INTRODUCTION
The scope of work is to show, using a few clinical applications as supporting examples, how personalised modelling of musculoskeletal pathophysiology can be used in clinical applications. We describe two clinical applications: the prediction of the risk of fracture of a biological skeletal reconstruction during rehabilitation exercises in paediatric skeletal oncology patients, and the prediction of the risk of low-energy fracture of the femoral neck in elders with osteoporosis and neuromotor control degradation. Before the methods described here can be adopted on at large-scale in the clinical settings, we need to automate and streamline the protocols so that they can be used on dozens of patients per day. More important, we need to produce data that convincingly show the efficacy of these methods. This cannot be limited to research validation experiments, but needs full-blown clinical trials, where the clinical efficacy of these simulation-based technologies is reliably quantified, and it is made clear in which cases the increase in cost and complexity these methods involve are justifiable form a cost-benefit ratio perspective.

METHODS

Paediatric skeletal oncology
Radio-opaque and reflective markers are attached to the skin all over the lower limbs, and kept fixed using an adhesive film. The patient is then examined with CT scan of the lower limb (which is part of the clinical protocol for these patients) and then brought to the movement analysis lab, where a full motion capture is performed, including ground reaction and EMGs. CT images are segmented to generate a 3D model of the lower limb skeleton. Markers are used as fiducial framework to register in space the 3D model with the motion data; global optimisation is used to deal with skin motion artefacts. A lower-limb musculoskeletal model is then fitted to the detailed anatomical information derived from the CT data. The model was improved over the years, and now is a 7-segment, 10 degree-of-freedom (DOF) articulated system actuated by 82 muscle-tendon units. Joint moments during specific movements are computed using inverse dynamics, whereas muscle and joint forces are estimated using a static optimisation scheme. EMGs data are used to verify that the activation patterns predicted by the model are correct. The CT data are further processed to derive from them two finite element models, one of the reconstructed bone and the other of its contralateral bone, using well-established methods. In a validation study on cadaver bones, these models were able to predict bone stains with an average error of 10% or less [1]. For each motion captured, muscles and joint forces predicted by the musculoskeletal model are applied as boundary conditions to the finite element model. These conditions are in turn used to constrain the optimisation so that the bone strain is realistically predicted and compared with the strain recorded in the CT data. Validation is performed by registering the predicted strain field and the experimental stain field in 3D, and estimating their difference. The strain difference is used as index of fit of the bone strain prediction. Prediction of bone strains in children and adolescents. As the tumour mass is surgically removed, the continuity of the skeleton must be reconstructed. One of the methods in use produces complex biological reconstructions that combine allografts and revascularised autografts; since the strength to physiological loading of these reconstructions is unknown, planning the rehabilitation program becomes a very delicate and potentially dangerous exercise. In the first clinical application we present here personalised body-organ predictive models are used to estimate such strength, guiding the post-operative rehabilitation planning.

Low-energy fractures in elders are usually associated with severe form of bone loss, called osteoporosis. However, most fractures can be explained only as a combination of reduced strength of the skeleton due to the bone loss and of skeletal overloading due to degradation of the neuromotor control. The use of personalised predictive models can combine these two aspects, providing estimates of the risk of spontaneous fracture for each patient.
conditions to the finite element models, and the risk of fracture of the reconstructed bone is computed relative to the contralateral intact.

Risk of low-energy fracture
The protocol used in osteoporotic patients to evaluate their risk of femoral neck fracture is quite similar to the previous one, except that in general in these patients whole body CT scan is not available, but only a small region of the skeleton can be examined with this modality, due to limitations on ionising radiation that can be used in prevention. Also a full motion capture exam is hard to justify in the clinical protocol. Thus, the joints and muscles forces are defined on the probabilistic basis, using a database of musculoskeletal models, parameterised over a number of information available for the patient, including body weight and height, femoral neck length and retroversion angle, etc. The advantage of this probabilistic approach is that we can also factor in the neuromotor degradation, by assuming that during a normal movement (walking, stair climbing) the neuromotor control can produce any possible sub-optimal activation pattern that ensures the observed kinematics. All infinite solutions can be parametrised over the hyperline that in the solutions space connect the solution that minimise the hip reaction with that which maximise it [2]. Thus, also the neuromotor degradation can be expressed probabilistically, expressing the probability as a function of the distance of the actual solution from the optimal one: the less optimal is the solution, the less probable it is. Since we are dealing with sub-optimal solutions, the effect of the tetanic muscle stress (TMS), which in optimal solutions is mild, here become significant. Thus, also the TMS, which is difficult to measure on the patient, is defined as a probabilistic variable over the range of values reported in the literature.

The bone finite element model is thus loaded by multiple loading cases, within a Monte Carlo scheme where load cases are generated randomly according to the distributions of the parameters (kinematics, TMS, neuromotor degradation, etc.). For each load case, we have a deterministic prediction of whether the femoral neck will fracture or not, but as we combine a spectrum of possible loading conditions, the resulting prediction becomes a probability of fracture.

RESULTS AND DISCUSSION
The described methods have been applied so far on small groups of patients. The method was applied to three paediatric oncology patients, one with the reconstruction of the whole proximal femur, the other two with intercalary reconstructions of the femur and of the tibia. As the methods were developed as we applied them, starting from lab research results, it is hard to draw any conclusion on the large-scale usability of such approach. With the appropriate level of automation for some of the most tedious data processing operations, we believe the time required to generate the personalised models could go down to one day, opposite the more than a week it takes now. The patient would do the CT and the motion analysis one day, and the model would be ready two days after. Currently, the model is then used a the basis for a team consultation between the bioengineer, the surgeon and the physiatrist; however, if the rehabilitation exercises can be standardised, the model could be used to produce a standard patient report, where the risk of fracture for each exercise, both at full or partial load, is estimated. One side advantage of this approach is that the CT exam can be processed also in the subsequent controls, not only updating the fracture risk estimates as the reconstructed bone grow and remodel, but also to provide the surgeon with a quantitative information of how the reconstruction is succeeding is restoring a full load-bearing functionality (fig. 1).

![Figure 1: changes of the risk of fracture during level walking over 44 months of follow-up after surgery.](image)

The protocol to predict the risk of femoral neck fracture in osteoporotic patients is currently being applied retrospectively to a collection of 200 cases, 100 of which had a low-energy femoral neck fracture. Meanwhile we are enrolling 20 patients for a first prospective study. The protocol involves an extended ambulatory visit, which includes also grip-force test, balance tests, etc., and a CT scan of the hip region. These data and then processed by an expert bioengineer, and a full probabilistic prediction can be provided, using a medium-sized cluster, in a few hours. Again, it is possible to produce a standardised patient report on a next-day basis.

Before the methods describe here can be adopted on at large-scale in the clinical settings, we need to address two problems. The first, which is a pure engineering and organisational problem, is to automate and streamline the protocols so that they can be used on dozen of patients per day. There is nothing conceptual here; it is just a matter of continuous improvement of the methods currently available. The second problem is instead more substantial: before such methods can be adopted, we need to produce data that convincingly show their efficacy. This cannot be limited to research validation experiments, but needs full-blown clinical trials, where the clinical efficacy of these simulation-based technologies is reliably quantified, and it is made clear in which cases the increase in cost and complexity these methods involve are justifiable form a cost-benefit ratio perspective.

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