In the Spotlight: Biomedical Signal Processing



Sergio Cerutti, *Fellow, IEEE*

I. Introduction

IT is well known that biomedical signals carry important information about the behavior of the living systems under study. A proper processing of these signals in principle enhances their physiological and clinical information. This is the ultimate goal in the widely diffused topic of "biomedical signal processing" (BSP) [1], [2]. Basically, the great majority of research centers in Biomedical Engineering (BME), Medical Physics, Bioinformatics, Biotechnology, etc., do present an activity in this area, more or less officially recognized in dedicated labs or strongly affiliated to other more topic-oriented labs. Further, in the most relevant programs of Biomedical Engineering curricula there are courses in Biomedical Signal Processing both in undergraduate and in graduate tracks as well as in Ph.D. programs. In the most recent annual conferences of the IEEE Engineering in Medicine and Biology Society (EMBS) an average of 350 papers per year were submitted to the BSP theme.

The applications of digital signal processing techniques for quantitative interpretations of physiological systems, vital signs management, or in general to biomedical data is central to the Biomedical Engineering mission (besides dealing with challenging and fascinating problems): in fact, significant innovation in this area might lead to the development of modern and advanced equipment for a better diagnosis and treatment of patients. Recently, many important and conspicuous research efforts both in North America and in Europe were dedicated to the development of new medical equipment and advanced worldwide networking in health environment, considering the single patient with his/her own vital signs as the terminal node of the overall net [3], [4].

Manuscript received September 24, 2008; revised October 07, 2008. Current version published December 02, 2008.

S. Cerutti is with the Department of Biomedical Engineering, Politecnico University, Milano 20133, Italy (e-mail: sergio.cerutti@biomed.polimi.it).

Digital Object Identifier 10.1109/RBME.2008.2008224

II. Traditional Approaches in Biomedical Signal Processing

It is certainly true that basically all methods of signal processing have been applied (more or less satisfactorily) to biomedical signals (ECG-electrocardiogram, EEG-electroencephalogram, EMG-electromyogram, EOG-electrooculogram, EGG-electrogastrogram, etc.) in various and differentiated experimental conditions. Many of these methods have been conceived in different research areas such as information processing, statistics, system and control theory, communication theory, medical informatics, lasers and electro-optics, digital signal, image analysis, etc. [5]–[7]; more recent approaches, connected with DNA information treatment, have been developed under the basis of observations of biological or physiological problems (bio-inspired methods or algorithms) [8].

The traditional approach of biomedical signal processing considers mainly second-order statistical analysis for stationary and linear systems based upon the Wiener–Khinchin theorem (which establishes a relationship between autocorrelation function in the time domain and the Fourier transform in the frequency domain) and the numerous related algorithms which may be implemented accordingly (digital filtering, convolution, power spectral density (PSD), auto/cross correlations, cross-spectrum and coherence, principal component analysis (PCA), time-invariant parametric modeling and others). Many important results have been obtained in biomedical signals which most often have the peculiarity of presenting strong sources of endogenous and/or exogenous noises and low signal/noise ratio [9], [10].

III. Nonstationary and Nonlinear Systems

The traditional cultural background of signal processing, as previously indicated, is certainly the first important step to be fulfilled in training young biomedical engineers and all this knowledge might be properly integrated with basic

1937-3333/$25.00 © 2008 IEEE

biological and physiological contents. The complex characteristics of biomedical signals in terms of their (sometimes multiple) generating systems, as well as the statistics of the superimposed noises which most often are not known, make the solutions of the more though problems in BSP extremely difficult with the traditional approaches. The actual state-of-art in the BSP research includes different methods which put into evidence other characteristics of the physiological or biological systems under study: i.e., *nonstationary behaviors* or *transient phenomena* which are emphasized by time-frequency distributions [11], time-scale decompositions or wavelet analysis [12], empirical mode decompositions [13], adaptive filtering and time-variant parametric modeling [14], [15], etc. Further, statistical independence on non-Gaussian data may provide interesting application of independent component analysis (ICA) or blind source separation (BSS) techniques in which an efficient signal decomposition might be achieved [16], [17].

Another area of modern research in signal processing is related to *nonlinear approaches*. Wiener–Khinchin theorem expanded to higher order cumulants (more than second-order) may express what is called "higher order statistical analysis," which gives rise to interesting BME application such as the bispectrum, bicoherence, and related parameters [18].

Other traditional techniques in this area employ dedicated kernels like Wiener kernel for nonlinear biological system studying or Lotka–Volterra equation data modeling in many examples of biological signals, mainly in epidemiology and in the study of populations, but there has been also much activity in nonlinear adaptive or time-variant filtering (i.e., Kalman filtering and particle filters) [19], [20], as well as in novel concepts of neural network applications [21] and of neural information processing [22].

Further, the paradigm of considering a biological signal as the realization of a nonlinear system with either stochastic or deterministic (and sometimes chaotic) behavior has found a wide acceptance in speculative research, as well as in some clinical problems. The challenge in this case is to be able to discriminate stochastic behavior from nonlinear deterministic chaotic dynamics in a signal which generally presents concurrently noises of different origins (and different statistical distributions, too); therefore, it could be argued that in many biological signals both stochastic and deterministic components might coexist: on the other hand, it is a very difficult problem to disentangle the single different components and to correctly interpret them. Surrogate data series (obtained from the signal itself and/or from other realizations of the same system) are useful approaches to determine whether the system is indeed chaotic or not [23], [24].

It is worth mentioning the hypothesis that many physiological systems may be modeled by a low-dimensional nonlinear chaotic system. Dimensionality estimation is a possible way to measure the complexity of the system itself. In many examples in cardiovascular system or in neurosciences, a wide consensus has been reached on the following link: a decrease of the complexity with respect to the normal case is in most instances bounded to a pathological condition (the statements "chaos is health" and "decreasing of chaos is pathological" has gained a certain popularity among clinicians). Therefore, the measure of chaotic system dimensionality (if this model fits to the data) is a parameter of potential clinical interest. Various applications have considered D_2 correlation dimension, α-coefficient (slope of the long-term signal power-law spectral density estimation), fractal dimension of the related chaotic attractor, Lyapunov exponents, etc. Other complexity measures may be applied to the data, i.e., entropy (Kolmogorov's, or approximated entropy ApEn), symbolic dynamics measurements, detrended fluctuation analysis (DFA) and the various measures of fractality (self-similarity) of the signal [25]–[27].

IV. Fusion of Biomedical Signal Processing and Physiological Modeling

An important innovative aspect is considering the integration between biomedical signal processing and physiological modeling of the biological system under examination [28], [29]. In this way, it is possible to directly attribute patho-physiological meaning to the parameters obtained from the processing, or vice versa, the physiological modeling fitting could certainly be improved by taking into account the results from the signal processing procedure. Generally, scientists who do signal processing do not do modeling: biomedical engineering must integrate these two aspects in order to proper train young scientists in the area and to provide a cultural vision for the implementation of important tools for newer investigations.

Along this direction, a significant milestone which was reached by a fruitful convergence between: 1) cardiovascular pathophysiology; 2) clinical medicine; and 3) advanced algorithms of cardiovascular signal processing, is the concept of "*dynamical disease*," i.e., a pathology which could be initially observed at an organ level (i.e., heart, circulatory system, etc) but it is a pathology of the correspondent controlling system [30], [31]. Many major pathologies of cardiovascular system (or involving cardiovascular system) are considered as dynamical diseases, like hypertension, diabetes, even some consequences of ischemic pathologies, etc. and may be accordingly described by measuring the activity of autonomic nervous system: this explains the strong interest in heart rate variability (HRV) analysis [32], with more than 14 000 papers which refer to this topic in recent years.

V. Multivariate, Multiorgan and Multiscale (MMM) Paradigm

A modern and very promising approach of biomedical signal processing, which is capable also to combine the outputs from physiological modeling, is the so-called MMM-paradigm (i.e., multivariate, multiorgan, and multiscale). Such an approach makes the system genesis explicit, where complexity is potentially allocated and how it is possible to detect information from it. No doubt that processing signals from multileads of the same system (*multivariate*), from the interaction of different physiological systems (*multiorgan*) and integrating all this information across *multiple scales* (from genes, to proteins, molecules, cells, up to the whole organ) could really provide a more complete look at the overall phenomenon of physiological system complexity, in respect to the one which is obtainable from its single constituent parts [33], [34].

A detailed analysis of the various implications of this paradigm is not possible in this short review. Very synthetically, it is possible to say that a *multivariate* approach does improve the information obtainable from the physiological system when compared to the monovariate case: ECG mapping, high resolution EEG recordings etc, but it is also true in statistical analysis where more parameters from the system under examination might significantly improve classification studies (for pathological assessment and risk stratification).

The expression *multiorgan* means that many physiological and pathological situations are the results of a combined relationship among different organs involved. A primary pathological disturbance and the resulting dysfunctions usually affect several other organs within the entire organism and do not appear as isolated disorder. Therefore, it is fundamental to know which are the systems involved and the new parameters obtainable from this interaction: they might be useful for a better diagnosis and treatment. Examples of this approach are sleep studies (sleep is certainly a multiorgan physiological phenomenon, by involving central and autonomic nervous systems, respiratory and cardiovascular systems, etc), connections between central and autonomic nervous systems in cardiovascular studies, other dynamical diseases (pathological situations of the controlling systems).

As far as the *multiscale* approach is involved, it is possibile to say that traditionally BSP is carried out at the organ level or system to be investigated (i.e., ECG or EEG signal, arterial blood pressure, respiration and so on). It is very clear the advantage of correlating this information with that one obtained about the same system, but at different scale level, i.e., at cellular level or even at subcellular level (for example, analysing possible genetic correlates or typical patterns of DNA/RNA or protein sequences). Biomedical engineering as a discipline may strongly contribute to this multiscale information processing. Along this line, even the long-QT syndrome can be efficiently studied at different scale level: a mutation in a portion of gene SCN5A, which presents a phenotype compatible to long-QT3 type is known to produce an altered function of Na+ channels [35]. Through a proper model describing the ventricular cell function, it is possible to say that this alteration may induce a prolongation of QT duration, as detected on ECG tracing. This event is further correlated with an increased risk of ventricular tachyarrhythmias. Hence, the path is completed: from the genetic expression up to the disease manifestation [36], [37]. Many different signal processing and modeling are involved in this paradigmatic example: an integration among the various scales of observation may undoubtedly contribute to a better understanding of the complex pathophysiological correlates.

A great effort is on course to create very large databases and networking of models and technologies for integrating such information (Physiome project [35], [38] is to be connected with Genome and Proteome projects and Virtual Physiological Human project – VPH – which are inserted into the activities of the 7th Framework EU Programme). Another example is the study of the profile of expressed proteins in 2-D gel supports, or after mass-spectrometry analysis, relative to a variety of pathologies (i.e., epilepsy, peripheral neuropathies or Amyotrophic Lateral Sclerosis (ALS), or in oncological studies) thus singling out the set of proteins which present a correlate with the pathology in respect to the control group [39]. This overall approach seeks a holistic view of the patient rather than an atomistic one which considers the whole as a simple sum of the single component parts.

REFERENCES

[1] E. N. Bruce, *Biomedical Signal Processing and Signal Modeling*. New York: IEEE Wiley, 2001.

[2] Rangayyan, *Biomedical Signal Analysis: A Case-Study Approach.* : IEEE Press, 2002.

[3] F. Ichihashi and Y. Sankai, "Development of a portable vital sensing system for home telemedicine," in *29th EMBS Annu. Conf.*, Lyon, Aug. 2007, pp. 5872–5877.

[4] C. Lin, R. Lee, and C. Hsiao, "A pervasive health monitoring service system based on ubiquitous network technology," *Int. J. Medical Informatics*, vol. 77, no. 7, pp. 461–469, 2008.

[5] G. E. P. Box and G. M. Jenkins, *Time Series Analysis: Forecasting and Control*. San Francisco, CA: Holden-Day, 1970.

[6] A. V. Oppenheim, R. W. Shafer, and G. R. Buck, *Discrete-Time Signal Processing*, II ed. Englewood Cliffs, NJ: Prentice Hall, 1999.

[7] J. S. Bendat and A. G. Piersol, *Random Data: Analysis and Measurement Procedures*, 3rd ed. New York: Wiley, 2000.

[8] G. L. Rosen, "Signal Processing for Biologically-Inspired Gradient Source Localization and DNA Sequence Analysis," Ph.D. dissertation, Georgia Inst. of Technol., Atlanta, 2006.

[9] A. Cohen, *Biomedical Signal Analysis*. Boca Raton, FL: CRC Press, 1986, vol. I, II.

[10] W. J. Tompkins, *Biomedical Digital Signal Processing*. Englewood Cliffs, NJ: Prentice Hall, 1995.

[11] L. Cohen, *Time Frequency Analysis: Theory and Applications*. Englewood Cliffs, NJ: Prentice Hall, 1995.

[12] P. L. Dragotti and M. Vetterli, "Wavelet footprints: Theory, algorithms, and applications," *IEEE Trans. Signal Processing*, vol. 51, no. , pp. 1306–1323, May 2003.

[13] P. Flandrin, G. Rilling, and P. Goncalves, "Empirical mode decomposition as a filter bank," *IEEE Signal Processing Lett.*, vol. 11, no. 2, pt. 1, pp. 112–114, Feb. 2004.

[14] S. Haykin, *Adaptive Filter Theory*, IV ed. Englewood Cliffs, NJ: Prentice Hall, 1996.

[15] , S. Haykin, J. C. Principe, T. J. Sejnowski, and J. Mc Whirtel, Eds. , *New Directions in Statistical Signal Processing: From Systems to Brains*, IV ed. Cambridge, MA: MIT Press, 2006.

[16] A. Hyvärinen, J. Karhunen, and E. Oja, *Independent Component Analysis*. New York: Wiley, 2001.

[17] F. Castells, J. J. Rieta, J. Millet, and V. Zarzoso, "Spatiotemporal blind source separation approach to atrial activity estimation in atrial tachyarrhythmias," *IEEE Trans. Biomed. Eng.*, vol. 52, no. 2, pp. 258–267, Feb. 2005.

[18] C. L. Nikias and J. M. Mendel, "Signal processing with higher-order spectra," *IEEE Signal Processing Mag.*, vol. 10, no. 3, pp. 10–37, 1993.

[19] S. Park and S. Choi, "A constrained sequential EM algorithm for speech enhancement," in *Neural Network*, Mar. 2008, doi:10.1016/j.neunet.2008.03.001.

[20] J. McNames and M. Aboy, "Statistical modeling of cardiovascular signals and parameter estimation based on the extended Kalman filter," *IEEE Trans. Biomed. Eng.*, vol. 55, no. 1, pp. 119–129, Jan. 2008.

[21] I. W. Sandberg, J. T. Lo, C. L. Fancourt, J. C. Principe, S. Katagiri, and S. Haykin, *Nonlinear Dynamical Systems: Feedforward Neural Network Perspectives*. New York: Wiley, 2001.

[22] S. Haykin, J. C. Principe, T. J. Seinowski, and J. McWhirter, Eds. , New Directions in Statistical Signal Processing: From Systems to Brains Cambridge, MA, MIT Press, 2006.

[23] T. Schreiber and A. Schmitz, "Surrogate time series," *PhysicaD*, vol. 142, no. 3-4, pp. 346–382, 2000.

[24] H. Kantz and T. Schreiber, *Nonlinear Time Series Analysis*, II ed. Cambridge, MA: Cambridge Univ. Press, 2004.

[25] S. Pincus, "Approximate entropy (ApEn) as a complexity measure," *Chaos*, vol. 5, no. 1, pp. 110–117, 1995.

[26] C. K. Peng, S. Havlin, H. E. Stanley, and A. L. Goldberger, "Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series," *Chaos*, vol. 5, no. 1, pp. 82–7, 1995.

[27] S. Cerutti, F. Esposti, M. Ferrario, R. Sassi, and M. G. Signorini, "Long-term invariant parameters obtained from 24-h Holter recordings: A comparison between different analysis techniques," *Chaos*, vol. 17, no. 1, p. 015108, 2007.

[28] J. L. Coatrieux, "Signal processing and physiological modeling, Part I and II," *Critical Rev. on Biomed. Eng.*, p. 27 + 18, 2002.

[29] A. Porta, G. Baselli, and S. Cerutti, "Implicit and explicit model-based signal processing for the analysis of short-term cardiovascular interactions," *IEEE Proc.*, vol. 94, no. 4, pp. 805–818, Apr. 2006.

[30] M. C. Mackey and J. C. Milton, "Dynamical diseases," *Ann. New York Acad. Sci.*, vol. 504, pp. 16–32, 1987.
[31] B. J. West, *Fractal Physiology and Chaos in Medicine*. Singapore: World Scientific, 1990.
[32] M. Malik *et al.*, "Heart rate variability: Standards of measurement, physiological interpretation, and clinical use," *Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, Circulation*, vol. 93, pp. 1043–1065, 1996.
[33] J. B. Bassingthwaighte, H. J. Chizeck, and L. E. Atlas, "Strategies and tactics in multiscale modeling of cell-to-organ systems," *Proc IEEE*, vol. 94, no. 4, pp. 819–831, Apr. 2006.
[34] S. Cerutti, D. Hoyer, and A. Voss, "Multiscale, multiorgan and multivariate complexity analyses of cardiovascular regulation," *Philosophical Transactions of the Royal Society A*, 2009, to be published.
[35] Y. Rudy, "From genome to physiome: Integrative models of cardiac excitation," *Ann. Biomed. Engineer*, vol. 28, pp. 945–950, 2000.
[36] C. E. Clancy and Y. Rudy, "Linking a genetic defect to its cellular phenotype in a cardiac arrhythmia," *Nature*, vol. 400, no. 6744, pp. 566–569, 1999.
[37] S. G. Priori, P. J. Schwartz, C. Napolitano, R. Bloise, E. Ronchetti, M. Grillo, A. Vicentini, C. Spazzolini, J. Nastoli, G. Bottelli, R. Folli, and D. Cappelletti, "Risk stratification in the long-QT sindrome," *N. Engla. J. Med.*, vol. 348, no. 19, pp. 1866–74, 2003.
[38] P. Hunter, P. Robbins, and D. Noble, "The IUPS human physiome project," *Pflugers Arch-Eur. J. Physiol.*, vol. 445, pp. 1–9, 2002.
[39] L. Lam, J. Lind, and S. Semsarian, "Application of proteomics in cardiovascular medicine," *Int. J. Card.*, vol. 22, no. 108, pp. 12–19, 2006.