Iberall, A. Dynamics of mammalian thermoregulation and its circadian component. *J. Appl. Physiol.*, 61:1230-1233, 1986.

Dynamics of mammalian thermoregulation and its circadian component

A. S. IBERALL
Department of Oral Biology, University of California, Los Angeles, California 90024

IBERALL, A. S. *Dynamics of mammalian thermoregulation and its circadian component.* J. Appl. Physiol. 61(3): 1230–1233, 1986.—This note attempts to focus a physical theory for the dynamics of mammalian thermoregulation, its relation to thermodynamic near-equilibrium, and its relation to a circadian component of that regulation. As such, it is an extension of the analysis and discussion carried on in earlier references. That earlier analysis is tested and extended by the use of two additional data sets not found in the earlier work.

thermo regulation; thermodynamics; physiological models; dynamic modeling

On Thermodynamic Near-Equilibrium in the Organism

In previous publications (2, 8–17, 19), the experimental result was established, and it was repeatedly discussed that thermodynamic near-equilibrium (process closure, as measured by first law energetics and viewed according to the second law of thermodynamics) was to be found in humans and dogs (more generally in all mammals) over a period of time of the order of 3 h. Few investigators have taken note of the constraining nature of this result in assessing what they might wish to view as near-equilibrium in organismic studies of various metabolic, biochemical, or behavioral systems in mammals.

The data set of a particular investigation (21) on the rectal temperature of a tethered (by cables used for measurement), but otherwise "free"-ranging, rat as a study in thermoregulation is offered as further support for the result and its general applicability to mammals. The first nominal observation of that data set (rectal temperature vs. time for 24 h) is that the generally expected mammalian level of deep body temperature regulation takes place. The second observation is that the temperature fluctuates at what appears to be a number of time scales (or frequencies). The first question that arises concerns the condition under which the regulation has been achieved. Why this question?

Suppose we look at the record at any point in time. What we find is that the temperature is changing (fluctuating). That change (gradient or slope) indicates that an equilibrium has not been achieved. Expressed as a power unbalance, the rates of change are extremely high.

Demonstration. To test thermodynamic closure according to the second law of thermodynamics, we write the first law in the form

$$\mathrm{W}c_P \frac{\mathrm{dT}}{\mathrm{d}t} = M - L$$

where W is the weight (or mass) of the animal, c_P the specific heat of average animal tissue, dT/dt the rate of change of average body temperature T with time t, M the metabolic power generated within the animal, and L the loss of body averaged heat power from the animal. The first law holds in this form, whether the system is controlled or not.

This relation states that storage change via specific heat = metabolic power − losses. No significant storage by phase change is assumed. At thermodynamic equilibrium, the left-hand side of the equation should be zero (e.g., when averaged over some minimum cycle). How significant is the metabolic unbalance for a nonzero left side? We decompose the metabolic power M into its time-independent mean value M_0 and its ongoing fluctuating component ΔM. Thus

$$\frac{\mathrm{dT}}{\mathrm{d}t} = \frac{M}{\mathrm{W}c_P} - \frac{L}{\mathrm{W}c_P} = \frac{\Delta M}{\mathrm{W}c_P} + \frac{M_0 - L}{\mathrm{W}c_P}$$

Let $M_0 - L \approx 0$ at equilibrium. (This, basically, is a definition of the mean "equilibrium" metabolic power, M_0. It is premised that the losses, L, are largely Newton-like heat losses and, thus, do not vary much in time. They depend on the body surface temperature and the ambient temperature, which do fluctuate but do not vary much in magnitude). Thus

$$\frac{\mathrm{dT}}{\mathrm{d}t} = \frac{M_0}{\mathrm{W}c_P} \frac{\Delta M}{M_0}$$

While M_0 is proportional to $\mathrm{W}^{0.8}$ for all mammals (14), it is close enough to assume $M_0 \propto \mathrm{W}$ and use human data for the common scale of mammalian sensitivity. M_0 approximates 2,100 kcal/day, W approximates 70 kg, and $c_P \approx 1$ kcal·kg^{-1}·°C^{-1}.

(While some readers might question whether adult body mass scales at the 0.8 power, preferring other values

0161-7567/86 $1.50 Copyright © 1986 the American Physiological Society

ranging from the 0.67 to 1.0 power, or question whether a specific heat of 0.8 is not more precise than 1.0, none of these changes affect the nominal sensitivity claimed of about 1°C/h in the near regulation range.)

$$\frac{dT}{dt} = 30\,\frac{\Delta M}{M_0}\,\frac{^\circ C}{\text{day}} \approx \frac{\Delta M}{M_0}\,\frac{^\circ C}{\text{hour}}$$

Thus a change (slope) of 1°C/h corresponds to metabolic imbalances on the order of one unit of normal "total" metabolism. The instantaneous derivatives in the data set are as high as 10°C/h, or 10-fold normal metabolism. Further, we have demonstrated the same "instantaneous" degree of dynamic imbalance for three mammalian species of considerably differing size, mouse, guinea pig, and human (17), suggesting common dynamics involved in the temperature regulation for all mammals.

Because of the high instantaneous metabolic change, one can only attempt to assess temperature regulation over some averaging period, e.g., a period over which regulation or control has taken place and some "initial" transient has been washed out. Note that the test animal of Pryzbylik et al. (21) is basically self-clamped in a constant low-activity schedule. Thus we are not concerned with transient processes but with a regulation or control period.

As a natural way to assess the regulation, one might choose temperatures at two points in time, some measure apart. How far apart must that time measure be?

If we take different time periods, e.g., 0.5 h apart, 1 h, etc., we see varying amounts of residual net slopes. That is, it is not until the net residual slopes are, say, less than 0.1°C/h (i.e., ±10% imbalance from normal metabolism) that we can sense a fair estimate of a regulation domain. Interestingly enough, we note that the "window" or "epoch" over which that determination must be made is relatively uniform for these data, approximately 3 h (i.e., examine the amount of imbalance for any arbitrary 3-h epoch).

This simple demonstration from this one set of rat data (supported by every other data set referenced in this paper) illustrates what closure according to the second law of thermodynamics is about. Over a period of 3 h, the metabolic machinery of the rat (more generally, all mammals) provides closure for its chemical-physical thermodynamics. (The system has operated over a cycle by drawing from stores and returned close enough to an effectively identical state of thermal equilibrium.)

This is the point made in our studies and presented in the mid-1950s to engineering, instrumentation, control, and physiological communities (1952 Gordon Conference, 1960 ASME publication). It has not yet been fully understood by the physiological community partly due, perhaps, to the fact that we have never presented long-term (e.g., 24-hr) data and depended instead on demonstrations involving independent experimental segments of 5 h (8, 17).

On Physiological Near-Equilibrium in the Organism

The demonstration of thermodynamic equilibrium, however, is no guarantee of physiological equilibrium. Examine, for example, another data set on mammalian core temperature (that of Czeisler for humans, Ref. 3, p. 154, 160, 164, 170, 172, 176, 177, and 180). This was a study of circadian characteristics in humans and has become widely known. As far as we know, the author has not published the entire set of findings elsewhere. A more common source of some of these data, e.g., "normal" light-dark and free-running data, is found in Fig. 3 Czeisler et al.'s study (4). Unfortunately, only p. 154, 160, 167 and 180 of Czeisler's thesis (3) are individual "normal" records of core temperature vs. time. Loosely speaking, these data are "square" waves, one temperature level during the active day and one lower temperature level during the sleeping night. (Actually, there is a ramp in falling asleep, and there are comparable day and night fluctuations.) Clearly, when one examines the data, the spiking measurements that define the temperature fluctuations have not been measured with sufficient time resolution to know what the high-frequency content may be, but there may be on the order of 8–10 0.25–0.5°F fluctuations per 24-h period. One finds residual derivatives on the order of 0.1°C/day, nominal, from 3-h segments of Czeisler's flat-top data. Thus, clearly, each of the two flat segments, sleeping and waking, are effectively thermodynamic equilibrium segments when these segments are filtered (averaged) over 3-h epochs. When the entire record is examined over the 24-h day, the sleep-wake response more closely represents physiological equilibrium, an epoch never tested for by us but extensively discussed in circadian literature and affording considerable opportunity for conjecture as to its mechanisms.

Czeisler's findings, then, make the next aspect of the thermoregulation problem clear. If there is a distinct 1.5°F difference between the "flat" responses of waking and of sleeping, there is no way that the core regulation can be regarded as a feedback set-point controller. (If there were a feedback controller, it would have to be a supracircadian controller, perhaps of an on-off nature. The thermodynamic closure guarantees decay of all local dynamic processes to near equilibrium in 3 h or less.) Such a "steady-state" error is absolutely incompatible with the notion of a control system. It may be regulated, e.g., the body may be a moderately poor regulator of its core temperature, but it is not a controller (see Ref. 9).

Thus we return to our original conclusion [see Iberall (8) and sequels (9–17, 19) and Hardy's summary (7) of our position]: the temperature regulation emerges from an "open-loop" regulator. The difference in regulation, in sleep, in waking, in health, in fever, still remains to be accounted for. If hypothalamic function is involved in such long-term regulation (e.g., these daily portions and longer), its role has still not been made explicit. If the effect is solely associated with posture, with activity or with the mean state of some circadian oscillator, none of these possibilities have been properly proven or rejected.

On a Feasible Model for Circadian Component of Thermoregulation

We would suggest that, by physical reasoning, we can now finally elect the most likely possibility for the ther-

moregulation. From the difference in Czeisler's data on core temperature, *1*) entrained by day-night and *2*) free running (also to be seen in Fig. 3 of Ref. 4), the former being a flat-top difference, day and night, the latter being dome-and-bowl shaped segments, awake and asleep, with an initial waking spike, we would have to reject posture, activity, and even a pure hypothalamic regulation. The most likely explanation of long-term thermoregulation would thus be regulation by a circadian oscillator [homeokinesis (15) as it involved some regulatory region within the body], possibly involving a domain of hypothalamic cells or possibly not. (We have no objection to involving hypothalamic regulation at a higher frequency. However, we reject the notion that it is necessarily involved in long-term temperature regulation.) What is particularly rejected is the notion that a measured set point in temperature is controlled by some group of cell sensors. A much more plausible explanation is that the metabolism of some group of cells, involving the particular temperature sensitivity of some particular enzymatic reaction, is what is involved in the regulation. We can imagine the free-running circadian performance of some two-distinct-state oscillator whose performance can be overridden by day-night determined states, wherein such an enzymatically sensitive central sensing domain might be involved in determining the bias of a rate controlling zonal vascular regulation. At this point, by pure physical reasoning, we could not precisely infer how such a region (e.g., hypothalamic) would be involved in the circadian oscillator. Thus we turn to a physiological point of view.

We can conjecture that the network defined by the superior cervical ganglion (SCG) coupled to the pineal and the eye possibly contains the mechanism for the circadian oscillator in mammals (1), with an exogenous light-dark (day-night) drive via the visual system and an endogenous drive via the pineal. We would tend to view coupling of the suprachiasmatic nucleus (SCN) to the circadian oscillator circuit and/or some other component, *X*, as a source for thermal biasing of the circadian oscillator at fractional day levels. Part of that bias may be associated with a high-frequency 7-min process that we conjecture represents the action of the hypothalamus in regulating regional blood flow in response to (as a follower at midbrain level of) central nervous system (CNS)-governed activity from higher centers. Another part, we conjecture, represents the leader-follower chemical coupling of 3-h cortisol pulsing and some integrated effect of motor action. At midbrain levels, that 3-h process seems to operate "routinely," i.e., fairly regularly, possibly with the cortisol pulse as the regularizing leader when the system is driven by exogenous night-day cycles. However, under endogenous circadian regulation, it appears that the election of motor action is biased into a considerably different form (see Refs. 5, 22). We are led to suspect, therefore, that *X* might be a higher level source such as the reticular activating system (RAS), but probably not the cortex.

We need not stress how very hypothetical the scheme is (and will have to be for a long time) for such complex dynamic characteristics as the multifaceted thermal regulation system.

It is appropriate to offer a few details about the higher frequency thermoregulatory response. For example, we may turn to the highest frequency (slower, though, than heartbeat and breathing rate) in the thermoregulatory record. (It is an interesting but simple piece of physical reasoning as to why one would look at periods longer than the breathing rate. Since the heat-producing metabolic reaction is an equivalent oxidation, producing metabolic by-products, and the breathing cycle involves alternating intake of O_2 and expulsion of by-products through a single source-sink vent, it is impossible to consider thermoregulatory equilibrium in anything less than one complete breath cycle.) It is also interesting that the Pryzbylik data have sufficient sensitivity to come close to such high-frequency results (fluctuating cycles in the minutes range). However, for quantitative results, one may turn to the studies of Goodman (6) and Lenfant (20). These two studies have verified our earlier results that there was a strong metabolic and heat production (exothermic reaction) cycle in the range of 1–2 min. Goodman, in particular, demonstrated that the fluctuating scale was quite nonstationary.

Beyond the highest frequency nonstationary fluctuating cycle of 1–2 min, there also exist lower frequency cycles, e.g., 7 and 30 min (examine our data and the data of both Goodman and Pryzbylik). These relate to other dynamic physiological mechanisms worthy of theoretical study (e.g., short-term hypothalamic regulation, perhaps carbonate regulation). However, these specific details do not advance the general nature of our thesis regarding long-term temperature regulation that is exhibited at 3 h and beyond.

Some Added Comments

The experimental results we have discussed for this and other regulations support the following general theses. *1*) For most physiological systems, there exist dynamic data in the literature that, however, have never been broadly presented or correlated. *2*) There often exists commentary on dynamic mechanisms, related or unrelated to these dynamic data. *3*) Quite commonly, these commentaries have not been critically assessed from a sufficiently general physical-physiological point of view (which has to become the essence of a physical biology).

On the basis of these theses, therefore, I would propose that a first "edition" of a handbook of dynamic signatures of physiological systems be assembled, preferably under APS guidance. Because of its scope, a "first" edition could succeed only in finding and assembling such data. It could be responsible for critically selecting the batch that is the clearest, most consistent with other findings, and most broadly descriptive of all the dynamic content in providing a modestly uniform level of feature extraction as data analysis, and it could also provide, at least, a first-round pass at a commentary on likely dynamic mechanisms. Our attempt to collect such data for temperature regulation in mammals is a most primitive first example.

Received 10 June 1985; accepted in final form 14 April 1986.

REFERENCES

1. BLOCH, E., S. CARDON, A. IBERALL, D. JACOBOWITZ, K. KORNACKER, L. LIPETZ, W. MCCULLOCH, J. URQUHART, M. WEINBERG, AND F. YATES. *Introduction to a Biological Systems Science.* (NASA Contractors Rept. CR-1720, p. 113–129, Feb. 1971. Available from NTIS, Springfield, VA.)
2. CARDON, S., AND A. IBERALL. Oscillations in biological systems. *Curr. Mod. Biol.* 3: 237–249, 1970.
3. CZEISLER, C. *Human Circadian Physiology. Internal Organization of Temperature, Sleep-Wake and Neuroendocrine Rhythms* (PhD dissertation). Stanford, CA: Stanford University, 1978.
4. CZEISLER, C., G. RICHARDSON, J. ZIMMERMAN, M. MOORE-EDE, AND E. WEITZMAN. Entrainment of human circadian rhythms by light-dark cycles: a reassessment. *Photochem. Photobiol.* 34: 239–247, 1981.
5. CZEISLER, C., J. ZIMMERMAN, J. RONDA, M. MOORE-EDE, AND E. WEITZMAN. Timing of REM sleep is coupled to the circadian rhythm of body temperature in man. *Sleep* 2: 329–346, 1980.
6. GOODMAN, L. Oscillating behavior of ventilation in resting man. *IEEE Trans. Biomed. Eng.* 11: 82–93, 1964.
7. HARDY, J. D. Physiology of temperature regulation. *Physiol. Rev.* 41: 521–606, 1961.
8. IBERALL, A. Human body as an inconstant heat source and its relation to clothes insulation. *Trans. ASME Ser. D J. Basic Eng.* 82: 95–112, 513–527, 1960.
9. IBERALL, A. A physical critique of the description of thermoregulation in the human. *Proc. Int. Conf. Med. Electron. 4th, New York 1961.*
10. IBERALL, A. A note on thermoregulation. *Curr. Mod. Biol.* 2: 140–148, 1968.
11. IBERALL, A. Regarding periodic phenomena. *Science Wash. DC* 168: 152, 1970.
12. IBERALL, A. On the general dynamics of systems. *Gen. Syst.* 15: 7–13, 1970.
13. IBERALL, A. Comments on "A review on mathematical models of the human thermal system." *IEEE Trans. Biomed. Eng.* 19: 67, 1972.
14. IBERALL, A. Blood flow and oxygen uptake in mammals. *Ann. Biomed. Eng.* 1: 1–8, 1972.
15. IBERALL, A., AND S. CARDON. Control in biological systems—a physical review. *Ann. NY Acad. Sci.* 117: 445–518, 1964.
16. IBERALL, A., AND S. CARDON. Human temperature regulation—a 1964 model. *Proc. Ann. Conf. Eng. Med. Biol. 17th Cleveland, Ohio, 1964.*
17. IBERALL, A., AND S. CARDON. *Further Study of the Dynamic Systems Response of Some Internal Human Systems.* (*NASA Contractors Rep.* CR-219, May 1965, p. 29–50, 79–89. Available from NTIS, Springfield, VA.)
18. IBERALL, A., AND S. CARDON. Oscillatory processes in biology. *Biophys. J. Soc. Abstr.* 8: MD1, 1968.
19. IBERALL, A., AND A. SCHINDLER. On a physical basis of a theory of human thermoregulation. *Trans. ASME Ser. G J. Dyn. Syst. Meas. Control.* 95: 68–75, 1973.
20. LENFANT, C. Time-dependent variations of pulmonary gas exchange in normal man at rest. *J. Appl. Physiol.* 22: 675–684, 1967.
21. PRYZBYLIK, A., G. MARTIN, AND N. SPECTOR. A method for the continuous measurement of core temperature in small animals. *Ann. Biomed. Eng.* 5: 122–129, 1977.
22. WEITZMAN, E., J. ZIMMERMAN, C. CZEISLER, AND J. RONDA. Cortisol secretion is inhibited during sleep in normal man. *J. Clin. Endocrinol. Metab.* 56: 352–358, 1983.