A time-series approach to assess physiological and biomechanical regulatory mechanisms

Ruben Fossion, Ana Leonor Rivera, Lesli Alvarez-Millán, Lorena García-Iglesias, Octavio Lecona, Adriana Robles-Cabrera, Bruno Estañol

Abstract In various areas of Medicine there is interest to incorporate information on homeostasis and regulation to increase the predictive power of prognostic scales. This has proven to be difficult in practice because of an uncomplete understanding of how regulation works dynamically and because a common methodology does not exist to quantify the quality of regulation independent from the specific mechanism. In the present contribution, it is shown that time series of *regulated* and *effector variables* from different regulatory mechanisms show universal features that may be used to assess the underlying regulation.

Ruben Fossion
Instituto de Ciencias Nucleares & Centro de Ciencias de la Complejidad (C3), Universidad Nacional Autónoma de México, 04510 Mexico City, Mexico
e-mail: ruben.fossion@nucleares.unam.mx

Ana Leonor Rivera
Instituto de Ciencias Nucleares & Centro de Ciencias de la Complejidad (C3), Universidad Nacional Autónoma de México, 04510 Mexico City, Mexico

Lesli Alvarez-Millán
Doctorado en Ciencias Biomédicas, Universidad Nacional Autónoma de México, 04510 Mexico City, Mexico

Lorena García-Iglesias
Doctorado en Ciencias, Universidad Autóoma del Estado de Morelos, Avenida Universidad 1001, Chamilpa, 62209 Cuernavaca, Morelos, Mexico

Octavio Lecona
Doctorado en Ciencias Biomédicas, Universidad Nacional Autónoma de México, 04510 Mexico City, Mexico

Adriana Robles-Cabrera
Doctorado en Ciencias Biomédicas, Universidad Nacional Autónoma de México, 04510 Mexico City, Mexico

Bruno Estañol
Laboratorio de Neurofisiología Clínica, Departamento de Neurología y Psiquiatría, Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán”, Mexico City, Mexico

1 Introduction

Apart from diagnosis and treatment, a third important task in medicine is *prognosis*. Short-term prognostic scales of the order of days and weeks as for use in critical and intensive care are based on vital signs, in particular point (one-time) measurements of heart rate, respiration rate, blood pressure, blood oxygen saturation, body temperature, state of consciousness, etc. Longer-term scales of the order of months and years as used in geriatrics and palliative care include different aspects of the patient's functionality (physical, emotional, social, etc.) because average values of physiological parameters tend to be within their normative ranges [4]. Attemps are being made to incorporate also measures related to regulation and physiological reserves, in particular in geriatric frailty scales, but these attempts have remained mostly theoretical because of problems related to how to assess and measure regulation [26, 38].

Physiological regulation was first advanced by Claude Bernard in the 2nd half of the 19th century as the approximate constancy of the internal environment ("milieu intérieur") of the human body in the face of perturbations received from the external environment. At the beginning of the 20th century, Walter Cannon included also adaptive physiological responses to these external perturbations in an extended concept which he coined *homeostasis*. Although homeostasis is one of the core concepts of physiology, several sticky points remain in its understanding, e.g., how constant is the approximate constancy of the internal environment, whether physiological regulation works as an on-off switch or whether it is active continuously, whether the setpoint of a homeostatic mechanism is stable or whether it may change over time, and how various homeostatic mechanisms interconnect hierarchically [23].

At least 3 different strategies exist to quantify homeostasis in clinical practice, but no strategy is 100% satisfactory [9]. First, point (one-time) measurements of vital parameters allow to check whether these are within their normal ranges. The most obvious example is measuring body temperature to detect fever. Unfortunately, only information on the end result of regulation is obtained but not on the dynamical adaptation that underlies regulation. Second, the stimulus-response approach where responses to standardized stimuli are measured, allowing to distinguish between adaptive and non-adaptive physiological responses. A typical example is the glucose tolerance test in the diagnosis of diabetes. The major drawback is that not all experimental stimuli are applicable in vulnerable populations such as elderly adults or critical care patients. Third, realizing that the human body is never really in rest but continuously responding to a wide variety of internal and external stimuli, the time series of the spontaneous fluctuations of specific physiological variables can be analyzed statistically in order to quantify the activity of the corresponding regulatory mechanisms. The most studied physiological time series is heart rate variability (HRV) which offers a non-invasive proxy to assess the autonomous nervous system [20, 32]. The disadvantage of this approach using physiological time series is that having no information on the perturbations that generate these fluctuations makes it difficult to compare between different subjects. Also, it is not obvious how the statistics of these fluctuations evolve from ideal conditions of youth and health to adverse

conditions of ageing or disease when physiological regulation becomes suboptimal. Two different hypotheses exist to interpret these fluctuations but appear to mutually contradict each other: the *loss of complexity* paradigm of Lipsitz and Goldberger which predicts that complexity and variability decrease [19], whereas the *critical transitions* paradigm of Scheffer et al. states that variability and non-gaussianity increase in adverse conditions [33]. Moreover, West argues that homeostasis and traditional gaussian statistics constitute conceptual barriers to understand the spontaneous fluctuations of physiological variables which should rather be studied within the context of the new field of *fractal physiology* [39].

In order to solve this paradox, we point to the fact that different variables may play different roles in physiological regulation. Indeed, recent advances in physiology education distinguish between on the one hand *regulated variables* such as core temperature and blood pressure that represent Bernard's internal environment and that are supposed to remain constant, and on the other hand *effector variables* such as skin temperature and heart rate that are responsible for Cannon's adaptive responses [23, 24]. We reasoned that these very distinct roles generate different statistics for the corresponding time series [9, 10, 11]: (i) in optimal conditions, regulated variables are characterized by a small variability around their respective setpoints which reflects the characteristic constancy of the internal environment, whereas effector variables have a large variability reflecting their adaptive capacity, and (ii) in adverse conditions, adaptive capacity and variability decrease for effector variables with as a consequence a loss of the constancy of the internal environment and therefore an increase of the variability of the regulated variables. In order to compare the variability from variables that often are measured in different units, we rescaled fluctuations to percentages around the median value,

$$\Delta X = 100 \times \left(\frac{X - \text{median}(X)}{\text{median}(X)} \right), \tag{1}$$

where X is the variable of interest, and we introduced a *homeostatic parameter*,

$$\alpha = \text{SD}(\Delta X_e)/\text{SD}(\Delta X_r), \tag{2}$$

which compares the relative variability of the regulated variable X_r of a specific regulatory mechanism and X_e a corresponding effector variable and where the standard deviation SD may be used as a measure of variability [10, 28]. It has been suggested that this approach may constitute a "bridge" between the loss of complexity and critical transition paradigms [25]. In the present contribution, we will focus on variables that are measurable continuously and in a non-invasive way, and we will compare examples from our previous publications (body temperature and cardiovascular variables) with new examples from physiology and biomechanics (ventilatory variables and gait), see Table 1.

Table 1 Regulatory mechanisms typically consist of one variable that is to be regulated and maintained constant and various effector variables that are responsible for adaptive responses to perturbations. Specific homeostatic mechanisms are often studied separately as if they function independently from each other which of course is an approximation; instead, homeostasis is known to work in a *hierarchical* or *nested* way, where a regulated variable such as blood pressure at the systemic scale may function as an effector variable at a local scale. Time series of regulated and effector variables may show universal behaviour independent from the specific field of study, from physiology to biomechanics.

regulated variable	effector variables
core temperature	skin temperature, vasomotor effects (vasoconstriction, vasodilatation), shivering, sweating, etc.
blood oxygen saturation	breathing rate, breathing amplitude, etc.
blood pressure[a]	heart rate, ejection fraction, cardiac output, vasomotor effects (vasoconstriction, vasodilatation), shivering, sweating, etc.
blood flow[b]	blood pressure, heart rate, ejection fraction, cardiac output, vasomotor effects (vasoconstriction, vasodilatation), etc.
average walking speed	step length, cadence, etc.

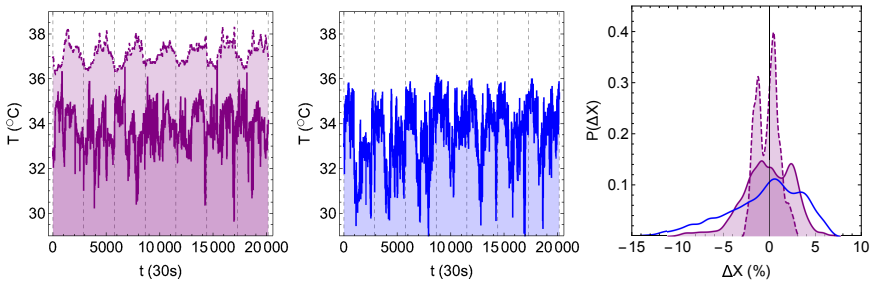
[a] systemic/extrinsic regulation
[b] local/intrinsic regulation or autoregulation

2 Selected physiological and biomechanical regulatory mechanisms

2.1 Physiological regulation of body temperature

The temperature of the human body depends on where it is measured [31]. It is the core body temperature which represents the internal environment and which is to be maintained constant in the face of changes of the external environment. One of the most important effector variables allowing adaptation to these external changes is skin temperature, which is modulated by limiting (vasoconstriction) or stimulating blood flow (vasodilatation) through the capillaries below the skin. Skin temperature depends on where on the body surface it is measured, in part because of variations in the local surface-to-volume ratio. Heat transfer is limited and a higher temperature is maintained proximally (on the trunk), whereas distally (on the extremities) heat transfer is enhanced and temperature tends to be lower. Temperature variations are slow and need to be measured over long time intervals, hours to days, to be studied as a time series, see Fig. 1. Core temperature T_{core} is a difficult variable to measure, because a sensor needs to be introduced in a body orifice and maintained there for the whole duration of the experiment. We explored body temperature regulation previously [8, 10], here we also aimed at exploring whether skin temperature when measured proximally, e.g., at the clavicula fossa T_{clav}, might function as a proxy for T_{core} to illustrate the dynamics of body temperature homeostasis in a more accessible way and we contrasted with distal skin temperature measured at the wrist, T_{wrist}. We compared the probability distribution functions (PDF) of all variables using the

dimensionless fluctuations of eq. (1) and calculated the homeostatic parameter α of eq. (2). It can be observed that the PDF of T_{core} is a superposition of 2 gaussian distributions corresponding to small variations of $\approx 1\%$ around a day and a night setpoint. In the PDF of T_{clav} the 2 local maxima of the circadian cycle are still present but in a less prominent way and variability is larger $\approx 5\%$. In the PDF of T_{wrist} the circadian cycle almost has become invisible, variability has increased dramatically $\approx 10\%$ and the distribution is non-gaussian and skewed to the left. We indeed observe a larger variability for the effector variable T_{wrist} than for the regulated variable T_{core} ($\alpha = 3.18$) or T_{clav} ($\alpha = 2.15$), which confirms our working hypothesis and indicates that indeed T_{clav} may possibly serve as a proxy for T_{core} to assess body temperature regulation. Previously, we also found that variability of T_{wrist} decreases with adverse conditions of being overweight and obesity which may indicate that adaptive capacity is lost [8, 10].



(a) core temperature and proxy (b) skin temperature at wrist (c) variability

Fig. 1 Homeostasis of body temperature. Shown are (a) the regulated variable of core temperature T_{core} and its possible proxy of skin temperature at the clavicula fossa T_{clav}, (b) effector variable of skin temperature at the wrist T_{wrist}, and (c) probability distribution functions (PDF) of fluctuations ΔX of eq. (1) for T_{core}, T_{clav} and T_{wrist} comparing their variability. Time series are measured continuously using thermochron iButtons at 30s sample intervals over 7 successive days (vertical gridlines indicate midnight) and the prominent 24h periodic pattern is the circadian cycle. All panels use the same color and style coding for the different variables, T_{core} (dashed and shaded purple curve), T_{clav} (continuous and shaded purple curve) and T_{wrist} (continuous blue curve). Data are from a healthy male adult.

2.2 Physiological regulation of blood oxygen saturation

Blood oxygen saturation, the percentage of arterial red blood cells carrying oxygen, is one of the only regulated variables that can be measured continuously and in a non-invasive way using a digital oximeter which can be developed in a well-equiped university lab at the undergraduate level [14, 21]. In optimal conditions, blood oxygen saturation is above 95% at sea level (above 90% at higher altitudes such as Mexico City located at 2000m), below 80% organ functionality is compro-

mised and below 70% consciousness is lost. Corresponding efector variables include breathing rate and breathing amplitude which can be measured using a chest strap. Fig. 2 compares conditions of rest and exercise (2km walking). It can be seen that during physical effort, muscles consume oxygen at an increased rate, breathing rate is increased but nevertheless blood oxygen saturation is slightly lower than during rest. The occasional large peaks in breathing amplitude during rest before the effort correspond to sighs; breathing amplitude is increased drastically during rest after the effort. Variability is larger for breathing amplitude (50-100%) than for breathing rate (20-30%), and variability of both effector variables is larger than in the case of the regulated variable (1%), with a homeostastic parameter of breathing rate with respect to blood oxygen saturation of $\alpha = 18.27$ (rest pre), $\alpha = 6.27$ (walk) and $\alpha = 10.71$ (rest post), and a homeostastic parameter of breathing amplitude with respect to blood oxygen saturation of $\alpha = 61.41$ (rest pre), $\alpha = 38.57$ (walk) and $\alpha = 37.59$ (rest post), which confirms our working hypothesis.

2.3 Physiological regulation of blood pressure

It is straightforward to realize point (one time) measurements of arterial blood pressure using a sphygmomanometer. It is much more difficult to continuously monitor blood pressure. Non-invasive devices exist, using volume-clamp techniques based on control theory, such as the Finapres of Finapres Medical Systems and the CNAP Monitor from CNSystems (CNAP stands for continuous non-invasive arterial pressure), but these very expensive [1]. Heart rate on the other hand can be measured easily using an electrocardiogram on the chest (ECG) or photoplethysmography (PPG) on the finger or earlobes, and which is the principle of measurement used by commercial smartwatches that monitor hear rate. There is a clear consensus that a high heart rate variability (HRV) constitutes a protective factor for health [20, 32]. The significance of blood pressure variability (BPV) is less clear, although there are indications that a high BPV represents a risk factor for negative health outcomes, which raises the question whether in the specific case of hypertension treatment should only focus on lowering high blood pressure levels or should try to reduce BPV as well [27]. In previous publications, we found evidence for a higher variability for heart rate than for systolic blood pressure in health [11], and a decrease of HRV and an increase of systolic BPV in the adverse condition of type-2 diabetes mellitus, in correspondence with our working hypothesis [9, 10, 28, 29]. In contrast, here heart rate and systolic blood pressure would seem to have similar variabilities, see Fig. 3, panels (a)-(c). A difference between both variables is that the distribution for systolic blood pressure behaves symmetrical and gaussian, whereas the distribution for heart rate is asymmetrical and right-skewed. Panels (d)-(f) compare average distributions over 5 min segments with the distribution for the whole time series of 2 hr for heart rate, systolic and diastolic blood pressure. It can be seen that variability increases only slightly for heart rate with time scale but that it increases much more importantly for systolic blood pressure. Diastolic blood pressure results to be much

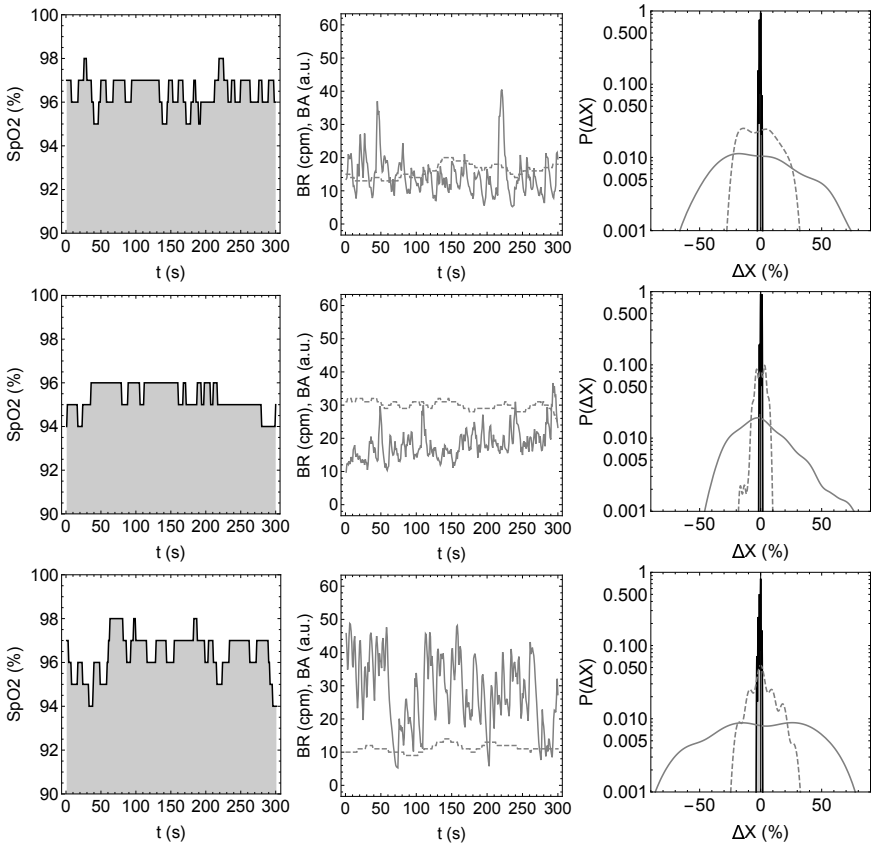
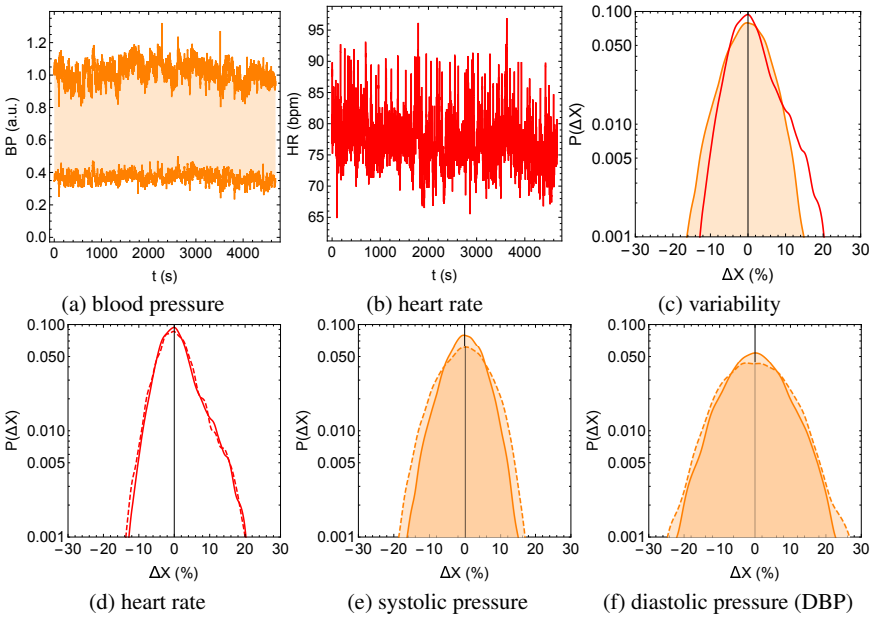


Fig. 2 Homeostasis of blood oxygen saturation in rest before (top row), after (bottom row) and during the physical effort of a 2km walk (middle row). Shown are (a) blood oxygen saturation SpO2 in percent, (b) breathing rate BR in cycles per minute and breathing amplitude BA in arbitrary units, and (c) probability distribution functions (PDF) of fluctuations ΔX of eq. (1) for SpO2, BR and BA comparing their variability. All time series are fragments of 5 min, measured at 1s sample intervals using a Masimo MightySAT oximeter (SpO2) and a Zephyr Bioharness (BA and BR). All panels use the same color and style coding for the different variables, SpO2 (continuous and shaded black curve), BR (dashed gray curve) and BA (continuous gray curve). Data are from a healthy female undergraduate student.

more variable than both heart rate and systolic blood pressure. Homeostatic parameters for heart rate with respect to systolic blood pressure are $\alpha = 1.07$ (average over fragments of 5min) and $\alpha = 0.83$ (over whole time series of 2hrs) and for heart rate with respect to diastolic blood pressure $\alpha = 0.66$ (average over fragments of 5min) and $\alpha = 0.61$ (over whole time series of 2hrs). Some physiological considerations may be able to explain these values. Systolic blood pressure depends mostly on cardiac output and in lesser degree also on arterial elasticity, whereas diastolic

blood pressure depends in the first place on arterial elasticity [36]. Therefore, it may be expected that systolic blood pressure participates actively in regulation whereas diastolic blood pressure possible plays a more passive role. Another consideration is that blood pressure may be a regulated variable at the systemic scale but plays an effector role at the local scale of specific organs, see Table 1, and the discussion section. This more passive role for diastolic blood pressure may be reflected by the homeostatic parameter α which appears to be independent from the time scale, whereas the variation in α with time for systolic blood pressure may indicate an alternation between the different roles of effector and regulator.



(a) blood pressure (b) heart rate (c) variability

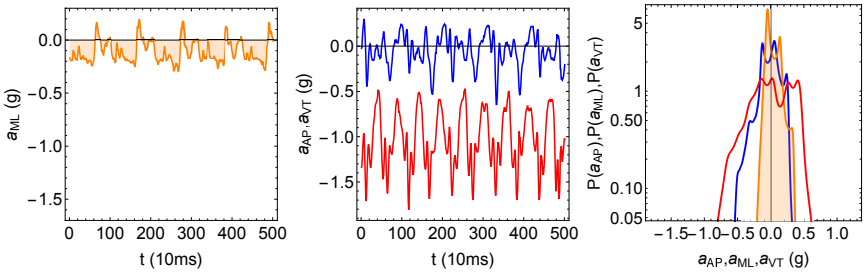
(d) heart rate (e) systolic pressure (f) diastolic pressure (DBP)

Fig. 3 Homeostasis of blood pressure. Shown are (a) systolic SBP and diastolic blood pressure DBP in arbitrary units, (b) heart rate HR in beats per minute and (c) average probability distribution functions (PDF) over 5min fragments of fluctuations ΔX of eq. (1) for SBP and HR comparing their variability. Average PDFs over 5min fragments are compared with PDFs of the complete 2hr time series for (d) heart rate HR, (e) systolic blood pressure SBP and (f) diastolic blood pressure DBP. Time series are on beat-to-beat basis with a length of 2hrs in supine rest. Data from a healthy young adult from the Physionet-Fantasia database [17, 13].

2.4 Biomechanical regulation of gait

The specific term of "homeostasis" is reserved for physiological regulation. Regulation also appears in other disciplines of medicine, e.g., the dynamics of biped

gait in biomechanics. Average walking speed v, possibly a regulated variable, is considered as the 6th vital sign because physical funcionality and independence are compromised when it drops below approx. 1m/s, e.g., in the case of age-associated frailty [12]. Elderly adults are often described to walk with a "cautious" or "senile gait", i.e., with small steps and a high step frequency or cadence [41, 18], both probably effector variables. When balance is altered, because of external factors such as walking in a moving train [2] or on a ship at sea [37] or because of internal factors such as pregnancy [22], obesity [5] or ageing [18], gait becomes similar to a "waddle", i.e., with an increased step width and larger associated mediolateral acceleration, also an effector variable. Fig. 4 shows fragments of time series of the effector variables of mediolateral a_{ML} and anterioposterior acceleration a_{AP} which oscillate around 0 and where each oscillation corresponds to an individual step, and vertical acceleration a_{VT} which oscillates around -1 because of the constant contribution of gravity. The PDFs of variability around the corresponding medians show that variability is smaller for a_{ML} than for a_{AP} and a_{VT}, in particular $\alpha = 1.53$ in the former case and $\alpha = 2.86$ in the latter case (comparing here different effector variables), which makes sense because the former component does not contribute to the forward movement whereas the latter two components do (this is obvious for a_{AP} but also applies to a_{VT} where especially for running vertical acceleration must be large enough to suspend both feet in the air simultaneously for each step). We have preliminary results that the variability of a_{AP} and a_{VT} decreases and that the variability of a_{ML} increases with age-associated frailty, constituting a suboptimal regulation of gait, which is also the reason that these variables are presented in different panels in Fig. 4.



(a) mediolateral (b) anterioposterior and vertical (c) variability

Fig. 4 Regulation of gait. Shown are (a) mediolateral acceleration a_{ML} in units of the Earth gravitational constant $g = 9.81\mathrm{m/s}^2$, (b) anterioposterior a_{AP} and vertical acceleration a_{VT} in units of g and (c) probability distribution functions (PDF) of fluctuations ΔX of eq. (1) for $a_{\mathrm{ML}}, a_{\mathrm{AP}}$ and a_{VT} comparing their variability. Time series fragments of 5s are shown and the PDFs are for the complete walk exercise of 2km (approx. 20min) of Fig. 2. Measured with the triaxial accelerometer of the Zephyr Bioharness with a sampling interval of 10ms. All panels use the same color and style coding for the different variables, a_{ML} (shaded orange curve), a_{AP} (blue curve) and a_{VT} (red curve). Data from a healthy female undergraduate student.

3 Discussion

Homeostatic principles of approximate constancy and therefore small variability of *regulated variables* associated to the internal environment and large variability because of adaptation to perturbations by *effector variables* are very clearly observed in time series related to body temperature homeostasis and the homeostasis of blood oxygen saturation, where skin temperature is much more variable than core temperature (Fig. 1), and breathing rate and breathing amplitude are much more variable than blood oxygen saturation (Fig. 2). In previous contributions, we have shown that in adverse conditions of ageing and/or disease the variability of regulated and effector variables deviates in opposite directions: decreasing for effector variables reflecting their diminished adaptive capacity and consequently increasing for regulated variables reflecting the more instable internal environment [9, 10]. This approach may offer a "bridge" between the paradigms of *loss of complexity* [19] and *critical transitions* [33].

This time-series approach can help to solve some of the "sticky points" mentioned in the introduction. The spontaneous fluctuations of physiological time series at all time scales clearly contradict the notion that physiological regulation would work as an on-off switch (on at some times and off at other times) and suggest that regulation is working continuously. Circadian cycles are a clear example of how the setpoint of a homeostatic mechanism may change over time, e.g., core body temperature is lower during the night than during the day, probably with the objective to save energy.

Another "sticky question" is how constant precisely the approximate constancy of the internal environment is. The answer may be that it depends on the specific homeostatic regulatory mechanism in question. In the cases of core temperature and blood oxygen saturation, we saw that they are maintained within a few percent of their median values. It may be interesting as well to consider the relative variability of specific regulated variables with respect to a corresponding effector variable. Since the work of Schrödinger where he interpreted the phenomenon of life from the perspective of physics, people have wondered about the order of internal structures and processes of the human body whereas according to the 2nd law of thermodynamics entropy should increase with time [30, 34]. Regulatory processes may function as an *entropy pump*, creating order in the internal environment by pumping excess entropy towards the external environment and creating extra entropy in the process. The homeostatic parameter α may express quantitatively how effective specific regulatory mechanisms are as an entropy pump. If true, then body temperature regulation and in particular blood oxygen saturation regulation would appear to work as good entropy pumps.

Standard textbooks on physiology discuss different homeostatic regulatory mechanisms one for one and separately, e.g., those listed in Table 1, as if they were independent from each other. This is not the case, different homeostatic regulatory mechanisms are interconnected as conveyed by the concept of *hierarchical* or *nested homeostasis* [6, 24]. One example may be blood pressure homeostasis. Although heart rate variability is one of the best studied physiological time series, its

statistics and that of the corresponding systolic and diastolic blood pressure is difficult to interpret in terms of regulatory mechanisms (Fig. 3). A possible reason is that blood pressure may play the role of a regulated variable at the systemic scale of the whole body but may function as an effector variable at the local scale of specific organs. Systemic blood pressure must be kept at a level which is convenient at average for all organs and tissues in the body, whereas some specific organs are so vital for survival, e.g., brain, heart, kidney, and possibly also eye [16], skin [40], etc., that their blood flow is very closely regulated and maintained constant by compensating between blood pressure on the one hand and vasomotor effects on the other hand [7, 15].

Regulated variables, such as core temperature and aslo blood pressure, tend to be more difficult to monitor continuously and non-invasively than corresponding effector variables, such as skin temperature and heart rate. We saw that regulated variables tend to be more symmetrical and gaussian, whereas effector variables appear to be characterized by more asymmetrical and non-gaussian distributions with a tail. Perhaps the focus on heart rate variability which is easy to monitor and which is well studied, has led West to conclude that homeostasis and gaussian distribution are obstacles to understand physiological time series [39]. Our results seem to indicate that gaussian statistics describes well regulated variables associated to the approximately constant internal environment, whereas fractal statistics and power laws may be better suited to describe the associated effector variables [11]. Homeostasis then is a concept which allows to combine the dynamics of regulated and associated effector variables within a same regulatory mechanism.

This time-series approach appears to capture general features of regulatory mechanisms and is applicable not only to physiological mechanisms, such as respiration and body temperature, but also biomechanical mechanisms, such as gait, and therefore is promising to incorporate information from regulation in prognostic scales in various medical disciplines.

4 Conclusions

Time series of physiological and biomechanical variables appear to reflect key aspects of the underlying regulatory mechanisms. The relative variability of a regulated variable and the corresponding effector variables would seem to offer a means to quantify the quality of the regulation. An advantage of focusing on such common and universal features would be that using the same methodology various regulatory mechanisms can be incorporated into prognostic scales.

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