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Introduction

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Advanced computation in cardiovascular physiology: new challenges and opportunities

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Recent developments in computational physiology have successfully exploited advanced signal processing and artificial intelligence tools for predicting or uncovering characteristic features of physiological and pathological states in humans. While these advanced tools have demonstrated excellent diagnostic capabilities, the high complexity of these computational 'black boxes' may severely limit scientific inference, especially in terms of biological insight about both physiology and pathological aberrations. This theme issue highlights current challenges and opportunities of advanced computational tools for processing dynamical data reflecting autonomic nervous system dynamics, with a specific focus on cardiovascular control physiology and pathology. This includes the development and adaptation of complex signal processing methods, multivariate cardiovascular models, multiscale and nonlinear models for central-peripheral dynamics, as well as deep and transfer learning algorithms applied to large datasets. The width of this perspective highlights the issues of specificity in heartbeat-related features and supports the need for an imminent transition from the black-box paradigm to explainable and personalized clinical models in cardiovascular research.

This article is part of the theme issue 'Advanced computation in cardiovascular physiology: new challenges and opportunities'.

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1. Editorial

Advances in non-invasive physiological investigations have significantly contributed to the possibility of continuous cardiovascular monitoring through innovative biomedical sensors, imaging techniques, and remote and wearable measurement tools. Technologies that were once in the hands of a few are now widely available, resulting in extremely large amounts of data. In turn, this results in both novel challenges and opportunities for the research community. But what does this mean for studies using standard clinical data measurement set-ups in small, controlled settings? How do the findings of such studies relate to experiments which generate and process very large amounts of data? Does quantity mean quality? What are the implications for healthcare?

Access to automatic advanced computational tools, especially in the field of cardiovascular physiology, is becoming dramatically important due to the tremendous amount of data available. On one hand, a large amount of data is being generated by biomedical sensors embedded in daily-use devices (e.g. smartphones and smartwatches) and, on the other hand, there is a widespread circulation of publicly available, ready-to-use software for processing biomedical data in a blind fashion (i.e. disjoint from any specific technical or physiological knowledge). In this context, it is of utmost importance to provide the research and industrial communities with unified guidelines in order to encourage exploitation of these emerging technological advances.

A key area of concern regards specificity issues in human cardiovascular pathophysiology. This field requires careful use of data-driven methods when healthcare monitoring occurs outside a clinically informed context. While different stages of severity of a specific cardiac disease may show a clear association with advanced computation-derived biomarkers (e.g. entropy measures or model parameter values), a number of other conditions, both physiological and pathological, may show biomarker variations similar to those observed in cardiopathic patients. For example, autonomic changes following congestive heart failure, which may comprise sympathetic activation and parasympathetic withdrawal, can also be observed in healthy subjects in e.g. postural changes, or physically or mentally stressful conditions. This may lead to inconsistencies due to the variety of experimental set-ups and methodological approaches used in validation studies.

Moreover, while automatic advanced computational approaches may achieve better-than-human performance for the diagnosis of cardiovascular diseases, several high-performing models generate results that are difficult to interpret by clinicians. As a matter of fact, it has been often proven extremely arduous to retrieve intuitive information that may explain physio-pathological mechanisms, as well as to identify model weaknesses and generalization properties, or to extract biological insights from computational 'black box' approaches.

Recently proposed machine-learning methods rely on the availability of large amounts of high-quality training data, which therefore may not be fully representative of the target patient population, because the latter are affected by various types of bias and noise that are typical of real-world scenarios like e.g. clinical environments. Moreover, methodologies for applying artificial intelligence (AI) tools (e.g. deep neural networks) to general diagnostics (e.g. the interpretation of signs and symptoms, past medical history, laboratory results and clinical course) and treatment selection are still under development. Also, while complex and nonlinear advanced signal processing strategies have contributed to the technical understanding and description of physiological signals, their clinical translation has been limited.

For these reasons, there is a real need for advanced computation-derived biomarkers and, more generally, advanced clinical decision support systems to be specific, reliable, trustworthy, accurate, capable of handling multimodal data, computationally efficient, explainable and interpretable.

In order to gain human-level interpretability for a model, we need to know the inner workings of the models, e.g. to infer what features, among the ones used by a model, carry the largest relevance and significance for the downstream prediction task. Indeed, some of the features, i.e. some specific underlying cardiac dynamics, have a higher impact than others in explaining a

specific pathophysiology scenario. All these aspects constitute open questions that invite new challenges for the ongoing research in the field of computational physiology.

The *Philosophical Transactions of the Royal Society A* theme issue 'Advanced Computation in Cardiovascular Physiology: New Challenges and Opportunities' focuses on recent transdisciplinary efforts towards the development of advanced computational tools for cardiovascular physiology and healthcare medicine. Cutting-edge research papers as well as review and perspective articles describe novel methods especially targeted to retrieving information that cannot be captured by traditional/existing strategies, and recasting this information into clinically actionable indicators.

In the context of AI methods for cardiology applications, Bodini *et al*. [1] review the interpretability issues of state-of-the-art machine-learning algorithms using electrocardiogram (ECG) signals to detect cardiac abnormalities. They also propose two novel frameworks to interpret the classification results of deep learning algorithms trained for 12-lead ECG-based classification; here, interpretability refers to the signal samples and waves (e.g. P-wave, QRS complex and T-wave) that contribute most to the disease classification. On the same topic, *Mollura et al*. [2] propose a novel AI approach to effectively predict sepsis from multimodal data continuously collected in an intensive care unit. By exploiting publicly available data, the proposed interpretable model highlights that a closed-loop cardiovascular control model may play a key role in the continuous monitoring of sepsis risk, together with patients' electronic health records. Two further AI-related studies exploit information from ECG data. *Lai et al*. [3] propose a deep learning model that selects an optimal ECG lead and automatically detects multiple ECG abnormalities. As diagnostic redundancy in 12-lead ECG signals may result in the overfitting of deep learning models, the proposed approach improves both the interpretability and the generalizability of the model. Venton *et al.* [4] show that noise in ECG data, including e.g. electrode movement and motion artefacts, impacts on automatic classification based on deep learning methods, highlighting that careful consideration should be given to the inclusion of noisy ECG signals in the training data when developing supervised methods for cardiac states classification. Two further developments of AI methods for cardiology research are included in the theme issue. Duggento *et al.* [5] show a novel multi-branch convolutional neural network architecture and pre-processing pipeline for a robust detection of pathological phonocardiograms. The study overcomes the high interpretation variability in human decision-making regarding abnormalities detected through heart sounds auscultation. On the bioimaging side, Banerjee *et al.* [6] propose an automated pipeline for three-dimensional reconstruction of the human heart from two-dimensional magnetic resonance images which are commonly acquired in clinical practice. The proposed methodology generates patient-specific three-dimensional biventricular representations and therefore allows for enhanced interpretability of clinical data.

Seven articles included in the theme issue deal with spontaneous beat-to-beat variations of heart rate, also known as heart rate variability (HRV). Starting from a brief history of HRV analysis, Saul & Valenza [7] provide methodological and clinical perspectives on the use of multivariate linear models, as well as on the issue of HRV specificity and complex HRV models which reveal nonlinear components of the underlying physiological processes. Multivariate models comprise additional physiological variables such as respiration, arterial blood pressure, central venous pressure and autonomic nerve signals. In this regard, Cairo *et al.* [8] propose an automated procedure for cardio-respiratory synchrogram analysis, with a particular focus on the identification of an optimal threshold for phase variability and related surrogate data analysis. Exemplary results show a decrease of cardio-respiratory phase-locking strength during vagal withdrawal induced by the modification of posture from supine to standing, as well as the effect of inspiratory muscle training in amateur athletes. Also with a focus on multivariate analysis, Faes *et al.* [9] introduce a novel methodological framework that combines cross-spectral and information-theoretic analyses. Through the analysis of HRV, systolic and diastolic arterial pressure, and respiration variability series gathered during postural changes, the framework allows us to retrieve information on cardiovascular and cardio-respiratory

oscillations within specific frequency bands, which are otherwise not detectable by standard time-domain information measures. By exploiting a recently proposed method for the estimation of causal influences in the spectral domain, Nuzzi *et al.* [10] show how to estimate instantaneous interactions between cardiovascular and cardio-respiratory oscillations, thus obtaining a novel index of undirected instantaneous causality and a novel measure of Granger causality including instantaneous effects. This study shows that the inclusion of instantaneous causality allows the baroreflex mechanism to be correctly disentangled from the effects related to cardio-respiratory interactions. González del Castillo *et al*. [11] show the importance of QT variability unrelated to RR variability during stress testing for the characterization of cardiac diseases. They show that low-frequency oscillations of unrelated QT variability are altered in the case of coronary artery disease as compared to healthy controls when measured during the first phases of exercise and last phases of recovery. In the frame of nonlinear analysis, Nakata *et al.* [12] propose a novel methodology for the assessment of long-range cross-correlations in cardiovascular and cardio-respiratory series. The higher order detrending moving-average cross-correlation analysis shows that, besides autocorrelations, respiratory and HRV series do not share long-range cross-correlations, whereas beat-to-beat systolic blood pressure and HRV series do share common long-range cross-correlated factors. Faini *et al*. [13] propose a novel multiscale index of multifractality, which is then tested on 24 h heart rate recordings. While the singularity spectrum failed to satisfy the concavity requirement for providing meaningful singularity spectrum width, the proposed methodology demonstrated a statistically significant heart rate multifractality at night and corroborates the presence of cardiac monofractality during daytime.

Finally, three articles focus on the exploitation of brain data analysis to collect meaningful insights on cardiovascular physiology. Through the computation of electroencephalographic and HRV series, Catrambone *et al*. [14] describe a novel methodological framework to study nonlinear functional brain–heart interplay in the non-Gaussian and multifractal domains. The proposed framework relies on a maximal information coefficient analysis between nonlinear multiscale features derived from electroencephalographic spectra and from an inhomogeneous point-process model for heartbeat dynamics. Hartmann *et al*. [15] study the dynamic interplay between the central and autonomic nervous system activity during sleep. Focusing on non-rapid eye movement sleep stages, they show the causal interplay between cortical and cardiovascular activity during cyclic alternating patterns. By exploiting a large functional magnetic resonance dataset, Duggento *et al*. [16] show a novel approach to estimate nonlinear, directed, within-brain network interactions through echo-state networks. Within the Granger causality framework, the authors show the existence of previously unknown, directed interactions, including interplays between brain networks and central vagal cardiac control dynamics that contribute to the thorough characterization of the so-called central-autonomic network in a causal manner.

To conclude, we strongly believe that the rich aforementioned body of work will stimulate a relevant multidisciplinary dialogue among scientists and clinicians on the importance of considering new ways of applying complex data processing methods for translational purposes in clinical cardiology. While easily accessible and affordable biomedical data may contribute to opening the floodgates to new improvements in cardiovascular research and empower-related clinical studies, a focus on improving basic scientific knowledge should also be encouraged, even if it is not an easy task. Also, US researchers should all contribute to the on-going technical and ethical discussions on medical management decisions made by computational machines. At the forefront of this debate is the importance of specificity and accuracy versus explainability and interpretability. If these issues are not addressed, the potential benefits and opportunities afforded by advanced computation in cardiology may be lost. Further integration of technical and biomedical disciplines should therefore be encouraged to develop more and more interpretable computational tools to evaluate patients and support diagnosis, treatment and prognosis.

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