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Revisiting concepts of thermal physiology: understanding negative feedback and set-point in mammals, birds, and lizards

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Abstract

The thermoregulatory system of homeothermic endotherms operates to attain thermal equilibrium, that is no net loss or gain of heat, where possible, under a thermal challenge, and not to attain a set-point or any other target body temperature. The concept of a set-point in homeothermic temperature regulation has been widely misinterpreted, resulting in such confusion that some thermoregulation specialists have recommended that it be abandoned. But the set-point concept has enjoyed a resurgence in a different domain, lizard microclimate selection. We review the principles of thermoregulation in homeotherms, endorse a negative feedback system with independent set-points for individual thermo-effectors as its core mechanism, and address the misconceptions about homeothermic set-point. We also explore the concept of set-point range in lizard microclimate selection and conclude that there is substantial convergence between that concept and the set-points of homeothermic thermo-effectors, as thresholds. In neither homeothermic nor lizard thermoregulation is the concept of a unitary set-point appropriate. We review the problems of measuring the set-points for lizard microclimate selection. We do not believe that the set-point concept in thermoregulation should be abandoned just because it has been misinterpreted by some users. It is a valid concept, identifying the threshold body temperatures at which regulatory thermo-effectors will be activated, to aid in attaining thermal equilibrium.

Key words: thermoregulation, body temperature, homeothermy, poikilothermy, hypothalamus, transfer function, evaporative cooling, microclimate selection, proportional control, shuttle box.

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I. INTRODUCTION

The stability of resting core temperature (see Table 1 for definitions of biological temperatures) in mammals and birds often is portrayed as an example of Claude Bernard's stable *milieu intérieur* or Walter Cannon's homeostasis (Modell *et al.* 2015). Despite large thermal challenges, from the environment or through changes in metabolic heat production, the core temperature of mammals and birds is remarkably stable, within and between individuals. Consequently, mammals and birds are considered homeothermic, even though not all are (e.g. naked mole-rat *Heterocephalus glaber*; see Buffenstein & Yahav, 1991). The level at which core temperature is held stable in homeotherms depends on time of day, because in most mammal and bird species, but again not all (e.g. Cape mole-rat *Georychus capensis*; Lovegrove & Muir, 1996), core temperature displays a circadian rhythm (Refinetti, 2020). The peak-to-trough range of the circadian rhythm typically is less than 2 °C in free-living large mammals without physiological stress (Hetem *et al.*, 2016; Maloney *et al.*, 2019), but is closer to 3 °C in smaller mammals (Mortola & Lanthier, 2004), and in birds (Prinzinger, Preßmar & Schleucher, 1991). The 24 h average, or the mesor of the circadian rhythm, of core temperature is not identical in all mammals and birds. It varies phylogenetically, tending to be higher in birds than in mammals (Gavrilov, Golubeva & Bushuev, 2023; Prinzinger *et al.*, 1991) and, within large mammals, to be higher in ruminants than in carnivores (Fuller *et al.*, 2016). It also varies allometrically, for example decreasing with body mass among large terrestrial herbivores (Hetem *et al.*, 2016) and in birds (Prinzinger *et al.*, 1991), but apparently not in all orders of mammals and birds (Clarke & Rothery, 2008). Nevertheless, the 24 h average of core temperature among different species of free-living mammals and birds, not under stress, lies in the range of about 34 to 42 °C, and placental mammals, loosely, often are said to have a core temperature of ~37 °C.

When they can do so behaviourally, several species of larger lizards, especially in the Iguanidae and Teiidae, select environments in which field active core temperatures cluster near to 37 °C (see, for example, DeWitt, 1967; Sanders *et al.*, 2015), although there is a large variation between lizard families (Clusella-Trullas & Chown, 2014). Indeed, a phylogenetic analysis of 1721 species of land tetrapods showed no significant difference between the body temperatures of field-active endotherms and ectotherms, and the temperatures of the Iguanidae and Teiidae overlapped with those of birds (Moreira, Qu & Wiens, 2021). Based on isotopic analysis of fossil teeth, the core temperature of large Jurassic dinosaurs also was 36–38 °C (Eagle *et al.*, 2011). There seems

to have been convergent evolution towards a core temperature near to 37 °C in terrestrial vertebrates when they are thermoregulating, though there clearly are many exceptions amongst ectotherms, for example nocturnal geckos (Huey *et al.*, 1989) and diurnal Australian elapid snakes (Lillywhite 1980), and even within families of mammals (McGowan *et al.*, 2020).

The advantage of a core temperature near to 37 °C is unknown. One suggestion has been that 37 °C simply was the temperature of the ocean from which terrestrial vertebrates emerged, and so was the temperature at which their biochemistry evolved. But vertebrates invaded the land in the late Devonian, when sea surface temperature was estimated to be about 30 °C (Joachimski *et al.*, 2009). The first mammals, small, insectivorous and nocturnally active, could have been homeothermic and indeed likely had a core temperature closer to 30 °C than to 37 °C (Crompton, Taylor & Jagger, 1978).

Another puzzle is why the body temperature of mammals and birds needs to be regulated at all. An explanation that is advanced frequently is that enzymatic, neurochemical, and other biochemical reactions function most efficiently at a high and stable temperature (Heinrich, 1977; Tan & Knight 2018; Tattersall *et al.*, 2012). However, if there had been the required selection pressure, there has been ample time for enzymes and neurochemical processes to have evolved to function adequately across a range of temperatures. Indeed, homeotherms are far outnumbered in the animal kingdom by poikilotherms that prosper without their biochemistry being held at a stable temperature. Presumably, though, if homeothermy had no advantages, endothermic homeotherms would not invest in the high physiological cost that is necessary to sustain it (Crompton *et al.*, 1978; Grigg, Beard & Augee, 2004), and those large lizards never would bother to maintain their core temperature stable for hours during the day. In some ectotherms, core temperature is regulated at temperatures close to their critical thermal maximum (Hamilton 1973; Heinrich 1977; Seely, Roberts & Mitchell, 1988). High and stable body temperature may benefit animals by allowing them to be active and escape predation at any ambient temperature (Heinrich, 1977; Montgomery & MacDonald, 1990), may improve rate of digestion in lizards (Alexander, van Der Heever & Lazenby, 2001; Harlow, Hillman & Hoffman, 1976) and snakes (Greenwald & Kanter, 1979; Tattersall *et al.*, 2004), may enhance reproductive success (Farmer, 2003), and may reduce susceptibility to pathogens (Evans & Cowles, 1959; Robert & Casadevall, 2009). Under the “hotter is better” hypothesis, some argue that warm-adapted genotypes will always outperform cold-adapted genotypes because chemical

Table 1. Temperatures of animal bodies and their surroundings.

Temperature ^a	Definition
Measured body temperatures	
Core temperature (T_{core})	Mean temperature of the internal tissues of the cranium, thorax, abdomen, and deep muscle, regions that are well perfused by arterial blood. Synonymous with “deep-body temperature”. In practice, usually it is represented by the temperature of one of the core tissues (IUPS, 2001).
Shell temperature	Mean temperature of tissues peripheral to the core. There is no convenient way to measure shell temperature so often it is approximated as skin temperature.
Skin temperature (T_{skin})	Mean temperature of the sentient skin surface, usually estimated as the weighted average of skin temperatures at a limited number of sites.
Surface temperature	Mean temperature of the outer surface of an animal, the surface that is involved in conductive, convective, and radiant heat exchange. This temperature may be the same as T_{skin} in naked animals, but not in animals with a pelage, scales, or feathers.
Subcutaneous temperature	The temperature in the tissue immediately below the skin.
Brain temperature	The mean temperature of the contents of the cranium.
Hypothalamic temperature	The temperature in or near the hypothalamus, considered to be the site of important temperature receptors and important integrating neurons in thermoregulatory neural networks.
Oesophageal temperature	Temperature in the oesophageal cavity. Oesophageal temperature at the level of the heart is considered the best external approximation of core temperature in humans (Brown & Brengelmann, 1970).
Rectal temperature	Temperature in the deep rectal cavity of mammals.
Vaginal temperature	Temperature in the deep vaginal cavity of mammals.
Cloacal temperature	Temperature in the deep cloacal cavity of birds and reptiles.
Gastrointestinal tract temperature	Temperature in the deep gastrointestinal tract, increasingly measured using ingested thermometers.
Tympanic membrane temperature	Temperature of the tympanic membrane, considered, by different researchers, to reflect either T_{core} or brain temperature, although it can differ substantially from temperatures at other sites in the body or even in the brain.
Calculated body temperatures	
Mean body temperature ($\bar{T}_b$)	(1) Arithmetic mean of the temperatures of all the tissues of the body, measured calorimetrically. This mean cannot be calculated accurately from any combination of T_{core} and T_{skin} (Snellen, 2000; Jay <i>et al.</i> , 2007), so $\bar{T}_b \neq T_{b*}$ (defined below). (2) The average body temperature of an animal over time. (3) The average body temperature of a group of animals.
Regulated body temperature (T_{b*})	An integrated temperature represented in the feedback signal to the temperature control system, generated by temperature receptors distributed throughout the body. Sometimes simplified as $T_{b*} = wT_{\text{core}} + (1-w)T_{\text{skin}}$, where w is a weighting factor that reflects the relative contribution of core temperature to the signal, and T_{skin} is skin temperature (defined above). The regulated body temperature stabilises when thermal equilibrium is reached (no heat stored in or lost from the body).
24 h maximum core temperature	(1) Highest individual value of T_{core} measured over a 24 h cycle. (2) Zenith of a curve fitted to the T_{core} measured over a 24 h cycle.
24 h minimum core temperature	(1) Lowest individual value of T_{core} measured over a 24 h cycle. (2) Nadir of a curve fitted to the T_{core} measured over a 24 h cycle.
Mesor core temperature	Mid-point T_{core} calculated from a curve fitted to the T_{core} measured over a 24 h cycle.
24 h amplitude of core temperature	(1) Strictly, the difference between the mesor and the maximum or minimum (from a fitted curve of T_{core} recorded over a 24 h cycle). (2) In many papers, what is called “24 h amplitude” or “range” is the difference between the measured peak temperature and the measured trough temperature in that 24 h period, which invariably is larger than twice the amplitude determined from a fitted curve.
Inferred body temperatures	
Selected temperature (T_{sel})	The range of core temperatures voluntarily selected by ectotherms through changes in behaviour.
Preferred temperature (T_{pref})	“The range of core temperature within which an ectothermic animal seeks to maintain itself by behavioural means” (IUPS, 2001, p. 263). Considered synonymous with selected temperature by some experts (e.g. Pough & Gans, 1982), and confined to laboratory measurements by Licht <i>et al.</i> (1966). See Camacho & Rusch (2017) for methods of measurement.
Optimal temperature	Temperature at which a particular physiological process performs optimally. Not the same for all physiological processes, so an organism does not have a single optimal temperature (e.g. Huey, 1982).
Pejus temperatures	The lower and upper body temperatures at which performance begins to decline on a thermal performance curve. See Pörtner (2002) and Miller & Stillman (2012).

(Continues on next page)

Table 1. (Cont.)

Temperature ^a	Definition
Critical thermal minimum	Core temperature at which the performance of a physiological process declines to zero, or an animal dies, because of a lack of heat. Usually applied only to ectotherms, and dependent on rate of body temperature decline.
Critical thermal maximum	Core temperature at which the performance of a physiological process (e.g. righting reflex) declines to zero, or pathological signs (e.g. spasms) set in, or an animal dies, because of an excess of heat. Usually applied only to ectotherms, and dependent on rate of body temperature rise.
Voluntary thermal maximum	Maximum core temperature displayed by a freely behaving ectotherm before moving to a cooler place
Microclimate temperatures	
Ambient temperature	(1) Mean temperature of a gaseous or liquid environment (usually air or water) that surrounds a body, as measured outside the boundary layer that overlays the body (IUPS, 2001, amended). In an air environment, this temperature is synonymous with air temperature. (2) Like room temperature, ambient temperature sometimes is used casually, and inaccurately, to describe the overall thermal effect of the prevailing environment.
Air temperature	Ambient temperature in an air environment shielded from radiation. More accurately “dry-bulb temperature”. By definition the thermometer measuring air temperature should be shielded from all radiation (Nakamura & Mahrt, 2005), but commonly used naturally ventilated radiation shields do not exclude all radiation.
Wet-bulb temperature	Lowest temperature to which air can be cooled by the adiabatic evaporation of water (IUPS, 2001). Under a prevailing wind regime, it is called “natural wet-bulb”. With forced ventilation it is called “ventilated” or “psychrometric” wet-bulb temperature. The natural wet-bulb temperature typically is higher than the ventilated wet-bulb temperature. Ventilated wet-bulb temperature can be calculated from dry-bulb temperature and relative humidity, but natural wet-bulb temperature cannot be calculated accurately in this way.
Globe temperature	The temperature at the centre of a matt-black hollow sphere, originally 150 mm diameter (Vernon, 1932), responsive to ambient dry-bulb temperature, radiation, and wind speed, and used to measure mean radiant temperature. Many other globe diameters have been used (see Mitchell <i>et al.</i> , 2024)
Mean radiant temperature	The temperature of an imaginary isothermal black enclosure that would exchange radiant heat with the object under test at the same rate as the actual environment.
Lower critical temperature	The lower limit of the thermoneutral zone.
Upper critical temperature	The upper limit of the thermoneutral zone, sometimes defined by increasing basal metabolic rate but more appropriately by an increase in evaporative cooling (see Mitchell <i>et al.</i> , 2018).
Operative temperature	“Temperature of a uniform (isothermal)” “black” enclosure in which a solid body or occupant would exchange the same amount of heat by conduction, convection, and radiation as in the actual non-uniform environment” (IUPS, 2001, p. 269). Alternatively and equivalently, “temperature of an inanimate object of zero heat capacity with the same size, shape and radiant properties as the animal exposed to the same environment” (Bakken & Gates, 1975, p. 261).

^aAbbreviations are given where they are used elsewhere in the text.

reactions will always be slower at low temperature, regardless of the temperature to which a species is adapted (Angilletta *et al.*, 2010; Pawar *et al.*, 2024). Experimental evidence does not always support the “hotter is better” hypothesis, though (e.g. Pietruszka, 1988; Ward, 1991).

Stable core temperature does not necessarily imply physiological regulation. The core temperature of the Antarctic icefish *Chaenocephalus aceratus* varies less than does that of large mammalian homeotherms, because it lives permanently in isothermal sub-zero sea water (Cheng & Detrich, 2007). Large vertebrate ectotherms may exhibit stable core temperatures, even in thermally variable environments, simply by virtue of their thermal inertia (Bicego, Barros & Branco, 2007; Harlow *et al.*, 2010; Nakamura, Matsumoto & Sato, 2020; Sato, 2014; Seebacher, Grigg & Beard, 1999). However, that core temperature is stable for species of different sizes under different environmental circumstances implies some form of active regulation by them.

While we may be uncertain about why core temperature is held stable, we know more about how it is held stable. The process of stabilising core temperature is not equivalent to setting the thermostat of a domestic air conditioner at a pre-determined fixed temperature, or to setting the cruise control of a vehicle at a fixed speed (Stone, Celi & Csete, 2015). Thermal challenges that cause body temperature to deviate elicit an array of corrective responses, behavioural and autonomic, which add thermal energy to the body or remove thermal energy from it, or redistribute the thermal energy within the body, processes aimed at attaining a state of thermal equilibrium, in which thermal energy is neither being gained nor lost. Provided that the environment is compatible with achieving a state of thermal equilibrium (said to be “compensable”) body temperature will re-stabilise at a new level. That level may be above or below that animal’s temperature when it is not challenged thermally. Except in pathological states, this array of

corrective responses can be controlled closely over a wide range of thermal challenges.

More than 50 years ago, James D. Hardy (Hardy, 1961, 1965) and then others (e.g. Wyndham, 1965; Wyndham & Atkins, 1968; Hammel, 1968) proposed a theoretical framework that described how temperature responses were organised in endothermic homeotherms, with a focus on humans. Those pioneers pointed out that these responses conformed to a negative feedback model of “systems engineering” or “control theory” (Carpenter, 2004). If body temperature (the “regulated variable” of thermoregulation) rises or falls, the control system institutes reactions that arrest the rise or fall. Picking up from Hardy (1961), James Heath transferred the framework to lizards (Heath, 1965). Indeed, in Heath’s view the control of behavioural thermo-effectors in ectotherms conformed better to the framework than did the control of autonomic thermo-effectors in mammals (Heath, 1970).

Incorporated within the negative feedback model was the concept of a set-point temperature, the base from which the deviations occurred. The set-point concept allowed ready explanation of seemingly incongruous physiological events in the regulation of body temperature. For example, elevation of the set-point temperature during fever provided a framework for explaining why a febrile mammal could shiver, or seek a warmer microclimate, when its body temperature already was elevated above normal. Oscillation of the set-point temperature provided a framework for explaining why mammals and birds, which are perfectly capable of preventing the deviations of body temperature, exhibit circadian rhythms of core temperature (e.g. Wenger *et al.*, 1976). Reduction of set-point temperature was advanced as a plausible explanation for mammals achieving a low but stable core temperature during hibernation and torpor (Nedergaard & Cannon, 1990). Depression of the set-point temperature provided a framework for explaining why women would sweat and vasodilate before body temperature changed during a menopausal hot flush (Kronenberg & Downey, 1987). However, the concept of a set-point soon would become distorted or misunderstood by some who sought to use it. Those pioneers who introduced the concept of a set-point into the field of thermoregulation, and so opened so many doors, could not have predicted that some contemporary experts in thermal physiology soon would reject the concept entirely. Indeed, a few actually would reject the idea that body temperature is regulated by a negative feedback system in homeotherms (see Section (1)).

Researchers in lizard thermal biology were well aware of negative feedback models of thermoregulation (e.g. Heath, 1965, 1970; Huey, 1982) but some seemed to use the term “set-point” in a way different to how the experts in control theory applied it to thermoregulation. For example, in lizards, Barber & Crawford (1977) considered “set-point” to be synonymous with “limit temperature” for thermoregulatory behaviour. In this review we will discuss the various ways that the term “set-point” has been defined and used, and we hope to demonstrate congruence between the control theory experts and lizard thermal

biologists. We also intend to identify where the concept of set-point has been misused. We shall endorse negative feedback as a fundamental process in the regulation of body temperature.

II. NEGATIVE FEEDBACK: NOT AN OBSOLETE CONCEPT IN THERMOREGULATION

(1) The historical master controller

The original negative feedback models of temperature regulation were simple and elegant. A “master controller” received a feedback signal from the body temperature that was to be regulated. That regulated temperature usually was assumed to be hypothalamic temperature. The master controller coordinated the full array of thermo-effectors (thermoregulatory control actions) when the regulated temperature deviated from a reference value, programmed into the controller. That reference value was called the “set-point” of the master controller. According to Kanosue *et al.* (1997), Roberts & Mooney (1974) were the first to question the idea of a master controller, that is a single controller that commanded all the thermo-effectors. A few years later, Satinoff (1978) proposed that, instead of a master controller, there are multiple negative feedback loops that work in hierarchical concert, each responsible for a different thermo-effector. For example, in lizards, microclimate selection would have its own control circuit, as would panting.

Further criticisms of the original “master controller” model emerged over the years, eventually resulting in the conclusion that the concept of set-point was confusing, misleading, unnecessary or fallacious, and should vanish (Kanosue *et al.*, 2010; Romanovsky, 2007; Werner, 1980, 2010). Others went further, to conclude that negative feedback was not the most efficient way to regulate body temperature (Ramsay & Woods, 2014; Somjen, 1992). Some went as far as saying that the entire control theory approach was irrelevant to physiological thermoregulation (Ramsay & Woods, 2016). According to Ramsay & Woods (2016, p. 361), the control theory approach has been responsible for “inserting terms such as error signals, set points, and central controllers, concepts that we, like many others, believe do not appropriately apply to physiological regulation, and that have misled several generations of scholars”.

In this review, we contend that not all scholars have been misled, that the control theory model of thermoregulation remains valid and useful, and that the primary physiological process of body temperature regulation is negative feedback control. We also contend that the model, and particularly the concept of set-point, needs to be revisited, because, far from vanishing in the face of criticism, the concept of thermoregulatory set-point has experienced a resurgence in thermal biology, driven largely by its incorporation into a model of behavioural thermoregulatory efficiency in lizards. In that resurgence, the term “set-point range” was used, and assigned to a range of stable body temperatures achieved by microclimate selection in a cohort of lizards, originally

by Hertz, Huey & Stevenson (1993) and later by other researchers (e.g. Corkery, Bell & Nelson, 2018; Kirchhof *et al.*, 2017; Sagonas *et al.*, 2017). During our review we address how the set-point range of Paul Hertz, Ray Huey, and Robert Stevenson, derived statistically, relates to the set-points in the control theory models of thermoregulation. Hertz *et al.* (1993) cited Heath (1965) but did not pursue the control theory model of lizard thermoregulation that he described, because they were concerned with the ecological significance of microclimate selection rather than with the underlying control mechanisms.

Scholars who have been exploring lizard thermal biology and those who mechanistically have been examining thermoregulatory systems have tended to operate in different domains. The degree to which the domains have differed is illustrated in Fig. 1. We considered citations, from *Web of Science* since 1993 (to normalise to the latest reference used), to four classic papers. First was Hammel's (1968) foundation review about set-point in control theory with, at the time of our search, 864 citations. We did not use Hardy's (1965) seminal paper because it was a book chapter that had far fewer citations within the same time window (33 citations). Second and third were Barber & Crawford's two classical papers (1977 and 1979) that provided a control-theory assessment of behavioural thermoregulatory control in reptiles and defined the "set-point range", with 131 citations. The final paper was Hertz *et al.* (1993) that employed, for ecological purposes, the concept of a set-point range based on microclimate selection by lizards, with 941 citations. We performed an analysis of overlap of the citations to each study, to examine how many studies that cited any one of those classic papers also cited one or more of the other papers. There was remarkably little overlap between any two pairwise comparisons. Only one paper cited all of the keynote papers and

only seven (of 1030) papers that cited the papers on set-point in the context of lizard thermal biology also cited Hammel's foundation paper on set-points.

So the thermal biologists, working later, who cited the concept of a set-point range based on microclimate selection as introduced by Hertz *et al.* (1993) rarely have cited mechanistic papers on thermoregulatory control theory. Similarly, those working on thermoregulatory control theory rarely have cited ectotherm work, a behaviour of authors that Firth & Turner (1982, p. 259) called "mammalian chauvinism". It could be that researchers in the different domains have asked different research questions, and so have required a different literature base. However, we believe that the disconnect between researchers in different domains is an obstacle to our understanding of how a stable body temperature is achieved, across the animal kingdom. Those studying set-points for sweating in humans have much to learn from the selection of body temperature in lizards, and *vice versa*. We hope to help overcome that divide. Much of what we shall say about lizard thermoregulation may apply to other terrestrial vertebrate ectotherms, but the concept of a set-point as a stable body temperature achieved by microclimate selection seems to have been applied so far only to lizards.

In the construction of their model of behavioural thermoregulatory efficiency, Hertz *et al.* (1993) measured the final core temperature that *Anolis* lizards attained when the lizards were allowed to move freely in a thermal gradient in the laboratory, and they called the central core temperature range that was selected the "set-point range". We hope to show that the set-points of their set-point range are compatible, in principle, with the concept of set-point that was incorporated in control-theory models of negative feedback regulation of body temperature. Those models were derived for homeothermic endotherms and could apply to ectotherms only while those ectotherms are regulating body temperature, which they do not do all of the time. Because set-points are constructs of negative feedback control, assigning a set-point range to lizard thermoregulation implies that lizard thermoregulation adheres to the essential features of negative feedback regulation of body temperature. Our first task will be to describe what those essential features are, more than 50 years after they first were invoked, and in the face of many contemporary misconceptions. We have to identify what "set-point" means in control theory before we can analyse how it relates to the statistical set-point range used for lizards. That task requires dealing not just with multiple negative feedback loops, but also with the concept of proportional control, and uncertainty about what the regulated body temperature is. We shall conclude that there is remarkable convergence, in principle, between the concept of set-point introduced by Hardy (1965) and that employed by Hertz *et al.* (1993). Shared processes underly the domains that seem not to overlap (Fig. 1).

A contemporary depiction of the original "master controller" model of body temperature regulation is presented in Fig. 2, showing how feedback elements (thermosensitive neurons) activate thermoregulatory control actions (thermo-effectors)

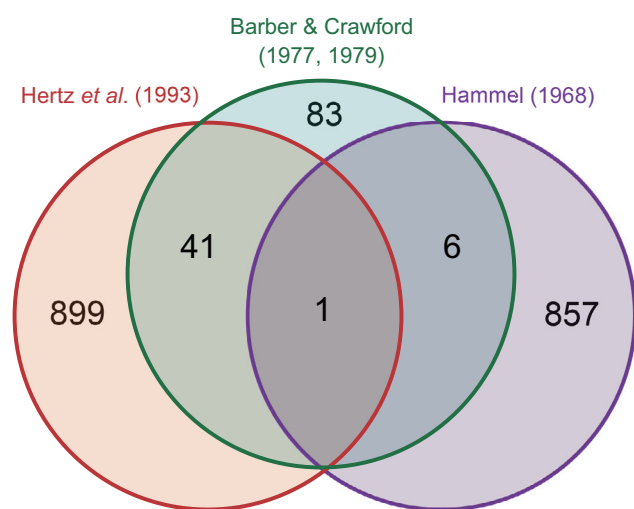


Fig. 1. Overlap in citations (post 1993) to four keynote papers concerned with thermoregulatory set-points. Citations to the two papers by Barber & Crawford are merged. Only Camacho & Rusch (2017) cited papers from all three domains.

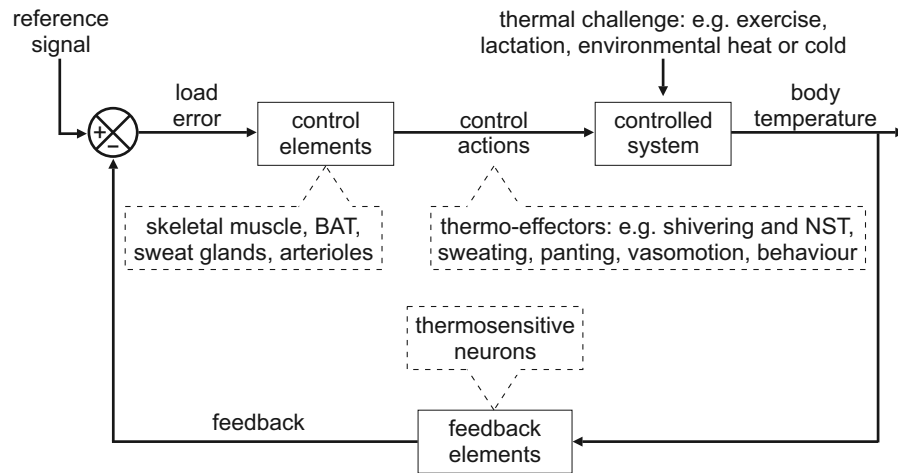


Fig. 2. Contemporary depiction of the historical “master controller” negative feedback model of body temperature regulation. Body temperature is detected by thermosensitive neurons and compared to a stable reference temperature. Deviations in body temperature under a thermal challenge generate a load error that activates the thermo-effectors. The thermo-effectors adjust the generation, exchange, and distribution of body heat, in a manner that opposes further deviations of the body temperature from the reference temperature, the “set-point” of the control system. The thermoregulatory system operates as a negative feedback system; the thermo-effector responses are corrective. If the activation of thermo-effectors is successful, body temperature will stabilise at a new value. The system will maintain the activity of the thermo-effectors at the level necessary to restabilise body temperature in the presence of the thermal challenge, and that level cannot be at the set-point (at which thermo-effectors would be inactive). In control theory terminology, thermal challenges are “disturbances” to the system. BAT, brown adipose tissue; NST, non-shivering thermogenesis. Original versions of the model (e.g. Bullard *et al.*, 1967; Mitchell *et al.*, 1972) lack some of the detail included here.

when body temperature deviates from a reference temperature, in a manner that arrests the deviation. In the historical model, that reference temperature defined the “set-point” of the control system. A physiological device was thought necessary to establish a set-point for the master controller. As Benzinger (1969, pp. 747–748) put it, “As an object of physiological reality and significance the set point must be defined as a temperature-dependent property of a definable anatomical or histological substrate”. Though most thermal physiologists now reject the master controller concept, and especially the need for a reference signal, we can use the model to address some issues concerning the physiological regulation of body temperature. In the words of another pioneer, John Brobeck, “it permits us to talk about phenomena for which we previously had no vocabulary” (Brobeck, 1965, p. 13).

There was evidence, apparently convincing at the time, that the thermoregulatory system in homeotherms was dedicated to the regulation of hypothalamic temperature (Benzinger, Pratt & Kitzinger, 1961; Hammel, 1965). Within the hypothalamus, neurons had been described that changed firing rate when hypothalamic temperature was changed experimentally, and others that did not change firing rate with a change in temperature (Griffin, Saper & Boulant, 2001). It seemed logical that those temperature-insensitive neurons of the anterior hypothalamic/preoptic area provided the neural substrate for a reference signal (Hardy, 1965).

The hypothalamus is exquisitely thermosensitive in many species, including in ectotherm species that have been studied (Boulant & Dean, 1986; Hammel, Caldwell & Abrams, 1967).

In mammals, the full range of autonomic thermo-effector actions that normally would be exhibited under heat or cold stress can be elicited by changing the hypothalamic temperature by about 1 °C (e.g. Van Someren *et al.*, 2002). There is an anomaly, though, originally highlighted by Bligh (1966) and still not understood more than half a century later (Notley, Mitchell & Taylor, 2023a): the hypothalamus responds, by implementing appropriate thermo-effector actions, to small (tenths of a degree) experimental manipulations of its temperature, but, at times, *in vivo*, will ignore deviations of greater magnitude. For example, unrestrained pigs exhibited frequent spontaneous deviations of hypothalamic temperature of 1 °C without any apparent thermo-effectors being activated (Fuller, Mitchell & Mitchell, 1999).

As well as containing temperature-sensitive and temperature-insensitive neurons (for review see Romanovsky, 2018), the hypothalamus was considered also to house the downstream neurons that activated the thermo-effectors (see Boulant, 2000; Nagashima, 2006). The hypothalamus is not the only region of the central nervous system that is involved in the integration of thermoregulatory signals. Within the brain, for example, the thalamus processes sensory information from temperature receptors, and the raphe nuclei process information ascending to, and descending from, the hypothalamus (Cristina-Silva, Gargaglioni & Bicego, 2021; Gordon & Heath 1986; Madden & Morrison, 2019). The spinal cord also contains functional temperature receptors (Brock & McAllen, 2016; Thauer, 1970) and, provided it is in communication with the brain, has substantial integrating power in the thermoregulatory system (Simon, 1974). The cardinal role

attributed to the mammalian hypothalamus in the late 1960s was endorsed at the time by evidence that the hypothalamus played the same key role, as both a site of thermosensitivity and as a site that generated thermo-effector responses, not just in mammals but in some birds (Richards, 1970) and in the thermoregulation of some ectotherms, notably lizards (Berk & Heath, 1976; Cabanac, Hammel & Hardy, 1967). Its thermoregulatory functions therefore extended to vertebrates other than homeothermic mammals and birds.

But evidence was available, even in Benzinger's time, that hypothalamic temperature could not be the only body temperature that is regulated. In the late 1960s, working in the field of mammalian comparative physiology, C. Richard Taylor (Taylor, 1966) discovered the phenomenon of selective brain cooling. Selective brain cooling is a process, available to some mammals, by which the hypothalamus, which is normally a few tenths of a degree warmer than the carotid arterial blood destined for the brain (Maloney, Mitchell & Blache, 2007), is cooled temporarily to below the temperature of that arterial blood. Researchers, like Benzinger, who then were investigating thermoregulatory systems, apparently did not become aware of Taylor's work, even after the mechanism was explained by Baker & Hayward (1967). The phenomenon was considered by Taylor, and many others subsequently (see Mitchell *et al.*, 2002), to be a mechanism to protect brain tissue from thermal damage, particularly during exercise, but is now known to be a mechanism for fine-tuning the hypothalamic control of evaporative cooling (Jessen, 2001; Strauss *et al.*, 2017). During selective brain cooling, the hypothalamic temperature can be reduced without affecting other deep-body temperatures (Baker & Hayward, 1967). Because animals at thermal equilibrium can have a variable hypothalamic temperature, hypothalamic temperature cannot be the only temperature that is regulated.

As the hydraulic model in Fig. 3 demonstrates, the maintenance of a variable at a regulated value (in this case the water level) is perfectly possible without a reference signal, contrary to the views of those who introduced the master controller model of thermoregulation (Fig. 2). It is now accepted widely that physiological thermoregulation does not require any neuronal circuit that generates a reference signal (reviewed by Romanovsky, 2018; Werner, 2010). In the model of Fig. 3B, a positive challenge, in this case additional water flowing into the tank (analogous to an additional heat load in thermoregulation), will result in the progressive opening of the outlet valve, until the flow out exactly balances the additional flow in. Then the water level in the tank will stabilise, but at a new higher level (analogous to a stable higher body temperature), necessary to keep the outlet valve open. Similarly, Fig. 3C shows what happens if a challenge results in water leaking out of the system; the system will stabilise at a new, lower, water level by admitting water (analogous to heat loss in the cold compensated by increased metabolic heat production). If the challenges cease (e.g. if the leak stops), the tank will revert to its original water level.

The processes of Fig. 3B, C illustrate an important principle of negative feedback control, namely that when the

system is challenged, the value of the regulated variable must deviate, and remain deviated, if equilibrium is to be achieved. It is not possible to be at thermal equilibrium under a thermal challenge and to be “normothermic” (Werner, 1978, 2010). Body temperature must rise to induce panting, and remain elevated to sustain panting. As Houdas *et al.* (1978, p. 16) put it, for thermoregulation, “The adequate response of the thermal controller is not the re-establishment of the initial level of the activity of the thermoreceptors, but the equalization of the loss and the gain, so that the heat storage rate becomes zero.... this is an experimental fact and not a hypothesis”. The outputs of the system cannot be at their basal values so the inputs cannot be at their thresholds (Kanosue *et al.*, 2010; Werner, 2010). To keep a motor vehicle going at constant speed up a steep incline requires the gas pedal to remain depressed, so not at its basal value. Endotherms are under a permanent thermal challenge, because they are always making heat as a by-product of their metabolism. They have to dissipate that heat if thermal equilibrium is to be achieved and their body temperature is to be stable. Consequently, endotherms never operate at, nor do they seek to attain, a set-point temperature, because one or more heat-loss thermo-effectors always has to be above threshold. We do not agree with Mekjavić & Eiken (2006, p. 2067) when they say “The controlling system attempts to minimize the error signal [our ‘load error’], thereby ensuring regulation of deep body temperature at a set point”. Restoring body temperature to the set-point of a thermo-effector would shut down that thermo-effector. Similarly, we do not agree with Firth & Turner (1982, p. 232) that the “fundamental problem” of thermoregulation is “to balance the various modes of heat exchange so that a given body temperature is maintained or achieved”. Stable body temperature must vary with the magnitude of the thermal challenge.

In the language of control theory, the new stable temperature that is attained is the “operating point” (Fig. 4). It is the body temperature at which the thermo-effector compensates the thermal challenge exactly, and so results in a new thermal equilibrium (e.g. Tansey & Johnson, 2015). In that context, the “balance point” terminology favoured by Romanovsky (2007) is a descriptive alternative to the operating point, not to the set-point (Werner, 2010).

In the hydraulic model depicted in Fig. 3, the gain (sensitivity) of the control system is determined by the length of the levers that extend from the valves to the floats. Changing the length of a lever, analogous to changing the slope of the line in Fig. 4, necessarily will change the water level at which a balance between input and output is achieved. In a physiological analogy, when humans become acclimated to heat, the gain of the sweating response increases (Notley Mitchell & Taylor, 2024b; Wyndham, 1967), and so the regulated body temperature will deviate less under heat load before thermal equilibrium is achieved, than it would have before acclimation.

The hydraulic model depicted has a single mechanism for responding to a challenge, namely the opening of a valve. The thermoregulatory system has many mechanisms that

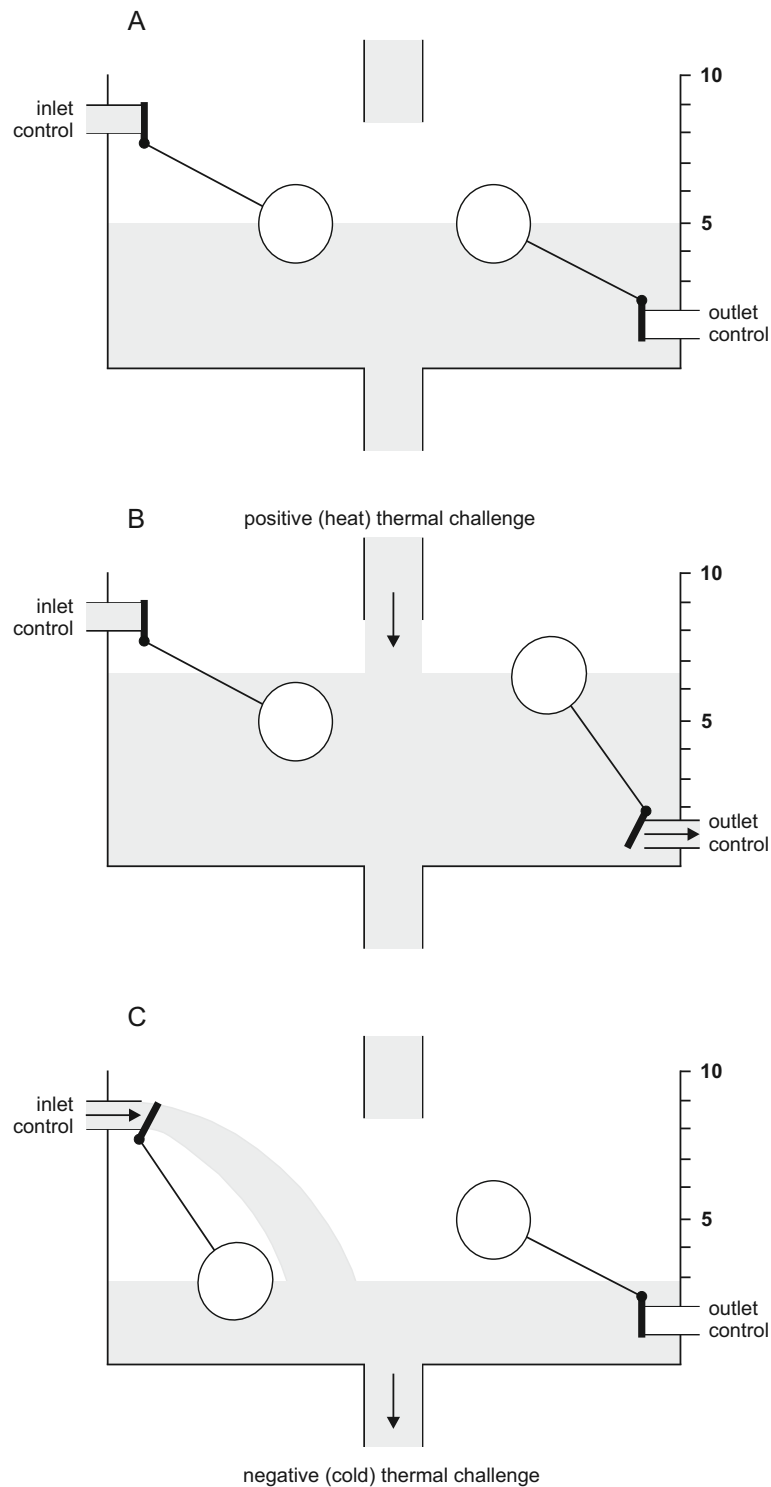


Fig. 3. A hydraulic model of negative feedback regulation, with water level as the regulated variable (equivalent to “body temperature” in Fig. 2), levers and floats as feedback elements, and inlet and outlet valves as control elements (equivalent to the sweat glands, brown adipose tissue, etc., in Fig. 2). In A, the system is at equilibrium with a constant water level because there is no inflow or outflow. In B, the system is subject to a challenge (water inflow, equivalent to a heat load on the body) that increases the water level (equivalent to an increase in body temperature), and in C to a challenge (leak of water, equivalent to heat loss from the body) that decreases the water level (equivalent to a decrease in body temperature). In both cases, after some time for adjustment, the water stabilises at a new level, different from the level in A, when the challenge is counteracted by the action of the control
(Figure 3 legend continues on next page.)

act in concert, to respond to a challenge. There are many thermo-effectors, for example escape behaviour, peripheral vasodilatation, and sweating, as responses to heat load. The value of the regulated variable at which each effector first is activated (the set-point or “threshold”, see Section (2)) is not necessarily the same for different effectors. That phenomenon creates an “inter-threshold zone” (Notley, Mitchell & Taylor, 2024a; Taylor & Gordon, 2019), often called a “dead band” in control theory. This phenomenon led to what Bligh (1966) called “broadband control”. As we shall see, the inter-threshold zone is analogous to the dual set-points described for lizards by Barber & Crawford (1977, 1979).

(2) Transfer functions, set-point and gain

Thermoregulatory systems are far more complicated, as we have said, than the simple hydraulic model depicted in Fig. 3, and even than the “master controller” model of Fig. 2. Figure 4 shows the “transfer functions” for the control of two representative thermo-effectors. Transfer functions are the quantitative relationships between the outputs (the thermo-effectors of Fig. 2) and the inputs to that controller (“body temperature” in Fig. 2). For all homeotherm thermoregulatory systems that have been studied, the relationship displays a progressive change of thermo-effector activity with progressive deviations in body temperature, like that depicted in Fig. 4. The more that the body temperature deviates from the set-point, the more the thermo-effector is activated. In the language of control theory, this type of control is called “proportional control”.

There is no expectation that transfer functions should be linear in biological systems. Indeed, they are likely to be sigmoid. However, over the range of body temperatures typical of thermoregulatory systems, they often are not distinguishable, statistically, from a linear relationship (see Tattersall & Milsom, 2009). So the transfer functions usually are expressed algebraically as $R - R_0 = \alpha (T_b - T_{b0*})$. Indeed, that was the format of the transfer function described by Heath (1965) for control of the body area that lizards of the genus *Phrynosoma* exposed to direct sunlight. The two examples of such linear relationships shown in Fig. 4 allow us to

define set-point and other terms. The basal value of a thermo-effector (R_0) can be zero, for example when R represents the evaporative cooling rate *via* sweating, or not zero, for example when R represents rate of thermogenic metabolic heat production. In Fig. 4A, R_0 then is the rate of resting metabolic heat production, and increases in R derive from shivering or non-shivering thermogenesis. The coefficient, α , is the slope of the line in each relationship, as each thermo-effector is activated by deviation from its set-point. The slope represents the gain (or sensitivity) of the control system for that thermo-effector.

In control theory terminology, the term “set-point” has just one definition, as depicted in Fig. 4. That definition is an algebraic concept (“purely a mathematical concept”, Périard, Eijssvogels & Daanen, 2021, p. 1876), not a physical phenomenon. It is the value of an input variable, in a transfer function, at which the output just becomes activated above the basal level (R_0). In the algebraic expression above, the set-point is T_{b0*} , the breakpoint in the line that describes how R changes with T_b . If the system output on the inactive side of the set-point is zero, as it is for sweat evaporation, then the set-point is equivalent to the threshold of a biological stimulus–response relationship, as pointed out by Huckaba, Downey & Darling (1971) and confirmed by Werner (2010), for whom the preferred terminology indeed is “threshold” not “set-point” (Notley *et al.*, 2023a).

When early models for temperature regulation with proportional control were proposed nearly 50 years ago (e.g. Hensel, 1973; Heller & Colliver, 1974), a set-point was attributed not to individual thermo-effectors, but to the thermoregulatory system as a whole, congruent with the then-prevalent concept of a master controller (Fig. 2). The same set-point was assigned to cold defence and to heat defence. After the “multiple controller” model of Satinoff (1978) was published and began to gain traction, Hammel’s (1965) original concept of a set-point for each individual thermo-effector was revived (e.g. Kanosue *et al.*, 1997; Sagot *et al.*, 1987; Werner, 2010; Wyndham & Atkins, 1968; Romanovsky, 2007, 2018). Although some contemporary researchers criticise the concept of set-point because they still consider it embedded in the now-abandoned construct of a

(Figure legend continued from previous page.)

valves, to match flow in to flow out (equivalent to achieving thermal equilibrium, with thermo-effectors, like sweat evaporation or shivering, balancing heat load or loss). That new level is sustained as long as the challenge continues, and will adjust if the rate of water flow in or leak out changes, but will not restore to the level in A. Opening the valve in B, to counteract the added water, does not restore the water level to that of A. Similarly, sweating during hyperthermia does not restore normothermia while the heat load is ongoing. In the thermoregulatory system, there always would be a small inflow from resting metabolism, compensated by a small outflow, not zero inflow as in the hydraulic model of A. The model also shows how the maintenance of a regulated variable in the face of a challenge does not require any reference signal. There is nothing that sets a target water level, just as there is no structure that sets a target body temperature. The water level comes about because of the interaction of each float with its lever arm and valves. If the length of one of the lever arms is changed, so too will be the level at which the water is regulated. Also, as a negative feedback system, the model compensates for errors. If, under a positive challenge (B), there is a partial obstruction to the response (partial block of the outlet control valve, equivalent to high water vapour pressure inhibiting sweating), water level will rise further (body temperature will rise further in thermoregulation). The rising water level will result in the outlet control valve opening more and more (sweating will increase) until equilibrium is restored. That will be at a higher stable water level (or higher stable body temperature). Based on a simpler version in Mitchell *et al.* (1972).

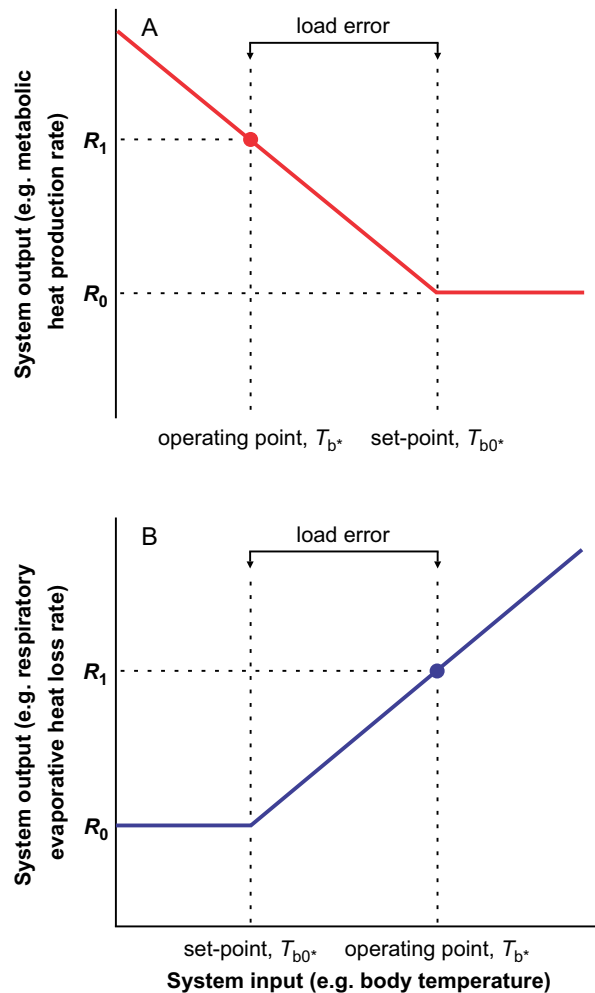


Fig. 4. Graphical depiction of two transfer functions of a negative feedback system with proportional control, as they operate in the regulation of body temperature. The transfer functions (drawn as linear) relate the thermo-effectors of rate of thermogenic metabolic heat production (A) and rate of respiratory evaporative heat loss during panting (B) to the regulated body temperature. R_0 depicts the basal value of each of the two outputs. The body temperatures that correspond to the points of inflection from R_0 (the thresholds) are the “set-points”, and are specific to each thermo-effector. When a cold challenge is imposed, heat will be lost (A), and when a heat challenge is imposed, heat will be gained (B). Body temperature therefore will fall or rise. It will stop falling or rising when it has changed enough to activate an effector response that balances that extra load or loss. R_1 depicts the rate of metabolic heat production (in a system challenged by cold, A) or the rate of respiratory evaporative heat loss (in a system challenged by heat, B) that have been activated just sufficiently to achieve a new thermal equilibrium, arresting further change in body temperature. R_1 thus defines the stable operating points, the body temperatures at thermal equilibrium. The temperature difference between the set-point and the operating point is the load error. In a proportional control system, the load error has to be sustained under a thermal challenge, to activate the thermo-effectors such that thermal equilibrium is achieved.

“master controller”, those researchers need to be reminded that, from the beginning, Hammel described set-points as specific to each thermo-effector (Hammel, 1965; Hellström & Hammel, 1967). Creating a unitary set-point for a “master controller” was an historical aberration.

A great deal of the confusion and mystique that has engulfed the concept of set-point in the context of physiological thermoregulation could have been avoided if researchers, including Hammel himself, had abided by his original definition (Hammel, 1965), with the proviso that we no longer consider hypothalamic temperature to be the sole input to the controller. But many researchers have departed from that definition (see Table 2). Some of these alternative definitions are compatible with the terminology of control theory, but most are not. The rejection of a control theory approach to thermoregulation, which is what Ramsay & Woods (2016) advocated, just because some users have misunderstood its structures is, we believe, unjustified.

(3) The regulated body temperature

Except for saying that it is not hypothalamic temperature alone, we have not identified the “regulated body temperature” input to the thermoregulatory system. In other words, we have not identified what the thermoregulatory system regulates. We cannot yet give it a simple physical identity. Werner (2010) concurs. Little has changed from Henry Cuthbert Bazett’s statement nearly a century ago: “The fact that the direction of temperature change is commonly not the same in different parts of the body makes it questionable as to what should be considered body temperature or even blood temperature” (Bazett, 1927, p. 545). In trying to identify what body temperature is regulated, it is tempting to look for the temperature that is the most stable (e.g. Cabanac, 1975; Ravanelli, Imbeault & Jay, 2020), assuming that this must be the temperature that is regulated. But, as the water bath model of Fig. 5 shows, this argument is fallacious. If, in animals, skin temperature is regulated, then core temperature still would be more stable than skin temperature. We do know that the controller must receive the information that it needs to attain thermal equilibrium for the entire body, but also it presumably must signal changes in the thermal status of individual body regions, and particularly to alert the system to potentially deleterious deviations in the temperature of those parts. Satisfying those requirements necessitates multiple and distributed sensors of body temperature (Jessen, 1985; Werner, 1986). As Hensel (1973, p. 952) pointed out 50 years ago, “the regulatory system tends to maintain the constancy of an integrated value of multiple temperatures more than that of a limited area of the body core”.

Within the mammalian central nervous system there are temperature receptors in the spinal cord as well as the brain (Carlisle & Ingram, 1973; Jessen & Mayer, 1971; Simon, 1974). Outside the central nervous system there are many peripheral temperature receptors in the skin (Romanovsky, 2014; Schepers & Ringkamp, 2010), as well

Table 2. Definitions for thermoregulatory set-point that have appeared in the literature.

<i>Definitions that are consistent with systems engineering/control theory</i>	
The value of hypothalamic temperature at which a thermo-effector departs from its basal value	Hammel (1965)
“That value of the controlled variable at which the control action is zero”	Hensel (1973, p. 987)
“The threshold hypothalamic temperature beyond which corrective responses are activated”	Cabanac (1975, p. 429)
“A threshold temperature that activates/deactivates the intrinsic thermosensitivity of the central T_b regulator”	Tattersall & Milsom (2009, p. 5270)
“Divergence from set point value activates homeostatic control mechanisms”	Kotas & Medzhitov (2015, p. 817)
“In stress, a homeostat senses a discrepancy between afferent information about the regulated variable and the set point for arousing a response”	Goldstein (2019, p. R312)
“The set point is purely a mathematical concept used to describe the thermal control of effector responses...It describes different recruitment stages within the magnitude of a load error, which is the difference between the input and set point”	Périard <i>et al.</i> (2021, p. 1876)
The value of an input variable, in a transfer function at which the thermo-effector just becomes activated. In the thermoregulatory system, the regulated body temperature at which each thermo-effector (e.g. sweating) becomes activated.	This paper, Section (2)
<i>Faulty definitions that identify set-point as a body temperature at which all thermo-effectors are at basal levels of activity; misconception confusing set-point with an hypothetical null point</i>	
“The temperature at which the regulation switches from a cooling action to a heating action”	Hardy (1965, p. 114)
The hypothalamic temperature at response zero	Cited in Nielsen (1969)
“The only pre-optic hypothalamic temperature which does not generate net driving force for heat gain or heat loss”	Heller & Collier (1974, pp. 587–588)
“A null-point core temperature at which effector functions are minimal”	Bligh (1978, p. 2)
“A range of T_b within which no thermoregulatory response is required”	Wang & Lee (1989, pp. 443–444)
The temperature at which heat loss and heat gain effectors are inactive	Cited in Kanosue <i>et al.</i> (1997)
Thermoneutral or null zone	Cited in, and rejected by, Werner (2010)
Body temperature in the endotherm thermoneutral zone	Angilletta <i>et al.</i> (2010)
“When the regulated variable is at a value where all effectors are at minimal or basal levels of activity, this would be considered the null point or null zone and would correspond to what is metaphorically considered as the set point”	Ramsay & Woods (2014, p. 11)
“In humans, 33 °C is the overall thermoneutral set point and temperatures above are sensed as warm and below as cool”	Grajales-Reyes <i>et al.</i> (2024)
<i>Faulty definitions that confuse the set-point with the operating point</i>	
“The value of a regulated variable which a healthy organism tends to stabilize by the processes of regulation”	IUPS (2001, p. 266)
“Regulated level of T_{core} in engineering terminology”	Kanosue <i>et al.</i> (2010, p. 9)
Steady state of body temperature	Cited in, and rejected by, Werner (2010)
A high and relatively constant body temperature (35 to 40 °C being the “set-point”) under diverse environmental conditions	Cited in Huey <i>et al.</i> (2012)
<i>Faulty definitions that confuse a set-point (or threshold) temperature with an optimal or target temperature</i>	
A fixed or constant input which sets the ideal value of the controlled variable	American Standards Association, cited by Hardy (1965)
“Core temperature of homeothermic mammals appears to be regulated at or near to an inherent but variable setpoint”	Maskrey & Bligh (1972, p. 794)
The target level of core temperature	Wenger (1995)
“The value defended by a regulation”	Cabanac (2006, p. 1339)
Innate or predetermined value for the regulated variable	Cited in, and rejected by, Werner <i>et al.</i> (2008)
“The most efficient level of regulation (set point)”	Kanosue <i>et al.</i> (2010, p. 9)
“The most frequently regulated body temperature”	Smit <i>et al.</i> (2013, p. 1142)
The mode of deep-body temperatures in the active phase	Boyles <i>et al.</i> (2013)
A hypothetically optimal level of a parameter that is monitored, maintained and defended (e.g. 37 °C for body temperature)	Cited and rejected by Ramsay & Woods (2014)
“Set point refers to the ‘desired value’ ... The range of values (range of magnitudes) of the regulated variable that the system attempts to maintain.”	Modell <i>et al.</i> (2015, p. 264)
“An optimal value of the regulated variable”	Kotas & Medzhitov (2015, p. 817)

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Table 2. (Cont.)

The body temperature “that coincides with the ideal or optimal temperature for organism function”	Corkery <i>et al.</i> (2018)
“The T_b set point is then defended by mechanisms for heat production or heat loss”	Ruuskanen <i>et al.</i> (2021, p. 2)
Faulty definitions that implicate a neural reference signal; misconception because there is no need, nor any evidence, for a generator of a reference signal	Vendrik (1959)
The intersection of the bell-shaped response curves of cold and warm temperature receptors	Hammel (1968, p. 645)
“The reference activity may be presumed to have a neural basis and may be thought of as transduced from a virtual not real temperature called the ‘set’ temperature”	
“A temperature-dependent property of a definable anatomical or histological substrate”	Benzinger (1969, pp. 747–748)
A neural reference generator that can be inactivated or seriously disturbed by a hypothalamic lesion	Maskrey & Bligh (1972)
The hypothalamic temperature at which the activities of high Q_{10} and low Q_{10} neurons are equal	Heller & Colliver (1974)
An optimum hypothalamic temperature “set” by the intersection of the firing rates of cold and warm temperature receptor populations in the hypothalamus	Lovegrove <i>et al.</i> (1991)
The core temperature at which the influences on heat gain and heat loss of warm-sensitive and temperature-insensitive neurons counterbalance	Benarroch (2007)
Value of a central reference signal	Cited in, and rejected by, Werner (2010)
Set-points are intrinsic properties of skin temperature receptors, which act as thermostats	Kobayashi (2015)

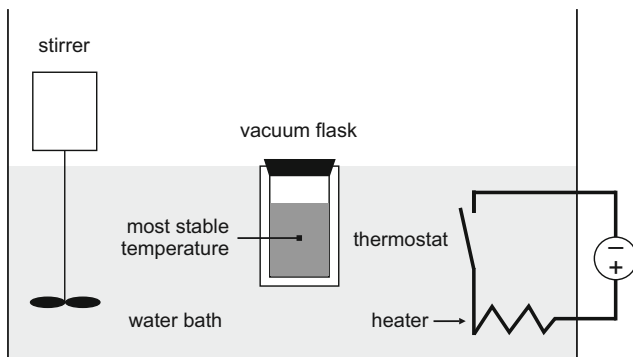


Fig. 5. An insulated flask in a water bath. The bath is warmed by an immersion heater, which is controlled by a thermostat. The temperature of the water bath is measured by the thermostat and a deviation activates or de-activates the heater, so that it is the bath temperature that is regulated. The temperature of the water in the flask is not detected anywhere in the control system, and has no influence on the thermostat, but will deviate much less than will the temperature of the water in the bath. The model illustrates that, in a thermoregulatory system, the most-stable temperature under a thermal challenge is not necessarily the temperature that is regulated actively. Endotherm temperature control systems do not operate as on–off thermostats as depicted here, but the principle about temperature stability applies. Based on Mitchell *et al.* (1972). Note the resemblance between our water bath and the 1887 water bath of The Reverend W. H. Dallinger (Fig. 22.1 of Huey & Rosenzweig, 2009).

as sensors capable of signalling trunk temperature, including intra-abdominal temperature (Riedel, 1976; Van Someren *et al.*, 2002). Peripheral temperature receptors are present in lizards too (Cabanac & Hammel, 1971), and in lizards both hypothalamic temperature and skin temperature contribute to the thermoregulatory feedback signal (Hammel

et al., 1967). In the iguanid lizard *Sauromalus ater* (previously *obesus*), raising hypothalamic temperature *via* an implanted thermode did not induce panting unless the rest of the body core exceeded 38 °C (Crawford & Barker, 1974), confirming that there must be extrahypothalamic temperature receptors in the core. The domestic fowl *Gallus domesticus* (Richards, 1970) and some other bird species (Cristina-Silva *et al.*, 2021) have a hypothalamus with thermosensitivity similar to that of mammals, but some bird species have to rely completely on extrahypothalamic temperature receptors as monitors of core temperature, because they do not display the hypothalamic thermosensitivity of mammals (Mercer & Jessen, 1978; Mercer & Simon, 1984).

The contribution of receptors that measure core temperature, but are outside of the hypothalamus, increases with body mass, so that in small mammals the input signal that represents core temperature derives almost entirely from hypothalamic temperature receptors (Heller, 1978; Tattersall & Milsom, 2009). In the goat *Capra hircus*, inventive experiments have shown that temperature receptors in the trunk and the brain contribute approximately equally to the input signal for the control of metabolic heat production and evaporative heat loss (Jessen & Feistkorn, 1984; Mercer & Jessen 1978). Although early studies failed to detect an influence of muscle temperature in body temperature regulation (Cabanac, 1975), there are temperature sensors in skeletal muscle (Hertel, Howaldt & Mense, 1976), and those sensors presumably provide input to the thermoregulatory system during exercise, when muscle temperature is higher than arterial blood temperature (Todd *et al.*, 2014). How much they contribute is unknown, because of the statistical covariance of muscle temperature with other measures of core temperature. Cooling the deep tissue in the legs of hyperthermic goats, while the temperature of the rest of the body was clamped, suppressed respiratory evaporative heat loss, but only by a little (Jessen, Feistkorn & Nagel, 1983).

Sensors that respond to the temperature of mixed venous blood returning to the heart would provide the system with integrated information about the thermal status of the whole body, but the search for such sensors on blood vessels (Cranston, Hellon & Townsend, 1978; Hellon, Townsend & Cranston, 1978) and in the right heart and lungs (Cranston, Hellon & Townsend, 1977) has not identified any temperature receptors there. Thermal stimulation of the femoral vein in cats *Felis catus* evoked blood pressure changes (Thompson & Barnes, 1970) and changes in the temperature of the human femoral vein were associated with abrupt changes in sweat rate at the beginning and end of work in one subject but not another (Gisolfi & Robinson, 1970), but temperature receptors have not been identified in the femoral vein. The tone of large arteries of mice *Mus musculus* increases with local temperature, but there is no evidence that the temperature receptors involved have any projections to the brain (Phan, Sahibzada & Ahern, 2023).

Because temperatures all over the body contribute to the input signal to the controller, and because temperatures vary over the body, for example when cutaneous vasomotion changes or muscles work, Bligh (1978) concluded that the regulated body temperature may not be definable. More optimistically, Werner (1986, p. 338) arrived at “a somewhat vague concept of control on the basis of spatial integration, which essentially means that temperatures measured all over the body contribute, according to definite weighting factors, to the measurement of the overall thermal state, which primarily determines all effector activities”. Though the thermosensitive neural pathways of homeotherms have been described well (e.g. Madden & Morrison, 2019), how the neural machinery integrates inputs from regions with different receptor densities, and receptors with different thermosensitivities, to arrive at a measurement of the overall thermal status of the body, remains unknown. We do not even know whether all animals that can thermoregulate have the same suite of temperature receptors. The distribution and contributions of temperature receptors have been explored inadequately in ectotherms.

Given that the stability of body temperature requires a balance between heat flow into and out of the body, some researchers have suggested that the input signal to the thermoregulatory system is not temperature at all, but heat flux through tissues (Bazett, 1951; Houdas *et al.*, 1973; Webb, 1995). It is possible to maintain the stability of a system by balancing inputs and outputs without measuring the variable that is stabilised. Brobeck (1965) gives the insightful example of a bank account; one can keep the account in balance by knowing what goes in and out without knowing how much is in it. However, flux detectors are rare in physiology (Brobeck, 1965) and detectors of heat flux have not been discovered anywhere (Werner, 2010), although Webb (1995) proposed that the temperature difference across the skin could serve as a measure of heat flux. However, if the body maintains constant mass and specific heat during the measurement, net heat flux between the body and the environment would be reflected in changes in the mean body

temperature (the average temperature of all body tissues; Table 1, first definition). So heat flux detectors are not required for net heat flux with the environment to be measured; the system could measure mean body temperature. Based on calorimetric experiments, some thermal physiologists have proposed that it indeed is the mean body temperature that is the regulated body temperature (Snellen, 1966). However, the physiological measurement of mean body temperature would require temperature sensors in all tissues, and computational capacity in the nervous system to weight the temperature of each body part according to its mass (or actually to its thermal inertia), requirements that are unlikely to be fulfilled in a physiological control system.

In the absence of information about how the temperature input signal to the thermoregulatory system is constructed, many thermal physiologists have adopted the pragmatic position that the input signal can be approximated by a combination of the core temperature (measured, for example, in the oesophagus, rectum, or cloaca) and the average skin temperature. The skin temperature is taken to represent not simply the temperature of the skin surface, but to also represent the temperature of all peripheral tissue (i.e. the “shell”; Table 1), just as the core temperature represents the temperature of all deep tissue. The assumption is that the input signal can be approximated as $T_{b*} = wT_{core} + (1-w)T_{skin}$, where w denotes the proportional contribution (i.e. weighting) of core temperature T_{core} to the input signal, with $0 < w < 1$, and T_{skin} is skin temperature. There are some who believe that the contributions of core temperature and skin temperature are not additive but multiplicative (e.g. Jacobson & Squires, 1970; Libert *et al.*, 1982; Stolwijk & Hardy, 1966). Some researchers have used that linear combination of core temperature and skin temperature not as an approximation for the input signal but as a surrogate for the average temperature of all body tissues, to estimate the rate of heat storage in the body. But no combination of core and skin temperatures correlates well with the change in total heat content of the body when the content is measured calorimetrically (Jay *et al.*, 2007; Jay & Kenny 2007; Snellen, 2000). Indeed, the core and skin temperature can both be falling when the calorimetric mean body temperature (that is, the body temperature derived from heat transfer measurements) is rising (Snellen, 2000).

The weighting factor w is not the same for the thermoregulatory control systems of different species or across all thermoeffectors in the same species. For example, the weighting factor is closer to 1 in larger mammals than in smaller ones (Cabanac, 1975; Hensel, 1973; Romanovsky, 2007) although small mammals still can respond powerfully to hypothalamic cooling (Tattersall & Milsom, 2009). The weighting factor is high in birds (Cabanac, 1975) but, as mentioned already, the high sensitivity to a change in core temperature does not originate in the hypothalamus in some bird species (Mercer & Simon, 1984). Except when the weighting factor is equal to 1, the approach recognises skin temperature (or shell temperature) as a component of the regulated body temperature.

That was not the role ascribed to skin temperature originally by Hammel (1968), who considered skin temperature to modulate the set-point in a control system that had core temperature as the only input. It also is not the role attributed to skin temperature by Romanovsky (2018), who considered skin temperature to contribute as an input signal and to be capable of initiating corrective control actions, but not to be part of the regulated variable.

The traditional method to measure a transfer function was to relate the magnitude of a thermo-effector, like sweat rate, to a measure of core temperature, often rectal temperature in humans, under a thermal challenge (e.g. Wyndham, 1967). While the method is still used (e.g. Ravanelli, Gendron & Gagnon, 2021), it can yield repeatable results only if skin temperature does not change when core temperature changes (see Notley *et al.*, 2024a) or if skin temperature changes consistently with core temperature. In some circumstances, the weighted average of prevailing core and skin temperatures does not reflect the thermal state of the body well enough, in which case thermo-effector intensity may not correlate well with that weighted average. After the start of exercise or a change in environment, human core temperatures may not stabilise within an hour, so measurements of rectal or even oesophageal temperature may not reflect core temperature faithfully soon after ambient conditions or exercise levels change (Notley, Mitchell & Taylor, 2023b).

The argument that the input signal can be approximated by a combination of core and skin temperature is supported by experimental evidence that, in many circumstances, the strength of thermo-effectors, like vasomotion, or the evaporative cooling rate, correlates quite well with body temperature calculated in that way. There is an important caveat about such evidence, though. Proper analysis of the relationship between inputs and outputs in a negative-feedback control system cannot be obtained in the closed-loop state, that is, when the negative feedback signal is functional (Hardy, 1965) because, then, the input is not independent of the output. Proper analysis must be done in the open-loop state, in which the input continues to affect the output, but there is no feedback of the output on the input. Opening the loop is not possible in an intact animal. As an alternative to abolishing the negative feedback, sophisticated laboratories can employ the technique of thermal clamping, whereby one or more purported thermal inputs is held constant (Notley *et al.*, 2023b; Von Euler, 1964). The technique allows for the analysis of the relationship between a selected input, say oesophageal temperature, and an output, say metabolic rate, by manipulating the input experimentally and measuring the output, while feedback from all other body regions is kept constant, by clamping their temperatures. Claus Jessen used a water spray and bath to clamp the skin temperature of goats, and intravascular heat exchangers to manipulate the trunk temperature and the brain temperature independently (Jessen, Mercer & Puschmann, 1977; Jessen, 1981). Less-invasive procedures have been used to clamp some body temperatures in humans while varying others (Cotter & Taylor, 2005; Van den Heuvel *et al.*, 2020). Such procedures

allow for the estimation of both set-point (threshold) and gain (sensitivity) of the relationship between a change in temperature at a specified site and the magnitude of a thermo-effector.

(4) Autonomous thermo-effectors

One of those who computes the input signal to the controller for human thermoregulation as $T_{b*} = wT_{core} + (1-w)T_{skin}$ is Jürgen Werner, who, for more than 40 years, has been a major contributor to discussions around the set-point concept. Based on that model, he created a set of simultaneous equations in which receptor firing rate, determined by T_{core} and T_{skin} , generates a measure of body temperature that is a linear function of the two temperatures. Thermo-effector activities governed by that input body temperature, in turn, influence both T_{core} and T_{skin} . He then solved those simultaneous equations for core temperature. There was just one value of core temperature that was consistent with thermal equilibrium. In his version of the control system (Fig. 6) there is no generator of a reference signal, and certainly no set-point of a master controller. The model incorporated equations for thermo-effectors in the form: thermo-effector activity $R - R_0 = \propto (T_{b*} - T_{b0*})$. So activity will be zero when $T_{b*} = T_{b0*}$, and, according to the Hammel (1965) definition, T_{b0*} is the set-point for that thermo-effector. Rather than “set-point”, Werner prefers the term “threshold”, which is compatible with our discussion around Fig. 4.

Werner's representation of the human thermoregulatory system (Fig. 6) has separate parallel control elements for each of the three thermo-effectors that it incorporates, namely shivering, vasomotion, and sweating. In Werner's representation, rather than a master controller, each thermo-effector has its own control system (McAllen *et al.*, 2010). For example, the system that controls vasomotion is functionally distinct from the system that controls sweating, although the two systems may share some neurophysiological elements. For example, they share the same input from temperature receptors. Also, in humans, peripheral vasomotion and eccrine sweating share the same sympathetic efferent nerves (Trbovich *et al.*, 2021). Although the thermo-effectors are not necessarily inter-connected functionally, they are coordinated in that they serve a common goal: to restore thermal equilibrium to the body (the body will be neither losing nor gaining heat) when the thermal status of the body has been challenged. In the face of an increase in radiant heat load, for example, activation of vasomotion that will increase heat transfer to the periphery may be supplemented by the activation of evaporative cooling, but the thermo-effectors of vasomotion and evaporative cooling each has its own separate controller.

The representation of the human thermoregulatory system in Fig. 6 still contains a relic of the obsolete “master controller” concept in that it assigns the same weighting factor to the inputs of T_{core} and T_{skin} for the three different thermo-effectors. This is not a requirement in a distributed control system, nor a reality in human thermoregulation, where it

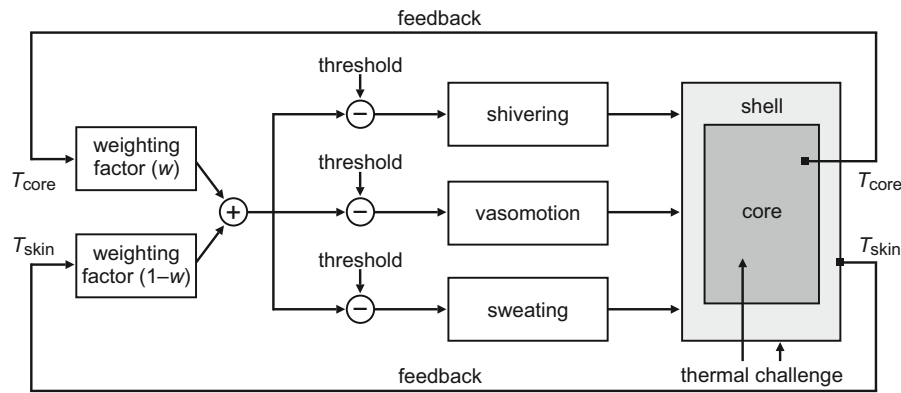


Fig. 6. Werner's conceptualisation of the system for the regulation of human body temperature, with thermo-effectors that work in parallel, with the input signal $T_{b*} = wT_{core} + (1-w)T_{skin}$ as the regulated variable, and with thresholds for each thermo-effector but no generator of a reference signal. Thermal challenges to the system initially may impact the skin (e.g. solar radiation) or the core (e.g. metabolic heat production during exercise). T_{core} and T_{skin} are defined in Table 1, and w denotes the proportional contribution (i.e. weighting, $0 < w < 1$) of core temperature to the input signal. Redrawn from Werner (2010).

has been studied best. The weighting factor is not necessarily the same for different thermo-effectors in the same animal. For example, the weighting factor is closer to zero for thermoregulatory behaviours in humans (absent in Fig. 6), implying a heavy influence of skin temperature on thermoregulatory behaviour, than it is for other thermo-effectors (Schlader *et al.*, 2009, 2013; Van Someren *et al.*, 2002; Vargas *et al.*, 2018). As we shall see (Section (4)), skin temperature also drives thermoregulatory behaviour in lizards. In Fig. 7 we present an amendment to Fig. 6 that includes behaviour as a legitimate thermo-effector and allows different weightings for the input from T_{core} and T_{skin} for each thermo-effector. It also allows for evaporative cooling other than sweating.

Satinoff (1978) proposed that the thermoregulatory control systems were arranged “hierarchically”, by which she meant that systems that are implemented by the more-distal central nervous system, including the spinal cord, were subject to supervision by the more-proximal central nervous system, and in particular by the hypothalamus. The contemporary view would be simply that they operate autonomously (Cabanac, 1975; Romanovsky, 2007), in what Werner (2010, p. 13) identified as a “a distributed multi-sensor, multi-processor, multi-effector proportional feedback control system” and Romanovsky (2018, p. 3) called a “dynamic federation of independent thermoeffector loops”. We should divorce the concept of set-point from the concept of a master controller, to which Kanosue *et al.* (1997), Romanovsky (2007), and others, believed it was wedded. We expect that what Werner calls the thresholds for each particular thermo-effector (which correspond to what Hammel, and we, call the set-points for those actions) to be staggered, perhaps according to how costly the implementation of each thermo-effector is. For example, among thermo-effectors that promote heat loss, the set-point for sweating is likely to be higher than the set-point for vasodilatation, so that vasodilatation will be implemented before sweating is, as body temperature rises (Kingma, 2018; Taylor & Gordon, 2019). Also, the set-points for behavioural responses to heat in

humans are likely to be well below those for sweating (Schlader *et al.*, 2013, 2018). It is the staggering of the set-points that leads to the inter-threshold zone or dead band that we have discussed. The staggering of set-points, however, does not mean that one thermo-effector needs to be at its capacity before the next one is implemented; evaporative cooling could start well before vasodilatation is maximal (Mitchell *et al.*, 2018). If the control systems are successful in working to their common goal following a change in thermal environment or metabolic rate, body temperature will stabilise, at an integrated operating point, when the body reaches thermal equilibrium and is no longer storing or losing heat.

III. THE RESURGENCE OF SET-POINT IN POIKILOTHERMIC ECTOTHERMIC LIZARDS

(1) Use of the term “set-point” for lizard thermoregulation

Since the concept of set-point was imported into thermal biology more than half a century ago, expert analysis of its meaning and role almost entirely has been the domain of a small group of specialists in control theory who have applied it to thermoregulatory physiology. Their interest has been in homeothermic endotherms, primarily humans. That no longer is the case. While several of those specialists in thermoregulatory physiology have advised that the term “set-point” should be abandoned, that has not happened. Rather, the term has experienced a resurgence in the research literature, and probably now is discussed more than it has been since the 1960s. The focus of that current interest is not homeothermic endotherms but poikilothermic ectotherms, notably lizards. The keynote paper of Hertz *et al.* (1993) about lizards has been cited more often since 1993 than has Hammel (1968) (see Fig. 1). Following the concepts and terminology of Barber & Crawford (1977), Hertz *et al.* (1993) measured a

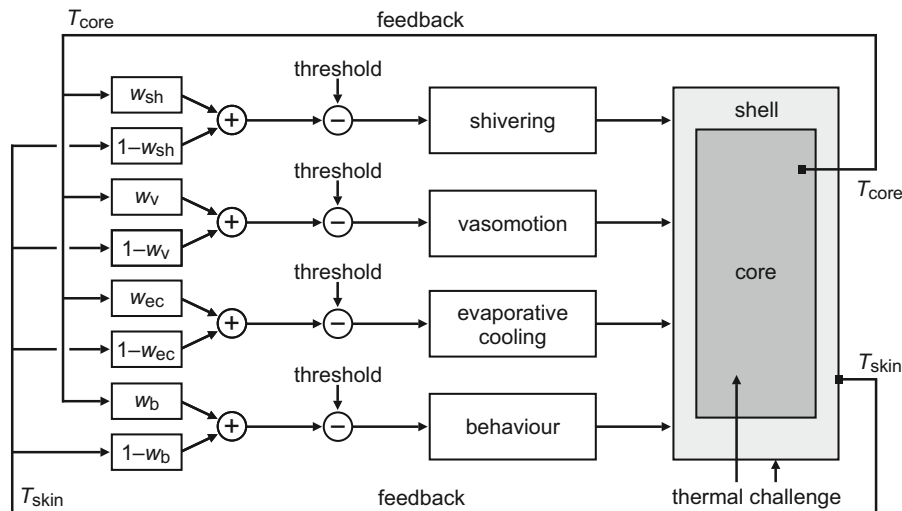


Fig. 7. Amendment to Werner’s conceptualisation of the system for the regulation of body temperature, to include thermoregulatory behaviour as a thermo-effector, and to eliminate a global input from core temperature T_{core} and skin temperature T_{skin} to all of the thermo-effectors. For example, T_{core} has more influence than does T_{skin} in the control of sweating, but less influence than does T_{skin} in the control of thermoregulatory behaviour. A further amendment is to allow forms of evaporative cooling other than sweating (e.g. respiratory evaporative cooling and saliva spreading) in non-human animals. In species that pant and sweat it is likely that there is a separate controller for each of panting and sweating. w is the weighting factor as in Fig. 6, but here each thermo-effector has a different weighting factor as specified by the subscripts.

“set-point range” as the stable body temperature attained by lizards in a thermal gradient, and used deviations from that range, relative to the scatter of ambient temperature in the habitat, as an index of thermoregulatory efficiency of lizards in the field. So, the term “set-point” now belongs as much to lizard biologists as to control-theory specialists.

The question that we now wish to address is whether the control-theory specialists and the lizard thermal biologists are discussing the same concept when they use the term “set-point”. Very few of the 941 citations to the paper of Hertz *et al.* (1993) would have emanated from control theory specialists also using the term “set-point”; they operate in a different domain (see Fig. 1). Hertz and colleagues did not seek to analyse whether their “set-point” was equivalent to the set-point of control theory. They were addressing ecological questions, not questions in mechanistic physiology. Indeed, they later expressed regret at having used the term (Hertz, Huey & Stevenson, 1999). We shall attempt to show that if the control theory specialists had paid attention to the set-point range of lizard thermal biology, and if Hertz *et al.* (1993) had ventured into mechanistic control theory, they would have discovered much common ground in their different domains.

Before we attempt to answer the question of whether the concepts of set-point are the same, we first must address the question of whether the constructs of proportional control theory apply to the relationship between body temperature and the thermal responses of lizards, and other poikilothermic ectotherms, because, if they do not, lizard set-point must have an alternative meaning. Many aspects of the thermal biology of ectotherms do not translate easily

to models that are designed to represent homeothermic endotherms. For example, Heath (1970) concluded that many insects employ on–off control of flight depending on their temperature, and not proportional control. Those insects generate heat when they fly, and they fly only if body temperature is below some threshold: “The insect either flies or does not fly, and the effector output, heat generation by the muscular activity of flight, is either maximal on or off” (Heath, 1970, pp. 403–404). That an insect flies when its body temperature is below a threshold does not prove that the flight is a thermo-effector, of course, and metabolic heat generation is not an on–off phenomenon in all insects (e.g. Vogt, 1986). Then again, the control of other thermo-effectors in insects does not necessarily adhere to on–off control. The control of evaporative cooling in desert cicadas *Diceroprocta apache* seems to adhere to proportional control (see Table 1 of Hadley, Quinlan & Kennedy, 1991).

The key question for us is whether thermo-effectors in lizards, on occasions when they are thermoregulating, conform to proportional thermoregulatory control, because the set-point employed by thermoregulatory physiologists for homeothermic endotherms is a construct of proportional control (Fig. 4). Early researchers were inclined to think that some did not, concluding that they conformed to on–off control, as in some insects (e.g. Garrick, 1979). Heath (1965) considered that panting and shuttling between shade and sun in lizards conformed to on–off control, but that control of the body area that a lizard exposed to direct sun conformed to proportional control. Later, Firth & Turner (1982) also considered panting in lizards to be subject to on–off control. Most of what we will say would apply, in

principle, to other ectotherms that show evidence of behavioural thermoregulation, including, for example, tortoises (e.g. McMaster & Downs, 2013; Zurovsky, Mitchell & Laburn, 1987b), snakes (e.g. Giacometti *et al.*, 2021; Zurovsky *et al.*, 1987a) and crocodiles (Downs, Greaver & Taylor, 2008; Seebacher, 1999). But it is only for lizards that we have the suite of data that is necessary to identify the mode of thermoregulatory control.

(2) Proportional thermo-effector control in lizards

Behaviour in a laboratory shuttle box (in or out of a chamber) or even shade-seeking (in shade or not in shade) is dichotomous, and so it is tempting to regard the control of such behaviour as on–off control in lizards (Black *et al.*, 2019). Some thermoregulatory behaviours in lizards, like heat-seeking postural changes, clearly are not under on–off control (Heath, 1965; Black, Aedy & Tattersall, 2021). Are they indeed under proportional control? There has been a plethora of studies exploring proportional thermoregulatory control in homeothermic endotherms, and especially in humans (see Notley *et al.*, 2023a, 2024a). Those studies have measured the transfer functions for various thermo-effectors. Typically, humans, rats, or other homeothermic endotherms have been subjected to graded thermal challenges, such as a progressive increase or decrease in ambient temperature, or graded exercise. Then, measurements have been made of the body temperatures that contribute to the putative input signal to the thermoregulatory system, often core and skin temperature but sometimes just core temperature, along with simultaneous measurements of the magnitude of one or more thermo-effectors, like sweat rate or metabolic rate.

By contrast, studies aimed at measuring thermoregulatory transfer functions in poikilothermic ectotherms are rare. Perhaps this rarity is not surprising given that “poikilothermic” implies that the animal does not regulate body temperature independently of environmental temperature, and therefore has no transfer functions to be studied. But, as we have observed, many poikilothermic species, and especially lizards, sometimes do regulate body temperature, when they have access to the thermal resources, and the opportunity and motivation to do so. It appears as if they have intrinsic access to some thermo-effectors, including cutaneous vasomotion (e.g. Baker, Weathers & White, 1972; Seebacher & Franklin, 2005) and respiratory evaporative cooling (e.g. Crawford & Barker, 1974). For much of the lives of the lizards, the gain (i.e. the sensitivity) of some thermo-effectors to which they have access seems to be zero; there is no response of that thermo-effector to changes in body temperature. It may well be zero for some thermo-effectors while, at the same time, not being zero for other thermo-effectors. The gain for an individual thermo-effector may even be zero in one season but not in others (Case, 1976; Huey & Pianka, 1977), and may be reduced in the dark phase of the light–dark cycle (Firth & Turner, 1982).

In circumstances in which lizards do regulate body temperature, just occasionally transfer functions have been

measured for autonomic thermo-effectors. An historical example is the linear transfer function, which reflects excellent proportional control, between cutaneous evaporative water loss and cloacal temperature in the iguanid lizard *Sauromalus ater* over the cloacal temperature range 26 to 44 °C (Crawford & Kampe, 1971). Those lizards also had a linear transfer function between metabolic rate and cloacal temperature, but the slope was positive, not negative as the slope of an equivalent transfer function would be in a homeothermic endotherm (Fig. 4A). Thus, the metabolic response in the lizards had nothing to do with the defence of body temperature in the cold, but likely reflected the Q_{10} (a measure of how much a process is affected by temperature) of metabolism, or the energy cost of panting (Loughran & Wolf, 2023), or both. Tegu lizards *Tupinambis merianae* have unusually high metabolic rates for lizards; their metabolic rate also increases, weakly, with body temperature (Tattersall, 2016; Toledo *et al.*, 2008), and that response also has nothing to do with defence against cold.

Respiratory evaporative heat loss of *S. ater*, although under proportional control, was of marginal importance in the lizards' heat balance (Crawford & Kampe, 1971). Only at the highest body temperature was there a marked increase in ventilation rate. Tattersall & Gerlach (2005) measured thermally induced gaping (rather than panting) in the Australian agamid lizard *Pogona vitticeps*. Open-mouth breathing or “gaping” is a complex phenomenon in lizards and appears to serve functions additional to whole-body cooling (Tattersall, Cadena & Skinner, 2006), to which its contribution may be only minor (e.g. Da Silveira Scarpellini, Bicego & Tattersall, 2015). Its thermoregulatory function also appeared to conform to proportional control. Not minor, though, was the panting that provided substantial evaporative cooling in 14 of 17 species of U.S. arid-zone lizards, resulting in a cloacal temperature that was 2–3 °C below air temperature in the heat (up to 50 °C air temperature) (Loughran & Wolf, 2020). Loughran and Wolf subsequently generated data from which they derived the body temperature threshold for panting, assuming proportional control. Re-analysis of the data showed that the relationship between evaporative cooling and cloacal temperature indeed conformed to proportional control for all 17 species (see Fig. 8 for three of those species; Loughran & Wolf, 2023), so validating their derivation of thresholds. Those thresholds would be equivalent to the set-points, in the language of control theory. The threshold varied between species, but always was high, ranging from 39.1 ± 0.2 °C in the 30 g *Sceloporus poinsettii* to 44.3 ± 0.3 °C in the 12 g *Callisaurus draconoides*. The lizards resorted to panting much less readily than would homeothermic endotherms that pant; lizard thresholds were close to the critical thermal maxima of the species (Camacho *et al.*, 2018).

When Hertz *et al.* (1993) used the term “set-point” it was not in the context of lizard autonomic thermoregulation like evaporative cooling, but in the context of a behavioural thermo-effector, namely microclimate selection. Behaviour is used far more frequently by lizards to alter heat exchange than

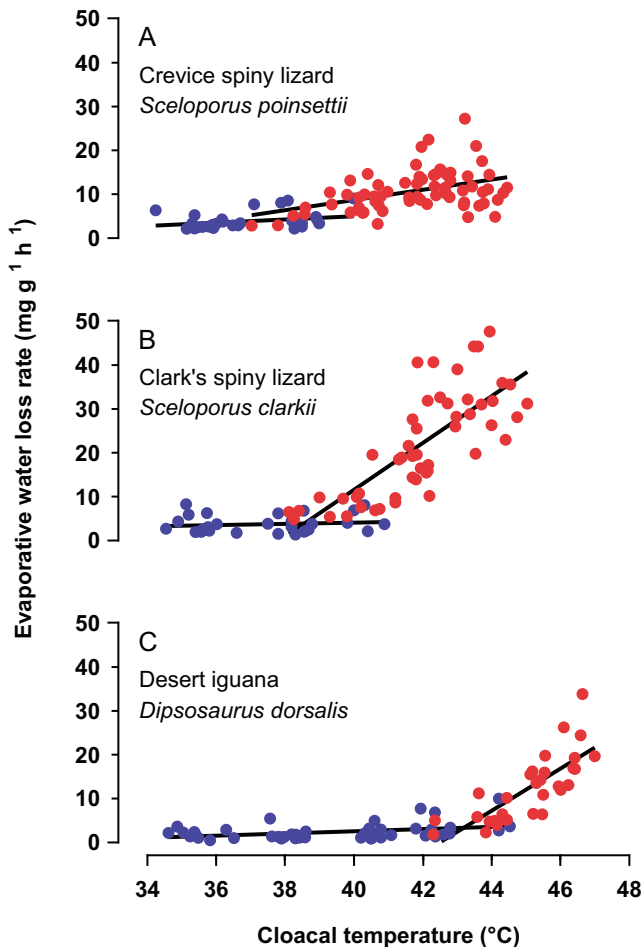


Fig. 8. Relationship between the rate of evaporative water loss and cloacal temperature in three species of diurnally active lizard from the arid south-west of the USA, exposed to progressively rising dry-bulb temperature in a metabolic chamber, and demonstrating proportional control above a threshold (set-point). Red symbols: lizards observed to be panting. Blue symbols: lizards observed to be not panting. *Dipsosaurus dorsalis* (C) inhabits hot lowland deserts, and appears to have evolved mechanisms to avoid evaporative cooling until cloacal temperature reaches about 43 °C. *Sceloporus poinsettii* (A) ranges from cool desert upland to montane habitats, and demonstrated low sensitivity (gain of the transfer function) of evaporative cooling to changes in cloacal temperature. *Sceloporus clarkii* (B), from the same genus, often is found on tree trunks or rock faces in a variety of habitats and demonstrated a higher sensitivity (gain of the transfer function) of rate of evaporative cooling to increases in body temperature. Also, the rate of evaporative cooling was higher, at high body temperature, in *S. clarkii* than in other *Sceloporus* species, perhaps because their rate of metabolic heat production was higher. Data extracted by Caleb Loughran from the data set of Loughran & Wolf (2023) and used with the permission of Caleb Loughran and Blair Wolf.

are autonomic thermo-effectors (Cowles & Bogert, 1944). It is much more difficult to establish whether behavioural thermo-effectors exhibit proportional control than it is to establish that

autonomic thermo-effectors exhibit proportional control, although Heath (1970) was convinced that at least some behaviours do so. Indeed, his data for the body surface area that horned lizards *Phrynosoma coronatum* expose to the sun plotted against body temperature (see Fig. 14 of Heath, 1965) portray a transfer function with threshold and proportional control. Further experimental evidence came later, but for a different thermoregulatory behaviour. Black & Tattersall (2017) attached a miniature thermometric data logger to the ventral abdomen of bearded dragons *Pogona vitticeps* and placed them in a thermal gradient with boundary temperatures of 15 °C and 45 °C. The lizards ultimately selected a median temperature of 34.1 ± 2.4 °C, but in the initial 3 h of exposure temporarily selected temperatures between 20 °C and 40 °C. Their probability of facing the hot end of the gradient, rather than the cold end, which presumably signalled intention to move to the heat, varied inversely, and almost linearly, with surface temperature. The colder was that surface temperature, the more likely they were to face the hot end. So, for both autonomic and behavioural thermo-effectors, the constructs of proportional control theory can be applied to the body temperature and thermal responses of lizards.

To establish proportional control specifically for microclimate selection would require the demonstration of a continuous relationship between a deviation in body temperature and the intensity with which the animals seek to select a microclimate. We can find no evidence that such a study has been conducted. We believe this could be investigated using the technique of operant conditioning. Lizards seeking warmth in a terrarium learn to activate a microswitch that turns on radiant heat and to de-activate the microswitch when they are too hot (Regal, 1971). That learned behaviour helps to stabilise body temperature (Kingsbury, 1993). It would be possible to design an experiment in which, by changing ambient temperature, the body temperatures of lizards could be driven by variable amounts from the temperature that they ultimately would select. The effort that those lizards put into working for a corrective thermal reward then could be measured. Regal (1971) and Kingsbury (1993) used reward from an overhead heat lamp, in a cool environment. Because it may be difficult, experimentally, to distinguish between the immobility that is typically induced in ectotherms by cold and a specific reluctance to work for heat, a better experimental design would be to elevate the ambient temperature and to have the lizards work for a cold thermal reward, which was the procedure used originally by Kemp (1969).

(3) Microclimate selection and set-point in lizards

If we had access to a plot of the intensity of microclimate selection against body temperature, then we could derive the set-point, as illustrated in Fig. 4, by extrapolating backwards to the body temperature at which the lizards just begin to seek a change in microclimate. However, this is not how Hertz *et al.* (1993) derived their set-point range. They used a variant of the formulation of set-point, in the context of

microclimate selection, that Crawshaw (1980, p. 476) had described: “Repeated measurements of the temperature where a particular animal is found typically exhibit a unimodal distribution skewed toward lower temperatures. From this information it is often inferred that the reptilian thermoregulatory system involves a set point (the peak of the distribution) and a proportional controller”. An important distinction between the approach of Hertz *et al.* (1993) and that of Crawshaw (1980) was that Hertz *et al.* (1993) identified a set-point range and not a peak in the distribution of body temperature. A set-point range had been proposed previously for the shuttling of lizards between the cool and hot chambers of a shuttle box (Berk & Heath, 1975; Firth & Turner, 1982; Kluger, Tarr & Heath, 1973). A set-point range, rather than a single set-point, indeed was considered to be essential for microclimate selection, for a reason given by Heath (1970, p. 405): “If a behavioral regulatory system were too tightly coupled, that is to say if the lizard both retreated to the shade and returned to sunlit areas at the same temperature, it would simply oscillate rapidly between sun and shade. As long as the sun shines it would be a very good thermoregulator but an ineffective lizard”.

Hertz *et al.* (1993) analysed the selected temperature of lizards of three Puerto Rican species (*Anolis cooki*, *A. cristatellus*, *A. gundlachi*), in five groups each of six lizards. The data were not generated *de novo* but obtained from a much-older study by Huey & Webster (1976), who had made their measurements in a static 2 m thermal gradient with a radiant heater at one end, in a 20 °C laboratory. The lizards were fasted; Hertz *et al.* (1999) later concluded that they should have been fed, because lizards typically have food in their stomachs (Huey, Pianka & Vitt, 2001). Body temperatures were measured with indwelling thermometers inserted *via* the cloaca into the intestine. One lizard at a time was placed in the gradient, and, after a 30 min familiarisation period, its body temperature was measured at 5-min intervals until 50 temperatures were recorded. The researchers then examined the distribution of body temperature for each lizard over that session and calculated the temperatures that bounded the middle 50% of observations for that lizard, assuming that the lizards would spend most time in a microclimate in which they wanted to be. They then averaged those bounds across the six lizards in each group, and called those averages the upper and lower limits of the set-point range for the lizards in that group. Standard errors were calculated between lizards. Hertz *et al.* (1993) acknowledged that the idea of expressing set-point range in terms of a central percentage of selected body temperatures had been advanced earlier by DeWitt & Friedman (1979). The body temperature distributions of lizards, and other ectotherms, tend to be left-skewed (Crawshaw, 1980; DeWitt & Friedman, 1979; Huey & Pianka, 2018) but this would interfere more with the extremes of the distribution than the middle 50%. The upper and lower bounds of the set-point range were 29.6 ± 0.4 and 31.6 ± 0.5 °C for *A. cooki*, and 24.3 ± 0.7 and 26.1 ± 0.8 °C for *A. gundlachi*. Three populations of *A. cristatellus* were studied, and their bounds lay within those of the other two species.

The association of those upper and lower limits with set-points originated from an idea of Cowles & Bogert (1944), consolidated by Barber and Crawford (1977, 1979), and expressed by Kingsbury (1993, p. 242) as follows: “Lizards, like most vertebrates that have been examined, thermoregulate in a manner consistent with a dual set point thermoregulatory mechanism. A lizard will avoid body temperatures below a lower set point temperature (LSP), as well as body temperatures above an upper set point temperature (USP), rather than defend a particular preferred body temperature. When body temperature is between LSP and USP, the lizard is indifferent to body temperature, and can carry out other activities unimpeded by a continuous thermoregulatory effort”. So it seems that lizards have access to two, independent, behavioural thermo-effectors related to microclimate selection, one active when their body temperatures are too low and the other when they are too high. Each thermo-effector then would have its own set-point, and the temperature interval between them would be the set-point range.

Although we would contest that dual set-point thermoregulatory mechanisms have been identified in “most vertebrates that have been examined”, the concept of the dual set-point is analogous to the concept of an autonomic inter-threshold range in homeothermic endotherms (Mekjavić, Sundberg & Linnarsson, 1991; Taylor *et al.*, 2019). The threshold, or set-point, for the thermo-effector of increased metabolic rate in the cold (Fig. 4A) and that for the thermo-effector of increased evaporative cooling in the heat (Fig. 4B) are independent and may be spaced at body temperatures quite different in magnitude (Notley *et al.*, 2023b), although not in all animals in all circumstances (Jessen & Clough, 1973). Within that inter-threshold range, though, homeothermic endotherms are not “indifferent to body temperature” but employ other thermo-effectors, like vasomotion and thermoregulatory behaviour. That lizards do not seek or avoid heat when their body temperatures are between the lower and upper set-points does not necessarily mean that they are indifferent to body temperature changes that might influence other thermo-effectors. Indeed, at body temperatures between the thresholds for heat-seeking and heat-avoidance, horned lizards engaged in thermoregulatory burrowing (Heath, 1965).

The body temperatures of lizards typically are not distributed evenly between their lower set-point and upper set-point for thermoregulatory behaviour but exhibit a peak frequency of body temperature. Some researchers interpret this peak as a “preferred” (Table 1) body temperature (e.g. Black *et al.*, 2019; Black & Tattersall, 2017; Crawshaw, 1980; Licht *et al.*, 1966; Murray *et al.*, 2014). However, the influence of body temperature on the capacity for movement in ectotherms can cause body temperatures to cluster and so create false evidence for a preferred body temperature (Dillon *et al.*, 2012). Also, the lower and upper set-points display statistical variability (they are “stochastically distributed”, according to Barber & Crawford, 1977) meaning that there is more likelihood of a selected body temperature appearing distant from the set-points than near

either one, so again creating a unimodal distribution of body temperatures (Firth & Turner, 1982). Counterintuitively, the distribution of temperatures even of inanimate objects (famously beer cans; Heath, 1964) in a sunlit environment may exhibit a peak.

We shall return later to questions about whether the experimental methods of Huey & Webster (1976), fit for purpose at the time, and the resulting data employed by Hertz *et al.* (1993), were ideal. First, in our endeavour to bridge the divide between domains, we address whether the concept of a set-point as it was used by Hertz *et al.* (1993) is compatible, in principle, with the concept of set-point that is incorporated in control-theory models of negative feedback regulation of body temperature. Were Hammel (1968) and Hertz *et al.* (1993) discussing the same kind of set-point, even though they used the term for different purposes? In control theory, as we have discussed earlier in this review, the term “set-point” has just one legitimate definition, the value of an input variable, in a transfer function, at which the output of a process just becomes activated. Hertz *et al.* (1993) did not seek to derive a transfer function for microclimate selection in the lizards. Indeed, no-one has done so yet. But their concept of set-point as a threshold implies that they inferred a proportional controller (in the words of Crawshaw, 1980) and therefore a proportional transfer function. The logic of their argument must have been that the further a lizard's body temperature was from the ambient temperature ultimately selected, the more strongly motivated that lizard would be to move in the thermal gradient. When the lizard demonstrated no further motivation to move, it was within its final range of selected temperatures.

The upper limit of the set-point range of Hertz *et al.* (1993), in principle, is not actually the upper set-point, according to control theory, but the balance point or operating point (Fig. 4), that is the body temperature required to achieve thermal equilibrium. In homeothermic endotherms, as we have said, a pervasive reason that an operating point is distinct from a set-point for a heat-loss thermo-effector is that to reach thermal equilibrium, homeothermic endotherms have to achieve heat balance under the substantial thermal load of endotherm metabolism, which requires substantial activation of heat-loss effectors. Body temperature has to rise to generate the temperature receptor activity that drives those effectors, and will stabilise when they are activated sufficiently to counteract the metabolic heat load. Lizard tissue also generates some metabolic heat, and, if they are to reach thermal equilibrium by microclimate selection, the lizards will have to seek a microclimate that is cool enough to dissipate that metabolic heat exactly. Thus, the elevation in body temperature that is caused by the metabolic heat will induce them to seek that cooler microclimate. We predict that if lizards in the set-point range of Hertz *et al.* (1993) were to perish, their body temperature would fall slightly. How much higher than threshold their body temperature will be will depend on how much metabolic heat they have to dissipate. Compared with metabolic heat production in a small endotherm, metabolic heat production in a small lizard is very

low (Seebacher & Franklin, 2005), and will cause a correspondingly small increase in body temperature to reach equilibrium. The displacement of the operating point from the set-point by metabolic load will be much smaller in a lizard than in an endotherm, and perhaps is not even measurable, although the elevation of body temperature caused by metabolic heat has been measured in a large lizard, the tegu (Tattersall *et al.*, 2016). Numerically, the operating points that actually were measured by Hertz *et al.* (1993) will differ very little, perhaps indistinguishably, from true set-points.

(4) Concerns and conclusions about selected temperature (and set-points for microclimate selection) in lizards

The accuracy of a numerical value attached to a set-point depends on the accuracy of the experimental data that are used to derive that set-point. With hindsight, how accurate were the data used by Hertz *et al.* (1993) (see Currin & Alexander, 1999; Hertz *et al.*, 1999)? The set-points were derived from laboratory data, rather than field data. There is a dispute about the merits of measuring any thermoregulatory variable for a wild-caught animal in the laboratory, compared to measuring the same variable in the field. As Harthoorn, Kanwisher & Tomkins (1970, p. 270) explained, “the measurement of the physiological parameters of wild animals poses a considerable problem, as even the sight and smell of man induces reaction. This reaction is manifested by changes in heart rate and even fluctuations in body temperature”. Apart from the issue of fear, animals in captivity may not be able to employ the full suite of thermo-effectors that they would normally employ in their natural habitats. Making measurements on captive animals, precluded from behavioural thermoregulation at night, has led not just to numerical errors but to fundamental flaws in our understanding of mammalian thermoregulation (Mitchell *et al.*, 2002). Hertz *et al.* (1993) were well aware of the hazards of measuring behaviour in the laboratory: “A laboratory setting is, of course, artificial and may potentially cause animals to behave unnaturally” (Hertz *et al.*, 1993, p. 801).

The dispute about laboratory *versus* field measurements to assess lizard thermoregulation relates mainly to which approach potentially imposes the greatest interference with the thermoregulatory behaviour. Any interference might result in lizards selecting a microclimate different from the microclimate that they would select without interference (Taylor *et al.*, 2021). More likely, though, under interference they would pay less attention to behavioural thermoregulation, and so introduce more variability into selected body temperatures. Those who defend laboratory measurements claim that lizards in the wild are subjected to complex ecological constraints that may reduce or distort the priority that they assign to microclimate selection; they have to decide how important the control of body temperature is, in a complex environment of competing demands (e.g. Basson *et al.*, 2017; Clusella-Trullas & Chown, 2014; Huey & Slatkin, 1976). Hertz *et al.* (1999, p. 46) doubted that

the body temperature realised in the field necessarily would be a target body temperature of thermoregulatory behaviour, because in the field “microhabitat selection probably represents a compromise among potentially conflicting needs that relate to thermoregulation, feeding, predator avoidance, and social interactions”. Indeed, Licht *et al.* (1966) and Clusella-Trullas *et al.* (2007, p. 64) argued not only that selected temperature should be measured in the laboratory but specifically in a laboratory thermal gradient: “selected temperature ... is defined as the range of body temperatures ... maintained by an organism in a laboratory thermal gradient”. Measurements of selected temperature in a laboratory thermal gradient certainly are not flawless, though; four species of cordylid lizard showed very low repeatability, because of high intra-individual variability (Clusella-Trullas *et al.*, 2007).

Others argue that distortions may well be equally serious in the laboratory (e.g. Christian & Weavers, 1996), especially because of fear of humans. The argument made by Harthoorn *et al.* (1970) regarding large mammals surely applies just as well to lizards in captivity, especially if the lizards have been freshly caught in the wild; in captivity, the presence of a large predator is a constraint that might reduce or distort the priority that a lizard assigns to microclimate selection, or result in stress-induced hyperthermia (Cabanac & Gosselin, 1993). For his laboratory studies of alligator lizards *Elgaria multicarinata*, Kingsbury (1993, p. 243) remarked “Alligator lizards are very secretive, thus the risk of exposure, even if minor, might inhibit thermoregulatory effort”.

Hertz *et al.* (1993) used departures from the set-point that they had measured, from data gathered in a static gradient in the laboratory, as a measure of thermoregulatory efficiency in free-living lizards, and others have followed their procedure (e.g. Kearney & Predavec, 2000; Kirchhof *et al.*, 2017). Essential to their approach was the requirement that lizards in their natural habitats, given the choice and the opportunity, will select exactly the same body temperature that they select in the laboratory. But there is good evidence, in other lizard species, that they do not do so; they tend to select higher temperatures in the laboratory than in the field (see Table 2 of Clusella-Trullas & Chown, 2014; Black *et al.*, 2019; Koziel *et al.*, 2021). Unless selection of a microclimate is given preference consistently over other behaviours, we would expect conflicting needs to increase the variance of the selected temperatures in the field, but the variance of body temperatures selected by lizards can be just as low in the field as in the laboratory [e.g. *Pedioplanis husabensis* (Kirchhof *et al.*, 2017; Murray *et al.*, 2014)].

Artificially high body temperatures selected by lizards in the laboratory may result from stress hyperthermia, but also could be a consequence of making the measurements in a static thermal gradient. In a gradient, ceasing to move is interpreted as microclimate selection, but there are other reasons that a lizard might be stationary (e.g. Dillon *et al.*, 2012). Other devices that are used to study microclimate selection compel lizards to move to achieve a thermoregulatory goal (Black *et al.*, 2019; Cadena & Tattersall, 2009a; Camacho & Rusch, 2017).

Despite the enjoyment to use thermal gradients (Clusella-Trullas *et al.*, 2007), shuttle boxes are favoured by many researchers who seek to measure selection of body temperatures in lizards and other ectotherms, especially slow-moving, cryptic, or shy species. Hertz *et al.* (1993) initially regretted having used data from a static gradient, but later also rejected the use of shuttle boxes because they would incur an energetic cost, and so a demand on the thermoregulatory system (Hertz *et al.*, 1999). Cadena & Tattersall (2009b) measured the cost of shuttling, and found that an impact of cost on thermoregulatory set-points was observed only in the most extreme case of forced shuttling, where lizards were constantly required to move from environments that were too hot to too cool. So, when reasonable demands are made on the lizards, the cost of shuttling should not confound the measurement of body temperatures that are selected. When a group of lizards was tested in a static gradient and in a shuttle box in the same laboratory, the lizards nevertheless selected different body temperatures in the two tests (Withers & Campbell, 1985). In the shuttle box tests, the lizards had to move at least 1 m for brief thermal reinforcement. Devices that force lizards to choose temperatures actively, rather than passively remaining at a temperature, lead to an increase in the variability of body temperature and a lower selected body temperature (Cadena & Tattersall, 2009a,b). Lizards of the species *Sceloporus cyanogenys* also selected higher temperatures in a static gradient than they did in an operant conditioning paradigm (Garrick, 1979).

Finally, the body temperature that Hertz *et al.* (1993) used to derive their set-point limits was a core temperature, namely intestinal temperature. If we are to conclude that lizard thermoregulation conforms to the control theory developed for homeothermic endotherms, we need to know whether core temperature drives microclimate selection in lizards. In homeothermic endotherms, as we have indicated, that drive often is assigned the simple form $T_{b*} = wT_{core} + (1-w)T_{skin}$, that is a linear combination of core and skin temperatures, with weighting factor $0 < w < 1$. For behavioural thermo-effectors in both endotherms and ectotherms, it seems that the weighting factor w approaches zero and, for lizards specifically, many workers have agreed with Crawshaw (1980, p. 476), that “peripheral skin temperature provides the major sensory input in the shuttlebox situation” (Cabanac & Hammel, 1971; Firth & Turner, 1982). The rate of change of skin temperature might be an even more powerful input. In humans, the strongest neurophysiological signal that the thermoregulatory control centre receives is the dynamic signal from skin temperature receptors when skin temperature is changing (Brown & Brengelmann, 1970). Consequently, in principle, the appropriate body temperature with which to correlate microclimate selection, if set-points are to be derived, is the skin temperature, not the core temperature. Barber & Crawford (1979, p. 250) concluded that “peripheral temperature was regulated ... deep body temperature is not the major directly regulated variable”, and Kingsbury (1993) implemented that idea. The surface temperature of a lizard might be quite different to that

of the core, especially if the lizard is exposed to a radiant heat source (Tosini, Jones & Avery, 1995). Infrared thermography is well-suited to the measurement of the skin temperature of lizards (Barroso *et al.*, 2016; Tattersall & Cadena, 2010; see Fig. 9). How lizards detect their skin temperature is not known yet. Indeed, Seebacher & Franklin (2005, p. 536) assert that “Pit organs are the only known thermal sensors among non-avian reptiles” and lizards do not possess pit organs. But they also “speculate that peripheral thermal sensors are present in

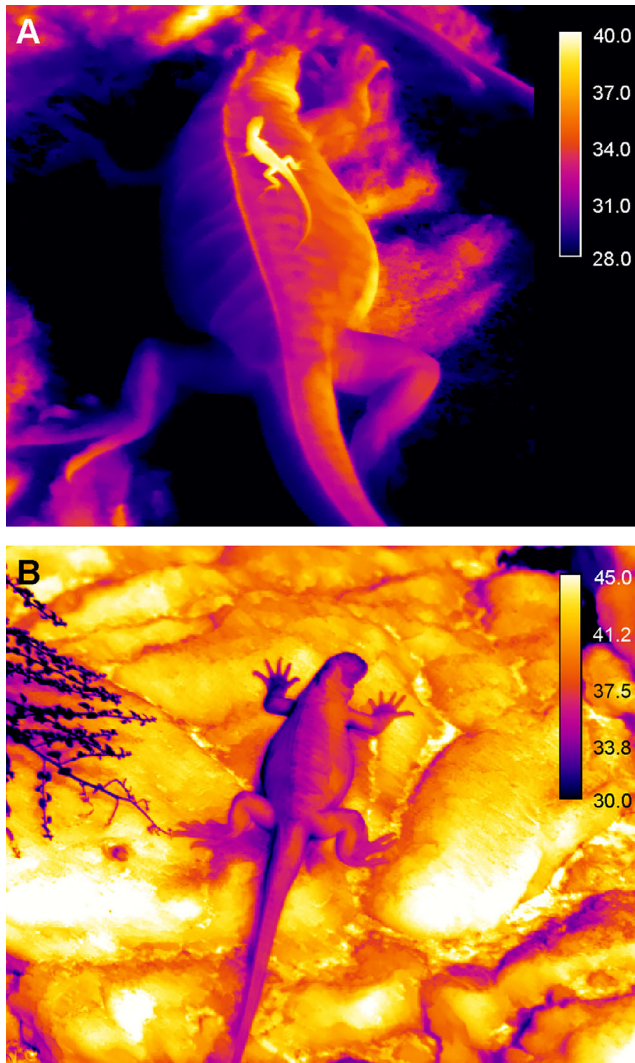


Fig. 9. Thermal images of basking lizards, depicting variation in surface temperature (in °C) according to size and orientation to the sun. (A) A lava lizard (*Microlophus albemarlensis*) sits atop a marine iguana (*Amblyrhynchus cristatus*) during early morning solar basking. The smaller lizard achieved higher surface temperatures from solar heating due to its lower thermal inertia. (B) A marine iguana at midday, recently had emerged from the sea and deriving heat from solar radiation and from the warm substrate. How lizards measure an integrated skin temperature remains unknown. Thermograms: G.J. Tattersall.

reptiles” (p. 539). Bailey (1969), decades earlier, had reported neurons that are sensitive to cold, but none sensitive to warmth, in the limb skin of the green lizard *Lacerta viridis*. At the time that Hertz *et al.* (1993) reported their analyses, data sets relating thermoregulatory behaviour to skin temperature in lizards were not available. In any case, in lizards as small as *Anolis* spp., the difference between core temperature and skin temperature likely will be too small to have any physiological significance. Thus, employing core temperature, rather than skin temperature, as the index of body temperature in *Anolis* lizards engaged in microclimate selection (Huey & Webster, 1976; Hertz *et al.*, 1993) is unlikely to have caused an appreciable aberration.

We asked earlier whether Hammel (1968) and Hertz *et al.* (1993) were talking about the same thing when they referred to “set-point”. We conclude that, in principle, they indeed were (see Fig. 10). They were talking about a body temperature input to the regulatory centre for a thermo-effector [in Hertz *et al.* (1993), microclimate selection] at which the thermo-effector just would become activated, as defined by Hammel (1965). In the lizards, the set-point temperatures

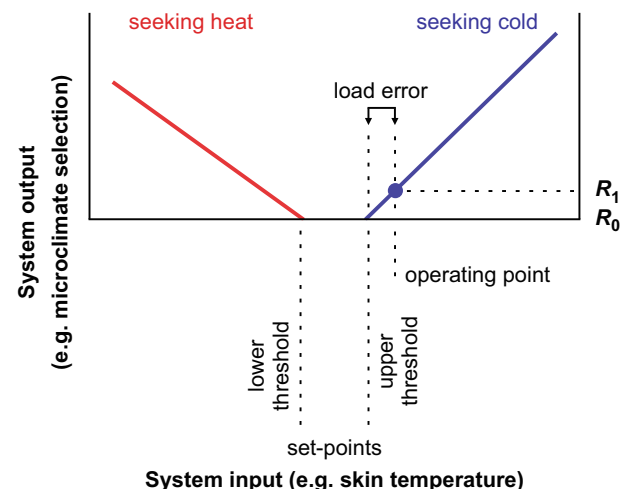


Fig. 10. Hypothetical transfer functions that describe the proportional control of microclimate selection in lizards. Output R_0 depicts inactivity in the selected microclimate. When body temperature exceeds an upper set-point, lizards will seek a cooler microclimate, and when it drops below a lower set-point, lizards will seek a hotter microclimate. In both cases, the intensity of the search for a different microclimate is depicted as proportional to the deviation of the body temperature from the set-point, although, in reality the responses likely will be curvilinear, and probably sigmoid. R_1 depicts the selection of a slightly cooler microclimate that is necessary to dissipate metabolic heat, and the corresponding operating point of body temperature has to be elevated above the set-point. However, because metabolic heat production is so low in lizards, compared with that of endotherms, the elevation will be small and perhaps not measurable, so the body temperature at the resulting operating point will be close to the upper set-point, an assumption made by Hertz *et al.* (1993).

were expressed as a range, which Hammel might have considered analogous to the inter-threshold range (dead band) of autonomic thermo-effectors in homeothermic endotherms. Figure 10 is similar to Fig. 2 of Barber & Crawford (1979) with the distinction that they envisaged dual thresholds for a single thermo-effector. We envisage single thresholds for two different thermo-effectors. Berk & Heath (1975) concluded that heat-seeking and heat-avoidance of *Dipsosaurus dorsalis* lizards in a shuttle box were separate thermo-effectors, controlled by different neuro-effector pathways. Their concept was endorsed by Firth & Turner (1982, p. 219): “the upper and lower set points for thermoregulatory shuttling appear to be regulated independently and by anatomically discrete brain regions”. We contend that seeking a hotter microclimate and seeking a cooler microclimate also are separate thermo-effector mechanisms in lizards, and, as Hammel (1965) specified for thermo-effectors generally, each will have its own set-point, with the difference between those set-points defining the set-point range. The thermosensitivity of temperature receptors relies on transient receptor potential (TRP) channels (e.g. Wetsel, 2011) and, in *Drosophila melanogaster* at least, the TRP channels involved in heat-avoidance and cold-avoidance are different (Rosenzweig, Kang & Garrity, 2008).

Hertz *et al.* (1993) did not seek, nor did they need, to demonstrate that microclimate selection conformed to the process of proportional control by body temperature, with set-points as depicted in Fig. 10. They had different objectives and were operating in a different domain. But their use of “set-point” as a threshold assumes that microclimate selection in lizards conforms to proportional control, an

assumption accepted but still unproven 30 years later. Some would consider that they used data from an inappropriate device, a passive thermal gradient in the laboratory, to measure body temperature following microclimate selection, but others would consider the laboratory thermal gradient to be the ideal device. They also did not measure set-point mechanistically, as one might measure the set-point for the onset of sweating in humans, but derived apparent set-points from a statistical distribution. They assumed that their statistical estimates would correspond to threshold temperatures for the activation of cool-seeking or warm-seeking behaviour, but, indeed, contended that “one should ideally determine the set points directly” (Hertz *et al.*, 1993, p. 801). Neither they nor DeWitt & Friedman (1979), who had used the concept earlier, tested that assumption of equivalence of set-points.

To test that assumption, we re-examined data from Cadena & Tattersall (2009b), derived from shuttle box assessments of thermoregulation in bearded dragons, *Pogona vitticeps* (see Fig. 11). The core temperature, measured by telemetry, at which a lizard began to escape from a cold or a warm environment, yielded lower and upper set-points of 34.1 °C and 35.6 °C, respectively. Hertz *et al.* (1993) employed the central 50% (interquartile range) of body temperatures realised during laboratory thermal gradient, while DeWitt & Friedman (1979) used the central 68% of their T_b data (mean $\pm$ SD). The bounds of the central 50% of selected body temperatures for the bearded dragons were 33.5 °C and 35.9 °C, respectively. Thus, the statistical bounds underestimated the lower escape set-point by 0.6 °C and overestimated the upper escape set-point

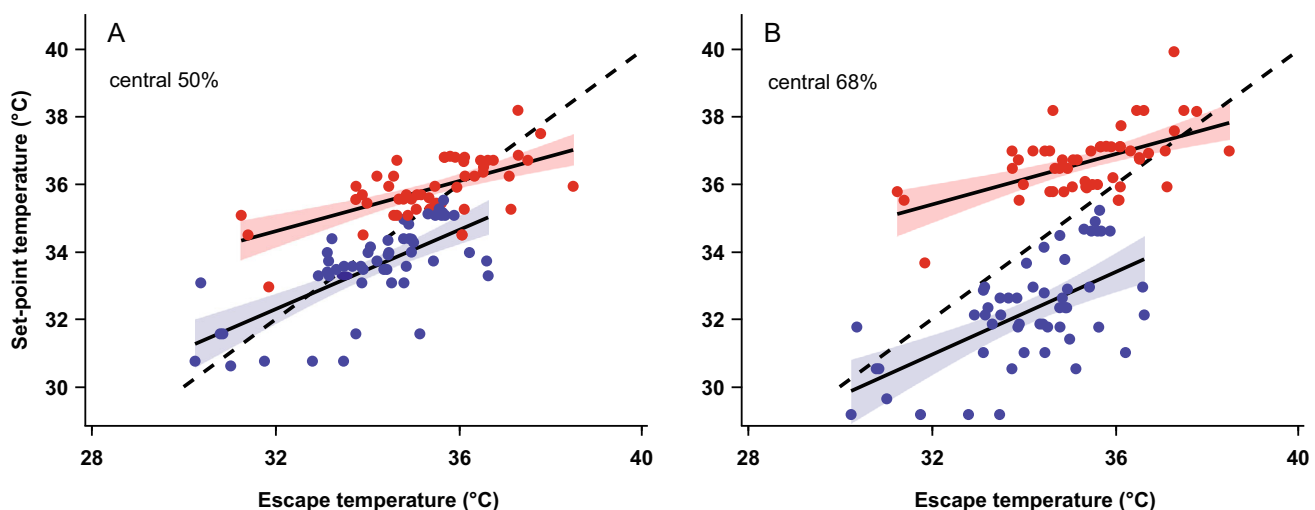


Fig. 11. Statistical estimation of set-points (y -axis) compared to direct measurements of threshold temperatures (x -axis), for bearded dragons *Pogona vitticeps* in a double shuttle box. (A) Set-points derived from central 50% of selected temperatures (following Hertz *et al.*, 1993). (B) Set-points derived from central 68% of selected temperatures (following DeWitt & Friedman, 1979). Each data point represents the set-point assessment for an individual animal (blue = lower escape temperature, red = upper escape temperature). Solid lines are least-squares regressions, and dashed lines are lines of identity ($y = x$). Data from Cadena & Tattersall (2009b); each lizard spent 8 h shuttling between ramping hot and cold chambers and exhibited multiple exits from each chamber.

by 0.3 °C. Thus, the agreement between mechanistic and statistical estimates of the set-points using the central 50% of selected body temperature was good. For bearded dragons, the central 68% had bounds of 32.2 and 36.7 °C, and so underestimated the lower escape set-point by 1.9 °C and overestimated the upper escape set-point by 1.1 °C. Had Hertz *et al.* (1993) measured set-point range directly, we suspect that they likely would have found very similar values.

When Hardy (1965) introduced the concept of engineering control systems into human thermoregulatory physiology, and Heath (1965) transferred the concept to lizards, they considered negative feedback to be sufficient to explain how body temperature is regulated. We now know that it is not sufficient. For example, negative feedback cannot explain how someone at rest but warmed up for exercise will increase sweat rate within 1.5 s of starting to exercise, long before any temperature receptor has been activated (Van Beaumont & Bullard, 1963). Negative feedback is supplemented by non-thermal feedforward control (Huey, 1982; Notley *et al.*, 2023a; Ramsay & Woods, 2014, 2016), a topic that deserves further discussion elsewhere.

In neither endotherms nor ectotherms are set-points fixed, even within one animal. They are subject to modulation by many influences. In lizards, for example, thermoregulatory set-points are modulated by hypoxia (Cadena & Tattersall, 2009a; Tattersall & Milsom, 2009). Circumstances in which set-points are and are not changed, which set-points are changed, and when they are, also require further exploration. Also, unlike well-fed well-habituated lizards in a thermal gradient in which they can devote their attention to thermoregulation, free-living animals in their natural habitats make choices, based on risk and reward, about how to employ their limited physiological resources and to manage their ecological contingencies, including how to prioritise competing homeostatic processes. Crucial to both endotherms and ectotherms that use evaporative cooling are the priorities given to thermoregulation and body fluid regulation, which compete for the same body water, including in lizards (e.g. Da Silveira Scarpellini *et al.*, 2015; Alomar *et al.*, 2024). We need to explore when animals give priority to thermoregulation and when they de-emphasise or abandon it in the face of more-pressing physiological needs.

IV. CONCLUSIONS

(1) This paper is the second in a series, following Mitchell *et al.* (2018), in which we revisit essential concepts of thermoregulation and identify misconceptions that may be held by some contemporary users of those concepts. Here we have tried to achieve two goals. First, we have tried to summarise the control-theory approach to thermoregulation, and to expel misunderstandings and confusions that have led some contemporary thermal physiologists to abandon it. Secondly, we have

tried to reconcile the set-point concept as employed extensively by biologists engaged in studies of lizard thermoregulation with the formal understanding of set-point that emanates from control theory (or systems engineering). Many biologists engaged with lizard thermoregulation are unlikely to have read papers on thermoregulatory control theory; many more thermoregulatory specialists are unlikely to have read papers about lizards (see Fig. 1). They may be surprised to discover how the two approaches converge.

(2) The confusion about set-point that has led some to lose faith in the concept may not have occurred if investigators had adhered to the definition of set-point that was advanced by Hammel (1965), as an algebraic property, analogous to a threshold, in the quantitative relationship between the magnitude of each thermo-effector and the body temperature change that stimulates that thermo-effector. The set-point concept should not be rejected just because the concept of a master controller for thermoregulation has been abandoned. It was incorrect to have considered set-point as an intrinsic property of a master controller. If we had adhered to Hammel (1965), “set-point” always would have belonged to individual thermo-effectors.

(3) Set-point is not the body temperature at which an animal operates, nor the body temperature that an endothermic system seeks to achieve, even though the expert literature is rife with these misconceptions. There are no neural networks that generate a set-point signal, in the way that the cruise control of a vehicle sets a speed that is to be defended (Stone *et al.*, 2015). Because of the low metabolic rate of lizards, and other ectotherms, the bounds of the body temperatures that are selected by small lizards, in a state in which they have access to a sufficient mosaic of microclimates and in which they can assign high priority to behavioural thermoregulation, while considered formally as operating points in control theory, are numerically close to the set-points. It is likely that the operating point and the set-point are numerically indistinguishable in small lizards. This conclusion relies on a reasonable, but unproven, assumption of proportional control of microclimate selection in lizards.

(4) A set-point is an algebraic property of a transfer function in a negative-feedback control system. Despite its dismissal by Somjen (1992), there is no mechanism other than negative feedback by which body temperature can be regulated precisely (Notley *et al.*, 2023a). Negative feedback is required to constrain thermo-effectors, and to correct errors in their activation.

(5) Despite Werner (2015, p. 338) urging not to “re-start on old confusing set-point discussion, which finally had come to a converging end”, we have done just that. The concept of regulation around set-points has not been abandoned in contemporary discussions of other homeostatic processes (Kotas & Medzhitov, 2015). Ramsay & Woods (2016) would have us reject not just the set-point discussion but the entire control-theory approach to thermoregulation. We believe that neither thermoregulatory systems specialists nor lizard biologists should abandon the set-point concept but should seek to attain and promote a rational understanding of set-point that is reconcilable with both domains.

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