I am particularly honored and glad to have the opportunity to introduce the comprehensive paper by Wacker and Witte [1] on "Time-frequency Techniques in Biomedical Signal Analysis: A Tutorial Review of Similarities and Differences", as well as the much relevant and deepened contributions by eight qualified discussants.

No doubt that Time-Frequency Analysis is a central topic in the evaluation of signal characteristics which are variable in time and in frequency and biomedical signals are very good examples in which these "variabilities" are present, constitute a major informative source of the signals themselves and, finally, are very strictly connected to diagnostic implications. That is the reason why we have in literature since from the '80s some earlier applications of T-F algorithms in the area of biomedical signal processing (Choi-Williams et al.,1987 [2]), just in the same time of the first seminal papers by Boashash, 1988 [3] and Cohen, 1989 [4].

The paper by Wacker and Witte has the significant merit of dealing with this topic starting from the unified concept of analytic signal and therefore the Short-Time Fourier transform (STFT), the Gabor transform (GT), the S-transform (ST), the continuous Morlet wavelet transform (CMWT) and the Hilbert transform (HT) are introduced as linear operators of the signal, while the Wigner-Ville distribution (WVD) is employed as example of the "quadratic transforms" class. The combination of WVD and GT with the matching pursuit (MP) decomposition and that of the HT with the empirical mode decomposition (EMD) are instead conceived as belonging to the class of signal-adaptive approaches. In this way, a comprehensive description of these tools is suggested which is elegant from a methodological point of view and also presents a unified approach which could indeed be proactive for a variety of applications in the biomedical context.

The Discussants have elicited important issues which basically confirm and complement the arguments expressed in the paper. I shall briefly point out some general aspects which I think are worth to be further remarked.

The traditional approaches of signal processing in time domain OR in frequency domain have been integrated and enriched by the time AND frequency domain [or time-frequency domain], originally carried out in T-F bidimensional plane. The objective is to optimize T-F resolution for a given implementation presented under the form of T-F atoms with constant T-F resolution or under multiresolution form [5]. In the quadratic case, the objective is instead to minimize the cross-term effects [6].

The solution of this global problem does not seem univocal: the Authors objectively remark that MP presents some attractive properties of optimization of T-F resolution and cross-term reduction; on the other hand, the atom-based structure in "greedy" form could present a bias which could be reduced via stochastic dictionary, with successive averaging operation.

Further, in more recent years [7, 8], EMD has undoubtedly found many applications in biomedical signal processing. Its decomposition into Intrinsinc Mode Functions (IMF’s) is generally processed via HT, by obtaining what is generally called Hil-
bert-Huang Transform (HHT) [9] and here again Authors emphasize pros and cons of this nowadays widely diffused algorithm of signal analysis which is often claimed to be a robust method for nonlinear, time-variant approach.

As Chichocki [10] has pointed out, a new and advanced method could tackle an overall and more complex problem, i.e. that one of introducing other domains like space; in this way we could have a 3-domain tensor constituted by space × time × frequency. Other examples are also possible, including protocol characteristics like subjects or trials, by achieving in this way a high complexity in the biomedical data as well as in their processing. Through tensor factorization it will be possible to optimize atoms of more dimensions which could take into account more signal contemporaneousness, i.e. EEG, MEG, more channels of the same signals, in combination with images, MRI or fMRI. An illustrative example is given in [11].

Along this direction, I think that an important and more general issue will be to consider the so-called "multi-paradigm" in Biomedical Signal Processing [12, 13], i.e. by taking into account more leads of the same signal (multivariate), more different modalities (multimodality), studying phenomena involving more organs (multiorgan) and finally integrating across different scales (multiscale), from the gene/protein scales up to the cell, the entire organ and the organism as a whole. Information exchange across these different items plays a crucial role in the modern concept of "integrative physiology" [14], with remarkable impact on clinical applications. In this global view, that would require suitable databases (the Virtual Human Physiome-VHP is a significant example [15]), advanced technologies for new data storing capabilities and, certainly, more advanced processing tools [16].

Further, I wish to stress the comments elicited by Mc Clintock and Stefanovska [10] on the nonlinearities which are usually present when studying biological phenomena. These nonlinearities not only make more complex the quantitative approach to the system under consideration, but also introduce information contamination under the form of harmonics, saturation, phenomena of entrainment, etc. A large variety of methods do exist which are capable to calculate important reliable invariants in these difficult conditions, like nonlinear coherence, coupling strengths, synchrograms as well as new causality relationships [17, 18]: on the other hand, it is clear that these methods are outside the objectives of Wacker and Witte paper.

Finally, I could not forget to stress the "golden rule" which has been recalled by the Authors as well as by most of the Discussants. It is very difficult to establish which is the "best" method for T-F analysis: in the same way that it is almost impossible to establish which is the "best" antihypertensive drug to be delivered to a patient . . . there are so many drugs with different active pharmacological principles which do exist! The basic problem is to choose the "best" one for that particular patient and for that particular form of hypertension in order to reach the goal of a more "personalized" and successful therapy! Analogously, it is important to have as much a-priori information as possible on the statistical characteristics of the signals as well as of the pathophysiological background of the patient under consideration.

Here, again, the problem concerns the fundamental connection between signal (and image) processing techniques with the physiological modeling underneath. The more "a-priori" information we have about these subject (or patient) conditions, the more successful will be the employed method for enhancing determined pathophysiological elements and I want to stress the fact that this is generally achieved mainly through a profound implication of models: that demonstrates again that physiological modeling and biomedical signal processing are strictly phenomenology related for the purpose of bringing significant innovation to this fascinating discipline.

References