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A definition of internal constancy and homeostasis in the context of non-equilibrium thermodynamics

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The constancy of the internal environment, internal homeostasis, and its stability are necessary conditions for the survival of a biological system within its environment. These have never been clearly defined. For this purpose nonequilibrium thermodynamics is taken as a reference, and the essential principles of equilibrium, reversibility, stationary steady state and stability (Lyapounov, asymptotic, local and global), are briefly illustrated. On this basis, internal homeostasis describes a stationary state of nonequilibrium, the actual state of rest, X(t), resulting from the relation $X(t) = X_S + x(t)$, between a time-independent steady state of reference (X_S), and time-dependent fluctuations of the state variables, x(t). In humans, two resting spontaneous homeostatic states are: (1) the conscious state of quiet wakefulness, during which time-dependent variables display bounded oscillations around the mean time-independent steady state level, this conscious state being thus stable in the sense of Lyapounov, and (2) the unconscious stable state of non-rapid eye movement sleep, in which the time-dependent variables would approach the lowest spontaneously attainable time-independent state asymptotically, sleep becoming a globally stable and attractive state. Exercise may be described as a non-resting, unstable active state far away from equilibrium and hibernation is a resting, time-independent steady state very near equilibrium. The range between sleep and exercise is neurohumorally regulated. For spontaneously stable states to occur, slowing of the metabolic rate, withdrawal of the sympathetic drive and reinforcement of the vagal tone to the heart and circulation are required, thus confirming that the parasympathetic division of the autonomic nervous system is the main controller of homeostasis.

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As Claude Bernard repeatedly stated, life is an expression of the physical reality and the maintenance of life is guaranteed by the constancy of the fluid matrix or ‘milieux interieur’ (Bernard, 1865, 1878). Cannon coined the term ‘homeostasis’ to describe the constancy of the internal variable and the regulatory integrated mechanisms directed to preserve it, and that of ‘emergency’ to describe the ‘efficiency in meeting sudden external demands on the body’ and linked both terms to the function of the sympathetic nervous system (Cannon, 1929, 1932, 1953; Cannon *et al.* 1929). Neurophysiological, behavioural and clinical data support the view that while the emergency function is mainly sympathetically driven, the constancy of the internal variable is mainly dependent on parasympathetic action (Hess, 1957; Recordati, 1984, 1989, 2002, 2003).

Regardless of the identity of the responsible controlling system a definition and quantification of the constancy of the internal environment and of the homeostasis of the internal variable is still lacking.

In the present paper an attempt is made at defining internal homeostasis and at quantifying constancy, the so-called ‘state of rest’ of the internal variables, on the basis of the systems theory by Bertalanffy and of the outstanding work by Prigogine on nonequilibrium thermodynamics and on the physical stability of thermodynamic systems (Bertalanffy, 1969; Nicolis & Prigogine, 1989; Kondepudi & Prigogine, 1998). Once homeostasis has been defined

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and preliminarily quantified it appears that amongst the known regulatory systems, the hypothalamic centres may be viewed as a complex thermodynamic controller which regulates exchanges of matter, energy and information with the external environment. The hypothalamus holds suitable 'set-points' through the reciprocal effects of the sympathetic nervous system, which moves the visceral apparatus away from equilibrium thus producing instability, and of the parasympathetic division which drives variables towards thermodynamic equilibrium favouring constancy and stability of the internal variable and environment (Recordati, 1984, 1989, 2002, 2003; Porges, 1995).

Basic principles

Systems and surroundings

From a mathematical point of view, a system can be defined as a set of interrelating elements (Bertalanffy, 1969), while physically it is a set of interacting elements, an arrangement or collection of things that can interact in a regular manner to form a unified whole (Yates, 1982). A system may be a reaction vessel, an engine, an electrochemical cell, and so on. Around the system are its surroundings, usually modelled as an infinitely large stable reservoir (Atkins, 1990).

Thermodynamic systems are classified into three types: (1) isolated (do not exchange energy or matter with the exterior); (2) closed (exchange heat and mechanical energy, but do not exchange matter with the exterior); (3) open (exchange both energy and matter with the exterior) (Kondepudi & Prigogine, 1998).

Already in 1905, on the basis of the second law of thermodynamics, Boltzman realized that the intrinsic organization of living being could only be understood as a part of the whole Earth system (Boltzman, 1905). A few years later Cannon introduced to physiology the concept of living being as open system (Cannon, 1929, 1939). Bertalanffy extensively quantified this approach and added the term 'information' to the definition of a biological system either to account for the functional role of the nervous system or as a measure of the internal order of the system (equivalent to 'negative entropy') (Bertalanffy, 1939, 1969). A schematic representation of an open system is illustrated in Nicolis & Prigogine (1989).

A biological system is an open system exchanging matter, energy and information with its environment (Recordati, 1989, 2002, 2003). Such a system may exist in many different states. The objective of the present paper is to describe those spontaneous states of rest which are characterized by the constancy of the internal variables and environment.

Equilibrium

The term 'equilibrium' describes the state of rest of a physical system. It may be either a mechanical or a thermodynamic state of rest. This term is hardly ever used in biology.

Mechanical equilibrium: a body is in a 'state of mechanical rest' when the net balance of forces acting on it is zero at each moment. If such balance is disturbed, motion is produced and thus equilibrium is broken (Nicolis & Prigogine, 1989).

Thermodynamic equilibrium: a system is in a 'thermodynamic state of rest' when there is no net exchange of energy and matter with its environment. A closed system is in this condition when its internal temperature and pressure equal the external temperature and pressure. If a temperature or pressure difference is present, a flux of heat or a variation of volume is produced, respectively. In an open system, where one or more chemical constituents can be exchanged with the environment, thermodynamic equilibrium requires the additional balance of chemical potentials. Thus thermodynamic equilibrium implies that certain internal variables X_i and external variables X_e (e.g. temperature, pressure, chemical potentials) attain identical values (Nicolis & Prigogine, 1989). In the case of isolated systems, the term equilibrium simply refers to the state of different internal compartements of the system itself (Kondepudi & Prigogine, 1998).

Biological systems reach a state of thermal and mechanical equilibrium with the external environment only when dead. With respect to temperature, the heart of homeothermic mammals ceases functioning between 10 and 15°C, while the heart of heterothermic (hibernating) mammals still functions at body core temperatures approaching 0°C and at ambient temperatures ranging from 0 to −16°C (Milsom *et al.* 1999; Buck & Barnes, 2000). Figure 1 schematically shows the different positioning of equilibrium points, with respect to body core temperature, for homeothermic and heterothermic mammals.

An example of a living biological system very near, but not at thermodynamic equilibrium, is the hibernating mammal during bouts of torpor. In the ambient temperature range of 6–12°C, while metabolic rate is held constant at a minimum level, heart rate is around 5 beats min^{-1}, and aortic systolic blood pressure ranges between 40 and 80 mmHg, body core temperature is always slightly above ambient temperature, but passively determined by the latter (Milsom *et al.* 1999; Buck & Barnes, 2000; Ortmann & Heldmaier, 2000). At ambient temperatures between 0 and −16°C, the metabolic rate of arctic hibernators increases again, to keep body core temperature near zero degrees centigrade (Buck & Barnes, 2000).

Reversibility. In the language of thermodynamics, the term 'reversible' indicates a process, a change, which may occur between two separate systems and between a system and its surroundings and which can be undone with no consequences for either the system or the environment. Only processes involving systems in equilibrium states may be reversible.

For example, the transfer of energy between two bodies with the same temperature is reversible, because if the energy content of either body is lowered by an infinitesimal amount, heat flows into it and temperature increases, but if energy content is raised by an infinitesimal amount, heat flows out of it and temperature declines (Atkins, 1990). Reversible processes are finely balanced changes, with the system in equilibrium with its surroundings at every stage (Atkins, 1990). Reversible processes are only present in those systems characterized by the absence of friction and by the absence of dispersion of energy, and therefore do not produce entropy. These systems are called 'ideal systems' and have been of great value for formalism of classical thermodynamics. In the real world, reversible processes do not exist either in physical or in biological systems.

The neurally mediated syncope (vasovagal syncope) offers an example of an acute state of equilibrium, at least for what the gravitational potential energy is concerned (Recordati, 1999), due to sudden increase in vagal tone, complete withdrawal of sympathetic vasocontrictor drive to the peripheral circulation, hypotension and, in some instances, asystolia. This pathophysiological state is completely reversible, in medical but not physical sense, and the healthy state may be re-established by maintaining the unconscious individual in an equilibrating supine position, thus facilitating venous return to the heart (Van Lieshout *et al.* 1997).

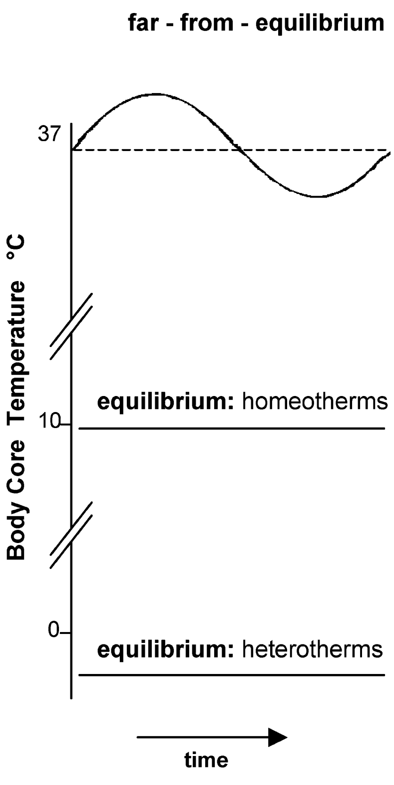

Figure 1. Schematic diagram of threshold levels of body core temperature and ambient temperatures for homeothermic and heterothermic mammals

These levels are extrapolated from the body core temperatures at which the heart of homeothermic and heterothermic mammals spontaneously stops beating. At these 'threshold' temperatures cellular functions are lost, and the organism is progressively and irreversibly driven to equilibrium with the external environment. Top trace represents a normal circadian harmonic oscillation of body core temperature at 37°C around the mesor and far from equilibrium.

Far from equilibrium

In contrast to equilibrium states, the states of nonequilibrium are associated with differences between some of the state variables X_i (set of internal variables) and X_e (set of external variables) and therefore with non-vanishing fluxes between system and environment. In nonequilibrium situations the system never identifies itself with its environment (Nicolis & Prigogine, 1989).

From the above definition it appears that since all living beings are open systems which exchange matter, energy and information with their surroundings, and the set of their internal variables (pressure, density, and temperature, for example) has different values from the set of the same external variables, they are away from the equilibrium, and are in nonequilibrium conditions with their environment.

As recognized by the pioneering work of Schrödinger, living beings need to be in a nonequilibrium state because of intrinsic reasons. He argued that the natural degradation of every form of energy into heat, formalized in the notion that entropy can be produced and transferred but not eliminated, implies that living beings need to develop schemes for the disposal of entropy in their environment and that better biological performances require more efficient means of dispersing heat (Schrödinger, 1944).

To exist far from equilibrium, a living being should develop gradients of the quantity X_i with its surroundings. Such gradients should be maintained utilizing energy imported from the outside. Depending on these gradients an open system may move from near to far from equilibrium (Recordati, 1989, 2002, 2003).

Figure 1, in addition to the levels of homeothermic and heterothermic mammalian equilibria, shows a body core temperature harmonic oscillation occurring with circadian rythmicity away from equilibrium and around a mean temperature level of approximately 36.5°C.

Irreversibility. Any heat transfer, expansion, composition change etc., taking place in systems far from equilibrium is necessarily irreversible and necessarily implies an irreversible loss of order, such as when heat is released into a colder environment or when chemical components diffuse from a concentrated to a dilute solution. Stated in other words an irreversible process brings about a degradation of available energy, a loss of 'free' energy which thus is no longer available to drive the process in the reverse direction. In these processes entropy is produced. In the real world all the spontaneous changes or changes due to work are accompanied by the production of degraded energy (entropy) and are irreversible (Atkins, 1990).

The energy budget associated with a cardiac beat offers a clear example of an irreversible process. Only a portion of the utilized biological energy is transformed into useful mechanical external work reaching an efficiency of about 40% on average. Part of the remaining energy is dissipated as heat and entropy is produced. Positive inotropic interventions, because of the O_2-wasting (Fenn) effect, are accompanied by a decline in efficiency and by an increased entropy (Suga, 1990).

Particularly in the case of homeotherms (isothermal conditions), metabolic rate and entropy production are simply proportional, so changes in one reflect changes in the other (Andresen *et al.* 2002).This observation has been useful to formulate the hypothesis that ageing of biological systems begins when their capacity to degrade energy starts to decline, as reflected by a decrease of specific entropy production (which is the entropy generated per unit time and per unit volume and weight of the system) (Toussaint *et al.* 2002). In this context the only intervention that appears to slow the intrinsic rate of ageing is caloric restriction, which simultaneously acts through a reduction of metabolic rate and metabolic reprogramming, resulting in lower production of toxic by-products of metabolism (Lee *et al.* 1999). Interestingly, while ageing is accompanied by an increase in sympathetic tone (Niima *et al.* 2000), caloric restriction is characterized by a decrease in sympathetic activity and an increase in parasympathetic tone (for references Recordati, 2003).

The increase in entropy allows the future from the past to be distinguished and the definition of the so-called 'arrow of time' (Kondepudi & Prigogine, 1998).

State of a system

In thermodynamics, the state of a system is specified in terms of the state variables, which are proportional to the size of the system (extensive variables) such as volume and amount of matter, typically expressed in moles, and of those which are independent of the size of the system (intensive variables) such as pressure and temperature, and by the functions of the state variables, such as internal energy, entropy and enthalpy (Kondepudi & Prigogine, 1998).

Due to the complexity of biological systems it is difficult to establish explicit relations (mathematical functions) between their state variables and therefore a state is defined only by the set of numerical values of its variables at a given instant and by 'balances' (Hobson & Steriade, 1986).

Nonetheless, many of the quantities usually accepted as the basic variables whose numerical values may be useful to describe a biological steady state have at the same time thermodynamic significance: temperature, arterial and venous pressures, volume and composition of body fluids, heart rate, frequency of breathing, oxygen consumption and the basal metabolic rate. All of these are thermodynamic variables which are usually scaled to the age, sex, mass and body surface area of the biological system under study. In clinical work on humans, two different healthy states are unanimously recognized as spontaneous states of rest: first, a conscious quiet state of wakefulness and second, the unconscious steady state of stages 3 and 4 of non-rapid eye movement (NREM) sleep. These two steady states, which can be identified on the basis of state variables, also differ with regard to the input of information, sleep being characterized by a definite disengagement from the external environment (Recordati, 2003). Before proceeding further by looking at the differences between these two states it is necessary to give a definition of the terms 'balance' and of 'stationary steady state' of rest.

Balance. The term 'balance' is used to describe the relationships between the system and its surroundings (external balance) or the relationship between different internal compartments of the same system (internal balance) (Valtin & Schafer, 1995). In bioenergetics it describes the relation between input and output of metabolic energy, with the inclusion of heat production and dissipation, while in renal physiology and clinical nephrology it describes the relation between the input, usually with diet, and the output through excretory organs of a given, specified, substance, for example Na and water. By definition, in the steady state an organism is in balance, which means that the output of a given substance is equal to the input, plus the internal production, of that substance (Valtin & Schafer, 1995). Hence the term 'balance' describes the final outcome of processes occurring inside the organism and between the living being and its environment, as an indirect index of average fluxes of energy and matter. The sympatho-vagal balance, for example, refers to the final outcome of the sympatho–vagal interactions at the target organ level. Heart rate may be viewed as the resulting vector of the opposing adrenergic and cholinergic influences on sinus node pacemaker cells.

Physicists use the term balance to indicate fluxes of matter, energy etc., to and from the environment and to indicate that such fluxes hold the system in a steady state. Open systems may show steady states and balances, which result from and are maintained constant far from thermodynamic equilibrium, which is to say in nonequilibrium conditions. Specific, crucial balances are the energy and the total entropy balance of an open system. The metabolism of living beings makes energy available to the system and, at the same time, generates entropy, which has to be disposed of. Thus entropy is not only produced inside the system, but it is also exchanged between the system and the environment. The total entropy can be constant only when the entropy flowing out of the system is equal to the entropy entering the system plus the entropy produced inside the system as the result of internal irreversible processes (Kondepudi & Prigogine, 1998). This thermodynamic balance is of relevance to understand entropy changes related to food intake and elimination of waste products (Recordati, 2003).

Stationary steady states

An isolated system at equilibrium is in a state of rest, which is called a steady state or stationary steady state.

The terms 'steady state' and 'stationary state' are also used to indicate a stable dynamic regime maintained by open systems away from thermodynamic equilibrium with the surroundings during which the system remains constant in its composition, in spite of continuous irreversible processes, import and export, building-up and breaking-down, taking place (Bertalanffy, 1969).

Hence, an open system which exchanges energy and matter with its environment can be maintained in a nonequilibrium state through a flow of energy and matter (Kondepudi & Prigogine, 1998). To underline the difference between an open and an isolated system at equilibrium this state is called a 'steady state of non-equilibrium' (Bertalanffy, 1969).

The defining characteristic of a steady state for both equilibrium and nonequilibrium systems is that both variables and fluxes are time-independent. For example, if the flow of heat from one body region to another is constant, i.e. it does not vary with time, its derivative over time is zero and therefore it may be described as time-independent (Kondepudi & Prigogine, 1998). Usually this is a final state which is reached after a transient period of time-dependency of the variable, and during which the phenomena of overshoot and false start may occur (Fig. 2). When such a final state is specific for a certain system in a certain environment, regardless of its starting ('initial') conditions, the tendency to attain such a steady state is described by the term 'equifinality' (Fig. 2) (Bertalanffy, 1969).

The term 'stationary steady state' is therefore a very general term encompassing both the steady state, constancy, of isolated systems at equilibrium and the steady state or constancy of internal variables of open systems away from thermodynamic equilibrium (Nicolis & Prigogine, 1989) *which is time-independent* (Bertalanffy, 1969) (Fig. 2).

In some remarkable cases the attained stationary steady state is independent from initial conditions. All human beings after 18–24 h of wakefulness, regardless of the previously perfomed activites, usually will fall asleep. Sleep deprivation, if prolonged, is not compatible with life (Recordati, 2003). During sleep each individual goes

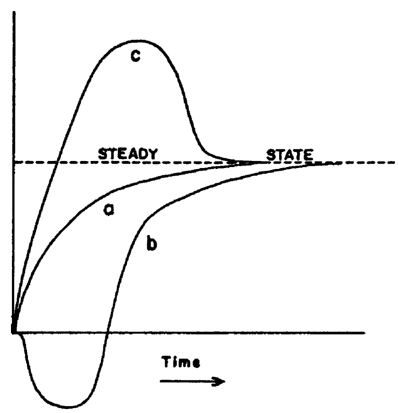

Figure 2. Steady state and state variables
This figure shows a steady state as a constant, time-independent state (horizontal dashed line), which is asymptotically approached by state variables along different time-courses: exponential-like relaxation (a), transitory with false start (b) and overshoot (c). In this example a common steady state is reached, which is thus called 'equifinal' state. From Von Bertalanffy (1969), Fig. 62.

through different stages of NREM sleep (Brebbia & Altshuler, 1965; Hobson & Steriade, 1986). In healthy humans, autonomic and cardiovascular systems will show definite and characteristic changes typical of this steady state, such as decreases in sympathetic activity, blood pressure, heart rate, oxygen consumption and metabolic rate and a clear increase in vagal tone. Sleep may be defined as a necessary, spontaneous (it does not require work to bring it about), equifinal steady state.

The reference steady state

A reference state, which may well be a stationary, time-independent, nonequilibrium state, is taken into consideration. This state may be indicated by the symbol X_S.

However, because of perturbations and fluctuations, many real-world systems oscillate around a reference state. Their state then becomes a time-dependent state $X(t)$, which is the observable, actual state, and which is related to X_S by the following relation

$$X(t) = X_S + x(t)$$

with X_S describing a time-independent state of rest and the average value of some physical quantity and with $x(t)$ describing time dependent fluctuations and perturbations.

While *perturbations* originate in the external environment and are the expression of the interference of the environment with the intrinsic dynamics of the system being investigated, *fluctuations* may be regarded as deviations from the average values of the macroscopic state variables that the system generate spontaneously, independent of the environment (Nicolis & Prigogine, 1989).

For example if the heart rate of an healthy individual performing deep breathing is the variable (x) under study, the average heart rate before and after the test will represent the steady state X_S, around which the fluctuations of heart rate induced by deep breathing, x(t), will occur. If circadian 24 h blood pressure changes are described as a harmonic oscillation, the mesor will become the X_S around which normal fluctuations will occur (Carandente, 1984). Temperature, arterial blood pressure and heart rate, extracellular fluid volume and composition, O_2 consumption, rate of breathing, tidal volume, muscle sympathetic nerve activity and metabolic rate are the main variables which may be described according to the above mathematical function. All these variables fluctuate with circadian rhythmicity and move from near equilibrium levels during sleep, to far away from equilibrium during strenuous muscular exercise. Hence the displacement of these variables along the ordinate axis may also be seen as directly related to the parallel changes in metabolic rate occurring during different behaviours. Thus X_S, the average value of the variable under consideration, is a function of the average value of the metabolic rate typical for a given behaviour. Hence if in a particular instance, the objective is to link neurohumoral regulation to energy balance, X_S will be represented by the mean level of metabolic rate for the behaviour under consideration, around which the variable, heart rate say, will show bounded oscillations under neurohumoral influences. The quantification of X_S by metabolism, besides dimensional problems (Ellis, 1966), will offer the opportunity to compare time-dependent oscillations and fluctuations of different variables at the same level of energy balance.

Stability and attractors

The concept of stability helps to characterize the fluctuating state of a system further offering a description of the behaviour of the time-dependent variable with respect to the steady state of reference X_S. Generally speaking the system is said to be stable if after a deviation from X_S the variable x tends to return to the reference steady state X_S, while the system is said to be unstable if the variable does not return to the reference state. For example, heart rate changes during testing of autonomic reflexes in autonomic failure patients, do not recover towards prestimulus values, allowing the conclusion that in this condition the system is unstable (Wieling & Karemaker, 1999).

Independently of time, stability may be quantified on the basis of the mutual dependence of the variables (Kreyszig, 1988). The graphical representation of such systems (the so-called autonomous systems) is reached by assigning each axis to a different variable, but not to time. The resulting space may be two-dimensional or 3 and n-dimensional (the phase space). Since the time dependence is eliminated from the description, a constant set of values for the variable, becomes a point in plane or space and is termed a critical point (Kreyszig, 1988).

Generally speaking a point P_0 is called a stable critical point if all paths that at some instant are sufficiently close to P_0 remain close to P_0atall future times. This is the Lyapounov definition of stability and the point P_0 is said to be stable in the sense of Lyapounov (Fig. 3*a*). Lyapounov's formulation gives conditions for stability in precise mathematical terms (Kondepudi & Prigogine, 1998). For example, respiratory sinus arhythmia during deep breathing offers an example of fluctuation of a variable around a mean steady reference state which may be considered stable in the sense of Lyapounov.

The point P_0 is called a stable and attractive (or an asymptotically stable) critical point if P_0 is stable and every path which has a point in a disk of given radius approaches P_0 as t (time) approaches infinity (Fig. 3*b*) (Kreyszig, 1988). The above mathematical definitions of stability are applicable to physical systems and allow a determination of whether the actual state $X(t)$ is stable, although characterized by the presence of fluctuations of the variables around a mean level (Nicolis & Prigogine, 1989).

A stable state may be globally or only locally stable (Nicolis & Prigogine, 1989). The difference between the last two states being dependent on the intensity of the perturbations needed to move the state of the system away from the reference steady state. If the state $X(t)$, the actual state, remains near the state X_S, the reference steady state, for all initial values of the perturbations, then the state $X(t)$ is a globally stable state, and it may also be a global attractor. Otherwise it is only locally stable or unstable (Nicolis & Prigogine, 1989).

Internal constancy and homeostasis

From the above physical definitions of stationary steady state, of the state of reference and of its stability, it is now possible to give a clear definition and description of internal homeostasis.

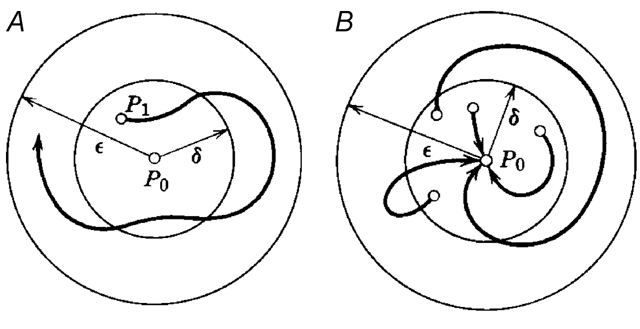

Figure 3. Phase plane representation of stable and attractive critical points

A, the point P_0 is called a stable critical point if, roughly speaking, all paths that at some instant are sufficiently close to P_0 remain close to P_0 at all future times. The variable's path initiating at P_1 stays in the disk of radius ϵ, and the point P_0 is said to be stable in the sense of Lyapounov. *B* The point P_0 is asymptotically approached by state variables. This point is said to be a stable and attractive critical point when every path which has a point in the disk of radius δ approaches P_0 as t (time) approaches infinity. From Kreyszig (1988), Figs 69 and 70. This material is used by permission of John Wiley & Sons, Inc.

Definition of internal homeostasis

In open systems which are maintained constant by continuous exchanges of matter,energy and information, the resting spontaneous reference state of internal homeostasis, should no longer be viewed as a state of mechanical or thermodynamic equilibrium, but rather as a thermodynamic stationary state of nonequilibrium (Nicolis & Prigogine, 1989). Since this state is stable over time, homeostasis should be a time-independent state, and, according to Bertalanffy, a state independent from initial conditions. Mathematically homeostasis may be represented by the actual state $X(t)$ composed of a time-independent steady state (X_S) and a time-dependent state variable, x(t), as previously illustrated. The teleological meaning implicitly present in the term 'homeostasis' is well expressed by the physical definition of equifinality (Recordati, 1984; Bertalanffy, 1969).

In healthy conditions the distance of the steady state X_S from thermodynamic equilibrium, hence its displacement along the ordinate axis, is dependent on prevailing behaviour. By assuming that X_S should be zero at equilibrium and maximal at the maximum possible distance from equilibrium it follows that the more precise representation of X_S is given by the metabolic rate of the living being under consideration. As a consequence, the definition of homeostasis in the frame of thermodynamics of nonequilibrium becomes strictly related to the level of energy balance and metabolic rate, as a description of a steady state at a given measurable distance from thermodynamic equilibrium. This definition will allow the linkage, through the allometric power function, of constancy and homeostasis to the mass, the biological efficiency, the entropy production and the physiological 'eigen time' of the biological system under consideration (Darveau *et al.* 2002; Gillooly *et al.* 2002; Toussaint *et al.* 2002; West *et al.* 2002).

Homeostatic states

At least two different spontaneous steady states of rest may be identified in humans.

First, the conscious resting state of quiet wakefulness. It may be considered a mean level around which all the internal variables rhythmically oscillate (heart rate, blood pressure, sympathetic and parasympathetic efferent activities) and fluctuate with a circadian rhythmicity (temperature) (Akselrod *et al.* 1981; Pagani *et al.* 1986; Badra *et al.* 2001). If these oscillations and fluctuations are bounded the reference state may be considered stable in the sense of Lyapounov. While in this state, however, the system threshold for moving away from stability is low. Either the subject may become drowsy favouring a prevalence of the parasympathetic tone and a concomitant fall in metabolic rate (Colrain *et al.* 1987; Fraser *et al.* 1989), or a sudden stimulus may elicit a sympathetic activation. Hence this state may be considered only locally and not globally stable (Nicolis & Prigogine, 1989). Secondly, the unconscious steady state of sleep, which is characterized by the lowest basal metabolic rate, temperature, rate of breathing, tidal volume, heart rate and blood pressure. In contrast to the previous state, this state is not a mean level around which the variables oscillate, but it is the lowest possible steady level to be asymptotically reached.

The decline in metabolic rate is very fast at the beginning of sleep, slowing as stage two of NREM sleep is approached and reaching the lowest possible value during phases three and four of NREM sleep. This time course results in a classic asymptotic approach to the basal metabolic baseline values (Fraser *et al.* 1989; Fontvieille *et al.* 1994; Zhang *et al.* 2002), as is shown in the accompanying figure for energy expenditure (Fig. 4). Similar asymptotic declines have been demonstrated for breathing rate and tidal volume (Colrain *et al.* 1987), temperature (Palca *et al.* 1986; Edwards *et al.* 2002), heart rate and blood pressure changes (Ohkubo *et al.* 2002; Sherwood *et al.* 2002) during sleep. Hence while the resting conscious state is stable in the sense of Lyapounov, the resting state of NREM sleep's stages three and four seem to be an asymptotically stable state, thus becoming a global attractor.

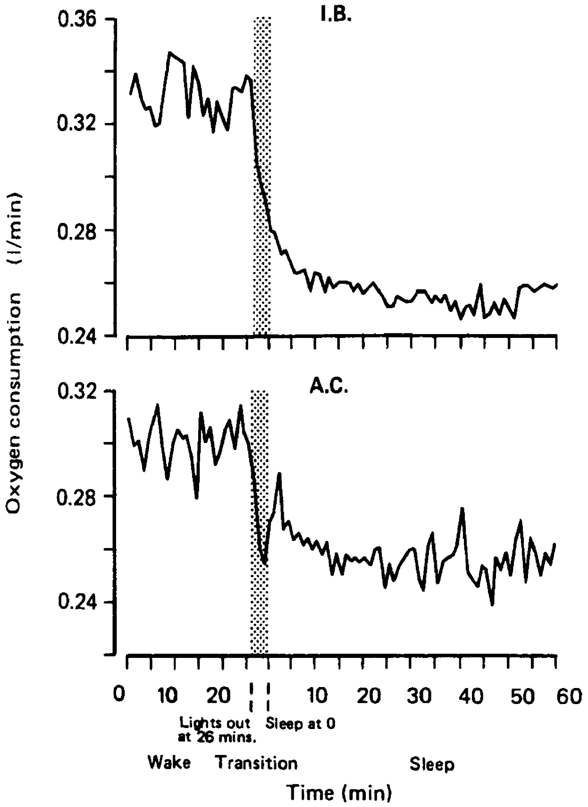

Figure 4. Example of an asymptotic approach of a state variable, the oxygen consumption, to a steady state at the beginning of sleep

Data shown are from 25 min before lights out to 60 min after onset of stage two sleep for two normal subjects (I.B. and A.C.). Variable duration transition period has been plotted as quartiles and is shown in shaded portion of the graph. After lights out the oxygen consumption spontaneously and asymptotically declines towards the steady state. Other cardiovascular and respiratory variables, and temperature, show similar time-course changes. Partial representation of Fig. 3 from Fraser *et al*. (1989). Reproduced with permission from the authors and the publisher.

Figure 5 schematically shows the two spontaneous resting steady states for the variable X as a function of time. These two spontaneous steady states of rest are representative of the constancy of the internal environment and of homeostasis. When in the appropriate environmental and subjective conditions healthy human beings, whatever race and culture, hence independently of inherited initial conditions, should be able to reach these stable states, thus confirming that the genome, metabolism and neurohumoral control have been progressively shaped in relation to environmental conditions (Recordati, 2002, 2003).

Sustained muscle exercise, although an active, non-spontaneous and non-resting state, is sometimes also called a steady state. It has been included in Fig. 5, top trace, to give the idea that it is positioned fairly above the resting states, in as much as it requires sympathetic activation, vagal withdrawal and maximum metabolic rate. Although stability for open systems far away from equilibrium has not yet been defined, it probably is an unstable state (Nicolis & Prigogine, 1989). This state is under volitional control, the so-called central command (Rowell, 1993). If heart rate and cardiac output are taken as representative state variables and expressed as percent of the final response, they tend to approach the maximum exercise level asymptotically (Rowell, 1993). As soon as the central command is halted, all these variables rapidly decline towards pre-exercise levels following a progressive and asymptotic time-course change. Figure 5 schematically illustrates variables changes during and after exercise according to the classic work by Rowell (1993) which recalls the top of a relief used by Prigogine to illustrate an unstable state (Nicolis & Prigogine, 1989).

An additional stationary steady state which has been represented in Fig. 4, is that of hibernation. As in the case of sleep, this behaviour is introduced by withdrawal of sympathetic tone and progressive reinforcement of vagal tone (Recordati, 2003). As a time-dependent variable

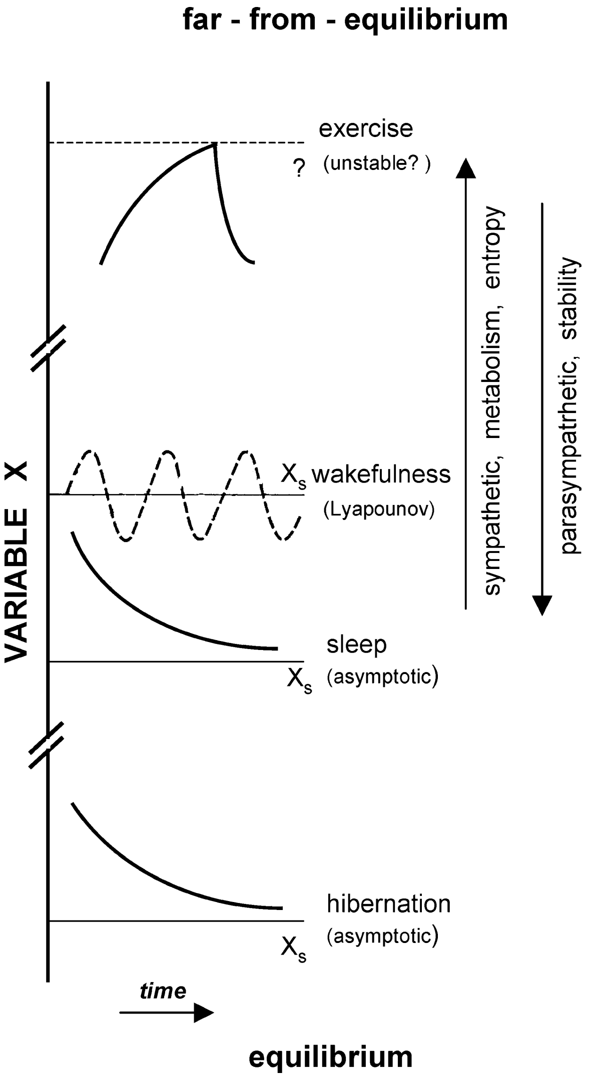

Figure 5. Schematic diagram of the two main spontaneous steady states of rest, quiet wakefulness and sleep, and of the unstable state of exercise in humans (top trace) and of the stable state of hibernation in eterothermic mammals (bottom trace)

Each state is composed of a time-independent state (X_S) and of a time-dependent state variable x(*t*), thus being asymptotically stable (hibernation and sleep), stable in the sense of Lyapounov (quiet wakefulness) or unstable (muscle exercise). With the exception of hibernation, all other states occur at an increasing distance from thermodynamic equilibrium. The upward and downward arrows on the right of the scheme indicate the directions of displacement of the reference states under prevailing sympathetic or parasympathetic influences. The parasympathetic drive moves the reference state towards equilibrium, favouring homeostasis and stability. Sympathetic dominance shifts the reference state away from equilibrium, simultaneously increasing metabolic rate and entropy production. The interval between sleep and exercise describes the normal range of neurohumoral control.

typical of this state, the body temperature of an hibernating alpine marmot is illustrated in Fig. 5, temperature asymptotically declining toward the steady level of ambient temperature (Ortmann & Heldmaier, 2000). During bouts of torpor, however, the hibernators accumulate sleep debt, and the central nervous system undergoes progressive disorganization and alterations, while visceral organs such as the liver and the kidneys halt their functionality (Buck & Barnes, 2000). These mammals should regularly arise from torpor reactivating their metabolism, to increase brain temperature to be able to sleep, and to recover and reorganize their nervous and visceral functions (Buck & Barnes, 2000).

The periods of transition from an active to a resting state (from exercise to quiet wakefulness, from this to sleep and from euthermia to torpor) are all characterized by an asymptotic decline of the variable towards the corresponding time-independent resting state and by sympathetic withdrawal and parasympathetic reinforcement. This asymptotic ‘off’ response may represent the final output of the complex interactions between autonomic nervous system, metabolism and target organ function and it has been used as a predictor of morbidity and mortality in cardiovascular function testing (Cole *et al.* 1999; Recordati, 2003).

The homeostatic controller

The hypothalamic centres integrating and regulating body temperature, fluid volume, composition (osmolality) and pressure, and metabolic energy exchanges, may be viewed as a complex thermodynamic controller. Within the general frame of nonequilibrium thermodynamics it appears that this neurohumoral control may start at a given distance from equilibrium, requiring metabolic rate and body temperature above a given threshold which has yet to be measured.

In homeotherms the displacement of the resting steady state X_S above this level is related not only to the stability of the system's state, but also to metabolism, entropy changes and the autonomic nervous system function. In heterotherms the downward displacement toward torpor metabolic rate is largely caused by a direct temperature effect and by metabolic inhibition (Song *et al.* 1997).

The range between sleep and strenuous exercise, inside which all the internal variables are under ordered neurohumoral control, may be increased by both physical (Rowell, 1993) and mental training (Wallace *et al.* 1971). It is known that, while physical conditioning improves cardiac output and oxygen utilization (Rowell, 1993), raising their upper level, transcendental meditation may induce a wakeful hypometabolic state (Wallace *et al.* 1971;

Recordati, 2003). Figure 5 therefore not only illustrates the two main spontaneous resting steady states which quantify the concept of the homeostasis of the internal variable, but also the normal range inside which ordered neurohumoral regulation should occur. The positioning along the ordinate axis of the two resting steady states is also the result of the sympathetic and parasympathetic interactions at the target organ level, thus becoming a measurable index of the so-called sympatho-vagal balance.

Figure 5 also illustrates that, with respect to the general nonequilibrium thermodynamic frame, the sympathetic moves towards far from equilibrium, for example by increasing gradients, while the parasympathetic moves towards equilibrium, increasing stability and favouring the steady states of rest. Amongst these two complementary and differently directed vectorial forces the main homeostatic agency is therefore the parasympathetic and not the sympathetic nervous system (Recordati, 2003). The disengagement from the external environment, which is essential to parasympathetic dominance, is addressed to favour self-protection, control and recovery and perhaps to minimize sympathetic nervous control with respect to driving influences from genome, metabolism and endocrine systems. In other words, if homeostasis is used to indicate an 'equifinal' spontaneous stable state of rest, an increase of the parasympathetic tone will address variables towards this state, while a sudden vagal withdrawal and a simultaneous increase in sympathetic activity will activate processes, fluxes and exchanges, which will displace the variables away from it.

Hence also from the approach proposed here it is possible to confirm the already reached conclusion that the parasympathetic division, and not the sympathetic division, is the main controller of homeostasis and stability (Recordati, 2002, 2003).

Stable states are also characterized by the minimum entropy production and maximum efficiency (Andresen *et al.* 2002), which is to say that during sympathetic activation which moves the system away from equilibrium, the efficiency of visceral organs probably declines, as it has been clearly demonstrated for cardiac contraction under adrenergic influences (Suga, 1990). Hence the parasympathetic drive contributes not only to stability but also to the efficiency of target organs function.

Conclusions

A thermodynamic approach has been proposed here to preliminarily quantify a basic concept of integrative physiology that is still waiting for dimensions. The definition of the constancy of the internal variables and environment and its attendant theory of homeostasis has been based on the description of two nonequilibrium stationary steady states of rest spontaneously occurring in mammals. Both these states are characterized by time-dependent variables fluctuating around or near time-independent constant states of reference. Amongst these states of rest, quiet wakefulness seems to be only locally stable, whereas NREM sleep stages III and IV are the globally stable and attractive states nearest thermodynamic equilibrium. The hypothalamus, which is the thermodynamic controller, handles these states as suitable homeostatic set-points through the integrated actions of sympathetic and parasympathetic nervous systems, the latter appearing to be the autonomic division in charge of control, stability and efficiency of visceral organs.

References

Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC & Cohen RJ (1981). Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* **213**, 220–222.

Andresen B, Shiner JS & Uelingher DE (2002). Allometric scaling and maximum efficiency in physiological eigen time. *Proc Natl Acad Sci* **99**, 5822–5824.

Atkins PW (1990). *Physical Chemistry*. 4th edn. Oxford University Press, Oxford.

Badra LJ, Cooke WH, Hoag JB, Crossman AA, Kuusela TA, Tahvanainen KUO & Eckberg DL. (2001). Respiratory modulation of human autonomic rhythms. *Am J Physiol* **280**, H2674–H2688.

Bernard C (1865). *Introduction a l'Etude de la Médicine Expérimentale*. JB Baillière, Paris.

Bernard C (1878). *Lècons Sur les Phénomènes de la Vie Communs aux Animaux et aux Vegetaux*. J.B.Baillière, Paris.

Boltzman L (1905). *Populare Schriften.* JA Barth, Leipzig.

Brebbia DR & Altshuler KZ (1965). Oxygen consumption rate and electroencephalographic stage of sleep. *Science* **150**, 1621–1623.

Buck CL & Barnes BM (2000). Effects of ambient temperature on metabolic rate, respirator quotient, and torpor in an arctic hibernator. *Am J Physiol* **279**, R255–R262.

Cannon WB (1929). Organization for physiological homeostasis. *Physiol Rev* **9**, 399–431.

Cannon WB (1932). *The Wisdom of the Body*. WW Norton, New York.

Cannon WB (1939). The William Henry Welch Lectures. I. Some new aspects of homeostasis. *J Mount Sinai Hosp* **5**, 587–597.

Cannon WB (1953). *Bodily Changes in Pain, Hunger, Fear and Rage*. 2nd edn. Charles T. Branford Company, Boston.

Cannon WB, Newton HT, Bright EM, Menkin V & Moore RM (1929). Some aspects of the physiology of animals surviving complete exclusion of the sympathetic nerve impulses. *Am J Physiol* **89**, 84–107.

Carandente F (1984). Mesor hypertension. *Chronobiology* **11**, 189–204.

Cole CR, Blackstone EH, Pashkow FJ, Snader CE & Lauer MS (1999). Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* **341**, 1351–1357.

Colrain IM, Trinder J, Fraser G & Wilson GV (1987). Ventilation during sleep onset. *J Appl Physiol* **63**, 2067–2074.

Darveau C-A, Suarez BK, Andrews RD & Hochachka PW (2002). Allometric cascade as a unifying principle of body mass effects on metabolism. *Nature* **417**, 166–170.

Edwards B, Waterhouse J, Reilly T & Atkinson G (2002). A comparison of the suitabilities of rectal, gut, and insulated axilla temperatures for measurement of the circadian rhythm of core temperature in field studies. *Chronobiol Int* **19**, 579–597.

Ellis B (1966). *Basic Concepts of Measurement*. Cambridge University Press, London.

Fontvieille AM, Rising R, Spraul M, Larson DE & Ravussin E (1994). Relationship between sleep stages and metabolic rate. *Am J Physiol* **267**, E732–E737.

Fraser G, Trinder J, Colrain IM & Montgomery I (1989). Effect of sleep and circadian cycle on sleep period energy expenditure. *J Appl Physiol* **66**, 830–836.

Gillooly JF, Charnov EL, West GB, Savage VANM & Brown JH (2002). Effects of size and temperature on developmental time. *Nature* **417**, 70–73.

Hess WR (1957). *The Functional Organization of the Diencephalon.* Grune & Stratton, New York.

Hobson JA & Steriade M (1986). Neuronal basis of behavioral state control. In *Handbook of Physiology.* Section 1, The Nervous System, vol IV, Lutrinsic regulatory systems of the brain, ed. Mountcastle VB, Bloom FE & Geiger SR, pp. 701–823. American Physiological Society, Bethseda, MD.

Kondepudi D & Prigogine I (1998). *Modern Thermodynamics. From Heat Engines to Dissipative Structures*. Wiley, Chichester, UK.

Kreyszig E (1988). *Advanced Engineering Mathematics*, 6th edn. Wiley & Sons, New York. p. 169.

Lee C-K, Klopp RG, Weindruch R & Prolla TA (1999). Gene expression profile of aging and its retardation by caloric restriction. *Science* **285**, 1390–1393.

Milsom WK, Zimmer MB & Harris MB (1999). Regulation of cardiac rhythm in hibernating mammals. *Comparative Biochem Physiol A* **124**, 383–391.

Nicolis G & Prigogine I (1989). *Exploring Complexity*. Freeman, New York.

Niima Y, Iwase S, Fu Q, Kamiya A & Mano T (2000). Effect of aging on muscle sympathetic nerve activity and peripheral venous pressure in humans. *Environ Med* **44**, 56–59.

Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, Matsubara M, Hashimoto J, Hoshi H, Araki T, Tsuji I, Satoh H, Hisamichi S & Imai Y (2002). Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypert* **20**, 2183–2189.

Ortmann S & Heldmaier G (2000). Regulation of body temperature and energy requirements of hibernating Alpine marmots (Marmota marmota). *Am J Physiol* **278**, R698–R704.

Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S & Piccaluga E (1986). Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho–vagal interaction in man and conscious dog. *Circ Res* **59**, 178–193.

Palca JW, Walker JM & Berger RJ (1986). Thermoregulation, metabolism, and stages of sleep in cold-exposed men. *J Appl Physiol* **61**, 940–947.

Porges SW (1995). Cardiac vagal tone: a physiological index of stress. *Neurosci Biobehav Rev* **19**, 225–233.

Recordati G (1984). The functional role of the visceral nervous system. A critical evaluation of Cannon's 'Homeostatic' and 'Emergency' theories. *Arch It Biol* **122**, 249–267.

Recordati G (1989). *The Visceral Nervous System: Homeostasis and the Dissipative Structure*. International Union of Physiological Sciences, Satellite Symposium on: Central and Peripheral Interrelations between Blood Pressure Control Mechanisms. *Abstract Book. Wilhelm Pieck University* Rostock/GDR, pp. 20–21.

Recordati G (1999). The contribution of the giraffe to hemodynamic knowledge: a unified physical principle for the circulation. *Cardiologia* **44**, 783–789.

Recordati G (2002). The visceral nervous system and its environments. *J Theor Biol* **214**, 293–304.

Recordati G (2003). A thermodynamic model of the sympathetic and parasympathetic nervous system. *Auton Neurosci* **103**, 1–12.

Rowell LB (1993). *Human Cardiovascular Control*. Oxford University Press, Oxford.

Schrödinger E (1944). *What Is Life ?* Cambridge University Press, Cambridge.

Sherwood A, Steffen PR, Blumenthal JA, Kuhn C & Hinderliter AL (2002). Nighttime blood pressure dipping: the role of the sympathetic nervous system. *Am J Hypert* **15**, 111–118.

Song X, Körtner G & Geiser F (1997). Thermal relations of metabolic rate reduction in a hibernating marsupial. *Am J Physiol* **273**, R2097–R2104.

Suga H (1990). Ventricular energetics. *Physiol Rev* **70**, 247–277.

Toussaint O, Remacle J, Dierick J-F, Pascal T, Frippiat C, Royer V & Chainieux F (2002). Approach of evolutionary theories of ageing, stress, senescence-like phenotypes, calorie restriction and hormesis from the view point of far-from-equilibrium thermodynamics. *Mech Age Dev* **123**, 937–946.

Valtin H & Schafer JA (1995). *Renal Function*. Little, Brown and Co., Boston.
Van Lieshout JJ, Wieling W & Karemaker JM (1997). Neural circulatory control in vasovagal syncope. *Pacing Clin Electrophysiol* **20**, 753–763.
Von Bertalanffy L (1939). The theory of open systems in physics and biology. *Science* **111**, 23–29.
Von Bertalanffy L (1969). *General System Theory*. G. Braziller, New York. p. 143.
Wallace RK, Benson H & Wilson AF (1971). A wakeful hypometabolic physiologic state. *Am J Physiol* **221**, 795–799.
West GB, Woodruff WH & Brown JH (2002). Allometric scaling of metabolic rate from molecules and mitochondria to cells and mammals. *Proc Natl Ac Sci* **99**, 2473–2478.
Wieling W & Karemaker JM (1999). Measurement of heart rate and blood pressure to evaluate disturbances in neurocardiovascular control. In: *Autonomic Failure*, ed. Mathias CJ & Bannister R, pp. 196–210. Oxford, New York.
Yates FE (1982). The 10th J.A.F. Stevenson Memorial Lecture. Outline of a physical theory of physiological systems. *Can J Physiol Pharmacol* **60**, 217–248.
Zhang K, Sun M, Werner P, Kovera AJ, Albu J, PI-Sunyer FX & Boozer CN (2002). Sleeping metabolic rate in relation to body mass index and body composition. *Int J Obes* **26**, 376–383.

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