PRoF Award abstract – Call 2015

<TEMPCOMPUTATION: Temperature complexity and acute inflammation >

1. Research Outline

Acronym	TEMPCOMPUTATION
Project name in English	TEMPerature COMPlexity and acUte inflammATION
Pitch (1 sentence)	Temperature complexity analysis in critically ill patients
Executive summary (max. 10 lines)	
Healthy state exhibits some degree of stochastic variability in physiologic variables, such as temperature. This variability is a measure of complexity that accompanies healthy systems and has been suggested to be responsible for their greater adaptability related to pathologic systems. In this project, we propose that reduced complexity of peripheral temperature curves could be considered as an early marker of microvascular alterations during systemic inflammation. Thus, complexity properties of temperature time series might serve as an early and 'smart' alarm for patients, even before systemic hemodynamics deteriorate, prompting early and accurate treatment in the Emergency department and the Intensive Care Unit.	

2. Cause and context of the research

Fever is a common problem in critically ill patients. While infections are the commonest cause of fever, other noninfectious inflammatory conditions may augment cytokine production with a subsequent febrile or hypothermic response, leading to the systemic inflammatory response syndrome (SIRS). Investigation of fever involves numerous diagnostic tests for differentiating infectious from noninfectious causes and determining the site of possible infection. In addition, the average annual cost to treat severe sepsis is estimated approximately $16.7 billion in USA [1], whereas every hour delay of antibiotic treatment in case of infection increases mortality by 5-10% [2]. Different biomarkers, such as procalcitonon (PCT), have been studied for their accuracy in discriminating patients with infectious and noninfectious acute inflammatory states. However, systemic reviews and meta-analyses have obtained contradictory results regarding the reliability of PCT in diagnosing sepsis [3].

Even though temperature is a continuous quantitative variable, its measurement in the clinical setting has been considered as a snapshot of a process, indicating if a patient is febrile or afebrile. Recently, other techniques have been proposed for the association between different properties of temperature with severity of illness in the Intensive Care Unit (ICU), based on complexity analysis of continuously monitored body temperature [4].

Physiologic systems' complexity is considered as arising from the interaction of numerous structural units and feedback loops operating over a wide range of temporal and spatial scales, constituting the basic adaptation mechanism of an organism. These characteristics give in principle a dynamic nature to the physiologic systems [5]. Briefly, complexity has been defined as the degree of 'irregularity' across time series [5]. Irregularity that can be assessed using entropy reflects either increased information content or increased disorder related to the number of 'microstates' that are accessible to the system [6]. Thus, greater entropy is associated with an uncertainty of the microstate-configuration of a stochastic process (such as a physiological process arising from a system with multiple feedbacks and interactions). Different methods, such as approximate and sample entropy, have been used for computing information content within a system [6]. Another signal processing technique is wavelet transformation (WT). A wavelet transform is a mathematical tool that can be used to process signals and provide salient information about both the time and frequency content of a transient signal, via the use of waveform pattern of limited duration. Wavelet analysis consists of taking a waveform with an average value of zero and moving it through the extent of the signal [7]. As the waveform is stretched out and scaled, coefficients are produced as a function of both scale and position, representing how well the waveform matches the signal.

It has been suggested that the complexity of a physiologic system is associated with long-range correlations, whereas complex variability arises from the nonlinear interaction of structural units and regulatory feedback loops [5]. Nonlinear is a term reflecting non additive coupling of different subsystems. Loss of complexity during illness might be attributed to altered coupling between system's components. In this respect, sepsis has been described as a manifestation of 'uncoupling of oscillators', which are responsible for a systems' dynamics [8]. For instance, loss of heart rate and blood pressure complexity during sepsis have been attributed to reduced baroreflex sensitivity, autonomic inputs upon pacemaker cells or central nervous system output [6,9].

Among different biosignals, temperature has been the less investigated system in critically ill patients so far. Although thermoregulation involves both core and peripheral temperature control through multiple feedback loops, mechanisms of local thermoregulation must be separated from those governing the hypothalamic set point. The reason is that due to external heat loss, a shift of the set point occurs only after failure of all peripheral defense mechanisms [10]. In general, skin temperature regulation could be considered as a complex system, since it depends on the interaction among blood-flow rate, local structure of subcutaneous tissues and sympathetic inputs upon vascular tone [5,10].

In this respect, the temperature signals are not periodic or completely random. They contain transients and localized components, whereas their statistics change over time. Thus, time-scale wavelet analysis could be considered as an optimum method to decompose the signal into a set of subsignals regarded at different scales/frequencies. Each subsignal contains localized information about the temperature changes in the specific time scale. It is thus possible to examine whether dominant scales are present (also corresponding to frequency content), and what is the dynamic of the temperature deviations at different scales (for example, in terms of complexity at different scales). Through such analysis we could also assess various thermoregulatory mechanisms that are reflected within different frequencies.

Wavelet-based spectrum analysis of blood flow oscillations has been used to quantify the contribution of different control mechanisms upon skin vasodilatory and vasoconstrictive response [11]. Moreover, their potential interaction can be evaluated by studying the complexity of each frequency component, using different entropy metrics, such as wavelet entropy. A few studies have shown that the low-amplitude fluctuations of skin temperature are caused by rhythmic alterations in peripheral blood flow, linked with oscillations of smooth muscle tone [12,13]. Particularly, only low- and very-low-frequency fluctuations of simultaneously recorded blood flow and temperature measurements seem to be correlated significantly because of the exponential decay of the temperature amplitude, in relation with the spectral content of the signal [14]. Different authors using a wavelet-based technique for assessing synchronization and coupling between peripheral skin temperature and blood flow signals, found increased coherence in two frequency intervals, around 0.1 Hz and 0.007 Hz [11,14]. While oscillations at approximately 0.1 Hz were attributed to myogenic activity, the latter spectral range was proven to correlate with biochemical processes at the level of endothelium [11].

Never-the-less, no study so far has evaluated potential associations between temperature complexity across different frequencies in critically ill patients and severity of illness. The rationale behind such an approach is that real-time or abrupt changes of patients' physiology cannot be captured early enough using conventional scoring systems, whereas no information is provided regarding potential pathophysiological mechanisms of organ impairment [6,9]. As a result, variability of different fluctuations of biological signals has been postulated as a more precise and informative measure for assessing severity of illness and predicting final outcome [9]. In addition, the development of novel online processing systems supporting real-time processing of multiple high-rate physiological data streams and extraction of different features, has already found correlations between heart rate variability (HRV) drop, that is a marker of autonomic nervous system output, and sepsis development even prior to clinical diagnosis [15].

3. Innovation results achieved

In this respect, we recently showed that the analysis of continuously monitored temperature, measured with a thermistor sensor (Datalogger Spectrum 1000, Veriteq, Canada) attached to the right hypochondrium and with a sampling frequency of 0.1 Hz in 22 critically ill patients was able to discriminate subjects with SIRS, sepsis and septic shock with an accuracy of 80

% [16]. In our study, low and very low frequency components of wavelet transformed temperature curves exhibited decreased complexity in patients proven to suffer from sepsis, compared with SIRS. Maybe, this could be attributed to reduced local blood flow in the first two groups that seems to decrease amplitude of vasomotion, related to blood flow redistribution during severe inflammation [17]. Additionally, the reduction in metabolic inputs (very-low frequencies) upon local thermoregulation could reflect changes in the dynamics of the release of different molecules from the endothelium, something that is markedly pronounced during infectious causes of acute illness [17]. Finally, in another study including 21 septic patients, we found that different wavelet entropy metrics of temperature curves reflecting complexity of metabolic inputs upon skin temperature and vasomotor activity, were significantly reduced in nonsurvivors compared to survivors [18]. Furthermore, such indices were able to predict mortality better than Specific Organ Failure Assessment (SOFA) score alone, with sensitivity and specificity higher than 80%.

In our two studies [16,18], we supposed that temperature complexity measurements could be useful for real-time monitoring of vascular activity, since it has been suggested that 'they are minimally sensitive to mechanical factors or accidental noise due to the low-pass filtering response of the thermal transfer function between blood vessels and skin temperature' [12]. Moreover, 'skin temperature variability is more closely related to blood vessel tone than to mean temperature, whereas mean temperature regulation might be more insensitive to stress and unrelated to short-term vasomotor activity' [12].

In conclusion, continuous temperature monitoring could provide physicians with early and 'smart' alarms regarding development of sepsis in a particular patient, which could add significant value to already established mortality or severity of illness indicators, such as SOFA score, as a real-time surveillance system [18]. Furthermore, temperature monitoring is inexpensive and easily performed at the bedside. Thus, its complexity analysis could be tested in future studies with larger data sets, as a routine real time monitoring for early detecting onset of sepsis, increasing at the same time specificity of clinical examination. In this respect, temperature wavelet transformation seems to have many advantages over other time-series processing techniques, since it can assess complexity of temperature oscillations in different frequency bands that have been found to be affected by both neurogenic and endothelial influences. Finally, the adoption of such methods could monitor response to treatment and predict a potential increase in severity of organ dysfunction despite resuscitation and systemic hemodynamics stabilization [19]. Subsequently, health care institutions and monitoring technology industry could save both lives and money from early and prompt response by carrying physicians, in the context of early directed therapy of sepsis, promoting a pro-active than a reactive model of care.

References

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4. Link to the PRoF values

Through this project, different PRoF values are being highlighted and fulfilled, since such a monitoring technology is totally non-invasive, with minimal cost (depends on high frequency peripheral temperature recordings), is applicable in a healthcare environment and can be used in different settings such as emergency departments, general wards and the ICU. Its potential implementation in routine monitoring systems could add significant value to the carrying physician, as a continuous surveillance system, prompting early personalised treatment of a febrile patient, before further clinical deterioration of systemic physiology.

5. Applicable IPR rules

This innovation concerns a new concept in critical care medicine and is at the late research phase (proof-of-concept). Both some background (information and knowledge held by the two beneficiaries-prof Papaioannou V and Dr Chouvarda I) and foreground (tangible and intangible results generated under this project) will be exchanged with potential stakeholders within the context of a grant agreement, in case of funding. Concerning access rights, project implementation will be royalty-free (access to both background and foreground) whereas use of results (implementation of future research) will be on fair and reasonable conditions.

6. Information on the partners

1. **Vasilios Papaioannou** MD, PhD, Assistant Professor of Intensive Care Medicine, Democritus University of Thrace, School of Medicine, Alexandroupolis Hospital, ICU, Greece.

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His research concerns applications of biosignal analyses tools in the ICU. He has been awarded with three European awards from European and Dutch Society of Intensive Care Medicine (2007, 2009, 2011) and an award from the Hellenic Society of Intensive Care Medicine (2010). His research has also been awarded from the Hellenic Ministry of Education (academic excellence in higher education, http://excellence.minedu.gov.gr/listing/487-icu).

2. **Ioanna Chouvarda** PhD, Biomedical Engineer, Senior Lecturer in Medical Informatics, Lab of Medical Informatics, Aristotle University of Thessaloniki, School of Medicine, Thessaloniki, Greece

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Her research concerns biosignal analyses in different clinical settings, such as cardiology, intensive care medicine and respiratory medicine, in silico modelling of cardiac tissues and numerous european projects about health informatics applications in primary care.

Addendum: Contact information

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