Modelling bone at the tissue scale: the missing link between drug design and clinical outcome

Viceconti, M[1,3], Dall'Ara, E.[2], Li, X.[3], Marzo, A.[3]

[1] Department of Industrial Engineering, Alma Mater Studiorum - University of Bologna

[2] Department of Oncology and Metabolism and Insigneo Institute for in silico Medicine, University of Sheffield

[3] Department Mechanical Engineering and Insigneo Institute for in silico Medicine, University of Sheffield

1. Introduction

The clinical assessment of new drugs against osteoporosis is a particularly expensive one. Ideally a clinical trial should have fragility fractures as primary outcome, and should follow-up patients for at least five years, but this would bring the cost and time-to-market to unacceptable levels. A quick search on https://clinicaltrials.gov shows that Romosozumab, one of the latest drugs brought to market has been studies either with indirect outcome metrics (such as bone density), or at most observing fractures over 24 months. While this is probably adequate for the specific purposes of those trials, the possibility to assess the efficacy of these new drugs with *in silico* trials is of extreme interest.

In the last 20 years computational medicine has developed, in relation to skeletal diseases, on two separate tracks. On one hand, computational pharmacology and systems biology models where able to describe the effect of small molecules on the activity of cell populations [1]; on the others computational biomechanics model were able to capture the physiopathological determinants of the disease progression [2].

There is a disconnection however, at the tissue scale. If we could predict how drug-induced regulation of cellular activity transforms the bone tissue, we could homogenise this at the organ scale and predict whether a new drug is effective in reducing the risk of osteoporotic fracture or not. The main limitations to this research agenda are the scalability of tissue-scale finite element models, and the experimental validation of such models, from a biomechanical and biological point of view.

In the framework of the CompBioMed project, a set of research results have been produced, that address at least in part such limitations, potentially opening the door to *in silico* trials for new bone drugs. These results are summarised, and put in context of developing large scale *in silico* trials of new bone drugs.

2. Scalability of tissue-scale finite element models

Bone tissue-scale finite element models pose considerable problems because of the extreme tortuosity of the tissue geometry at that scale, especially for the most porous regions (cancellous bone). The models are usually generated starting from micro computer tomography (microCT) of a bone tissue specimen; benchtop microCTs can reach resolutions around 10 microns, while synchrotron-light microCT (SnCT) can go down to 0.1 microns of spatial resolution. If we use

the simplest mesh generation process, where all bone voxels are homogenised and then converted into a cartesian mesh (sometime referred to as voxel meshes), the minimum level of homogeneisation for microCT images (four voxels per finite element) would provide an element size of around 20 microns. Such models can typically have around 100-200 million degrees of freedom, and in many cases required a non-linear solution involving 10-20 steps to convergence.

In a previous study [3], we explored the convergence of mesh refinement for these models. Models were solved with MPI implementation of a preconditioned conjugate gradient solver, and the non-linearities handle with a conventional Newton-Raphson scheme. The largest model had 158 million degress of freedom, and the solution required 255 GB of memory and 29 hours over a two nodes, 16 cores Infiniband cluster.

More recently [4], we used automatic segmentation of microCT images and an automated tetrahedral mesh generator to produce 10-node tetrahedral finite element meshes. The largest model had an average element edge size of 11 microns, 275 million degrees of freedom, and was solved in 1.7 hours using 437 GB of memory on an SGI UV-2000 Intel Xeon E5-4650, 2.70 GHz, 104 cores, 1.6TB of RAM, using an OpenMP implementation of a preconditioned conjugate gradient solver.

In our most recent study [5], a model with 962 million degrees of freedom was solved in around two hours and with 311 GB of memory, using the University of Sheffield SHARC HPC system (121 nodes with two Intel Xeon E5-2630 v3 each, for a total of 2024 cores).

The generation of finite element models from SnCT produces models that can exceed the ten billion degrees of freedom, which need to be solved for at least 10-20 iterations. While this calls for much large HPC systems than those used in these previous studies, it appears the solutions of even such larger problems is well within the reach.

3. Biomechanical validation of tissue-scale finite element models

A well known problem in bone tissue computational biomechanics is that until recently no experimental measurments of displacement or strain were available at such small spatial resolution that could be used to validate tissue-scale finite element models. Digital Volume Correlation (DVC) has addressed this limitation. A specimen of bone tissue is scanned with a microCT in its undeformed state, and then again after deformation under a known loading. A 3D image elastic registration algorithm is used to compute the displacement field required to trasform the underfomed 3D image into the deformed 3D image. Such displacement field can then be spatially differentiated to compute strain.

Using a DVC implementation developed at the Insigneo Institute, starting from the ShIRT image registration library [6], we were able to establish a ocomplete validation framework for these tissue-scale models [5], [7].

However, ShIRT was designed to register medical imaging datasets, typically of much lower resolution of microCT or SnCT. This motivated the development, as part of the CompBioMed

project of the pFIRE library[1]. pFIRE is an open source re-implementation of ShIRT that uses the PETSc scientific toolkit[2] to provide a parallelised image registration tool that can scale up to handle very large 3D images. Once its development is completed, a complete workflow could be made available for microCT or SnCT -based modelling of bone tissue and its validation using scalable BoneDVC algorithm based on pFIRE.

4. Biological validation of tissue-scale models

The *in silico* trials scenario we are exploring here would require that the effect of new drugs on specific cell types (as predicted by molecular dynamics and systems biology models) be used to update the initial tissue morphology over time, as measured by the microCT through a model coupled to the tissue-scale finite element model. This bone remodelling model would predict how cellular activity changes the tissue morphology over time, while the finite element models would predict how the biomechanical stimulus that bone cells experience and their activity would change as tissue morphology changes.

How can we validate such models? The best opportunity is offered by murine experimental models, coupled with the use of *in vivo* microCT; the whole process is represented in figure 1.

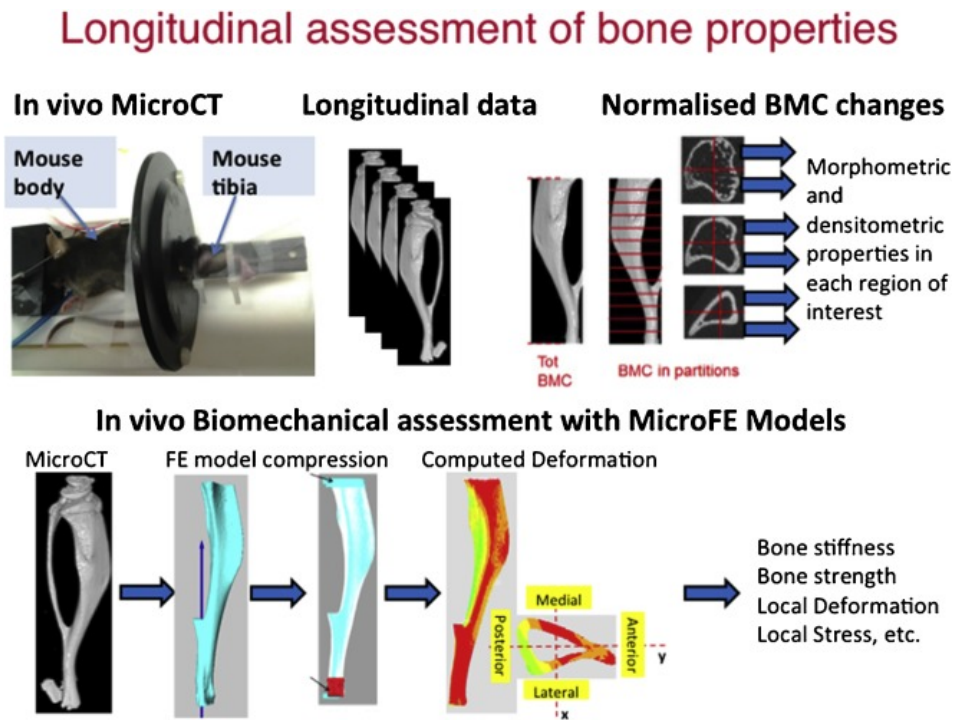

Figure 1 *Top: workflow to assess morphometric, densitometric and mechanical properties of the mouse tibia over time from longitudinal microCT images. The longitudinal microCT data are used to evaluate the change in total bone mineral content (Tot BMC) over time with respect to baseline. Bottom: each microCT image can then be converted into a micro finite element (microFE) model in order to estimate the changes in mechanical properties over time. Reproduced with permission from [8].*

[1] https://github.com/INSIGNEO/pFIRE
[2] https://www.mcs.anl.gov/petsc/

Mice are treated with the new drug or with placebo, and we can observe the longitudinal changes that this induces in their bones using *in vivo* microCT at multiple time points. For each time point, a finite element model of the mouse bone can be built from the microCT data, which can predict the level of biomechanical stimulus at each specific time point. The changes in tissue morphology as predicted by the bone remodelling algorithm can then be validated by comparing them with the microCT measurments at the various time points.
The HPC challenge that emerges from this scenario is that we need to solve a very large Ordinary Differential Equations (ODE) system at each time step which is coupled with the large-scale finite element model. The scalable model to predict mechano-regulated bone adaptation is one of the target of the CompBioMed2 project, that will start in October 2019.

5. Conclusions

The scalability work that has been done in the framework of the CompBioMed project on the solution of tissue-scale finite element models, and the elastic registration of high-resolution microCT and SnCT images is finally enabling the development of complete computational workflow to generate, solve and validate tissue-scale models able to predict the biomechanics and the mechano-biology. The last element, the ODE-PDE coupled models we plan to port to HPC architectures during the CompBioMed2 project should complete this long-term research project.

6. References

[1] S. Scheiner, P. Pivonka, D. W. Smith, C. R. Dunstan, and C. Hellmich, "Mathematical modeling of postmenopausal osteoporosis and its treatment by the anti-catabolic drug denosumab," *Int J Numer Method Biomed Eng*, vol. 30, no. 1, pp. 1–27, Jan. 2014.

[2] P. Bhattacharya, Z. Altai, M. Qasim, and M. Viceconti, "A multiscale model to predict current absolute risk of femoral fracture in a postmenopausal population," *Biomech Model Mechanobiol*, vol. 18, no. 2, pp. 301–318, Apr. 2019.

[3] Y. Chen, M. Pani, F. Taddei, C. Mazza, X. Li, and M. Viceconti, "Large-scale finite element analysis of human cancellous bone tissue micro computer tomography data: a convergence study," *Journal of biomechanical engineering*, vol. 136, no. 10, p. 101013, Oct. 2014.

[4] Y. Chen, "Verification and validation of MicroCT-based finite element models of bone tissue biomechanics," PhD thesis, University of Sheffield, UK, 2016.

[5] M. C. Costa, G. Tozzi, L. Cristofolini, V. Danesi, M. Viceconti, and E. Dall'Ara, "Micro Finite Element models of the vertebral body: Validation of local displacement predictions," *PLoS One*, vol. 12, no. 7, p. e0180151, 2017.

[6] D. C. Barber and D. R. Hose, "Automatic segmentation of medical images using image registration: diagnostic and simulation applications," *Journal of Medical Engineering & Technology*, vol. 29, no. 2, pp. 53–63, Jan. 2005.

[7] Y. Chen *et al.*, "Micro-CT based finite element models of cancellous bone predict accurately displacement once the boundary condition is well replicated: A validation study," *J Mech Behav Biomed Mater*, vol. 65, pp. 644–651, Jan. 2017.

[8] M. Viceconti and E. Dall'Ara, "From bed to bench: How in silico medicine can help ageing research," *Mech. Ageing Dev.*, vol. 177, pp. 103–108, 2019.