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Editorial

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Physiological variables exhibit oscillatory patterns on many time scales (Mackey and Glass 1988, Buzsaki and Draguhn 2004, Stefanovska 2007). Compared to random behavior these periodical patterns convey to the whole system flexibility in presence of changing demands and variable environment. Indeed, a rhythmical activity enables temporal coordination among physiological process via synchronization and entrainment, guaranties efficient hierarchies among separate parts of the system, facilitates prediction of repetitive events favoring the preparation of the organism before the occurrence of event, minimizes energy expenditure, and allows storage and transmission of an infinite amount of information via frequency encoding (Rapp 1987). The multiplicity of the observed scales is the consequence of the need of living organisms to cope with sudden demands, such as during fight, and slow adaptations, such as those driven by seasons or aging, and the result of the natural selection that might have favored individuals able to extend the aforementioned advantages over a range of frequencies as wide as possible.

Periodical fluctuations of physiological variables are the result of the activity of self-sustained oscillators located in various places in our body. One of these autonomous oscillators is the heart responsible for oscillations of several physiological variables including arterial pressure and blood flow at the cardiac frequency and its multiples. Self-sustained oscillators interact with each other in such a way that their rhythmical activity might be modulated by the action of others. For example, the frequency of the heart is modulated by the respiratory centers located in the brain stem through the vagal innervation of the sinus node imposing changes to the heart period synchronous with the respiratory rate that contribute to the respiratory sinus arrhythmia (Eckberg and Karemaker 2009). The activity of these autonomous oscillators perturbs mechanisms responsible for controlling physiological variables and the resulting response might appear as a periodical activity as well. For example, the cardiac-related rhythm of the integrated muscle sympathetic nerve activity is mainly due to the periodical modification of the central inhibition induced by pulse-synchronous baroreceptor nerve activity driven by arterial pressure variations (Barman *et al* 2003). The oscillatory behaviors of physiological variables are not only the consequence of the incessant activity of internal rhythmical sources but also of periodical external inputs. For example, synchronization between heart rate and stride frequency, usually termed cardiolocomotor synchronization, was observed during running (Kirby *et al* 1989) and circadian variations are observed in many physiological variables (Millar-Craig *et al* 1978). Physiological fluctuations occurring at frequencies below the cardiac one (i.e. below 0.5 Hz in humans in resting supine condition) is usually referred to as variability. This term gained popularity with the spreading of the analysis of the variations of inter-beat interval from the electrocardiogram (Task Force 1996). Physiological fluctuations

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are referred to as vasomotion, and usually assessed below 0.15 Hz, when analyzed from signals related to blood circulation through the vascular system. Variability was widely assessed with special focus on cardiovascular system (Cohen and Taylor 2002). Although variability could be interpreted as a measurement error or as a harmless side effect of the application of the homeostatic principle aiming at maintaining the relative constancy of the internal milieu of the organism, its more profound significance was immediately recognized (Billman 2011). Some pioneering works (Akselrod *et al* 1981, 1985, Colantuoni *et al* 1984, Pagani *et al* 1986, Berger *et al* 1997) made possible the quantitative analysis of variability and proved that it carries information about regulatory mechanisms. The analysis of spontaneous variability became more important when it was realized that an abnormal or missing response could be utilized as a hallmark of a pathological state and variability markers were very sensitive in identifying a dysfunction (Task Force 1996). However, given the intricate nature of interactions among physiological systems featuring autonomous rhythm generators, complex nonlinear relationships, and nested reflexes with different hierarchies and latencies, disentangling mechanisms, assessing the gain of specific pathways, disambiguating causal effects, identifying closed loop relations, evaluating associations in specific temporal directions and conditioning out confounding factors are challenging tasks. Modern signal processing can be fruitfully exploited to provide the separate characterization of the internal perturbations and evoked responses and to estimate the strength of the dependency of the response on the stimulus while accounting for indirect influences and the eventual presence of buffering effects (Stankovski *et al* 2015, Muller *et al* 2016, Penzel *et al* 2016, Porta and Faes 2016).

Vasomotion, on the other hand, attracted much attention from those studying hemodynamic properties of the cardiac activity and blood flow evaluated by quantification of rhythmic diameter changes of the vessels (Colantuoni *et al* 1984), optical methods such as laser Doppler flowmetry (Stefanovska *et al* 1999), or white light or near infra-red spectroscopy (Obrig *et al* 2000). Simultaneous recording of electrical and hemodynamic activity in resting humans have identified involvement of oscillatory activities at frequencies as low as 0.01 Hz and below, attributable to myogenic, neurogenic, endothelial and metabolic processes (Shiogai *et al* 2010, Aalkjaer *et al* 2011), The contribution of the vascular system to the oscillatory behavior originates from rhythmic activity of the smooth muscle cells in the vascular walls, the rhythmic activation of sympathetic nerves innervating the vessels and the involvement of endothelial cells lining the inner layer of the vascular walls. The ultimate goal of the cardiovascular system activity is to bring the nutrients to each cell and take the waste products of their metabolism, processes that presumably need to be synchronized with the cellular metabolic oscillations that have already been observed *in vitro* (Aon *et al* 2003, Gustavsson *et al* 2012). The flow of the blood, as well as the neuronal signaling processes, requires close coordination of cardiovascular and brain activity (Stefanovska 2007). Monitoring changes in these interactions with various conditions, like e.g. anesthesia (Stankovski *et al* 2016) may be expected to yield new insights into the underlying physiology.

Applications of modern signal processing techniques to fluctuations of physiological variables acquired over time with a given temporal resolution is not only a mere exercise of computational skills but a practice useful in physiology to understand dependences among variables, in medicine to typify pathological states and improve diagnosis and in clinics to predict outcome of an intervention and performing risk assessment. Just to provide few examples of relevant applications of signal processing techniques to physiological oscillatory patterns that led to practical advancements in clinics and provided turning points in understanding the complexity of the physiological interactions, we recall that: (i) Bauer *et al* (2008) demonstrated the clinical value of characterizing the physiological variations of heart rate following an internal stimulus such as the isolated premature ventricular contraction; (ii) La

Rovere *et al* (2011) proved the prognostic value of cardiac baroreflex sensitivity estimated from spontaneous variations of heart period and systolic arterial pressure and its nonredundant value compared to the gold standard invasive estimate based on the administration of vasoactive drugs; (iii) Bashan *et al* (2012) put physiology under a system-wide perspective in which a pathophysiological state can be fully typified by estimating via signal processing techniques the strength of the connections among the constituents of a physiological network describing the functioning of the entire organism; (iv) Park and Friston (2013) and Seth *et al* (2015) suggested that modeling and causality approaches might allow one to move beyond the information associated to regional activations of cerebral areas toward the characterization of functional circuits; (v) Tononi *et al* (2016) postulates that information theory could provide tools to unveil consciousness and measure the quality and quantity of a subjective experience. Remarkably, conclusions reached by the aforementioned studies were drawn without being necessary to implement new experimental setups or inventing original devices but by looking at the already acquired signals under new perspectives that have in common the exploitation of rhythmical changes of physiological variables.

The European Study Group on Cardiovascular Oscillations (ESGCO) and the Berlin Biosignal Group (BBG) focused their respective meetings, namely the 9th ESGCO meeting, 10–14 April 2016, Lancaster, UK, www.physics.lancs.ac.uk/ESGCO2016/ and the BBG meeting, 7–8 April 2016, Berlin, Germany, http://2016.biosignal.berlin/, on the rhythmical variations of physiological variables and on the tools needed for their measurement, processing and interpretation. This area, at the crossing between biology, biophysics, bioengineering, physiology, medicine and technology, is the core of the activity of both groups since their beginnings. More specifically, the ECGCO conference was centered on complexity and multiscale analyses of oscillatory biological signals and their nonlinear interactions and featured also a rich and deep discussion on the origins and nature of cellular, microvascular, cardiovascular and neurophysiological oscillations. Moreover, it was recognized that all biological oscillations can be treated in the same way mathematically, i.e. as resulting from non-autonomous continuously perturbed and mutually interacting systems. However, a better understanding of their underlying biophysics and their physiological origin is needed. The BBG meeting was centered on the acquisition and analysis of electrical and magnetic fields of the body and, in particular, on the similarities and differences of methodological approaches and their clinical relevance. Some of the work presented at these two meetings is published in this focus issue of Physiological Measurement. A common feature is the signal processing approach to the problems of biological oscillations. Selection was made via the regular peer-review process of the journal over expanded versions of the contributions originally presented in the aforementioned meetings and submitted to this focus issue. The resulting collection of articles covers advanced methods for multivariate time series analysis, spectral decomposition, information processing, complexity assessment, causality estimation and synchronization quantification with applications to cardiovascular control, neurophysiology, cardiovascular physiology and neuroscience.

The common denominator of the contributions listed in the present issue is to exploit unconventional signal processing techniques over physiological variations recorded routinely in standard hospital facilities to characterize the functioning of the underlying system and the interactions among parts of the same system or among different systems according to a holistic view. The final practical aim is to facilitate the identification of deviation from the normal behavior, the characterization of a population and its separation from groups with apparently similar features, the monitoring of the evolution of system characteristics over time and the quantification of dynamical interactions among system constituents. The contributions can be roughly divided into three categories according to the complexity of the approach as categorized by the number of different signals necessary to perform the analysis. Among the applications of univariate approaches requiring the acquisition of one signal Castiglioni and Merati (2017) performed fractal analysis of heart rate variability series in paraplegic individuals and found that this analysis was superior to more traditional power spectral analysis in a subgroup of paraplegic individuals featuring an intact cardiac control; Hoyer *et al* (2017) summarized the novel developments in monitoring fetal maturation using heart rate variability recordings; Corino *et al* (2017) performed atrial fibrillation detection from interdiastolic pulse wave interval series recorded via a wristband device with remarkable sensitivity and specificity in discriminating atrial fibrillation from sinus rhythm and different arrhythmias; Masé *et al* (2017) evaluated the dependence of the ventricular response on atrial activity and atrioventricular conduction variability markers computed in time and information domains during episodes of atrial flutter and atrial fibrillation; Wejer *et al* (2017) computed the complexity of patterns extracted cardiovascular variability series in patients with an history of vasovagal faints during orthostatic challenge; Gizzi *et al* (2017) proposed an original approach for the quantification of action potential amplitude alternans recorded from isolated right canine ventricles and applied it in hypothermic conditions; Elstad *et al* (2017) studied the oscillatory patterns of acral skin blood flow below 0.1 Hz during the lowering of the ambient temperature within the thermoneutral zone via wavelet transformation in healthy subjects; Sorelli *et al* (2017) addressed the issue of spatial heterogeneity of microcirculation in healthy individuals through a model-based approach fitting the response of skin blood flow to local heating and a wavelet transformation evaluating the spectral content of the signal below 1 Hz. Among the applications of approaches requiring the acquisition of two signals Javorka *et al* (2017) assessed directionality of the interactions between heart period changes and slow oscillations of arterial pressure during situations of sympathetic activation with the specific aim of understanding how the structure of the interactions varied as a function of the fiducial point selected over arterial pressure recordings; Mazzucco *et al* (2017) studied phase synchronization between heartbeat, as detected from surface electrocardiogram, and the ventilator in respiratory failure patients admitted in critical care units and proved that cardioventilatory phase interactions depended on the mode of mechanical ventilation; Berg *et al* (2017) demonstrated that cardiorespiratory coordination increased in preeclampsia using an approach where respiratory activity was inferred from surface electrocardiogram; Kuhnhold *et al* (2017) compared five different methods for quantification of cardiorespiratory phase synchronization in a large cohort of post-myocardial infarction patients. Among the applications requiring the acquisition of three or more signals, Porta *et al* (2017) proposed a method in the information domain to estimate the redundancy of physiological control mechanisms in contributing to spontaneous fluctuations of heart period and arterial pressure in healthy subjects and applied it to a cohort of subjects with different ages; Krefting *et al* (2017) applied a time delay stability approach to polysomnographic recordings in healthy subjects to describe the interactions among different physiological systems and assess their modifications with gender and age; Bari *et al* (2017) proved that an information domain directionality method applied to cerebrovascular and cardiovascular variabilities can identify the impaired regulatory mechanisms in patients prone to develop postural syncope.

We hope that the contributions presented in this issue can, on the one hand, stimulate the design of new tools devoted to improve specificity of the information derived from variations of physiological variables and, on the other hand, encourage the application of existing methods to larger databases with the main purpose of validating observations, standardizing approaches and indexes and accelerate the utilization of the methods in clinical settings.

References

Aalkjaer C, Boedtkjer D and Matchkov V 2011 Vasomotion—what is currently thought? *Acta Physiol.* **202** 253–69

Akselrod S, Gordon D, Madwed J B, Snidman N C, Shannon D C and Cohen R J 1985 Hemodynamic regulation: investigation by spectral analysis *Am. J. Physiol.* **249** H867–75

Akselrod S, Gordon D, Ubel F A, Shannon D C, Berger R D and Cohen R J 1981 Power spectrum analysis of heart rate fluctuations: a quantitative probe of beat-to-beat cardiovascular control *Science* **213** 220–3

Aon M A, Cortassa S, Marban E and O’Rourke B 2003 Synchronized whole cell oscillations in mitochondrial metabolism triggered by a local release of reactive oxygen species in cardiac myocytes *J. Biol. Chem.* **278** 44735–44

Bari V, De Maria B, Mazzucco C E, Rossato G, Tonon D, Nollo G, Faes L and Porta A 2017 Cerebrovascular and cardiovascular variability interactions investigated through conditional joint transfer entropy in subjects prone to postural syncope *Physiol. Meas.* **38** 976

Barman S M, Fadel P J, Vongpatanasin W, Victor R G and Gebber G L 2003 Basis for the cardiac-related rhythm in muscle sympathetic nerve activity of humans *Am. J. Physiol.* **284** H584–97

Bashan A, Bartsch R P, Kantelhardt J W, Havlin S and Ivanov P Ch 2012 Network physiology reveals relations between network topology and physiological function *Nat. Commun.* **3** 702

Bauer A *et al* 2008 Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use *J. Am. Coll. Cardiol.* **52** 1353–65

Berg K, Kraemer J, Riedl M, Stepan H, Kurths J and Wessel N 2017 Increased cardiorespiratory coordination in preeclampsia *Physiol. Meas.* **38** 912

Berger R D, Kasper E K, Baughman K L, Marban E, Calkins H and Tomaselli G F 1997 Beat-to-beat QT interval variability: novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy *Circulation* **96** 1557–65

Billman G E 2011 Heart rate variability—a historical perspective *Front. Physiol.* **2** 86

Buzsaki G and Draguhn A 2004 Neuronal oscillations in cortical networks *Science* **304** 1926–9

Castiglioni P and Merati G 2017 Fractal analysis of heart rate variability reveals alterations of the integrative autonomic control of circulation in paraplegic individuals *Physiol. Meas.* **38** 774

Cohen M A and Taylor J A 2002 Short-term cardiovascular oscillations in man: measuring and modelling the physiologies *J. Physiol.* **542** 669–83

Colantuoni A, Bertuglia S and Intiglietta M 1984 Quantification of rhythmic diameter changes in arterial microcirculation *Am. J. Physiol.* **246** H508–17

Corino V, Laureanti R, Ferranti L, Scarpini G, Lombardi F and Mainardi L 2017 Detection of atrial fibrillation episodes using a wristband device *Physiol. Meas.* **38** 787

Eckberg D L and Karemaker J M 2009 Point:Counterpoint: respiratory sinus arrhythmia is due to a central mechanism versus respiratory sinus arrhythmia is due to the baroreflex mechanism *J. Appl. Physiol.* **106** 1740–4

Elstad M, Zilakos I and Bergersen T K 2017 Oscillatory pattern of acral skin blood flow within thermoneutral zone in healthy humans *Physiol. Meas.* **38** 848

Gizzi A, Loppini A, Cherry E, Cherubini C, Fenton F and Filippi S 2017 Multi-band decomposition analysis: application to cardiac alternans as a function of temperature *Physiol. Meas.* **38** 833

Gustavsson A K, van Niekerk D D, Adiels C B, du Preez F B, Goksor M and Snoep J L 2012 Sustained glycolytic oscillations in individual isolated yeast cells *FEBS J.* **279** 2837–47

Hoyer D *et al* 2017 Monitoring fetal maturation—objectives, techniques and indices of autonomic function *Physiol. Meas.* **38** R61

Javorka M, Krohova J, Czippelova B, Turianikova Z, Lazarova Z, Javorka K and Faes L 2017 Basic cardiovascular variability signals: mutual directed interactions explored in the information domain *Physiol. Meas.* **38** 877

Kirby R L, Nugent S T, Marlow R W, MacLeod D A and Marble A E 1989 Coupling of cardiac and locomotor rhythms *J. Appl. Physiol.* **66** 323–9

Krefting D, Jansen C, Penzel T, Han F and Kantelhardt J 2017 Age and gender dependency of physiological networks in sleep *Physiol. Meas.* **38** 959

Kuhnhold A, Schumann A, Bartsch R, Ubrich R, Barthel P, Schmidt G and Kantelhardt J 2017 Quantifying cardio-respiratory phase synchronization—a comparison of five methods using ECGs of post-infarction patients *Physiol. Meas.* **38** 925

La Rovere M T, Maestri R, Robbi E, Caporotondi A, Guazzotti G, Febo O and Pinna G D 2011 Comparison of the prognostic values of invasive and noninvasive assessments of baroreflex sensitivity in heart failure *J. Hypertension* **29** 1546–52

Mackey M C and Glass L 1988 *From Clocks to Chaos: the Rhythms of Life* (Princeton, NJ: Princeton University Press)

Masè M, Disertori M, Marini M and Ravelli F 2017 Characterization of rate and regularity of ventricular response during atrial tachyarrhythmias. Insight on atrial and nodal determinants *Physiol. Meas.* **38** 800

Mazzucco C E *et al* 2017 Mechanical ventilatory modes and cardioventilatory phase synchronization in acute respiratory failure patients *Physiol. Meas.* **38** 895

Millar-Craig M W, Bishop C N and Raftery E B 1978 Circadian variation of blood pressure *Lancet* **311** 795–7

Muller A, Kraemer J F, Penzel T, Bonnemeier H, Kurths J and Wessel N 2016 Causality in physiological signals *Physiol. Meas.* **37** R46–72

Obrig H, Neufang M, Wenzel R, Kohl M, Steinbrink J, Einhaupl K and Villringer A 2000 Spontaneous low frequency oscillations of cerebral hemodynamics and metabolism in human adults *Neuriomage* **12** 623–39

Pagani M *et al* 1986 Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog *Circ. Res.* **59** 178–93

Park H-J and Friston K 2013 Structural and functional Brain networks: from connections to cognition *Science* **342** 1238411

Penzel T, Kantelhardt J W, Bartsch R P, Riedl M, Kraemer J F, Wessel N, Garcia C, Glos M, Fietze I and Schöbel C 2016 Modulations of heart rate, ECG, and cardio-respiratory coupling observed in polysomnography *Front. Physiol.* **7** 460

Porta A, Bari V, De Maria B; Perseguini N M, Milan J, Rehder-Santos P, Minatel V, Takahashi A and Catai A 2017 Assessing the evolution of redundancy/synergy of spontaneous variability regulation with age *Physiol. Meas.* **38** 940

Porta A and Faes L 2016 Wiener–Granger causality in network physiology with applications to cardiovascular control and neuroscience *Proc. IEEE* **104** 282–309

Rapp P E 1987 Why are so many biological systems periodic *Prog. Neurobiol.* **29** 261–73

Seth A K, Barrett A B and Barnett L 2015 Granger causality analysis in neuroscience and neuroimaging *J. Neurosci.* **35** 3293–7

Shiogai Y, Stefanovska A and McClintock P V E 2010 Nonlinear dynamics of cardiovascular ageing *Phys. Rep.* **488** 51–110

Sorelli M, Stoyneva Z, Mizeva I and Bocchi L 2017 Spatial heterogeneity in the time and frequency properties of skin perfusion *Physiol. Meas.* **38** 860

Stankovski T, Petkoski S, Raeder J, Smith A F, McClintock P V E and Stefanovska A 2016 Alterations in the coupling functions between cortical and cardio-respiratory oscillations due to anaesthesia with propofol and sevoflurane *Phil. Trans. R. Soc.* A **374** 20150186

Stankovski T, Ticcinelli V, McClintock P V E and Stefanovska A 2015 Coupling functions in networks of oscillators *New J. Phys.* **17** 035002

Stefanovska A 2007 Coupled oscillators—complex but not complicated cardiovascular and brain interactions *IEEE Eng. Med. Biol. Mag.* **26** 25–9

Stefanovska A, Bračič M and Kvernmo H D 1999 Wavelet analysis of oscillations in the peripheral blood circulation measured by laser Doppler technique *IEEE Trans. Biomed. Eng.* **46** 1230–9

Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology 1996 Heart rate variability—standards of measurement, physiological interpretation and clinical use *Circulation* **93** 1043–65

Tononi G, Boly M, Massimini M and Koch C 2016 Integrated information theory: from consciousness to its physical substrate *Nat. Rev. Neurosci.* **17** 450–61

Wejer D, Graff B, Makowiec D, Budrejko S and Struzik Z 2017 Complexity of cardiovascular rhythms during head-up tilt test by entropy of patterns *Physiol. Meas.* **38** 819

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