VPHOP: multiscale modelling to fight osteoporotic fractures

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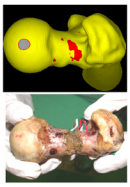
Osteoporosis is a killer

Osteoporosis is a life threatening disease. OP fractures kill as many women as breast cancer. 30 to 50% of all women and 15 to 30% of all men will face an osteoporotic fracture in their lifetime. 4,000,000 fractures cost the European health system more than 30 billion Euro per year. This figure is likely to double by 2050. 250,000 elders will die of related complications within 12 month; all others will remain impaired. The technology in current clinical practice is clearly insufficient. The accuracy in predicting fractures is as low as 60%. Even if we see the drugs are not working we wait for the fracture, and only then surgically fix it. We need better ways to prevent osteoporotic fractures.

Predictive, Personalised and Integrative medicine (PPI)



Bone physiology is as complex as any other organ, but the biomechanics of bone fracture is in itself a purely mechanical event. This is one of the few domains where organ-level models already achieve predictive accuracies of over 90%.
The VPHOP project will make possible Predictive and Personalised (P2) medicine for osteoporosis:

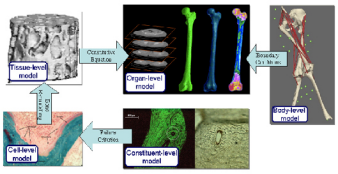
-Predictive: multiscale models representing the skeletal mechanobiology from the whole body down to the molecular constituents, simulate the skeletal loading in various conditions and predict if the bones will fracture in each of them.

-Personalised: the multiscale model is personalised using specific patient information. The more available information, the more personalised the model becomes.

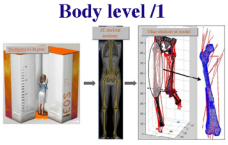
The Integrative model

OP fracture is multiscale:

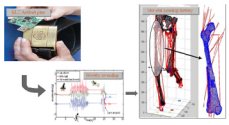
-**Body** musculoskeletal anatomy and neuromotor control define the daily loading spectrum, which includes paraphysiological overloading events
-Fracture events occur at **Organ** level
-**Tissue** morphology defines the bone elasticity
-The **Cell** activity changes the tissue morphology and composition over time
-The **Constituent** of the extracellular matrix are the prime determinants of the tissue strength



Body level /1



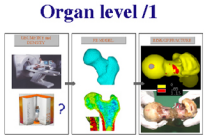
Body level /2



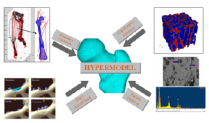
Body level-Challenges

Technology	Available now	Challenge
BOS	3D skeletal anatomy	3D musculoskeletal anatomy
ActiBelt	Monitor 1 week of physiological activities	Monitor overloading and stumbling events
Chaste model	Predict joint contact forces under normal conditions	Predict probabilistic spectrum of skeletal overloading

Organ level /1



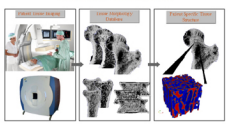
Organ level /2



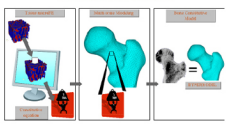
Organ level-Challenges

Technology	Available now	Challenge
Screening OP	Statistical regression from DEXA-patient's data	From a 3D FE models DB through registration on patient's data
BOS	3D skeletal anatomy	3D skeletal density distribution
IOF FE model	Failure load prediction under simplified BCs	FE prediction integrating multi-scale models

Tissue level /1



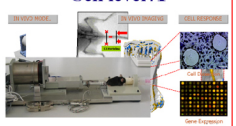
Tissue level /2



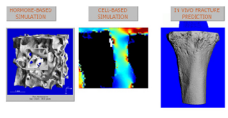
Tissue level-Challenges

Technology	Available now	Challenge
Tissue imaging	XperCT, XtremeCT	Optimization of highest resolution at tolerable radiation exposure
Patient specific tissue structure	Diverse human bone morphology data	Build and use database w/registration images of patient tissue structure
Bone constitutive model	Multiscale FBA	Accurate prediction of bone strength

Cell level /1



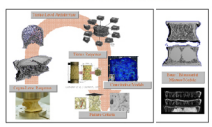
Cell level /2



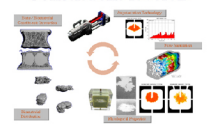
Cell level-Challenges

Technology	Available now	Challenge
In vivo model	Mouse tail loading and in vivo imaging; molecular cell assays	Gene expression profile linked to skeletal status in disease and treatment
In silico model on animals	Cell based prediction models in vitro	Validation of in silico biology using real experiments
In silico model on humans	Simulation of age-related bone loss	Extrapolation of animal models to humans

Constituent level /1



Constituent level /2

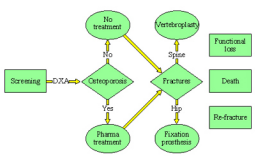


Constituent level-Challenges

Technology	Available now	Challenge
Constituent models	Discrete isotropic bone and cement models	Multi-scale mixture models non-linear formulations
Failure criteria	Maximum shear strain	Damage accumulation and bone-biomaterial interaction
Rheological models	Isotropic Darcy flow model	Patient-specific anisotropic cellular model

Current standard of care:

Current fracture predictions are based on historical, fracture-patient data sets to identify key factors which contribute to the increased probability of an osteoporotic fracture. This approach oversimplifies the mechanisms leading to an osteoporotic fracture and fail to take into account numerous, hierarchical factors which are unique to the individual.



VPHOP clinical protocol

Prognosis

-Predicting the absolute risk of femoral or vertebral fracture under low energy loading.

-Predicting the probability of developing micro-fractures at the tissue level.

Pharmacological treatment planning

-Predicting changes over time due to the evolution of osteoporosis.

-Predicting the changes in risk due to the pharmacological treatment.

Interventional treatment planning

-Predicting the most clinical location within each bone.

-Predicting the changes in risk due to interventional augmentation.