e-Seminar #26

Phase III In Silico Trials of new treatments for osteoporosis using exascale computers

Presenter:
Marco Viceconti
(Rizzoli Orthopaedic Institute, University of Bologna)

2 September 2022

The e-Seminar will start at 2pm CEST / 1pm BST

Moderator:
Tim Weaving
(University College London)

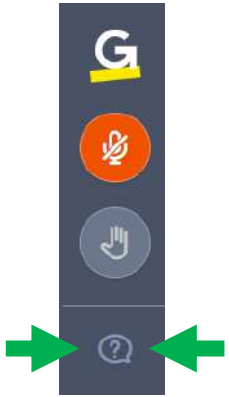
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823712

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

The e-Seminar series is run in collaboration with:
VPH Institute
Building the Virtual Physiological Human

Q&A

To pose a question, please click on the symbol and send your question via the 'Ask the staff a question' panel



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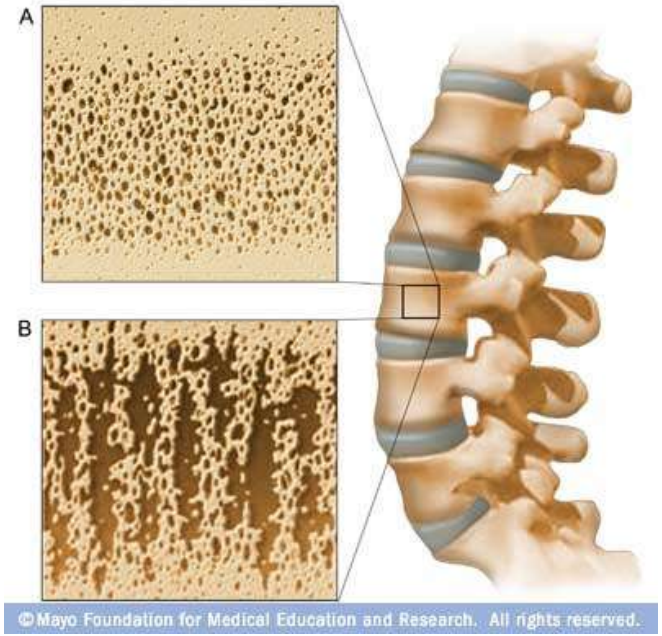
Phase III In Silico Trials of new treatments for osteoporosis using exascale computers

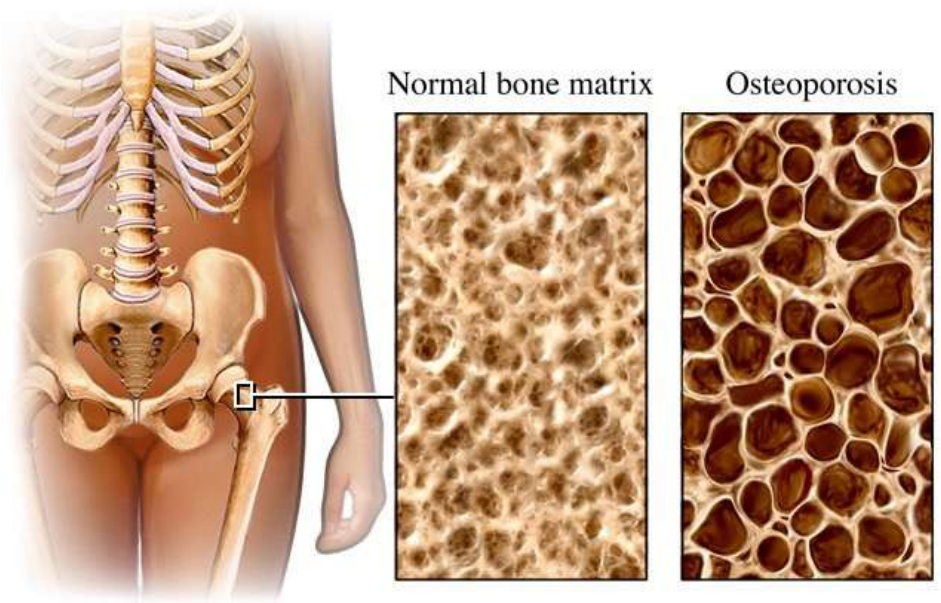
Marco Viceconti

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

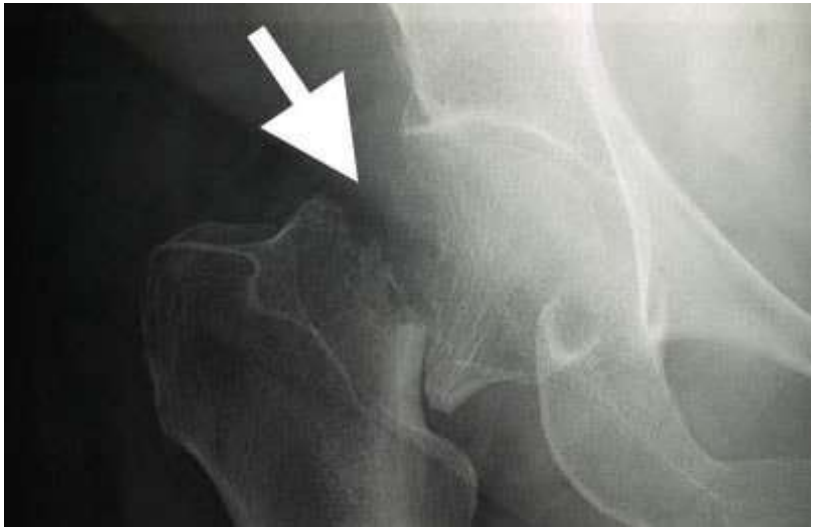
CompBioMed e-Seminar #26
Sept 2nd, 2022

Osteoporosis

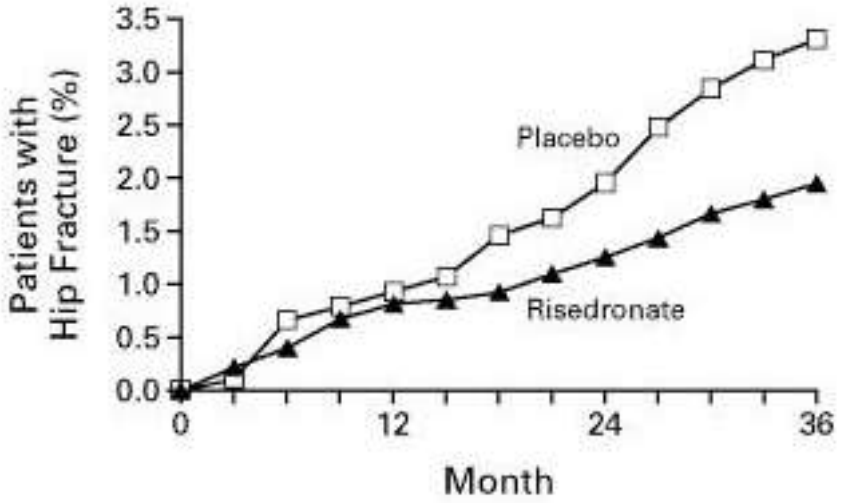




Clinical need



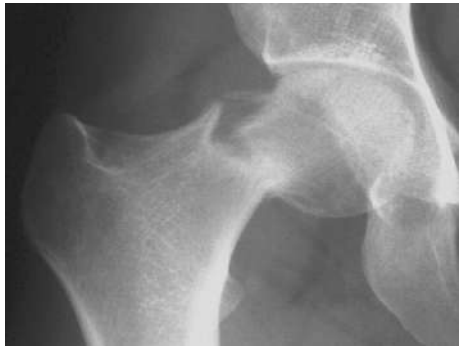
Proximal femur fracture is the most dangerous of all fragility fractures:
≈ 20% die within 12 months



Current drugs reduce incidence of hip fracture only of 40-60%:
in 2019 >3M fracture in EU

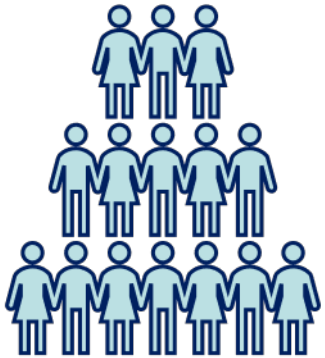
Currently no new drugs in phase I clinical testing

RCTs cost too much



Only 4% of women over 55 have an hip fracture in the following 5 years

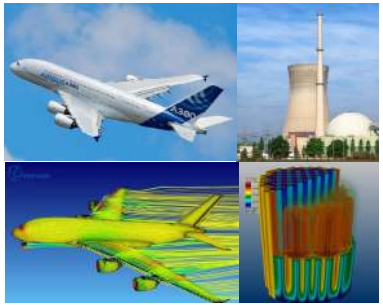
EMA requests RCT vs placebo; ethics impose low risk patients (<1%)



To observe 100 fracture, we need 10,000 enrolled and followed for 5 years
Cost > €300M

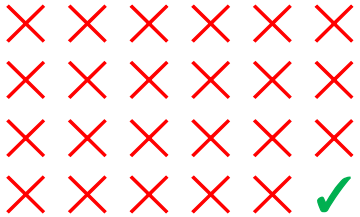
Why not use computer simulation?

In any other industrial sector



Testing is now done mostly with computer simulation

In healthcare



We test safety and efficacy of new products only by trial and error

Can models predict health changes?

2001: a ML model predicts biochemical failure after radical prostatectomy with a 75% accuracy

Tewari A. *et al* Mol Urol. 2001 5(4):163-9.

2014: FDA allows marketing of HeartFlow vFFR-CT tool for optimal treatment of coronary stenosis

Gaus S, *et al*, JCCT 2013, 7(5):279-88.

2018: patient-specific models of bone strength are more cost-effective that DXA in clinical trials of bone drugs

Viceconti M, Curr Ost Rep 2018 16(3):216-223

2008: FDA approves Kovatchev-Cobelli diabetes simulator to replace animal experimentation

Zisser *et al* Diab Tech Th 2014 16(10):613-22.

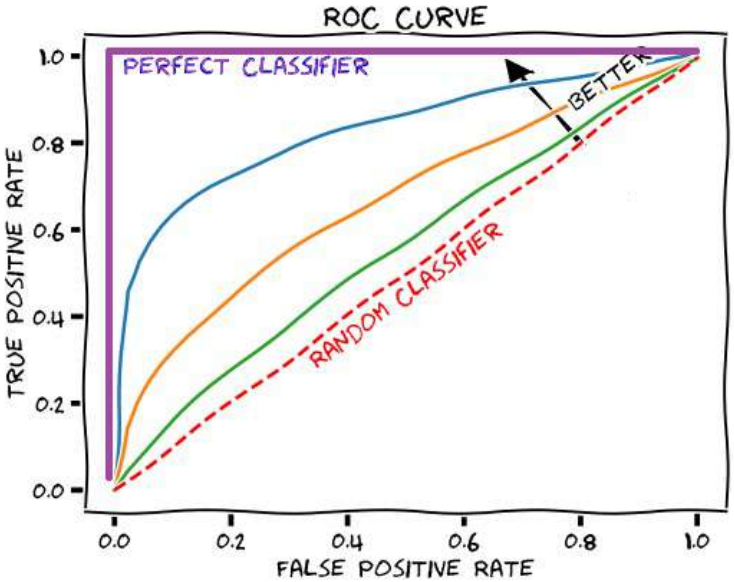
2015: Oxford Virtual Assay in silico cardiotoxicity test wins 3R prize for animal replacement

Britton OJ, *et al* PNAS 2013 110 (23) E2098-E2105

2019: FEops HEARTguide in silico tool for planning transcatheter aortic valve implantation is CE-marked

El Faquir N, *et al* Int J Cardiov Img 2019

Accuracy of F/NF predictors



Stratification accuracy: given a cohort half fractured, the area under the ROC curve provide a robust estimate of the ability of the predictor to separate F vs NF

Prediction	F at 5y	Accuracy
YES	YES	1
NO	YES	0
NO	NO	1
NO	NO	1
YES	NO	0
YES	YES	1
NO	NO	1
NO	NO	1
NO	YES	0
Predictive accuracy		**67%**

Prediction accuracy: given a threshold to decide, the F/NF prediction is compared to the observation over a period of time (e.g., 5y)

Biomarkers of hip fracture risk

- Biochemical
  - Bone metabolism biomarkers can detect increased bone loss ➔ stratification accuracy ≈ 60%
- Statistical
  - Statistical predictors like FRAX correlate risk of fracture with information such as age, sex, weight, height, risk factors, etc. ➔ stratification accuracy ≈ 65%
- Bone mass
  - Dual x-ray absorptiometry (DXA) measure with great accuracy the areal bone mineral density (aBMD) in the region of interest ➔ stratification accuracy ≈ 65% - 75%

The clinical cohorts

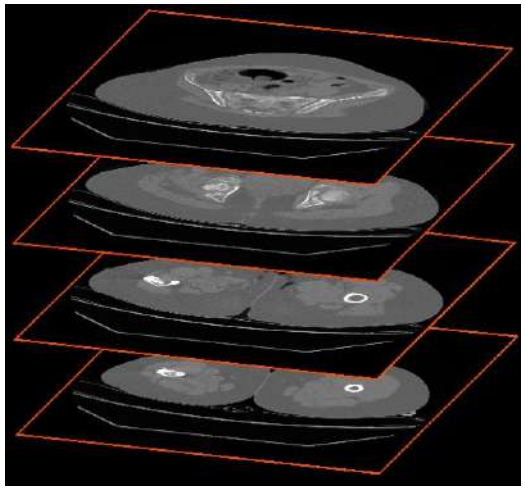
- **The Sheffield cohort**: CT scan and clinical data collection of 100 post-menopausal women; 50 were recruited when they arrived in the ER with a low-energy impact hip fracture; the other 50 were pair-matched by age, weight, and height, among patients referred to the osteoporosis clinics, but had not yet experienced a fragility fracture.

- **The Bologna cohort**: CT scan and clinical data of 100 post-menopausal women, who has the femoral scan done for other reasons. 5 of them experienced a fragility hip fracture within 5 years form the CT scan.

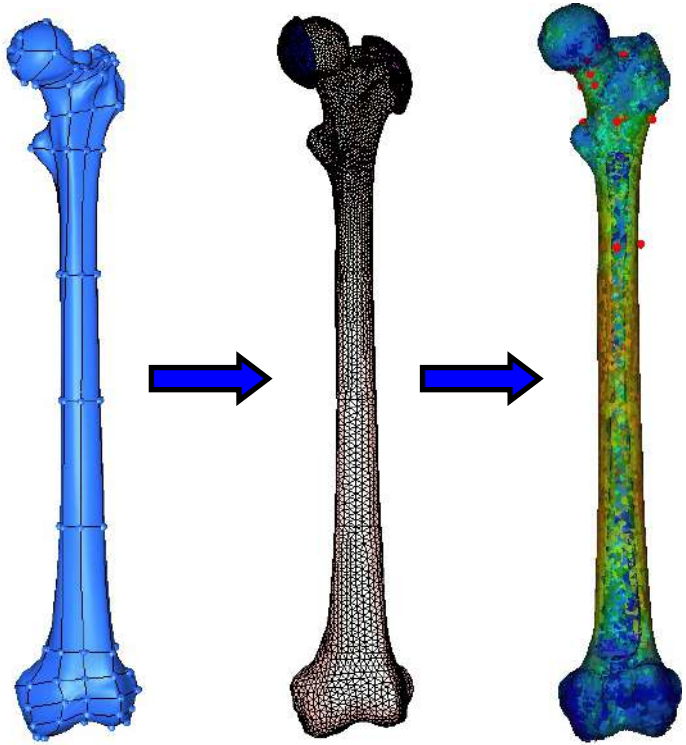
Bologna Biomechanical Computer Tomography (BBCT) Digital twin

QCT-SSFE: BBCT

Quantitative Computed Tomography based Subject Specific Finite element model

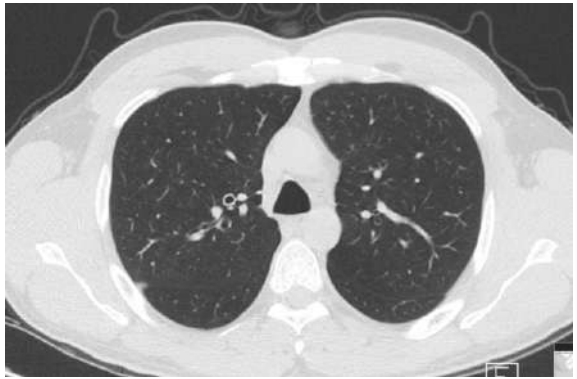


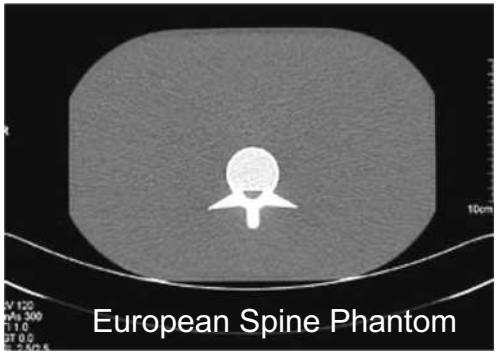
Basu PK, *et al*. Biomater Med Devices Artif Organs. 1985; 13:163-186.

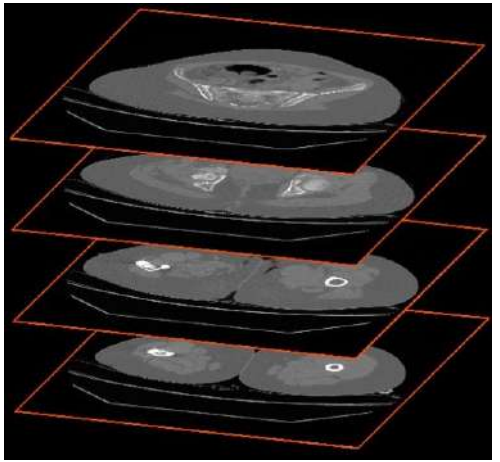


The Bologna Biomechanical CT

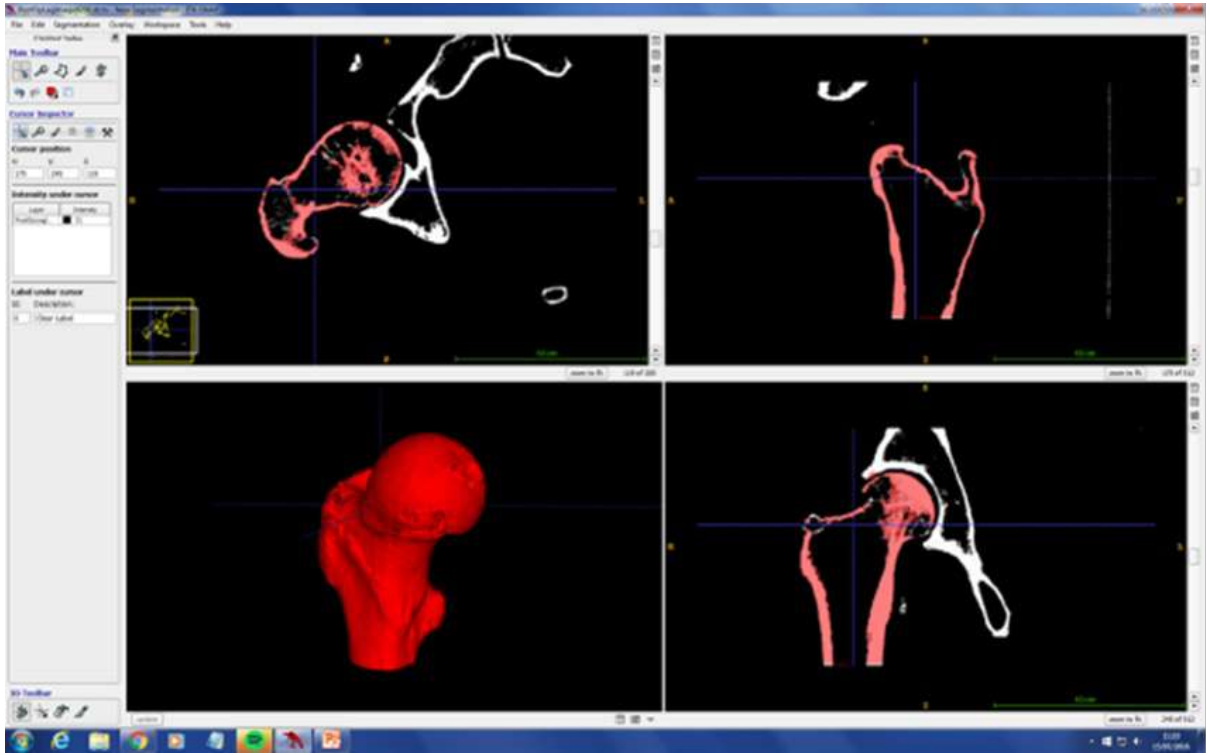
Computed Tomography



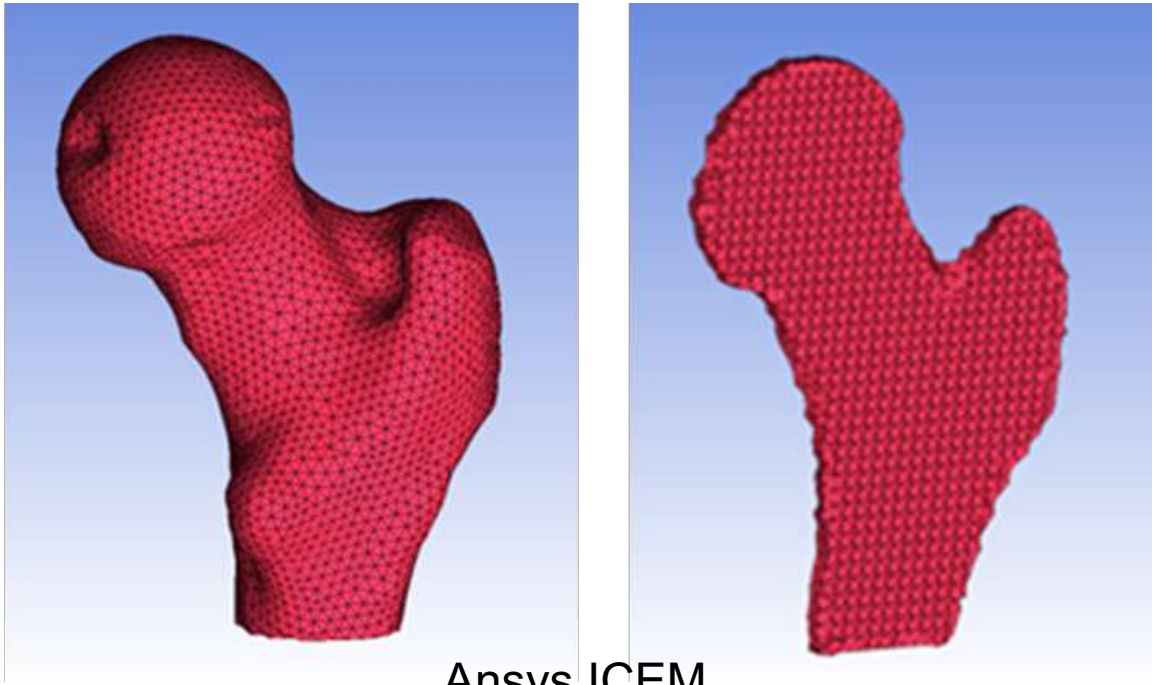




3D Segmentation

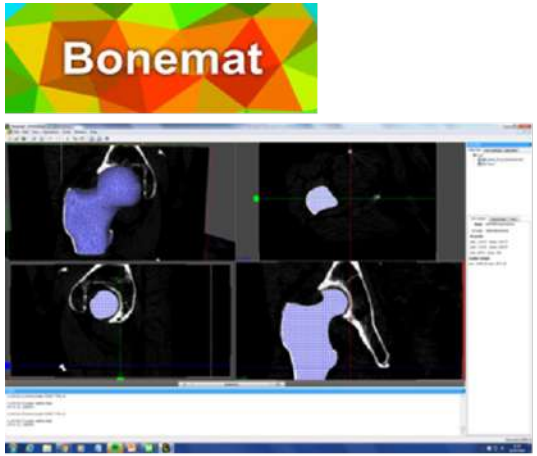


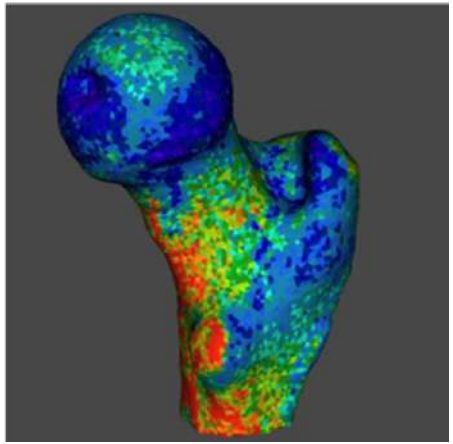
Volume meshing



Ansys ICEM
Direct Volumetric Mesher

Materials' mapping





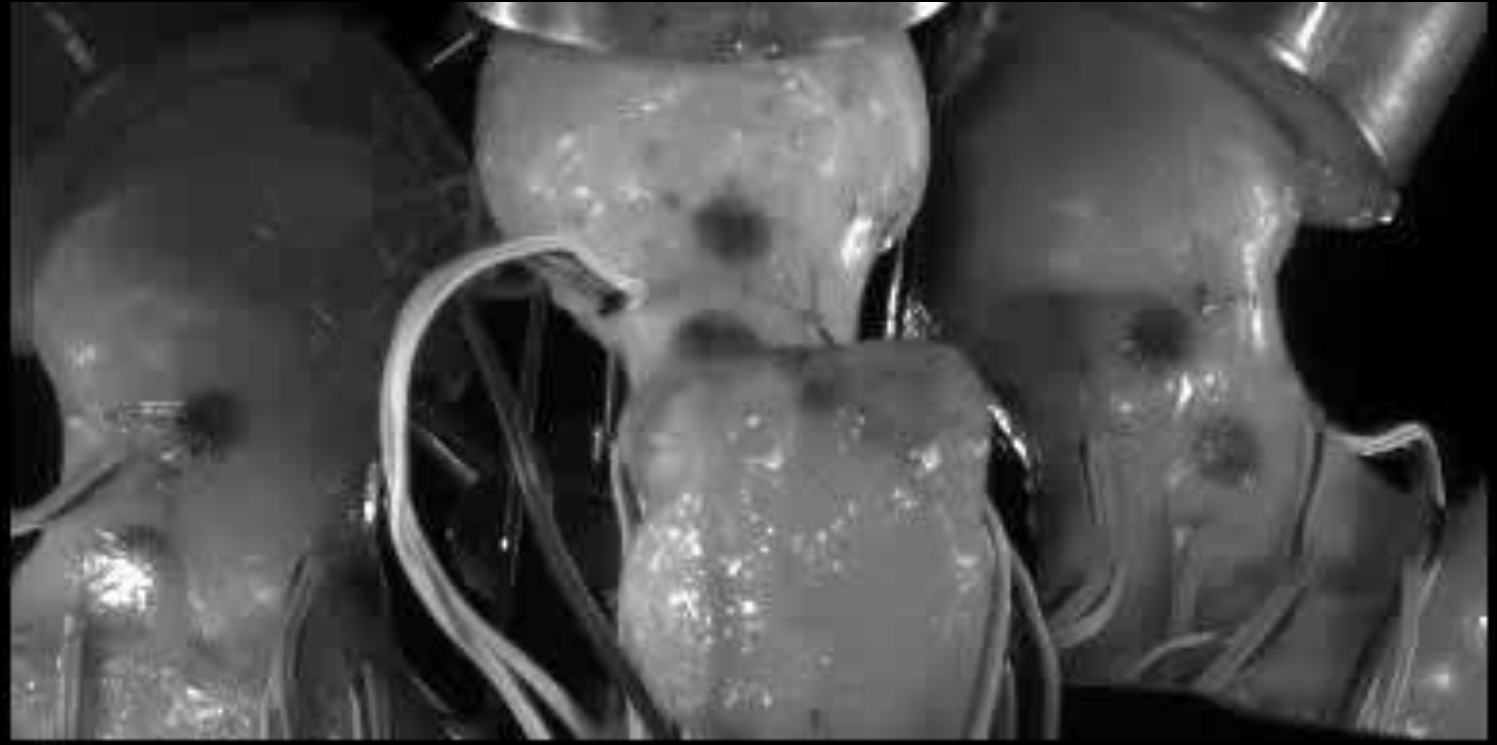
http://www.bonemat.org

Meshed volume and the associated CT scan are then imported into BoneMat. Elastic modulus (E) is then mapped on to the mesh based on the CT values (HU)

$\rho = a*HU + b$ $\quad E= 6.950(\rho)^{1.49}$

(a & b determined from Calibration phantom)

Taddei F, Schileo E, Helgason B, Cristofolini L, Viceconti M. (2007) The material mapping strategy influences the accuracy of CT-based finite element models of bones: an evaluation against experimental measurements. Med Eng Phys. 207 Nov;29(9):973-9.


Photron
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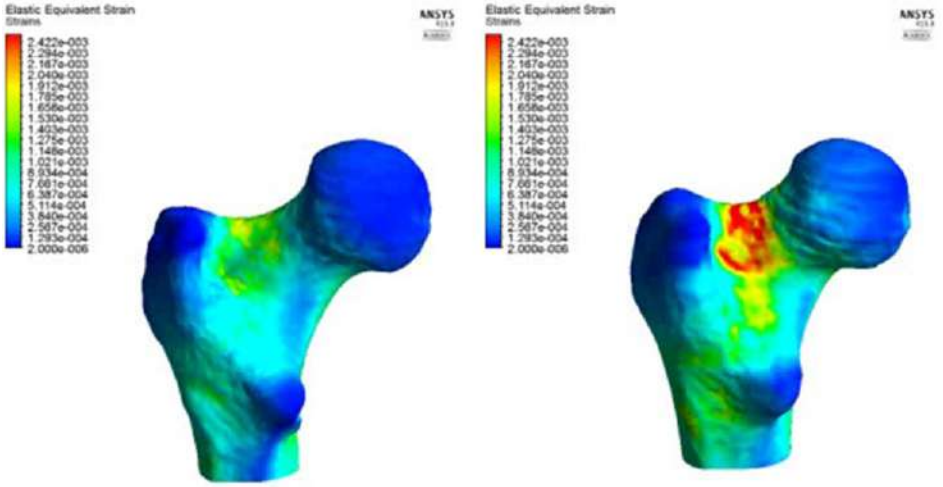
384 x 192
frame : -5090
-00:00:00.5090
Test 3155

Failure criterion

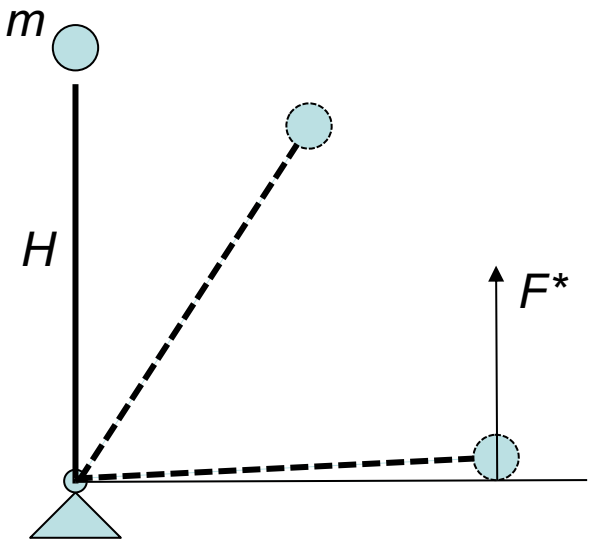


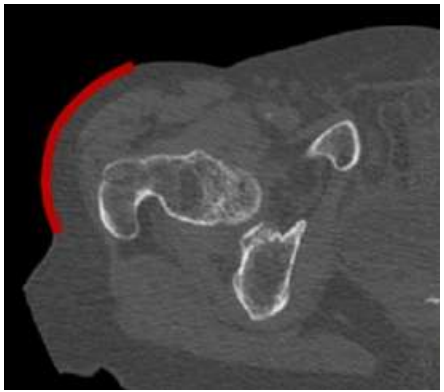
All femur fractures propagate in less than 2ms
➔ fragile fracture ➔ Strain-based, linear-elastic
Bayraktar *et al*. *J Biomech* (2004), 37:27-35

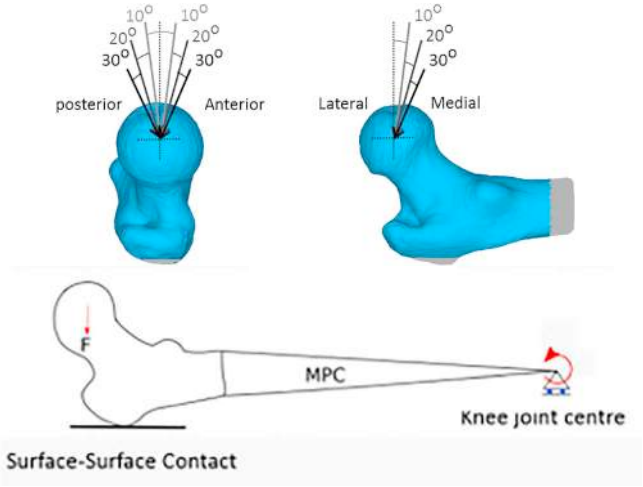
Falls in fragile elders

- 95% hip fractures can be associated with a fall
- Even fall that initiate frontally or posteriorly tend to produce lateral impacts (protection)
- We can model side fall as an inverted pendulum
- All the complexity of posture during fall can be reduced to postural attenuation coefficient

Fall: biophysics model







$$e = c^2H^2\ddot{\theta}_i\left(\frac{\pi}{2} + \theta_f - \theta_i\right) + \frac{1}{2}c^2H^2\dot{\theta}_i^2 + gcH\left(\cos\theta_i + \sin\theta_f\right)$$

$$u = \sqrt{2(1-\eta_P)e}$$

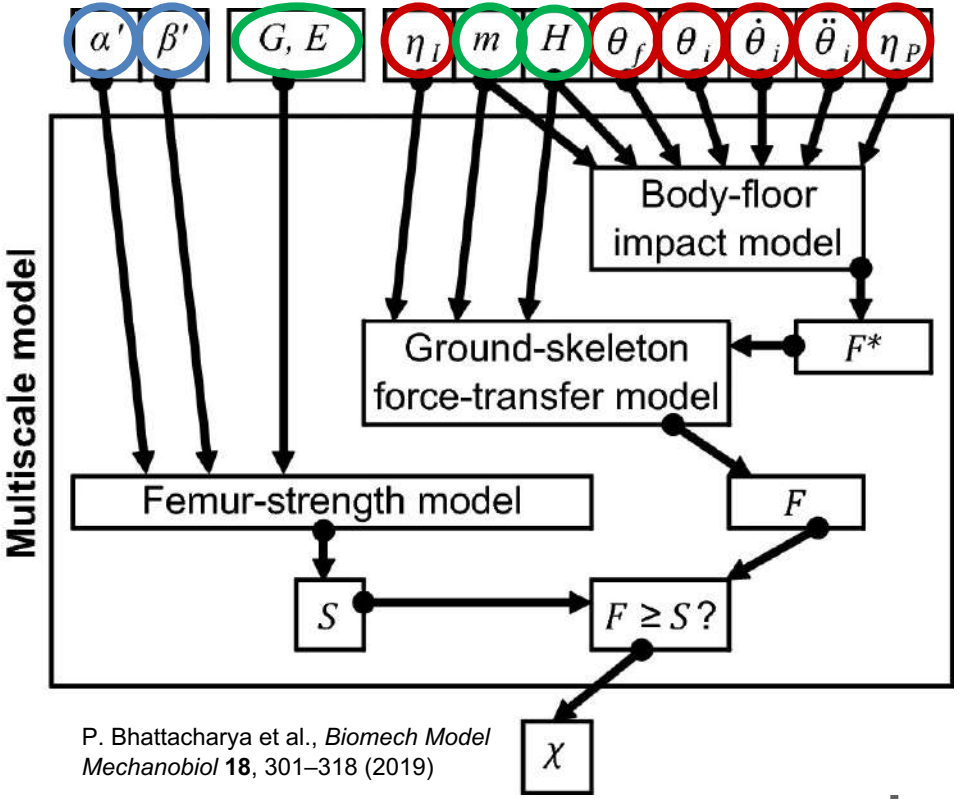
$$F^* = k \cdot 2m\,u/\Delta t$$

$$F = F^* \cdot \left(1-\eta_{IFloor}\right) \cdot \left(1-\eta_{IExt}\right) \cdot \left(1-\eta_{IAct}\right) \cdot \left(1-\eta_{ST}\right)$$

$$\partial\Pi = \int_V \sigma_{ij}\partial e_{ij}dV - \int_V \mathbf{F}\partial\mathbf{u}dV - \int_S \mathbf{T}\partial\mathbf{u}dS = 0$$

Multiscale model

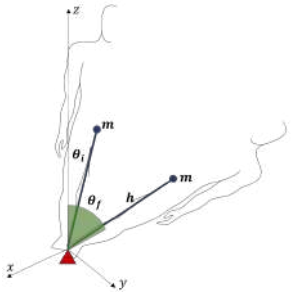
- 8 stochastic inputs
- 4 patient-specific inputs
- Probability distributions from the literature
- Latin Hypercube sampling for Monte Carlo scheme
- Surrogate model of FE

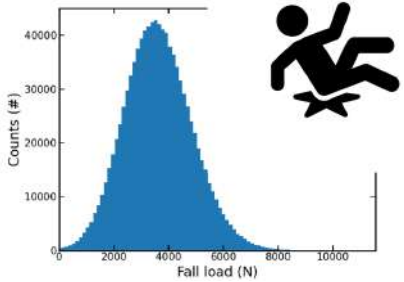


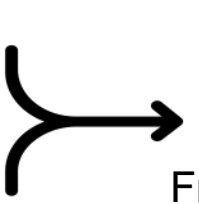
P. Bhattacharya et al., *Biomech Model Mechanobiol* **18**, 301–318 (2019)

Bologna Biomechanical CT

Falls simulation to predict **impact loads**

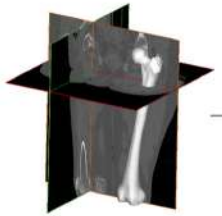


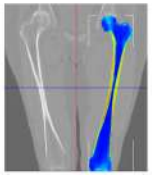




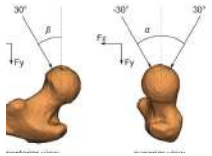
Fracture Risk (ARF0)
over 1 million
simulated falls

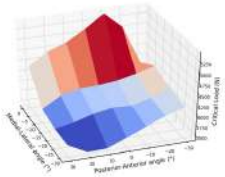
QCT-based patient-specific **load to failure**



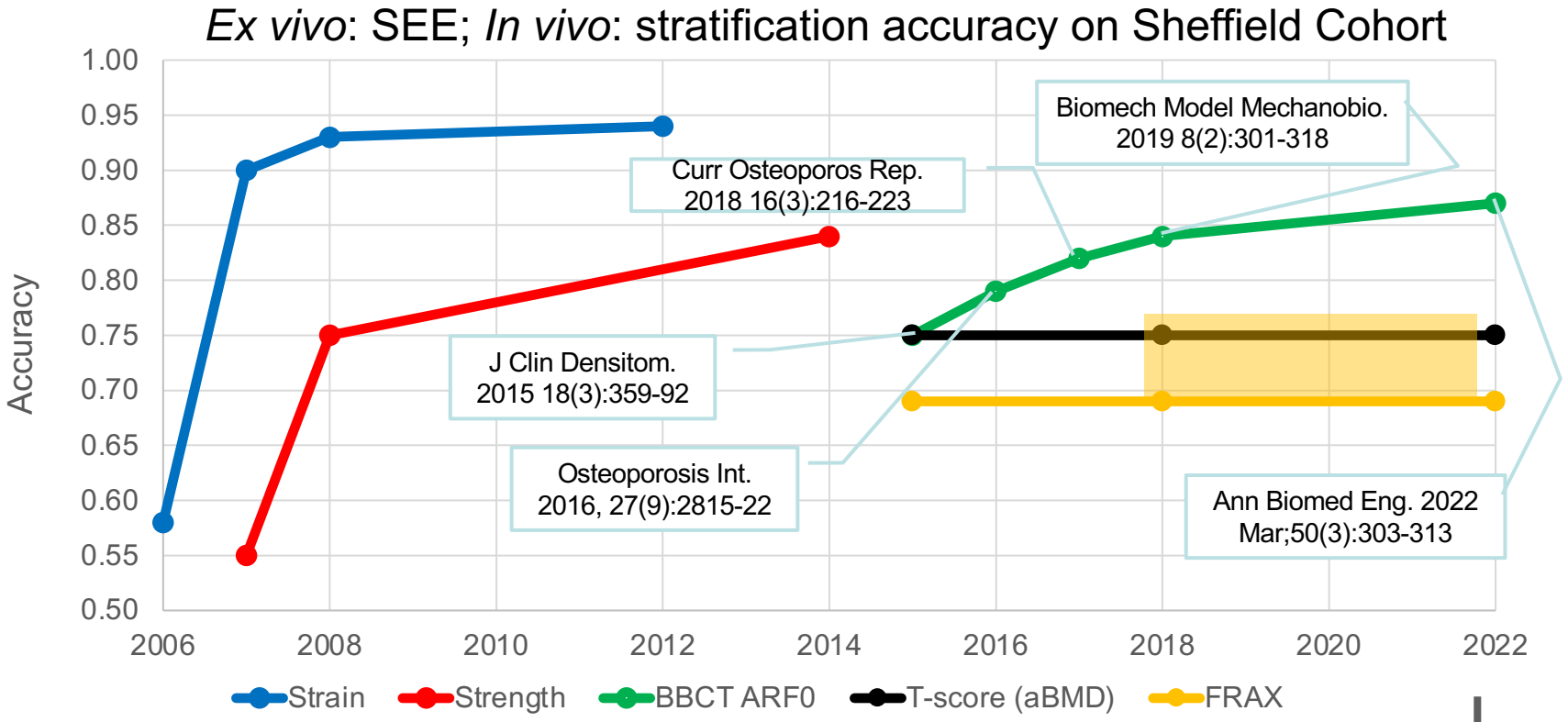


Bonemat





Is BBCT better than aBMD?



BBCT: Technical validation

- BBCT can predict the biomechanical deformation induced by side fall loads in cadaver femurs with an error of only 6%
- BBCT can predict the force required to fracture each cadaver femur with an average error of 15%
- In a retrospective cohort of 100 women, half with a hip fracture, BBCT has stratification accuracy (AUC) of 87%, aBMD only 75%

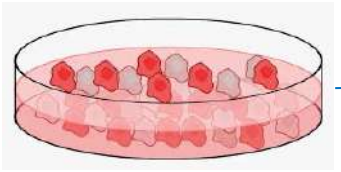
BBCT: computational cost

- BBCT requires ≈ 100 core-hour per patient to predict:
  - **MSF** (Minimum side fall strength): the lowest force caused by the fall that produce fracture among all possible impact directions
  - **ARF0** (Absolute Risk of Fracture at time 0): the number of simulated falls for which fracture is predicted, divided by the total number of simulated falls (1 million)
  - BBCT requires the solution of a non-linear Finite Element model of ≈ 3M DOF. The FE model should be run for 1 million fall patterns; instead is run with different boundary conditions for 30-40 time to inform a surrogate model of the side-fall strength as a function of the impact direction

From a Digital Twin to an In Silico Trial

BBCT ➔ BoneStrength

Many use of DT in drug development



Estimated drug efficacy

Drug Trial Design

Estimated drug efficacy

Augmented RCT

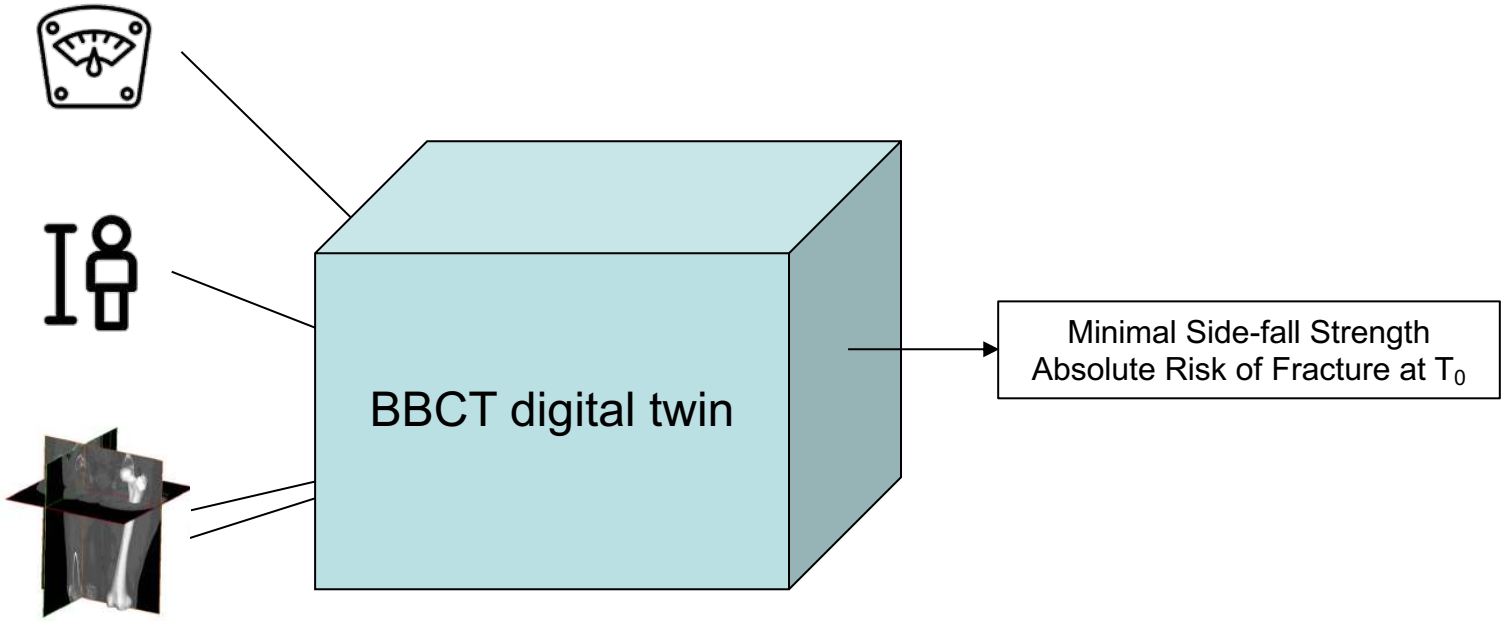
Estimated Dose-response

Virtual Placebo, Virtual Follow-up

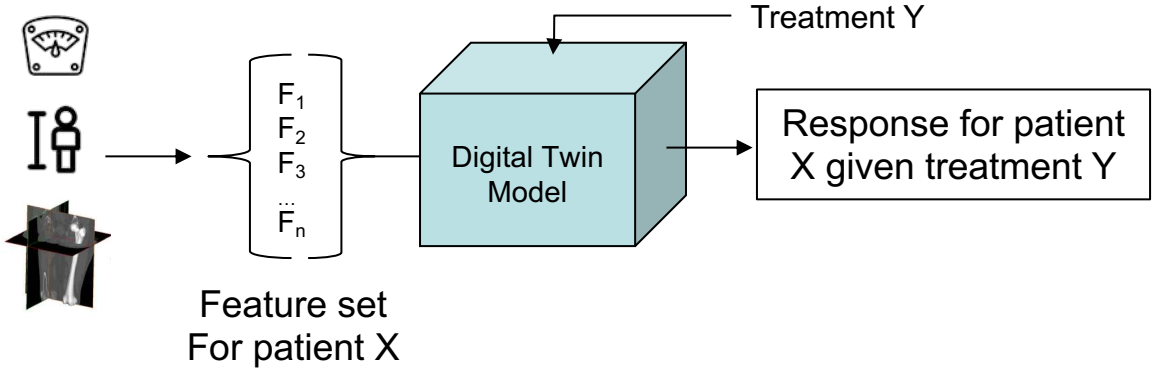
Refined Dose-response

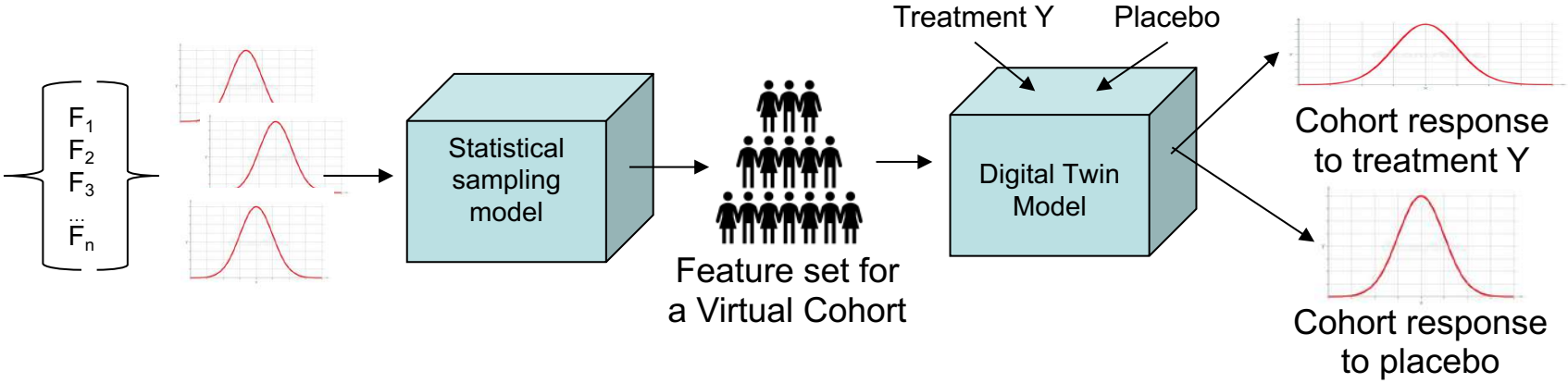
Virtual HTA

BBCT digital Twin



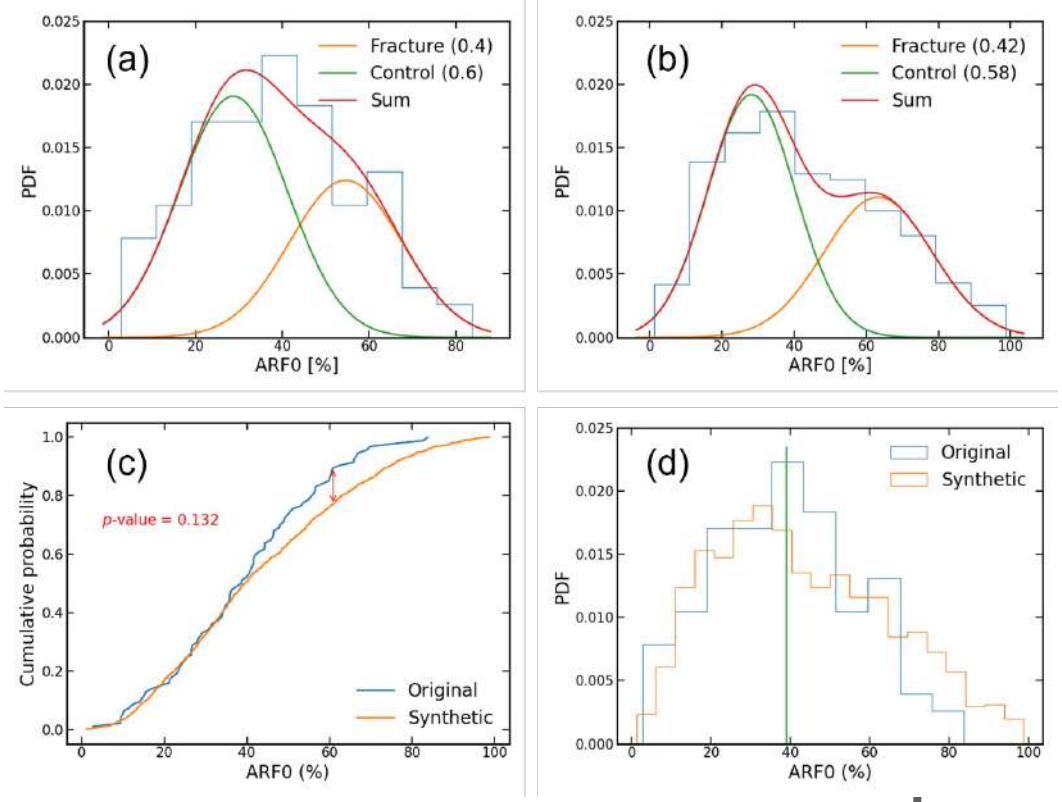
From a Digital Twin to an In Silico Trial





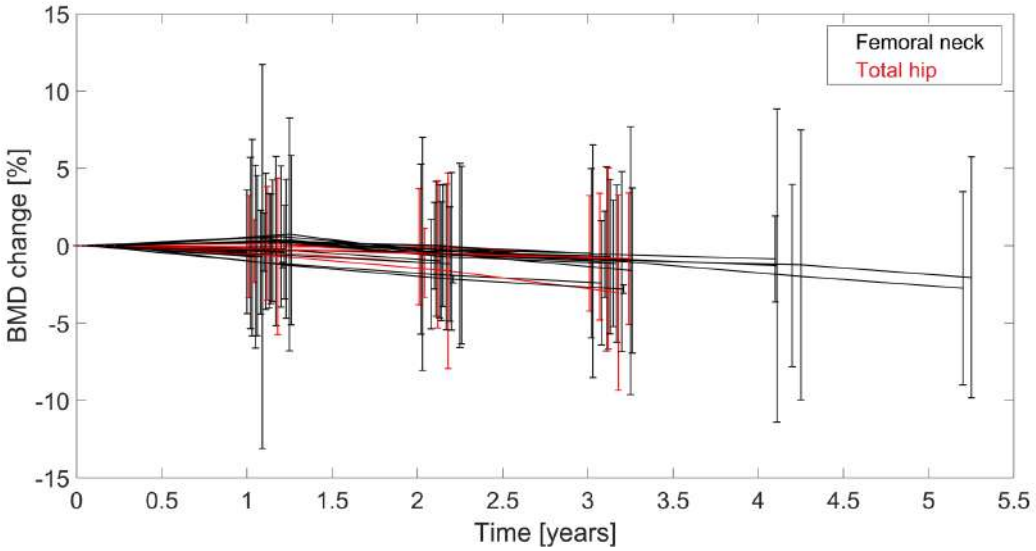
Cohort expansion

- La Mattina *et al,* Annals of Biomedical Engineering, 2022 *in press*
- Expanded 98-cases Sheffield cohort into 1000-cases virtual cohort
- ARF0 distribution for NF is nearly identical; that for F is lower (long tail effect)
- Same threshold divide expanded cohort still in half

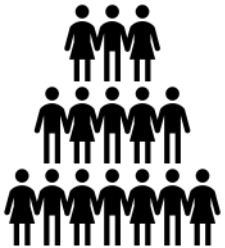


Disease progression

- Oliviero *et al, 2022* Curr Osteop Rep, *in revision*
- Systematic review of 28 clinical studies, for a total of 27,089 patients
- On average untreated OP patients loose 0.5% of bone mass / year, with peak of 2%
- Data-driven stochastic model of disease progression



BoneStrength Placebo Trial



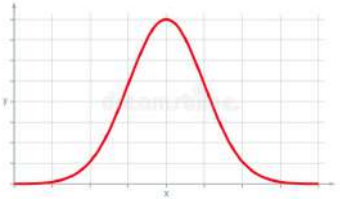
1000 VP with different:

- Height
- Weight
- Anatomy
- Initial BMD
- Resop. Rate
- Fall rate

BBCT digital twin

Disease progression model

Placebo arm

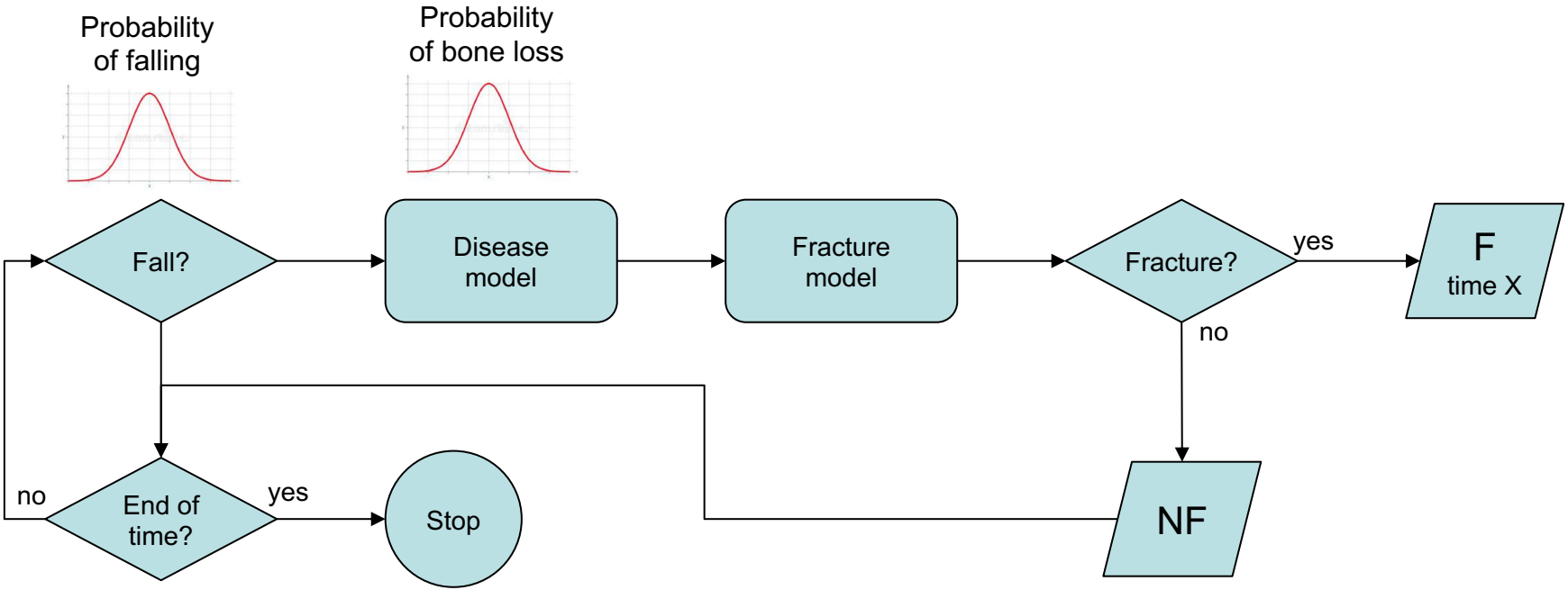


ARF10

Placebo arm: computational cost

- Frontal solution
  - 100 core-hour X 1,000 virtual patients X 10 time-steps (12m) = 1,000,000 core-hour
  - On the Leonardo pre-exascale HPC system:
    - Assuming 16 jobs per node, 5000 nodes
    - 12.5 hours using the whole HPC system!!

Markov-chain Monte Carlo



Placebo arm: computational cost

- Frontal solution
  - 100 core-hour X 1,000 virtual patients X 10 time-steps (12m) = 1,000,000 core-hour
  - On the Leonardo pre-exascale HPC system:
    - Assuming 16 jobs per node, 5000 nodes
    - 12.5 hours using the whole HPC system!!!
- Markov-chain
  - 3 core-hour per FE, 10 time steps, 1000 patients *0.65 falls/y
  - < 200,000 core-hour x 10 realisations
  - On the Leonardo pre-exascale HPC system
    - ≈ 7 hour on 2000 nodes

Development of a treatment model

How to model the treatment effect?

1. Modulate the resorption rate
   a. For drugs already tested on humans we can reduce resorption rate accordingly (validation)
   b. For new drugs we can infer reduction in resorption rate from animal studies, using the same scaling function for placebo

2. Bone remodelling with ODE
   a. Various mechanistic models exist (e.g. Pivonka) that describe a small volume (e.g. 1 mm^3) as a bone multicellular unit (BMU)

3. Bone remodelling with ABM
   a. Agent-based models can also be used to model single BMUs

Phenomenological model /1

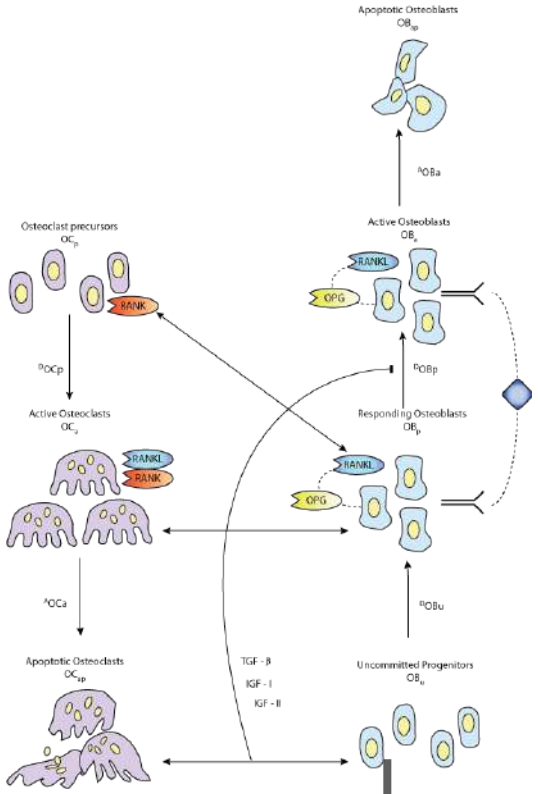
- Phenomenological treatment models are easy to implement: simply change the resorption rate to account for the drug effect
- You handle all co-factors in probabilistic response factor
- Easy to implement for drugs already tested on humans ➔ easy validation

Phenomenological model /2

- Animal effect scaling is quite unreliable
- But remain the only viable option for new drugs for which the mechanism of action is unclear
  - Perform ovariectomy on female mice to simulate osteoporosis
  - Observe bone resorption rate in untreated mice
  - Observe bone resorption rate in treated mice
  - Scale untreated rate to human placebo rate
  - Use the same scaling factor to scale treated rate from mice to humans

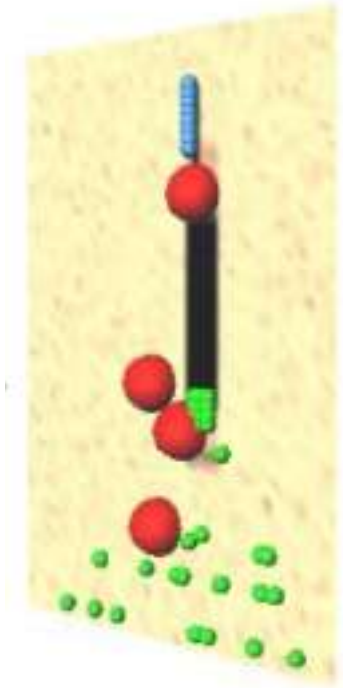
ODE models

- ODE-based bone remodelling add the solution of one ODE system with a different initial condition for each FE element
- New GPUs nodes can solve over 5000 ODE in parallel
- Add ≈ 20 core-min to each time step

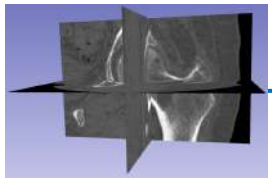
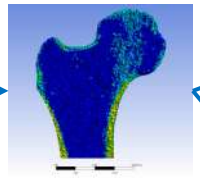
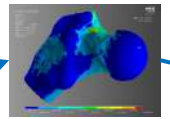
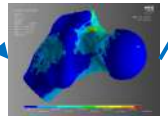
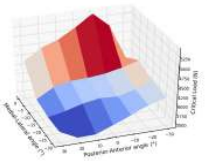


Agent-based models

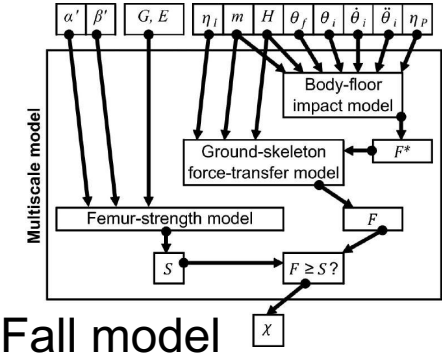
- Bone marrow cellularity is 10^6 / mm^3; Bone tissue cellularity is 10^4 / mm^3. ➔ an 8 mm^3 FE element contains ≈ 4 million cells
- Current ABM solvers run ≈ 1 M cells in 20 min
- Multi-GPU code, add 20 core-min



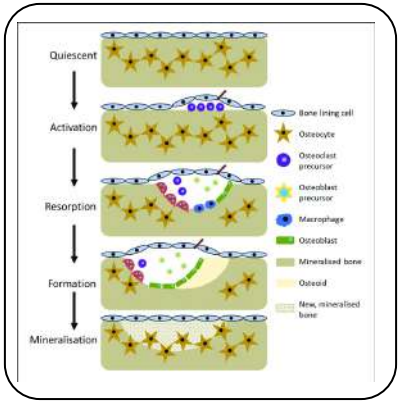
BoneStrength: a full In Silico Trial

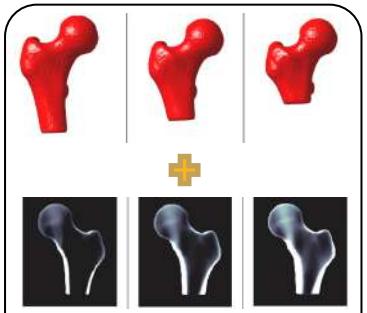
Femoral Strength model



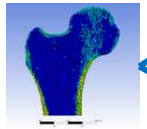
Fall model



Flinders UNIVERSITY



Virtual cohort

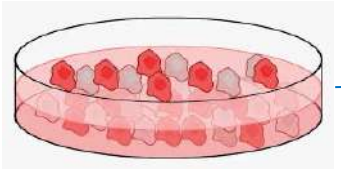


Virtual trial

BoneStrength: computational cost

- Markov-chain for treatment arm
  - < 260,000 core-hour x 10 realisations
  - On the Leonardo pre-exascale HPC system
    - ≈ 10 hour on 2000 nodes
- Full In Silico Clinical Trial
  - 200,000 x placebo arm + 260,000 for treatment arm
  - On the Leonardo pre-exascale HPC system
    - ≈ 17 hour on 2000 nodes

Current use without qualification



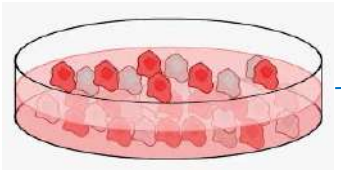
Estimated drug efficacy

Estimated drug efficacy

Estimated Dose-response

Drug Trial Design

Future use with EMA/FDA qualification



Estimated drug efficacy

Drug Trial Design

Estimated drug efficacy

Augmented RCT

Estimated Dose-response

Virtual Placebo, Virtual Follow-up

Refined Dose-response

Virtual HTA

BoneStrength: regulatory qualification

Medicinal products: no standards

- What we describe are authors' opinions informed by:
  - Current regulatory practices for the qualification of other "technological" drug development tools
  - Informal conversations with officers of FDA and EMA
- Predictive models are treated like any other technology producing a **biomarker**
- The focus is not on the technology or its precision, but on the use that such biomarker has in the regulatory decision process

Qualification of new methodologies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

"A qualification submission should provide insight into the reliability, accuracy, precision, clinical validity, generalisability and clinical applicability of the methodology to be qualified"

FDA U.S. FOOD & DRUG ADMINISTRATION

"Qualification is a conclusion that within the stated context of use, the methodology can be relied upon to have a specific interpretation and application in drug development and regulatory review"

Credibility

Context of Use

"BBCT-predicted ARF0 is to be used as a **response variable** in multi-dose Phase II studies in place of the measured DXA-based aBMD"

Step #1: technical validation

V&V for specific model types

Separation of model's layers:
- Physiology
- Disease
- Treatment

Predicted

Accuracy & Precision

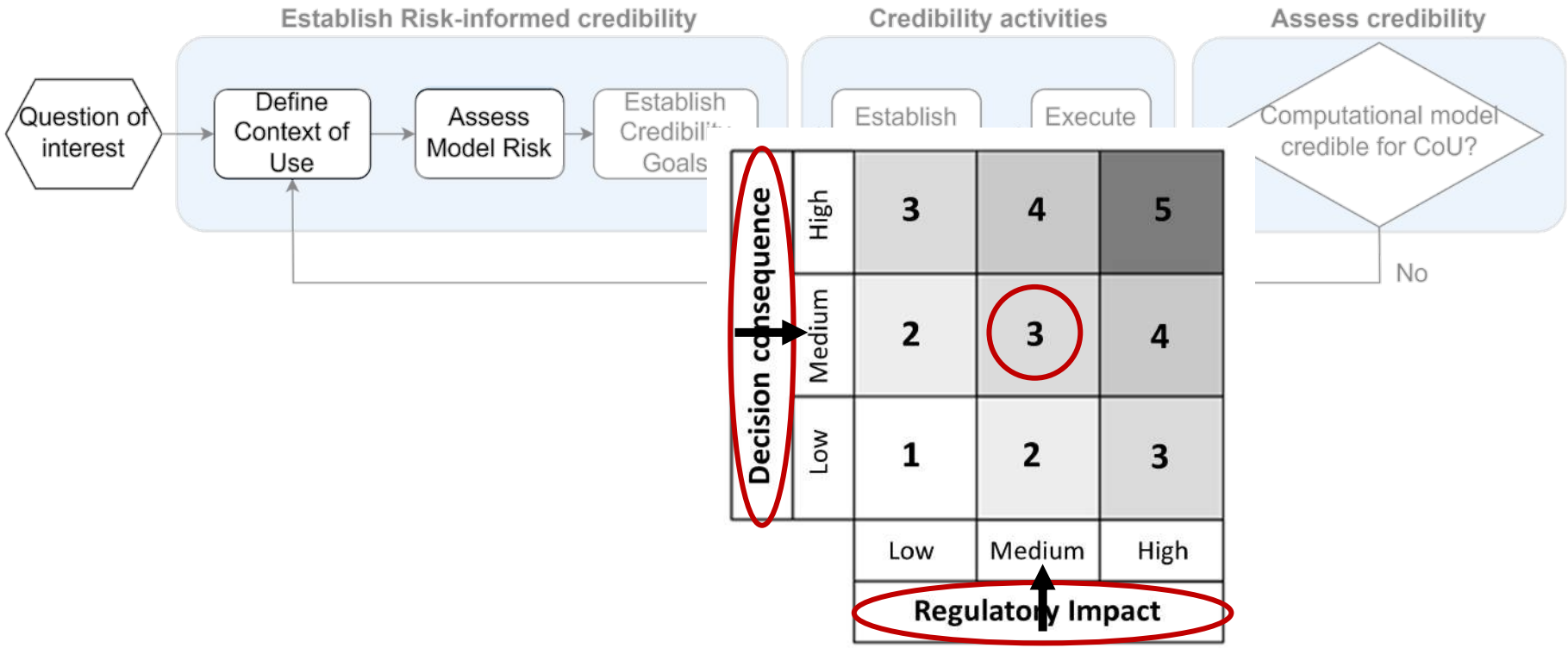
Measured

Reference samples

Measured

Repeated measurements

V&V-40 pipeline: Risk analysis



V&V-40 pipeline: verification

Code verification **Calculation verification**

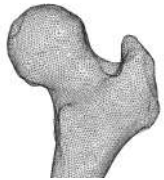
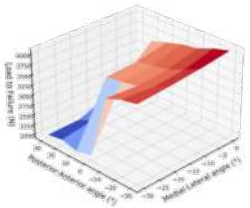
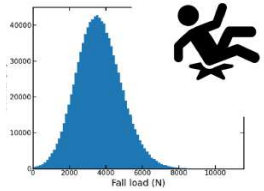
Mathematical model → Computational model → Simulation results

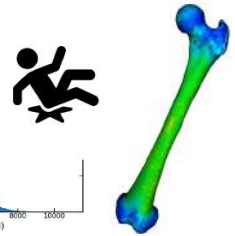
- SQA procedures from the vendors are referenced

  Ansys MATLAB

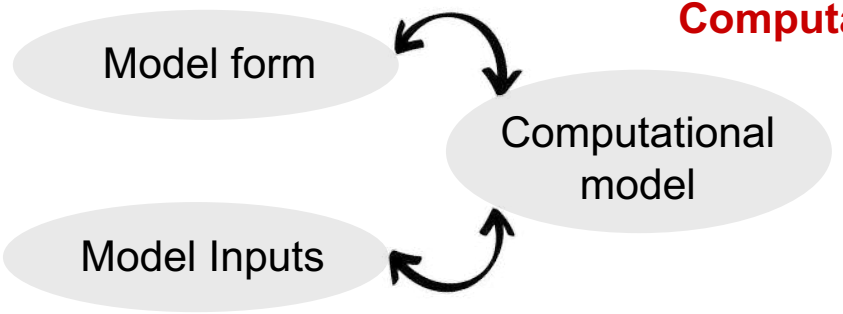
- Multiple benchmark test cases are used to verify the numerical solution

- Newton-Raphson convergence criteria
- Discretization error



V&V-40 pipeline: validation



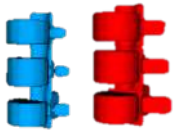
Model form

- Governing equations: density–elasticity relationship
- System configuration: CT-derived femur geometry
- System conditions: applied boundary conditions to simulate a fall on the side

Model inputs

- Governing equations: $\mathrm{E} = A \cdot \rho_{App}^{B}$
- Governing equations:

$$\rho_{QCT} = C + HU \cdot D$$



- Svstem configuration: anatomical landmarks

- System conditions: boundary conditions
- System conditions: contact parameters

V&V-40 pipeline: validation

Model form

Model Inputs

Computational model

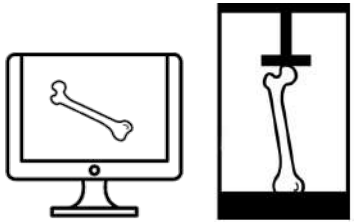
Comparator – Observed Data

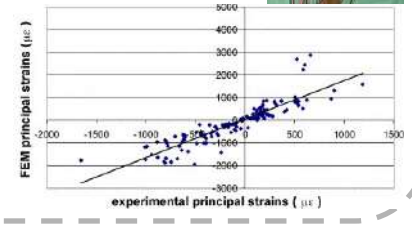
Simulation outcomes

Experimental outcomes

In vitro comparator:

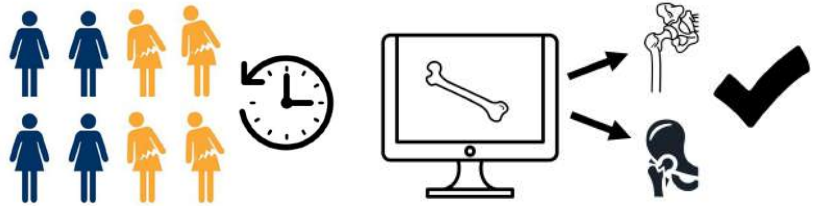
predictive accuracy



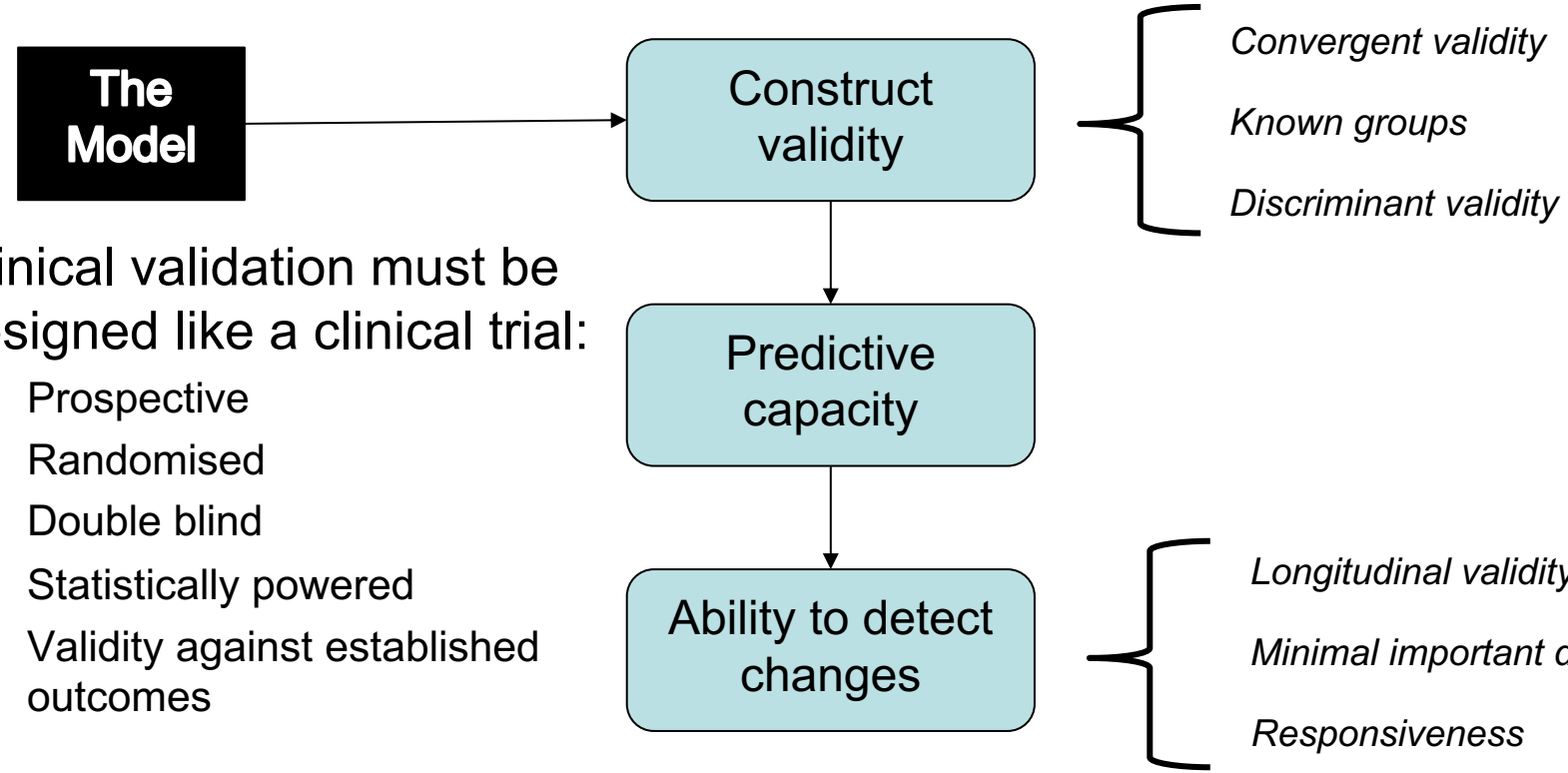


In vivo comparator:

stratification accuracy



Step #2: clinical validation



- Clinical validation must be designed like a clinical trial:
  - Prospective
  - Randomised
  - Double blind
  - Statistically powered
  - Validity against established outcomes

BoneStrength Qualification Advice

- EMA accepts the technical validation plan based on VV-40, but request highest possible risk level, even for a low-risk CoU
- EMA requests a clinical validation based on a full-scale prospective interventional RCT

Economic analysis

- Current cost for a full In Silico Trial with Bone Strength ≈ €200,000
- “The median cost of conducting a study from protocol approval to final clinical trial report was […] **$21.4 million** for phase III trials” Nature Reviews Drug Discovery volume 16, pages381–382 (2017)

BoneStrength: availability

BBCT Digital Twin
(as research tool)

Q4/2022

BoneStrength ISCT
(non-regulatory use)

Q3/2023

Conclusions

- Digital Twin models can be transformed into In Silico Trials, but at a considerable computational cost
- HPC systems are indispensable for the simulation of Phase III clinical trials

The people

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Insigneo Institute, USFD

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Thank you!!!

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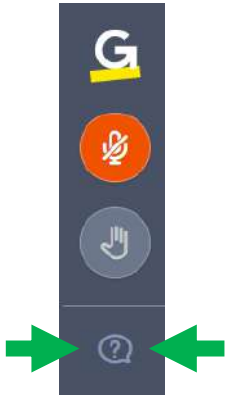

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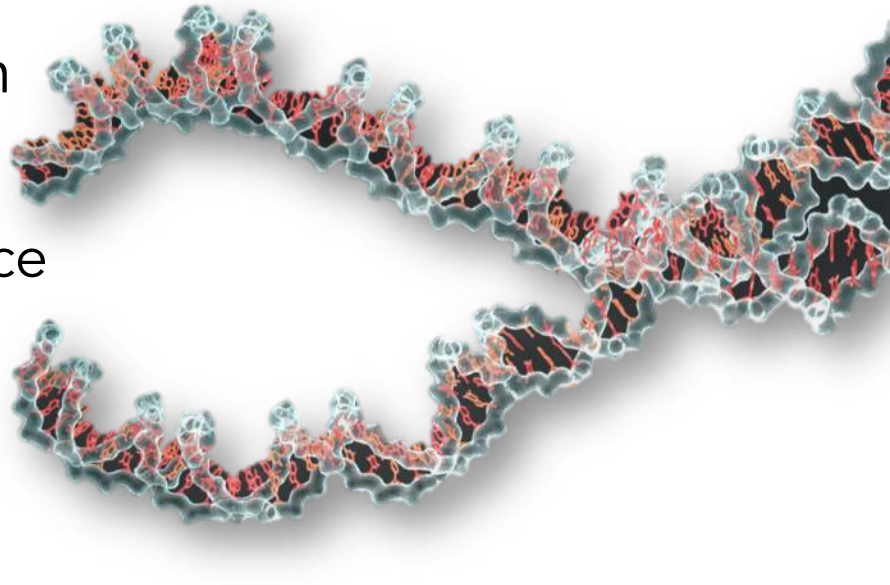

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www.insilico.world/community

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Collaboration	• Join teams and collaboratively work on shared goals, projects, concerns, problems or topics
Safe space	• A pre-competitive space where experts from academia, industry, and regulatory agencies can ask for and exchange advices

More than 500 experts have already joined the community and its channels

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Thank you for participating!

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