DEVELOPMENT OF A MARKOV CHAIN MONTE CARLO ALGORITHM TO PREDICT HIP FRACTURES IN POSTMENOPAUSAL WOMEN

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Introduction

Fragility hip fractures associated with osteoporosis (OP) represent a significant social burden as they lead to reduced quality of life, high mortality (17-32%) and healthcare costs. These injuries are particularly common in postmenopausal women [1].
Intervention clinical trials for the development of OP treatments are associated with high costs due to the need for large sample sizes and lengthy follow-up periods. Therefore, there is a need for more efficient methods to evaluate the effectiveness of OP interventions, and computational models could be used to improve drug development (In Silico Clinical Trials) (ISCT).
Finite Element (FE) models of the femur have been extensively validated for the prediction of failure load in a sideway-fall configuration [2] and can be applied in this framework.
The aim of this study was to develop an ISCT method based on a Markov Chain Monte Carlo algorithm to simulate clinical trials for OP treatments and predict fracture incidence in a virtual cohort.

Materials and methods

1089 virtual patients were generated by sampling a statistical atlas obtained from a set of 94 subject-specific CT-based proximal femur FE models of post-menopausal women [3]. Baseline characteristics matched the population recruited in a previous clinical trial [4] (aBMD = 0.722 ± 0.096 g/cm^2). The synthetic models consisted of quadratic tetrahedral elements (average mesh size = 3 mm) with isotropic linear elastic material properties.
At each simulated follow up year, 3 in total, the occurrence of falls was randomly determined from the probability density function of falls in the population of interest [5]. For each fall, impact direction is determined stochastically from the relative probability distribution. Failure load in the corresponding direction is obtained using a well-established FE procedure [2].
The impact force associated with each fall is obtained stochastically with a multiscale model, considering subject-specific height and weight, attenuation parameters and kinematic of fall [6]. We assumed the effect of muscle co-contraction was negligible due to the increased reaction time associated with aging [7].
At each fall, if impact load exceeds the failure load, a patient is considered fractured and excluded from the virtual cohort.

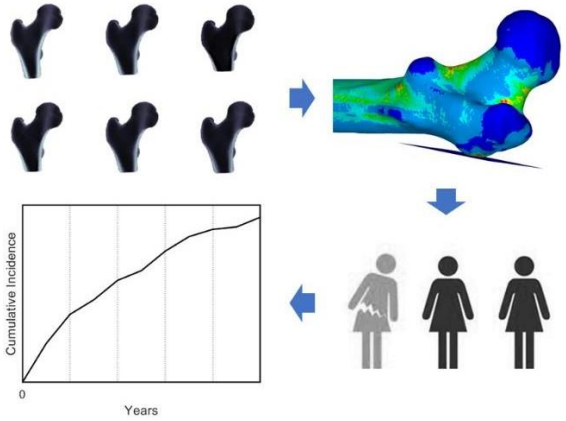

Figure 1: Workflow of the Markov Chain Monte Carlo algorithm.

Results

Preliminary results showed that in 3 years of simulated follow up, 37 of hip fractures occurred among the cohort, which is in the same order, although slightly overestimating) with data reported for the placebo group of a concluded clinical trial, where a total of 14 hip fractures was reported [4].

Discussion

The present study shows the ability of this Markov Chain Monte Carlo algorithm to predict the number of hip fractures as consequence of falls in a population of postmenopausal women. Future work will be focused on calibration of the stochastic parameters to reproduce the specific features of the population of interest, and on validation of the model using clinical data. The potential of In *Silico Clinical Trials* is to improve time- and cost-effectiveness of the drug development process.

References

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