower time domains, has been effected through the cardiovascular system and the kidney system. It is likely that the blood levels of such constituents as sugar, oxygen, water, electrolytes, etc.—Cannon's homeostasis—are regulated through separate flow regulating mechanisms for each constitutent. This would require an oscillating process for introducing the constituent into the blood (similar to the heart action in producing the arterial pressue pulse wave) or an oscillating process for regulating discharge from the blood, or both. This may account for the many different hormones, since each major constituent probably requires an independent hormonal mechanism for its regulation. The necessity for hormones, or chemical signals generally, may arise from the following consideration: namely, while it appears to be fairly straightforward to construct oscillators with electro-mechanical or electro-chemical-mechanical elements, it is more difficult to construct them with chemical elements alone. The use of a catalyst and especially negative or inhibitory effects are possible solutions. Thus the main function of the hormones may be to provide "grid coupling" so that unstable oscillatory action can develop in each power amplifier loop.

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DISCUSSION

H. M. Paynter*

First, I would like to say that each time I hear Mr. Iberall explain his distinctly original and valuable contributions to control processes in biological systems, my understanding and appreciation increases.

Nevertheless, even after his exposition today, I still find it hard to appreciate the distinction between biological processes defined as collections of oscillators and the similar sounding formalism of quantum mechanics to describe dynamical systems which are presumably not living. Is the human organism simply a well-instrumented, well-controlled chemical plant?

REPLY

The key is contained in Academician Trapeznikov's remarks during the opening session, pointing out that one must have recourse to statistical mechanics to treat complex systems such as a national economy, or in our case, the biological system. If the collection of all active subsystem elements are equally indifferent, or have equal status, then the appropriate "mechanics" of the system leads to some partition in a suitable phase space of these subelements, and some idea of the fluctuations about some averaged equipartitioned state. Various statistics such as the Maxwell statistics, have been suitably derived in physics, if the number of subelements is considerable then; the fluctuations are small, and the deviation of states from equilibrium is small. The formalism begun by Helmholz and Gibbs permits discussion of the return to equilibrium and the relation between system states in space and time. Finally equations of change, in states near equilibrium may be derived from the formalism started by Maxwell and Boltzmann. These lead to phenomenological equations appropriate to a wide but much slower time scale than the energy interchanges on the subelement level.

Even though subelements, as active systems, may have involved regulation and control characteristics, we must now jump to a higher hierarchical level. Now the "plant" (of subsystems), described by equations of change, may no longer have the same large number of "degrees of freedom," of indifferent subsystems. If the number is large, for example many vibrational modes in an elastic system, they may again be treated statistically, this time by phenomenological laws. A superstatistical mechanics would require that these subsystems now be active, large in number, and equally indifferent.

The biological "plant" has two lower levels that can be treated (at least speculatively) by a statistical mechanical program, the atoms and molecular made up cells. The derivation of "equations of change" for cells is an (ultimate) aim of molecular biology. However the organization of cells into subsystems, the cardiovascular system, liver, heart, brain, pancreas, stomach, etc, are not sufficiently large in number to permit anything but a crude approximation to the equations of change for a continuum mechanics, perhaps similar to a liquid droplet or ideal gas model for atomic nuclei. In fact our program may be best viewed as an attempt to develop a macroscopic biological spectroscopy that will permit future assessment at a count of the internal modes of this plant.

Our present view is that the number of state variables required to characterize the biological system are not great in number (having teen-age children, emotionally we are tempted to believe the number to be much smaller than the number we suspect scientifically). However the number strikes us as being sufficiently great that Gibb's ergodic hypothesis and a view of behavior according to a rather narrowly drawn microcanonical ensemble offers a most apt description. It is just individual instantaneous state fluctuations that seem considerable.

J. H. Milsum*

To the author's excellent presentation of his new and stimulating ideas, I am stimulated to add three comments.

(i) *On oscillators*. While completely convinced that many oscillators do exist, I do not think it helps to force all stable limit-cycles into this term with the result that a new word like "homeokinesis" is suggested. House thermostatic control does indeed produce cycles but the purpose and functional achievement is still that of constant regulation within acceptable tolerances.

Therefore "homeostasis" would seem to me a perfectly acceptable term.

(ii) *On control algorithms*. Open-loop predictive control of the neuromuscular systems seems to be the rule for learned, "skilled" actions, such as walking, jumping etc. Certainly this makes good sense and control engineers equally make such provision whenever the disturbances can be measured. In such cases the muscle "engines" do not have to wait until a velocity is established before the power commands can be given.

(iii) *On purpose*. In so far as evolution has achieved the fear of photosynthesis only at the cost of consider-

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*McGill University, Montreal, Quebec, Canada able "plant" complexity and therefore development. I think the author belittles his case in suggesting that the only certain thing about the purpose of animals in that they merely burn this fuel to return the process to the starting point. Instead of course regimes of high order are increased in this process, thus characterizing the peculiar ability of living systems to "build-up from its own bootstraps."

REPLY

(i) While it is obvious that all internal systems do not operate in oscillating modes, it was quite surprising to us how many did. It remains always open that any particular system may be aperiodic. However it must be recognized that the systems will in general be active.

Second, while we would have accepted small amplitude "on-off" oscillation, or any other simple linear automatic control description, if the limit cycle oscillations were small, it was quite disconcerting to find regulation of mean quantities to take place by oscillating amplitude changes comparable to the mean. Such dominant nonlinear behavior, in our view, is worth a casting in its own right in the form of a new suitable nonlinear control theory.

Third, to emphasize to the biologist both the dynamic time dependant nature of his system; to attempt to steer him away from a too easy acceptance of elementary control theory; and not to do violence to Cannon's basic organizing concept, the term homeokinesis is proposed.

(ii) While we are quite in agreement that some sort of "open-loop predictive" control exists in the brain in its response for both learned and new experience, we are referring to quite a different time scale in the power adaption of the muscle "engine." The immediate response of the muscles is at the neurophysiological scale that includes the predictive control that Dr. Milsum alludes to. However the follower characteristics (following the neurophysiological computation) of the capillary oxygen choke system is delayed into the tens of seconds before tissue depletion requires readjustment of the oxygen choking pattern by local work demand. This does not preclude another system, the sympathetic-adrenaline system from hurling the capillary beds in specific regions into immediate action at more nearly neurophysiological time scale.

(iii) In my oral presentation, I concluded with a new proposal for a mechanistic definition of life, and with what appeared to be a shocking overstatement that the "purpose" of a living system was to maintain and preserve in time the operation of the chemical reaction oxygen plus fuel equals carbon dioxide plus water. We intended no literary shock but an emphasis on the following technical implications: the "purpose" of the biological plant is to sustain this reaction. Every internal system that we have examined in the body, *regardless of the time scale of operation*, appears to us to be clearly related to the regulation spectrum associated with one or more elements of this reaction. The body as a self-actuated self-locomotory complex plant uses its system at many time scales from 0.01 second to nearly 100 years and involves many kinds of actions, including internal computation and external adaptive search, but in very significant ways both physiological and psychological behavior seem to be related to sustaining the performance of this reaction.