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## PAPER

# A physicist's view of homeostasis: how time series of continuous monitoring reflect the function of physiological variables in regulatory mechanisms

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## Abstract

**Objective:** Homeostasis is one of the key concepts of physiology and the basis to understand chronic-degenerative disease and human ageing, but is difficult to quantify in clinical practice. The variability of time series resulting from continuous and non-invasive physiological monitoring is conjectured to reflect the underlying homeostatic regulatory processes, but it is not clear why the variability of some variables such as heart rate gives a favourable health prognosis whereas the variability of other variables such as blood pressure implies an increased risk factor. The purpose of the present contribution is to quantify homeostasis using time-series analysis and to offer an explanation for the phenomenology of physiological time series. **Approach:** Within the context of network physiology, which focusses on the interactions between various variables at multiple scales of time and space, it may be understood that different physiological variables may play distinct roles in their respective regulatory mechanisms. In the present contribution, we distinguish between *regulated variables*, such as blood pressure or core temperature, and *physiological responses*, such as heart rate and skin temperature. **Main results:** We give evidence that in optimal conditions of youth and health the former are characterized by Gaussian statistics, low variability and represent the stability of the internal environment, whereas the latter are characterized by non-Gaussian distributions, large variability and reflect the adaptive capacity of the human body; in the adverse conditions of ageing and/or disease, adaptive capacity is lost and the variability of physiological responses is diminished, and as a consequence the stability of the internal environment is compromised and its variability increases. **Significance:** Time-series analysis allows one to quantify homeostasis in the optimal conditions of youth and health and the degradation of homeostasis or homeostenosis in the adverse conditions of ageing and/or disease, and may offer an alternative approach to diagnosis in clinical practice.

## 1. Introduction

The term *homeostasis* attempts to convey two key ideas: (i) the internal *stability* of the human body, and (ii) coordinated *adaptive* responses in order to maintain this internal stability (Modell *et al* 2015). Physiology suggests that distinct types of variables are responsible for these two different aspects of homeostasis, where *regulated variables* such as blood pressure and core temperature are contained within a narrow range of values around a certain setpoint, whereas *physiological responses* such as heart rate and vasomotor action adapt to perturbations to ensure the stability of the former; see table 1. Homeostasis has become one of the key concepts to understand (patho)physiology, and the major regulatory mechanisms responsible for maintaining homeostasis have been identified: the sympathetic (SNS) and parasympathetic (PNS) branches of the autonomous nervous system (ANS), the endocrinological system and protective systems such as the immune system and the integumentary system (Hall 2011). The simplest measures of homeostasis are *point measurements* of

**Table 1.** Examples of homeostatic regulatory mechanisms where *regulated variables* are distinguishable because of their specific sensors and are maintained close to normative values by means of *physiological responses* which absorb or adapt to perturbations from the inner and outer environments. With permission on Modell *et al* (2015), Copyright 2015 by the American Physical Society.

Examples of homeostatic regulatory mechanisms			
Variable	Regulated variable		Physiological responses
	Normative value	Sensor	No sensors nor normative values
Systolic blood pressure (BP)	120 mmHg	Baroreceptor	Cardiac output (heart rate, stroke volume) Vasomotor action (constriction, dilation)
Core temperature ( $T_c$ )	37 °C	Thermoreceptor	Vasomotor action (constriction, dilation) Skin temperature Shivering, sudomotor
Blood oxygen saturation ( $SpO_2$ )	95%	Chemosensor	Respiration dynamics (rate, volume)
Blood glycemia	10 mg dl <sup>-1</sup>	Chemosensor	Insuline, glucagon

vital parameters, i.e. single measurements made at a specific moment in time, which can be compared with population-based *normative ranges*, and where deviations from these ranges may be an indication of disease (Hall 2011). These point-measurements and normative ranges, however, are the end-result of the homeostatic regulatory processes, which gives information on the stability of the internal environment, but do not provide insight into the dynamics or adaptive aspects of homeostasis. For this purpose, *standardized clinical ‘stress’ tests* have been developed where the patient is submitted to specific standardized challenges or stimuli to study the corresponding physiological responses. Non-adaptive responses, i.e. responses which are too strong, too weak, or which come too delayed in order to cope efficiently with the challenge, may be an indication for disease. Examples of such standardized clinical tests are cardiac exercise stress testing to investigate chronic heart disease (Pescatello *et al* 2014), Ewing’s battery of autonomic reflex tests for neuropathy (Ewing *et al* 1985), and the glucose tolerance test for diagnosis of early-stage diabetes (Stumvoll *et al* 2000). However, these tests are time-consuming and intensive, both for the patients and for the treating clinician, and it may not be possible to perform these tests in vulnerable populations of weak patients or elderly adults, and these tests do not form part of a routine screening of the general population. On the other hand, recent technological advances allow one to monitor many different physiological variables in a non-invasive and continuous way, and the time evolution or *time series* of these variables is conjectured to reflect the dynamics of the underlying homeostatic regulatory mechanisms and to correlate with the health status of the organ, process or system under study (Seely and Macklem 2004). Most—if not all—of these variables spontaneously fluctuate in time, even when the monitored subject is in rest, possibly because the human body is always subjected to a wide variety of minor stimuli, which can come from the outside environment such as ambient temperature variations, and/or from the internal environment such as digestion, mental stress or internal reparation or restorative processes (Goldberger *et al* 1990). Intriguingly, for some variables a high variability is interpreted an indication of good health, as in the case of heart rate variability (HRV) (Malik *et al* 1996), whereas in other cases—on the contrary—it implies a risk factor, as in the case of blood pressure variability (BPV) (Parati *et al* 2013).

The study of the variability of most physiological variables is at the level of basic research, and it is not at all clear how diverse physiological systems and organs coordinate their functions over broad ranges of space and time. The focus of the recently proposed field of *network physiology* is to better understand how homeostasis and its counterpart of homeostenosis emerge as different *physiological states*, optimal versus maladaptive, respectively, from the interaction between many different physiological variables, with as an objective to improve clinical diagnosis, prognosis and preventive medicine, and to better understand ageing and chronic-degenerative disease (Bashan *et al* 2012, Ivanov *et al* 2014, Bartsch *et al* 2015, Liu *et al* 2015, Ivanov *et al* 2016). In the present contribution, we will study time series of the simultaneous monitoring of various physiological variables, at different time scales, and subjected to either a dominant stimulus or a wide variety of stimuli. We will illustrate how in optimal conditions of youth and health the statistics of these time series reflects the different roles these variables play in the corresponding regulatory mechanisms, and how in adverse conditions of ageing or disease the alteration of these statistics indicates a degeneration of physiological regulation.

## 2. Physiological time series while subjected to a dominant stimulus

Figure 1 illustrates the effect of rest and physical exercise on cardiac and respiratory physiology in a healthy male young adult. Physical activity can be quantified at the level of individual movements using triaxial accelerometry,

where the acceleration vector  $\vec{a} = \vec{a}_X + \vec{a}_Y + \vec{a}_Z$  is composed of contributions from the sagittal (X), lateral (Y) and vertical (Z) directions. The absence of physical activity during supine rest ( $a \approx 0$  g) is characterized by physiological time series with high moment-to-moment variability, both for heart rate (HR) and breathing rate (BR). For low-intensity activity ( $a < 0.2$  g), such as leisure activities inside the house with repeated sitting down and standing up, heart rate variability (HRV) and breathing rate variability (BRV) appear to be even higher than during supine rest. On the other hand, for high-intensity physical activity ( $a > 0.8$  g), such as running in a treadmill, HR and BR increase proportional to the physical effort and HRV and BRV become minimal. After the exercise, average HR and BR gradually return to their basal levels and also their variability recuperates over time.

Figure 2 shows the effect of the alternation of day and night on the physiology of the same male young adult of figure 1 during 7 days of continuous monitoring. Panel (a) shows an actigraphy (act) time series, which is an average measure based on accelerometry, such as in figure 1(a), but where the number of movements is counted per sample time interval or ‘epoch’, in the present case arbitrarily chosen as 1 min. Simultaneous to the actigraphy time series, panel (b) shows the cardiovascular variables of heart rate (HR) and systolic blood pressure (BP), and panel (c) shows body temperature variables of skin temperature  $T_s$  and core temperature  $T_c$ . The dominant feature of these time series is the *circadian rhythm*, i.e. the degree by which these variables are modulated by the periodic 24 h day–night cycle. The standard way to study the circadian rhythm contained in a time series  $x_n = x_1, x_2, \dots, x_N$  with  $N$  data points, is so-called cosinor analysis (Fossion *et al* 2017) where a cosine function  $y(t) = M + A \cos(2\pi t/T + \phi)$  is fitted to the data in order to calculate the circadian parameters of the average or mesor  $M$ , amplitude  $A$ , period  $T$  and acrophase  $\phi_0$  (time of day for which the circadian rhythm maximizes). As shown in table 2, all variables of figure 2 adapt to the day–night cycle with an oscillation  $T \approx 1440$  min (24 h). The circadian cycle for act, HR, BP and  $T_c$  maximizes in the early afternoon, whereas the maximum for  $T_s$  is early during the night. The coefficient of determination  $R^2$  quantifies what fraction of the variance of the time series is explained by the model function  $y(t)$ .  $R^2$  is 50%–70% for BP and  $T_c$ , about 30% for HR and  $T_s$  and minimal for act, indicating that for the former variables the major part of the variance is due to the circadian rhythm, whereas for the latter variables there is additional variance that cannot be explained by the circadian rhythm.

### 3. Physiological time series while subjected to a wide variety of stimuli

#### 3.1. Optimal conditions of youth and health

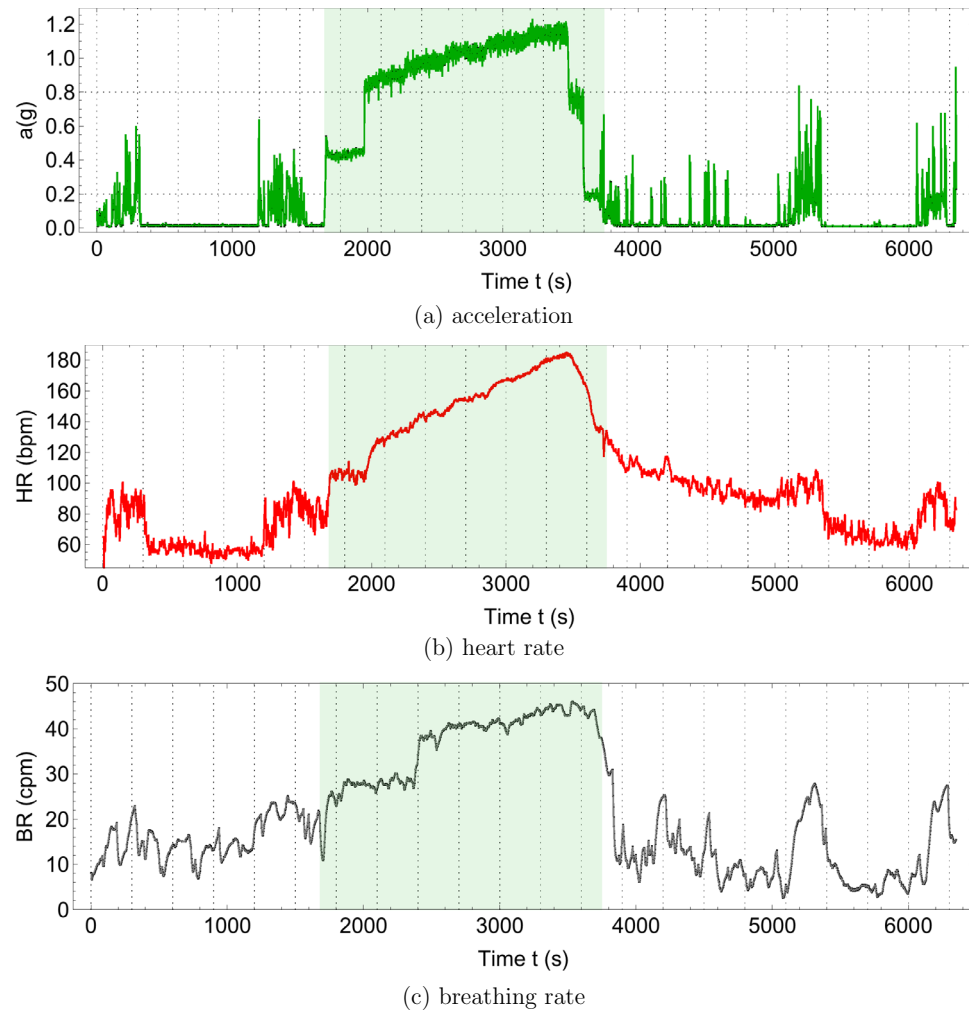
In order to compare the statistics of the fluctuations of each of the variables  $X(t)$  of figure 2, dimensionless fluctuations  $\Delta X$  can be defined around their respective average value  $\langle X \rangle$  and expressed as a percentage of this average value,

$$\Delta X(\%) = 100 \times \frac{X(t) - \langle X \rangle}{\langle X \rangle}. \quad (1)$$

The behavior of these fluctuations can be illustrated using probability density functions (PDFs), which show the relative probability of a specific fluctuation  $\Delta X$  with respect to the range of fluctuations of the measured time series of that variable  $X$ , and where the area of each PDF has been normalized to 1 (unitary total probability). Figure 3 shows the PDFs of the fluctuations  $\Delta X$  of the behavioral, cardiovascular and body temperature variables of figure 2, where positive values of  $\Delta X$  indicate fluctuations above and where negative values of  $\Delta X$  show fluctuations below the respective average  $\langle X \rangle$ . Variability of BP is small with respect to HR, variability of  $T_c$  is small with respect to  $T_s$ , and all physiological variables HR, BP,  $T_s$  and  $T_c$  are less variable than the behavioural variable act. The PDFs of BP and  $T_c$  correspond to the superposition of two Gaussians, with small fluctuations around two representative average values, which are the day and night setpoints. The PDFs of act, HR and  $T_s$  correspond to non-symmetric and skewed distributions with a broad maximum of small but frequent fluctuations at one extreme and a tail with large but less frequent fluctuations at the other extreme; comparison with the time series allows one to identify the broad maxima with night-time and the tail with day-time fluctuations.

#### 3.2. Adverse conditions of ageing and disease

We collected 5 min HR and BP time series in  $N = 30$  control subjects,  $N = 30$  asymptomatic subjects with recently diagnosed type-2 diabetes (DMA) and  $N = 15$  long-standing patients with type-2 diabetes (DMB) in supine resting position, see Rivera *et al* (2016). Average age increases from the controls to the DMA and DMB groups because chronic-degenerative disease needs time to develop; see table 3. Exclusion criteria included smoking, cardiac arrhythmia, hypertension and having taken medication up to 48 h previous to the study. Examples of time series for individual subjects are shown in figure 4 (left-hand panels). Average heart rate  $\langle \text{HR} \rangle$  was similar for controls and the DMA group, but was significantly higher for the DMB group, whereas  $\langle \text{SBP} \rangle$  was comparable for the three groups. Figure 4 (right-hand panels) shows for each population the PDF for the fluctuations  $\Delta \text{HR}$  and  $\Delta \text{BP}$ , according to equation (1). For the control group, the distribution  $P(\Delta \text{HR})$  is wider than  $P(\Delta \text{BP})$ , in particular, for  $\Delta \text{HR}$  there is an asymmetric tail towards positive fluctuations up to 40% whereas  $\Delta \text{BP}$  is

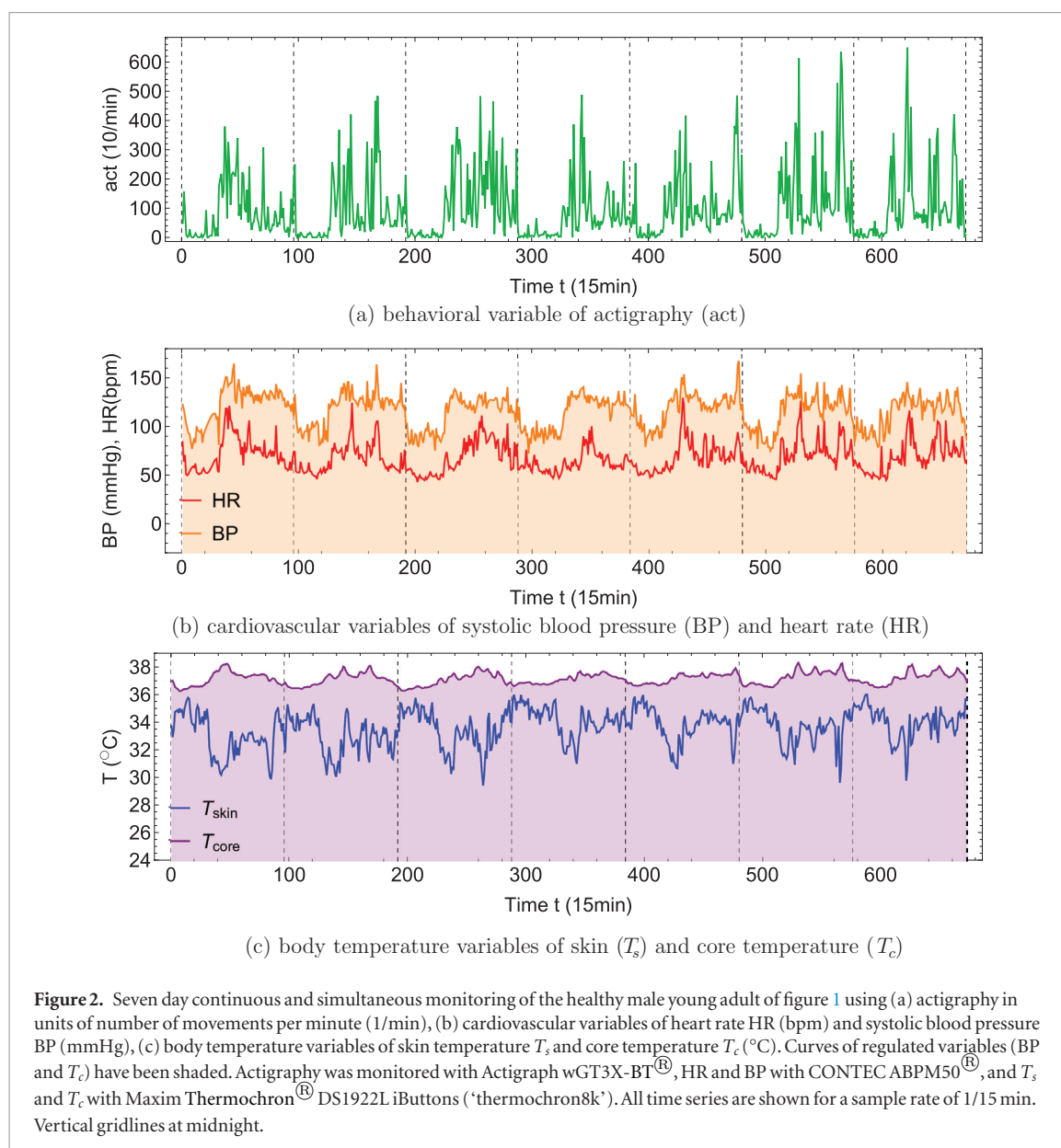


**Figure 1.** Effect of rest and physical exercise on cardiac and respiratory physiology in a healthy male young adult, (a) acceleration vector magnitude  $a$  in units of gravitational constant  $g = 9.81 \text{ m s}^{-2}$ , (b) heart rate (HR) in units of beats per minute (bpm), (c) breathing rate (BR) in units of cycles per minute (cpm). Physical activity (shaded area) corresponds to warming up by walking on the treadmill for 5 min at 4 miles per hour (mph), running on a treadmill at increasing velocities of 5, 6, 7, 8 and 9 mph for 5 min each, and cooling down by walking at 4.5 and 2 mph for 2 min each. Resting or minimal-intensity physical activity intervals (non-shaded areas) before and after the exercise correspond to supine or seated rest ( $a \approx 0 \text{ g}$ ) or low-intensity activities inside the house ( $a < 0.2 \text{ g}$ ). All data were collected using a Zephyr Bioharness3® device and are shown for a sample rate of 1 Hz. Vertical gridlines at 5 min intervals. Horizontal gridlines at limiting values  $a = 0.2 \text{ g}$  (walking) and  $a = 0.8 \text{ g}$  (jogging) according to the Bioharness manual.

constrained within the range  $-20\%$  to  $+20\%$ . For the DMA group, the width of  $P(\Delta\text{HR})$  is greatly reduced and in particular the positive  $\Delta\text{HR}$  fluctuations have decreased below  $30\%$ , whereas now the probability distribution of  $\Delta\text{BP}$  has become wider than that of  $\Delta\text{HR}$  towards the negative side. For the DMB group, the situation is reversed with respect to the control group, where  $P(\Delta\text{BP})$  has become wider than  $P(\Delta\text{HR})$ , in particular, the positive  $\Delta\text{HR}$  fluctuations are now limited to  $20\%$ , whereas the negative  $\Delta\text{BP}$  fluctuations have increased up to  $30\%$ .

#### 4. Discussion

In section 2, the effect on physiology of a dominant stimulus is studied. High-intensity physical exercise on a treadmill, see figure 1, is an example of a continuous dominant stimulus, evoking a response of the sympathetic nervous system (SNS) which increases average heart rate  $\langle\text{HR}\rangle$  and breathing rate  $\langle\text{BR}\rangle$  proportionally to the physical effort, in order to increase the oxygen supply to the muscles and the disposal of  $\text{CO}_2$  to the lungs (Hall 2011). Systolic blood pressure (BP) has also been reported to increase with exercise (Palatini 1988). The SNS decreases variability, as shown here for heart rate variability (HRV) and breathing rate variability (BRV), because the whole of physiology is focussed on the realization of one single task, and supply and disposal rates should be as constant and reliable as possible to maximize efficiency. The overall effect is not unlike a steam locomotive, the SNS being the train driver, where steam pressure and steam flow are increased in proportion to the desired speed. On the other hand, the parasympathetic nervous system (PNS) lowers HR, and temporal inhibition of

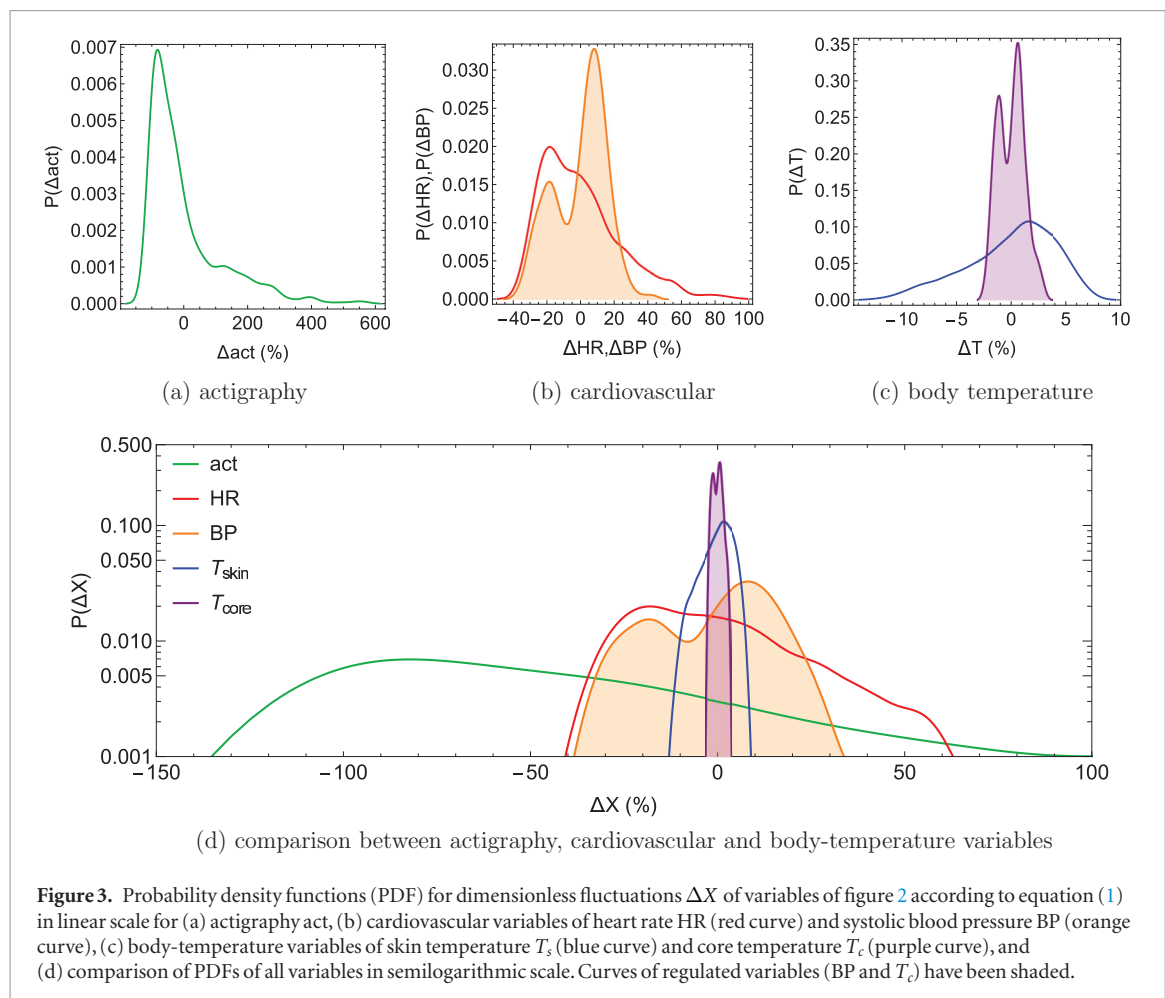


**Table 2.** Circadian parameters of average or mesor  $M$  (\*), period  $T$  (min), amplitude  $A$  (\*), acrophase  $\phi_0$  (in degrees ° or hours and minutes hh:mm after midnight) and coefficient of determination  $R^2$  for the 1 week time series of actigraphy (act), heart rate (HR), systolic blood pressure (BP), skin temperature ( $T_s$ ) and core temperature ( $T_c$ ) of figure 2.  $M$  and  $A$  are measured in the same units as the corresponding variable (\*). See Fossion *et al* (2017) for technical details on the cosinor method used.

		Act (1/min)	HR (bpm)	BP (mmHg)	$T_s$ (°C)	$T_c$ (°C)
$M$	(*)	964.68	67.96	115.78	33.57	37.12
$T$	(min)	1470	1470	1440	1425	1470
$A$	(*)	645.50	13.84	18.38	1.03	0.52
$\phi_0$	(°)	228.75	236.25	236.35	26.25	243.75
	(hh:mm)	15:15	15:45	15:45	01:45	16:15
$R^2$		0.160	0.387	0.518	0.295	0.693

the PNS induces episodes of HR accelerations, such that a modulation of the PNS is sufficient to take care of low-intensity leisure activities inside the house, and also internal processes such as digestion and restoration or reparation, and HRV is a reflection of the multitasking capabilities of the PNS. Measures of heart rate response to and heart rate recovery from a dominant stimulus are the basis for cardiac exercise stress testing (Pescatello *et al* 2014), and similar responses of various variables are used in other standardized clinical stress tests (Ewing *et al* 1985, Stumvoll *et al* 2000). On the other hand, circadian rhythms are an example of how physiological variables are modulated by the repetitive dominant stimulus of the 24 h day–night alternation, see figure 2, where the most obvious feature of the time series is a periodic behavior which can be described approximately by a cosine function.





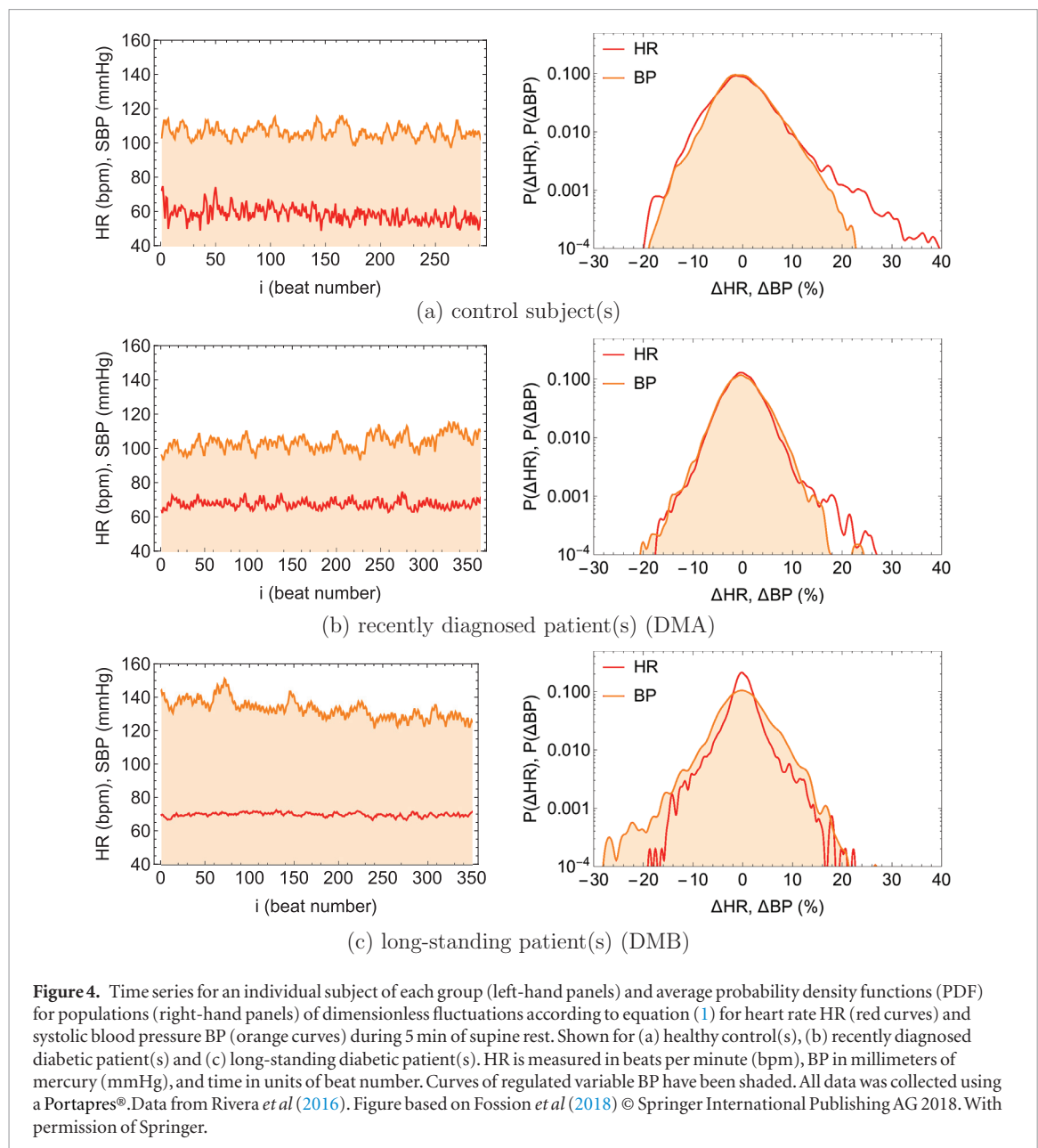
**Figure 3.** Probability density functions (PDF) for dimensionless fluctuations  $\Delta X$  of variables of figure 2 according to equation (1) in linear scale for (a) actigraphy  $act$ , (b) cardiovascular variables of heart rate  $HR$  (red curve) and systolic blood pressure  $BP$  (orange curve), (c) body-temperature variables of skin temperature  $T_s$  (blue curve) and core temperature  $T_c$  (purple curve), and (d) comparison of PDFs of all variables in semilogarithmic scale. Curves of regulated variables ( $BP$  and  $T_c$ ) have been shaded.

**Table 3.** Heart rate ( $HR$ ) and systolic blood pressure ( $BP$ ) for the control group, recently-diagnosed diabetic patient group (DMA) and the long-standing diabetic patient group (DMB) of figure 4.  $HR$  for DMB is significantly different from controls and DMA at the  $p = 0.05$  level according to a Kruskal–Wallis test (\*). Age and gender constitution of the three populations is also indicated.

	Control ( $N = 30$ )	DMA ( $N = 30$ )	DMB ( $N = 15$ )
Gender	17 females, 13 males	16 females, 14 males	10 females, 5 males
Age (years)	$33 \pm 8$	$41 \pm 5$	$53 \pm 18$
$HR$ (bpm)	$68 \pm 11$	$67 \pm 9$	$81 \pm 12$ (*)
$BP$ (mmHg)	$107 \pm 11$	$118 \pm 23$	$113 \pm 24$

The baseline value of physiological variables is reassigned according to a specific setpoint for day-time or night-time to allow a more efficient use of energy and resources, not unlike the different gears we use in bicycles or cars at different speeds. Loss of regularity of circadian rhythms may indicate underlying pathologies such as attention deficit hyperactivity disorder, age-associated frailty or insomnia (Fossion *et al* 2017). In hypertension, patients that display a nocturnal decrease in their  $BP$  profile (‘dippers’), tend to have a more favourable clinical outcome than patients that do not exhibit circadian modulation (‘non-dippers’) or that have a nocturnal increase (‘risers’ or ‘reverse dippers’) (Mancia *et al* 2014). The conclusion of section 2 is that physiological variables tend to adapt to a dominant stimulus, and maladaptation to such a stimulus (responses that are too strong/weak or that arrive too early/late) may be an indication for adverse health conditions.

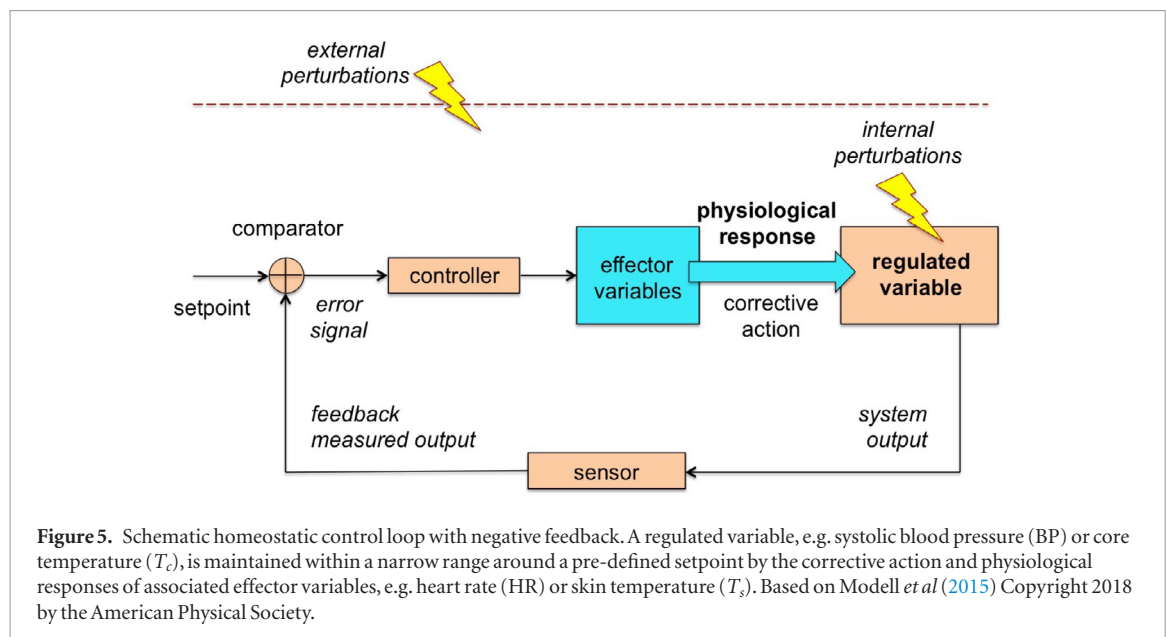
Section 3 discusses the effect on physiology of a wide variety of stimuli at ultradian time scales. Figure 3 suggests that some variables such as heart rate ( $HR$ ) and skin temperature ( $T_s$ ) tend to adapt to this wide variety of stimuli of various magnitude and time scales and therefore are characterized by a large variability, whereas other variables such as systolic blood pressure ( $BP$ ) and core temperature ( $T_c$ ) tend to remain approximately constant and close to a predetermined setpoint. The reason may be that for an organism it cannot be efficient to adapt as a whole to every single stimulus from its external environment, and a more optimal strategy would be to maintain some specific variables of the internal environment constant, so-called *regulated variables*, while absorbing as well as possible perturbations from the outer environment in the *physiological responses* of other so-called effector variables. Control theory and negative feedback loops indeed assign distinct roles to different



variables, depending on their specific place in the control circuit, see figure 5, and also physiology and anatomy acknowledge that different variables may carry distinct responsibilities in homeostatic regulation; see table 1. The opposing statistics that we observed in figure 3, Gaussian distributions for regulated variables versus non-Gaussian, asymmetric and skewed distributions for physiological responses, reflects the complementary roles these variables play in the corresponding regulatory mechanisms in optimal conditions of youth and health. In the adverse conditions of ageing or chronic-degenerative disease, adaptive capacity of the physiological responses is increasingly lost which is reflected by a diminished variability of the associated time series, and as a consequence the stability of the internal environment is compromised and its variability increases. Figure 4 illustrates the adverse effects of type-2 diabetes mellitus on cardiovascular homeostasis, possibly aggravated as well by the aging process. Although by study design hypertensive patients were excluded such that no population differences could be observed for  $\langle BP \rangle$ , variability analysis reveals that adaptive capacity of HR decreases whereas the increase of temporary perturbations of BP indicates that homeostatic control is failing. In this way, we may understand intuitively the empirical observation in the literature that heart rate variability (HRV) is a protective factor for health Malik *et al* (1996), whereas blood pressure variability is a risk factor (Parati *et al* 2013).

We argue that existing paradigms to explain the very rich phenomenology of the variability of time series have each focussed on either one of the two types of variables of table 1. On the one hand, the paradigm of *early-warning signals* of Scheffer (2009) and Carpenter *et al* (2011) discusses regulated variables of dynamic systems, which behave in a Gaussian way with low variability and little correlation or memory of past events while in a state of stability and equilibrium, whereas when the system approaches a critical threshold at the





**Table 4.** Scheme that incorporates various existing paradigms to interpret the phenomenology of physiological time series depending on their role in homeostatic regulation and depending on the type of stimulus they are subjected to.

	Dominant stimulus	Variety of stimuli	
		Regulated variables	Physiological responses
	All variables	Stability	Adaptability
Optimal conditions (youth and health)	Normative response	Gaussian statistics	Fractal physiology (West 2010) Self-organized criticality (Bak 1996, Muñoz 2018)
Adverse conditions (ageing or disease)	Non-normative response	Early-warning signals (Scheffer 2009, Carpenter <i>et al</i> 2011)	Loss of complexity (Lipsitz and Goldberger 1992)

brink of collapse, statistical parameters such as variance, non-Gaussianity, correlations and memory tend to increase. The term ‘early-warning’ refers to the fact that countermeasures can be taken to avoid a catastrophe for dynamical systems such as the economy or the climate if these statistical fingerprints are detected early enough. On the other hand, the *loss of complexity* paradigm of Lipsitz and Goldberger (1992) discusses physiological responses, which are inherently ‘complex’ with a large variability that is increasingly lost with ageing and/or chronic-degenerative disease. West (2010) has suggested that these variables are characterized by heavy-tailed distributions such as power laws and that a new paradigm, *fractal physiology*, is needed to understand their behaviour. The fractal nature of physiological responses indicates that they are not white noise and that they behave according to specific correlations, although they do not obey any regulation that is hardwired into the feedback control loop as is the case of regulated variables. Therefore, one possibility is that they behave according to *self-organized criticality*, which operates in the vicinity of the critical point of a phase transition halfway between order and disorder (Bak 1996, Muñoz 2018), where physiological responses may strike an optimal balance between possibly opposite requirements from different corresponding regulated variables. For example, BP and  $T_c$  both depend on vasomotor action for their regulation, see table 1, such that vasomotor action might self-organize in a critical point in the case of opposite requirements of BP and  $T_c$ . Table 4 makes an attempt to integrate the above paradigms of fractal physiology, early-warning signals and loss of complexity in a single scheme to explain the phenomenology of physiological time series. The present discussion is based on the pair-wise association of a regulated variable and a corresponding physiological response, e.g. blood pressure versus heart rate, or core temperature versus skin temperature, see table 1, where different homeostatic regulatory mechanisms are thought to be independent from each other. This approximation is of course not completely correct, because different regulation loops may be coupled by shared physiological responses (e.g. vasomotor action in the regulation of body temperature and blood pressure), and variables which are regulated at one time scale may play the role of physiological responses at another time scale (called nested homeostasis or hierarchy of homeostasis, see Carpenter (2004) and Modell *et al* (2015)), and a more general framework is needed to integrate these pair-wise relations into a more global network. The many new tools and methodologies offered by network physiology, including time delay stability (Bashan *et al* 2012, Ivanov *et al* 2014, Bartsch *et al* 2015, Liu *et al* 2015, Ivanov *et al* 2016), may explain how many different physiological vari-

ables from distinct homeostatic regulatory mechanisms interact together at many scales of time and space such that a physiological state of homeostasis emerges at the level of the organism.

## 5. Conclusion

Technological advances allow one to monitor an ever increasing 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 is 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 versus 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. We demonstrated these concepts for experimental data of heart rate and blood pressure for healthy controls and diabetic patients and we make the prediction that other pairs of regulated variables versus physiological responses, such as blood oxygen saturation versus respiration dynamics, or blood glycemia versus insulin and glucagon concentrations, should follow similar patterns. It will be up to the new field of network physiology to integrate these different pairwise relations of regulated variables versus physiological responses from distinct homeostatic regulatory mechanisms into a network in order to explain how homeostasis may emerge as a physiological state at the level of the organism.

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