Autumn 2005

QuBQu²

- Qualifying Bone Quantity
-Quantifying Bone Quality
www.hull.ac.uk/QuBQu

Ongoing Projects

Volumetric Density from Conventional BMD: BMD-TM
Finite Element Analysis of X-ray Images: FEXI
Sensitivity of FEXI to Anatomical Variations of the Proximal Femur: FEXI-Sim
Paediatric Infra-Red Skeletal Assessment: PIRSAN
Quantitative Ultrasound: QUS
Prediction of Propensity to Fall: Hull Stabilometer
Bone Remodelling Simulation Environment: BMU-Sim

- Bone is a fascinating human tissue that continually undergoes a remodelling process where old is replaced with new. It automatically adapts to better serve the functional demands placed upon it. Unfortunately though, the remodelling process falters in later life, often leading to osteoporosis related fragility fractures.
- Assessment of the mechanical integrity of the skeleton has for the past 40 years been based predominantly upon bone mineral density (BMD), an areal measure of **Bone Quantity**. With the emergence of anabolic agents and increasing interest in metabolic bone disorders affecting children, there is a need to **Qualify** our measurements of **Bone Quantity**.
- The term **Bone Quality** is increasingly being used to describe the factors in addition to **Bone Quantity** that determines the mechanical integrity of the skeleton. These factors include the anatomical geometry (e.g. length of femoral neck), the degree of mineralisation, and the spatial distribution of bone (cortical and cancellous). It is important however that we **Quantify Bone Quality** in order to fully elucidate its contribution to the mechanical integrity of the skeleton.
- The aim of the **QuBQu²** research initiative is to better understand the relationships between the **Quantity** and **Quality** of bone with the mechanical integrity of the skeleton. Allied to this are emerging clinical topics such as paediatric bone assessment. We may also consider the role of computer simulation, where different physiological and physical scenarios may be readily investigated in a fraction of real-time.
- The **QuBQu²** research initiative is undertaken within the University of Hull's Clinical Biosciences Institute, and forms in part a collaboration with the Centre for Metabolic Bone Disease and the Centre for Medical Engineering and Technology.
- This Newsletter aims to update you on projects currently being undertaken within the **QuBQu²** research initiative, and hopefully to encourage you to collaborate with us in the future.

THE UNIVERSITY OF HULL

Hull and East Yorkshire Hospitals NHS Trust

ClinBio

CMET

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BMD-TM
Volumetric Density from Conventional DXA-derived Bone Densitometry

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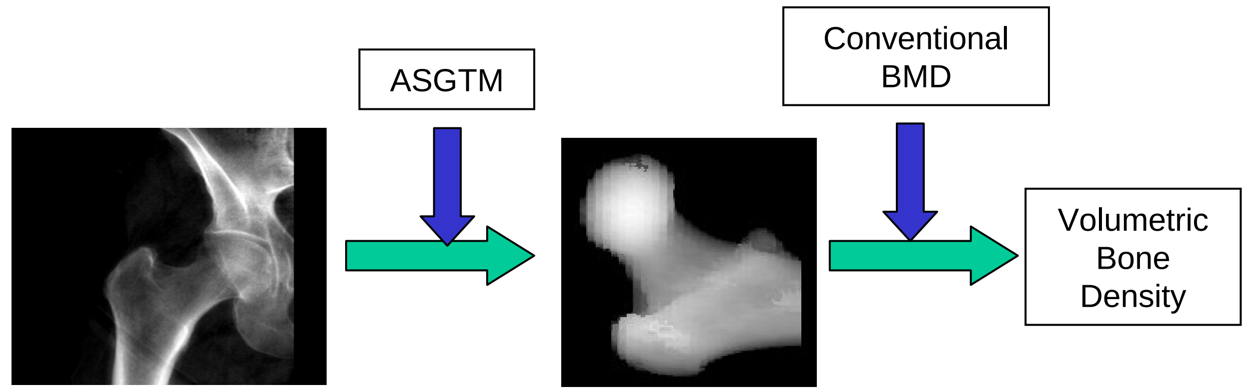
Background

- Conventional assessment of osteoporosis is via measurement of BMD, generally via DXA at the proximal femur and lumbar spine
- BMD (g cm^{-2}) is an areal parameter, describing the amount of bone over a known cross-sectional area. The thickness of bone interrogated is not known.
- BMD is dependent upon bone size - problem for assessment of children and new anabolic agents; need to measure volumetric density (g cm^{-3}).

Concept

- For a given bone (proximal femur), there is consistent relationship between the shape and size of a 2D projection and its orthogonal thickness mapping.



Derived Thickness Map

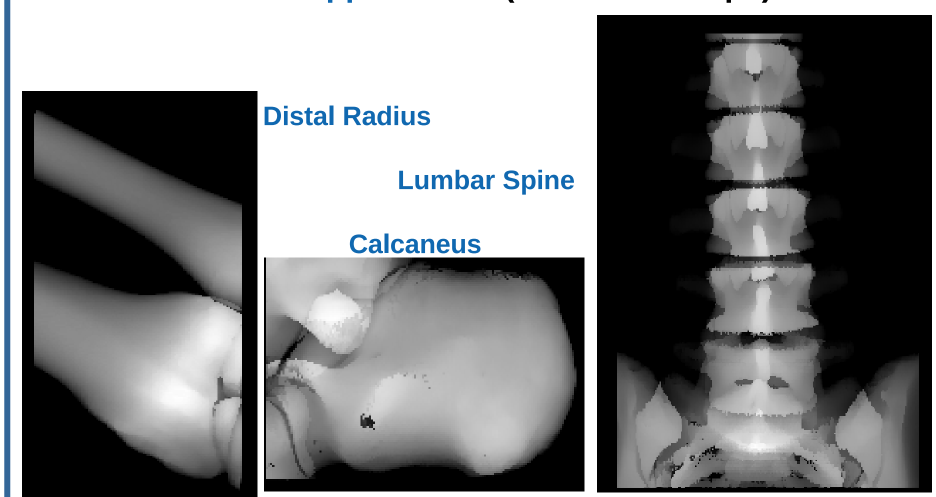
Methodology

- Thickness Maps are derived from a Training Set of CT scans using a bespoke program, CAST2D.
- Using an Annotation technique, an 'Average Shape Generic Thickness Map' (ASGTM) is derived for the Training Set.
- The ASGTM is warped to suit the shape and size of any new 2D projection, deriving an 'individual' Thickness Map.
- Division of conventional BMD by the derived Thickness Map yields the volumetric density (g cm^{-3}) for the bone.

Ongoing Validation Study

- An 'ASGTM' will be derived from a Training Set of proximal femur CT scans.
- For each femur, we will derive & compare true and ASGTM-derived Thickness Maps.
- True and ASGTM-derived Thickness Maps will also derived and compared for an independent Test set of proximal CT scans.

Other Anatomical Applications (Thickness Maps)



FEXI
Finite Element Analysis of X-ray Images

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Background

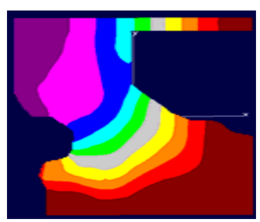
Currently, the preferred method of assessing the risk of an osteoporosis related fracture is a measure of bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA). Other factors however contribute to the overall risk of fracture including anatomical geometry and the spatial distribution of bone. Although spatial information is currently recorded in the form of a DXA image, this information is not utilised clinically.

Concept

We are working on the technical development and clinical evaluation of a novel 2D plane-stress FEA based technique utilising conventional 2D radiographic images (e.g. DXA scan or plain radiograph) that will hopefully provide a quantitative and accurate measure of a subject's fracture risk. FEXI (finite element analysis of X-ray images) provides a computer simulation of a bone being mechanically tested which is equivalent to a person falling on their hip.

Methodology

- Convert X-ray image into 8-bit .BMP = 256 pixel grey levels (≡ areal density)
- Isolate bone of interest, apply loading & support platens
- Consider bone image as 2D thin plate for FE analysis
- Consider each image pixel as finite element of defined Young's modulus
- Simulate mechanical test, applying known load
- Record vertical displacement of platen
- Calculate stiffness = applied load / platen displacement
- Validate with clinical trials & experimental studies
- Clinical pilot studies to date most encouraging!



Clinical Validation Study

Hypothesis

That FEXI provides greater discrimination than conventional BMD between subjects who have, and have not, suffered an osteoporotic fracture.

Materials & Methods

15 female subjects were recruited who had recently suffered a non-traumatic hip fracture. Within a week of them being chair-mobile, they were transported by private ambulance from the Orthopaedic Ward at Hull Royal Infirmary to Centre for Metabolic Bone Disease. A DXA hip scan was performed on a Lunar Expert XL Densitometer, from which Total Hip BMD was recorded and the hip image exported for FEXI analysis. A control cohort was identified that was matched for sex, age, and most importantly, total hip BMD. These subjects had not suffered a previous non-traumatic fracture and had not taken steroids.

Results

Parameter	Control (C)	Fracture (F)	Pairs (C – F)	p-value
Age (years)	78.5 ± 2.0	79.1 ± 5.0	-0.6 ± 5.7	0.691
Weight (Kg)	55.2 ± 7.8	60.4 ± 8.8	-5.2 ± 9.1	0.045
Total Hip BMD ($g\ cm^{-2}$)	0.701 ± 0.118	0.700 ± 0.119	0.0004 ± 0.006	0.801
FEXI ($N\ mm^{-1}$)	24.7 ± 1.6	25.7 ± 2.0	-0.96 ± 1.74	0.051

Discussion

- The fracture cohort was significantly heavier than the control cohort, contrary to expectation
- The fracture cohort also exhibited higher stiffness of the proximal femur, as defined by FEXI. This is an interesting finding, suggesting that the fractured hips may have been more brittle.
- The design of this clinical study was based upon 50 recent hip fracture and 50 matched control subjects, recruitment continues.

Relative Sensitivity of BMD along with 3D & 2D FEXI to Variations in Geometric Parameters of the Proximal Femur

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Background

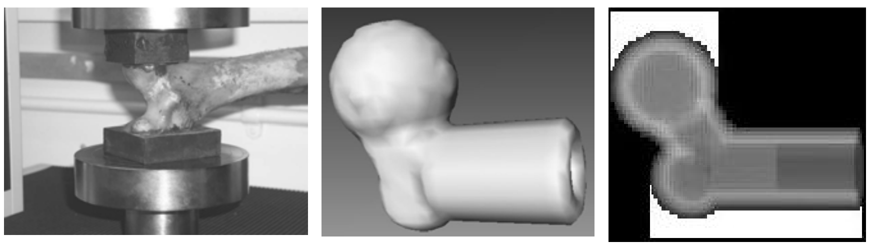
The preferred method of assessing the risk of an osteoporosis related fracture is currently a measure of bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA), yet other factors contribute to the overall risk of fracture, including anatomical geometry and the spatial distribution of bone.

Concept

Finite element analysis may be performed in both 3D and 2D, and predicts the deformation or induced stress when a load is applied to a structure (such as a bone) of defined material composition and shape. The simulation of a mechanical compression test provides a measure of whole bone stiffness (N mm^{-1}).

Methodology

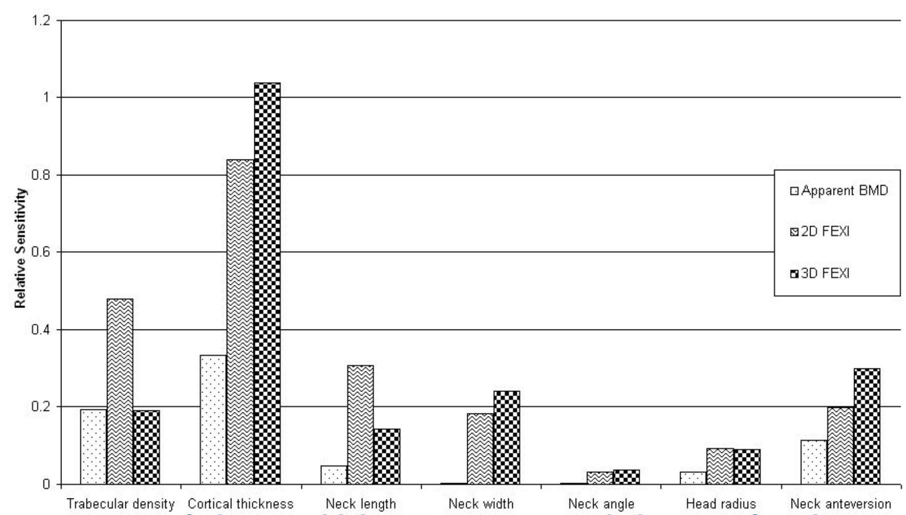
A simulation system was developed to study the sensitivity of BMD, 3D and 2D finite element analysis to variations in geometric parameters (trabecular bone density, cortical shell thickness, neck length, neck-shaft angle, neck width, neck anteversion and head radius) of a virtual proximal femur model. 2D projections were also generated, thus creating plain radiograph-like images.



Photograph of mechanical compression test, 3D and 2D simulation models for proximal femur

Results

- all three measurement parameters increased non-linearly with increased trabecular bone density and cortical shell thickness, decreased linearly with increased neck length, and decreased gradually with increased neck anteversion angle and head radius.
- Multi-parameter sensitivity analysis (MPSA) was performed to determine the relative sensitivity of each measurement and geometric parameter on the overall stiffness of the bone. Cortical thickness had the highest sensitivity for all three measurement parameters.
- When all geometric parameters were considered, 3D and 2D finite element analysis had statistically equal sensitivities (0.41 ± 0.20 and 0.42 ± 0.16 respectively) being significantly higher than the sensitivity for BMD (0.24 ± 0.07).



Relative sensitivity to parameter variations, analysed separately for BMD, 2D FEXI & 3D FEA

PIRSAN
Paediatric Infra-Red Skeletal Assessment

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Experimental scanning frame

Background

- Conventional bone assessment utilises ionising radiation and necessitates large scanning systems.

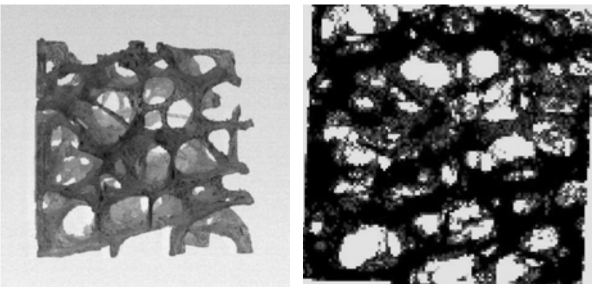
Concept

- The aim of this project is to develop a non-ionising bone assessment system for paediatric subjects based upon infra-red imaging. Potential applications include incubator-based assessment of premature neonates and bone age.

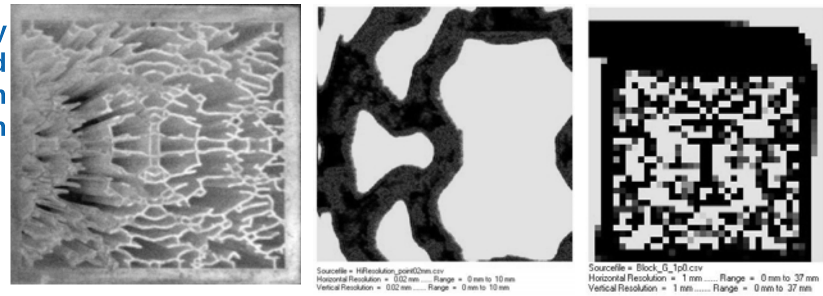
Methodology

- We have developed a prototype infra red scanning system, consisting of a 3D stepper motor driven rectilinear scanning frame, a yoke housing 785 nm laser diode module and co-axial photodiode detector, a 12-bit ADC, and associated software.
- Experimental studies to date have imaged stereolithography replicas of human cancellous bone, and studied the effect of spatial resolution.

Validation



Photograph of Stereolithography Model (60mm x 60mm) and corresponding Infra-Red scan image at 0.5mm resolution



Photograph of Stereolithography model (40mm x 40mm) and Infra-Red scan image at 0.02mm and 1mm resolution

Future Developments

- Improve the signal-to-noise ratio via incorporation of an avalanche photo diode
- Investigate scattered radiation in addition to through-transmission
- Undertake *ex vivo* animal & *in vivo* human validation.

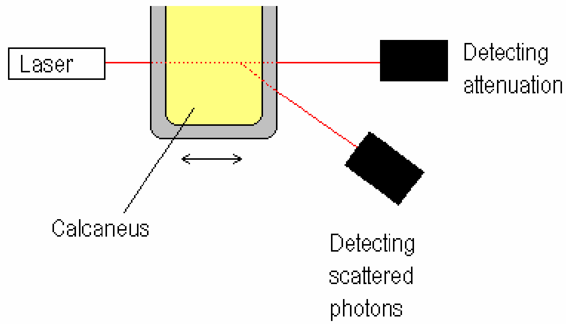


Diagram demonstrating detection of scattered in addition to through-transmission attenuation

QUS
Quantitative Ultrasound

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Background

- The Clinical application of Quantitative ultrasound (QUS) for the assessment of osteoporosis was first demonstrated in Hull by Dr Chris Langton via the measurement of broadband ultrasound attenuation (BUA) at the calcaneus.
- QUS has been scientifically validated both in terms of fundamental in-vitro and clinical in-vivo studies. We know that ultrasound velocity is related to the elasticity and density of cancellous bone, whereas BUA is related to the density and structure of cancellous bone, noting that as the structural variability decreases the relationship between BUA and density increases.
- Clinical studies have shown that QUS parameters are sensitive to age-related changes; may discriminate osteoporotic subjects; and exhibits a prospective fracture risk prediction comparable to axial DXA. Normative data have been defined for several devices.
- QUS offers the potential to serve 2 major clinical roles: to predict fracture risk independent of established bone densitometry; or to be a case-finding referral tool for subsequent conventional densitometry.

QUS Highlights

1984 – first clinical demonstration of clinical utility of BUA, C M Langton, PhD thesis

1985 – first commercial system, Walker Sonix UBA575, Langton & Palmer patent US 4774959

1993 – first dry commercial system, McCue CUBAclinical, Langton patents GB 2257253, US 5452722

1996 – electronic bone phantom, Langton patents GB 9502448.5, US 08/599338

1996 – demonstration of parabolic relationship between BUA and density, Langton et al, Physics in Medicine & Biology; 41, 2411-2420

1996 – demonstration of linear relationship between BUA and fractal dimension, Langton et al, Physics in Medicine & Biology; 43, 467-471 l

1997 – first demonstration of cost effectiveness of QUS, Langton et al, Clinical Rheumatology; 16(1), 117-118

Current Research

- One of the long-outstanding clinical QUS questions is what 'high velocity / low BUA' etc is telling us.
- It is hypothesised that velocity and BUA are primarily related to the elasticity and density of bone respectively.
- Following recent successful research utilising wavelength-dimension spatially-matched acoustic propagation through sterolithography replica models, samples exhibiting a range of material properties will be studied.

Hull Stabilometer & Activity Logger

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Hull Stabilometer

Background
Propensity to fall is known to be a significant risk factor for an osteoporotic fracture.

Concept
The purpose of the Hull Stabilometer is to predict the propensity to fall by monitoring and analysing the response of a subject to a physical perturbation simulating for example, a trip or slide. Additional clinical applications include assessment of diabetic neuropathy and other disorders that affect postural stability.

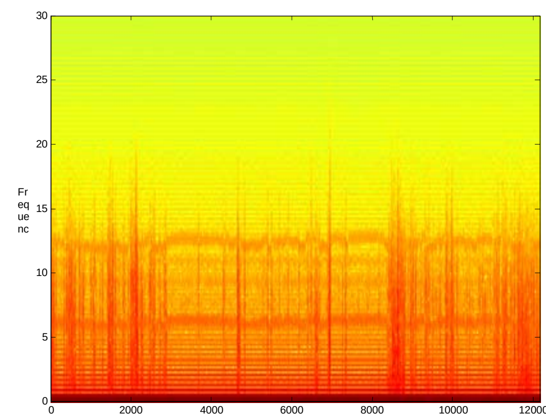
Methodology
- Subject stands on a motor-driven platform that may be moved in any profile within a 2D plane.
- Number of movement profiles may be selected, describing the directions, acceleration and distance.
- We are currently concentrating on profiles that simulate both a trip and slide.
- The platform also serves as a force plate, thereby recording the postuography response of the subject to the movement profile.
- Data analysis consists of both time domain and frequency domain.
- The device is currently undergoing assessment of healthy volunteers prior to clinical evaluation.

Activity Logger

Aim
To develop a reliable, portable, and non-intrusive device that can be used routinely to evaluate body movements, measure physical activities, and determine the relationships with heart rhythm in all age groups over long periods of time.

System
- Motion Sensor: based on a 3-axis accelerometer. Sensors will generally be attached to two identifiable locations on the subject, e.g. on the thorax and thigh, or thorax and head. For Sports Science applications, the system will be multi-sensor but operate over a shorter measurement period.
- Heart Rhythm Sensor: this will acquire a one-lead ECG signal from a chest electrode.
- Memory Card Data Recording and Reading.

Logger & Battery Pack



24 hour Spectral Analysis; x-axis = time, y-axis = acceleration

BMU-Sim
Bone Remodelling Simulation Environment

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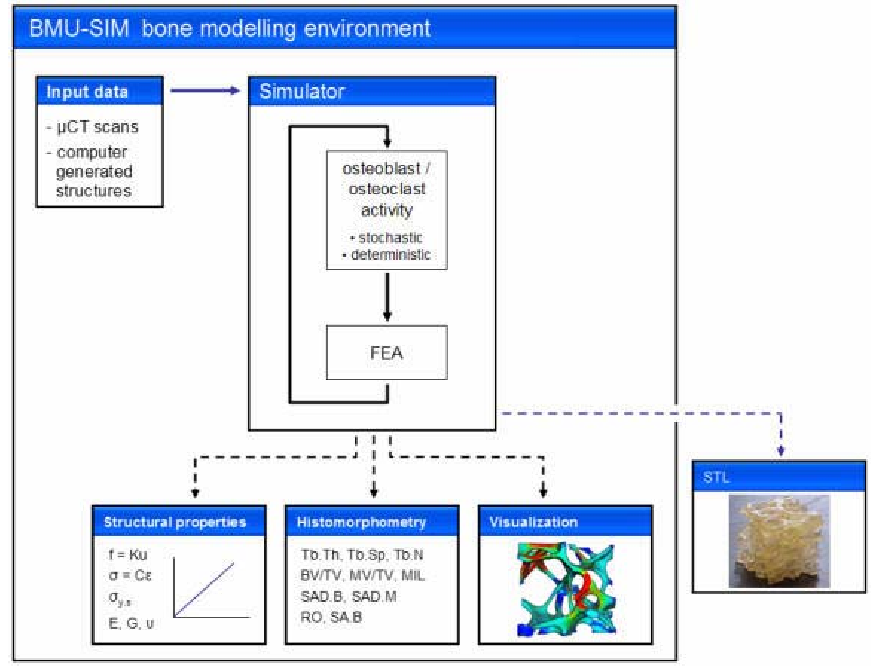
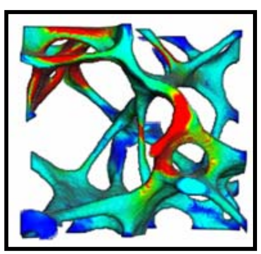
Concept
BMU-SIM is a flexible and adaptable bone remodelling environment that predicts the resultant mechanical integrity of a bone structure.

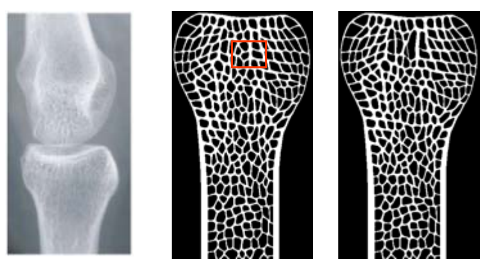
Methodology
- The simulator works by identifying pixels / voxels at the bone-marrow interface and adding or removing bone at those locations.
- The operational rules may range from wholly Stochastic (completely random selection of voxels) to wholly Deterministic (selection of voxels identified by stress / strain / SED *etc*, and/or age and location in model).
- The integral Finite Element Solver can model an unlimited number of material types implemented on a parallel processor machine. The model is distributed between the processors by partitioning the structure along an axis of the model. The estimated maximum model size is 160 million elements/voxels.
- The Eagle High Performance Cluster has 32 nodes with 2Gbit bandwidth Myrinet interconnect; each node has two 2.6GHz Xeon CPUs and 2Gbyte RAM; exchange rate between nodes is 230 Mbytes/second.
- Typical solution time of only 40 minutes for 6.2 million voxels.



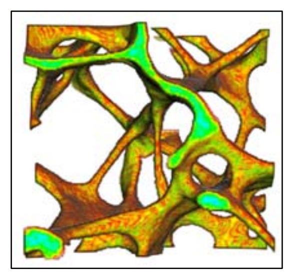
Results



Strain based Adaptation



Rheumatoid Arthritis Simulation



Bone Age Mapping

Clinical Applications
- Osteoporosis and Rheumatoid Arthritis
- Development & Growth
- Effect of Drug Therapies
- Design and Optimization of Prostheses
- Remodelling around Prostheses
- Fracture Healing
- Dental Research
- Understanding Function and Morphology
- Anthropological Research

Associated Facilities & Expertise

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Centre for Metabolic Bone Disease

CMBD is a joint development between Hull & East Yorkshire Hospitals Trust and the University of Hull. The Centre provides a multi-disciplinary approach, combining Medical Physics with the clinical specialities of Gynaecology and Rheumatology which are closely involved with the detection, prevention and management of osteoporosis.

The Centre has a strong research track-record with projects ranging from fundamental studies, through technological developments, to Phase II & III pharmaceutical trials. A number of research collaborations have been established with Surgery, Cardiology, Orthopaedics, and Rehabilitation.

Centre for Medical Engineering and Technology

CMET has access to an unrivalled range of state-of-the-art facilities and equipment. These include: a **Biomechanical Test Laboratory** with universal testing and fatigue machines plus sophisticated strain gauge and data-logger equipment to support the development of implants, prostheses and medical devices; a **Biomaterials Laboratory** equipped with an instrumented nano-indenter and dynamic mechanical analyser for detailed characterisation of man-made materials and human/animal tissue; an **Advanced Imaging Laboratory** which includes a microCT system capable of scanning to 10 microns; a **Modelling, Simulation and Visualization Laboratory** with a wide range of software for image processing and visualization, CAD, finite element analysis and kinematic analysis software for advanced modelling and simulation studies; and access to the Sport Science / HYMS **Gait Analysis Laboratory** and **Hull Immersive Visualization Environment** (HIVE).



microCT Scanner, Dynamic Mechanical Analyser & Differential Scanning Calorimeter, Nano-Indenter, Universal Test Machine

Publications & Head of QuBQu^2 Initiative

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Book Editorship

The Physical Measurement of Bone
Eds. C M Langton & C F Njeh
IOPP, 2004, ISBN 0 7503 0838 9

Book Chapters

Quantitative Ultrasound; C M Langton & C F Njeh; pp 412-474
Radiogrammetry: C M Langton & J A Thorpe; pp 337-354

Publications

Sisias G, Phillips R, Dobson CA, Fagan MJ, Langton CM; 2002; Algorithms for accurate rapid prototyping replication of cancellous bone voxel maps; J. Rapid Prototyping; 8, 6-2

Langton C M; 2003; Ultrasound and the assessment of osteoporosis; Nat. Assoc. Primary Care Review; 3(1), 117-118

Phillips R, Grunchec JA, Ward JW, Fagan MJ, Dobson CA, Langton CM, Sisias G; 2003; Stereovisualization of 3D trabecular bone structures produced by bone remodelling simulation; Stud Health Technol Inform; 94, 258-264

In Press

Attenborough K, Qin Q, Fagan MJ, Shin H-C, Langton CM; Measurements of tortuosity in stereolithographical bone replicas using audio-frequency pulses; J Acoustic Soc America

Dobson CA, Sisias G, Phillips R, Fagan MJ, Langton CM; 3D stereolithography models of cancellous bone structures from µCT data: testing and validation of finite element results; Proc. Int. Mech (Part H)

Submitted

Fagan MJ, Bernard CP, Dobson CA, Jones BJ, Ong EK, Phillips R, Langton CM; Examining the depletion of cancellous bone structures using a novel 3D bone simulator

Pisharody S, Phillips R, Langton CM; The Relative Sensitivity of Bone Mineral Density (BMD) along with 3D and 2D Finite Element Analysis of X-ray Images (FEXI) to Variations in Geometric Parameters of the Proximal Femur – a Simulation Approach

Dr Christian McDonald Langton

Christian Langton studied for his BSc in Physics and Chemistry at Hull University and MSc in Medical Physics at Aberdeen University before returning to Hull University to study for his PhD, awarded in 1984 titled ‘Measurement of Broadband Ultrasonic Attenuation in Cancellous Bone’. Following two years in industry, developing the BUA technique with Walker Sonix, he returned to academia, with Lectureships in Applied Physics at City of London Polytechnic and Sheffield Hallam University. In 1992, he was appointed Director of the Health Research Centre at Sheffield. In 1994, he again returned to Hull University, as the Senior Lecturer in Medical Physics within the School of Medicine, Faculty of Health. In 1999, he was awarded the Personal Title of Reader in Medical Physics.

Dr Langton has maintained an active research interest in the ultrasonic assessment of osteoporosis, serving on three European Community Research Management Committees, being the co-ordinator for a European consensus on the clinical role of ultrasound in osteoporosis. He has patented the CUBA ultrasonic bone analyser, commercially developed by McCue Ultrasonics, Winchester, UK and a novel electronic calibration phantom for BUA. In recognition of his contribution to scientific and technical developments applied to Clinical Practice, Dr Langton was awarded the IPSM ‘Manufacturer’s Award for 1995-96’ and Associate of Royal College of Physicians in 2001.

Current research projects include relationships between ultrasonic parameters with material and structural properties of cancellous bone, computer simulation of cancellous bone remodelling and osteogenesis, finite element analysis of X-ray images (FEXI) incorporating tissue thickness mapping, infra-red imaging of bone, automated left ventricular cardiac MRI segmentation. He has over 1300 publication citations. Dr Langton was one of only three entries from University of Hull in Universities UK’s ‘50 years of Research’ book published in honour of the Queen’s Golden Jubilee.

Dr Langton serves as Deputy Director of the Postgraduate Medical Institute (in Association with Hull York Medical School) with particular responsibility for Research and Reach-Out; and Head of the Technology Development Group within Hull & East Yorkshire Hospitals NHS Trust’s Medical Physics Service. He also serves as strategic lead for R&D within the Trust.