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Title: Comment on "Time-frequency techniques in biomedical signal analysis: A tutorial review of similarities and differences" by M. Wacker and H. Witte

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In commenting on the review by Wacker and Witte [1], we would like to applaud the authors' emphasis on the importance of being able to treat signals with time-varying properties: this feature is universal in time series derived from measurements on living systems. From a physics perspective, life always corresponds to a thermodynamically open system, for which energy and matter are being exchanged freely with the environment. Consequently, the oscillatory processes associated with life have natural frequencies and amplitudes that are continuously modulated by external influences. From the perspective of mathematics, they are non-autonomous oscillators and must be treated as such.

The authors have provided a systematic review of the main methods currently available for time-frequency analysis of biomedical signals. The continuous wavelet transform has indeed been the main work-horse for the analysis of such time-series, ever since it was introduced for the study of oscillatory processes in e.g. heart rate variability [2,3] and blood flow [4]; and the other methods reviewed [1] certainly have their merits. We would like to point out, however, that there are additional approaches of which the reader should also be aware. We describe some of them below, but first we expand slightly on the physiological and medical applications of the continuous wavelet transform, complementing the mainly EEG-related discussion of [1] by mentioning some applications to signals derived from the cardiovascular system.

Multiresolution wavelet analysis was reported to discriminate between healthy subjects and those with cardiac pathology [5]; the continuous wavelet transform, using the Morlet mother wavelet, enabled the extraction of characteristic frequencies in blood flow [6], and their association with particular physiological processes [7]. The wavelet transform has been used e.g. as a filter for de-noising single events [8] and to reveal endothelial dysfunction in diabetes mellitus [9], post-acute myocardial infarction [10], congestive heart failure [11], hypertension [12], and ageing [13,14]. Its great advantage lies in the possibility of logarithmic frequency resolution, enabling a very wide range of frequencies to be encompassed, a feature that is often essential in the analysis of physiological time series. The synchrosqueezed wavelet transform [15] has brought some additional advantages, being especially useful for phase detection [16] as it provides optimal time-frequency localisation.

In dealing with time series from systems whose frequencies and amplitudes vary in time, several distinct, often coexisting problems must be overcome: (i) To identify basic oscillatory components, despite the time-variations; (ii) to discriminate between oscillatory components that may have nearby characteristic frequencies which, with noise and time-variability, may pose a very difficult problem; (iii) furthermore, there may be a mixture of harmonics and basic components, all with nearby frequencies to be distinguished. Where there are several oscillatory components, it may be useful to investigate the interactions that occur between the underlying physiological processes by studying measures of e.g. synchronization, coherence, phase coherence, bispectral density, couplings, coupling functions, and direction of coupling. We will enlarge briefly on these methods.

Ambiguities can arise in the analysis of signals containing oscillatory contributions at different frequencies, as commonly occur in physiological applications. Because of inherent nonlinearities, higher harmonics will be present in addition to basic frequencies, and an observed component may either be due to a real oscillatory process at that frequency or may just represent a harmonic of another lower-frequency process. The distinction can be especially hard to draw when several time-variable frequencies are present, combined with random noise, but a method [17] based on mutual information combined with surrogate testing [18] enables the question to be settled in most cases.

As indicated in [1], wavelet phase coherence analysis [19-21] can be used to establish whether there is a relationship between the oscillatory processes giving rise to two complex signals, even where there is time variability and noise. Time-localised wavelet phase coherence has been applied to test [21] the possible influence of arterial blood pressure on intracranial pressure (ICP) in intensive care, related to the preservation or otherwise of ICP auto-regulation.

Synchronization analysis [22] provides another method that is robust in the face of time-varying frequencies in the presence of noise. It has been applied to investigate the cardio-respiratory interaction by many authors. Where bivariate data are being analysed, it is quite possible for both frequencies to vary together with time, mutually locked at a particular synchronization ratio (which in general is not 1:1). Alternatively, the ratio may evolve discontinuously with time e.g. during the induction of, or awakening from, anaesthesia [23], or during exercise [24]. The ratio can be found either by plotting a synchrogram [22] or by the calculation of synchronization indices [25].

Where two oscillatory processes are tending to synchronise, thus demonstrating an underlying interaction, it is interesting to ask which process is dominant, i.e. which oscillator is mainly the driver and which of them is adjusting its frequency and amplitude mainly on account of being driven? This directionality of interaction can be established either by an analysis of phase dynamics [26], by the use of information theory [27], or by wavelet-based bispectral analysis [28]. For example, evaluation of coupling strengths showed causal interaction between the phases of respiration and δ-waves in the EEG and how it changes in anæsthesia [29]. Arguably, however, one the most complete way of describing the interaction between two oscillatory processes, based on measurements of their time series, is by calculation of their coupling functions [30]. Bayesian inference enables coupling functions to be followed efficiently as they change with time in the presence of noise, as demonstrated by application of this method to study the cardio-respiratory interaction as a function of time [31,32].

In conclusion, we agree with Wacker and Witte [1] that the use of time-frequency methods is virtually mandatory for the meaningful analysis of biomedical time series. It is a rapidly evolving area of scientific endeavour, with a steady stream of new methods being proposed and validated.

References

1. Wacker, M and Witte, H. Time-frequency techniques in biomedical signal analysis: A tutorial review of similarities and differences. Method Inform Med. 2013 (this issue).
2. Yang, F and Liao, W. Modeling and decomposition of HRV signals with wavelet transforms. IEEE Engin Med Biol Mag. 1997; 16(4): 17-32.
3. Bračič Lotrič M, Stefanovska A, Štajer D, Urbančič-Rovan V. Spectral components of heart rate variability determined by wavelet analysis. Physiol Meas. 2000; 21: 441-457.
4. Bračič M, Stefanovska A. Wavelet based analysis of human blood flow dynamics. Bull Math Biol. 1998; 60: 919-935.
5. Thurner S, Feurstein MC, Teich, MC. Multiresolution wavelet analysis of heartbeat intervals discriminates healthy patients from those with cardiac pathology. Phys Rev Lett 1998; 80: 1544-1547.
6. Stefanovska A, Bračič M. Physics of the human cardiovascular system. Contemp Phys 1999; 40: 31-55.
7. Stefanovska, A. Coupled oscillators: Complex but not complicated cardiovascular and brain interactions. IEEE Eng Med Biol Mag 2007; 26: 25-29.
8. Effern A, Lehnertz K, Grunwald T, Fernandez G, David P, Elger CE. Time adaptive denoising of single trial event-related potentials in the wavelet domain. Psychophysiol 2000; 27: 959-865.
9. Urbančič-Rovan V, Bernjak A, Stefanovska A, Ažman-Juvan K, Kocijančič A. Macro- and microcirculation in the lower extremities - Possible relationship. Diabetes Res Clin Pract. 2006; 73: 166-173.
10. Ažman-Juvan K, Bernjak A, Urbančič-Rovan V, Stefanovska A, Štajer D. Skin blood flow and its oscillatory components in patients with acute myocardial infarction. J Vasc Res. 2008; 45: 164-172.
11. Bernjak A, Clarkson PBM, McClintock PVE, Stefanovska A. Low-frequency blood flow oscillations in congestive heart failure and after beta 1-blockade treatment. Microvasc Res. 2008; 76: 224-232.

12. Rossi M, Bradbury A, Magagna A, Pesce M, Taddei S, Stefanovska A. Investigation of skin vasoreactivity and blood flow oscillations in hypertensive patients: Effect of short-term antihypertensive treatment. J Hypertens. 2011; 29: 1569-1576.
13. Humeau A, Chapeau-Blondeau F, Rousseau D, Rousseau P, Trzepizur W, Abraham P. Multifractality, sample entropy, and wavelet analyses for age-related changes in the peripheral cardiovascular system: Preliminary results Med Phys 2008; 35(2): 717-723.
14. Shiogai Y, Stefanovska A, McClintock PVE. Nonlinear dynamics of cardiovascular ageing. Phys Rep. 2010; 488: 51-110.
15. Daubechies I, Lu J, Wu H. Synchrosqueezed wavelet transforms: An empirical mode decomposition-like tool. Appl and Comput Harmon Anal. 2011; 30, 243-261.
16. Sheppard LW, Stefanovska A and McClintock PVE. Testing for time-localized coherence in bivariate data''. Phys Rev E. 2012; 85: 046205.
17. Sheppard LW, Stefanovska A, McClintock PVE. Detecting the harmonics of oscillations with time-variable frequencies. Phys Rev E. 2011; 83: 016206.
18. Paluš M, Vejmelka M. Directionality of coupling from bivariate time series: how to avoid false causalities and missed connections. Phys Rev E. 2007; 75: 056211.
19. Le Van Quyen M, Foucher J, Lachaux JP, Rodriguez E, Lutz A, Martinerie J, Varela FJ. Comparison of Hilbert transform and wavelet methods for the analysis of neuronal synchrony. J Neurosci Methods. 2001; 111(2): 83-98.
20. Bandrivskyy A, Bernjak A, McClintock PVE, Stefanovska A. Wavelet phase coherence analysis: application to skin temperature and blood flow. Cardiovasc Engin. 2004; 4(1): 89-93.
21. Sheppard LW, Stefanovska A, McClintock PVE. Testing for time-localized coherence in bivariate data''. Phys Rev E. 2012; 85: 046205
22. Schäfer C, Rosenblum MG, Kurths J. Heartbeat synchronised with respiration, Nature. 1998; 392: 239-240.
23. Stefanovska A, Haken H, McClintock PVE, Hožič M, Bajrović F, Ribarič S. Reversible transitions between synchronization states of the cardiorespiratory system. Phys Rev Lett. 2000; 85: 4831-4834.
24. Kenwright DA, Bahraminasab A, Stefanovska A, McClintock PVE. The effect of low-frequency oscillations on cardio-respiratory synchronization''. Eur Phys J B. 2008; 65: 425-433.
25. Tass P, Rosenblum MG, Weule J, Kurths J, Pikovsky AS, Volkmann J, Schnitzler A, Freund H-J. Detection of n:m phase locking from noisy data: Application to magnetoencephalography. Phys Rev Lett. 1998; 81: 3291-3294.
26. Rosenblum MG, Pikovsky AS, Detecting direction of coupling in interacting oscillators, Phys Rev E. 2001; 64(4): 045202.
27. Paluš M, Stefanovska A. Direction of coupling from phases of interacting oscillators: An information-theoretic approach. Phys Rev E. 2003. 67: 055201(R).
28. Jamšek J, Paluš M, Stefanovska A. Detecting couplings between interacting oscillators with time-varying basic frequencies: instantaneous wavelet bispectrum and information theoretic approach. Phys Rev E. 2010; 81(3): 036207.
29. Musizza B, Stefanovska A, McClintock PVE, Paluš M, Petrovčič J, Ribarič S, Bajrović F. Interactions between cardiac, respiratory and EEG-delta oscillations in rats during anæsthesia. J Physiol. 2007; 580.1: 315-326.
30. Kralemann B, Cimponeriu L, Rosenblum M, Pikovsky A, Mrowka R. Phase Dynamics of coupled oscillators reconstructed from data. Phys Rev E. 2008; 77: 066205.
31. Stankovski T, Duggento A, McClintock PVE, Stefanovska A. Inference of time-evolving coupled dynamical systems in the presence of noise Phys Rev Lett. 2012; 109: 024101.
32. Duggento A, Stankovski T, McClintock PVE, Stefanovska A. Dynamical Bayesian inference of time-evolving interactions: From a pair of coupled oscillators to networks of oscillators. Phys Rev E. 2012; 86: 061126.