Reprinted from the "Record of the IEEE Systems Science and Cybernetics Conference," October 1969.

HIERARCHICAL REGULATION IN THE COMPLEX BIOLOGICAL ORGANISM

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Abstract

1. Preliminaries. The biological system can be described at the molecular biological level, the cellular level, the organ level, the entire systems level, the total behavioral level in the environment, or the genetic level. We are interested in the dynamics of the 3rd, 4th, and 5th levels. Our tools of analysis are the dynamic systems analysis of the electrical engineer and physicist, the 'spectroscopy' of its operating chains. For a first round, we have dealt with the power engineering, not the communications engineering. We find an extensive spectrum of biochemical chains. We call the dynamic life scheme exhibited homeokinesis, to augment the quasi-static idea of homeostasis.

2. Dynamic limit cycles in mammals. The experimental foundation for our belief in homeokinesis is referenced. Dynamic cycles in various biochemical events are mentioned.

3. Describing homeokinesis. Dynamic regulation of the organism's interior is discussed briefly.

4. Our new thesis - hierarchical regulation. Biochemical regulation in the system is truly achieved by an overlay of system upon system.

Biophysical Preliminaries

The following outlines our physiologically founded view of the biological organism.

1. Its understanding may be organized around the following levels:

a. biochemistry at the molecular level;
b. process maintenance and exchange at the cellular level;
c. process maintenance and exchange at the organized level of organs;
d. internal process organization and logic for the macrosystem (i.e., overall systems analysis);
e. 'factory' operation of the biosystem in its total environment (i.e., both internal and external dynamic systems behavior);
f. genetic and epigenetic coding for reliable reproduction of biosystems that are operative in total ecological environments.

We selected the exposition of levels c-e for our first long term task. Our experimental-theoretical program, predominantly limited to organ and total system levels, have led us to the need for formulating a position for the level of factory operation. This represents our second such position paper. (For the first, see (1, 2).)

2. Preferred tools for analysis of a gross system and its major subcomponents, studied at that structural-hierarchical level, is its dynamic response, both steady state and transient. This involves the determination of the time and spatial course of the major identified fluxes and potentials, and the modes of motor actions (of switches, valves, pumps, motors, etc.) that the system exhibits. (We call this process of analysis 'biospectroscopy', since it relates to physical-chemical spectroscopy.) If these are well identified, then the 'chains' of causality, as these fluxes and modes course through the system, may perhaps be identified, by physical-chemical hypothesis.

3. The two great logical divisions of the nature of flux (i.e., flow) are the separations into power and information. While modern electrical engineering may favor the information fluxes, a more classically oriented physics might start by examining the power fluxes.

4. Operationally, we define the human, our prototype complex biosystem, as a self-actuated motor system ('automobile') that intermittently roams through its physical environment in search of food. Its principle dynamic properties are that it hungers, feeds, and moves about so that it can continue to hunger, feed, and move about. At the right unfolding time, it couples and reproduces so that the newly formed unit can hunger, feed, and move about. This implies that by his fundamental nature, man involves one or more major internal thermodynamic engines, and engine cycles (for motor capability). Such study involves straightforward power engineering. (Fuel is taken in, energy is liberated and made available for work.)

5. Our first choice, therefore, was to explore the dynamics of the metabolic processes, (3-11), and then, having found a ubiquity of internal biochemical oscillators, to explore additional variables.

6. Finding a near stationary spectrum for the many biochemical parameters that we explored (although the cycles warbled or 'wowed' in frequency, with considerable noise, their power spectra indicated large amounts of energy tied up in these spectral regions), we formally (1, 2, 7, 14, 15, 16) identified the chains in which they were in-

Iberall, A.S., S.Z. Cardon. Hierarchical regulation in the complex biological organism. *Record of the IEEE Systems Science and Cybernetics Conference*, Philadelphia, PA, October, 145-151, 1969.

volved as nonlinear limit cycles, everbeating, with internally lossy mechanisms, independent of the starting conditions. Since it seemed clear that the mean state of these variables were those regulated parameters identified with homeostasis, the central concept of the constancy of the internal environment independent of external change, we were forced to propose its modification. For such dynamic regulation of the mean state, we suggested the modified name homeokinesis, to denote mediation, mainly by inhibition or release from inhibition, of a manifold of oscillatory processes which make up the many biochemical chains in the organism.

7. Having demonstrated thermodynamic consistency in describing some of the basic metabolic processes, and having postulated causal chains involving hormone interaction for a number of those identified, we proceeded to the behavioral logic of the entire system. The biosystem is not an idiot thermodynamic system that tracks a routine path, doing its 'thing' over and over again. Instead the system has indeterminate gain at zero frequency. It is essentially marginally unstable.

Roughly speaking this means that if the system is put down it will not stay at rest indefinitely. If in a disturbed state, it will calm down in time when put into a confined region. To completely describe its character, we had to postulate a large number of operational modalities in the biosystem. Because of its inherent instability, the biosystem threads these modalities, its 'hungers', to form a satisfactory pattern. This was covered in our first position paper, a proposed extension of physiological to include behavioral homeokinesis.

8. However, this scheme is still not sufficient to stabilize fully the unstable biosystem. We, therefore, had to postulate a hierarchical nature to the total system's behavioral regulation. Regulation is achieved by overlay of system upon system. For preliminary exposition, see (17). A second description is in progress for cardiovascular system regulation. However, from these essays, we have caught a glimpse of the overall scheme, which we propose to discuss in this paper.

Dynamic Limit Cycles in Mammals - The Foundation for Our Belief in Homeokinesis

To prevent our schemes from being viewed as pure speculation, we have searched out a quantity of spectral data. (Alluded to in (11), they will appear in assembled form soon (18). Also see Richter (19) and Jenner (20).) A common feature in these oscillator chains is a relatively slow cycle, suggesting that their dynamics are not single rate governing steps at the cellular level; yet the cycles are quite fast for the amplitudes exhibited (visualize that it is large power that these nonlinearly stable oscillators put into transit). The amplitude ranges tend to be near-normally (Gaussian) distributed but with finite cut-offs. Typically their maximum to minimum amplitude ratio over an observation of many cycles is 5-6 to 1. Thus we are not discussing small changes.

The observations are of ventilation gases, metabolism, thermal power, heart rate, blood gases, blood fuel constituents, blood hormones, capillary red cell flow, water content, weight, sex, circadian rhythms, activity, and some of psychic state.

Describing Homeokinesis - Dynamic Regulation of The Organism's Interior

We find that when interested scientists finally grasp the fact that there really is a fairly determinate spectrum of repetitive chains in the biosystem, with relatively little stochastic signal (a characteristic signal to noise ratio is of the order of 4 to 1), rather than the more commonly expressed idea of 'inherent biological variability', the next question they raise is what is the significance of these 'rhythms'. We have carefully tried to lay out the genesis of our ideas in a number of references. ((5, 15, 1, 16) is the shortest introduction.)

As a brief summary: There is a matrix whose columns represent the chemical materials, chemical process chains, and behavioral modalities of the system, and whose rows represent ordered time scales. All intersections are not filled. However, in any column, the many temporal levels of regulation of that material, process, or modality are catalogued. In any row, the elements may or may not be coupled. The coincidence of time scales, where processes are not coupled, may be due to the use of similar or comparable physical-chemical steps or spatial domains, so that the rate governing processes are similar. We have indicated that the pertinent frequency range is quite broad, approximately 10 decades (1, 2).

To repeat, the system and its many chains are marginally unstable. It is this character that keeps the system and its internal fluxes in intermittent motion, always in process of responding to the changing inputs to the system, to the vicissitudes of the milieu which appear as an impulsive spectrum.

The net resultant of this instability and the chains of organization that emerge both genetically and epigenetically, are that the system locks into behavioral modalities, perhaps 10-20 in all. (Ethologists identify 10, we count 20.)

As a correlary of the system instability and its emergent behavioral modalities, regulation in the complex system is multi-hierarchical. The system cannot be viewed as at an indefinite quiescence from which its regulation emerges. It truly has indeterminate gain at zero frequency. Instead, it is in overlay of system upon system by which total regulation takes place. Reference (17) attempted to make this clear with regard to thermoregulation. One must always think of system's regulation as taking place against a total scheduled background of normal activities that make up a standardizable behavioral pattern for the biosystem. (Detailed moment by moment, hourly, daily, weekly, monthly, yearly activity, and finally life pattern.)

Hierarchical Regulation

What are we trying to say? Consider an analogue. As explorers in a strange land, we note complex 'factories' in operation. We don't know their logic, the 'purpose' of these systems. However, we infer that the ensemble is ergodic. What any one individual 'factory' does resembles what others do. Each individual seems to repeat epochs of much the same behavior. The 'factories' have a start-up, a life, and a degradative phase, and appear to have internal loss mechanisms. From this we infer that the observed 'factories' are systems. This requires qualification by the first and second laws of thermodynamics, i.e., in the system, energy is neither created nor destroyed; the system goes through an energetic cycle, which thus is the minimum period for thermodynamic equilibrium; an irreversible production of entropy takes place.

Next, we determine their frequency response characteristics, of both autonomous oscillators and transients. This helps suggest some of the detailed internal mechanisms.

Now we are ready to attack the logic of the system. If we succeed, then we may go on to the 'purpose' of the factory. In the biosystem, we are up to these questions. What is the logic of its spectra and subsystems?

What we propose to do is outline the temporal-hierarchical levels that are associated with the metabolic and automotive process (namely, the system does eat and move about). Some of the levels are speculations based on a number of observations, others are based on much tighter arguments.

1. 0.1-0.3 second level - detailed motor activities can take place at this scale which are programmed by the brain (e.g., highest frequency segments in motor actions). Energetic demands can be put on the system, and individual motor units can put forth energy packets within this time domain (at what is considered to be the reaction time level). A first behavioral response shows itself at the highest frequency for which motor activity can be changed in local regions.

2. 7-20 seconds level - storage capacitance of oxygen as a blood gas provides this magnitude of time constant. At this level, a first small behavioral modality begins to arise. The body tends to shift its postures. (Noted in a number of mammalian species. Contrarily, birds, illustratively gulls, change posture more frequently. It is suggestive that the behavior is a visual-neocortical response.)

3. 30-120 seconds level - fuel oscillations in the blood, and a cyclic supply of red cells through small capillaries (i.e., 2-5 microns in mammals) take place with cycles of this periodic magnitude (21). The red cell flow in these capillaries seems to be independent of plasma flow at this time scale, although in arterioles, which supply many capillaries, red cells and plasma flow are proportional (uniform hematocrit). Most recently, the production of hemoglobin has been shown to be synthesized in this time scale. Thus, overall equilibrium in the system within 100 seconds cannot be assumed, i.e., a full cycle of chemical supply for motor performance has not taken place in less time. Yet the organism can perform a complex behavioral task and leave an oxygen debt whose repayment follows with a time constant of this order of magnitude.

4. 400 seconds level - this seems to be the first overall systems level. (An illustration is offered from Brouha (22). In starting up a long term task involving the entire set of the body, the time constant for increased oxygen consumption is the previous 100 seconds. On the other hand, the time constant for increased heart rate support is about 7 minutes. Similar observations in a number of different metabolic systems led us to appreciate the general nature of Brouha's results.) It apparently arises from the integrative response of the hypothalamus in redistributing the systemic blood circulations to satisfy a hypothalamic algorithm.

Major overall shifts to 'stress', i.e., to overall cardiovascular support for a changed activity, take place with this time constant (e.g., skin vascularity, hypothalamic thermoregulation response). There likely are one or more hormones, involved with local organ systems, that help in the blood redistribution with this time constant. However, this autonomic level is not sufficient to run the system. With only this level available, the system would die (i.e., it is not sufficient that cardiovascular system and local organ hormones provide supportive follower action. The system's total actions are not thereby regulated).

5. 20-60 minutes level - because of the high buffer capacitance of carbonate, this is likely the epoch of CO_2 equilibrium in the body. At this domain, it is possible that a CNS segment leads to a deactivating-activating epoch, in which the system shifts tasks toward major behavioral modalities. At this level, CO_2 makes the system stir toward a different activity. (Twenty minutes of sustained activity probes at the overall body commitment. It is difficult to concentrate on one thing for longer periods when in a warm, humid, or stale atmosphere, as compared to a fresh breezy atmosphere low in CO_2.)

6. 3½ hours - the overall body thermal balance takes place at this time scale, i.e., it is the primary thermodynamic time constant of the system. The system requires an extensive integrative communicational 'vote' whether to persist in accepting the behavioral pattern of modalities or to change to something new. (At this time constant, the body makes a volitional, i.e., computed, decision whether to persist in a state or not; whether to work for the next four hours, whether to take an extensive walk in the cold, etc. It requires a complete body commitment.)

7. 24 hours - the circadian epoch involves the automatic making of large scale decisions - with regard to rest-wake, water, ingestion. A major patterning cycle of behavior takes place. The complete higher nervous command-control system emerges for the first time. Behavior is patterned into rest,

wake, eliminate, forage, etc., back to sleep and rest. Corticosteroids and a number of other hormones, as well as the reticular core and other major CNS compartments are involved.

8. 3½-7 days - both physiological and social behavioral rhythms emerge mediated by hormones with longer action times. A water cycle exists, namely, weight rises and falls with this rhythm. Such cyclic changes in total body water occur via cyclic unbalances in intake and excretion. This perhaps influences the food and social cycle. (For example, it is approximately the rebalance period required for reacclimatization after time or climatic zone shifts. One may suspect that these involve a water escapement.) The social week, with its complex behavioral rhythm, fits physiological cues. (Would men accept very rigid daily schedules without weekly or longer variation?)

9. 20-60 days behavioral rhythms - we believe that a case exists, centered on the menstrual cycle cue, for major behavioral rhythms at this scale. Anxiety-euphoria, intellectual, sexual, 'creative', 'learning' phenomena, it is proposed, possess such periodic epochs. (Taking on a total 'postural' frame of CNS reference - such as intense grief, high excitement, intense activity preoccupation, a complete change of pace of a vacation - can only be held for time scales of this magnitude.)

10. 1 year rhythms - the seasonal cues drive the complex animal, from rigid seasonal movements in birds and fish to smoother ones in mammals. One can suspect that the mammal, such as the human, who exists in a one climate environment - whether hot or cold - does not show much color in his behavioral patterning. His creativity is more limited; his depths and heights - of aggression; of sex activity; of ranging patterns, etc., seem to be less.

11. 10-20 years - the life epoch, the behavioral foci of life, exhibit such time scales in their behavioral patterns.

Metabolic regulation takes place with regard to all of these levels. However, the first integrative level is of the order of 400 seconds.

Can we prescribe an 'average' activity which will resemble the average behavior of a human? It will neither be rest nor high activity. There are many body postures possible - rest, eating, motor activity, etc. We see these as physically cast atomistic fragments of the behavioral modalities. However, the time averaged metabolism over some such moderate behavioral activity patterns sustained over a few such time constants (i.e., approximately 20 minutes or longer) is not very dissimilar from the time averaged metabolism over an entire day, an entire weather season, or a 20 year epoch. Thus we can conceive of a systems description of time averaged metabolism over such 400 or more seconds epochs. This measure can be regarded as an elementary 'normal' metabolism, rather than a 'basal' metabolism.

However, let's not look at the problem as the determination of the average metabolic event. We want instead to know what is a dynamic 'equilibrium' physiological state in which the regulatory functions of interest (here metabolic, thermoregulatory, activity, and behavioral) are implied, i.e., what is it that describes the system moving to eat so that it can move to eat. It will be patterned rhythmically around the average metabolism.

Such regulation does not take place at one level, nor is it rigid. As homeokinesis, it is a comfortable threading of all the hungers by small integral numbers per relevant epoch so that all systems are kept near their regulated state. This requires chains with both internal and external links, even for the apparently 'pure' physiological ones.

Thus there are many normal physiological patterns. All we can do for test purposes, if we want to characterize the system's ergodic character, is to choose an artificial one that samples all of the hungers.

Let us arrive at it by the following personalized dialogue: Will you be my body slave? More palatably, will you (as employee) be my (as employer) body slave? Yes, for a few minutes or a 5 hour experiment. More dubiously for a rigid 8 hour, 24 hour, or 30 day experiment.

For each succeeding level, more accomodative schedules must be permitted. For example, up to five hours, one can request a nearly pure single activity. (Lie quietly on a bed, sit quietly in a comfortable seat, exercise steadily at moderate rate, eat slowly but steadily, enter into a sustained argument.) For 8 hours, the subject wants a food break and an elimination break. For 24 hours, the subject wants rest-wake, a few food breaks, one or more elimination breaks, a number of no attention (i.e., relaxation) breaks, and a few interpersonal attentions. For two weeks, the subject wants these and a few more, on a repetitive, near circadian rate. However, he may be willing (barely) to accept them as a rigid routine. For 30 days, he is no longer willing to accept these schedules as a rigid daily routine. Yet at the time scale of a month, by introducing a few periods (at least hours, perhaps days) of more patterned threading of modalities, a 'normal' life is feasible.

We have proposed the following list as necessary modalities in the human. We will not assert their independence (they are certainly not 'normal modes' in the physical sense), nor their certainty, nor their uniqueness. Yet, intuitively, even after comparing with others which we have subsequently found, we still believe that the list furnishes nearly an upper bound to the number of salient mammalian modalities. A more unique identification of modalities may take a full generation to study.

sleep
'work'(directed motor activity)
'interpersonally attend' (body, verbal or sensory contact)

eat and drink
'communicate' (e.g., talk in humans)
'attend' (indifferent motor activity, involved sensor activity)
'motor practice' (run, walk, play, etc.)
sex
rest (no motor activity, indifferent internal sensory flux)
anxious
euphoric
fear
aggress
void
flight
'escape' (negligible motor and sensory input)
anger
laugh
envy
greed

Thus I (employer) do in fact tie you (employee) up for years. I (entrepeneur) am in fact also tied by my boss (customer) up for years. Loosely speaking, in that time scale, I am willing to pattern my life almost on a rigid yearly schedule with a minimum amount of variation (e.g., comparable to the 4 to 1 signal to noise ratio referenced before. However, like martinis, a 9 to 1 ratio is also acceptable, and perhaps even a 30 to 1 ratio).

Whether incarceration can deal with man or animals on more rigid schedules needs considerable looking into. Laboratory animals are quite different from wild animals; they require a large measure of support of function for their maintenance; and their schedule is less rigid than might appear.

Since some may regard this as far a field from behavior, let us exemplify the problem once more. The topic will be my thermoregulation and me in my branching choices in life.

At the 10 Hz. level, my individual muscle fibers and nerve fibers can be used for very fragmentary actions. (For example, I may play mandolin duets with a friend. We will tend to compete, and while chasing the music, we will step the tempo up to play nearly 10 notes per second, involving individual motor actions.)

However, my blood follower system must power this activity. Thus a complex of metabolic blood followers will be found cycling away at the 30-120 seconds level to provide fuel, oxygen, and the hormone drive to sustain that activity. As evidence for this, if I stop the activity, a metabolic decline can be shown with about a 100 seconds time constant. Alternately I can (and do) conduct my system to nearly any all-out activity for a few minutes. (Almost anyone can be trapped to run around a gym; swim two laps, etc. under ordinary circumstances.) Heat pulsing from the body can be found at this time scale.

However, I wish to sustain my new activity pattern. I can no longer do this on 'nerve' and one cycle of circulating hormone alone. The body follower system must drag the supporting cardiovascular system along. It is here where the hypothalamus comes in, particularly its thermoregulatory response.

It is our best hypothesis that the hypothalamic algorithm involves putting the 'fires' of temperature out. We believe that there is a blood division among the peripheral systemic circulations to increase the flow to reduce the local temperature. Thus demands put on systems - the skin heat exchanger, the GI tract, the kidney, etc. - result in an increased flow to that zone. It is a zonal control of blood flow. We find evidence for the seven minute temperature cycle from Benzinger's hypothalamic measurements (23); from Brouha's heart rate rise with activity; from the time constant for pooling of fluids at the extremities; from temperature changes seen in whole body thermography. We find, upon examining Fusco's data (24), that it is this thermoregulatory response which is abolished for weeks with hypothalamic lesions.

It is this level that we believe is controlled by nervous action at the level of arteriolar sphincters, etc. (We do not believe in the ubiquity of precapillary sphincters (21). Instead we believe and find support for an electrical gating of red cells in capillaries at the 100 second level; and a nervous control of the muscles regulating small vessel flow at the 7 minute level.) As sustained body demand changes, there is a cycling through the body zones, with whatever system having the major duty getting an augmented blood supply, controlled by arterioles actuated from the hypothalamic level.

This is what keeps me thermoregulated at the 7 minutes level. Namely, the hypothalamus has arranged a blood subdivision commensurate with power and oxygen demand and its central regulated temperature.

Will I persist in this task? No, I may get bored in 20 minutes. Here there is a 'vote' from the body as a whole, likely through the CO_2 and pH system as the resultant appears at a coordinating 'center', which reports the result to the reticular formation. Our scheme is, of course, somewhat hypothetical, but it has been adapted to fit a near 20 minutes CO_2 time constant.

If I work in a CO_2 laden, stale, warm, humid atmosphere, I get sleepy or bored. If the speaker is not colorful and doesn't know how to stir my internal faster hormones, I poop out on him (typically, he can use adventure, danger, or sex in his talk, but not tons of data, abstract equations, or too many ideas). Conversely, fresh air, a change in pace or activity will change my status.

Thus my reticular core votes to continue this silly state or change the activity level. One of the signals that is pressing is the temperature regulating response. After the 7 minutes response, my extremities go down in temperature, if it is cold. I have to vote whether to persist in the activity or not. It is only my extremities that are signalling discomfort. Yet I can make the overriding decision for my body to continue or change the activity.

The body algorithm is ruthless. If you want to persist, it says, you may, but it will no longer waste the heat (algorithm: if a region is warm - give it blood, if it's cold - take it away). Your extremities begin to shut off. The large body follower begins to make large thermal adjustments. Behind it stands the overall chemical balance in which the CO_2 and pH system and its related hormones likely dominate.

I am thus capable of voting locally, i.e., major body zones push up their satisfaction-discomfort level at me, and we vote to persist or desist.

Now for a more integrative level. "Come with me and be my love." I say, "Let us take a long walk in the cool damp woods." "How long?" says my wife. "Oh, three or four hours!" say I. "Not me," says my wife, "Take your friend for the walk." "O.K." says he.

Note at this level there is already a near conscious vote through all of the systems, making use of remembrances of things past. "Shall we commit ourselves to this action," they ask. They know or can estimate the level of physical discomfort, the possible level of joy and satisfaction ("Will he talk me to death?" my friend says to himself, "Or will the thoughts be so illuminating that I can stand all the pain? Perhaps I should ask him to play the mandolin instead," i.e., trade-offs of goods and evils). The time constant here is a full thermal time constant of the entire body. It is also, incidentally, the approximate relaxation time constant for food satiety.

If my friend commits himself to the action, the entire body thermal equilibrium will shift. Within limits the system is capable of readjustment that will keep its hypothalamus temperature regulated (not controlled - Benzinger's data (23) show there can be a near $1^{\circ}C$ shift in level). There is a range of environment and sustained activity over which the body can perform. It is a wide range, but not infinite.

Of course, the human has augmentors, extensions. "Perhaps I better take a sweater, or put my Arctic clothing on," says my friend. However, nearly nude, he can tolerate 0 to $40^{\circ}C$ by activity regulation.

In longer term, he cannot sustain the activity. Day-night enters. His reticular core finally votes and tells him to turn off the day. He sleeps.

With regard to a circadian temperature cycle (25), we do not believe that there is an autonomous thermal cycle. We believe there exists a rest-wake-activity cycle (food foraging, etc.), and that temperature changes are concomitant with the activity changes. In an experiment on a bedridden subject, temperature was measured upon waking and after. Normal mild bed activity would jump the temperature up, as parts of the vascular circulation were brought into play. If one remained 'absolutely' still, there was no jump in temperature. With cooperation and interest, we are willing to attempt an experiment that we doubt has ever been done. Namely, we will attempt to stay very quiet, with essentially no motion, for 24 to 48 hours, while measuring temperature.

Note that the experimental situation of clamping a person in a fixed modality; or actually in a pattern involving very minimal modalities is almost an impossible task to perform. This is the essential meaning of the statement that the system has indeterminate gain at zero frequency (i.e., at frequencies smaller than 1 cycle per 12 hours or 1 cycle per 24 hours). The problem is even more aggravated with sensory deprivation, as more modalities are excluded. (Namely, we would doubt that a total sensory deprivation experiment could be conducted for 24 hours.)

Thus we suspect that temperature regulation at the 24 hour level is a concomitant of the rest-wake pattern of life.

At the next level, while there is a strong social basis for weekly patterns (e.g., the Thank God It's Friday syndrome), we also find a strong $3\frac{1}{2}$ day water cycle in humans and in guinea pigs. We have not been able to completely divorce the cycle from the social week. Nevertheless, we are convinced that the time constant for water is of the order of $3\frac{1}{2}$ days, and are reasonably convinced that the food cycle entwines that water cycle. We have reason to believe that acclimatization, say under movement from one time zone to another, from one temperature zone to another, from one altitude to another, from one heavy activity pattern to another, has a time constant of this magnitude (3-5 days) and that it is associated with the water balance. Thus water and long term metabolism - we believe - are certainly coupled in one direction, and possibly have nearly symmetric coefficients, coupling them the other way. Thus the longer term thermoregulation is possibly tied to this water-metabolism-activity cycle.

Now we enter the near purely behavioral range of 20-40 days. In this domain, the chains certainly have external links. (In fact, we consider that the distinction between psychological, as opposed to physiological behavior, should be made on the basis of how strongly the chains of causality depend on external links that are directly in the chain, rather than at boundaries.) A major polarization is afforded by a wife's (or involved female's) autonomous menstrual rhythm. Beach (26) points out both female humans' and rats' activity levels vary over the menstrual cycle.

However, we believe the female influences the brood within her sphere - husband, boyfriend, and children. Thus a subtle emotional cuing exists. This tends to entrain other emotional derived phenomena.

On the other hand, we believe, with mostly behavioral evidence so far, that there are autonomous emotional, intellectual, sexual, anxiety-euphoria, and other rhythms vaguely in this time domain, that involve definite internal, mainly biochemical chains. However, they have strong external links, i.e., it is a time constant of the order necessary to have a good vacation, get an important idea, work up courage to get married, or to get drunk, to get a new job, to become very anxious, or euphoric, etc. All of these 'chosen' patterns lead to very definite physical-physiological involvement. In social life, the female's menstrual period sits there as a gentle signal rocking the system's frequency response. Temperature regulation in this domain is more subtle. It is the follower pattern on the activity patterns of a busy life.

Since that temporal level may have seemed a little strained (for temperature, not for living) the next one may be more clear. We come to the seasonal cue.

The human chooses a thermal environment he can make out in. (One may not overlook his clothing and his environmental thermal conditioning.) On earth, man responds - if he is temperate zone adapted (or even if he is not) - to work out a seasonal roaming. He may go to Florida in the winter, and north in summer!

While this intentionally exaggerated the reaction for the affluent human, it is clear that many species adapt to the warm-cold of seasonal changes in a great variety of ways. Birds migrate, many mammals change their insulation. Many primates change their environment winter and summer. The complex human tends to control both his locomotion state, his local living milieu, and his location. Thus, in civilized society, he simply shows an even more complex reaction pattern.

However, basically, the human works out motor patterns that hold his thermoregulating signal within bounds. He does not conduct himself with heavy activity in very hot climates, nor does he overexpose himself in very cold climates. At near $0^{o}C$ with little clothes, he has to have a very active kind of daily and seasonal pattern.

Beyond lies a slow adaption. We suggest that the mammals (suppose them to be driven by changing weather cues, such as a cold season to season spell, or a warm one, or a dry one, etc.) begin to explore the ecological environment, drifting slowly in it, in search-seek patterns which have a strong thermoregulatory cue. This is at the seasonal or greater level. Animals change their roaming habits over years, not necessarily over days. This seems to be the record read from the archeological evidence of past ice ages (e.g., wandering of mammalian species over Europe).

Thus the thermoregulatory homeotherm does not achieve his regulation by one hierarchical level, but by overlay of level upon level.

While so far we have discussed this for only one signal, with the temperature signal in the foreground, the ideas and modeling are true for all other essential fluxes - for light, food, sex, etc.

Should any man think that he can stay in one physiological state without being driven into patterns, we offer him the challenge. Let him join us, and we'll both try to remain quiet for a day!

In such fashion, we propose hierarchical homeokinetic regulation with its strong behavioral overtones.

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This program is jointly supported by Army Research Office and NASA under Contract NASW 1815.