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SPECIAL ISSUE ON "COMPUTATIONAL MODELLING IN MEDICINE": GUEST EDITOR INTRODUCTION

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SPECIAL ISSUE ON "COMPUTATIONAL MODELLING IN MEDICINE": GUEST EDITOR INTRODUCTION

It has been an honour and a pleasure to serve as Guest Editor for this special issue of the Journal of Engineering in Medicine dedicated to "Computational Modelling in Medicine". In my role of Director of the Insigneo institute for *in silico* Medicine I have the opportunity to see the rapid and radical innovation that is taking place in this sector, but in spite of this, reading the manuscripts that were accepted for this special issue, I was surprised and delighted to see how the idea of using mathematical and computer modelling to model the physiology and the pathology of the human body has matured in the last 15 year, and how its application is starting to make a tangible impact in biomedical research.

The issue opens with "Capturing complexity in respiratory system modelling" by Alys Clark, Haribalan Kumar, and Kelly Burrowes, which reviews the different strategies reported in the literature to model the respiratory system, with particular reference to the delicate problem of balancing the anatomo-functional complexity with the computational cost as these models move from speculative research to clinical translation scenarios, where their predictions are used to support clinical decisions.

The paper "Mechanobiological modelling of tendons: review and future opportunities by Mark Thompson, Nazri Bajuri, Hanifeh Khayyeri, and Hanna Isaksson, reviews the mechanobiology of tendons, offering an interesting window in an important but to some extent neglected aspect of the mechano-adaptation of connective tissues.

In "A Multi-Scale Modelling Approach to Understand Atherosclerosis Formation: A Patient-Specific Case Study in the Aortic Bifurcation", Mona Alimohammadi, Cesar Pichardo Almarza, Obiekezie Agu, and Vanessa Díaz-Zuccarini face the "test of fire" for any subject-specific model, by comparing the size and spatial location of atherosclerotic plaques in the aortic bifurcation of a patient, with those predicted by a multiscale subject-specific model that predicts the early stages of the atherosclerotic plaque formation by modelling the blood transport and the migration to the arterial lumen of the low density lipoprotein. Considering the complexity of the mechanobiology process being modelled, the agreement is impressively good.

The following two papers dig into a central problem of computational medicine: constitutive equations. While the mechanical behaviour of conventional engineering materials is well described and characterised, that of complex biomaterials like shape-memory alloys, or of biological materials like bone tissue are still an important research topic. The paper "The role of inelastic deformations in the mechanical response of endovascular shape memory alloy devices" by Lorenza Petrini, Alessandro Bertini, Francesca Berti, Giancarlo Pennati, and Francesco Migliavacca explores how in a trans-catheter aortic valve during its crimping/expansion cycle can be modelled the accumulation of inelastic strains, finding that their inclusion makes significant difference in the model predictions.

I am well aquainted with the work "Nonlinear homogenisation of trabecular bone: effect of solid phase constitutive model" by Francesc Levrero-Florencio, Krishnagoud Manda, Lee Margetts, Pankaj Pankaj, having had the pleasure of being recently external examiner of Francesc PhD thesis. Francesc has developed a sophisticated finite element modelling code to simulate the biomechanical post-elastic behaviour of cancellous bone; in this paper he and his co-authors compare two yield criteria or the solid phase, Drucker-Prager and Eccentric-Ellipsoid, finding the first to predict much higher strains in some loading conditions.

Somewhere in between the characterisation of methods and the clinical application is the manuscript "Sensitivity of a juvenile subject-specific musculoskeletal model of the ankle joint to the variability of operator dependent input" by Iain Hannah, Erica Montefiori, Luca Modenese, Joe Prinold, Marco Viceconti, and Claudia Mazzà. The study investigates the sensitivity to operator-dependent inputs of a musculoskeletal dynamics model used to predict the ankle joint resultant force during level walking in children affect by Juvenile Idiopathic Arthritis. It is concluded that the MRI-based spatial determination of origins and insertion of the muscles shows a significant inter-operator variability, which can bias the force predicted for certain muscles by up to 64%. This calls for a more robust way to personalised these models.

The next three papers move markedly toward the clinical translation; they use computational medicine methods to explore, with a level of detail otherwise impossible, the effect of complex interventions.

In "Computational modeling of long-term effects of prophylactic vertebroplasty on bone adaptation", Sandro Badilatti, Patrik Christen, Stephen Ferguson, and Ralph Müller complete a complex investigation started in the frame of the VPHOP project, aimed to explore the long-term effect in terms of bone tissue adaptation to an intervention of vertebroplasty. While some changes are predicted, the paper concludes that "the impact of vertebroplasty on the bone at the microstructural level is less detrimental than previously thought".

In "Virtual Flow-Diverter Treatment Planning: The Effect of Device Placement on Bifurcation Aneurysm Haemodynamics" by Thomas Peach, Katerina Spranger, Yiannis Ventikos the effect of the placement of a flow-diverter device on the efficacy of the intervention for three different aneurysm geometries is investigated. It is concluded that one placement strategy seems to be superior, but it is also suggested that such technology could be used for pre-operative planning, in order to decide, on a subject-specific basis, the most effective placement strategy.

The last of these three more translational papers, "Load Application for the Contact Mechanics Analysis and Wear Prediction of Total Knee Replacement" by Jing Zhang, Zhenxian Chen, Ling Wang, Li Dichen, and Zhongmin Jin revise critically the ISO 14243 standard used to quantify pre-clinically the wear of total knee-joint prostheses. This standard uses a single eccentric load to simulate the complex system of forces transmitted to the medial and lateral compartments. However, studies with telemetric implants and musculoskeletal dynamics models now give us a much more detailed understanding of such loading patterns during daily living. The study uses computational medicine methods to predict the wear produced under the ISO standard loading, and under a more realistic medial-lateral loading conditions; they conclude that the latter "could produce more reasonable contact mechanics and wear prediction".

The special issue closes with a manuscript, in which I have the honour to narrate the emergence of the use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention, now referred to as"*In silico* clinical trials". In "*In silico* assessment of biomedical products: the conundrum of rare but not so rare events" by Marco Viceconti, Claudio Cobelli, Tarek Haddad, Adam Himes, Boris Kovatchev, and Mark Palmer we describe two success stories in this field: the adoption of the Padova – UVA simulator for the assessment of artificial pancreas technologies as the first FDA-accepted in silico alternative to animal testing, and the "*in silico*-augmented clinical trial" approach developed by a group of researchers at Medtronic Corp., which allow to mix physical and virtual patients in a clinical trial, making possible the

exploration of "patients' phenotypes that are unlikely to appear in the trial cohort, but are still frequent enough to be of concern".

The publication of this special issue happens very close to the tenth anniversary of the release of "Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human[1]" the road-mapping report we published in 2007, which painted a vision where subject-specific computer models could transform biomedical research and clinical practice. The extraordinary work that our research community worldwide has expressed in these ten years, of which this special issue is a representative sample, transformed this vision a thriving reality. We do live in interesting times; long live the Virtual Physiological Human!

[1] http://www.vph-institute.org/upload/step-vph-roadmap-printed-3_5192459539f3c.pdf