Homeostasis from a Time-Series Perspective: An Intuitive Interpretation of the Variability of Physiological Variables

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Abstract Homeostasis implies the approximate constancy of specific *regulated variables*, where the independence of the internal from the external environment is ensured by adaptive physiological responses carried out by other so-called

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effector variables. The loss of homeostasis is the basis to understand chronic-degenerative disease and age-associated frailty. Technological advances presently allow to monitor a large variety of physiological variables in a non-invasive and continuous way and the statistics of the resulting physiological time series is thought to reflect the dynamics of the underlying control mechanisms. Recent years have seen an increased interest in the variability and/or complexity analysis of physiological time series with possible applications in pathophysiology. However, a general understanding is lacking for which variables variability is an indicator of good health (e.g., heart rate variability) and when on the contrary variability implies a risk factor (e.g., blood pressure variability). In the present contribution, we argue that in optimal conditions of youth and health regulated variables and effector variables necessarily exhibit very different statistics, with small and large variances, respectively, and that under adverse circumstances such as ageing and/or chronic-degenerative disease these statistics degenerate in opposite directions, i.e. towards an increased variability in the case of regulated variables and towards a decreased variability for effector variables. We demonstrate this hypothesis for a simple mathematical model of a thermostat, and for blood pressure and body temperature homeostasis for healthy controls and patients with metabolic disease, and suggest that this scheme may explain the general phenomenology of physiological variables of homeostatic regulatory mechanisms.

1 Introduction

Homeostasis is one of the core concepts of physiology [1]. The origins of this concept can be found with the French physiologist Claude Bernard (1813–1878) who observed that living systems possess an internal stability that buffers and protects the organism against a continuously changing external environment [2]. Although Bernard was highly honoured and was the most famous French scientist during his lifetime, his hypothesis of a constant *milieu intérieur*, first proposed in 1854, was largely ignored for the next 50 years, one of the reasons being that the technology necessary to measure the internal environment was not yet available [3]. These ideas were expanded and popularized by the American physiologist, Walter Cannon (1871–1945), who coined the term *homeostasis* from the Greek words όμοιος [omoios] "similar" and στάσις [stasis] "standing still", together to mean "staying similar" (but not to be misunderstood as "staying the same") [4]. Homeostasis thus describes the *self-regulating processes* by which a biological system maintains internal *stability* while *adapting* to changing environmental conditions [1, 4]. Homeostatic ideas are shared by the science of *cybernetics*, from the Greek κυβερνητικός [kybernitikos] "steersman", defined in 1948 by the

Jewish American mathematician Norbert Wiener (1894–1964) in collaboration with the Mexican physiologist Arturo Rosenblueth (1900–1976) as "the entire field of control and communication theory, whether in the machine or in the animal" [5]. *Negative feedback* is a central homeostatic and cybernetic concept, referring to how an organism or system automatically opposes any change imposed upon it that could move it away from a predefined *setpoint* [6]. More recently, it has been proposed that there may be other or additional mechanisms important for physiological regulation, not explicitly contained within the original homeostatic concept, in particular *anticipatory regulation*, *behavioural homeostasis* and *feedforward* or *positive feedback*, such that numerous alternative explanatory models have been suggested in an effort to address these apparent gaps in homeostatic thinking, as listed in Ref. [7]: enantiostasis [8], predictive homeostasis [9], reactive homeostasis [9], homeorhesis [10–13], homeorheusis [14], homeokinetics [15], rheostasis [16], homeodynamics [17–19], teleophoresis [20, 21], poikilostasis [22], heterostasis [23], allodynamic regulation [24, 25] and allostasis [26–28]. Others argue that it is not clear whether these alternative concepts offer anything that was not already apparent, or at least readily derivable, from the original concept of homeostasis, and—on the contrary— criticize that these neologisms may unnecessarily complicate the understanding of the unifying principles of physiological regulation [29, 30].

Recently, technological advances allow to monitor a great variety of physiological variables in a non-invasive and continuous way and it came as a surprise that most—if not all—of these variables spontaneously fluctuate in time, even when the monitored subject is in rest. Often, these fluctuations behave in a stochastic and fractal-like way and without obvious periodic patterns [31]. The *variability* of these time series can be studied with various statistical techniques and is conjectured to correlate with the health status of the organ, process or system under study [32], as found, e.g., for the variability of blood oxygen saturation (SpO_2) [33], blood glucose variability [34], variability of gastro-esophageal acidity [35], brain signal variability [36], gait variability [37], heart rate variability (HRV) [38], blood pressure variability (BPV) [39], variability of breathing dynamics [40], skin temperature variability [41, 42] and variability of core body temperature [43, 44], variability of electrodermal activity (EDA) [45], variability of equilibrium and balance function [46] and variability of physical activity (actigraphy) [47– 50]. Measurement devices capable of continuous physiological monitoring have become ubiquitous, not only in the medical world but also in the consumer market with a wide variety of activity trackers, smartphones, smartwatches and dedicated applets for data collection, analysis and visualization [51]. These specialized and commercial devices generate huge amounts of data, which are also continuous in time. It is not always clear how to extract the useful information from this new type of continuous data, which is exactly the quest of *time series* analysis [52] in the so-called *Big Data* problem [53]. Also, the phenomenology of these physiological time series is not always well understood, where curiously, for some variables a high variability is interpreted an indication of good health, as in the case of HRV [38], whereas in other cases—on the contrary—it has been suggested to imply a risk factor, as in the case of BPV [39].

In literature, at least two different theoretical frameworks have been proposed to explain the variability of experimental time series in physiology and other fields of knowledge. The *loss of complexity* hypothesis of Goldberger and Lipsitz proposes that the geometrical patterns of anatomical organ structures and the time series of the dynamics of physiological processes are inherently "complex" with a large variability that is increasingly lost with ageing and/or chronic-degenerative disease [31, 54–57]. In the same context, based on the empirical observation that physiological time series tend to follow long-tailed distributions with rare but large deviations away from the mean as opposed to a gaussian distribution with frequent but small fluctuations around a setpoint, Bruce West suggested that the ideas of homeostasis and normality are obstacles for the progress of medicine and that a new paradigm, *fractal physiology*, is needed [58–60]. On the other hand, the framework of *early-warning signals* of Scheffer, Carpenter and collaborators, particularly popular in complex dynamical systems such as the climate, ecology and finance, states that—on the contrary—variables of a system in a state of stability and equilibrium behave in a gaussian way with low variability and little correlation or memory of past events, whereas when the system approaches a critical threshold at the brink of collapse, statistical parameters such as variability, non-gaussianity, correlations and memory tend to increase, and—if they are detected early enough—offer the opportunity to take countermeasures to avoid a catastrophe [61–65].

Homeostatic thinking divides physiological variables in two broad categories of regulated variables as opposed to effector variables, see Table 1 and Ref. [1]. *Regulated variables*, such as blood pressure (BP) or core body temperature, are variables that are to be controlled and to be maintained within a very restricted homeostatic range to ensure the stability of the *milieu intérieur* and they are anatomically distinguishable because of the presence of specific sensors that measure the value of these variables directly; an alternative name could be that of essential variables [66]. On the other hand, *effector variables* and the corresponding *physiological responses*, such as heart rate (HR) or skin temperature, have an adaptive function, they oppose and thereby buffer against perturbations from the inner and outer environment with an objective to maintain the regulated variables as constant as possible; they do not have their own specific sensors,[1] which may suggest that their absolute values are not of primary importance but matter only because of the effect they have on the regulated variables. In the present contribution, we hypothesize that time series of regulated and effector variables can be expected to exhibit very contrasting statistical properties given their different functions in a homeostatic regulatory mechanism, which may explain the apparent contradictions between the loss of complexity and early-warning paradigms. We test this hypothesis in various systems, in Sect. 2 using a simple mathematical model of a thermostat, in Sect. 3

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[1]The skin of course does have its own thermosensors, but they are part of a *reflex loop* and not of a local *homeostatic control loop*: when touching something extremely warm or cold, there will be an automatic reaction to move the fingers away, but not a physiological response to locally cool off or warm up the skin to maintain a constant skin temperature.

Table 1 As a first approximation, different homeostatic mechanisms may be considered to coexist in a more or less independent way. The focus of each homeostatic mechanism is a specific *regulated variable* that is to be maintained within a restricted homeostatic range, and therefore use is made of one or more supporting *effector variables* and corresponding *physiological responses* whose function it is to absorb or adapt to variations of the inner and outer environments, with as an objective to safeguard the constancy of the regulated variable as much as possible, based on Refs. [1, 67]. In the present contribution, we will focus on the first few mechanisms of which the variables can be monitored in a continuous and non-invasive way

Homeostatic regulatory mechanisms	
Regulated variable	Effector variable(s) and physiological response(s)
(specific sensors available for direct measurement)	(indirect estimation by effect on regulated variable)
Arterial blood pressure (BP)	Cardiac output (heart rate, stroke volume)
(baroreceptors)	Vasomotor (vasodilatation, vasoconstriction)
Core body temperature	Vasomotor and superficial skin temperature
(thermoreceptors)	Metabolism
	Shivering vs. sudomotor
	Behaviour and physical exercise
Blood oxygen saturation (SpO$_2$)	Respiration dynamics (rate, volume)
(chemosensors)	Erythropoietin (EPO) increasing hematocrit (Ht)
Blood oxygen P$_{O_2}$ and carbon dioxide partial pressure P$_{CO_2}$ (chemosensors)	Respiration dynamics (rate, volume)
	P$_{CO_2}$ closely related to extracellular fluid pH
Extracellular fluid pH	Bicarbonate concentration [HCO$_3$]
(chemosensors)	Carbonic acid concentration [H$_2$CO$_3$]
Blood glucose	Insulin
(chemosensors)	Glucagon
Plasma ionized calcium concentration [Ca^{2+}]	Parathyroid hormone (PTH)
(chemosensors)	Calcitonine
Extracellular sodium concentration [Na]	Renin and related aldosterone
(chemosensors)	
Extracellular potassium concentration [K]	Aldosterone
(chemosensors)	
Volume of body water and electrolyte-water balance	Vasopressin or antidiuretic hormone (ADH)
osmolality or osmolarity	Atrial natriuretic peptide (ANP)
(osmosensors)	Thirst

analysing HR and BP time series of healthy controls and diabetic patients, in Sect. 4 focussing on time series of skin temperature as a function of body weight, while in Sect. 5 we propose an intuitive scheme that may explain the phenomenology of variability of physiological variables in general, and finally, in Sect. 6 we present our conclusions.

2   The Thermostat as a Paradigm for Homeostasis

The term *thermostat* is derived from the Greek words ϑερμός [thermos] "hot" and
στατός [statos] "standing, stationary" and refers to a controlling component which
senses a system's temperature and allows for this temperature to be maintained near
a desired setpoint. In cybernetics and control theory, a *setpoint* is the desired or
target value for a specific regulated variable of a system. A thermostat can often
be the main control unit for a heating or cooling system, in applications such as
ambient air control and sometimes a thermostat combines both the sensing and
control action elements of a controlled system, such as in an automotive thermostat,
see Fig. 1. It is an example of a *closed-loop control* device and departure of a variable
from its setpoint is the basis for *error-controlled regulation*, that is, the use of
negative feedback to return the system to its norm, as in homeostasis. A thermostat
is most often an instance of a *bang-bang controller* where the heating system is
switched on and off as often as necessary. It works by sensing the air temperature,
switching on the heating when the air temperature falls below the thermostat setting,
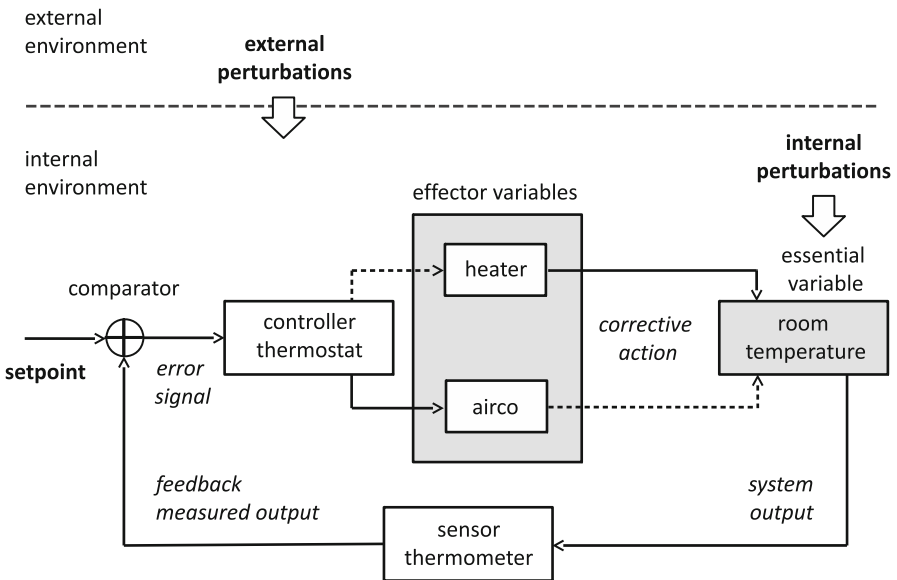

Fig. 1 The control mechanism of a thermostat. The control mechanism is based on a negative
feedback loop which acts to maintain the regulated variable of the room temperature within a
narrow homeostatic range. The effector variables of the heater and/or the airconditioning allow for
the system to adapt to perturbations from the outside and inside environment. A negative feedback
loop necessarily consists of an odd number of inhibitory/negative couplings (dashed lines) where
connected components are inversely related (an increase in one component induces a decrease
in the other component and vice versa) and an arbitrary number of excitatory/positive couplings
(continuous lines) where connected components are directly related (an increase in one component
induces an increase in the other component and vice versa). Image based on Refs. [1] and [67]

and switching it off once this set temperature has been reached. The heating or cooling equipment runs at full capacity until the set temperature is reached, then shuts off. Other, more advanced controller mechanisms include *proportional controllers*, *proportional–integral–derivative controllers* (or *PID controllers*) and *optimal controllers*. More advanced controllers will be more adaptive, will absorb the perturbations of the inner and outer environment more effectively in the effector variables, or will incorporate a memory of past events, to predict and anticipate future perturbations, with a general objective to minimize more efficiently the error signal between the expected and the obtained values of the regulated variable.

In what follows, in Figs. 2 and 3, we will show the numerical results for a simple mathematical model of the thermostat of Refs. [68, 69], which includes a heater but no airconditioning, to illustrate the statistical differences of time series corresponding to a regulated variable (the inside air temperature) and an effector variable (the heater). The model includes the following variables: outdoor air temperature T_o, indoor air temperature T_i, water temperature of the radiators T_w and a binary function θ_f that indicates whether the furnace of the boiler is active (state 1) or not (state 0). The initial values at $t = 0$ are $T_i(0) = 13\,°C$ and $T_w(0) = 10\,°C$. The thermostat is fixed at the constant setpoint $T_s = 20\,°C$. Heat is transferred between the radiators and the indoor air at a rate $r_1 = 0.03$ proportional to the temperature gradient, heat is lost from the indoor to the outdoor air at a rate $r_2 = 0.01$ due to imperfect insulation, heat is transferred between the indoor air and the water of the boiler at a rate $r_3 = 0.02$, and $r_4 = 1.0$ is the rate at which the water of the boiler heats up when the furnace is switched on. The system is controlled by three coupled difference equations that update the values at time $t + 1$ depending on the values at the previous time step t. We assume that the system updates its values each minute.

$$\theta_f(t + 1) = \begin{cases} 1 \text{ if } T_i(t) < T_s(t) \\ 0 \text{ if } T_i(t) \geq T_s(t) \end{cases} \tag{1}$$

$$T_i(t + 1) = T_i(t) + r_1\Big(T_w(t) - T_i(t)\Big) + r_2\Big(T_o(t) - T_i(t)\Big) \tag{2}$$

$$T_w(t + 1) = T_w(t) + r_3\Big(T_o(t) - T_w(t)\Big) + r_4\theta_f(t) \tag{3}$$

Figure 2 shows results for a numerical simulation of Eqs. (1)–(3) during three successive hypothetical winter days. The variation of the outside air temperature T_o was modelled using a slow linear trend and small random fluctuations superposed on a 24-h periodic cycle, with day temperatures being higher than temperatures during the night, but always lower than the thermostat setpoint $T_o < T_s = 20\,°C$, such that the thermostat control system is always active. The thermostat controller θ_f of Eq. (1) does not include memory of past events, it does not think ahead, and the value for $t + 1$ is updated taking into account only the last known inside air temperature $T_i(t)$. It can be appreciated that the thermostat switches on and off at a faster rate during the night when it is cold outside, and at a slower rate during the day when the outside air temperature is higher. The switching on and
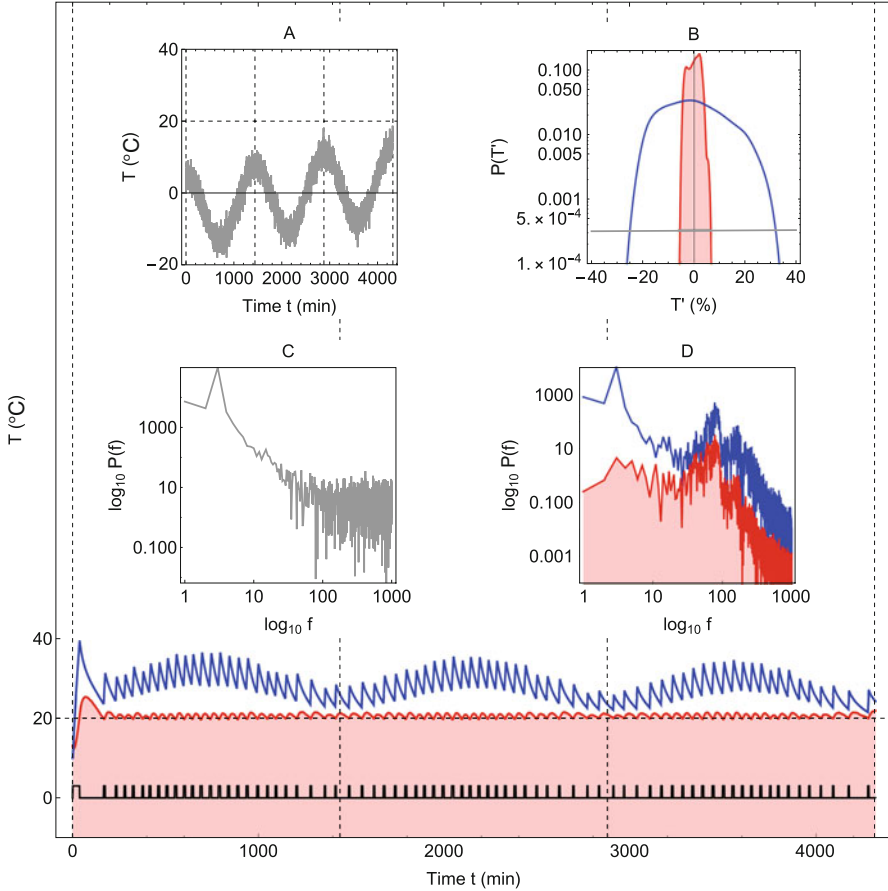
Fig. 2 Mathematical simulation of a simple thermostat based on Refs. [68, 69] for three successive hypothetical winter days. The main figure shows the dynamics of the central heating θ_f switching on and off (black curve, states 1 and 0, respectively), the water temperature in radiators T_w (blue curve) and the inside air temperature T_i (red curve) in response to the outside temperature T_o (grey curve of inset A). Shown are also the probability distributions $P(T')$ of the fluctuations T' of temperature time series T_i, T_w and T_o as a percentage of their respective average values (inset B), the Fourier power spectrum $P(f)$ for T_o (inset C) and for T_w and T_i (inset D). The horizontal gridline indicates the temperature setpoint $20\,^{\circ}$C and vertical gridlines indicate midday of the three successive days (main figure and inset A). Frequency f is in units of total number of oscillations for the whole duration of the time series

off rate of the thermostat is reflected in small but rapid fluctuations of the water temperature of the radiators, but also slower and larger periodic oscillations are present because the water of the radiators will be heated up to a higher average temperature during the night than during the day to offset the day-night difference of the outside air temperature. As a result of the heating of the radiators, the inside air temperature always stays very close and within very small rapid fluctuations from
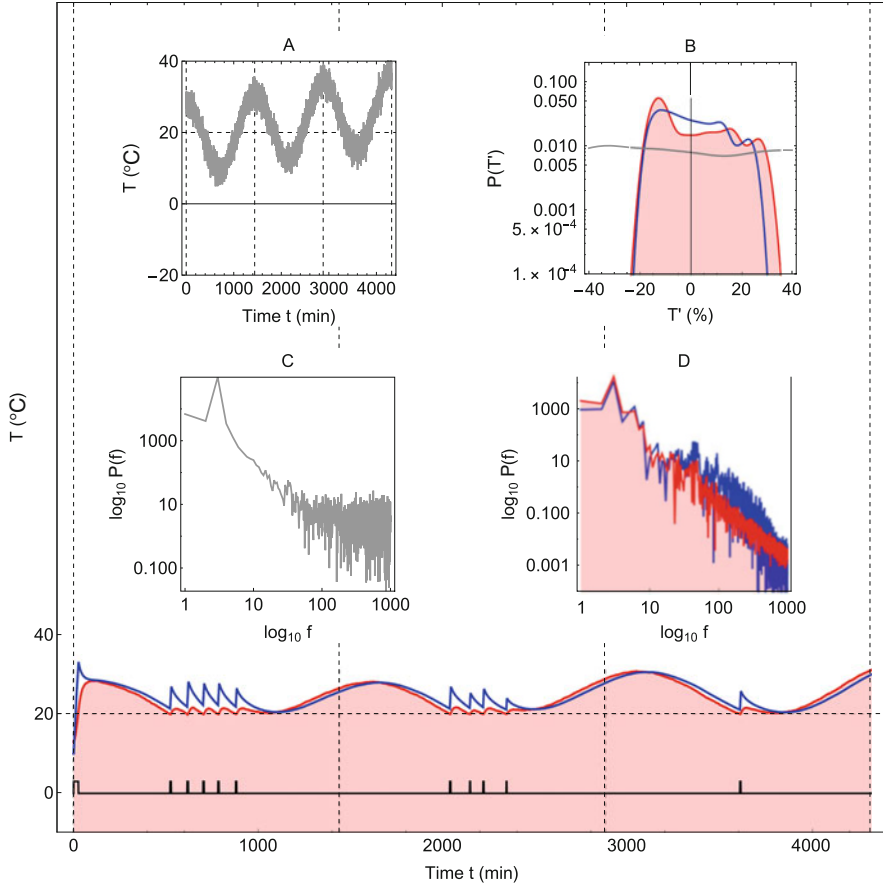
Fig. 3 Similar to Fig. 2 but for three successive hypothetical spring days

the setpoint, $T_i \approx T_s = 20\,°C$. Indeed, when we compare the probability distribution functions $P(X')$ for the fluctuations X' around the average value μ of time series $X(t)$ expressed as a percentage of this average value,

$$X(t)' = 100 \times \frac{X(t) - \mu}{\mu}, \qquad (4)$$

for the inside air temperature T_i, the outside air temperature T_o and the water of the radiators T_w, then it is clear that the variability of T_i is well controlled within a restricted range and is much smaller than the variance of T_w and that both are smaller than the variations of T_o. A Fourier spectral analysis of the corresponding time series offers additional insight into how the control mechanism works. The power spectrum $P(f)$ of the time series for T_o shows a dominant peak at $f = 3$, reflecting the periodic day-night cycle over three successive days, and is rather flat

for higher frequencies indicating random white noise. The power spectrum $P(f)$ for T_w shows the same dominant peak at $f = 3$ and an additional broad peak at higher frequencies $50 < f < 100$ corresponding to the rapid cycles of heating and cooling of the water in the radiators at multiple times during the day. On the other hand, the power spectrum $P(f)$ for T_i shows that the outside perturbation at $f = 3$ is successfully suppressed with over 2 orders of magnitude and the dominant feature of $P(f)$ is the peak at $50 < f < 100$ in response to the rapid heating and cooling cycle of the radiators. In other words, it appears that the automatic thermostat system creates its own *intrinsic rhythms*, which have small amplitude but high frequency, and with which the larger but slower outside perturbations are canceled out. For more advanced types of controllers, e.g., capable of incorporating memory about past events, we can expect that more of the outside perturbations will be absorbed in the effector variable T_w to keep the error signal $e(t) = T_i(t) - T_s$ closer to 0; in those cases, the statistical differences between the time series of the effector variable T_w and the regulated variable T_i will be even larger than in the present example.

Figure 3 shows the behaviour of the system during three successive hypothetical days in spring time when the temperature during the night is still below the setpoint, $T_o < T_s$, but the temperature during the day rises above the setpoint, $T_o > T_s$. Therefore, the thermostat will be inactive for most of the daytime, during which the system is incapable to influence neither the water temperature of the radiators T_w nor the inside air temperature T_i, and both are subjected to the perturbations of the outside air temperature T_o. Of course, a heating system can only correct for too-low temperatures, and an extra cooling effector device would be needed to correct also for too-high temperatures, as shown for the full climate control system of Fig. 1, but here, we are interested in studying time series of a control system where the control fails. The probability distributions functions $P(T')$ show that the fluctuations T' of the would-be regulated variable T_i now exhibit a larger variability than the fluctuations of the effector variable T_w. The power spectrum $P(f)$ shows an almost absence of intrinsic rhythms with which the outside perturbations were controlled in Fig. 2 and consequently T_i and T_w follow here the same dynamics as T_o.

3   Arterial Blood Pressure and Heart Rate

Figure 4 shows the control mechanism for blood pressure homeostasis where blood pressure (BP) is the regulated variable and with heart rate (HR), stroke volume (SV) and total peripheral resistance (TPR) as physiological responses of the effector variables, where

$$\text{cardiac output} = \text{heart rate (HR)} \times \text{stroke volume (SV)} \tag{5}$$

$$\text{blood pressure (BP)} = \text{total peripheral resistance (TPR)} \times \text{cardiac output.} \tag{6}$$
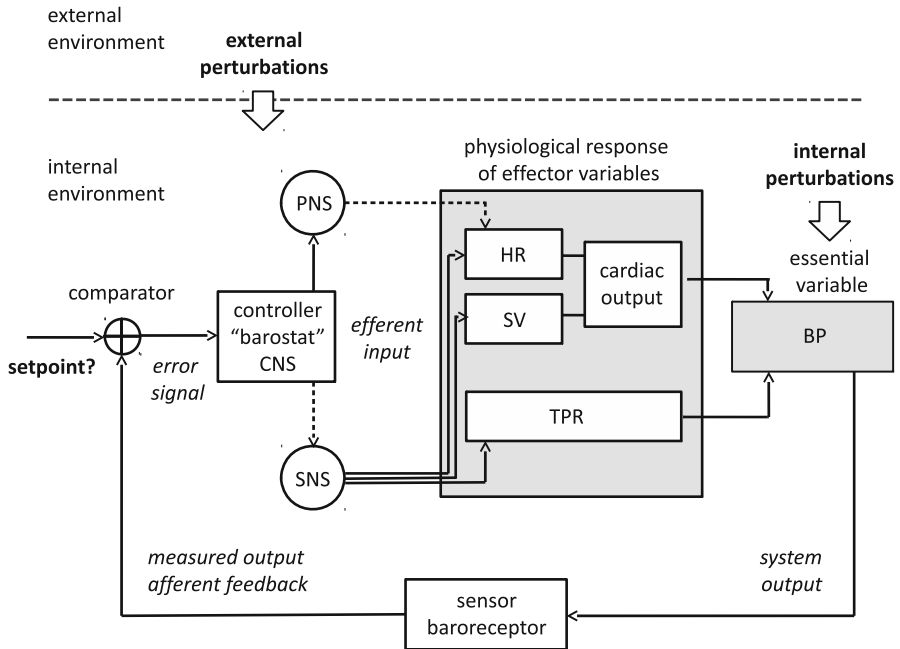
Fig. 4 Similar as for Fig. 1 but for the control loop of arterial blood pressure. The control centrum of the barostat is located in the central nervous system (CNS) which passes commands through the sympathetic (SNS) and parasympathetic (PNS) branches of the autonomous nervous system to the effector variables of heart rate (HR) and stroke volume (SV), whose product is the cardiac output, and the total peripheral resistance (TPR), which together act to maintain blood pressure (BP) in a restricted homeostatic range as measured by the baroreceptor. Image based on Refs. [1] and [67]

Of all the variables mentioned here, HR is easiest to measure on a continuous (beat-to-beat) basis, using, e.g., a common electronic electrocardiographic (ECG) registration. Also BP can be measured continuously, although in this case very specialized (and expensive!) equipment is required, such as a Finapres®, Portapres® or CNAP® device. Using a Portapres®, we collected 5-min HR and BP time series in supine resting position in 30 control subjects, 30 asymptomatic subjects with recently diagnosed type-2 diabetes (DMA) and 15 long-standing patients with type-2 diabetes (DMB), see Refs. [70, 71]. Exclusion criteria included cardiac arrhythmia, hypertension and having taken medication up to 48 h previous to the study. Time series for individual subjects are shown in Fig. 5 (left-hand panels). Average heart rate $\langle HR \rangle$ was similar for controls and the DMA group, but was significantly higher for the DMB group, whereas $\langle SBP \rangle$ was comparable for the three groups, see Fig. 6. Subtle group differences were found between the three populations for the higher-order moments of the distributions of HR and BP, such as standard deviation (SD), the coefficient of variation (CV=SD/mean) skewness
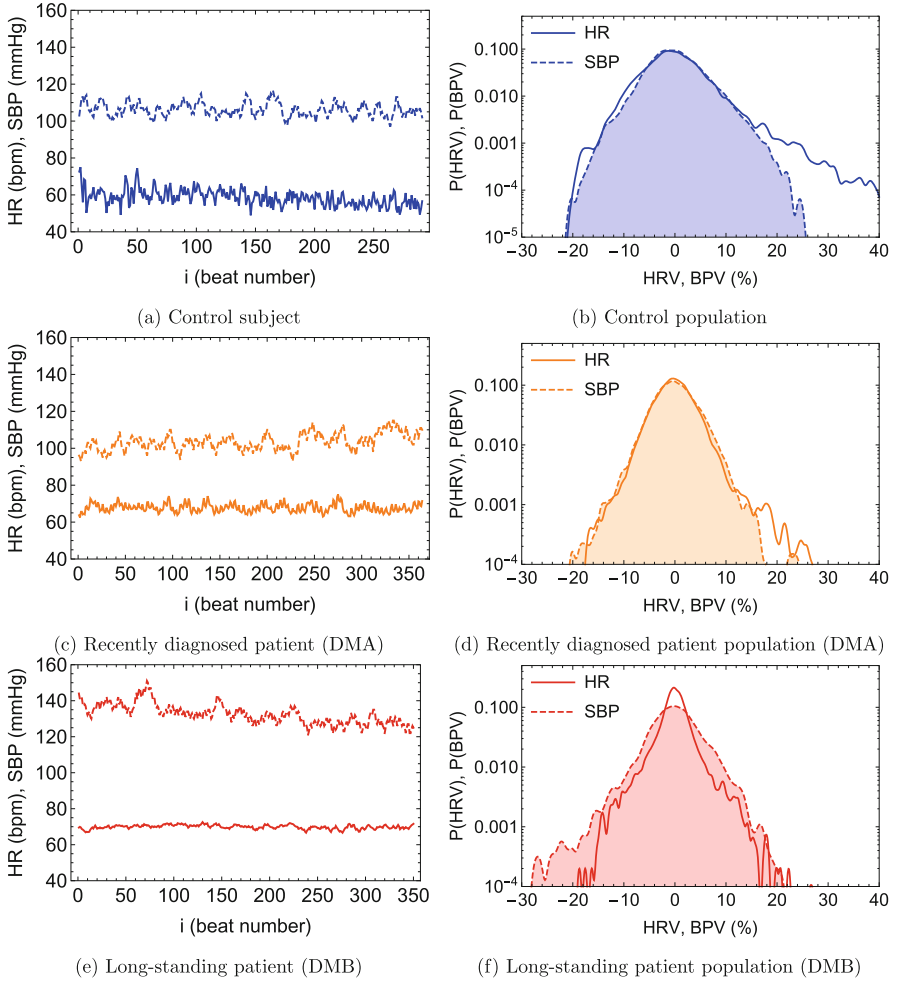
Fig. 5 Time series of individual subjects (left-hand panels) and probability distributions for populations (right-hand panels) for heart rate (HR) and blood pressure (BP) during 5min of supine rest. Shown for (**a-b**) healthy control(s), (**c-d**) recently diagnosed patient(s) and (**e-f**) long-standing patient(s). HR (continuous curves) is measured in beats per minute (bpm), BP (dashed curves) in millimeters of mercury (mmHg) and time in units of beat number. In the case of the probability distributions, in order to show both HR and BP in the same graph, fluctuations of both variables are shown as a percentage of their average value according to Eq. (4). Data from Refs. [70, 71]

(Skew) and kurtosis (Kurt), but statistical significance was obtained only when combining heart rate variability (HRV) and blood pressure variability (BPV) in a single parameter,

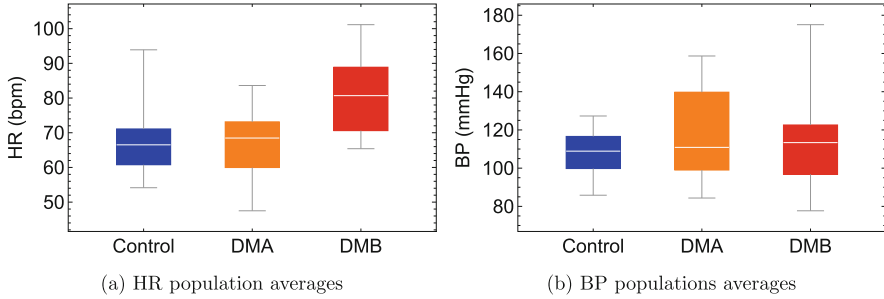$$\alpha = \frac{\text{HRV}}{\text{BPV}}, \tag{7}$$

Fig. 6 Box whisker charts of (a) average heart rate ⟨HR⟩ and (b) average systolic blood pressure ⟨BP⟩, for the control group (blue), recently diagnosed patients DMA (orange) and long-standing patients DMB (red). According to a Kruskal-Wallis nonparametric test, there are significant differences between the control-DMB and DMA-DMB pairs for ⟨HR⟩ at the $p = 10^{-4}$ level, but no significant group differences for ⟨BP⟩. Data from Refs. [70, 71]

where α is large for the control group and is found to decrease as a function of the development of the disease [70]. The interpretation of α is that HRV is a protective factor whereas BPV is a risk factor and that there is a correlation between both. Furthermore, it would seem that more than the absolute values of HRV or BPV separately, it is the relative magnitude of HRV with respect to BPV that appears to correlate with the health status of the populations considered here.

Figure 5 (right-hand panels) shows for each population the probability density functions for the fluctuations of HRV and BPV, where positive values indicate fluctuations above the average and negative values fluctuations below the average. It can be appreciated that for the control group the distribution for HRV is wider than for BPV, in particular, for HRV there is a long tail towards positive fluctuations up to 40% whereas BPV is contained within the range from -20% to $+20\%$. In the case of the DMA group, the width of the HRV probability distribution is greatly reduced and in particular the positive HRV fluctuations have decreased below 30%, whereas now the probability distribution of BPV has become wider than that of HRV towards the negative side. In the case of the DMB group, the probability distribution of BPV has become wider than that of HRV, in particular, the positive HRV fluctuations are now limited to 20%, whereas the negative BPV fluctuations have increased up to 30%. It has been argued that 5-min HR registrations are too short to contain modulations by the sympathetic nervous system (SNS) [72], especially if the registrations are made in supine resting position. Therefore, in the case of the controls, the large positive HRV fluctuations are most probably due to vagal withdrawal (vagolysis) causing temporary HR accelerations, which are probably necessary for the homeostatic control of BP. In the case of DMA, vagolytic capacity is reduced, possibly resulting in a loss of BP control and episodes of hypotension. In the case of DMB, vagolytic capacity is lost completely and BP excursions towards hypotension dominate the probability distribution of BP. It is possible that in the DMB group HR is significantly increased to counter this danger of hypotensive episodes.

4 Body Temperature

The regulation of body temperature depends on the species and the specific body part under study, see Fig. 7. Reptiles, such as lizards, are called *exotherms* and their core temperature adapts to the temperature of the outside environment. Mammals, on the other hand, are *endotherms*, and their core temperature is—over a certain range—approximately independent from the outside temperature. Humans achieve a core temperature near a constant setpoint of about $36.5\,°C$ independent from the outside circumstances by creating a dynamic balance between *thermogenesis* (heat production) and *thermolysis* (heat dissipation), see Fig. 8. In striking this balance, adaptive mechanisms play a very important role, such as cutaneous vasoconstriction when it is cold outside and cutaneous vasodilatation when it is warm, which control the amount of heat radiated from the body towards the outside environment, and consequently skin temperature can be expected to exhibit a large variability in order to keep core temperature constant.

We carried out a pilot study where we monitored skin temperature continuously over seven successive days as a function of the body mass index (weight divided by height squared, $BMI = kg/m^2$). We considered three groups, a control group with normal weight (ten subjects with $18 < BMI < 25$), a group of overweight subjects (ten subjects with $25 < BMI < 30$), and a group with obese subjects (ten subjects with $BMI > 30$) [42]. Skin temperature can be measured easily and continuously, using, e.g., a thermochron iButton® fixed at the non-dominant wrist using medical tape; core temperature is much more difficult to measure, because a probe should be introduced in a body orifice (mouth, anal, etc.) which is uncomfortable, especially in
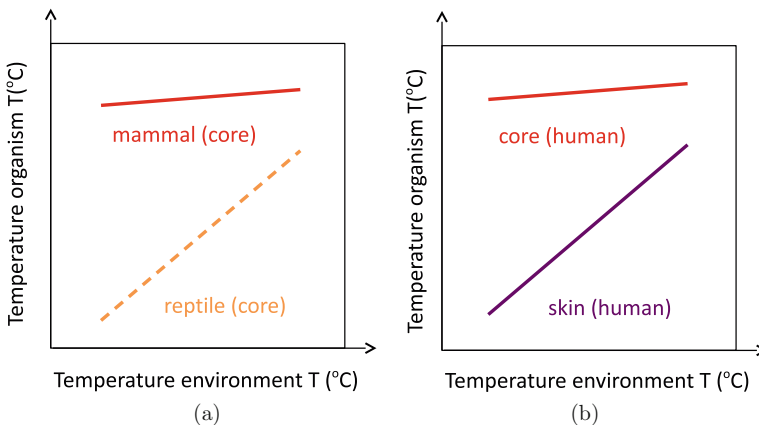

Fig. 7 Schematic representation of body temperature vs. the temperature of the outside environment, (**a**) for endotherms (e.g., humans, continuous red curve) and exotherms (e.g., reptiles, dashed orange curve), based on Ref. [73], and (**b**) for human core temperature (red continuous curve) and human skin temperature (purple continuous curve), based on Ref. [74]
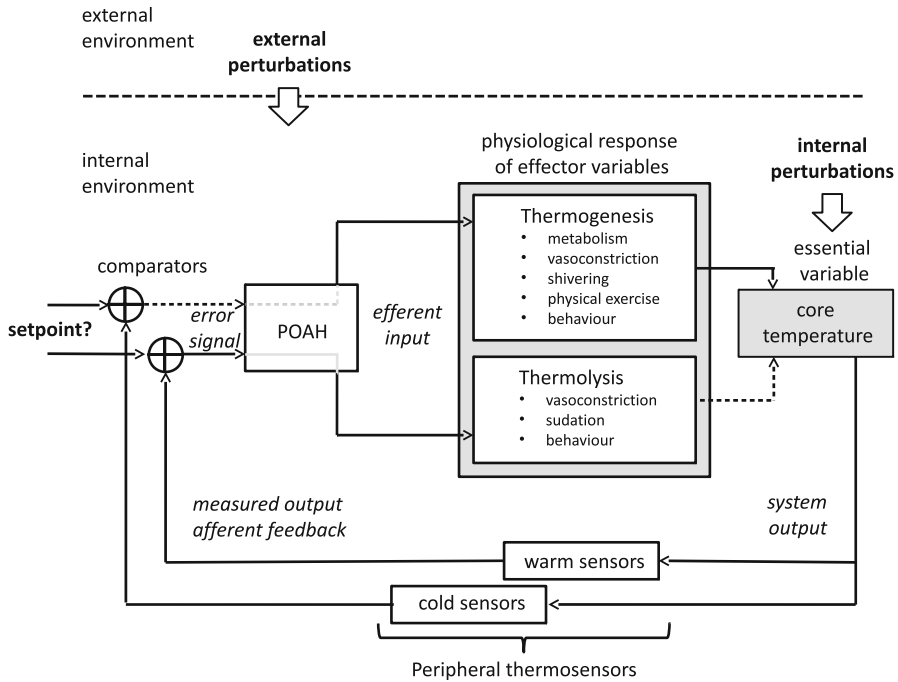
Fig. 8 Similar as for Fig. 1 but for the control loop of core body temperature. The control centrum of core temperature is located in the preoptic anterior hypothalamus (POAH) which activates thermogenetic or thermolytic responses which together act to maintain core temperature in a restricted homeostatic range. Physiological responses include vasomotor effects which determine skin temperature. Behavioural responses include seeking shade when it is hot or putting on a sweater when it is cold. Image based on Refs. [67] and [75]

an ambulatory setting on a long-term basis. In another study, in agreement with our working hypothesis, we have found that skin temperature variability is much larger than core temperature variability [51]. Here, we restrained to the monitoring of skin temperature. Figure 9 shows an example of a continuous 7-day time series of skin temperature in a control subject with normal weight, and the probability distribution of skin temperature for the control group, the overweight group and the obese group. It is clear that the probability distribution is wider for the controls, becomes narrower for the overweight group, and is narrowest for the obese group. The box-whisker plots of Fig. 10 show that there would seem to be a trend for average skin temperature $\langle T \rangle$ to increase with body weight but without statistical significance, possibly because of the small population sizes; on the other hand, variability as measured with the standard deviation (SD) can be seen to decrease with body weight, obtaining statistically significant differences between the control group and the obese group at the $p = 0.022$ level; the skewness of the distribution increases with body weight, but without statistical significance; the kurtosis increases with body weight, from a platykurtic (Kurt < 3) distribution for the controls towards a
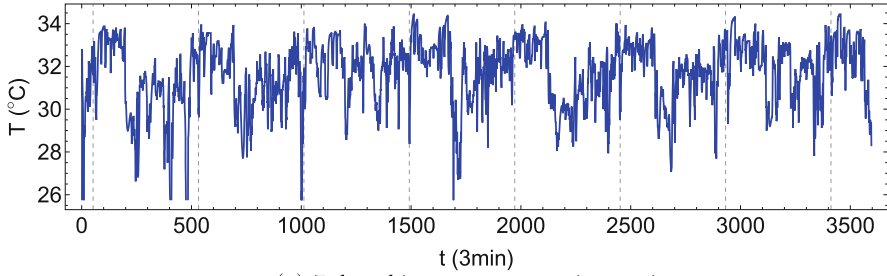
(a) 7-day skin temperature time series
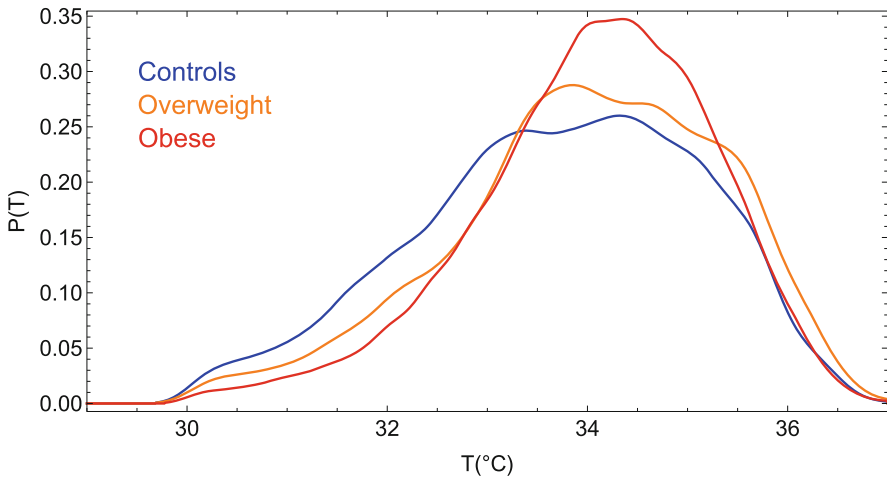
(b) Skin temperature probability density functions

Fig. 9 Continuous monitoring of skin temperature during seven successive days in controls with normal weight, overweight and obese subjects, (**a**) example of a time series of a control subject with vertical gridlines at midnight, and (**b**) probability distribution of the time series of the three groups. Data from Ref. [42]

leptokurtic (Kurt > 3) distribution for the obese population, and in this case there is again statistical significance in the difference between the control group and the obese group at the $p = 0.033$ level.

5 Discussion

When studying a new physiological variable, it is not always clear a priori what type of statistics to expect for the corresponding time series, how this statistics may degenerate under adverse circumstances, and whether any physiological meaning may be contributed to these fluctuations in a clinical context. Although it has been
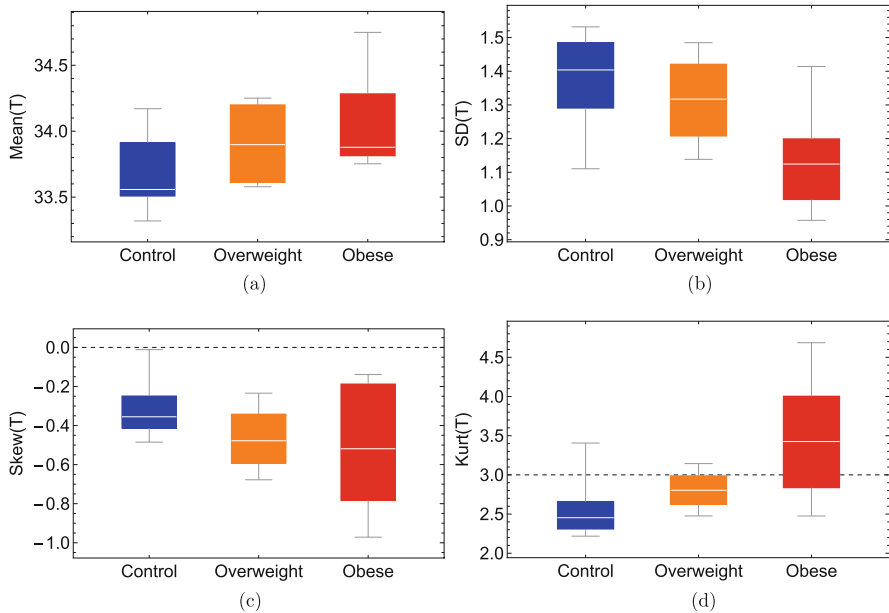
Fig. 10 Box-whisker plots of the moments of the distribution of the skin temperature time series of the control group with normal weight, the overweight group and the obese group, (**a**) mean, (**b**) standard deviation (SD), (**c**) skewness (Skew), and (**d**) kurtosis (Kurt). According to a Kruskal-Wallis nonparametric test, there are significant differences between the control group and the obese group for SD at the $p = 0.022$ level and for Kurt at the $p = 0.033$ level. Horizontal gridlines indicate values for a normal distribution Skew$= 0$ and Kurt $= 3$. Data from Ref. [42]

proposed that blood pressure variability (BPV) is a risk factor [39] and heart rate variability (HRV) an indicator of good health [38], it is not clear whether BPV has diagnostic relevance for specific pathologies such as hypertension [76]. Core body temperature time series have been analysed from the perspective of periodic circadian rhythms, e.g. when studying the effect of body weight and obesity [77–79], but without taking into account the ultradian fluctuations. Fluctuations of skin temperature have been studied, e.g. in intensive care patients [41], but without an interpretation of the physiological implications of the different statistics observed in patients and healthy controls. The research question of the present contribution is whether it is possible to propose a universal guiding principle that helps to explain the statistical behaviour of time series of physiological variables in general, and which can predict how this behaviour degenerates with adverse circumstances such as ageing and/or chronic-degenerative disease.

In the present contribution, we focussed on control theory and the concept of homeostasis, where it is common to distinguish between regulated variables and effector variables, which perform very different functions in the corresponding regulation mechanisms, see Table 1. We studied a variety of different homeo-

static mechanisms: in Sect. 2, we investigated a simple mathematical model of a thermostat, in Sect. 3 we focussed on blood pressure homeostasis in healthy controls and diabetic patients, and in Sect. 4, we analysed time series related to body temperature homeostasis as a function of body weight. Regulated variables are explicitly controlled by the pre-programmed feedback loop, whereas the control of effector variables is implicit and may *self-organize* [80] by interacting with other effector variables and the associated regulated variable. In all the examples that we studied, in optimal conditions, we found that effector variables are more variable than the corresponding regulated variable, reflecting the adaptive function of the former and the narrow homeostatic range to which the latter is confined. In adverse conditions, these variables do not adequately play their distinctive roles in the homeostatic regulation mechanism, i.e. effector variables become less adaptive and the corresponding time series less variable, whereas control over regulated variables is increasingly lost, and consequently the variability of their time series increases. The appropriate framework to describe the degeneration of effector variables would appear to be the *loss of complexity* paradigm [31, 54–57], whereas regulated variables seem to degenerate according to the predictions of the *early-warning signals* paradigm [61–65], see Table 2. This may be a universal principle obeyed by all physiological variables of Table 1 and which may explain the rich phenomenology observed in the statistics of physiological variables.

The field of *fractal physiology* was first proposed after technological advances allowed to monitor physiological variables in a non-invasive and continuous way. We noted that it is more difficult to monitor regulated variables (such as BP and core temperature) than effector variables (such as HR and skin temperature), possibly due to the fact that effector variables mediate between the internal and the external

Table 2 Hypothesis of a general guiding principle to interpret the statistics of experimental time series of physiological variables depending on their role in the homeostatic control mechanism

	Homeostatic regulatory mechanism	
	Regulated variable	Effector variable(s)
	Synonyms: controlled or essential variable	Synonyms: supporting, non-regulated, regulating or self-organized variables
	e.g., *blood pressure (BP)*	e.g., *heart rate (HR)*
Youth health	Properties: controlled, stable, confined	Properties: adaptive, variable
	Framework: gaussian statistics	Framework: fractal physiology
	Small variance	*Large variance*
	Gaussian statistics	*Non-gaussian (fractal and long-tailed) statistics*
	Non-correlated (no memory)	*Correlated (memory)*
Ageing disease	Framework: early-warning signals	Framework: loss of complexity
	Increased variance	*Decreased variance*
	Increased non-gaussianity	*Increased gaussianity*

environment and thus are more readily accessible from outside, whereas regulated variables by definition are related to the *milieu intérieur* which is more difficult to access. Because of these practical reasons, the best studied time series tend to be effector-like variables, which might have introduced the bias that all physiological variables are highly variable and fractal-like, and leading to the impression that gaussian statistics and the concept of homeostasis are obstacles for the advancement of medicine. The main conclusion of the present contribution is that health needs both the fractal (adaptive) properties of effector variables and the gaussian (stability) characteristics of regulated variables to survive.

6   Conclusions

Technological advances allow to monitor an ever larger variety of physiological variables in a non-invasive and continuous way. It is not clear a priori how the time series of newly measured variables should behave statistically, or why a large variability of one variable represents a risk factor (e.g., blood pressure) whereas a large variability of another variable could be an indication of health (e.g., heart rate). In the present contribution, we argue that the role a particular variable plays in the homeostatic control mechanism, a regulated variable vs. an effector variable, determines the way the corresponding time series will behave statistically. With youth and health, a *regulated variable* such as blood pressure is maintained within a restricted homeostatic range with low variability, whereas *effector variables* and the corresponding *physiological responses* that adapt to perturbations from the inner and outer environment are characterized by a large variability. With ageing and/or chronic-degenerative disease, the capacity of these variables to play their respective roles is increasingly lost which is reflected by diminished statistical differences of the corresponding time series, or the regulated variable can become even more variable than the effectors variables. We demonstrated these concepts for a mathematical model of a thermostat, for experimental data of heart rate and blood pressure for healthy controls and diabetic patients, and for experimental data of skin temperature as a function of body weight. We make the prediction that other pairs of homeostatic variables, such as blood oxygen saturation vs. respiration dynamics, or blood glucose vs. insulin and glucagon concentrations, will follow similar patterns.

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