FROM MUSCULOSKELETAL DIGITAL TWINS TO IN SILICO TRIALS OF NEW INTERVENTIONS: A JOURNEY

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Introduction

Digital Twins in Healthcare (DTH) are subject-specific quantitative predictive models used as clinical decision support systems in diagnosing, prognoses, and treating disease. The management of musculoskeletal pathologies is frequently informed by biomechanical quantities, but in many cases, measuring these quantities is difficult or impossible. DTH can provide accurate estimates of these quantities on a patient-specific basis, supporting the clinical decision process.

Another important role of predictive models is their use in developing and de-risking new treatments, whether drugs, medical devices, tissue engineering solutions, physical therapies, surgical procedures, etc. These models, called *In Silico Trials* (IST), need to predict how specific quantities of interest represent the disease progression, how this progression changes because of the treatment, and whether the treatment may also cause adverse effects. But this prediction needs to be done not for a single patient but for cohorts of patients large enough to represent the whole target population.

There are many ways to develop IST solutions, but one particularly effective is using, at the core, a DTH model. However, transforming a DTH into a full-blown IST is a complex project. In this perspective talk, we use biomechanical DTHs as a guiding example to show the challenges of transforming a DTH into an IST pose.

Background

BBCT-Hip is a DTH to predict the risk of proximal femur fracture in osteopenic subjects. BBCT combines a stochastic model of falling with a CT-based finite element model of the femur to predict whether the femur will fracture for a given fall condition. ForceLoss is a DTH for the differential diagnosis of dynapenia. ForceLoss use a patient-specific musculoskeletal dynamics model to test the various diagnostic hypotheses. DIIP is a DTH that predicts the risk of the most common failure modes for a patient treated with a joint replacement. DIIP currently test for aseptic loosening, dislocation, intra-operative fracture, and massive wear.

We aim to transform these three DTHs into IST solutions: the first, to estimate in silico the efficacy of new anti-resorptive drugs; the second, to estimate the efficacy of anti-sarcopenia drugs; the third, to run in silico a complete risk analysis for new joint replacement designs.

Results

The transformation of BBCT-Hip into an in silico clinical trial required the generation of a virtual cohort, a disease progression model, and a treatment model. We summarise our recent work in cohort expansion, through which we transformed a collection of 94 patient-specific models in a cohort of 1000 virtual patients [1]. We also report on using a Markov-Chain Monte Carlo to reduce the computational costs of the In Silico Trial. Last, we report using the newly developed In Silico Trial to investigate the effect of compliance on the efficacy of a hip protector.

For ForceLoss, we discuss the challenges we faced in generating a virtual cohort and present tentative solutions.

For DIIP, we will discuss the challenge of automating the model's generation and how to account for both patient and surgical variability. We will report some preliminary results on the risk of intraoperative fracture in a cementless hip stem and on the risk of massive wear in a knee replacement [2].

Discussion

Although limited, this experience helps explain the main challenges in transforming a digital twin in healthcare into a full-blown In Silico Trial. As part of the discussion, we also touch on IST's regulatory challenges [3].

References

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