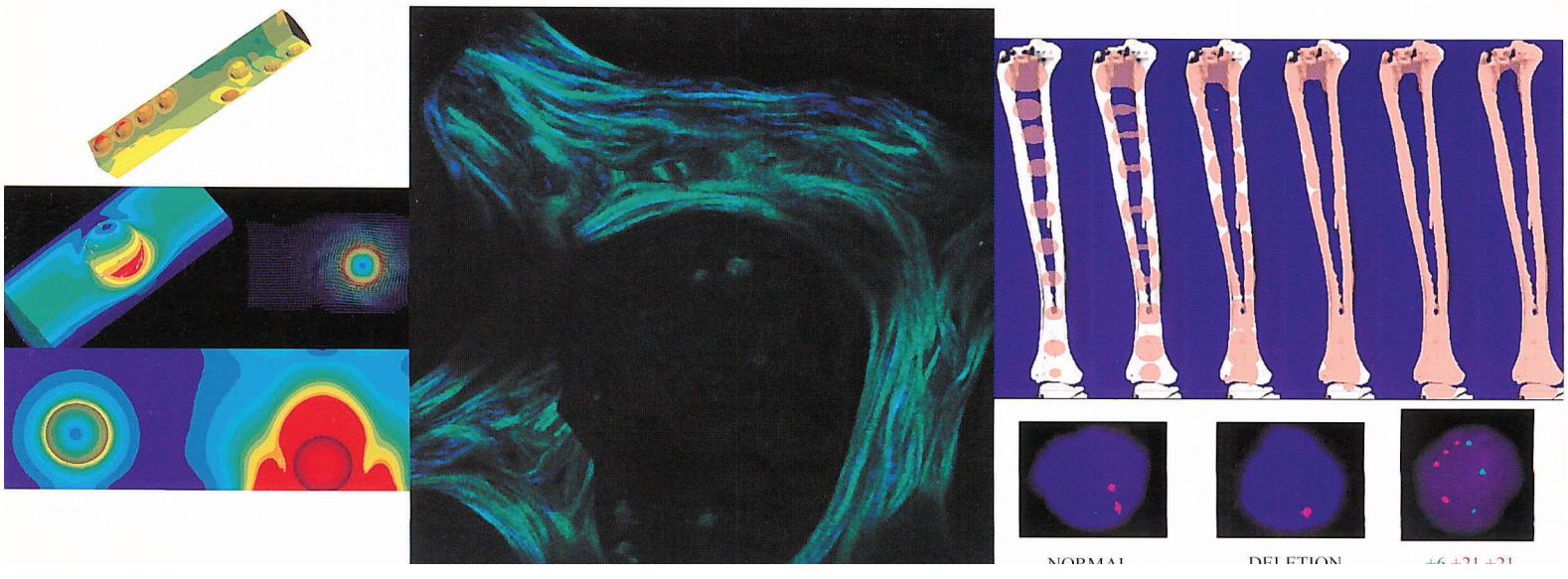
Bio-Medical Engineering Research

at the Faculty of Medicine of the University of Lisbon



Editorial board:

Members of the committee for Bio-Medical Engineering at FML:

Fernando Lopes da Silva
Teresa Paiva
Ana Sebastião
Jacinto Monteiro
João Eurico Fonseca

and Antónia Lomba

With special thanks to the FML and IST researchers who
supplied information and illustrations.

Sponsor:

Bio-Medical Engineering at Faculty of Medicine of the University of Lisbon

Date: October 2007.

Lisbon Medical Faculty (FML)

Bio-Medical Engineering

formal collaboration between the Instituto Superior Técnico and the Faculty of Medicine of the University of Lisbon

Instituto Superior Técnico (IST)

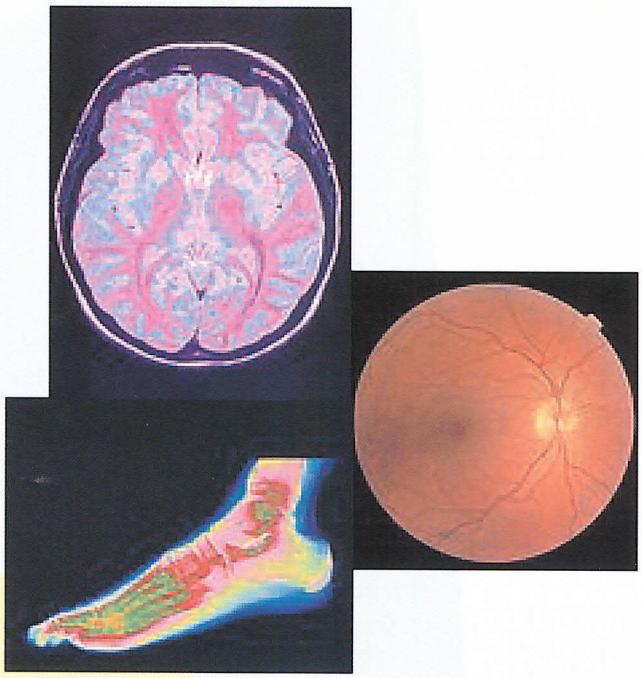
Contacts

Lisbon Medical Faculty (FML)
Secretariat:
Antónia Lomba
Phone: 21 7999416
Email: mlomba@fm.ul.pt or biomedica@fm.ul.pt
www.fm.ul.pt

Instituto Superior Técnico (IST)
Secretariat:
Martinha Sousa
Phone: 21 8419013
Email: biomedica@fisica.ist.utl.pt
www.ist.utl.pt

Contents

Preface

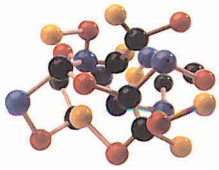


In 2006 the Committee responsible for Teaching and Research in Bio-Medical Engineering published a booklet containing an account of the research being carried out in the IST within the field of Bio-Medical Engineering where the research of the Medical Faculty was only mentioned in very abbreviated form. Therefore in this booklet we assembled the descriptions of the research projects where the Medical Faculty plays a central role. The present booklet complements that of 2006. We took this opportunity to include also in this booklet some projects of the IST in the area of Bio-Medical Engineering that were not included in that of 2006.

We consider that it is important to realize that Bio-Medical Engineering is a multi- and inter-disciplinary research area that needs inputs from many scientific and engineering groups and also an active interaction with bio-medical groups. This is essential not only to determine appropriate choices of research themes but also to guarantee an efficient implementation of the research results.

In some cases the research theme and the questions formulated have their origin in a bio-medical context, although in many cases the impulse for a research project arises in the scientific/ engineering environment. What is certain is that the chance of success of a research line in this field is enhanced by a close collaboration of both sides. Only in this way the research context and the proper environment can be matched in an optimal way.

Naturally the results of Bio-Medical Engineering research should prove their usefulness in the applied field of the Health systems. To realize this aim in an optimal way it is necessary to include in the staff of the Health institutions, both those involved primarily in research but also, most important, those dedicated to patients diagnosis, care and revalidation, bio-medical engineers. The new generation of bio-medical engineers is trained to understand the medical context and to master the know-how given by the scientific/engineering environment. Thus they are optimally placed to act as important protagonists within the contemporary Health systems. In Portugal this intense collaboration between medical professionals and engineers is still very limited. It is hoped that bio-medical engineers will pave the way to change this situation and will prove in practice that the investment of Health systems in these new highly educated professionals will pay both in enhancing the level of the Health services to the public in general, and to make them more efficient.



In 2007 two main events of great importance for the M.Sc. in Bio-Medical Engineering took place: the accreditation of the M.Sc. degree by the professional Association of Engineers of Portugal, and the creation of a Consortium with the aim of promoting research in the field of Bio-Medical Engineering and stimulating collaborations with organizations in the field of Health and Engineering, both public and private. From the document in which the objectives of the Consortium are presented we single out the following quotation:

"As a sequel of the positive evolution of the initiatives associated with the creation and functioning of the course in Bio-Medical Engineering (EBM), that now constitutes an integral M.Sc. course and a Ph.D. program, it became evident that it was indispensable to create the conditions to promote an enhanced cohesion between the different research groups, with respect both to teaching and research.

The interdisciplinary character of this scientific domain requires an adequate environment, which may be provided by an organizational structure such as the Consortium. Such structure may help to develop interdisciplinary projects and competitive research programs at the European level that can attract the best students, both nationals and foreigners. This may promote the eligibility of these programs to compete for external funds, and to participate strongly in programs of the European Union."

These considerations led the Instituto Superior Tecnico and the Faculty of Medicine of the University of Lisbon, and associated organizations as the Instituto de Medicina Molecular and the INESC, to create an interdisciplinary research organization that comprises a large variety of fields within Bio-Medical Engineering, namely: biomaterials, biotechnology, biomechanics, biomedical imagiology, microsystems, biosystems and biomedical nanotechnologies, analysis of biomedical signals, neurosciences , bioinformatics, computational biology and management of health systems.

Fernando Lopes da Silva

Research projects

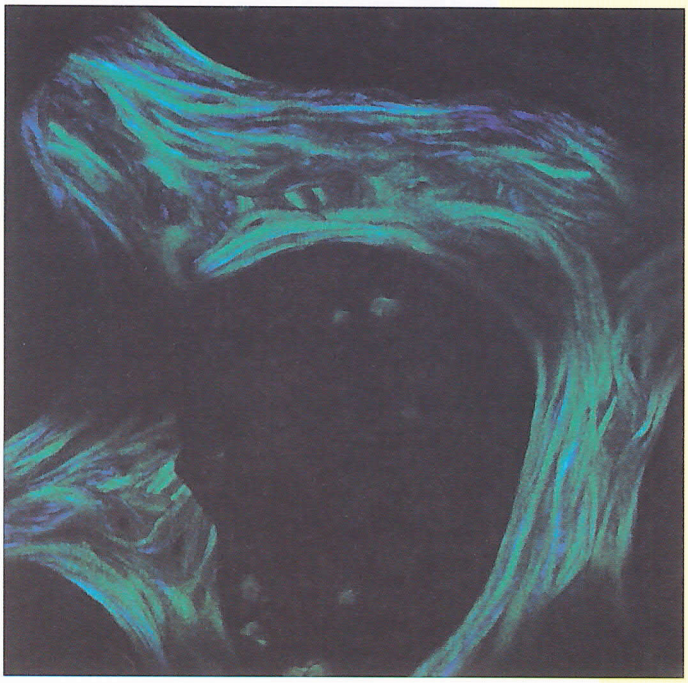
1. Biomechanical tissue properties

1.1. Effects of inflammation on bone and cartilage: collagen pattern and biomechanical properties (2007-2010)

Coordinators: João Eurico Fonseca (FML); Fátima Vaz (IST)

Brief description of the research group activities:

The aim of the Rheumatology Research Unit is the study of the pathogenesis of inflammatory joint diseases and bone disorders in order to characterize potential tools for early diagnosis and prognosis, and potential targets for novel therapies. Ongoing research projects are devoted to the study of neutrophils and B cells in very early arthritis and to the relevance of TNF-alpha polymorphisms in the prognosis and pharmacogenetics of several inflammatory joint diseases. In the context of the collaboration with IST this Unit is also involved in research in the field of bone and soft tissues biomechanics.



Summary of the project:

Bone and cartilage characterization of matrix structure degradation and of biomechanical properties might contribute to a better understanding of joint destruction mechanisms in inflammatory diseases and may lead to new therapeutic paradigms, particularly if we could verify how do drugs used to treat joint inflammation influence the organization of bone and cartilage matrix. On the other hand, the capacity to early identify the individuals who will suffer more severe organic and mineral matrix destruction, and therefore greater biomechanical degradation, may constitute new predictive parameters for disease progression. The main goal of the project is to characterize the correlation between bone collagen matrix structure, bone mineral density in patients with rheumatoid arthritis evaluated by dual X-ray absorptiometry, bone chemical elements quantification in mice with arthritis by spectroscopy (EDS) associated with scanning electron microscopy and bone mechanical properties evaluated by mechanical tests.

1.2. Contribution for the prevention of osteoporotic fractures and bone quality evaluation – a new method for the evaluation of the extracellular matrix (2007-2008)

Project coordinators: João Eurico Fonseca (FML); Jacinto Monteiro (FML); Fátima Vaz (IST)

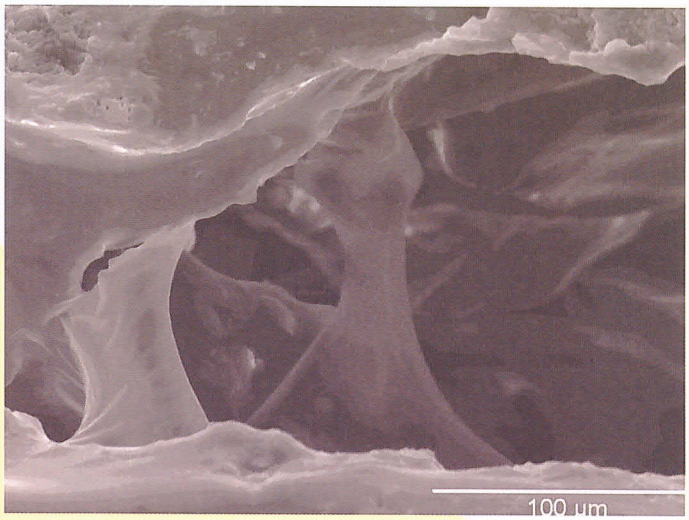
Summary of the project:

The clinical diagnosis of osteoporosis (OP) is still based in the finding of a bone mineral density (BMD) that is 2,5 standard deviations inferior to the peak bone mass. However BMD has only a 0,4 correlation with bone biomechanics and it does not fully explain fracture risk. The correct identification of the individuals that are at the higher risk for fracture is critical for the therapeutic decision. With this goal, in femoral epiphysis obtained from hip replacement surgeries and in an animal model of osteoporosis it will be characterized:

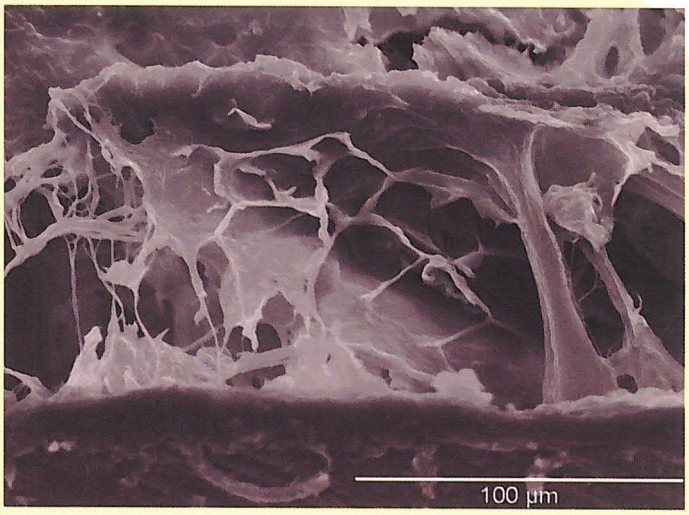
1-The structure of the bone matrix in osteoporotic bone through multiphoton microscopy;

2-The correlation between collagen structure and mechanical strength;

3-The correlation between microscopic and biomechanics data with bone remodelling markers and epidemiological data, in order to identify the clinical and laboratorial variables that are predictive of bone fragility.



Arthritic mouse vertebra 400x (a)



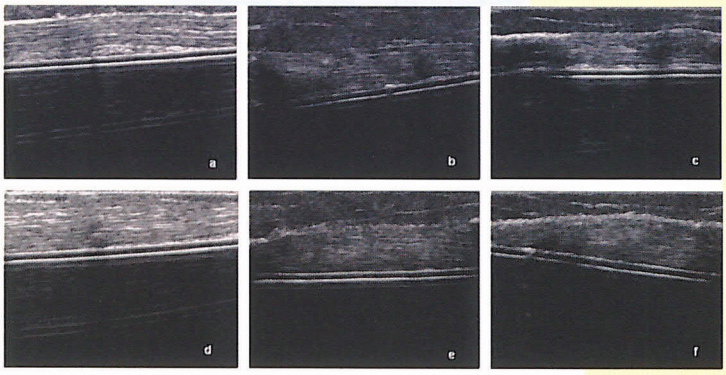
Normal mouse vertreba 500x (b). SEM microscopy.

1.3. Ultrasonography of tendons (2007-2008)

Project coordinators: João Eurico Fonseca (FML); Fátima Vaz (IST); Fernando Saraiva (HSM)

Summary of the project:

Soft tissue ultrasonography allows the visualization of tendon ruptures and tendonitis. However, qualitative changes caused by inflammation or repetitive movements, usually described as "tendinosis", are not precisely known and are considered to be the consequence of structural modifications of the tendons, which can constitute a risk factor for rupture and a contraindication for corticosteroid injection. The goal of this study is to understand the structural and biomechanics meaning of "tendinosis". In animal tendons the changes of "tendinosis" will be induced and a complete ultrasonography, mechanical (tensile) tests and microscopic (multiphoton) analysis will be performed. Tendons will be also injected with corticosteroids in order to understand the effects of this drug on the biomechanics and histology of tendons.



Ultrasonographic images of two tendon samples. a) and d) tendons before tensile test, b) and e) tendons in yield region, c) and f) tendons in rupture region. Arrows represent areas of hypoechogenecity.

List of current projects (P.I. and other researchers) and external collaboration:

- Effects of inflammation on bone and cartilage: collagen pattern and biomechanical properties. PTDC/SAU-BEB/65992/2006.
- Sequencing of the promoter of the tumour necrosis factor alpha (TNF-alpha) gene - contribution for new genetic markers of rheumatoid arthritis prognosis and of anti TNF-alpha response. POCI/SAU-ESP/59111/2004.
- The role of neutrophils and B cells in the initiation and perpetuation of Rheumatoid Arthritis. SPR-SP 2005/2007.
- Polymorphisms of the tumour necrosis factor alpha promoter and Juvenile Idiopathic Arthritis- identifying subtypes and prognosis in Portuguese patients. FML-Astra Zeneca 2005-2007.
- Polymorphisms of the tumour necrosis factor alpha promotor and seronegative spondyloarthropaties- descrimination between subtipes, prognosis and pharmacogenetics of TNFα blocking terapeutics. Hospital de Santa Maria Research Grant 2006-2007.
- Contribution for the prevention of osteoporotic fractures and bole quality assessment- new method for bone matrix evaluation. Hospital de Santa Maria Research Grant 2007-2008.

Publications (2002-2007)
Peer-reviewed journals:

- Fonseca JE, Cavaleiro J, Teles J, Sousa E, Andreozzi VL, Antunes M, Amaral-Turkman MA, Canhão H, Mourão AF, Lopes J, Caetano-Lopes J, Weinmann P, Sobral M, Nero P, Saavedra MJ, Malcata A, Cruz M, Melo R, Braña A, Miranda L, Patto JV, Barcelos A, Canas da Silva J, Santos LM, Figueiredo G, Rodrigues M, Jesus H, Quintal A, Carvalho T, Pereira da Silva JA, Branco J, Viana Queiroz M. Contribution for new genetic markers of rheumatoid arthritis activity and severity: sequencing of the tumor necrosis factor-alpha gene promoter. Arthritis Res Ther, 2007;9 :R37 (1-10).
- Ligeiro D, Fonseca JE, Abade O, Abreu I, Cruz M, Nero P, Cavaleiro J, Teles J, Trindade H, Caetano JM, Branco J. Influence of human leucocyte antigen-DRB1 on the susceptibility to rheumatoid arthritis and on the production of anti-cyclic citrullinated peptide antibodies in a Portuguese population. Ann Rheum Dis, 2007; 66: 246 – 248
- Abreu I , Laroche P, Bastos A, Issertr V, Cruz M, Nero P, Fonseca JE, Branco JC, Machado Caetano JA. Multiplexed Immunoassay For Detection of Rheumatoid Factors By Fidistm Technology. Ann NY Acad Sci, 2005;1050:357-6.
- Fonseca JE, Carvalho T, Cruz M, Nero P, Sobral M, Mourão AF, Cavaleiro J, Carmo-Fonseca M, Branco JC. Polymorphism at position -308 of the tumor necrosis factor a gene and rheumatoid arthritis pharmacogenetics. Annals of Rheumatic Diseases, 2005; 64:793-794.
- Fonseca JE, Cortez-Dias N, Francisco A, Sobral M, Canhão H, Resende C, Castelão W, Macieira C, Sequeira G, Saraiva F, Pereira da Silva JA, Carmo-Fonseca M, Viana Queiroz M. Inflammatory cell infiltrate and RANKL/OPG expression in rheumatoid sinovium - Comparison with other inflammatory arthropaties and correlation with outcome. Clinical and Experimental Rheumatology, 2005; 23:185-192.
- Pereira Silva JA, Costa Dias F, Fonseca JE, Canhão H, Resende C, Viana Queiroz M. Low bone mineral density in professional scuba divers. Clinical Rheumatololy, 2004; 23:19-20.
- Mackiewicz Z, Hukkanen M, Povilenaite D, Fonseca JE, Virtanen I, Konttinen YT Dual effects of caspase-1, interleukin-1, tumour necrosis factor-alpha and nerve growth factor receptor in inflammatory myopathies. Clinical and Experimental Rheumatololy, 2003; 21:41-8.
- Fonseca JE, Edwards JC, Blades S, Goulding NJ (2002). Macrophage subpopulations in rheumatoid synovium: reduced cd163 expression in cd4+ t lymphocyte-rich microenvironments. Arthritis & Rheumatism 46: 1210-6.

Research projects

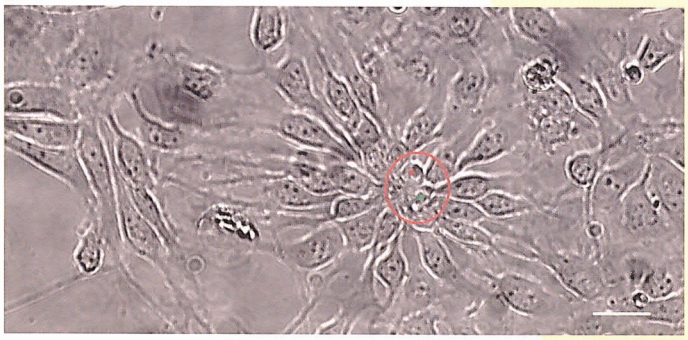
2. Biotechnology and replacement therapy

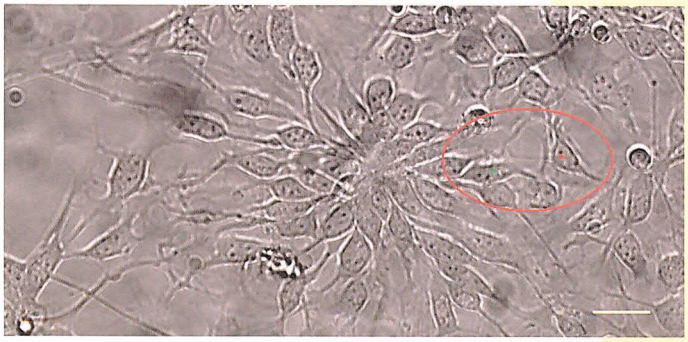
2.1. Embryonic stem cell neuronal differentiation (2007)

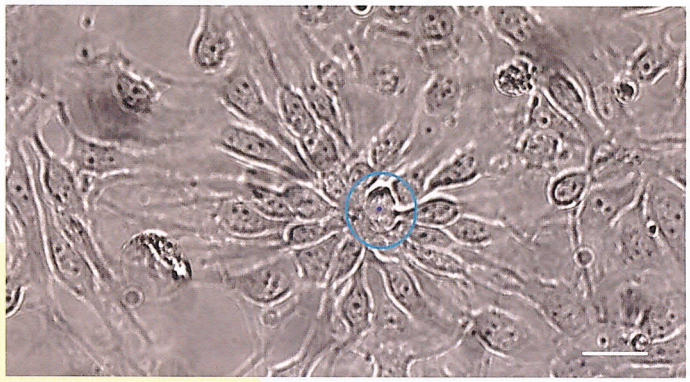
Project coordinator: Domingos Henrique (FML)

Brief description of the research group activities:

The main objective of the Developmental Biology Unit is to investigate the molecular mechanisms that regulate the genesis of neurons in vertebrate embryos. Our aim is to characterize the molecular events that control the establishment of neural stem cells in the embryo, how these cells are maintained and how they give rise to the multitude of neurons that compose the adult CNS. A better knowledge about these fundamental mechanisms is a pre-requisite for the development of cellular replacement therapies that can be applied in the future to treat neurodegenerative diseases, and might have a significant impact on human health.







Summary of the project:

We are trying to apply the knowledge about embryonic neurogenesis to the *ex vivo* production of neurons, starting from mouse embryonic stem (ES) cells. To achieve this, we have established an *in vitro* culture system in which ES cells can be driven through a process of controlled differentiation into committed neural precursors. We have also derived various Neural Stem cell lines from ES cells and shown that they are capable of generating various populations of fully differentiated neurons and glial cells in culture. This research is being carried out in the context of the FunGenES European Consortium (www.fungenes.org), where our goal is to develop new tools to follow the process of neuronal differentiation from ES cells, aiming to increase the efficiency and robustness of in vitro neuronal differentiation.

We have also been collaborating with the Bioengineering Research Group at the Instituto Superior Técnico (Lisbon), to develop strategies for the ex vivo expansion of stem cells and their controlled differentiation into the major cell types in bioreactor systems.

List of current projects (P.I. and other researchers) and external collaboration:

- "Expansion and differentiation of Neural Stem Cells in Bioreactors" (POCTI/BIO/46695/02). Joint Project with Prof. Joaquim Cabral, I.S.T., Lisboa.
- "FunGenES- Functional Genomics in Engineered ES cells", 6th Framework Integrated Project.

Publications (2002-2007)

Peer-reviewed journals:

- Abranches E, Bekman E, Henrique D, Cabral J (2007). Expansion of mouse embryonic stem cells on microcarriers. Biotechnology and Bioengineering 96:1211-21.
- Roszko I, Afonso C, Henrique D, Mathis L (2006). Key role played by RhoA in the balance between planar and apico-basal cell divisions in the chick neuroepithelium. Dev. Biology 298:212-224.
- Afonso C, Henrique D (2006). PAR3 acts as a molecular organizer to define the apical domain of chick neuroepithelial cells. J. Cell Science 119:4294-4304.
- Fior R, Henrique D (2005). A novel hes5/hes6 circuitry of negative regulation controls Notch activity during neurogenesis. Dev. Biology 281:318-333.
- Alsina B, Abelló G, Ulloa E, Henrique D, Pujades C, Giraldez F (2004). FGF signalling is required for determination of otic neuroblasts in the chick embryo. Dev. Biology 267:119-134.
- Duarte A, Hirashima M, Benedito R, Trindade A, Diniz P, Bekman E, Costa L, Henrique D, and Rossant J (2004). Dosage-sensitive requirement for mouse Dll4 in artery development. Genes & Development, 18:2474-2478.
- Abranches E, Bekman E, Henrique D, Cabral J (2003). Expansion and neural differentiation of embryonic stem cells in adherent and suspension cultures. Biotechnology Letters 25:725-730
- Kawakami Y, Rodríguez-León J, Koth C, Büschen D, Itoh T, Raya A, Ng J, Esteban C, Henrique D, Takahashi S, Asahara H, Belmonte JC (2003). MKP3 Mediates the Cellular Response to FGF8 Signalling in the Vertebrate Limb. Nature Cell Biology 5:513-19.
- Bekman E, Henrique D (2002). Embryonic expression of three murine genes with homology to the Drosophila prickle gene. Mechanisms of Development (GEP) 119:77-81

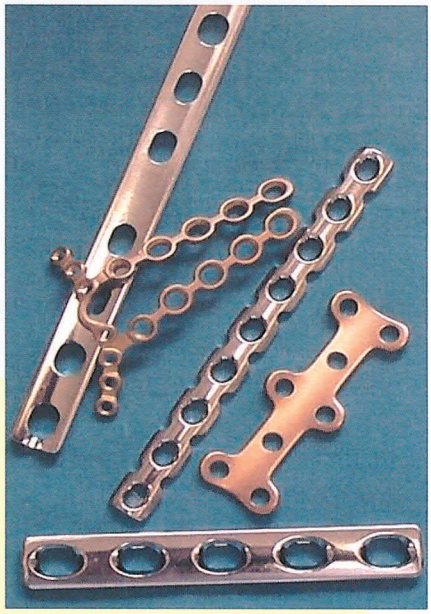
Ph.D. and M.Sc. Theses (2002-2007):

- Cristina Maria Paulino Afonso - "Cell polarity in the embryonic chick neuroepithelium: role of the PAR polarity complex", PhD Thesis, F.M.L., 2006
- Rita Leonor Alves Cabral Figueiredo Fior - "The role of *hes* genes in the controlled production of neurons", PhD Thesis, F.M.L., 2007
- Tiago Alexandre Mestre - "Ontogeny of the CB1 receptor mRNA in the nervous system", M. Sc. Thesis on Neuroscience, F.M.L. 2007.

Research projects

3. Biomechanics and orthopaedics

3.1. Surgical correction of scoliosis by the Resina-Alves method: in vivo measurement of forces and its comparison with results obtained from a numerical simulation (2007)

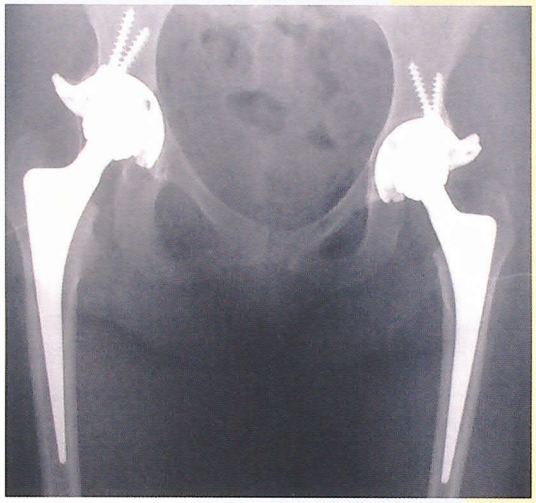


Project coordinators: Jacinto Monteiro (FML), E. Borges Pires (IST)

M.Sc. thesis of Susana Palma

Brief description of the research group activities:

Biomechanic behaviour of orthopaedics prothesis envolving simulation analysis has been included in several research projects. The aim is to compare these simulation studies with the implants "in vivo" (mainly hip prothesis).



Summary of the project:

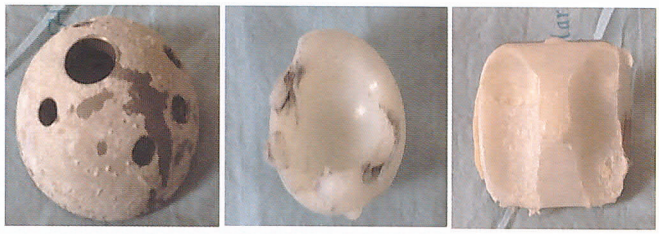
Scoliosis is characterized by an abnormal curvature of the spine when viewed in the frontal plane, an axial rotation of the vertebrae and a deformation of the thoracic cage. In this work some experiments were performed at Hospital Ortopédico de Santiago do Outão during corrective surgeries of adolescent idiopathic scoliosis by the Resina-Alves method. These experiments allowed the measurement of the forces generated in the vertebrae by the fixation system when connecting two metallic rods to the spine. The forces were measured by means of strain gauges placed at the forceps used by the surgeons to bring the rods together with the column. These experimentally obtained forces were compared with the results of numerical simulations performed with a previously developed model of the vertebral column. With this model and using ABAQUS finite element program, geometrically non-linear three-dimensional analysis was performed. The resulting final configuration of the column was compared with a frontal X-ray obtained after the surgery.

List of current projects (P.I. and other researchers) and external collaboration

- "Structural Biomechanics – Study of Implants and Analysis of Soft Tissues". P.I.: E. Borges Pires; Other Researchers: João Martins and Fernando Simões. Contract GRICES (Portugal)/CAPES (Brasil) – 2006/2008.

Publications (2002-2007)
Edited proceedings

- Palma SJ, Pires EB, Rodrigues RP, Ferreira JG, Dinis PB, Martins JAC. Correcção Cirúrgica de Escolioses pelo Método de Resina-Alves: Medição In Vivo de Forças e sua Comparação com os Resultados de uma Simulação Numérica. 2º Encontro Nacional de Biomecânica, Évora, H. C. Rodrigues, P. R. Fernandes, A P. Veloso, J. A. Simões e M. A. Vaz (eds.), IST Press, 299-304, 2007.
- Palma SJ, Pires EB, Dinis PB, Martins JAC. Resultados Numéricos Adicionais Relativos à Correcção Cirúrgica de uma Escoliose pelo Método de Resina-Alves. Congresso de Métodos Numéricos e Computacionais em Engenharia CMNE/CILAMCE 2007, FEUP, Porto, 2007 (artigo completo nos Proceedings em CD-ROM).
- Bettencourt A, Calado A, Amaral J, Alfaia A, Vale FM, Monteiro J, Castro M. Surfaces studies on acrylic bone cement. Int. J. Pharm, 278, 181-186, 2004.
- Dinis PB, Pires EB, Martins JAC, Domingues S., Perdigão N. Surgical Correction of a Scoliotic Spine using the Resina–Alves Method: Numerical Simulation of a Clinical Case. International Congress on Computational Bioengineering, M. Doblaré, M. Cerrolaza e H. Rodrigues (eds.), Saragoça, Espanha, 471-476, 2003.



- Dinis PB, Pires EB, Martins JAC, Thibieroz B. Correcção Cirúrgica de uma Coluna Escoliótica pelo Método Resina-Alves: Outros Resultados Numéricos. VII Congresso de Mecânica Aplicada e Computacional, J. I. Barbosa (ed.), Universidade de Évora, Évora, 1341-1350, 2003.
- Dinis PB, Pires EB, Martins JAC. Finite Element Simulation of the Surgical Treatment of Scoliosis by the Portuguese Method. Numerical Methods in Engineering V, J. Goicolea, C. Mota Soares, M. Pastor, G. Bugeda (eds.), SEMNI, Madrid, 2002 (artigo completo nos Proceedings em CD-ROM).
- Bettencourt A, Calado, A, Amaral J, Vale FM, Rico JMT, Monteiro J, Montemor MF, Ferreira MGS, Castro M. The effect of ethanol on acrylic bone cement. Int. J. Pharm., 241, 97-102, 2002.

Theses (2006-2007)

- Susana Isabel Conde Jesus Palma – "Surgical Correction of Scoliosis by the Resina-Alves Method: *In Vivo* Measurement of Forces and its Comparison with the Results of a Numerical Simulation", Final Course Project for the Biomedical Engineering Degree, IST and FML, 2007. Supervisors: Jacinto Monteiro (FML), E. Borges Pires (IST).

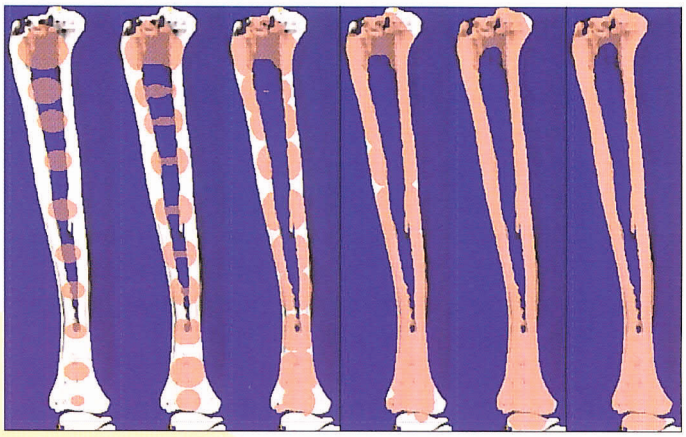
- Susana Isabel Conde Jesus Palma – "Surgical Correction of Scoliosis by the Resina-Alves Method: *In Vivo* Measurement of Forces and its Comparison with the Results of a Numerical Simulation", M. Sc. Thesis, IST and FML, 2007. Supervisors : Jacinto Monteiro (FML), E. Borges Pires (IST).

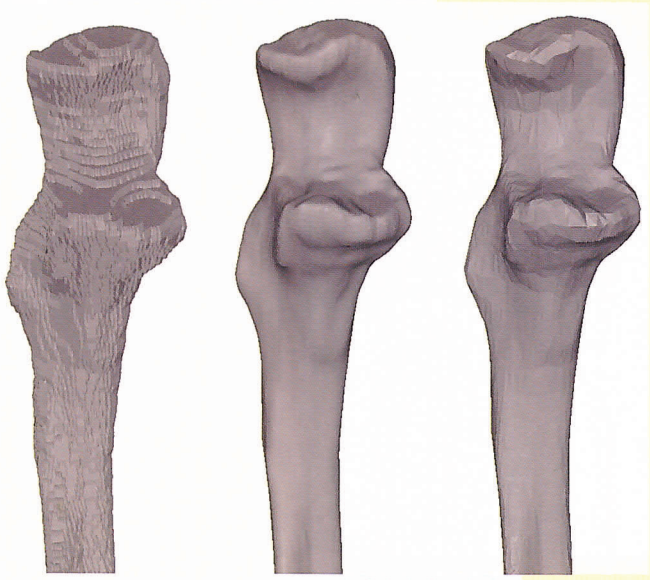
3.2 Geometric modeling of biomechanical structures

Project coordinators: Jorge Campos (FML), João Martins (IST)

Brief description of the research group activities:

Development of a software pipeline for geometrical modeling, based on CT data and having in mind biomechanical studies of bone structures.





Summary of the project:

The geometric modeling of biomechanical structures is a large systematic process whose input is an ordered stack of medical images that involves a cascade of digital image operations and meshing algorithms, and that outputs accurate 3D surface and volume meshes: the digital representations of the tissues being modeled. Despite the usage of several computational methods, modeling human structures requires keen visual capabilities and anatomy knowledge.

A software pipeline was developed for modeling the bones of the upper and lower extremities based on computed tomography (CT) images. The CT-based pipeline relies on anisotropic diffusion for image enhancement and restoration, semi-automatic segmentation using 3D active contour methods, algorithms for surface mesh generation and Delaunay tetrahedralization for volume mesh generation. The 3D models that were obtained demonstrate the great detail and realism achieved by the modeling process.