CT2S: QCT-based Strength prediction service

Scientific background

The primary function of the human skeleton is biomechanical in nature (support, protection, etc.); thus, its ability to sustain mechanical loading without substantial damage (hereinafter referred to as *strength*) is a biomarker of primary importance in a large part of related clinical research. Unfortunately, mechanical strength can be measured directly only invasively and only destructively; thus, we can measure the strength of bones only *ex vivo*, from bone dissected from cadavers. For this reason, in most clinical studies that have bone strength (or related indicators such as risk of bone fracture) as an end point, surrogate biomarkers provided by medical imaging modalities are used instead. The most common are those that measure the average Bone Mineral Density (BMD) over a given region, either areal (aBMD, provided by DXA), or volumetric (vBMD, provided by QCT). However, while the BMD is strongly correlated to the bone strength, it is a poor *predictor* of bone strength, typically with accuracies of 75% or lower (Cody et al., 1999; Dragomir-Daescu et al., 2011; Srinivasan et al., 2012).

Since strength is a mechanical property, regulated by well-established physical laws, in principle it should be possible to build computational models based on such laws that accurately predict for each subject the biomechanical strength of each bone in their skeleton. Prof Marco Viceconti has worked to the development of such technique since 1998. He proposed the first CT scan sequence specifically optimised for 3D reconstruction of the femur (Zannoni et al., 1998), its segmentation to extract the bone geometry (Viceconti et al., 1998), the early techniques to derive from the segmentation accurate finite element meshes (Viceconti et al., 1998), and the first implementation of the *Bonemat* algorithm to map the heterogeneous tissue properties as derived from the CT images onto the finite element mesh (Zannoni et al., 1998). He then worked extensively on the use of DXA images to predict bone strength (Testi et al., 1999; Testi et al., 2001; Testi et al., 2001; Testi et al., 2002; Testi et al., 2004), reaching the conclusion that only CT-based models could provide the necessary accuracy (Viceconti et al., 2004). Interestingly, a recent re-visitation of this approach, using state-of-the-art DXA technologies reached similar conclusions (Dall'Ara et al., 2016).

Using human bones dissected fresh from cadavers Prof Viceconti's team developed a robust experimental set-up to validate the predictive accuracy of these subject-specific CT-based computer models (Taddei et al., 2006; Cristofolini et al., 2007). The first validation study published in 2007, reported an error of 40% (Taddei et al., 2006); refining the methods we reached in a few years a predictive accuracy of 95% or better (Schileo et al., 2007; Schileo et al., 2008; Schileo et al., 2008; Juszczyk et al., 2011; Grassi et al., 2012; Schileo et al., 2014; Zani et al., 2015) both under stance and side fall loading conditions.

Once validated this method has been used to investigate the biomechanical possibility of spontaneous fractures (Viceconti et al., 2012), the safety factor of the femur during level waking (Taddei et al., 2014), the bending strength of infant femurs (Li et al., 2015), and the effect of laterality on femoral strength (Taddei et al., 2016). In all these cases this subject-specific CT-based modelling method provided an accurate, robust and reproducible estimate of bone strength from imaging data, which made these physiology research studies possible.

In 2014 we demonstrated that using the method to estimate the minimum femoral strength under physiological (hereinafter called Minimum Stance Strength, or MSS), and pathological (hereinafter called Minimum Fall Strength, or MSF) could accurately predict the risk of femoral neck fracture in a small cohort of osteoporotic women (Falcinelli et al., 2014). In 2016 we confirmed these conclusions on a much larger cohort of 100 women (Qasim et al., 2016); in this retrospective cohort the MSS biomarker was able to correctly identify fractured and non-fractured women only form their CT data, with an accuracy of 79% (Qasim et al., 2016).

Recently, we have further improved the MSS prediction, which now classify the same cohort with an accuracy of 83% (Ak Al Tai Z, *et al.* 2017; in preparation). Also, we demonstrated that the MSS biomarker is much more robust than other clinical biomarkers such as aBMD; when we restrict the analysis to

"difficult" patients, those with T-score between -1.0 and -2.5, aBMD accuracy is only 60%, while MSS accuracy remains 75% (Qasim M, *et al.* 2017; in preparation).

While the MSS biomarker is clearly superior to any other available clinical biomarker in estimating the bone strength of a subject non-invasively, the derivation of this biomarker from CT data require a fairly sophisticated set of proprietary software tools and specifically trained operators, which only our institute can provide. In order to make this biomarker widely available, we are now offering the prediction of MSS from CT data as an on-line service accessible by any clinical research team in the world. This service, denominated "CT to Strength" or CT2S for short, makes possible to return within 48 hours an accurate prediction of the subject strength from a properly calibrated CT dataset that is uploaded to our on-line service. This document gives a brief description of the process.

Data generation

The most important factor in the achievement of high predictive accuracy is the appropriateness of the medical imaging protocol used. In this situation the CT system is not used to generate pictures that the radiologist has to interpret, but as a measurement machine, whose outputs are processed quantitatively. For this reason, the radiological protocol we propose (see annex #1) must be respected rigorously and the first step in our modelling process involves an inspection of the CT data; we reserve the right to reject any case where the CT data were not collected following our recommended radiological protocol, as the results of the model would be unreliable.

At the outset of the study, one of our experts would visit the clinical site where the CT scan will be performed, meet the radiology team (primarily the radiographers) who will be responsible for scanning the patients, and assist the execution of a full scan on the first patient; the resulting protocol should be stored in the memory of the CT system, so as to ensure that all future patients will be scanned using the same plan. The key elements of this protocol are:

a) Scan covers the full length of the bone plus 2 cm beyond its proximal and distal ends;

b) Current and voltage settings are specified and cannot be changed during the scan (exclusion of automatic current modulation); the voltage is set lower than usual to keep the effective radiation dose within acceptable limits;

c) Pitch, slice thickness and slice spacing are imposed;

d) At the beginning of the study, the European Spine Phantom (QRM, GmbH) should be CT scanned using the same parameters used in the CT protocol for patients. For long studies, the scanning of the European Spine Phantom should be repeated every 12 months, to correct for drifts of the CT system. The images of the phantom should be submitted alongside those of the patients, and will be used to calibrate accurately the mineral content scale of the CT images. Upon request we can perform the first phantom scan during our on-site visit;

We strongly recommend that all scans in a study be performed with the same CT scanner. If this is not possible, then the European Spine Phantom should be scanned on each CT scanner, and for each scan the indication of which CT machine has been used.

Data transmission and handling

The CT data should be stored in digital format following the DICOM Standard. Before submission the DICOM files must be processed with anonymisation software that removes any information that could be used to identify the patient. Clinical studies typically assign a unique ID to each patient; this ID should be used to name the DICOM files, and will be also used by us to report the results of our analysis. The association between the Patient ID number and the actual patient identity should be stored safely behind the hospital firewall, so as to ensure the highest level of confidentiality. Please do not use the NHS Number as patient ID as this can be converted into the patient identity. In order to avoid any liability, the CT data that

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are found upon inspection not properly anonymised will be immediately and permanently delated, and the requesting clinical team informed.

The CT DICOM files should be saved in a single directory and then zipped into a single file, named with the local patient ID, which will be uploaded to one of our secure servers following the detailed instructions that we will provide. The data will be stored safely behind the University of Sheffield firewall, and will be made accessible exclusively to those who need it to provide the requested service.

When you upload the data we will ask you to sign a declaration confirming that you have all the necessary legal and ethical permissions to share these data for research purposes; upon request, we will provide you with pro-forma templates for informed consent that we recommend to include, but the ultimate responsibility for ensuring that you are authorised to collect and give us those data will remain entirely with you.

The DICOM data you provide, all associated metadata, and any link to the PatientID, will be destroyed once our analysis is complete and once the results have been transferred to you. However, in projects that are not commercially sponsored, we ask as a condition for the application of the non-commercial discount the permission to retain all derivative data obtained by the processing and modelling of the original CT image, including voxel level information, for research and service improvement purposes. After the removal of the metadata and the association with the PatientID, such derivative data will completely and fully anonymised, and it will be impossible to relink them to the patient's identity.

Reporting procedure

Once CT data of a patient have been properly uploaded, and have passed our quality check, an expert operator will process them in to a patient-specific model that will be used to generate one or more predictors. Whilst we are happy to discuss *ad hoc* predictors for specific research purposes, for normal clinical studies we recommend two strength predictors:

- Minimum Stance Strength (MSS): this predictor evaluates the strength of the patient's bone under a wide range of loading conditions representing the spectrum of possible loads that act on that bone during daily life, under physiological conditions. The minimal strength is chosen as the predictor value. In retrospective studies, this predictor has been found to classify patients correctly into 'fractured' and 'non-fractured' groups with an accuracy of between 75% and 84% (Falcinelli et al., 2014; Qasim et al., 2016).
- Minimum Fall Strength (MSF): this predictor evaluates the strength of the patient's bone under side-fall loading conditions; a wide range of side-fall events is simulated varying the direction of the fall; the minimum strength is chosen as predictor. In retrospective studies, this predictor has been found to classify patients correctly into 'fractured' and 'non-fractured' groups with an accuracy of between 79% and 89% (Falcinelli et al., 2014; Qasim et al., 2016).

A report, in PDF format, will be sent by email to the person requesting the study; in addition, upon request, our operator can log the strength results directly into your clinical research system (such as OpenClinica).

The typical turnaround time from receipt of usable DICOM data to release of results is 48 hours; however, to provide a contingency to accommodate extraordinary events, we reserve the right to return our report within 60 days. Currently we have the capacity to process about 200 cases per year, but this can be increased upon need.

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