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Institute for *in silico* Medicine

Use of machine learning and modelling to improve diagnosis and treatment of ischaemic stroke

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NHS Foundation Trust

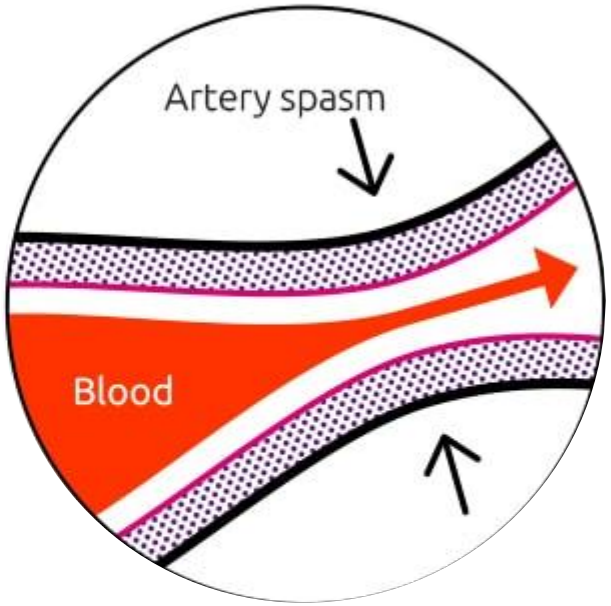
Outline

- Cardiovascular applications
- Musculoskeletal applications

The goal

Use of machine learning methods to develop a methodology for differentiating between **cerebral vasospasm (VS)** and **ischaemic stroke (IS)**

Cerebral vasospasm (VS)

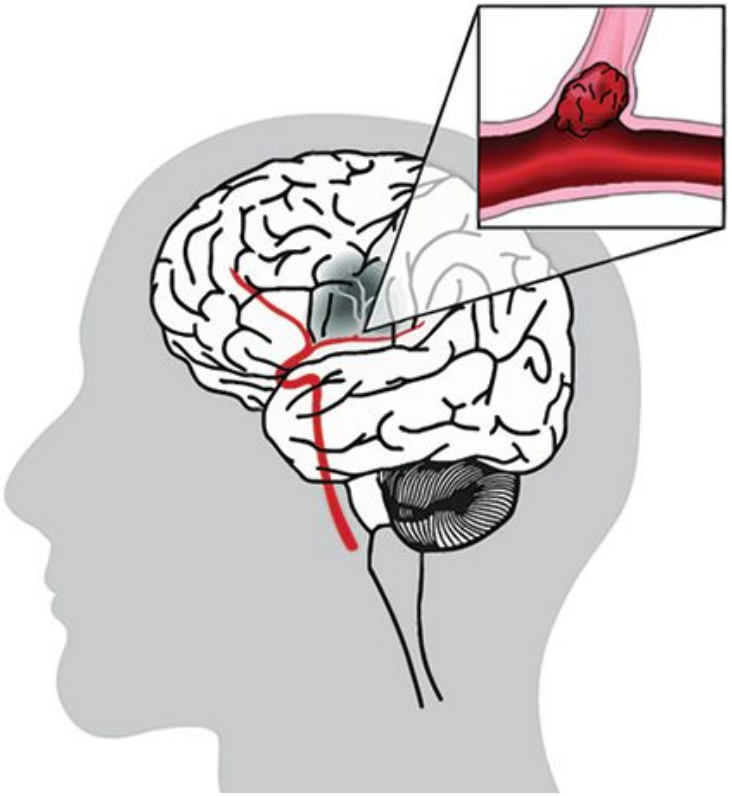


http://www.idorsia.com

- Progressive narrowing of arteries after stroke/SAH
- Major cause of cerebral ischaemia

Findlay et al., *Can J Neurol Sci*, 2016

Ischaemic stroke (IS)



http://www.enableme.org.au

- Blood supply to brain is cut off or severely reduced
- Leading cause of long term disability

Phipps, et al., *BMJ,* 2020

VS or IS?

Different treatment strategies:

Treatment of VS

- Pharmacological
- Endovascular (balloon and catheter **angioplasty**)

Treatment of IS

- Thrombolytic drugs
- Mechanical removal (balloon and catheter **thrombectomy**)

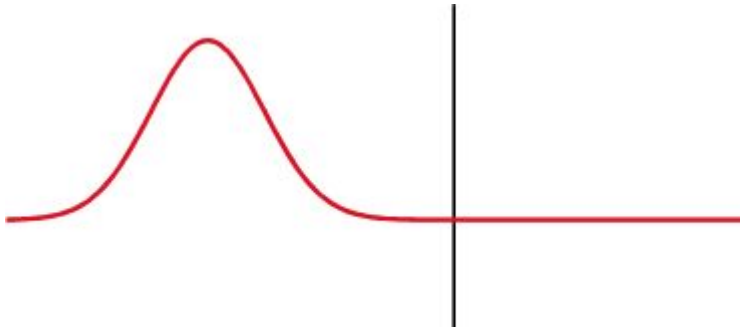
Similar diagnostic techniques:

- Imaging (CT, MRI, …)
- Transcranial Doppler

Transcranial Doppler

- Measurement of Doppler frequency shift to estimate the blood velocity
- Portable and non-invasive
- Abnormal waveforms in arteries affected by VS and IS
- Low sensitivity to alterations in peripheral vessels

Pulse waves in the cardiovascular system



O. Alexandrov
https://commons.wikimedia.org/w/index.php?curid=3148138

- Pressure waves originate from intermittent contractions of the heart
- Wave propagate through the network of elastic vessels
- Waves are reflected at discontinuities

Pulse waves in the cardiovascular system

T. Walsh
http://www.ophysics.com

- Incident and reflected waves superimpose to determine the observed waveform

- Waveforms are rich in diagnostic information about the system through which they propagate

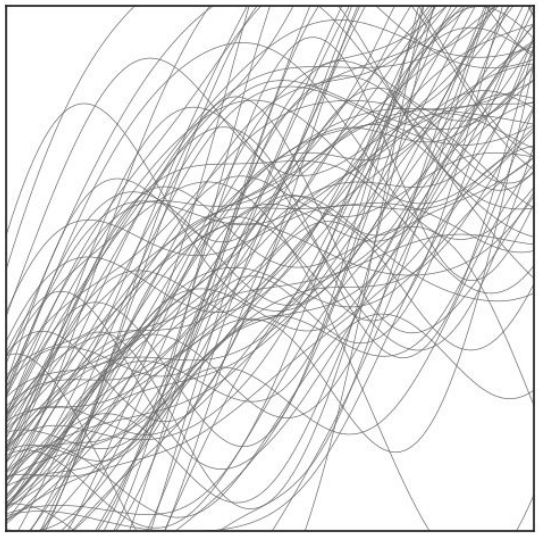
1D cardiovascular model (openBF)

- Incompressible flow in tapered elastic vessels
- Method of characteristics
- Finite volume method
- Open source

$$
\begin{cases}
\dfrac{\partial A}{\partial t} + \dfrac{\partial (Au)}{\partial x} = 0, \\
\dfrac{\partial (Au)}{\partial t} + \dfrac{\partial \left(Au^2\right)}{\partial x} + \dfrac{A}{\rho}\dfrac{\partial P}{\partial x} = -8\pi\dfrac{\mu}{\rho}u, \\
P = P_{ext} + \beta\left[\left(\dfrac{A}{A_0}\right)^{1/2} - 1\right], \quad \beta = \sqrt{\dfrac{\pi}{A_0}}\dfrac{Eh_0}{1-\sigma^2},
\end{cases}
$$

Melis et al., Int J Numer Meth Biomed Eng, 2017

Gaussian process statistical emulators

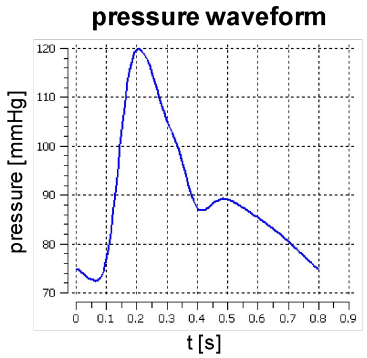


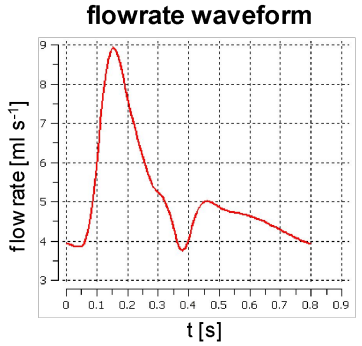
Melis et al., Int J Numer Meth Biomed Eng, 2017

- GPE is trained with few runs of the original model
- GPE is used to perform sensitivity and uncertainty analysis, reducing computational time
- Identification of waveform features strongly correlated with the pathology in exam

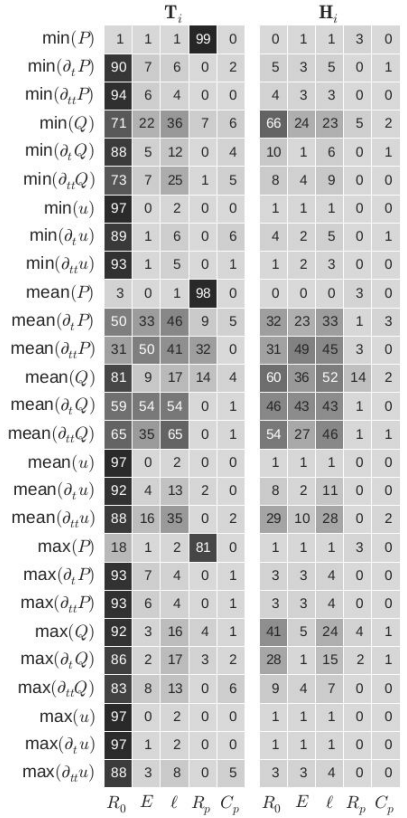
Sobol's sensitivity analysis: VS biomarker

Which inputs, or combination of inputs, have the greatest effect on output variables that can be observed in a clinical setting?





Melis et al., J Biomech, 2019



CV biomarker	$\mathbf{T}_{R_0}$	$\mathbf{H}_{R_0}$
$\mathrm{mean}(u)$	97.43	0.82
$\max(u)$	97.28	0.84
$\min(u)$	97.23	0.93
$\max(\partial_t u)$	96.83	0.90
$\min(\partial_{tt} P)$	93.76	3.62
$\max(\partial_{tt} P)$	93.05	3.35
$\min(\partial_{tt} u)$	92.98	1.16
$\max(\partial_t P)$	92.52	3.48

Distal arteries:
$\min(u_t)$

Proximal arteries:
mean(u)

The plan: IS

- Simulate complete physiological cerebral network to have a baseline
- Simulate IS in a variety of common locations
- Identify pool of biomarkers through GP based SA

Ideas for collaboration?

- Waves reflect due to tortuosity, bending and other 3D geometric features: does the same analysis in 3D FSI CFD confirm the findings of 1D models?

- Explore the use of other statistical emulators

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Musculoskeletal modelling in CompBioMed2

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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 5000 patients

The problem /2

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

The problem /3

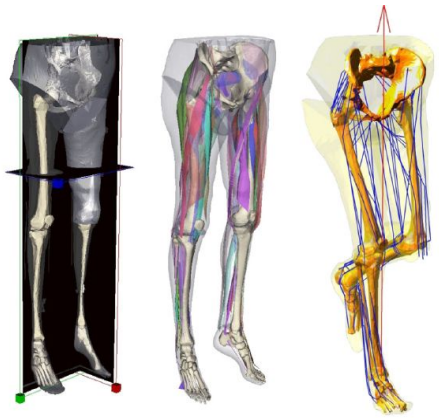
- Many of these new drugs can be used only once during the patient life, and only for limited time: it would be important to know when is the best time to use them

- Clinical trials aimed at optimising the treatment protocol with two or more drugs would be prohibitively expensive, so alternatives are required

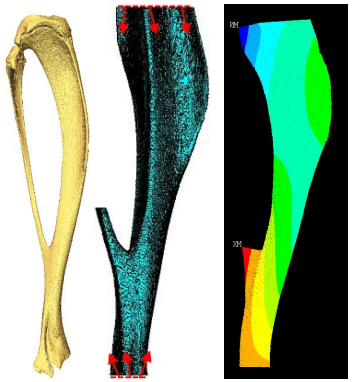
The goal

To develop collaboratively an *in silico* trials platform to evaluate the efficacy of new bone drugs on human cohorts, from limited pharmacodynamics data on the new drug obtained on mice

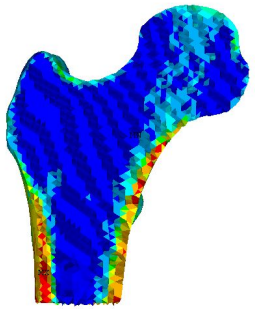
An hypothetical model



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

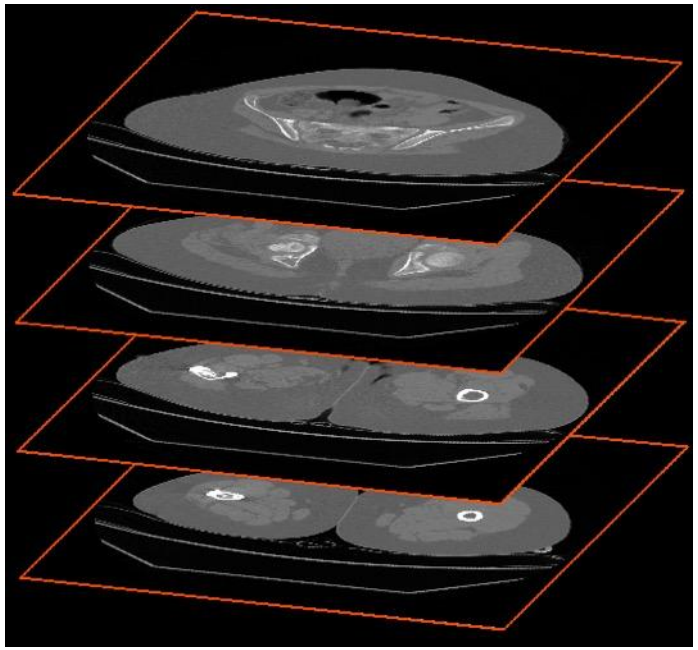


2: A **validated** mouse-specific model that can provide an estimate of the drug effect

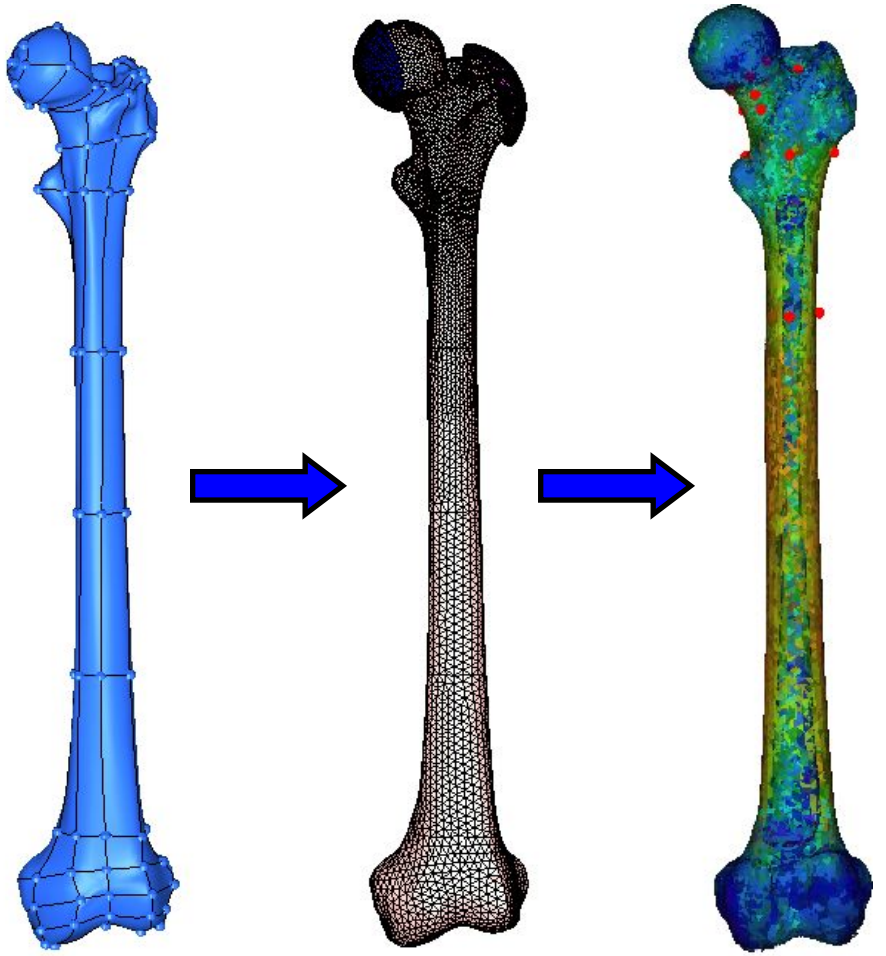


3: A **validated** stochastic population-specific bone remodelling algorithm model that predicts changes in bone over time

1 - CT2S: from imaging to models

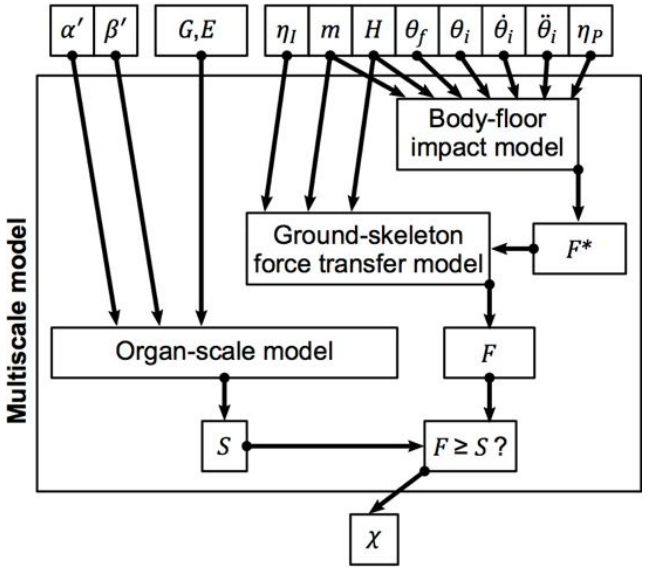


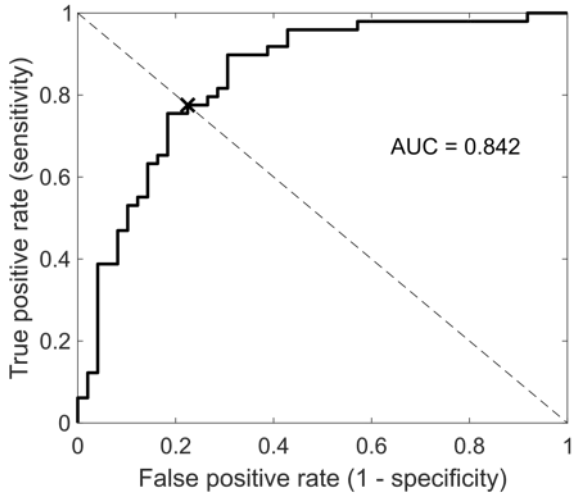
Basu et al., Biomater Med Devices Artif Organs. 1985



1 - ARF0 fall simulator

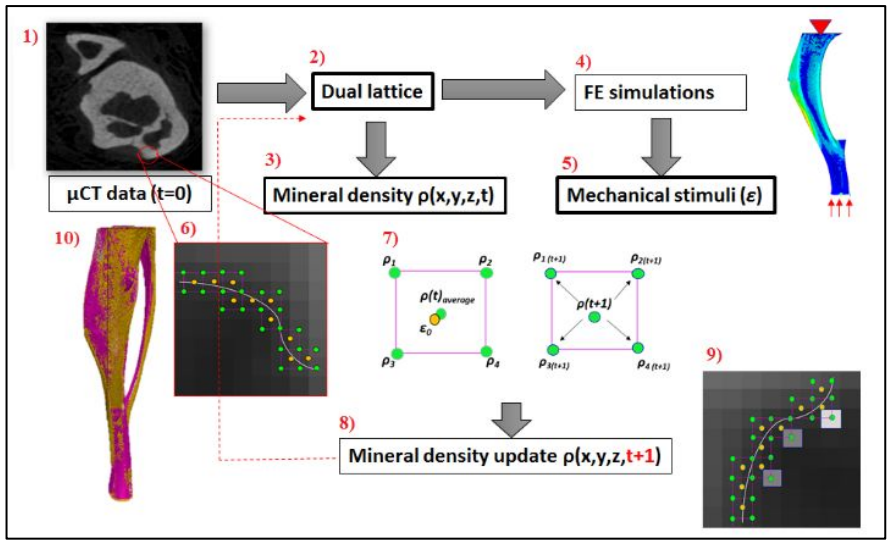
- Multiscale model of fall, body-floor damping, femur deformation
- Full stochastic modelling of fall
- Stochastic modelling of uncertainties (i.e. soft tissue damping)
- Accuracy: 0.82 □ 0.84





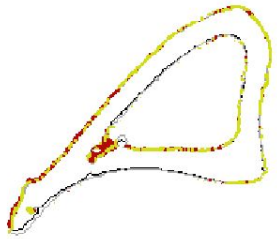
3 - Bone remodelling algorithm

Input

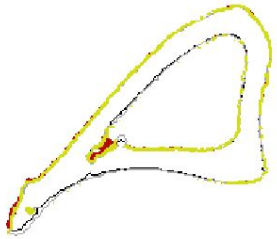


Prediction

Strain energy



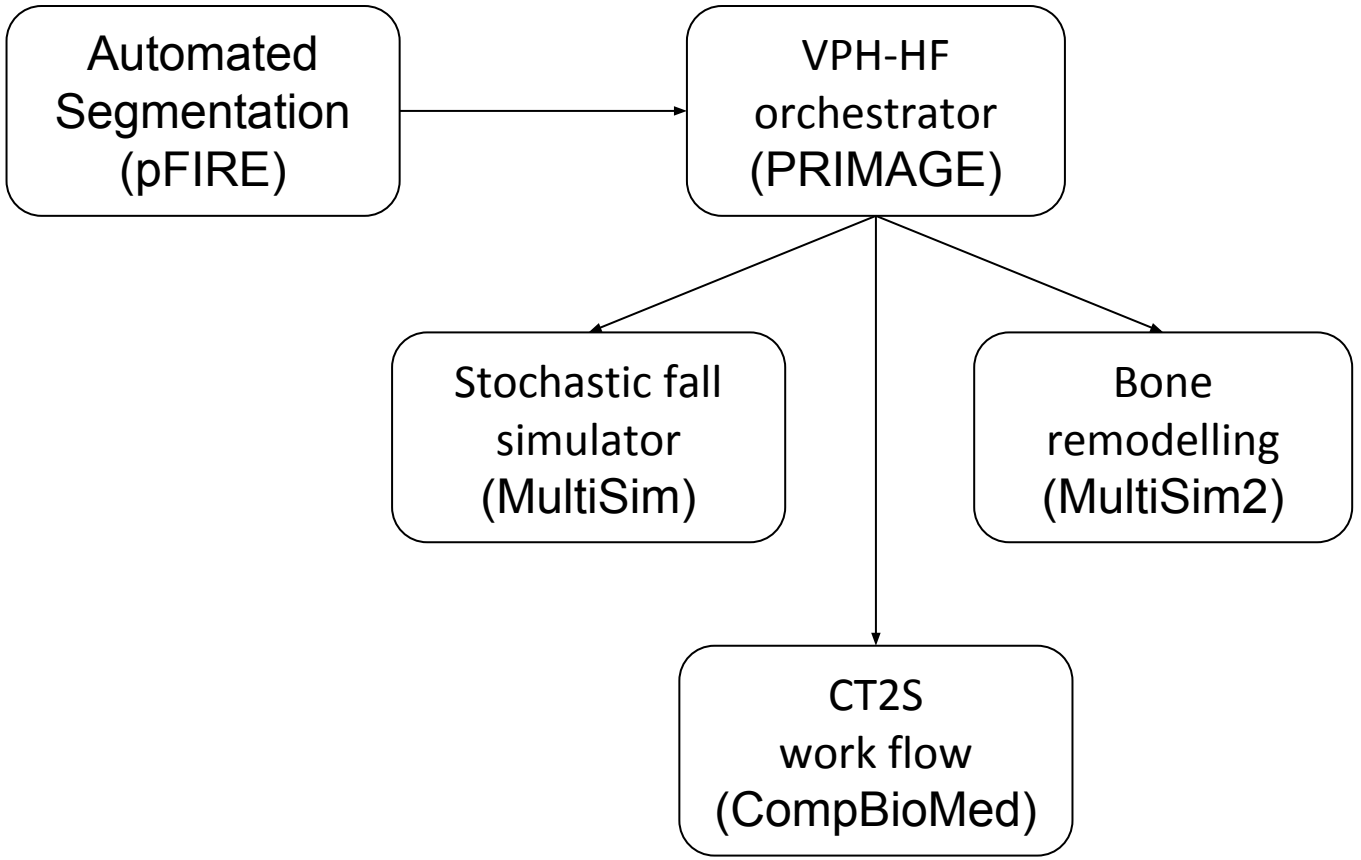
Maximum



Red = experimental remodelling
Yellow = predicted correctly by model

Cheong et al., BMMB, under revision

Software architecture



Clinical studies

1. Sheffield cohort
   a) 98 women, 50% with hip fracture
   b) Perfect controlled validation cohort
   c) Simulations run on USFD cluster
2. Virtual cohort
   a) 1000 virtual patients generated by statistical atlasing of the Sheffield cohort
   b) Simulations run on SurfSara HPC
3. Bologna cohort
   a) Up to 500 cases, 5% with hip fracture
   b) Validation cohort for virtual population
   c) Simulations run on UNIBO cluster

Acknowledgements

Thank You!

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