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Signal Processing Guided by Physiology: Making the Most of Cardiorespiratory Signals

Biomedical signals convey information about biological systems and can emanate from sources of such varied origins as electrical, mechanical, or chemical. In particular, biomedical signals can provide relevant information on the function of the human body, e.g., related to muscle contraction, neuronal activity, or heart beating, to name a few. This information, however, may not be apparent in the signal due to measurement noise, presence of signals coming from other interacting subsystems, or simply because it is not visible to the human eye. Signal processing is usually required to extract the relevant information from biomedical signals and convert it into meaningful data that physicians can interpret.

RELEVANCE OF PHYSIOLOGY-GUIDED PROCESSING

It is fundamental to know the physiology behind the biomedical measurements under analysis. Not considering the underlying physiology may lead to processing methods that do not fully exploit the biomedical signals or even distort/remove the information of interest [1], [2]. An example can be found in applications that use filtering to remove powerline noise in situations where micropotentials, spectrally overlapping with the powerline interference, want to be analyzed. Another example refers to infinite impulse response filters, which, when used to remove baseline wandering in the electrocardiogram (ECG), produce highly distorted T-waves due to their nonlinear phase response.

Digital Object Identifier 10.1109/MSP.2013.2266961
Date of publication: 20 August 2013

Biomedical signal processing (BSP) tools are typically applied on only one signal recorded at a unique level of the functional system under investigation and with limited knowledge of the interrelationships with other components of that system. However, in most instances, BSP can benefit from an analysis in which multiple signals are simultaneously evaluated (multimodal processing), different levels of function are considered (multiscale processing), and scientific input from different disciplines is incorporated (multidisciplinary processing). For each problem at hand, the BSP researcher should decide to what extent information from a number of signals, functional levels, or disciplines needs to be incorporated to solve the problem [3], [4]. As an example, a multiscale model may be necessary when a deeper knowledge of the cell and tissue mechanisms underpinning alterations in a body surface signal is required, whereas a simplified, single-scale model may be sufficient in other cases, as when investigating the relationship between two signals measured on the whole human body.

At present, there are many biomedical signals that can be acquired and processed using relatively low-cost systems, which makes their use in the clinics very extensive. In particular, noninvasive signals readily accessible to physicians are increasingly being used to improve the diagnosis, treatment, and monitoring of a variety of diseases [5]. The following sections illustrate the role played by BSP in the analysis of cardiovascular signals. A set of applications is presented where BSP contributes to improve our knowledge on atrial and ventricular arrhythmias, the modulation of cardiac activity by the autonomic nervous system (ANS), and the interactions between cardiac and respiratory signals.

CARDIOVASCULAR SIGNALS

The cardiovascular system, composed of the heart, blood vessels, and blood, is the network responsible for distributing blood and nutrients to the body's tissues. The heart is a four-chambered organ, with left and right atria and ventricles, whose muscle cells have the property of excitability. This means that, when stimulated with a sufficiently large electrical current, cardiac cells are able to generate an active electrical response, called action potential (AP), which acts as the trigger for mechanical contraction. The AP is the result of ion charges (mostly sodium, calcium, potassium, and chloride) moving in and out of the cell through voltage-gated channels. Under normal conditions, each cardiac cycle is started by an AP originated at the sino-atrial node, which then propagates to the atria, passes through the atrio-ventricular node, and finally spreads out via a specialized conduction system throughout the ventricles. Coordinated contraction of atria and ventricles allows the heart to pump deoxygenated blood to the lungs and oxygenated blood to the rest of the body. The two phases of each cardiac cycle, which in mechanical terms correspond to contraction and relaxation, are named in electrical terms as *depolarization* and *repolarization*, respectively.

The AP cannot be typically measured in vivo, or its measurement requires invasive procedures. However, the resulting electrical activity of the whole heart can be noninvasively recorded at the body surface by a proper setting of electrodes and acquisition system. The signal recorded at

the body surface is known as the ECG and reflects the spatial summation of the electrical activity of the heart's cells activated at a given time. A simple model to visualize the electrical activity manifested on the ECG is given by the dipolar model, which considers an electrical heart vector defined as the sum of all the cell current dipoles activated at a time instant and describes the ECG as a projection of this electrical vector. The projection direction is given by the positions of the electrodes from which the ECG is measured. Although the ECG is an integrated measure of processes occurring at the cellular level, the fact that it can be used for massive scrutiny due to its characteristics of simplicity and accessibility make it a fundamental tool to extract information about cardiac function.

A closer view of the electrical activity of the heart can be obtained by locating electrodes on the myocardium surface. The signals obtained in this way are called electrograms (EGMs). EGMs can be measured from a single electrode (unipolar EGM), reflecting the regional myocardium electrical activity, or as the voltage difference between two electrodes (bipolar EGM), which essentially reflects the passing of the wavefronts through the area between both electrodes. Obviously, these signals can only be obtained in an invasive way, and thus lack the universality of the ECG, but play a crucial role in the operation of implantable devices, such as cardioverter-defibrillators, cardiac resynchronization devices, or pacemakers, and also in guiding electrophysiological interventions such as atrial and ventricular ablation.

Coordination of heart contraction determines the effectiveness of blood distribution to the body. The mechanical effects of blood flowing through the vessels can be measured from biomedical signals such as pulse photoplethysmography (PPG) or blood pressure (BP). The PPG is a simple and useful method to measure the relative blood volume changes in the microvascular bed of peripheral tissues and thus evaluate peripheral circulation. The PPG signal is obtained based on blood light absorption through noninvasive pulse oximetry systems. The technique is simple, cheap, and widely used in the clinical routine.

BP is defined as the pressure of the blood against the vessel walls of the cardiovascular system, and it constitutes one of the most important determinants of cardiovascular function. Direct measurement of BP requires the insertion of a catheter into different areas of the cardiovascular system. Noninvasive continuous measurement of the BP signal is possible based on finger plethysmography or applanation tonometry.

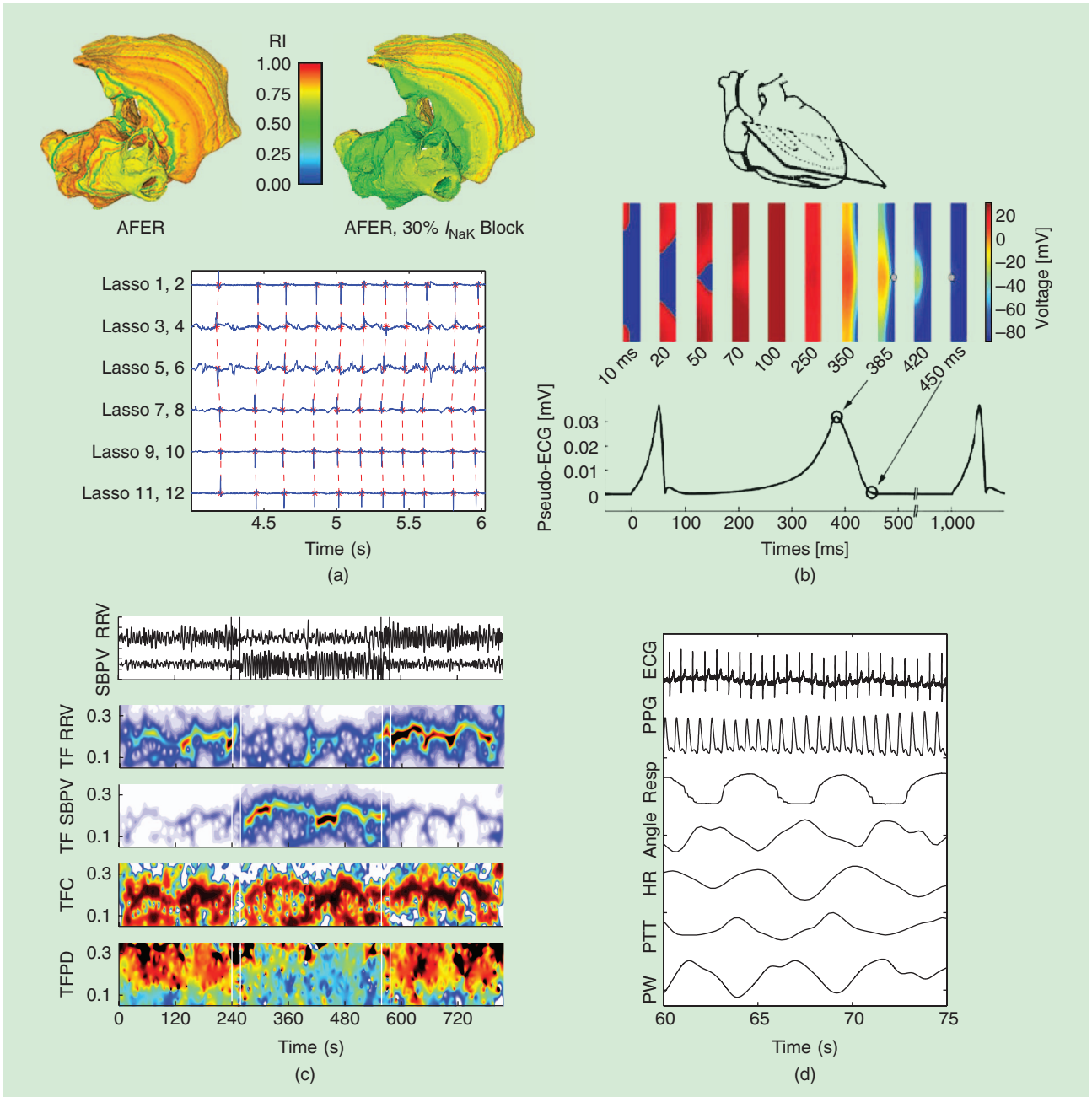
THE ATRIAL MYOCARDIUM: GUIDING TREATMENT OF ATRIAL ARRHYTHMIAS THROUGH SIGNAL PROCESSING

Cardiac arrhythmias, defined as disturbances in the normal rhythm of the heartbeat, represent a common cause of mortality in industrialized countries. Specific types of arrhythmias include the so-called *re-entrant arrhythmias*, which occur when a propagating electrical impulse fails to die out after normal activation of the heart and persists to re-excite other regions that have already recovered excitability. Atrial fibrillation (AF) and ventricular fibrillation (VF) are examples of re-entrant arrhythmias.

AF is the most commonly diagnosed cardiac arrhythmia. It is characterized by very high atrial excitation rates and a loss of coherence of atrial contraction. Ineffective atrial beating favors the formation of blood clots, increasing the risk of stroke four- to fivefold. Procedures currently used for AF management remain rather empirical [6]. Pharmacological management is still the main option for AF treatment, although there is growing acceptance of catheter ablation to treat AF [7]. In the following, an illustration is provided on how BSP can aid in the identification of more effective anti-AF pharmacological therapies and in successfully guiding ablation of AF substrates.

Currently available drugs used to treat AF show limited efficacy, and many of them present serious adverse effects. Major advances in the development of more effective anti-AF compounds are needed, and BSP can make a significant contribution to this end. Most research in this area has so far focused on assessing the effects of sodium or potassium channel block, usually either before or after the AF-related electrical remodeling (AFER) caused by persistent AF. A more systematic characterization of the effects of transmembrane ionic currents in modulating human atrial electrophysiology, both in short-term AF (before AFER) and long-term AF (after AFER), has been published in recent studies [8]. Multiscale atrial models have been built based on several previously published formulations of human atrial AP dynamics to confirm model independence. Properties related to excitability, refractoriness, and re-entrant dynamics have been investigated in cell, tissue, and whole atria, and descriptors of AF organization, including temporal regularity, spatial coupling, and dominant frequency of activation, have been computed by time- and frequency-domain analyses of EGMs [Figure 1(a)]. Results have shown that the sodium-potassium pump (I_{NaK}), generally ignored in the screening of drug compounds, is an important modulator of human atrial electrophysiology, both in short-term AF and long-term AF. Results have also confirmed the relevant role played by the inward rectifier potassium current (I_{Na}) and the sodium current (I_{K1}) in modulating excitability, refractoriness, and re-entrant dynamics of the human atria, in agreement with previous experimental and theoretical studies focused on the particular action of one of these two currents. In all cases, the sensitivity of the investigated atrial properties to ionic current variations has been shown to be inferior after AFER, which is concordant with the fact that pharmacological AF therapies targeting specific ionic currents present lower efficacy in patients with long-term AF versus short-term AF. The characterization provided in the above-described BSP studies offers new avenues to guide the development of compounds with improved anti-AF efficacy.

Ablation is another option for AF management. Catheter ablation of the AF



[FIG1] **The top part of (a) is the dorsal view of the atria showing interpolated maps of temporal regularity computed from EGMs after AFER and AFER with a 30% block of the sodium-potassium pump current (I_{NaK}). In the bottom part of (a), bipolar EGMs at six different atrial sites are shown. In the top part of (b), the left ventricle tissue slice used in the simulation is shown; the middle part shows a simulated sequence of isochronic voltage representation, with indication of the cells' positions whose repolarization corresponds with the peak and end of the T wave (gray points); and the bottom part shows the derived pseudo-ECG signal. (c) From top to bottom: RR variability (RRV), with RR being inverse of HR, and systolic BP variability (SBPV); TF representation of RRV; TF representation of SBPV; TF coherence (TFC); TF phase differences (TFPD). (d) From top to bottom: ECG, PPG, respiration, rotation angle series, HR, pulse transit time (PTT), and pulse width (PW).**

substrate, usually by application of radiofrequency energy, has been shown to give good results for a large number of patients resistant to pharmacological or electrical cardioversion. However, it may present both short- and long-term risks due to the destruction of cardiac tissue. There is not yet clear evidence of which is the optimal strategy for catheter ablation in terms of treatment success and minimization of complications. Isolation of pulmonary veins is commonly effective for paroxysmal AF, but ablation of other regions of the atria is usually needed to treat persistent or permanent AF. Areas with high activation rates and with fractionated atrial electrograms have been shown to have an important role

in sustaining the arrhythmia and are common targets for ablation [9]. Significant research is being performed in analyzing and quantifying patterns of activation by means of BSP applied to EGM signals, including the characterization of spatial interactions between different atrial sites. The objective is to combine this characterization with electroanatomic mapping systems to identify the regions that play a central role in maintaining AF, and should be ablated, while minimizing the area of tissue death.

THE VENTRICULAR MYOCARDIUM: PREDICTING RISK OF VENTRICULAR ARRHYTHMIAS THROUGH SIGNAL PROCESSING

Ventricular tachycardia (VT) and VF are among the most dangerous cardiac arrhythmias. VT is characterized by high ventricular excitation and contraction rates and a decrease in cardiac output (i.e., in the volume of oxygenated blood delivered to the body). VT may degenerate into VF, characterized by even higher ventricular excitation rates and a loss of coherence of ventricular contraction. This produces almost zero cardiac output and will cause sudden cardiac death unless an electrical shock is immediately delivered to defibrillate the heart. A number of methods have been proposed in the literature to quantify the susceptibility to suffer from ventricular arrhythmias such as VT or VF [10], [11]. However, very few of them have been implemented clinically, mainly due to the fact that their fundamental bases and the connection to arrhythmic risk have not been clearly established [12], [13]. In the following, we illustrate the role played by BSP in linking ECG markers of ventricular arrhythmic risk with their underlying mechanisms and origin of risk.

Enhanced temporal and spatial variability in ventricular repolarization, and in particular variability in the QT interval of the ECG, has been suggested as a marker of increased propensity for VT/VF in both experimental and clinical studies. Different investigations have postulated that temporal fluctuations in transmembrane ionic currents due to random ion channel gating contribute to beat-to-beat repolarization variability, while spatial heterogeneities in current amplitudes due to differences in channel numbers contribute to cell-to-cell repolarization variability [14]. Recent BSP studies have thoroughly investigated the causes and modulators of spatiotemporal repolarization variability using combined experimental and computational approaches that involve the development and validation of multiscale stochastic models of ventricular electrophysiology [4], [15]. Intrinsic noise associated with random ion channel gating has been modeled by using, among others, stochastic Langevin equations dependent on the number of channels [4]. Extrinsic noise associated with cell-to-cell differences in channel numbers of each ionic current has been modeled by fitting statistical distributions to current measurements. Channel numbers have been derived from experimental data by applying stationary and nonstationary fluctuation analysis techniques [4]. The stochastic current formulations, including intrinsic and extrinsic noises, have been incorporated into different models of ventricular cell dynamics. Propagation in tissue and whole ventricle has been simulated, and extracellular potentials (pseudo-ECGs) have been calculated. Under physiological conditions, both sources of noise have been shown to contribute to significant spatiotemporal repolarization variability in isolated cells. At higher scales (tissue, ventricle, and ECG), electrotonic coupling mitigates the effects of noise, reducing variability levels in a very substantial way. Pathologies involving electrotonic uncoupling (like ischemia) or reduced repolarization reserve (like certain types of long QT syndrome) uncover the manifestation of noise at all levels and result in enhanced variability that leads to electrical abnormalities such as afterdepolarizations (spontaneous depolarizations during or immediately after normal AP repolarization) and alternans (alternate-beat variations in the timing or morphology of repolarization), both of which have been linked to increased risk for VT/VF.

Ventricular repolarization dispersion (VRD) has been proposed as another arrhythmia risk marker. Dispersion is a measure of the spatial variation in the AP duration (APD) of different myocardial areas. Increments in the dispersion of the APD, as well as in its restitution (APDR), have been associated with greater propensity to suffer from VT/VF. The reason behind it is that higher dispersion increases the probability that a tissue area acts as an exciting trigger for another area that has already repolarized and is thus ready to get re-excited, setting the stage for the generation of an arrhythmia loop. A proposal to quantify VRD from the ECG is by measuring the T-wave width. Another approach is the computation of the ratio between the dipolar and nondipolar components of the singular value decomposition of the T wave. When the dispersion, in addition to have a spatial signature, has a beat-to-beat variation, it is reflected as a subtle alternation in the morphology of the ST segment and the T wave, so called T-wave alternans, which can be successfully detected using BSP techniques [10]. On other occasions, it is known that adverse arrhythmic episodes occur in association with sudden changes in heart rate (HR), and then it is worth to associate VRD with the change in HR. In this framework it has been shown that APD adaptation to HR changes has a different profile for distinct areas of the ventricular myocardium [1], and it is thus in the transient after the HR change when a substantial increase in VRD would occur. In relation to this, delayed adaptation of the QT interval to HR changes has been suggested as an ECG-derived marker of increased arrhythmic risk.

Other approaches have been proposed to estimate dispersion in the APDR by measuring rate-normalized differences in the steady-state T-peak-to-T-end (T_{pe}) interval of the ECG [16]. The evolution of this dispersion as a function of HR is reflected on the divergence of the APDR curves for different HRs, which is a well-known risk marker at the cell level and, consequently, the rate-normalized differences in the T_{pe} interval represent a surrogate of it at the ECG level. Simulation of electrical tissue behavior has

provided a first validation of those principles [Figure 1(b)] [16].

THE AUTONOMIC NERVOUS SYSTEM: EVALUATING ITS ROLE THROUGH SIGNAL PROCESSING

The ANS plays an important role in maintaining cardiovascular homeostasis. Its dysfunction has been associated with a variety of diseases including hypertension, heart failure, obesity, diabetes, sleep apnea, and mental disorders. Analysis of ANS activity can help in the prognosis, diagnosis, and follow-up of the former diseases [17]. Direct measurement of ANS activity has been usually addressed by animal experimentation or by the administration of drugs inhibiting ANS activity, and requires standardized laboratory conditions. However, ANS activity prints characteristic patterns in cardiovascular signals, such as HR and BP, which motivates the noninvasive measurement and interpretation of ANS activity through signal processing.

HR variability (HRV) analysis is an established noninvasive tool for the assessment of autonomic regulation of HR at rest [18]. The spectrum of HRV at rest is characterized by two main components: 1) a high-frequency (HF) component in the band 0.15–0.4 Hz, synchronous with respiration and mainly mediated by the parasympathetic branch of the ANS, and 2) a low-frequency (LF) component in the band 0.04–0.15 Hz, influenced by sympathetic as well as parasympathetic modulation. Latest trends in HRV analysis are devoted to the characterization of the ANS in nonstationary situations where the cardiovascular system needs to adapt to changing conditions or perturbations.

An interesting application of that characterization is in the field of exercise. The prospect of a noninvasive measurement of ANS activity during exercise is attractive for sport physiologists to understand how the cardiovascular system responds to the stress of exercise. It is also appealing for physicians since exercise pushes the system to the limit and ANS alterations, such as those related to ischemia, may be more evident than at rest. However, analysis and interpretation of HRV as a measure of ANS activity during exercise is still a matter of debate. The increase of mean HR with exercise intensity influences HRV measurements. It has been demonstrated that if ANS evolution is derived from HRV analysis, a correction of HRV measurements with the time-varying mean HR should be considered to avoid over- or underestimation of ANS activity due to changes in mean HR [19]. The fact that the respiratory frequency during exercise is not restricted to the range 0.15–0.4 Hz makes it necessary to redefine the HF band [19]. Cardiolocomotor coupling manifests in the HRV of subjects during an exercise test as a component centered at the stride frequency (if exercise is running) or at the pedaling frequency (if exercise is cycling). Stride frequency (SF) aliases have been shown to appear due to the undersampling of the SF component and its harmonics when the mean HR does not satisfy the Nyquist criterion. The consideration of the SF component as well as its aliases is very important when the evolution of the ANS activity is to be assessed from HRV analysis, since SF aliases may overlap with the LF and HF components, making it impossible to distinguish in those cases if the power measured in the LF and HF bands has an autonomic and respiratory origin, or a cardiolocomotor origin [2].

NONINVASIVE MEASUREMENT OF ANS ACTIVITY THROUGH THE ANALYSIS OF HRV CAN BE ENHANCED BY THE ANALYSIS OF ITS RELATION WITH BP VARIABILITY.

Another application of noninvasive measurement of ANS activity through the processing of cardiovascular signals is in the monitoring of the stress level. Stress has been associated with dysfunctions in the immune system, psychiatric disorders, evolution of cardiac diseases, emotional states, traffic accidents, and concentration level. Analysis of HRV has been proposed to monitor the stress level of a subject as well as to characterize ANS response to physical or psychological stress in healthy subjects and patients.

Noninvasive measurement of ANS activity through the analysis of HRV can be enhanced by the analysis of its relation with BP variability (BPV), which allows the noninvasive characterization of the baroreflex system. The baroreflex is a negative feedback system that buffers short-term fluctuations of BP by modifying HR, among other cardiovascular variables. The use of time-frequency (TF) coherence and TF phase differences gives insight into the relationship between HRV and BPV, beyond classical baroreflex measurements, especially in response to perturbations of the cardiovascular system, such as tilt test [Figure 1(c)] [3].

An indirect characterization of the interactions between HR and BP is also possible by studying the response of HR to ventricular premature beats (VPBs). It has been shown that, in healthy subjects, the drop in BP induced by a single VPB triggers a baroreflex-mediated response consisting in a HR acceleration followed by a deceleration to its baseline level. This phenomenon is known as heart rate turbulence (HRT) [20]. Even if HRT is a subtle phenomenon, not evident in the HR series after a VPB, it can be unveiled by averaging the response to several VPBs, usually during 24-h ambulatory recordings. The absence or attenuation of the HRT response reflects ANS dysfunction and has been shown to be a powerful predictor of cardiac death risk in different populations, mainly in postinfarction [20] and congestive heart failure (CHF) patients [21]. Recently, a statistical detection theoretical approach was introduced for HRT analysis, aiming at physiologically modeling the HRT response and the background HRV. In a population of mild-to-moderate CHF, the proposed detection statistic exhibited much stronger association with risk of cardiac death than other most commonly used heuristic parameters, and remained predictive of cardiac death when computed from 4-h data instead of 24-h data [21].

CARDIORESPIRATORY INTERACTIONS: DERIVING RESPIRATION THROUGH SIGNAL PROCESSING OF CARDIOVASCULAR SIGNALS

Respiration is a vital sign and therefore its measurement has a great relevance in the clinical routine. It is well known that respiration and circulation are closely related through the ANS and several reflex mechanisms, and these cardiorespiratory interactions are reflected in biomedical signals [22]. Consequently, isolating a physiological phenomenon in this context is a great challenge from a BSP point of view.

Deriving respiration from the ECG or the PPG are two examples of how the knowledge of the underlying physiology in cardiorespiratory interactions is essential for obtaining the desired information. Respiratory activity influences electrocardiographic measurements in various ways. During the respiratory cycle, chest movements cause electrical heart vector displacement that affects beat morphology in the ECG. Moreover, changes in the thorax impedance due to the filling and emptying of the lungs also affect ECG morphology. Respiration can be derived from the ECG signal by estimating the rotation angles of the heart's electrical axis through BSP techniques [23]. Furthermore, ANS modulates respiration in such a way that autonomic balance increases during inspiration and decreases during expiration. These changes in autonomic balance during the respiratory cycle are reflected in the HR, in the pulse rate and also in the PTT. The PTT signal gives a quantitative measure of the time that the pulse wave needs to pass from one artery to another. Although respiratory information can be extracted from the PTT signal, this method requires both ECG and PPG signals. An alternative to derive respiration only from the PPG by exploiting this physiological relationship is based on measuring the PPG PW, since PW has been shown to depend on the PTT [Figure 1(d)] [24].

BSP techniques aimed at combining respiratory information obtained from different physiological interactions are of great interest since they improve the accuracy and offer a more robust method to derive respiration, for example from PPG-based methods by means of pulse rate, PW, and pulse amplitude [24].

CONCLUSIONS

Physiology-oriented processing of biomedical signals is a powerful instrument in relevant areas such as the diagnosis, therapy, and follow-up of a wide range of diseases. In this column, we have presented examples of multimodal, multiscale, and multidisciplinary processing of cardiovascular signals. Some of those examples have illustrated how signal processing can aid in the identification of patients who are at high risk of developing cardiac arrhythmias as well as in the development of more effective strategies to treat them. Other examples have shown that signal processing of cardiovascular signals serves to noninvasively characterize the ANS activity and robustly derive respiratory information, both of which find great application in the clinical routine.

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applications CORNER (continued from page 135)

[TABLE 1] ERROR RATE.

$\mu_{\text{error}} \pm \nu$	SYNTHETIC DATA	HANDWRITTEN DIGITS
K-MEANS	0.3090 ± 0.0865	0.2661 ± 0.0349
USC	0.3483 ± 0.0620	0.3704 ± 0.0219
NCUT	0.5020 ± 0.0474	0.3228 ± 0.0204
SOQ	0 ± 0	0.1603 ± 0.0192

150 sample points. For spectral clustering algorithms, an affinity matrix is needed. Let the generated 2-D points be $\mathbf{p}_1, \mathbf{p}_2, ..., \mathbf{p}_N$ with $\mathbf{p}_n = (\mathrm{x}_n, \mathrm{y}_n)$ for $1 \le n \le N$. We generate the affinity measure $s_{i,j}$ between any two points $\mathbf{p}_i$ and $\mathbf{p}_j$ by $s_{i,j} = \exp\left(-||\mathbf{p}_i - \mathbf{p}_j||_2^2/(2\sigma^2)\right)$, where $\sigma = 1$ in this experiment. In this way, we obtain an affinity matrix S.

We run the algorithms 20 times, each with a different randomly permuted input, to obtain 20 clustering results. By comparing to the ground truth in Figure 3, we obtain the error rate for each experiment. For the 20 experiments, we calculate the mean clustering error rate and 95% confidence interval, which are listed in the second column of Table 1, where μ_{error} denotes the mean clustering error rate and $\mu_{\text{error}} \pm \nu$ denotes upper/lower bound of the confidence interval, respectively. Table 1 demonstrates that SOQ significantly outperforms K-means, USC, and Ncut for this synthetic data set.

The second experiment uses real-world data, consisting of images of handwritten digits, which are described in [9] and are downloadable from [10]. The ten digits data set is used in our experiment. There are ten clusters in the data set, with 100 members in each cluster. Again, we run the algorithms 20 times, each with different randomly permuted input. For the 20 experiments, we calculate the mean clustering error rate and 95% confidence interval, which are listed in the third column of Table 1. Table 1 demonstrates that SOQ significantly outperforms K-means, USC, and ncut for this set of handwritten digits.

CONCLUSIONS

In this column, we have discussed kernel methods as pattern analysis tools, and provided insights in two important pattern analysis problems: feature extraction and clustering.

Kernel methods have been widely applied to computer vision, image processing, information retrieval, text mining, handwriting recognition, geostatistics, kriging, bioinformatics, chemoinformatics, and information extraction, among others. It is expected that kernel methods will provide valuable pattern analysis tools for emerging big data applications.

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