

EDITORIAL

## Addressing the complexity of cardiovascular regulation

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The cardiovascular system plays a key role in complex living organisms since it provides supplies for maintaining vital functions and, contemporaneously, gets rid of waste materials. It is formed by highly specialized subsystems that interact with each other to accomplish tasks (e.g. the optimization of arterial and pulmonary circulation) and even compete for resources as in, for example, the maintenance of the cerebral circulation during a massive haemorrhage. Subsystems have their own local regulatory mechanisms (e.g. mechanisms regulating blood flow in proximal microvascular districts) that interact with central neural commands reflecting the activity of the vasomotor and respiratory autonomous oscillators, with reflex neural commands occurring in response to changes in some controlled variables (e.g. arterial pressure) and with humoral factors. All these regulatory mechanisms act rhythmically, producing incessant adjustments in cardiovascular variables visible from beat-to-beat recordings. These variations are referred to as ‘cardiovascular variability’ and occur over a wide frequency range including very slow rhythms (e.g. ultradian periodicities) and oscillations even faster than heart rate. The magnitude of these variations depends on the gross amount of the activities of the autonomous central oscillators, on the resonance of the closed-loop mechanisms, on the gain of the relationship between variables and on the possibility that a network of distributed oscillators with negligible activities becomes entrained or remains sparse.

The presence of multiple regulatory mechanisms contemporaneously active over different time scales and capable of varying over time the relationships among variables generates the dynamic complexity of cardiovascular variables. This complexity also depends on the presence of mechanisms favouring synchronization among the activities of subsystems according to  $n : m$  coupling ratios (i.e.  $n$  cycles of activity of one subsystem correspond to  $m$  cycles of the other), thus reducing dimensionality of the cardiovascular system, and on the amount of information exchanged among subsystems (i.e. on their degree of isolation).

Current evidence suggests that the assessment of the complexity of cardiovascular regulation could provide important information about the underlying regulatory mechanisms. In particular, it has been shown that a modification of complexity indices, resulting from depressed organ function, a loss of interaction among subsystems, an overwhelming action of a subsystem over others and an impairment of regulatory mechanisms, is a clear hallmark of a pathological situation. Interestingly, since the complexity of cardiovascular regulation can be evaluated from variables that are routinely and non-invasively estimated during the most common medical examinations, this assessment does not require additional procedures and devices. On the contrary, it necessitates

One contribution of 15 to a Theme Issue ‘Addressing the complexity of cardiovascular regulation’.

methods that facilitate the integration of a large number of different signals derived from different districts and that extract information from the contemporaneous presence of several temporal scales originated by various mechanisms.

The primary aim of this theme issue is to propose the application of signal processing tools to fruitfully address the dynamic complexity of cardiovascular regulation via the analysis of cardiovascular variability. Advanced signal processing techniques based on system identification, parametric modelling, time-varying spectral approaches, complexity, irreversibility, synchronization and fractal analyses, directionality and causality are exploited to derive pathophysiological information. The final aim is to extract clinical indices useful to typify a pathological state, to screen subjects at risk, to tailor individual treatments and to improve medical diagnostics and therapy.

This theme issue, collecting contributions from experts bridging many disciplines from physiology to medicine, from computer science to biology, from physics to bioengineering, is designed to review the field of the assessment of cardiovascular regulation through the application of state-of-the-art signal processing techniques and concepts of complex system theory. In addition, this theme issue includes a tribute to Solange Akselrod (Cerutti & Davrath 2009). She was a pioneer (Akselrod *et al.* 1981) in the analysis of cardiovascular variability and in understanding the information coded in it. The contributions can be roughly subdivided into three categories: (i) contributions proving the relevance of the assessment of cardiovascular complexity not only in clinical settings but also in animal laboratories (Aubert *et al.* 2009; Huikuri *et al.* 2009; Montano *et al.* 2009; Retzlaff *et al.* 2009), (ii) contributions exploring the complexity of specific cardiovascular control mechanisms (Couderc 2009; Di Rienzo *et al.* 2009; Panerai 2009), and (iii) contributions proposing or applying specific signal processing tools for the evaluation of certain aspects of cardiovascular complexity (Batzel *et al.* 2009; Cerutti *et al.* 2009; Keissar *et al.* 2009; Nollo *et al.* 2009; Porta *et al.* 2009; Riedl *et al.* 2009).

Within the set of contributions demonstrating the importance of quantification of cardiovascular complexity, Huikuri *et al.* (2009) review the studies assessing complexity indices over heart period variability in humans and elucidate the physiological and clinical information that can be extracted from them. Aubert *et al.* (2009) follow the same approach as Huikuri *et al.* (2009), but cardiovascular variability signals are recorded from small animals that are routinely used in laboratories. Retzlaff *et al.* (2009) provide a good example of how a large set of linear and nonlinear indices can be integrated and fruitfully exploited to derive clinical information helpful in categorizing patients. More basically, Montano *et al.* (2009) directly investigate the complexity of neural recordings in humans and small animals as the basis to better understand the information that can be derived from the analysis of less invasive cardiovascular variables.

Within the set of contributions exploring the complexity of specific cardiovascular control mechanisms, Couderc (2009) reviews the mechanisms influencing the timing and the morphology of the T wave and affecting the relationship between heart period and ventricular repolarization duration, Di Rienzo *et al.* (2009) deal with the time scales, nonlinearities and complexity of the baroreflex, i.e. the most important reflex mechanism for the maintenance of blood pressure homeostasis, and Panerai (2009) challenges the complexity of human cerebral regulation.

Within the set of contributions proposing or applying specific signal processing tools for the evaluation of certain aspects of cardiovascular complexity, [Cerutti \*et al.\* \(2009\)](#) provide a list of issues that can benefit from the application of temporal and spatial multiscale analyses in the context of multivariate recordings derived from different subsystems. [Porta \*et al.\* \(2009\)](#) show that irreversibility analysis, based on the evaluation of the invariance of statistical properties of a process after time reversal, can be helpfully exploited to typify complexity and detect specific nonlinear patterns in heart period variability recordings obtained during normal daily life. The issue of estimating the relationships among cardiovascular variables is discussed by [Batzel \*et al.\* \(2009\)](#) using modern identification techniques based on linear or nonlinear models. This approach allows the separation of influences and the disjoining of mechanisms directly from real data obtained without artificially opening closed-loop regulations via pharmacological or surgical interventions. At variance from [Batzel \*et al.\* \(2009\)](#), who mainly focused on the estimation of gain and phase of the relationships between signals, [Keissar \*et al.\* \(2009\)](#), [Nollo \*et al.\* \(2009\)](#) and [Riedl \*et al.\* \(2009\)](#) emphasize the indices capable of quantifying interactions between variables according to the degree of correlation and the amount of information exchanged between them: [Keissar \*et al.\* \(2009\)](#) estimate the strength of linear coupling, as assessed by the coherence function, between heart period and respiration using a time-variant approach based on continuous wavelet transform during a fast change in posture from a supine to a standing position; [Riedl \*et al.\* \(2009\)](#) check for the presence of synchronization between the foetal and maternal heart beats using a data-driven model-based analysis; and [Nollo \*et al.\* \(2009\)](#) test directionality (or causality) of the interactions between heart period and systolic arterial pressure according to the Granger paradigm.

In conclusion, we hope that this theme issue will demonstrate how the application of modern signal processing tools for the assessment of nonlinear and complex dynamics can facilitate the understanding of cardiovascular function in health and disease and provide non-redundant clinical information without any need of introducing new, highly sophisticated devices. In addition, we hope that concepts and ideas included in this theme issue could stimulate future research, thus accelerating the development of techniques for the assessment of patients' health status and the transfer of the results into clinical practice.

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