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Introduction to the Special Section on Computational Modeling and Digital Twin Technology in Biomedical Engineering

This special section collects six original articles that carried their studies *in silico* and one narrative review on digital twins (DTs) of biological systems.

As the Merriam-Webster dictionary defines, *in silico* (virtual) literally means "in silicon" in New Latin and is a nod to the importance of silicon in creating computer chips.

In silico medicine uses mathematical modeling and computer simulation to mimic human systems' anatomy, physiology and pathology to understand their mechanisms and processes at different levels, i.e., organ, cellular, molecular and genetic levels. Furthermore, computational modelling serves to study, diagnose and treat or prevent disease and as a predictive tool for the effect of different interventions. Compared to traditional modelling approaches, a digital twin (DT) of the human body is still a virtual representation of an individual's physiological state, but it is created using real-time data from sensors and medical devices, with the purpose of simulating, predicting and optimizing health outcomes through advanced analysis and modelling.[1] Although the clinical uptake of modelling and DT have not been consistent, increased numbers of experiences have been reporting the use of *in silico* tools in clinics [2].

The articles collected in this special section have as the ultimate goal the clinical adoption of their computational models. In particular, the authors developed and applied computational modelling *i)* to improve early detection of acute respiratory distress syndrome (ARDS) using datasets from different Intensive Care Unit (ICU) determined solely by medical conditions, reducing biases introduced by learning from heterogeneous datasets; *ii)* to develop an automated post-traumatic stress disorder (PTSD) screening tool to be used as a self-assessment for early PTSD diagnosis and treatment; *iii)* to design a performance-based arousal decoder that estimates the arousal level of persons based on their performance task, in presence of exciting and calming music; *iv)* to continuously estimate respiratory rate (RR) and blood pressure (BP) as vital signs for the prediction of cardiovascular diseases, using a (non-invasive) wearable photoplethysmogram (PPG) sensor; *v*) to better understand the physiological changes in arterial compliance associated with aging and therefore, to identify potential interventions for age-related cardiovascular diseases; *vi)* to investigate the electrical impedance spectroscopy as a method to distinguish between the thyroid and parathyroid tissue during surgery. Finally, the narrative review defined DTs of biological systems and discussed benefits, risks and challenges associated.

In the paper of Sharafutdinov and colleagues, the authors showed that mechanistic virtual patients, which were created using a high-fidelity and highly integrated computational model of the cardiopulmonary systems [3], [4], [5], could be applied to large ICU patient cohorts to infer model-derived parameters on individual patients with suspected ARDS. The authors used patients' data from five different hospitals. They compared the results of clustering, an unsupervised learning method, using two datasets to compare original measured parameters, used as inputs to the simulator, calculated before and after suspected ARDS onset with model-derived data. The model showed an adequate quality of fitting for 95.9% of patients before suspected ARDS onset and for 84.5% of patients after suspected ARDS onset. Clustering on the original data was unable to divide an entire cohort into homogeneous groups and find a stable cluster configuration while clustering on the model-derived data revealed significantly better clustering quality for all configurations of the number of clusters. The model-based clustering reduced biases introduced by the inclusion of data from the different hospitals, improving detection of patients driven exclusively by medical conditions and providing a tool for early diagnosis of ARDS.

Quatieri and colleagues developed a digital emotional twin for the early detection of PTSD, a psychiatric disorder that may occur in subjects who have experienced or witnessed a traumatic event, series of events or set of circumstances. [6] The digital emotional twin is a tailored computational model of the effect of emotions on speech and language, to detect PSDT and to improve its accuracy of diagnosis and early diagnosis. The screening tool developed by the authors used vocal biomarkers, which are emotional changes quantified by arousal (i.e., the intensity ranging from calm/drowsy to excited/alarmed) and valence (i.e., from pleasure to displeasure). The PTSD prediction system relied on emotion filtering, which passes segments of low-level features corresponding to low arousal or positive valence, followed by the extraction and classification of high-level features. The low-level features were based on the respiratory, phonatory, and articulatory speech production subsystems as PTSD can be associated with changes in these subsystems. High-level features include representations of correlation structure and dispersion, which characterize the levels and complexity of coordination in the aforementioned subsystems. These features were then used in a machine-learning model to predict PTSD severity. The algorithm was tested on TSD Check List Civilian (PCL-C) rating scores and achieved an AUC (area under the curve) of 0.80 in detecting PCL-C ratings when using valence filtering emotional and arousal, outperforming models without an emotion filter (AUC = 0.68) and on an emotional filter using high arousal and negative valence (AUC = 0.70). The digital emotional twin introduced in this study is novel and may be used to select the most significant temporal regions of an audio recording to improve PTSD detection performance.

Khazaei and colleagues investigated cognitive arousal, i.e., the intensity level of emotion associated with the sympathetic nervous system and, developed an arousal-performance model based on the Yerkes–Dodson law. [7] The Yerkes–Dodson law, also known as the inverted-U law, states that performance increases with physiological or mental arousal, but extremely low arousal levels can lead to a lack of attention and high arousal may result in a distraction. The study focused on the evaluation of the arousal-performance link through a cognitive task in the presence of music.

The authors decoded the arousal and performance in the presence of two types of music, calming and exciting, since different types of music can be an effective factor in cognitive performance regulation. Moreover, they presented performance indices within each music session and task difficulty (1-back and 3-back tasks [8]) evaluated the arousal-performance link, and developed a performance-based arousal decoder. Six participants were recruited and asked to select personalized music to simulate low and high-arousing environments.

To decode the continuous performance and arousal state the authors used peripheral physiological data and behavioural signals, using the Bayesian filtering approach within an expectation-maximization framework. Among the quantitative arousal index, the authors measured electrodermal activity. Behavioral data, i.e., the sequence of correct/incorrect responses and reaction time, showed better performance (i.e., the number of correct responses and time of reaction) with exciting music in five out of six patients and during the 1-back task. These data aligned with the decoded arousal and performance data, which fitted the inverted U shape.

The learning effect, the nature of the task, and the participant's baseline (different perception of music) may be other factors involved in the performance. In this study, the exciting music was executed as the second session and therefore, it is possible to consider that the learning effect played a role in the participant's performance. The proposed arousal-performance model will be investigated in different behavioral experiments.

In the paper of Sultan and Saadeh, the authors presented a patient-independent approach to estimate RR and BP using robust spectro-temporal features derived from a single channel PPG signal.

The PPG signal was pre-processed to remove baseline shifts and artefacts due to body motion, and then multiple parameters, independent of individual patient PPG morphology were extracted for RR and BP. Only peaks and onsets of PPG were considered because of their independency nature from the patient. Three respiratory morphological features for RR estimation were obtained, i.e., respiratory-induced intensity, frequency and amplitude variations, whilst for BP estimation, six morphological parameters were obtained: i.e., systolic and diastolic time, systolic and diastolic branch widths (i.e., systolic or diastolic time calculated at a fraction of beat amplitude), heart rate and PPG intensity ratio (the ratio of peak and onset amplitudes). For BP estimation also spectral and statistical features were derived. The spectral features, in the frequency domain, included energy, entropy and area bands, whilst the statistical features, in the time domain, included the PPG signal's kurtosis, skewness, and temporal entropy. Extracted features were checked for their relative significance in determining RR and BP. To determine RR, three robust modulation quality indices (MQI) were considered: power spectrum (frequency content), autocorrelation (signal periodicity) and template matching (signal similarity) MQIs. The features selected to determine BP were the Pearson correlation coefficient (to check linear relationships), mutual information coefficient (to see non-linear dependency between signals) and minimal redundancy and maximal relevance (to check if there is redundancy). Finally, to estimate RR, a peak detector was used with a moving average filter with a frequency range of 0.1 to 1 Hz whilst to estimate BP a deep neural network regression.

Validation of the approaches was conducted using open datasets, namely, the TBME Benchmark Capnobase Dataset & BIDMC Dataset from MIMIC-II Physionet (n patients = 95) for RR and Open-Source MIMIC-I Database (n patients = 2064) for BP. To the current state of the art, both RR and BP approaches were superior having the mean absolute error and standard deviations of error similar or lower. In this study, the authors proposed a powerful approach to continuously estimate RR and BP, which are vital signs for the prediction of cardiovascular diseases, using only one physiological signal (PPG) acquired in a single channel and with a wearable (non-invasive) device.

Bahoul and colleagues investigated the application of fractional-order modeling of arterial compliance - the amount by which a vessel will increase in volume for a given increase in distending pressure - in human vascular aging. The authors implemented five fractional-order models, with different numbers of elements to describe the apparent (i.e., dynamic) vascular compliance to simulate the active relationship between blood pressure and volume. Each configuration incorporates a fractional order capacitor element – FOC– that combines both resistive and capacitive attributes, to lump the apparent arterial compliance's complex and frequency dependence properties and compare them to the standard integer-order models. Furthermore, the authors formed a novel fractional order modified arterial Windkessel [9] combining the simplest fractional-order representation into a global arterial lumped parameter representation. This was aimed at capturing the complex and frequency-dependent properties of proximal (large arteries - more elastic) and distal (muscular arteries – stiffer) compliances. The unknown parameters and the fractional differentiation order were estimated using aortic pressure and flow rate values from three human subjects at different ages (28, 52, and 68 years), using the non-linear least square minimization method. The results showed that the FOC model accurately fits the dynamics of arterial compliance, showing a good reconstruction of the proximal blood pressure. Therefore, the novel tool developed in this study may be used to better understand the pathophysiological changes in arterial compliance.

Matella and colleagues developed computational – numerical – models as tools to simulate and evaluate the mechanisms that influence the thyroid and parathyroid tissues on the impedance spectra. Finite element models of thyroid and parathyroid implemented were chosen and used to evaluate connections between the impedance spectra and the tissue characteristics. The differences in the thyroid and parathyroid impedance can be recorded with an electrical impedance spectroscopy (EIS) probe, but the EIS measurements solely do not provide information on the connection between the recorded impedance spectra and the tissue characteristics. The computational simulations were compared with the EIS experimental (*in vivo*) results. Both thyroid and parotid tissues' structures were implemented at different scales, from the cellular level (microscale) to the tissue level (macroscale). For the thyroid tissue, also the follicle was modelled introducing an additional scale (mesoscale).

To investigate the impact of various geometrical and electrical properties of the compartments in all sub-models, the authors performed a local intercompartmental sensitivity analysis to determine the isolated effects of the parameters on the simulation results. Baseline impedance spectra parathyroid showed higher impendence compared to thyroid when both models were at their default configuration of morphological and electrical properties, although the overlap between the computed results increased with the frequency. Compared with *in vivo* measurements at frequencies below 100 kHz, the computed thyroid spectra corresponded to the lower impedance values from the experimental data, whilst the parathyroid showed the opposite.

Thyroid impedance results were predominantly sensitive to changes in the size of the follicles at low frequencies and the thickness of the connective tissue at high frequencies. Whilst for the parathyroid, extracellular space thickness and cell length had the most significant influence at the low frequencies. Colloid and fascia compartments had a significant effect on simulated impedance spectra characteristics. *In vivo* EIS data measurement accompanied by computational models could be used as a tool to differentiate thyroid and parathyroid tissue during thyroidectomy.

In the narrative review by Alsalloum and colleagues the authors provided the history, definition and construction of DTs of biological systems. The review found the first definition of DTs in 2002 under the names of 'Mirror Space Model' and 'Information Mirror Model'. With the time and the rapid advancements in computing and technology, the concept of DTs has evolved into intelligent systems and incorporated smart sensors, Internet of Things and AI for enhanced prediction and optimized medical treatment. The authors defined the DT *as a computational model representing the structure, behavior, and context of a unique physical asset, allowing for thorough study, analysis, and behavior prediction*. A DT differs from simulation-only models in that it operates in real time, integrates various data sources, and provides continuous, bidirectional data exchange between physical and virtual twins, improving patient data monitoring and prediction response of the treatment.

The authors discussed the five phases necessary for building DTs, namely planning, development, customization, testing and validation, and the continuous learning phases. The authors also provided socio-ethical benefits (better diagnostics, patient empowerment, less invasive treatments, cost reduction) and risks (data privacy and security, equity and accessibility, trust and autonomy, regulatory compliance), as well as key challenges to face. Finally, the review summarized the DTs of biological systems at their different levels of organization (i.e., systems, organs, cellular, subcellular and molecular level) and provided a detailed list of studies which includes DTs of cells, stem cells, brain and neurons, heart, blood circulation, colon, vertebrae, liver, joints, cardiovascular and autonomic nervous system, diabetes, stroke, lung cancer, breast cancer, multiple sclerosis patients, tumor tissue, cognitive model and immune response.

In summary, this special section encompasses studies on the development of broad computational models to be applied to critical and intensive care, psychiatry, psychology, cardiopulmonary and cardio-vascular medicine, and otolaryngology. Although in the last years, computational modelling has been used for numerous applications and great progress has been made, there is still a lack of understanding of the pathophysiology of human systems and room for improvement for their best development and use. The studies on this issue have made great additions to the current state of the art, providing us with novel and appropriate skills to interpret the results of research based on such methodologies [10].

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APPENDIX

RELATED WORKS

A1) K. Sharafutdinov et al., “Computational simulation of virtual patients reduces dataset bias and improves machine learning-based detection of ARDS from noisy heterogeneous ICU datasets,” *IEEE Open J. Eng. Med. Biol.*, early access, Feb. 08, 2023, doi: 10.1109/ojemb.2023.3243190.

A2) T. F. Quatieri et al., “An emotion-driven vocal biomarker-based PTSD screening tool,” *IEEE Open J. Eng. Med. Biol.*, early access, Jun. 13, 2023, doi: 10.1109/OJEMB.2023.3284798.

A3) S. Khazaei, M. R. Amin, M. Tahir, and R. T. Faghih, “Bayesian inference of hidden cognitive performance and arousal states in presence of music,” *IEEE Open J. Eng. Med. Biol.*, vol. 5, 2024, Mar. 18, 2024, doi: 10.1109/OJEMB.2024.3377923.

A4) M. A. Sultan and W. Saadeh, “Continuous patient-independent estimation of respiratory rate and blood pressure using robust spectro-temporal features derived from photoplethysmogram only,” *IEEE Open J. Eng. Med. Biol.*, early access, Nov. 02, 2024, doi: 10.1109/OJEMB.2023.3329728.

A5) M. A. Bahloul, Y. Aboelkassem, Z. Belkhatir, and T.-M. Laleg-Kirati, “Fractional-order modeling of arterial compliance in vascular aging: A computational biomechanical approach for investigating cardiovascular dynamics,” *IEEE Open J. Eng. Med. Biol.*, early access, Dec. 14, 2023, doi: 10.1109/OJEMB.2023.3343083.

A6) M. Matella, K. Hunter, S. Balasubramanian, and D. C. Walker, “Multiscale model development for electrical properties of thyroid and parathyroid tissues,” *IEEE Open J. Eng. Med. Biol.*, early access, May 11, 2023, doi: 10.1109/OJEMB.2023.3275536.

A7) G. A. Alsalloum, N. M. Al Sawaftah, K. M. Percival, and G. A. Husseini, “Digital twins of biological systems: A narrative review,” *IEEE Open J. Eng. Med. Biol.*, to be published, doi: 10.1109/OJEMB.2024.3426916.

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