CompBioMed
A Centre of Excellence in Computational Biomedicine

e-Seminar #28

Predicting and preventing bone fractures with HPC

23 November 2022

The e-Seminar will start
at 2pm CET / 1pm GMT

Presenter:
Dr La Mattina
(University of Bologna)

Moderator:
Tim Weaving
(University College London)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823712

INSILICO WORLD

https://insilicoworld.slack.com/archives/C0151M02TA4

The e-Seminar series is run in collaboration with:

VPH Institute
Building the Virtual Physiological Human

e-Seminar series

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ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

CompBioMed e-Seminar #28
Nov 23rd, 2022

Predicting and preventing bone fractures with HPC

Antonino A. La Mattina

Outline

- Introduction: osteoporosis and hip fractures
- Digital Twin model development
- Evolutions and derived models
  - In Silico Trials for osteoporosis drugs
  - Integration with neuromuscular control
  - Not only falling femurs
- Conclusions

Osteoporosis

- Pathological bone mass loss and microarchitecture degradation
- Mainly affects postmenopausal women

Image by Blausen Medical on Wikimedia Ccommons

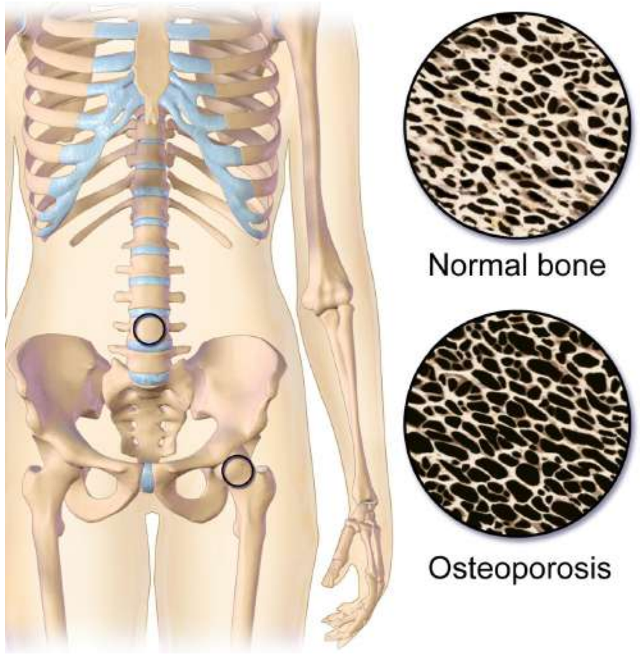


Image by Smart Servier on Wikimedia Commons

Fragility femur fractures

- Fragility fractures at wrist, ankle, ribs, spine, …
- The most catastrophic at femur

Image by iem-student.org on Flickr

Image from Carl Jones on Wikimedia Commons

Social impact

- Every year more than 600 000 hip fragility fractures in EU
  - Every year > 20 billions €
  - 20% die within 12 months
  - Reduced life quality
- 75% are women
- 5% of falls cause fractures
- Not only falls
  - Severe osteoporosis + impaired motion control can cause spontaneous fractures

J. D. Kosy *et al.*, *J Orthopaed Traumatol* **14**, 165–170 (2013)

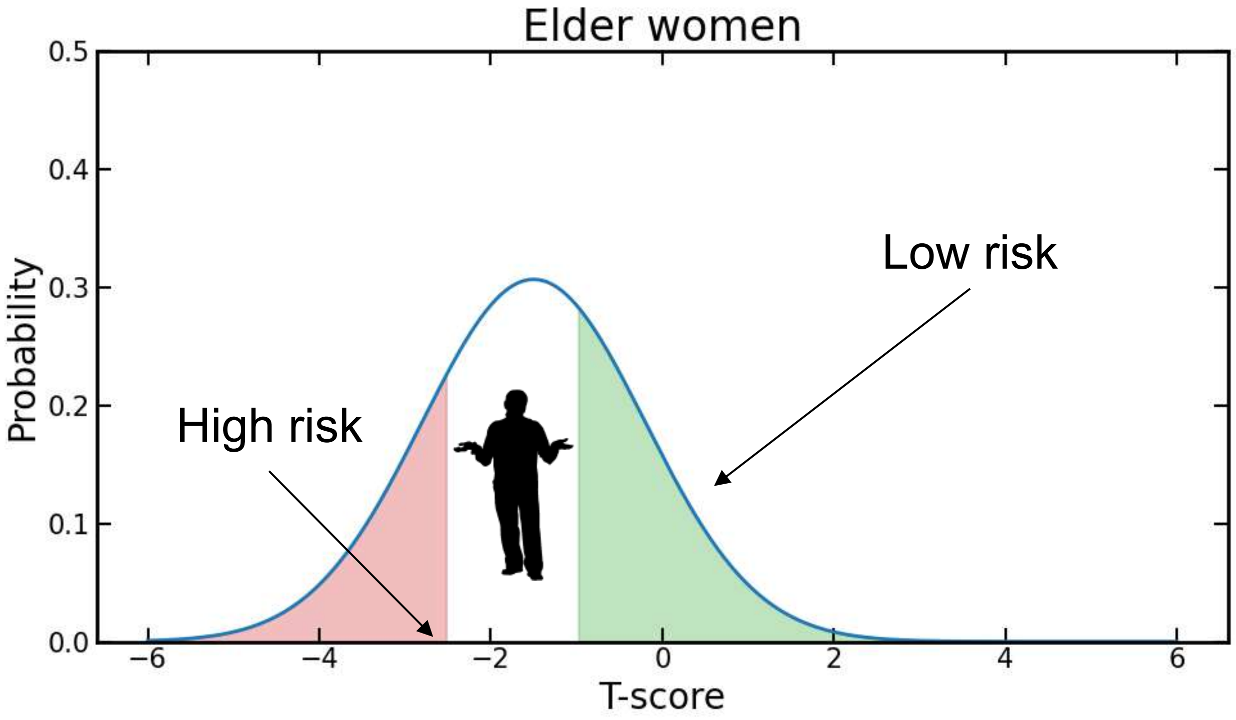
K.-G. Thorngren *et al.*, *Injury* **33**, 1–7 (2002)

F. Borgström *et al.*, *Arch Osteoporos* **15**, 59 (2020)

M. Viceconti *et al.*, *Journal of Biomechanics* **45**, 421–426 (2012)

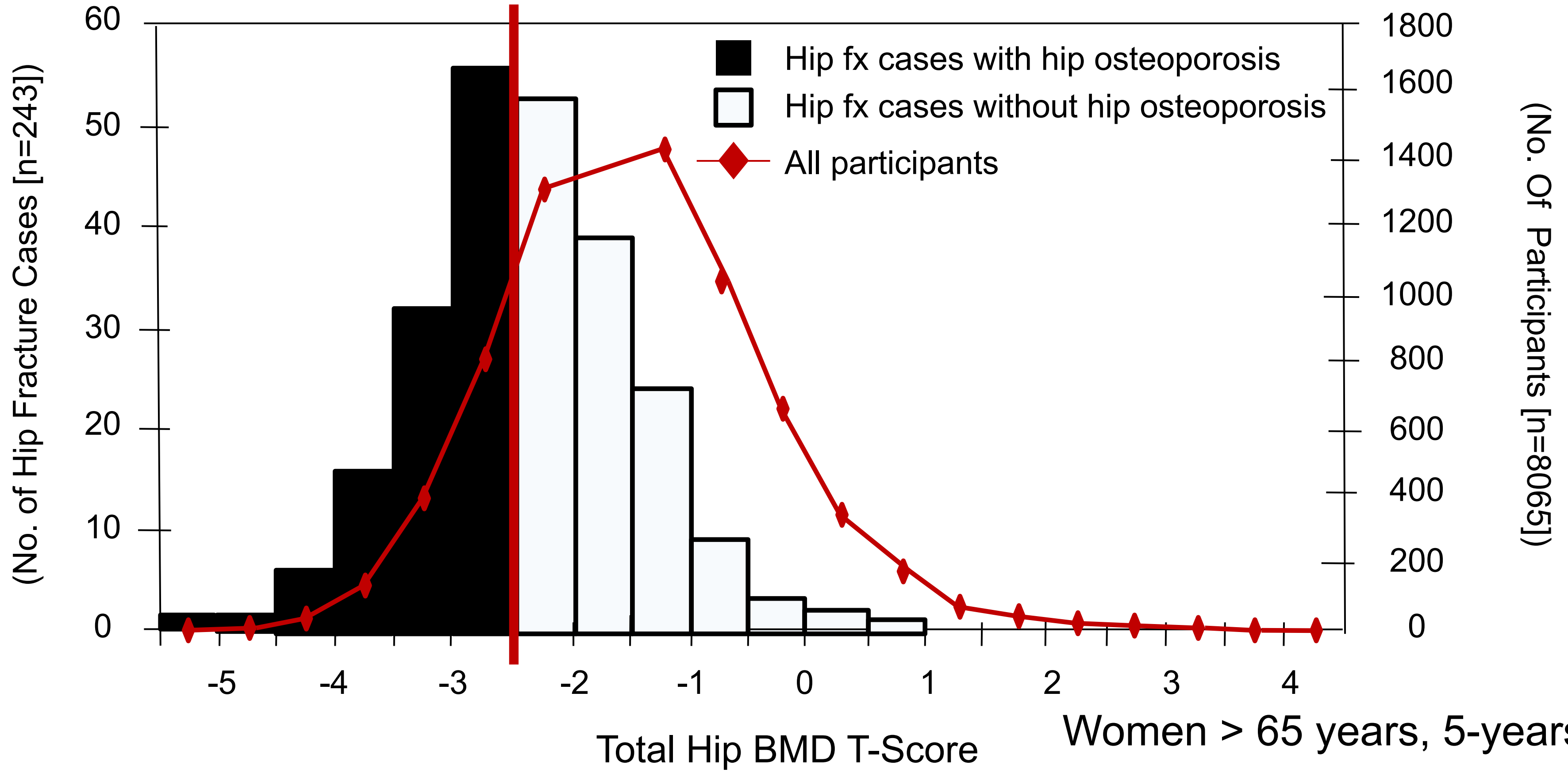
Diagnosis and prediction

- Osteoporosis diagnosis based on bone mineral density measured by dual energy X-ray absorptiometry (DXA)
  - Comparison with healthy young population density (T-score)



Unrecognised fragility

50% of hip fractures in non-osteoporotic subjects

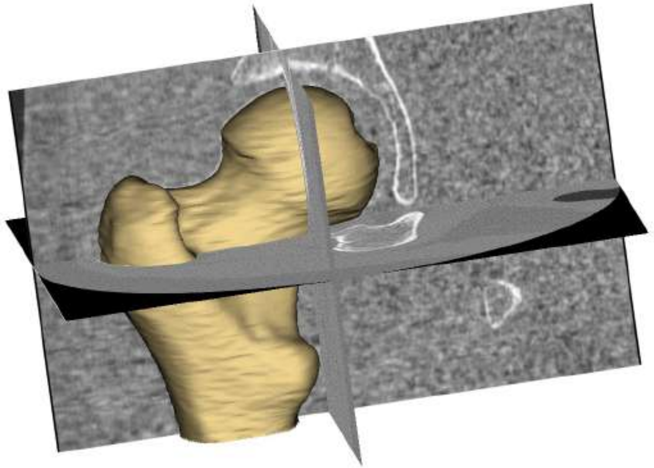
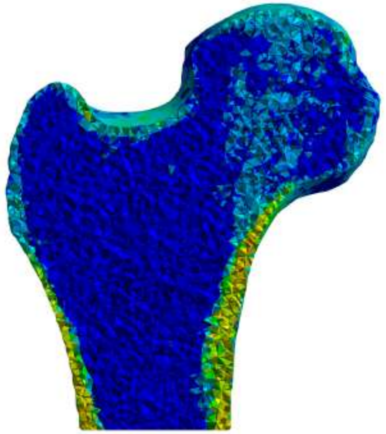
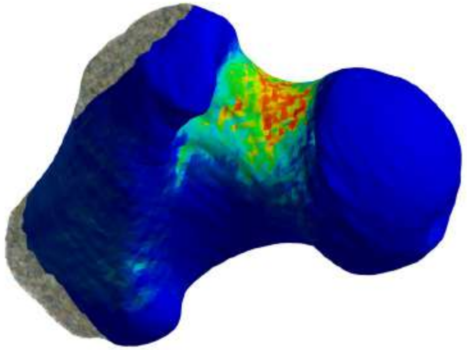


Women > 65 years, 5-years follow-up

S. A. Wainwright *et al.*, *J Clin Endocrinol Metab.* **90**, 2787–2793 (2005)

Digital Twin: QCT-SSFE

- Subject-specific finite element models informed by quantitative computed tomography
  - Bone geometry extraction, local stiffness calculation
- Physics-based, no reference healthy population

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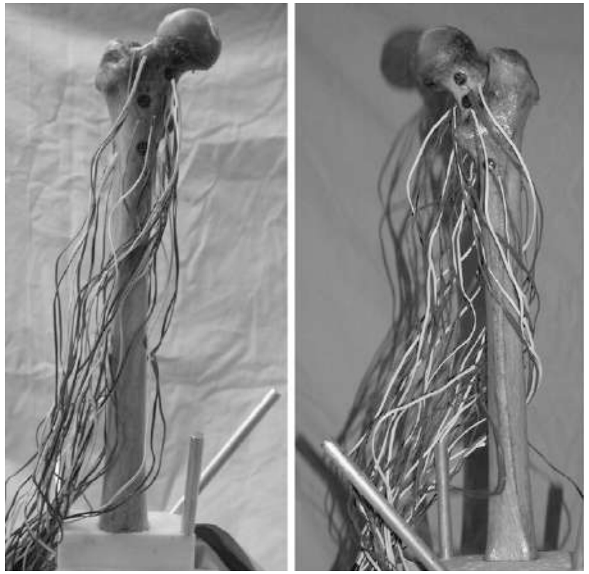
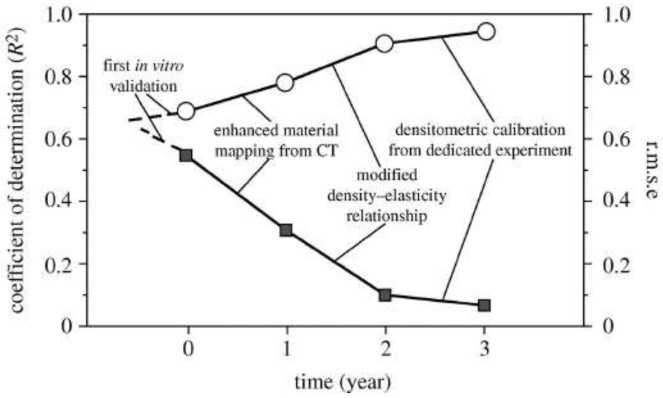
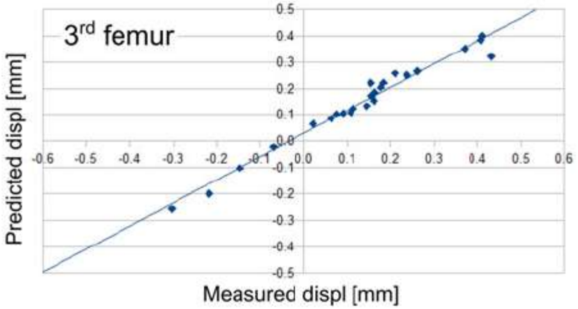
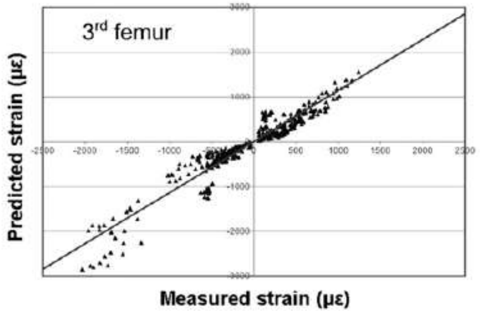
Where we started

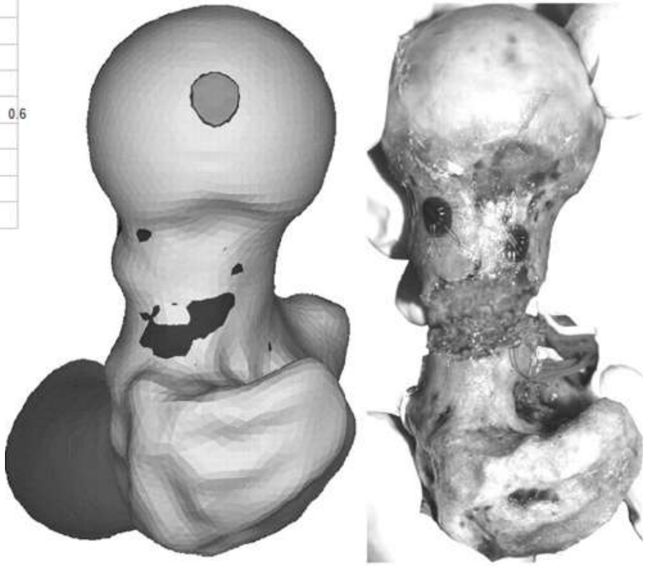
- FE models extensively validated on cadaver femurs
  - Displacement, strain, failure load, fracture position











F. Taddei *et al.*, *Medical Engineering & Physics* **29**, 973–979 (2007)

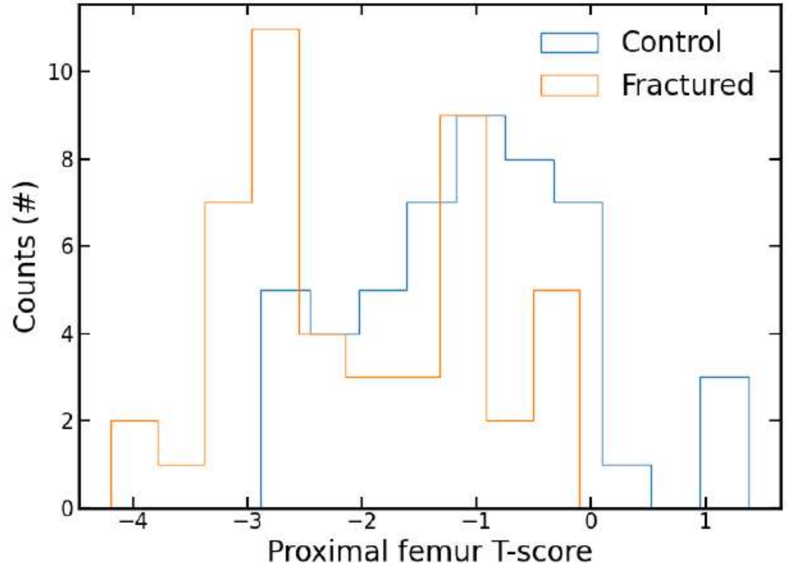
L. Cristofolini *et al.*, *J Biomech* **40**, 2837–2845 (2007)

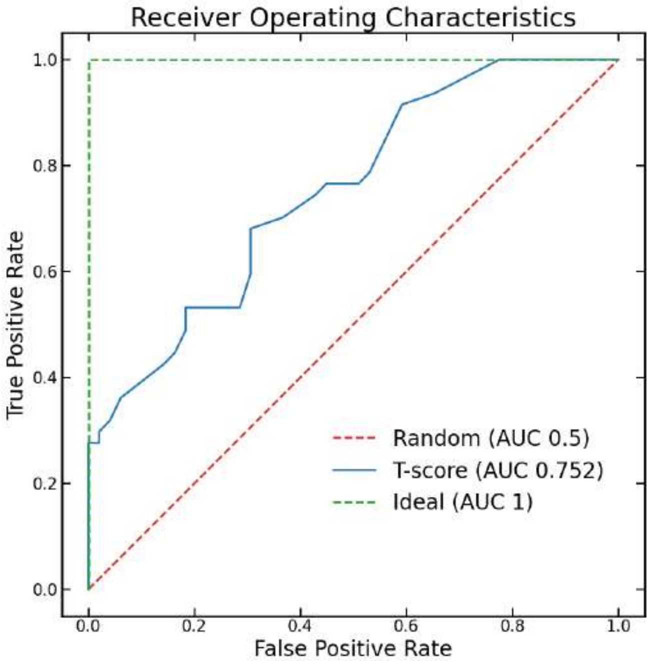
L. Cristofolini *et al.*, *Phil. Trans. R. Soc. A* **368**, 2725–2763 (2010)

L. Grassi *et al.*, *Journal of Biomechanics* **45**, 394–399 (2012)

Sheffield cohort

- Retrospective pair-matched cohort
  - 49 women with proximal femur fracture + 49 non-fractured (at the time of the CT scan) women with same age, height, and weight
- For each patient, DXA and proximal femur QCT scan

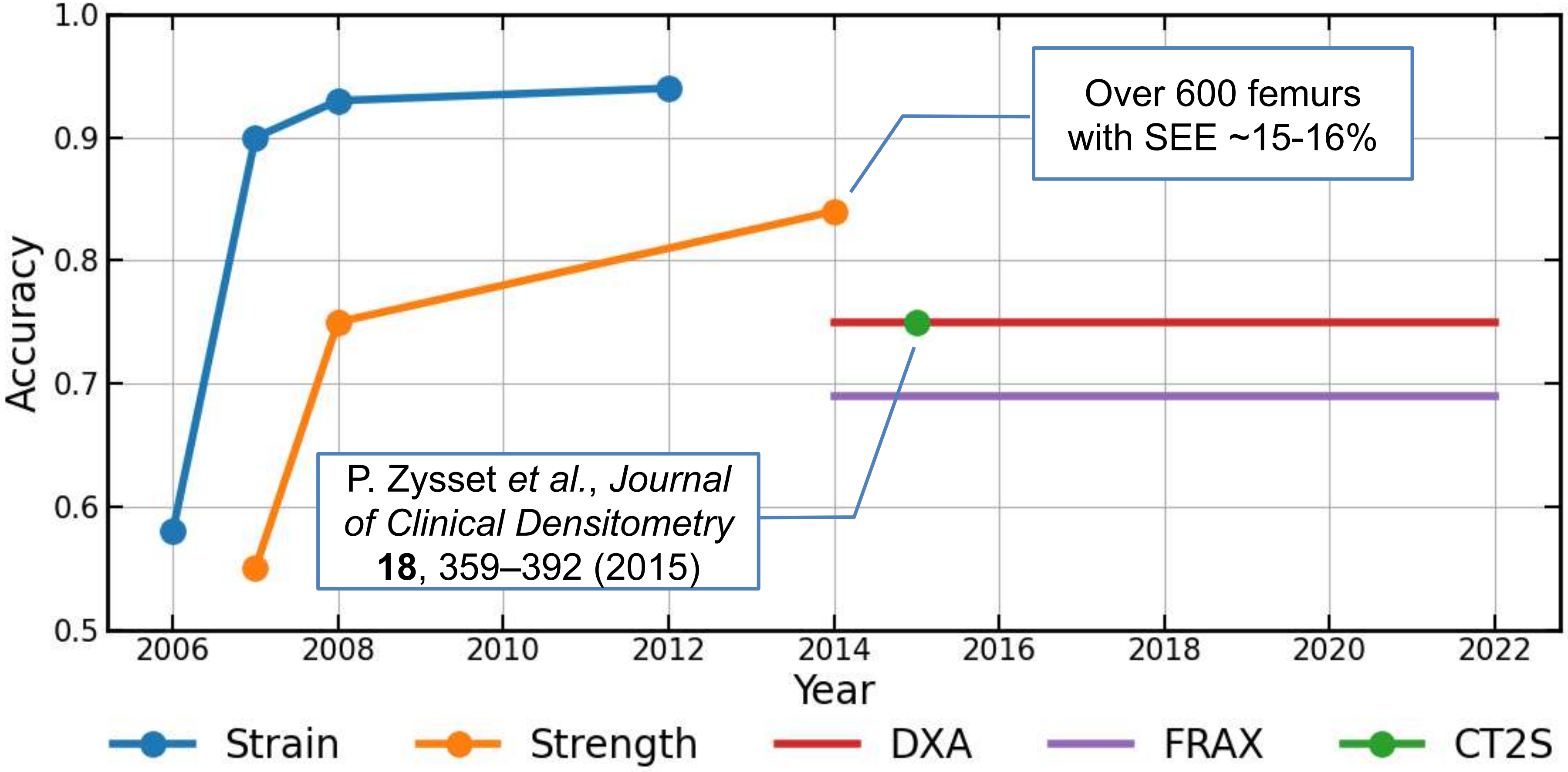




L. Yang *et al.*, *Osteoporos Int* **25**, 251–263 (2014)

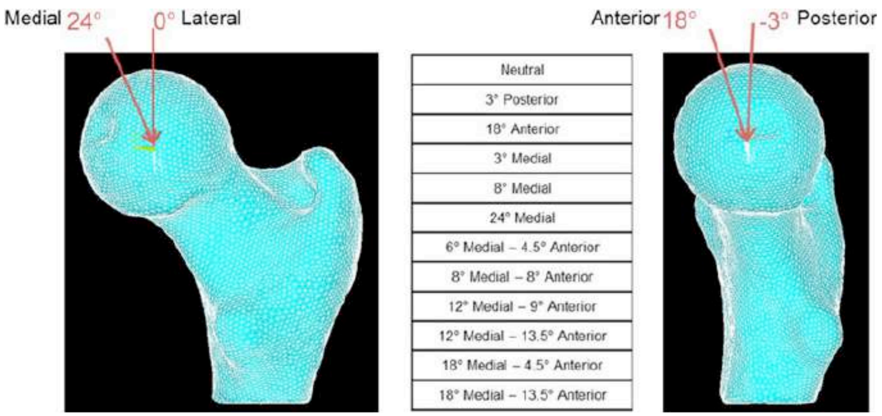
Model accuracy

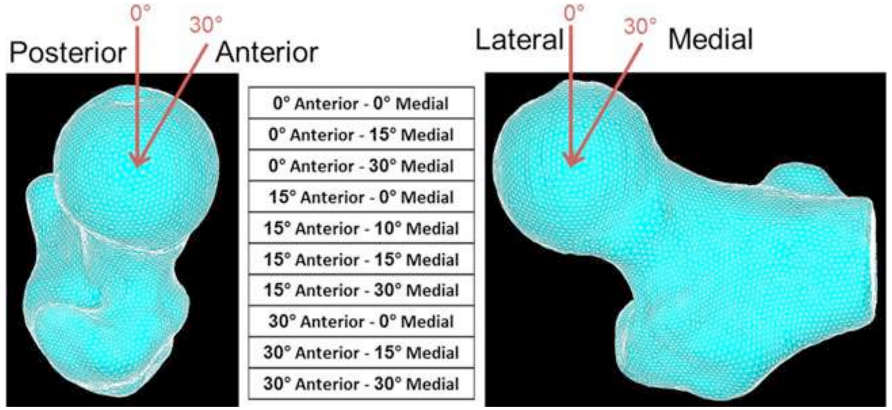
Ex vivo: SEE
In vivo: stratification accuracy of the Sheffield Cohort (AUROC)



Femur orientation and fall angles

- Anatomy atlas to estimate whole femur orientation
- Multiple standing and falling angle simulations

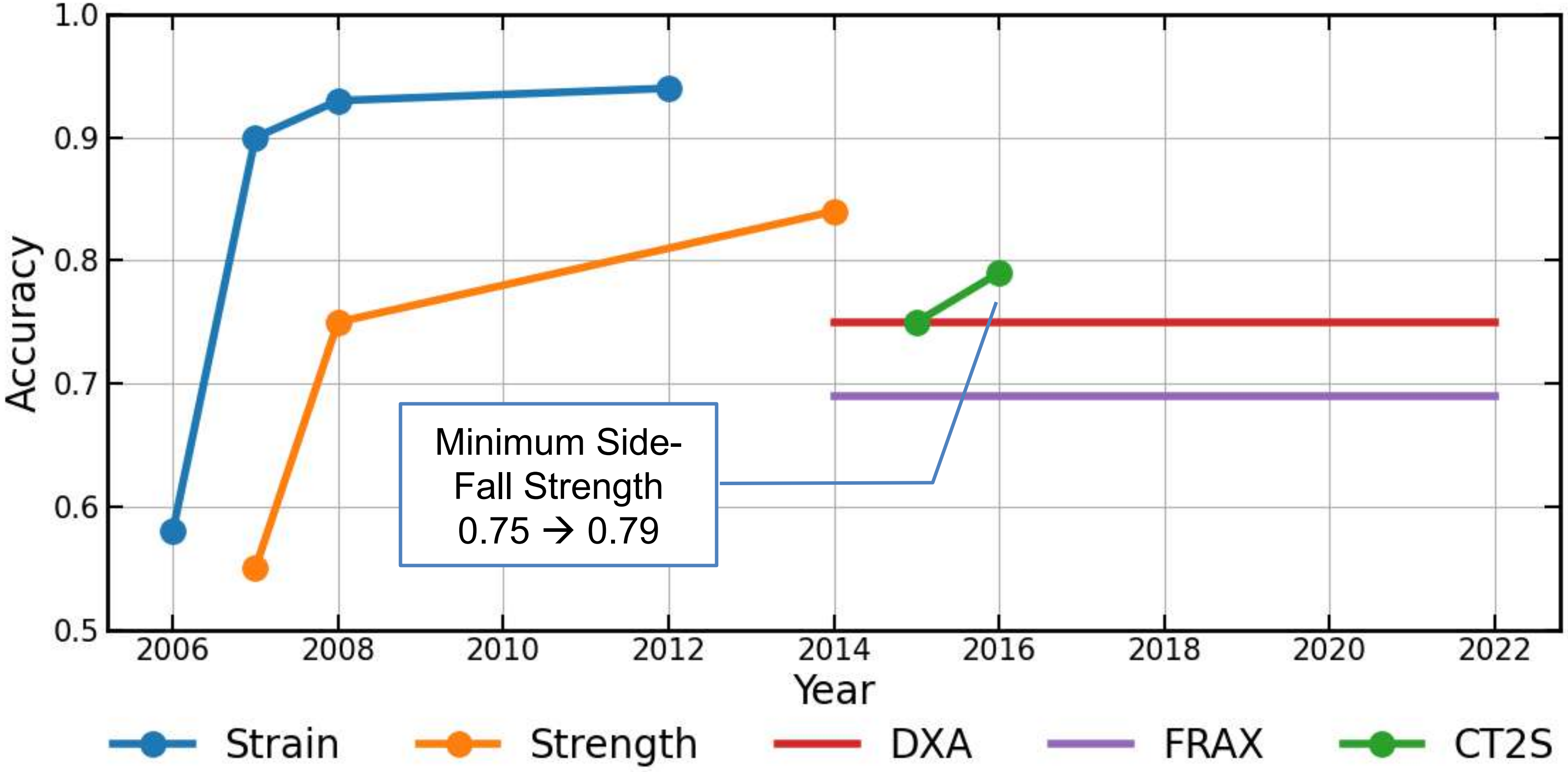




M. Qasim *et al.*, *Osteoporos Int* **27**, 2815–2822 (2016)

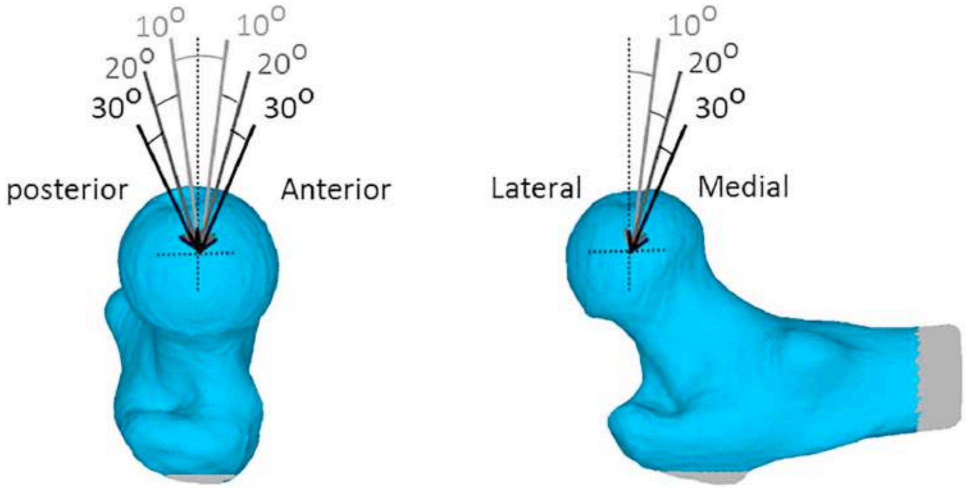
Model accuracy

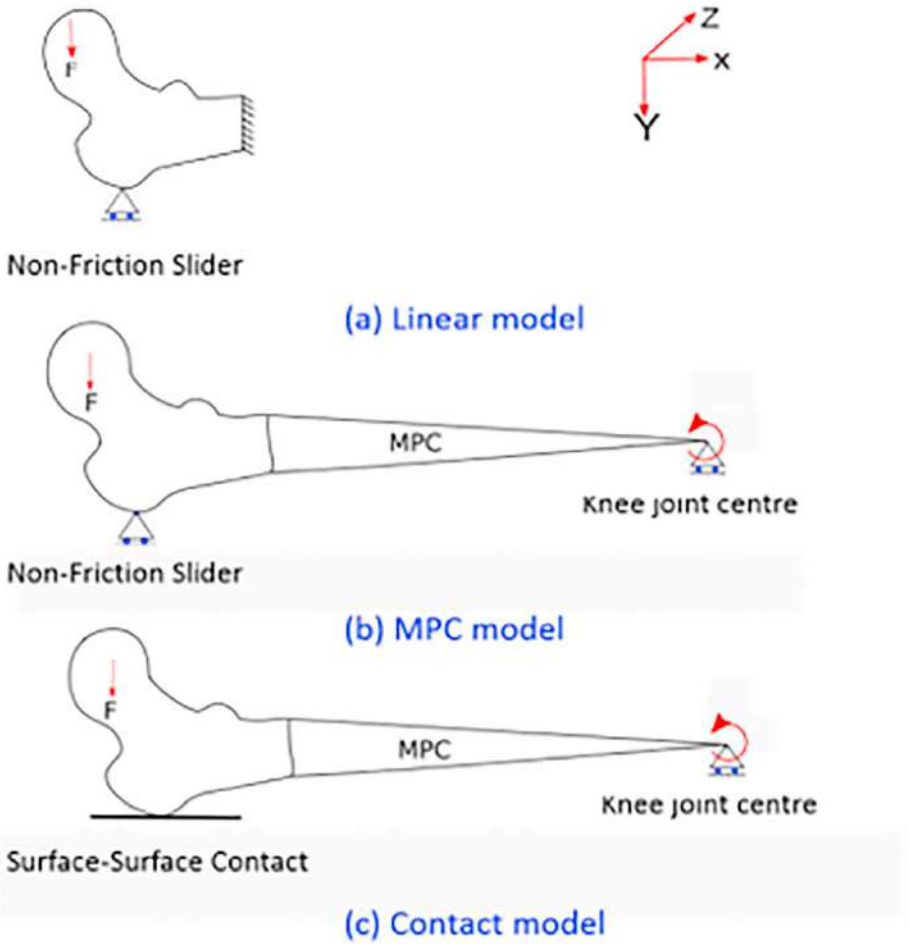
Ex vivo: SEE
In vivo: stratification accuracy of the Sheffield Cohort (AUROC)



Boundary conditions

- Non-linear contact between bone and “floor”
- Wider range of fall angles





Z. Altai *et al.*, *Clinical Biomechanics* **68**, 137–143 (2019)

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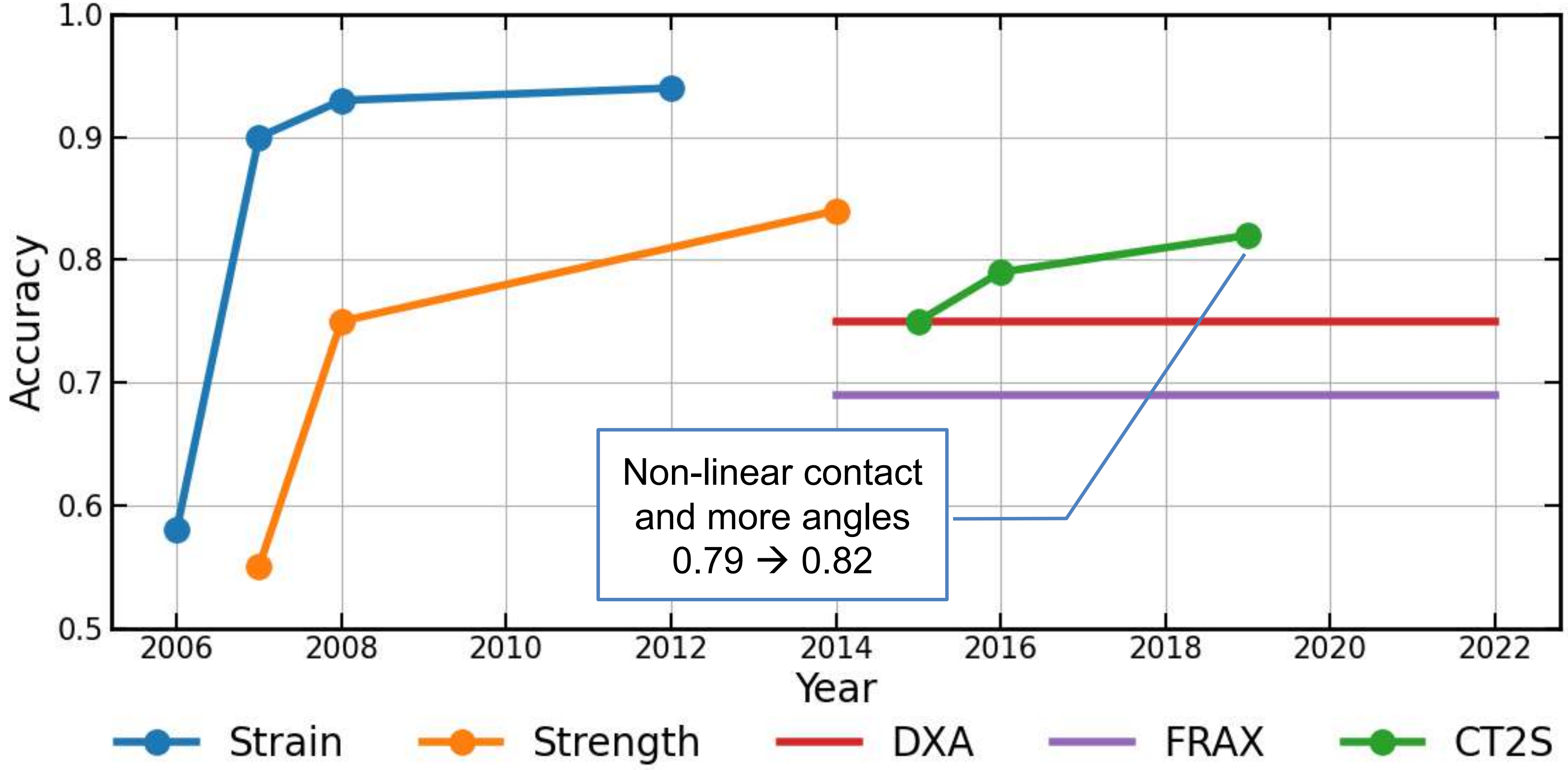
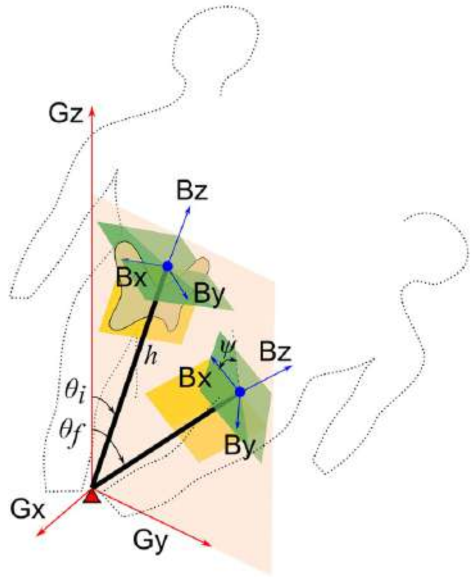
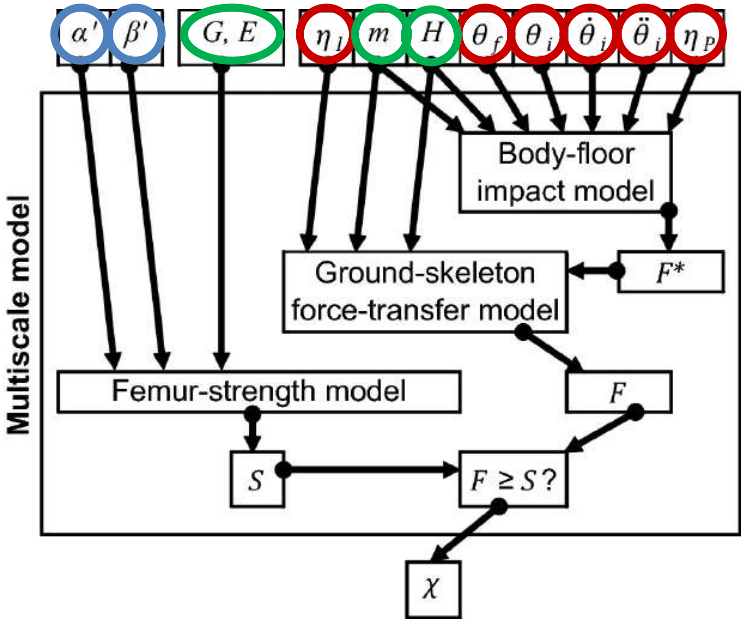
Ex vivo: SEE
In vivo: stratification accuracy of the Sheffield Cohort (AUROC)



Stochastic falling

- Stochastic multiscale patient-specific model to estimate impact force
- Monte Carlo integration of fracture probability





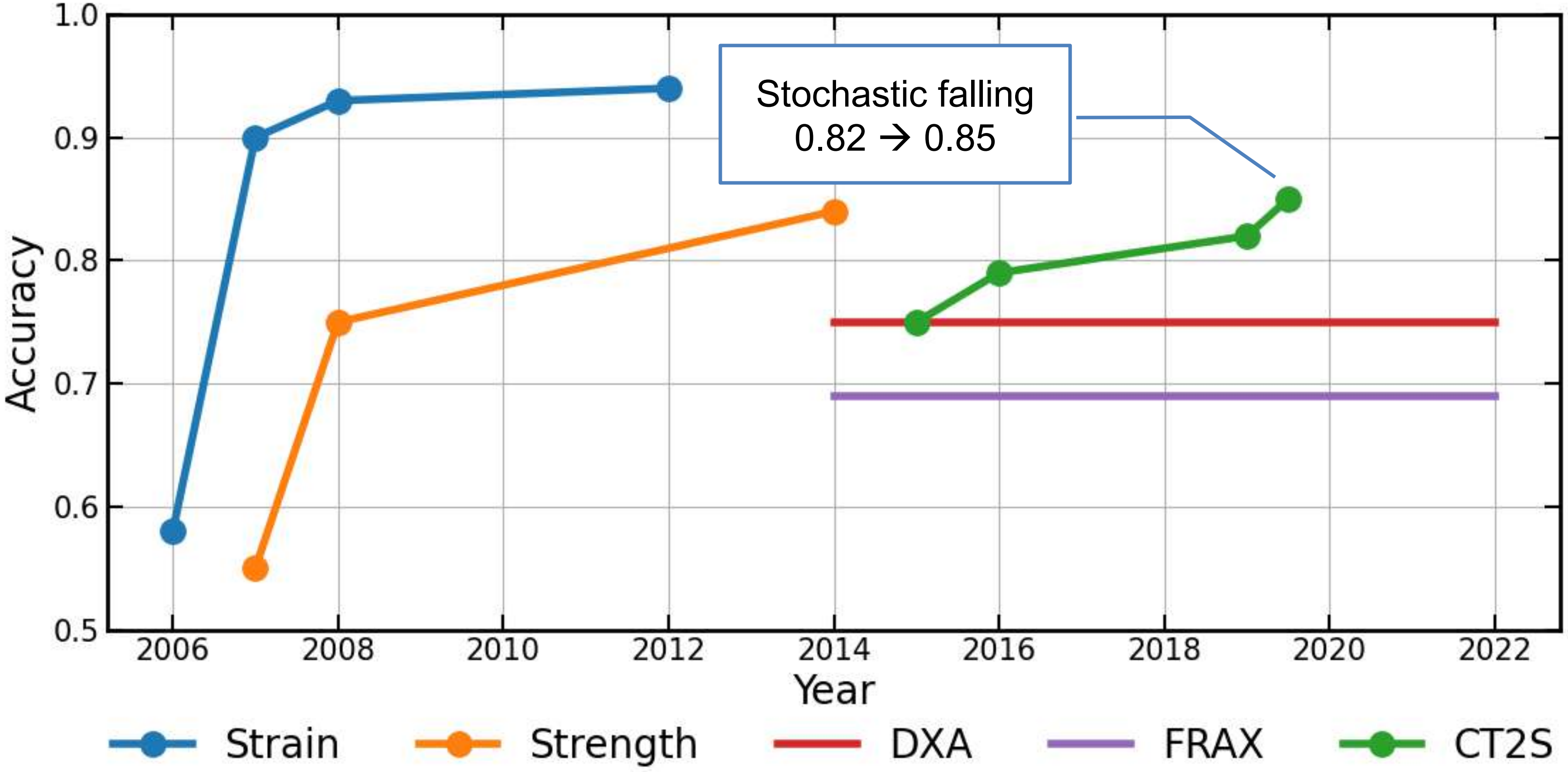
6 stochastic variables +
2 impact force angle

Patient height, weight, and CT scan

P. Bhattacharya *et al.*, *Biomech Model Mechanobiol* **18**, 301–318 (2019)

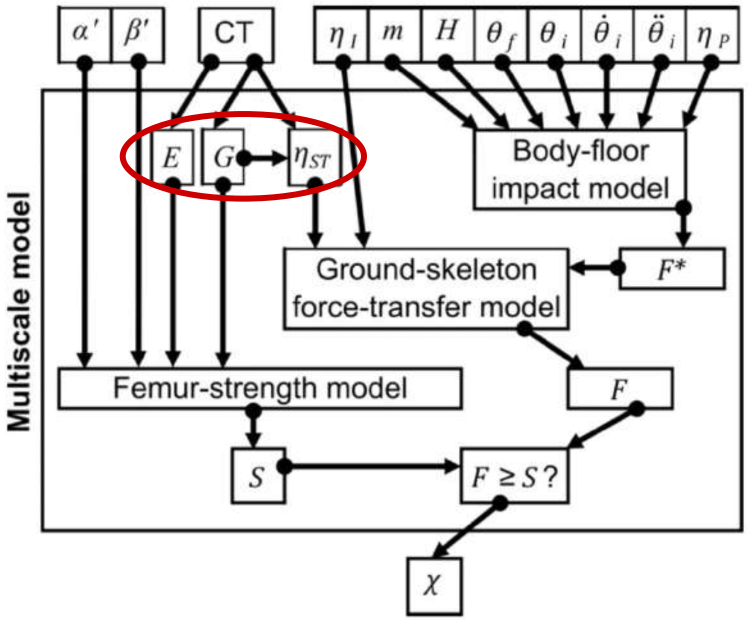
Model accuracy

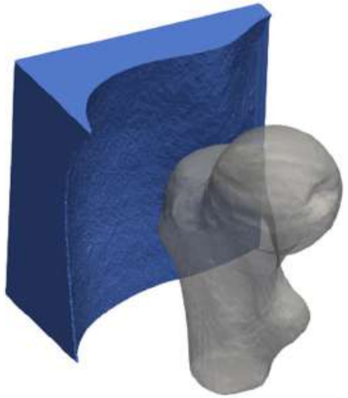
Ex vivo: SEE
In vivo: stratification accuracy of the Sheffield Cohort (AUROC)

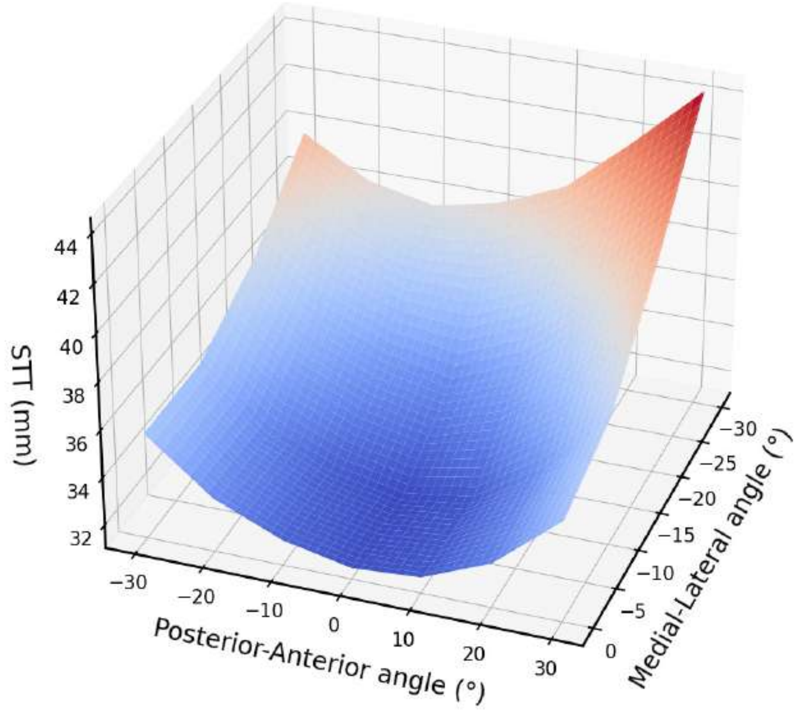


Soft tissue thickness

- Segmentation of patient's hip soft tissues
- Patient-specific angle-dependent damping factor







A. Aldieri *et al.*, *Ann Biomed Eng* **50**, 303–313 (2022)

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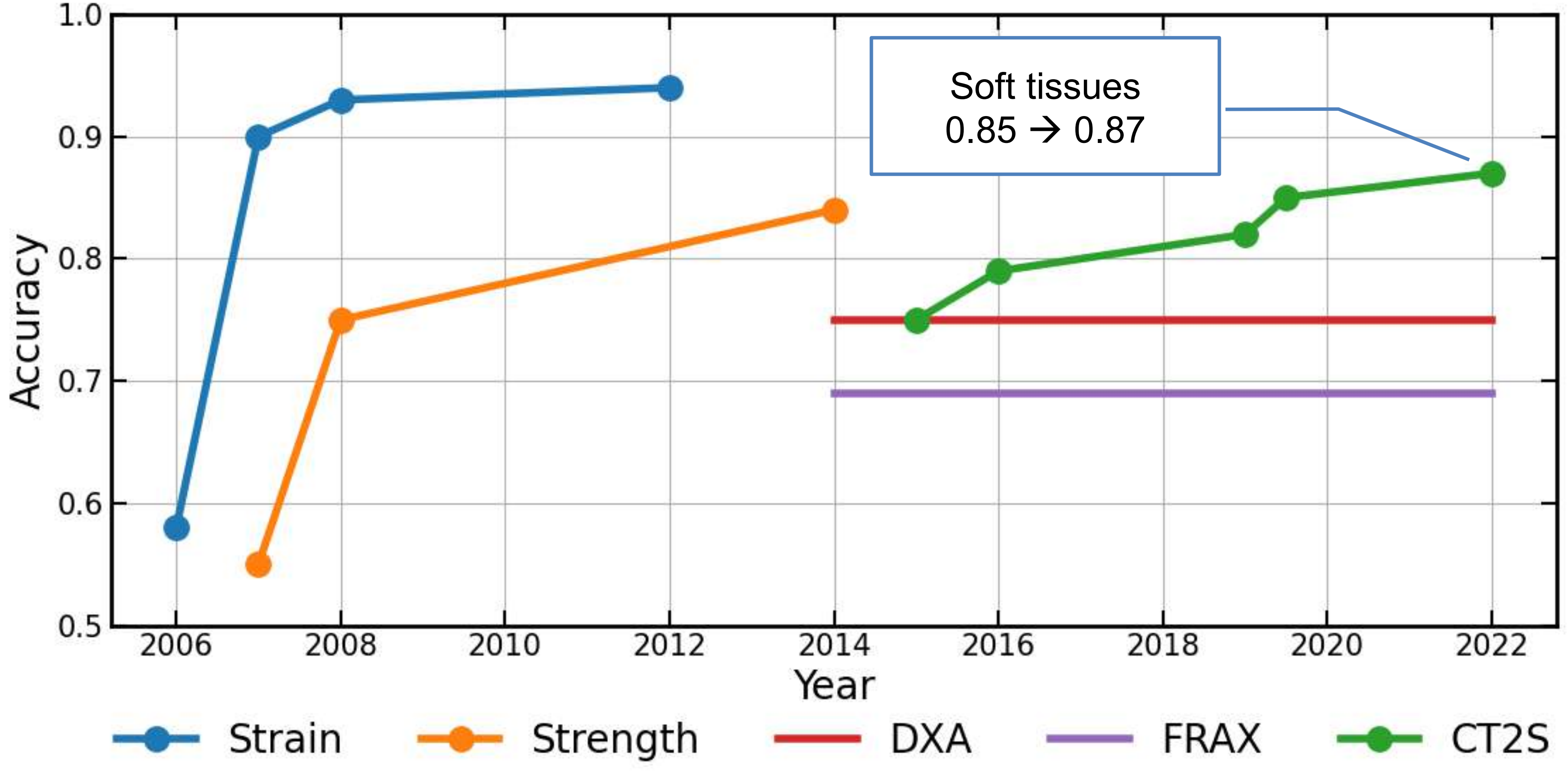
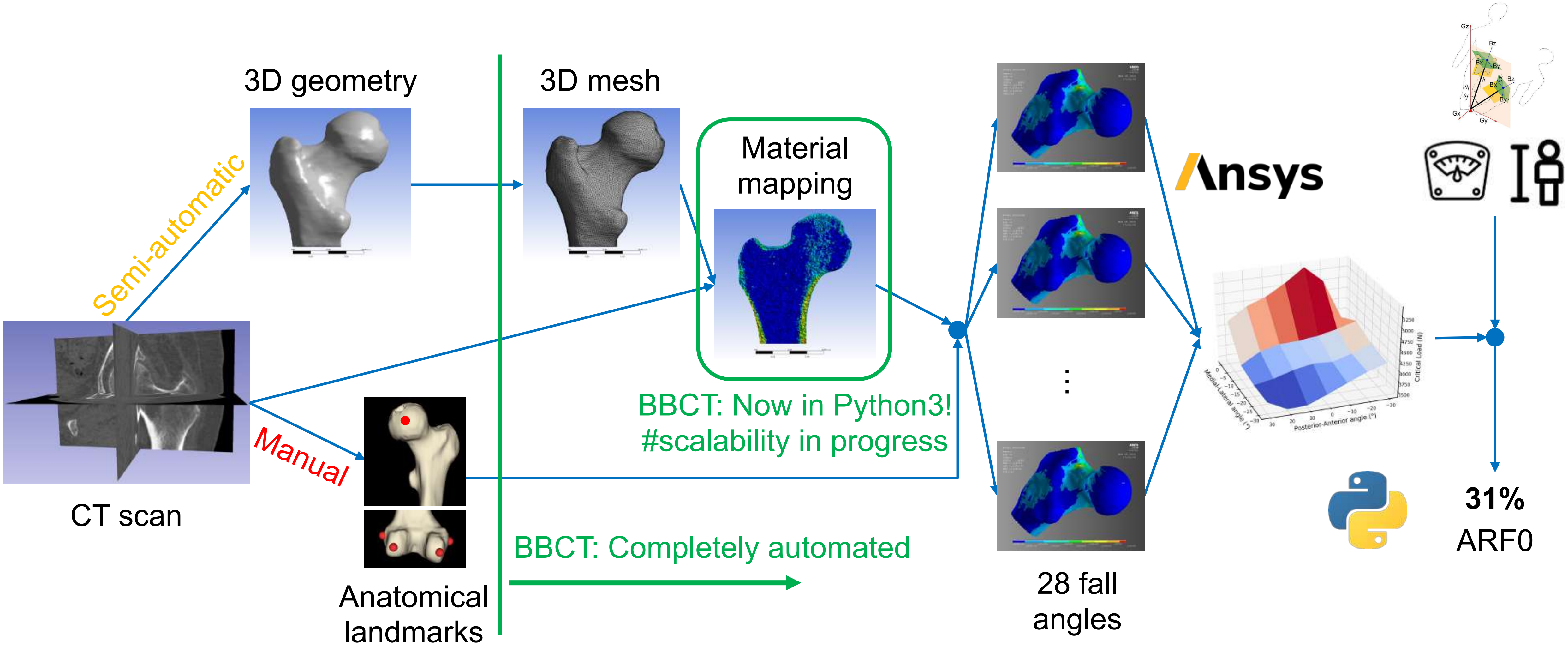


Digital Twin: CT2S and BBCT



~50-100 core-hours per patient

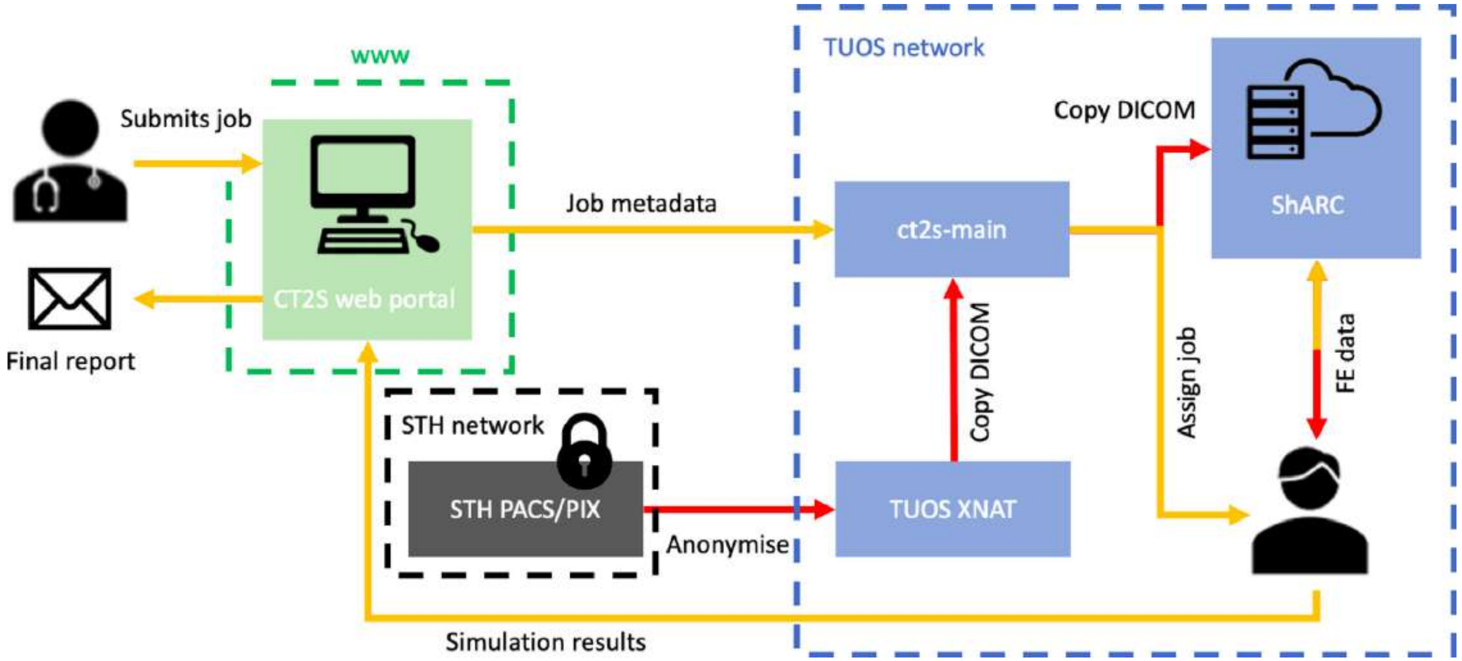
BBCT: validation and EMA QA

- Ongoing workflow validation with Rizzoli cohort
  - 101 women, age ≥ 55 years
  - 4 of them fractured within 5 years after CT scan
  - From *stratification* to *prediction* accuracy

- Requested Qualification Advice to EMA to use BBCT as DXA substitute in clinical trials

CT2S: delivery to clinicians

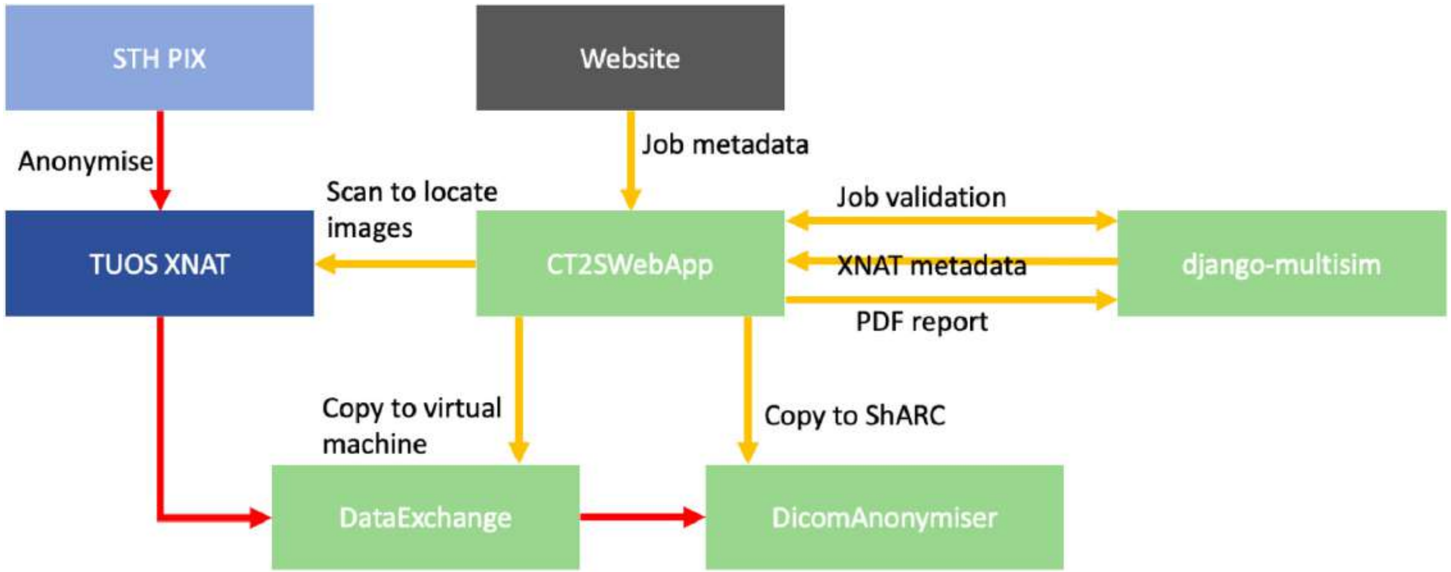
- Simple web interface for clinicians
- Simplified image transfer from hospital PACS
- Manual segmentation and technical supervision



I. Benemerito *et al*., *Comput Methods Programs Biomed* **208**, 106200 (2021)

CT2S: delivery to clinicians

- Background components and data transfer



I. Benemerito *et al*., *Comput Methods Programs Biomed* **208**, 106200 (2021)

CT2S: delivery to clinicians

- Clinician user-experience

Create a new job

Job ref.

Job ref.

Age (years)

Gender

--

Weight (kg)

Height (cm)

Project

Ethnicity

--

Submit

3.5 – 8 h

INSIGNEO Institute for *in silico* Medicine — The University Of Sheffield. — Sheffield Teaching Hospitals NHS Foundation Trust

CT2S: Patient-specific bone strength estimation from QCT data

Insigneo Predictive Medicine Online Services

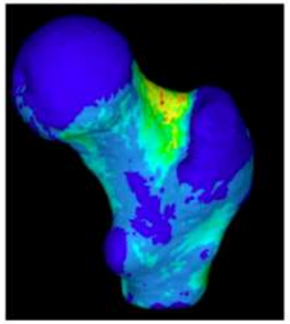
Job No. 125

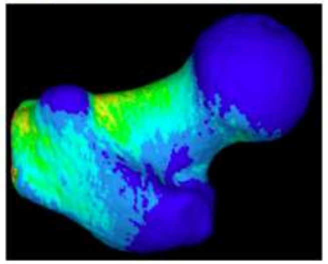
Reference		Materials	
Job Ref.	**001-subj001-reg001**	Patient Scan ID	**Obs001**
Requesting Organisation	**University of Sheffield**	Phantom Scan ID	**ESP001**
Date Submitted	**Jun 19, 2017**		

Results - Stance		Results - Fall	
Femur strength under stance loading		Femur strength under side-fall loading	
Minimum	**4136N***	Minimum	**2658N**
Maximum	**7622N**	Maximum	**4271N**

*strengths are provided in Newtons; a kilogram force is approximately 10 Newtons.

Loading Condition - Stance	Loading Condition - Fall
Picture showing the location of fracture for the loading case with minimum strength.	Picture showing the location of fracture for the loading case with minimum strength.

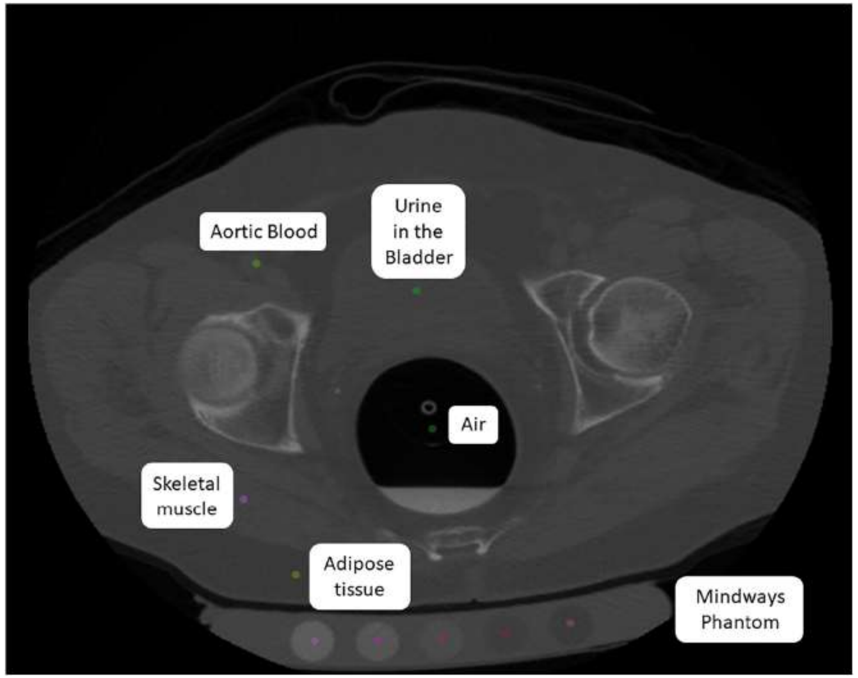




I. Benemerito *et al.*, *Comput Methods Programs Biomed* **208**, 106200 (2021)

Phantomless calibration

- Reference tissues from patient CT scan
  - No need of off-line phantom scan
  - Opportunistic use of pre-existing CT scans



C. Winsor *et al.*, *Bone* **143**, 115759 (2021)

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- Introduction: osteoporosis and hip fractures
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Towards phase III In Silico Trials

- Phase III clinical trials require thousands of patients enrolled and monitored for some years
  - Very expensive and time-consuming
- Simulation of clinical trials could save time and money
  - FE models used to predict hip fractures

- Apply BBCT workflow to the study population (BoneStrength)

What do we need for IST?

Large (virtual) population

Ph. by James Crisland on Flickr

Physiological ageing model

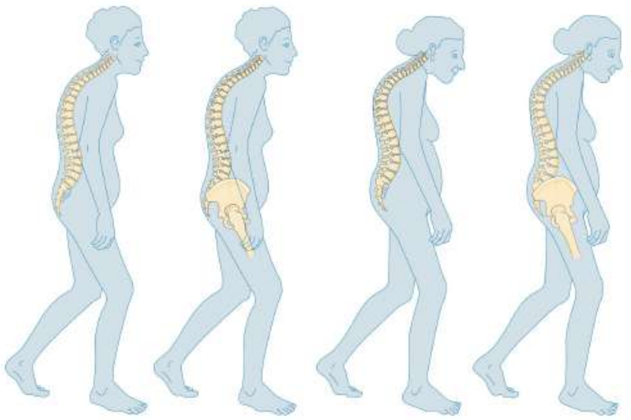
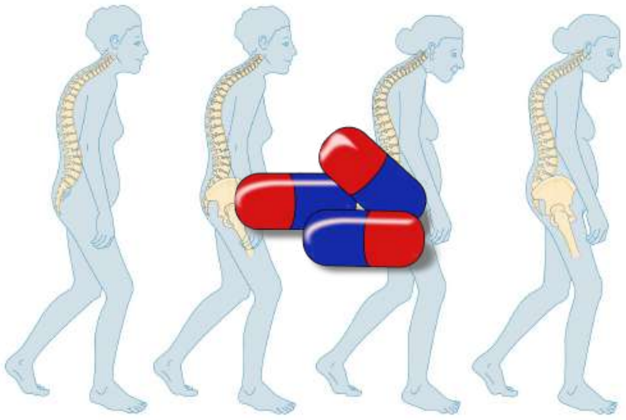


Image by Smart Servier on Wikimedia Commons

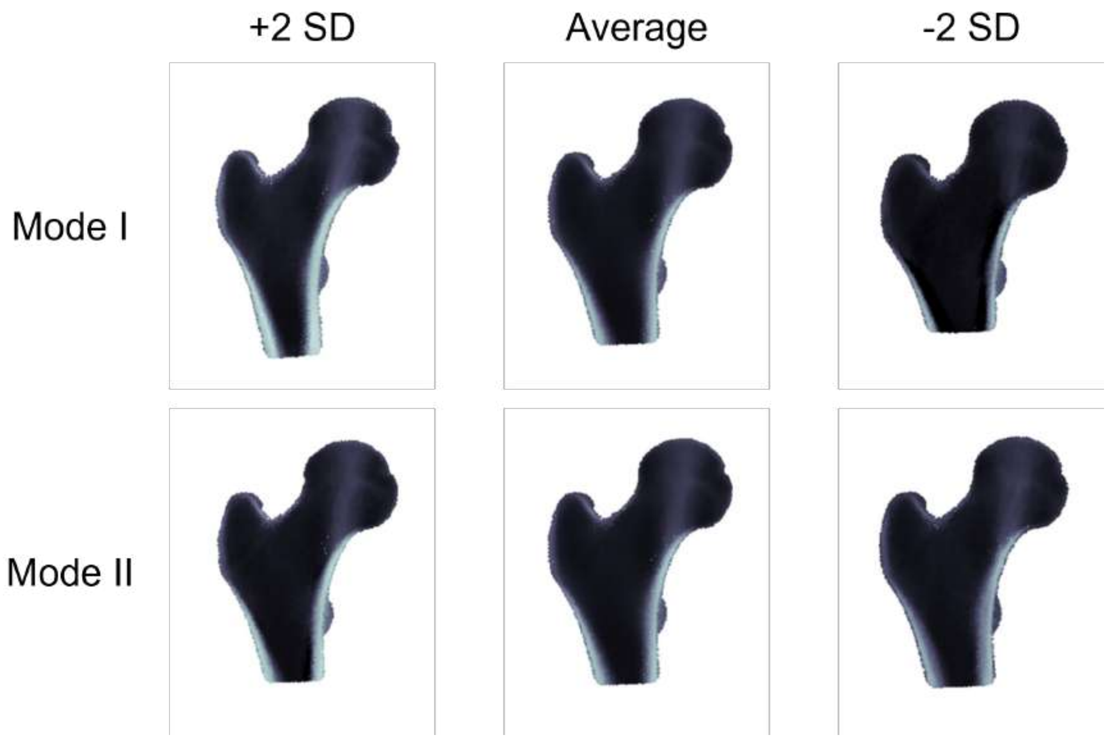
Disease and treatment effects



Adequate compute power

Statistical anatomy atlas

- PCA-based statistical anatomy atlas
  - Statistical shape and appearance (local stiffness) model
  - Created from 94 femurs of Sheffield cohort

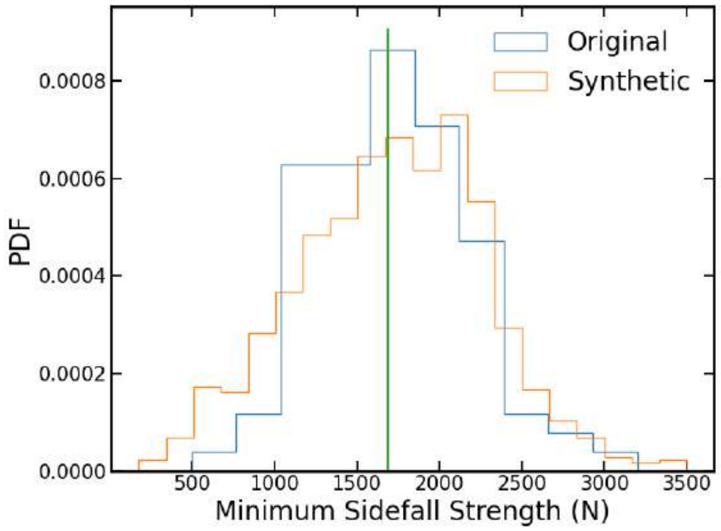


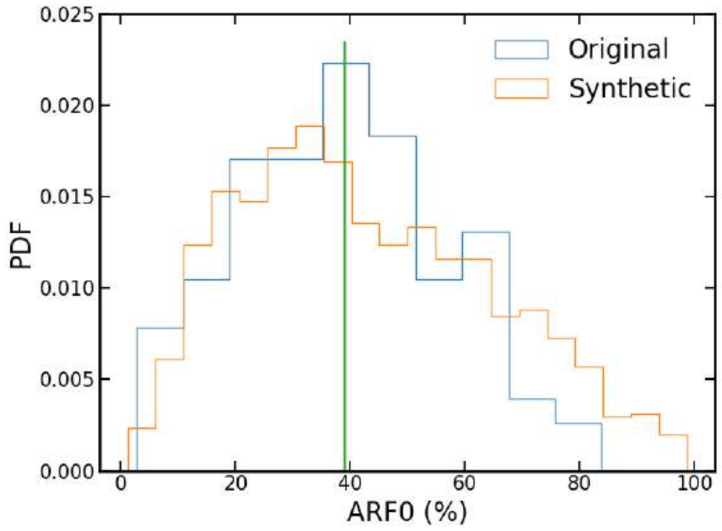
M. Taylor *et al.*, *J Mech Behav Biomed Mater* **118**, 104434 (2021)

A. A. La Mattina *et al.*, *Ann Biomed Eng* (2022)

Cohort expansion

- Statistical aliasing of Sheffield cohort
  - Inverse transform sampling of PC
  - Height and weight randomly assigned
- ARF0 workflow on 1044 synthetic subjects





A. A. La Mattina *et al.*, *Ann Biomed Eng* (2022)

Ageing model: step 0

- Phenomenological law based on DXA measurements
- Linear regression on Sheffield cohort
  - Porous bone eroded faster than cortical
- Mineral loss rate from literature
  - Systematic review of placebo arms of phase III clinical trials from literature

S. Oliviero *et al.*, *in preparation*

Ageing model: next steps

- Biology-informed ODE and/or agent-based model
  - Disease and treatment effects at cell and tissue levels
- Embarrassingly parallel workload
  - ~ 20 core-min per time step
- Need efficient coupling between ageing and FE models

Paradigm shift for IST

- Full-fledged BBCT workflow prohibitive computational cost
  - 1000 patients, 2 arms (placebo/comparator + treatment), 10 years
  - ~ 1-2 millions core-hours

- FE models predicts single-patient fracture risk, but…
- Clinical trials record fractures within observation time

Markov-BoneStrength

- Fall probability for each (virtual) patient
- If falling, stochastic parameter extraction and simulation
  - If fractured, out of cohort
  - If not fractured (or not fallen), goes to next year
- Repeat until end of observation time (for each patient)

- At the end of the simulation, count the observed fractures

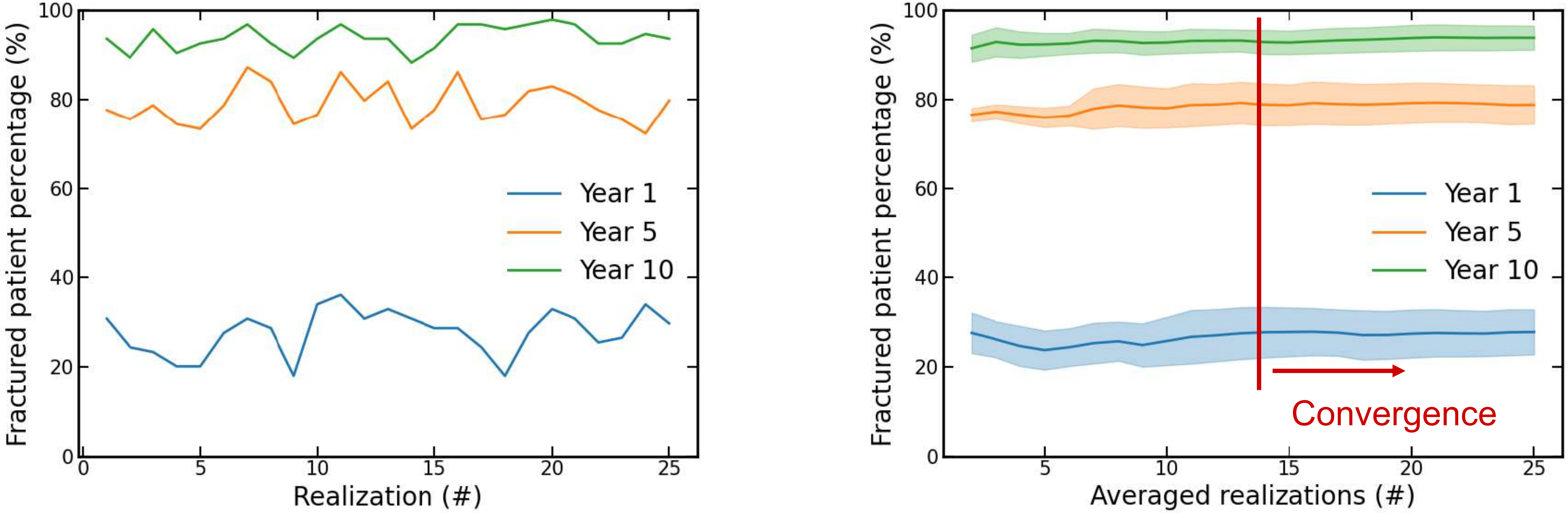
Convergence tests

- Different bone loss time-steps → different material properties for the same fall conditions
  - Ensure time sampling is fine enough

- Input stochasticity → different fall parameters for the same model
  - Averaging of realization results to ensure output convergence

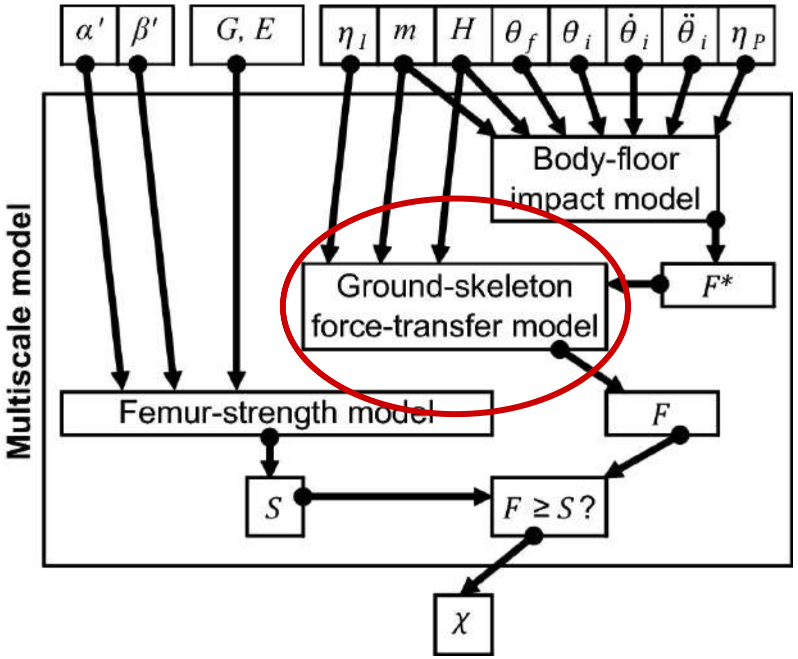
Output convergence

- 94 patients reconstructed from Sheffield cohort
  - 1-year bone loss time-step
  - 25 realizations



Validation and work in progress

- Overestimated observed fractures (~60% vs ~1% in 3 years)
  - Need better estimation of stochastic fall parameter distributions (attenuation coefficients and falling strategies)



S. R. Cummings *et al.*, *N Engl J Med* **361**, 756–765 (2009)

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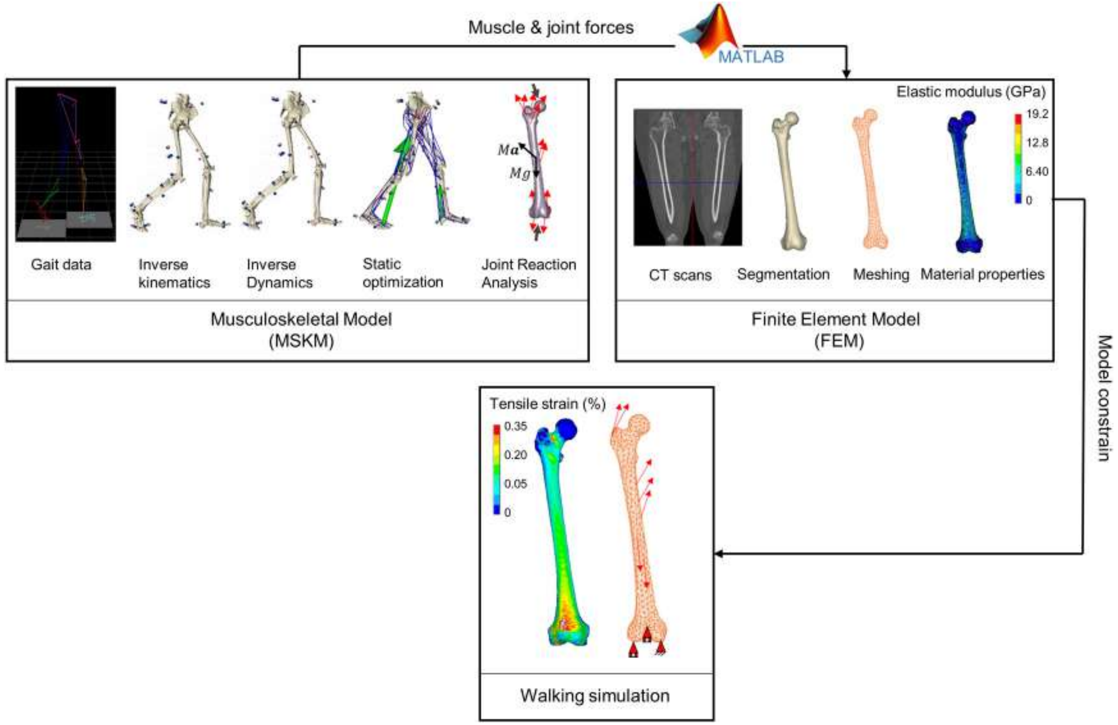
Muscle control in FE models

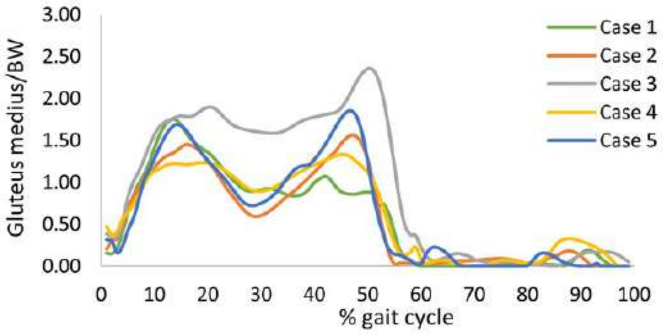
- Neuro-muscular model informed by gait analysis
- Muscle forces as boundary conditions for FE models

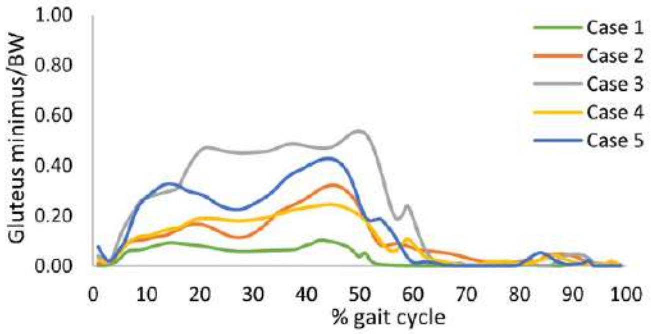


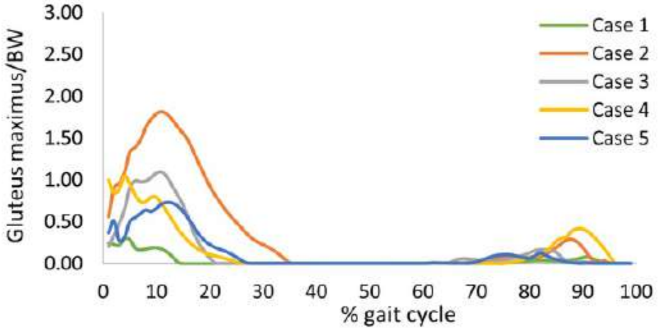
Z. Altai *et al.*, *Plos ONE* **16**, e0245121 (2021)

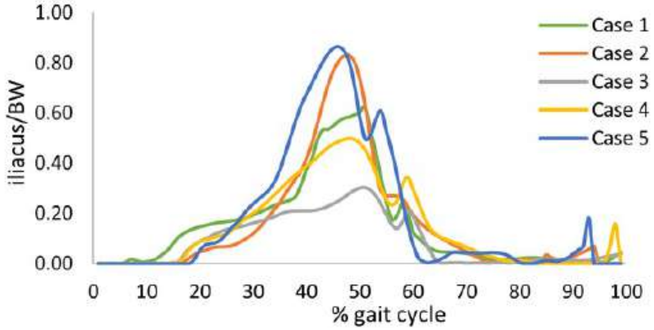
Muscle effects in FE models

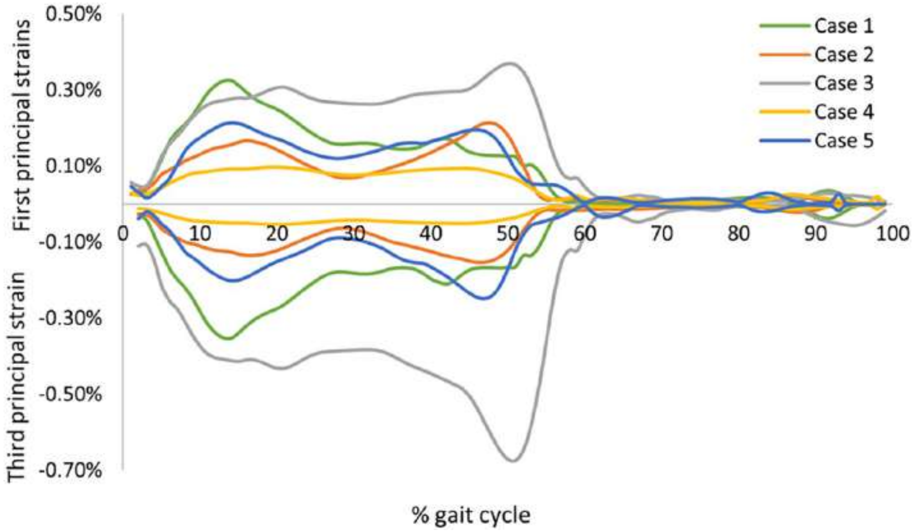
Time discretization: 100 substeps per cycle

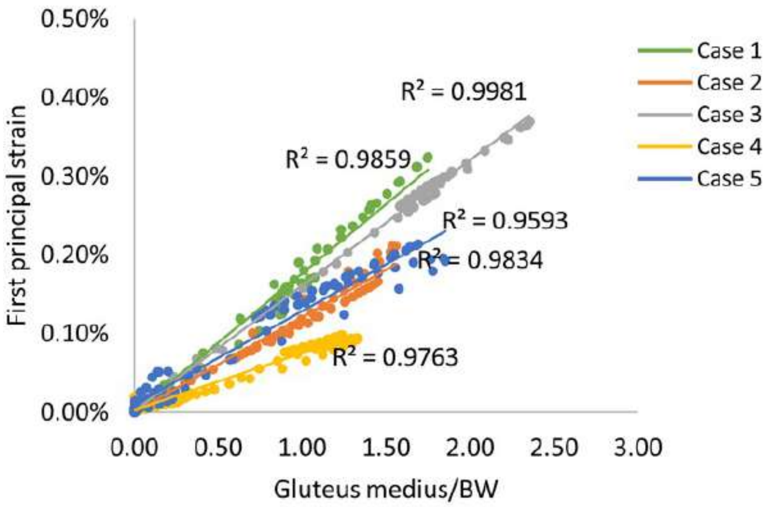












Z. Altai *et al.*, *Plos ONE* **16**, e0245121 (2021)

HPC for movement dynamics

- The biomechanics of human movement has two open challenges:
  - Prediction of the muscle activation patterns in patients with sub-optimal neuromuscular control
  - Simulation of motor control in forward dynamics

- Long-term goal: solve these problems in less than 200 ms to allow naturally walking exoskeletons for spinal cord injury patients

Quantum biomechanics

- Two quantum algorithms are being explored:
  - **Quantum Annealing**: annealing can be used to solve the muscle indeterminacy problem with respect to a specific optimal control target. Preliminary tests with a D-WAVE system suggest a 10^3 speed-up. Possibility to use a similar algorithm to solve the uncontrolled manifold problem, with a potential speed-up of 10^6 factor.
  - **Quantum walk**: the quantum version of the random walker algorithm could be used to implement a forward dynamics controller fast enough to provide real-time control.

Outline

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Intraoperative femur fractures

- Femur fractures during total hip replacements
- Generally low incidence (~3-5%), highly design-dependent


Images by Jmarchn on Wikimedia Commons

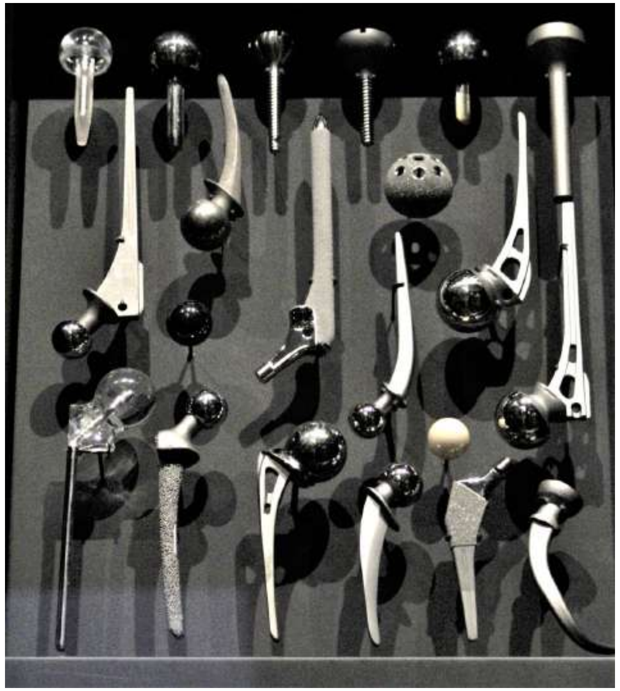
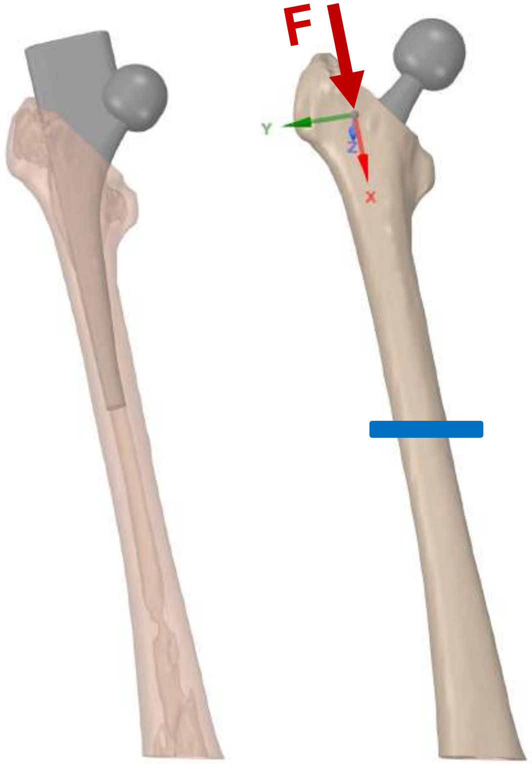


Image from Wikimedia Commons

IFF simulation: early results

- Simple approach: Incremental Element Deletion
- Reasonable crack propagation
  - Need to be validated

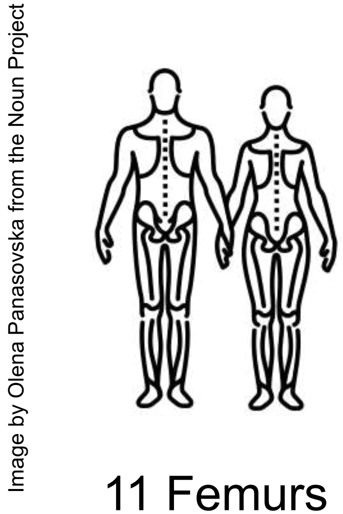


<u>200 core-hours per simulation, 50 GB RAM, I/O bounded</u>

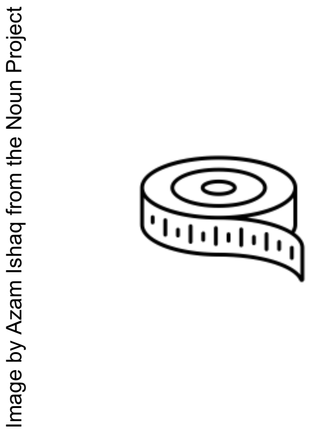
M. Petrucci *et al.*, *in preparation*

IFF: In Silico Trial platform

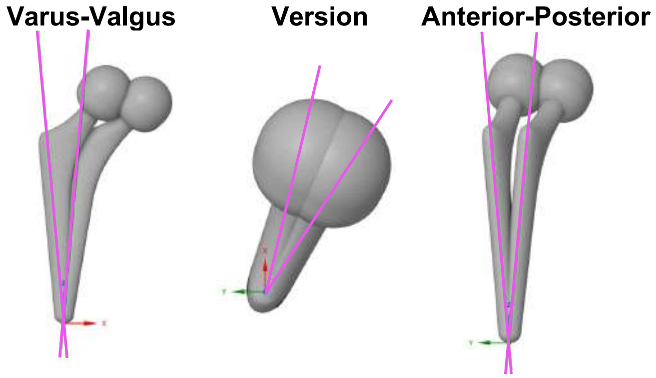
- Test new prosthesis designs before production
- Consider anatomo-densitometric and surgical variability



11 Femurs



3 Sizes



7 Orientations

3 Osteoporosis level

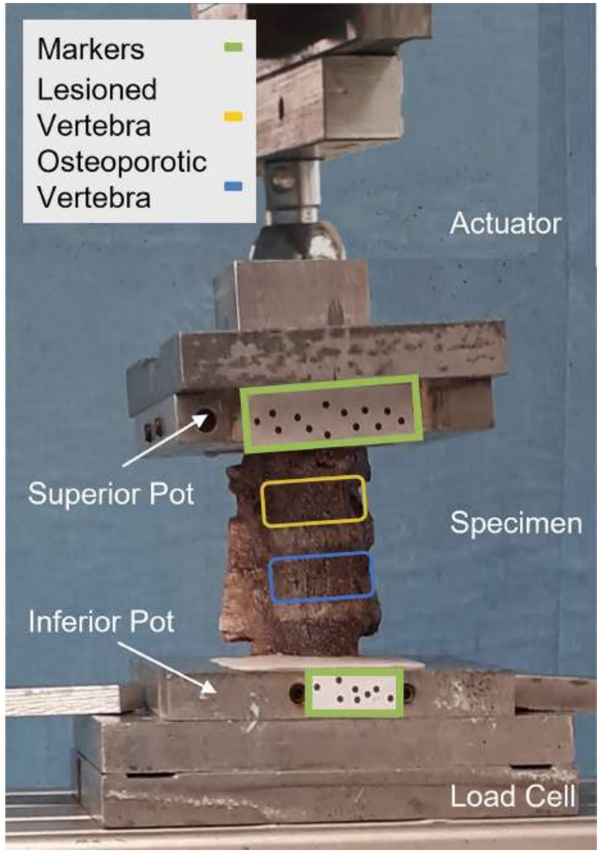
693 FE models

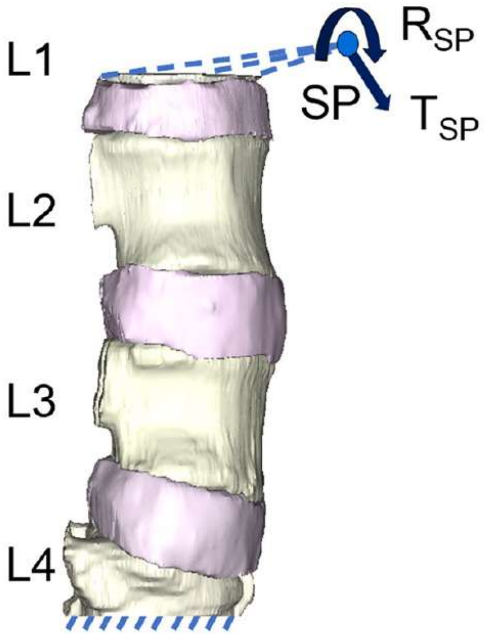
~150k core-hours per stem design

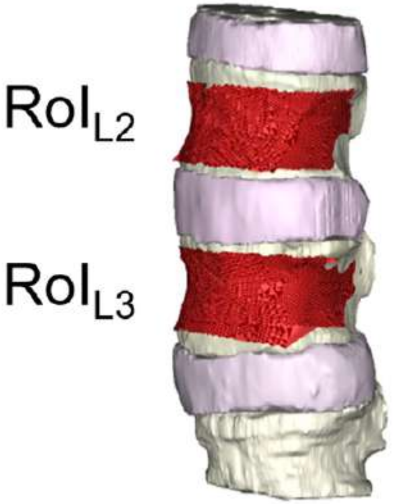
Even more with a full Monte-Carlo approach…

Vertebrae: model validation

- FE model validation on displacements
  - Digital Image Correlation measurements

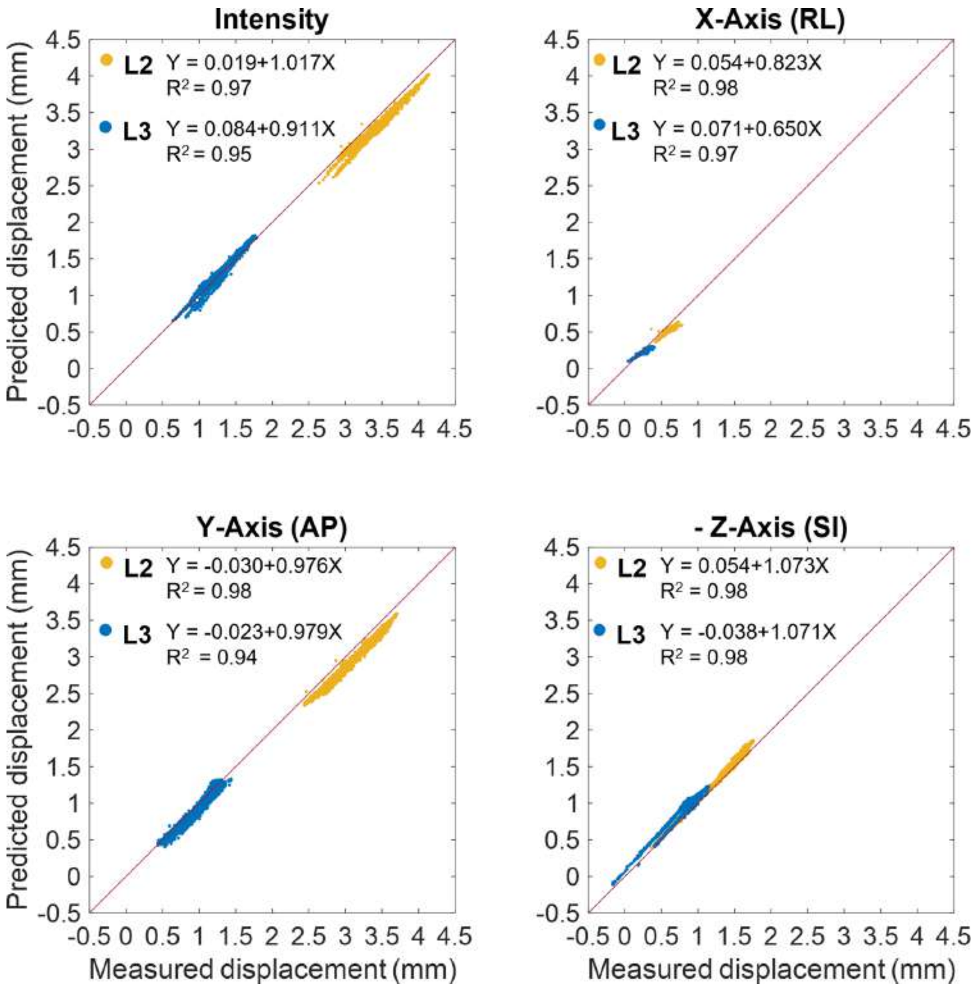


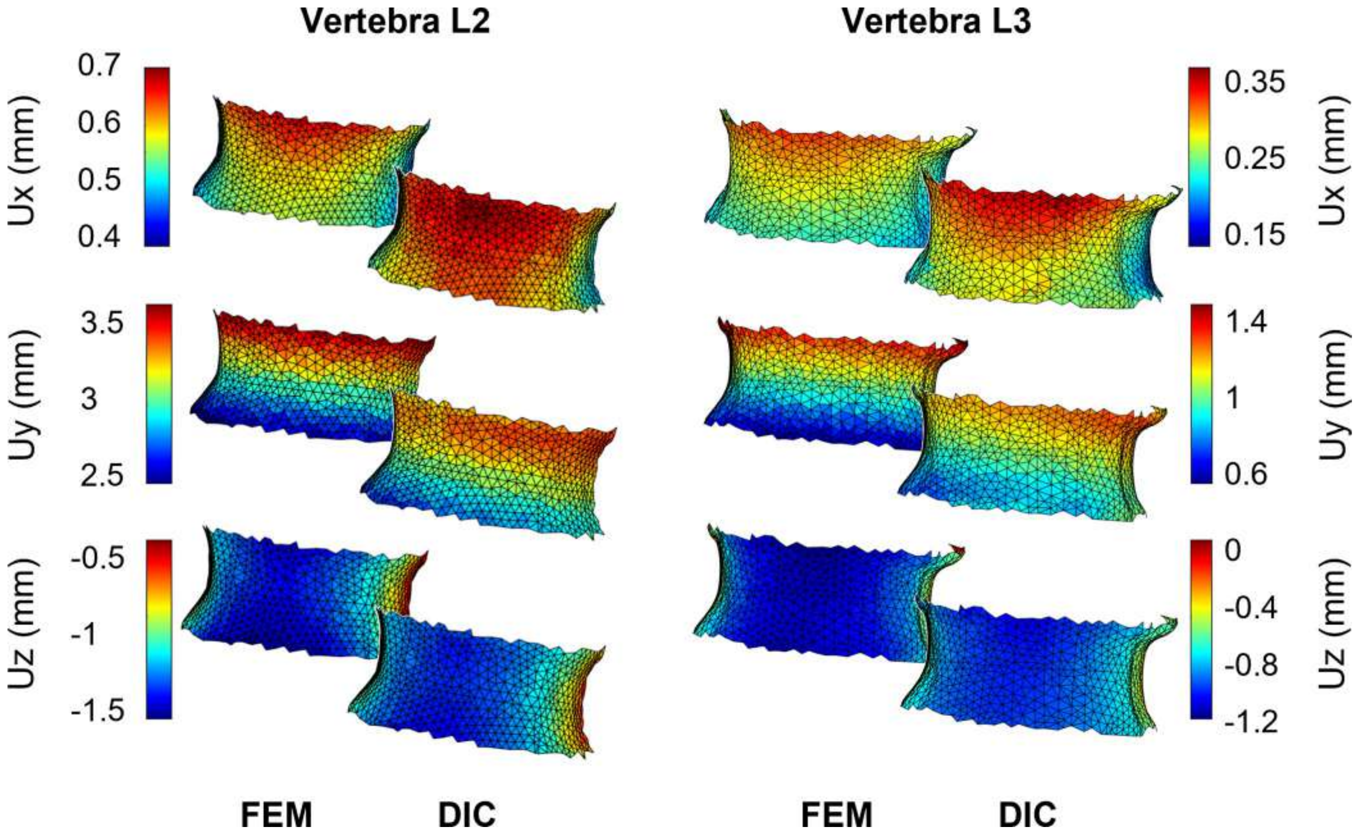




C. Garavelli *et al.*, *Plos ONE* **17**, e0272529 (2022)

Vertebrae: model validation





C. Garavelli *et al*., *Plos ONE* **17**, e0272529 (2022)

Vertebrae: microarchitecture

- Validation against Digital Volume Correlation data
  - MicroCT scans (voxel sizes of few μm) during mechanical testing

- Voxel-based linear hexahedra: @XX M degrees of freedom
  - @XX GB RAM, @XX CPU cores
  - @XX core-hours

M. Palanca *et al.*, *J Mech Behav Biomed Mater* **125**, 104872 (2022)

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Conclusions

- Validated Digital Twin workflow, automated and HPC-ready
  - Deployed in hospitals for patient femur fracture risk estimation
- Development of In Silico Trial platform
  - Simulation parameter tuning, ongoing bone remodelling formulation
- Muscle contraction influence
  - Real life stress-test, highly compute-demanding
- Ongoing extension to other human bones and applications

The University Of Sheffield.

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Thank you

SURF

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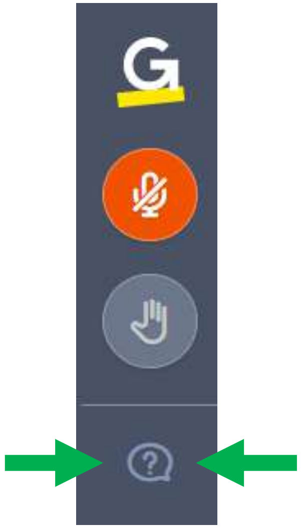

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823712

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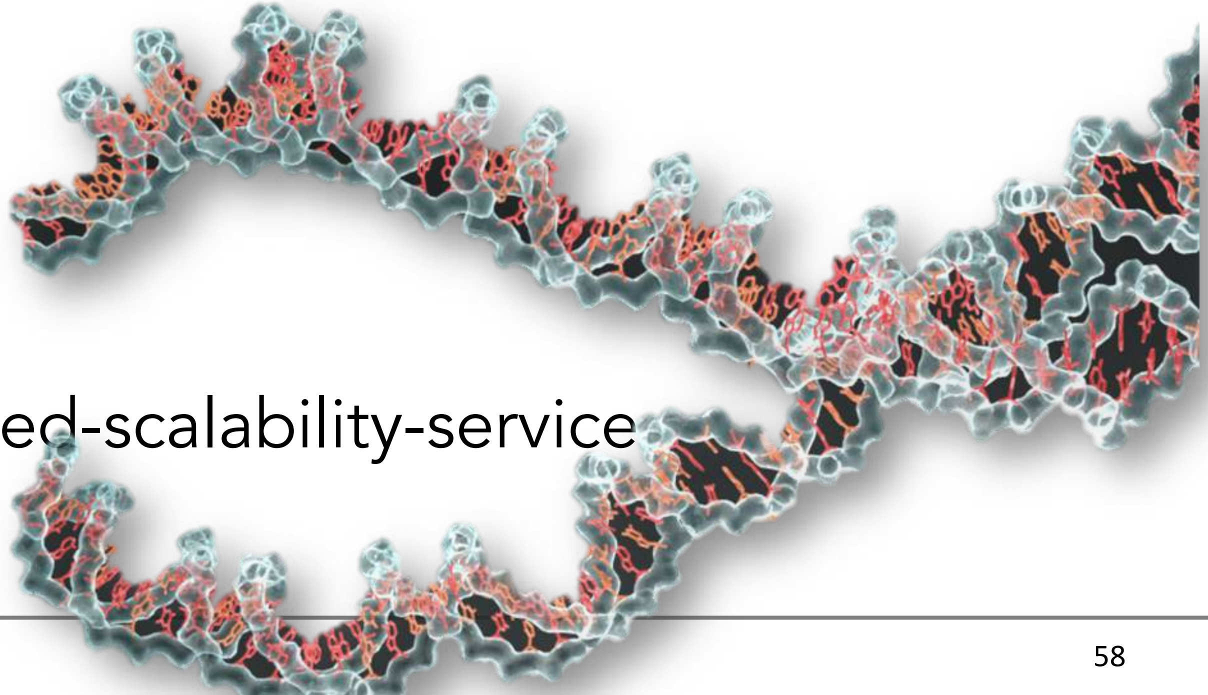

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