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

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The problem /1

- Bone drugs are long-term therapies that aim to reduce the risk of bone fracture associated with low-energy impacts (fragility fractures)
- The risk of hip fracture in the general population over-50 is only 2% over ten years
- To observe 100 hip fractures we would need to follow up for 10 years over 5,000 patients

The problem /2

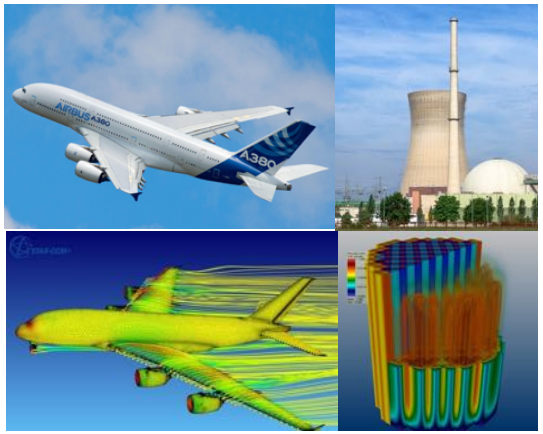
- Efficacy of recent bone drugs was demonstrated indirect endpoints, such as changes in bone mass
- But bone mass can explain only 60-70% of hip fractures
- This creates the serious possibility that the efficacy found in the phase III clinical trial, will not translate into effectiveness in future HTA studies

Problem /3

- Many of these new drugs can be used only once the patient life, and only for limited time; it would be important to know when is the best time to use them
- But clinical trials aimed to optimise the treatment protocol with two or more drugs would be prohibitively expensive, so no one does them

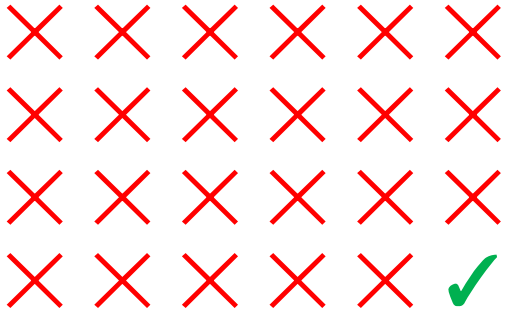
Why not use computer simulation?

In any other industrial sector



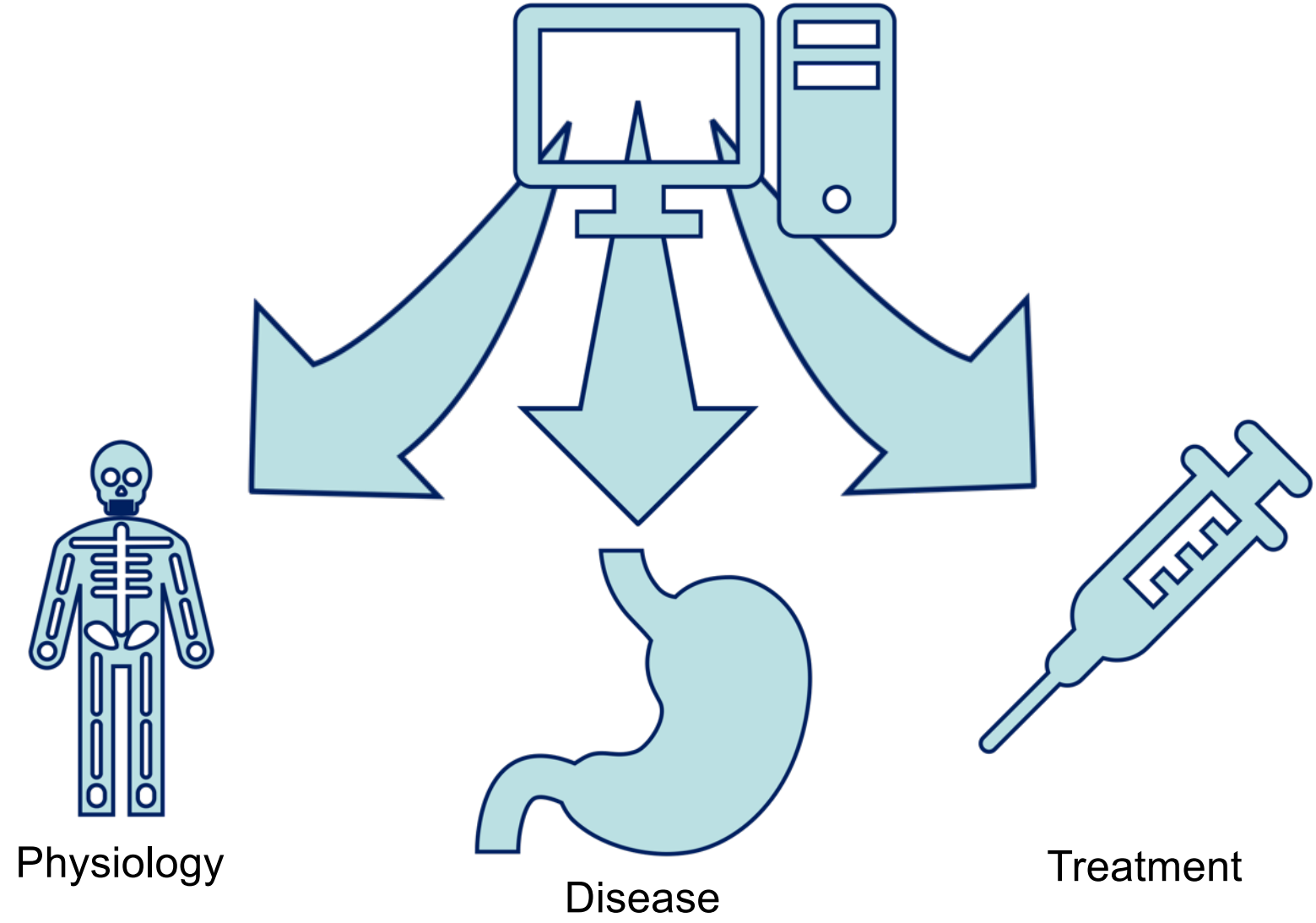
Testing is now done mostly with computer simulation

In healthcare

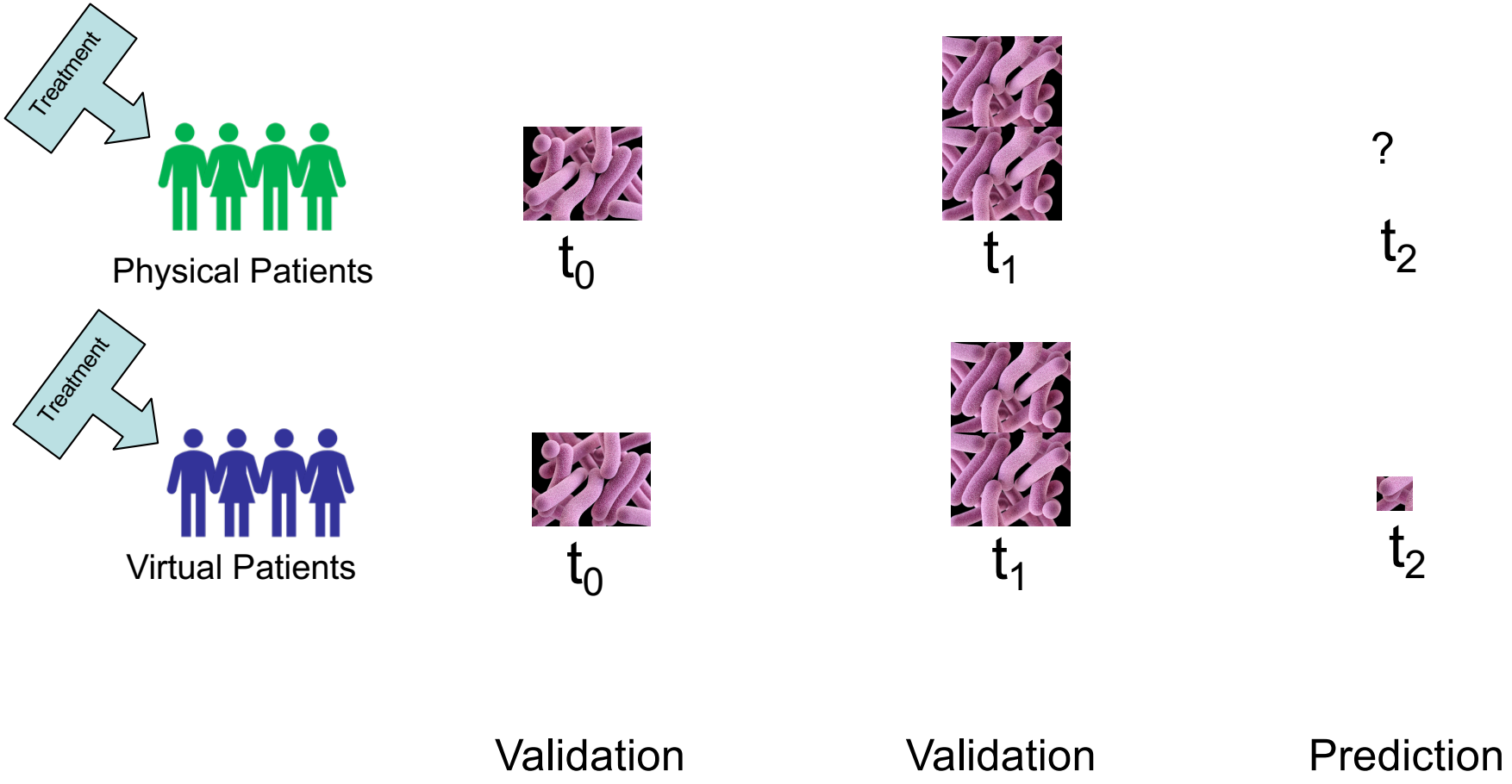


We test safety and efficacy of new products only by trial and error

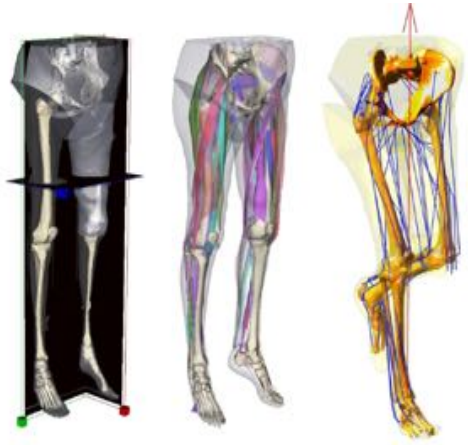
A model for In Silico Trials



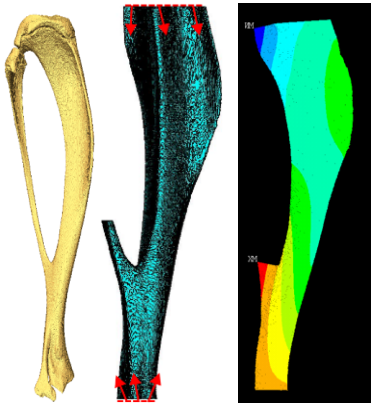
Simplest use: time extrapolation



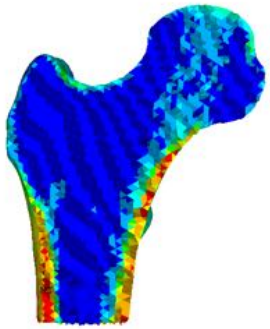
An hypothetical model



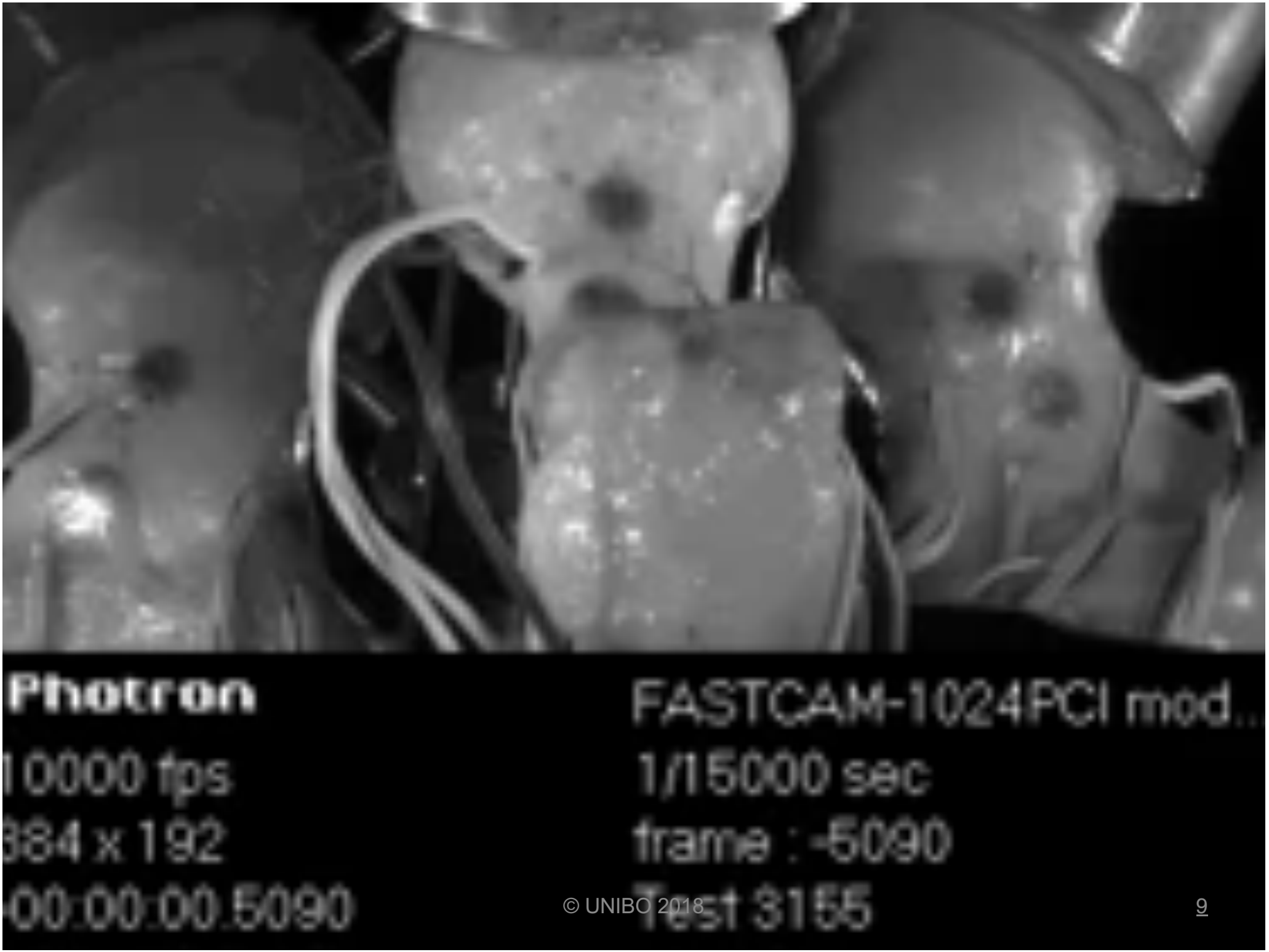
A **validated** patient-specific model that predicts the risk of hip fracture today



A **validated** mouse-specific model that can provide an estimate of the drug effect



A **validated** stochastic population-specific bone remodelling algorithm model that predicts changes in bone over time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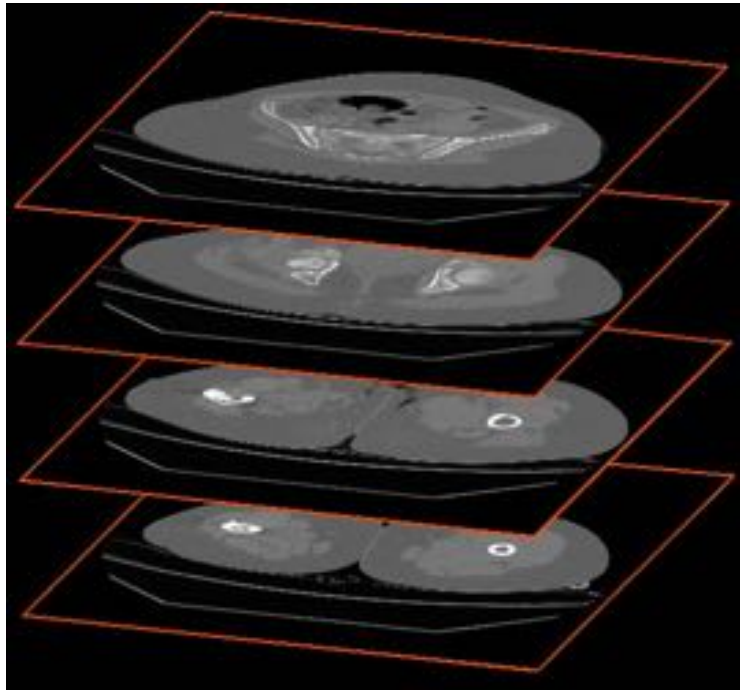
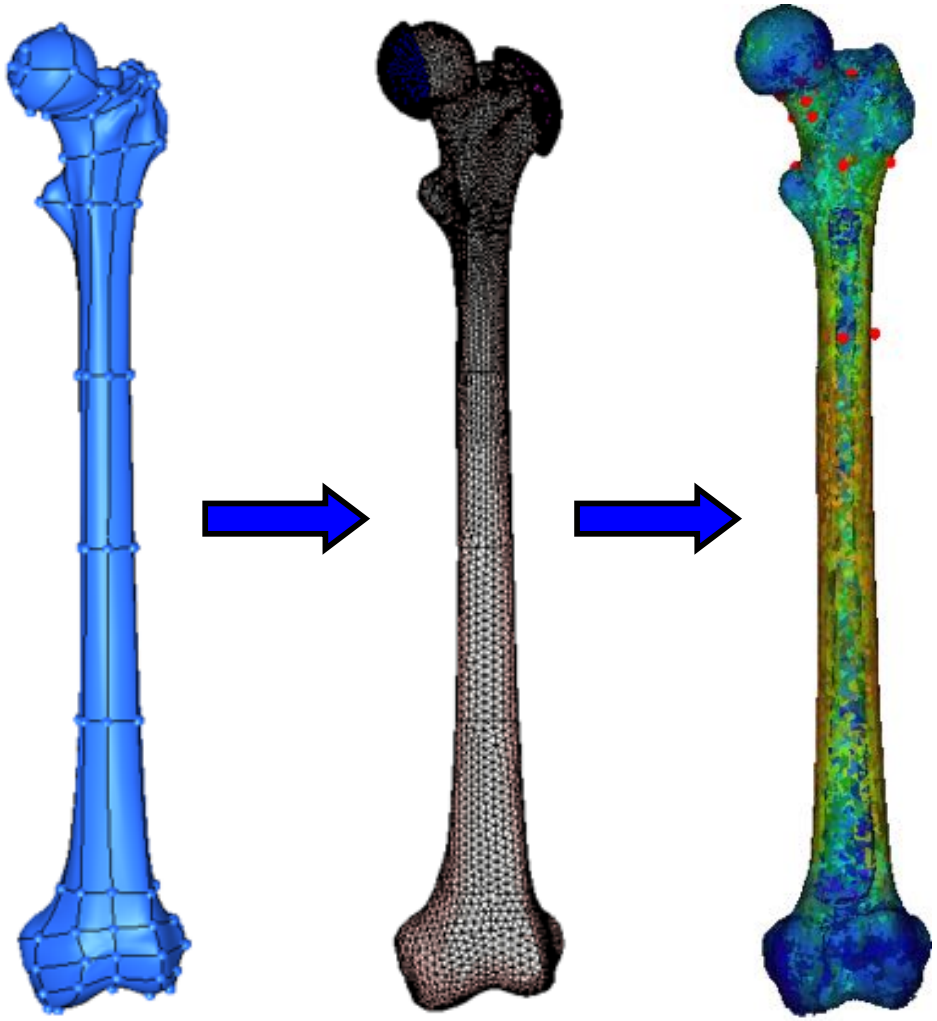
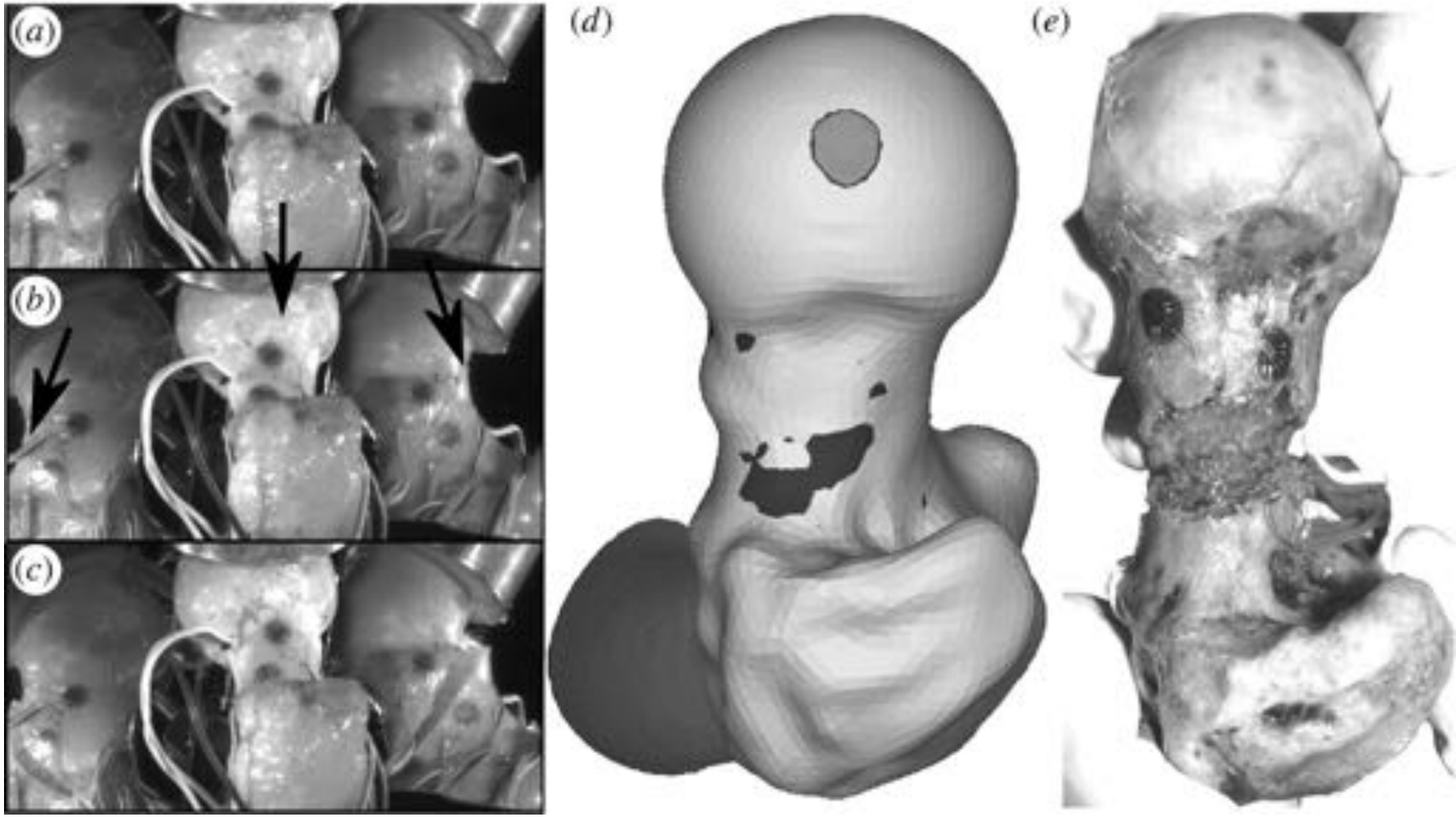
CT2S: from imaging to models



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



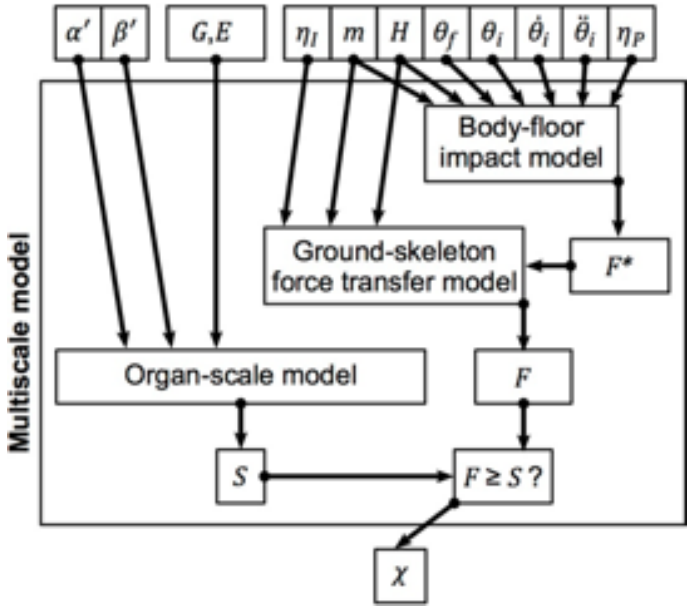
Experimental validation

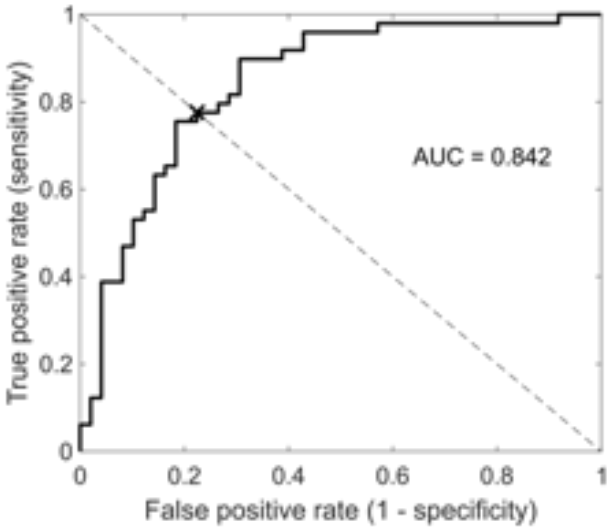


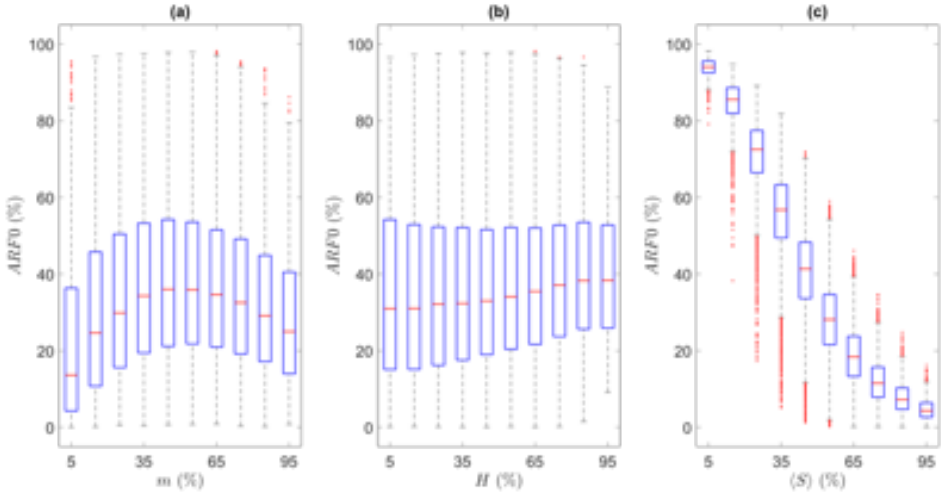
Cristofolini L. et al. Phil. Trans. R. Soc. A 2010;368:2725-2763

ARF0 fall simulator

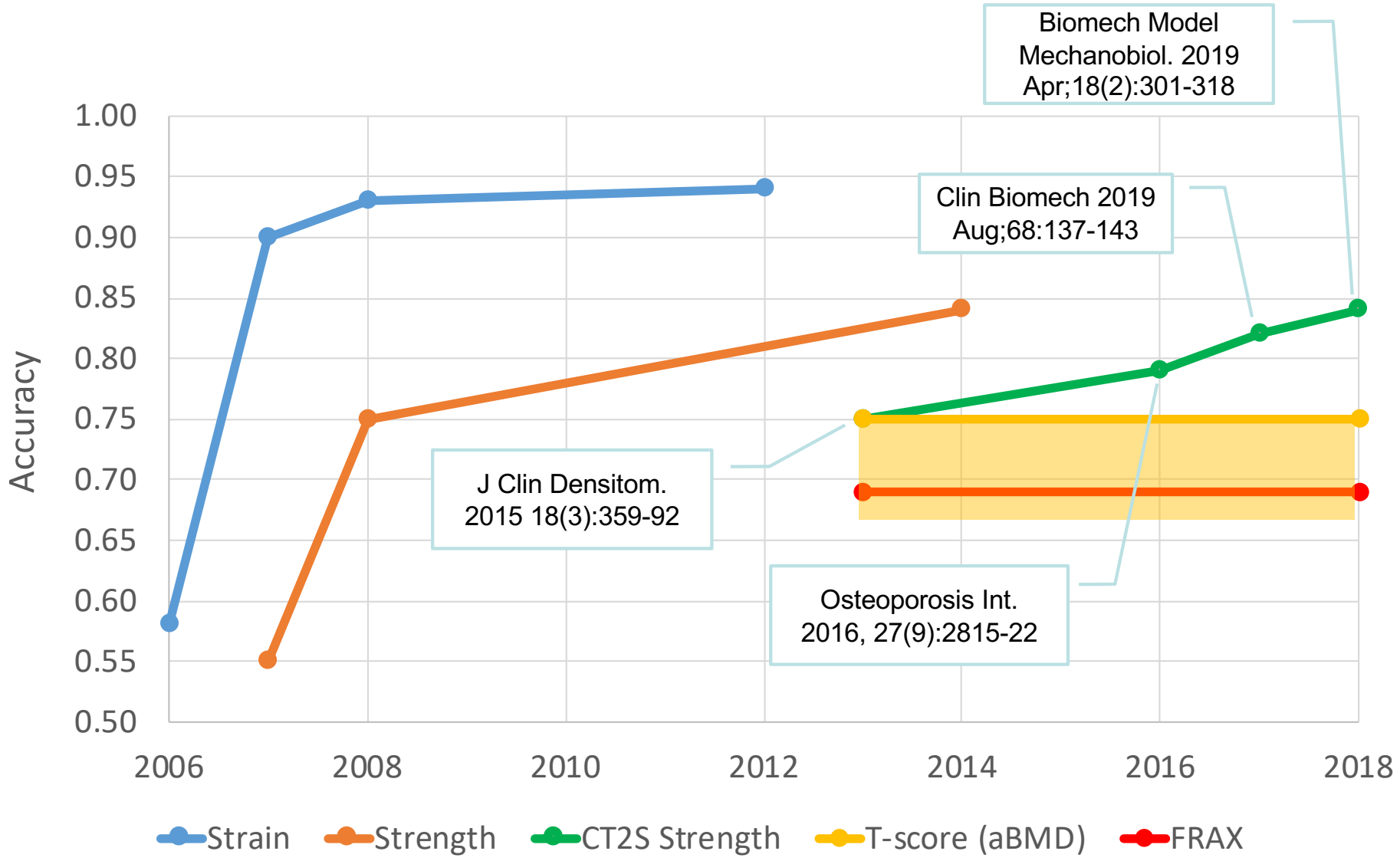
- Multiscale model of fall, body-floor dumping, femur deformation
- Full stochastic modelling of fall
- Stochastic modelling of uncertainties (i.e. soft tissue dumping)
- Accuracy – 0.82 ➔ 0.84





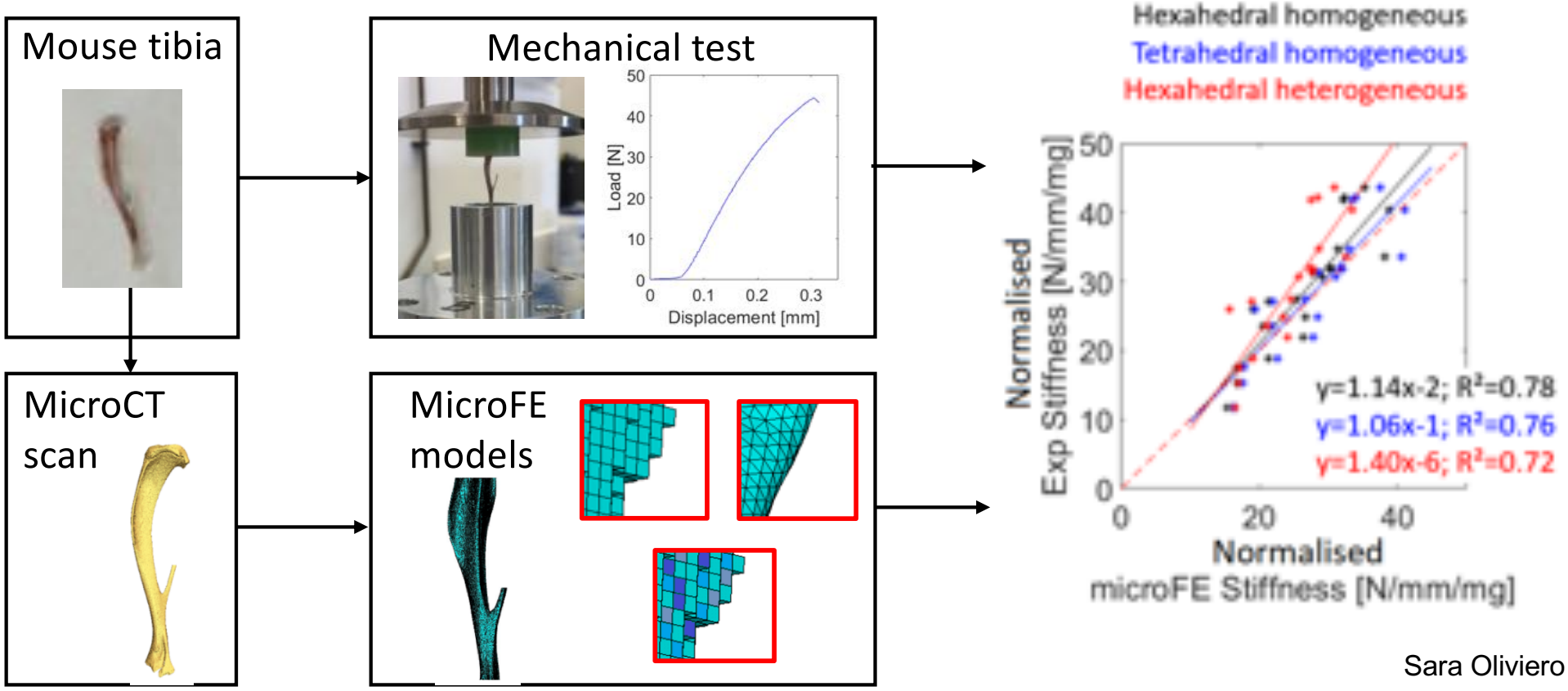


Not an easy journey



Validation of FE models of mouse tibia

- 20 tibiae from C57BL/6 and BALB/c mice, 16-24 week-old
- Validation of structural mechanical properties



Sara Oliviero

INSIGNEO

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

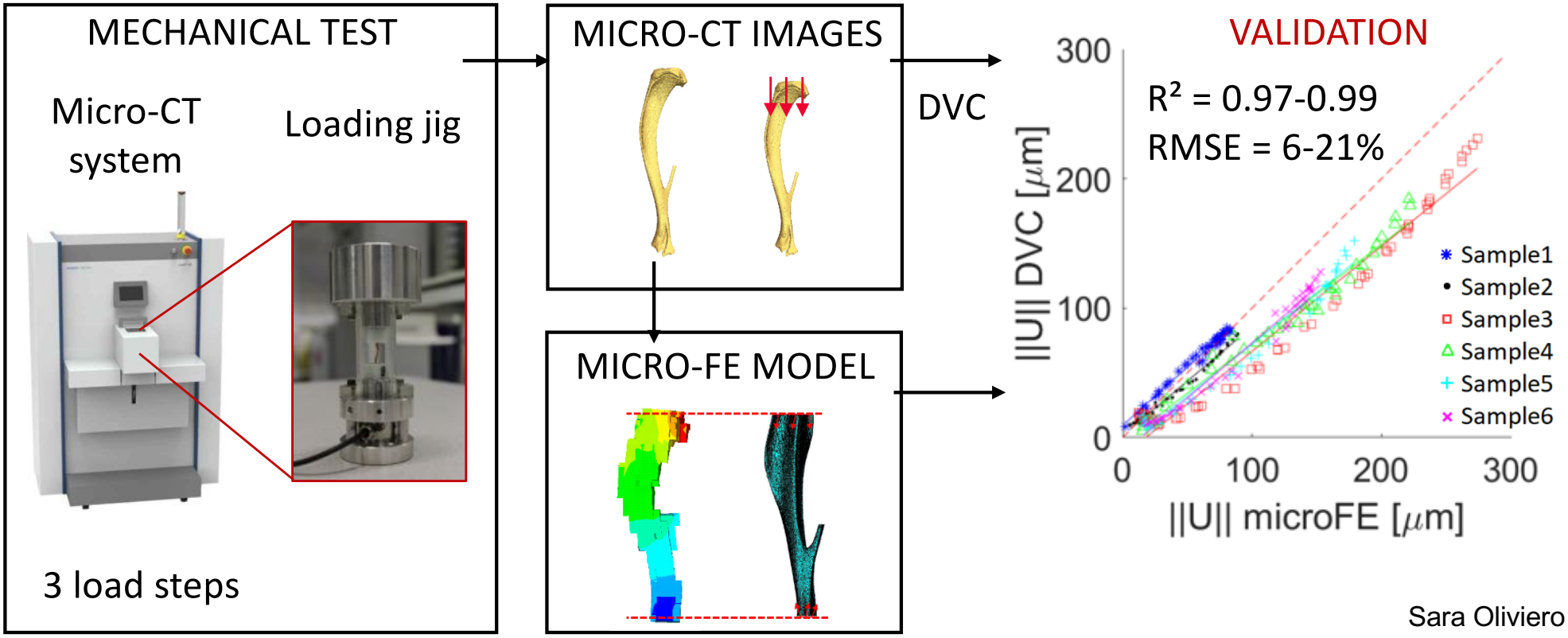
skelet.AL

EPSRC

MultiSim

Validation of FE models of mouse tibia

- 6 tibiae from C57BL/6 mice, 16-24 week-old
- Validation of local displacements



Sara Oliviero

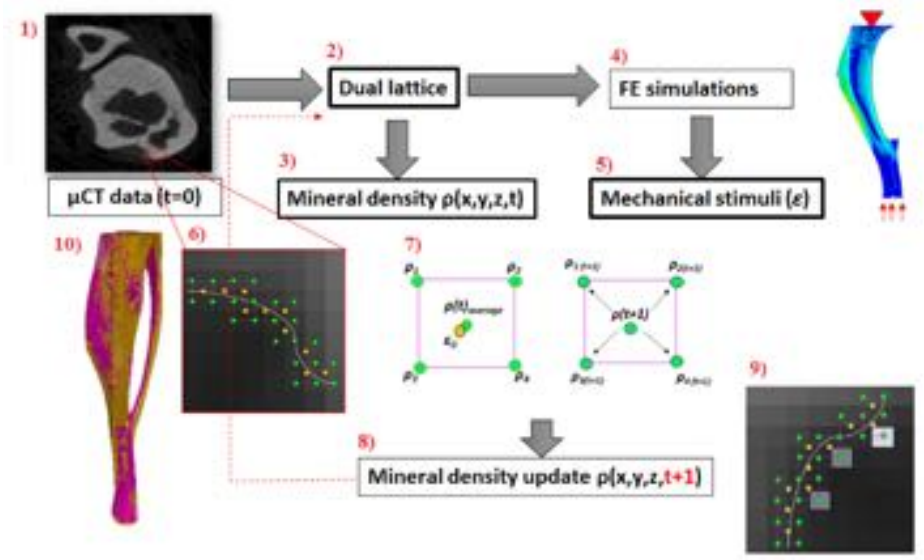
1. Oliviero et al., JMBBM, 2018

skelet.AL EPSRC MultiSim

Bone remodelling algorithm

Input

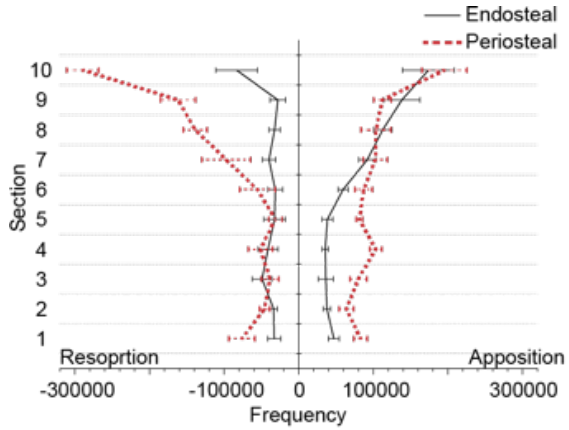
t=0

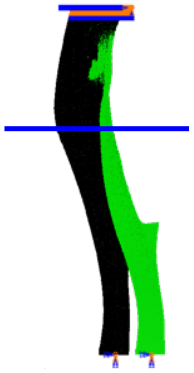


Prediction

t=n

Experimental remodelling





Strain energy density

Maximum principal strain

Red = experimental remodelling
Yellow = predicted correctly by model

Vee San Cheong

INSIGNEO 1. Cheong et al., BMMB, under revision

EPSRC Engineering and Physical Sciences Research Council
MultiSim

Conclusions

- It is a long journey to develop and validate In Silico Trials models

- In CompBioMed2 we plan to:
  - complete the development
  - Complete the validation of the BR simulator
  - run large scale in silico trials of drugs already in use to provide a final clinical validation

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