IN SILICO TRIALS: A SYSTEMATIC APPROACH TO THE ASSESSMENT OF MODEL CREDIBILITY

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Background

While computer modelling appeared very early in biomedical research [1–4], it is only in the early 2000 that it becomes evident that it is possible to predict with good accuracy how certain measurable quantities representing a certain aspect of the health status of an individual patient change over time because of the progression of the disease, or because of a treatment [5–10]. This can be used in two ways: to support the medical decision about an individual patient (hereinafter referred to as Digital Patient technologies) or to assess in silico the safety or the efficacy of a new medical product (hereinafter referred to as In Silico Trials). Regarding Digital Patients applications we are seeing a number of commercial solutions reaching the market such as HeartFlow [11], FEOPS [12], O. N. Diagnostics [13], VASCOPS [14], also thanks to a robust regulatory framework on the so-called "software as a medical device" which has been extensively harmonized between Europe and USA in the last years [15]. But until a couple of years ago, no regulatory agency in the world would normally accept as primary evidence of safety or efficacy for a new medical product (whether drug or medical device) an in silico prediction; primary evidences had to be produced experimentally, in vitro, in vivo with animal experimentation, or with clinical trials on humans. This changed recently, when both the US congress and the European Parliament made similar recommendations to their respective regulators to reconsider this position (see these reviews for more information [16,17]). Now the challenge is back in our hands: how can we demonstrate the credibility of the evidences provided by a computer model with respect to the regulatory process? In traditional computational engineering this is usually referred to as Verification, Validation, and Uncertainty Quantification (VV&UQ). However, the complexity of the processes being modelled, the incompleteness of the knowledge on the mechanisms behind physiology pathology processes, the insufficient of the information required to fully identify the model, and cultural barriers that this approach faces in the regulatory world, present unique challenges.

Recent Advances

Starting from a systematic review of recently published new technical standard "Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices" (ASME V&V-40) [18], we will present a general mathematical framework for VV&UQ of biomedical models that attempts to address a) the combination of mechanistic and phenomenological knowledge in a single model, and b) the problem of "model extrapolation", i.e. how the predictive accuracy degrades as we get near to the limits of validity of the model itself. We will also briefly discuss how the problem of credibility is being approached for drugs, and the challenges that this poses.

Marco Viceconti is currently Full Professor of Computational Biomechanics at the University of Bologna. He is a key figure in the emerging field called *in silico* medicine: founder, director, and now President of the VPH Institute; first author of the Europhysiome roadmap that set the early research agenda for the field; founder and director of the Insigneo Institute for in silico Medicine at the University of Sheffield (UK), the largest in Europe on this topic; lead of the Avicenna initiative that drove the concept of In Silico Trials. Since 2016, he focused on the regulatory aspects of in silico medicine. He authored or co-authored over 300 publications (Google Scholar H-Index = 60).

Future directions

The computational biomechanics research community has an opportunity and an obligation. The opportunity is to drive the birth of a new industrial sector, where new biophysics models are used to refine and expand the scope of regulatory activities, with the ultimate goal of replacing animal and human experimentation for regulatory purposes. The obligation is to take lead in this critical review of current methods and their credibility for regulatory purposes, taking our rightful side next to the regulatory authorities.

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