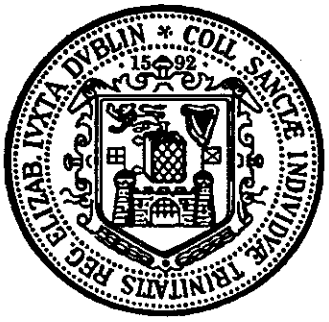
Papers in Biomechanics and Bioengineering



Patrick John Prendergast
BA, BAI, PhD, CEng, FIEI, MRIA

Doctor in Science

University of Dublin

2009

Volume 1

Page

Contents

I. INTRODUCTION

This is my account of the papers hereby submitted for the degree of Doctor in Science. The papers address the following topics in biomechanics and bioengineering:

a. Mechanobiology and tissue engineering,

b. Implant design and testing,

c. Historical, educational, and research topics.

Mechanobiology and tissue engineering

Papers on mechanobiology and tissue engineering deal mainly with modelling bone adaptation and tissue differentiation, and experiments to ascertain the effect of mechanical forces on cells and tissues.

Modelling bone adaptations

Modelling bone adaptation was the subject of my PhD work done between 1987 and 1991 under the supervision of David Taylor. I proposed the hypothesis that accumulative damage regulates bone mass [1] and I tested this hypothesis by performing computer simulations of bone adaptation around an intramedullary prosthesis [2]. I also contributed to work comparing predictions with animal experiments [3]. I presented the concept behind damage-adaptive bone remodelling at a conference in Swansea in 1991; the concept is that bones have evolved to be metabolically efficient to move and maintain by having within them continuous damage accumulation and repair processes – therefore bones do not have to be so strong that they never break; in fact damage accumulates and a continuous repair process normally prevents it from causing a fracture [4]. Damage accumulation is physiological and damage-stimulated bone adaptations are evolutionarily favoured over strain-adaptive remodelling, or so the argument went.

Later I went to the University of Nijmegen in the Netherlands to do postdoctoral work with Rik Huiskes, and together we predicted that damage could be sensed as changes in the local strain fields occurring in the region of microdamage [5, 6]. At this time I also wrote two papers showing that damage-adaptive remodelling and strain-adaptive remodelling are not mutually exclusive [7, 8].

Before leaving Nijmegen I collaborated with Harrie Weinans on a theoretical examination of how bone remodelling and tissue adaptations are non-linear dynamical processes [9]. When I returned to Dublin, I

conducted a theoretical analysis of this idea in terms of the then popular chaos theory [10]. In the end we could show that the non-linearity of remodelling 'traps' the tissue in metastable states; these metastable states are the end-states observed anatomically [11]. Although I still believe this is true, the findings were not really highly regarded by anyone, ourselves excepted – and we both decided to pursue other research. At this time, back in Dublin, David Taylor had taken up the issue of modelling microcrack growth in compact bone, and we collaborated on a paper to predict non-linear microcrack propagation rates as a function of bone microstructure [12]. A final paper from Brian McNamara's PhD work appeared using these ideas to predict damage-stimulated remodelling around a cementless prosthesis [13]. Later Professor Taylor further developed these concepts to a comprehensive analysis of microdamage-stimulated adaptation of bone tissue, backed up by experimental and histological observations of Clive Lee and Fergal O'Brien, our colleagues at the Royal College of Surgeons in Ireland. In fact, Dublin bioengineers soon had such a reputation in the field of bone mechanics that we later christened it (no false modesty here) as the "Dublin School of Bone Mechanics" [14].

I then forgot about damage-adaptive bone remodelling for eight years and returned to it when supervising the PhD research of Laoise McNamara and Paul Scannell. With Laoise McNamara's work, we showed that stresses sufficient to cause microdamage could occur in bone [15]; this work was done partly when Laoise McNamara visited the laboratory of Professor Weinans in Rotterdam and was helped in her experimental work by Jacqueline van der Linden.

Next we came up with a new algorithm that revised the theory first put forward by Prendergast and Taylor [1]. In papers [16] and [17] we proposed that bone remodelling is a response to strain when strain is below a critical damage threshold whereas if microdamage accumulates above the threshold then damage-stimulated remodelling is activated. Paul Scannell and I wrote two papers on simulation of stain/damage remodelling around a cementless prosthesis [18, 19] – the previous paper on this topic [13] had only been an analysis at different time-steps and therefore had not involved simulations in the sense that simulations predict changes over the course of time. Brianne Mulvihill implemented this in three-dimensions and came up with some very interesting results: first the patient-specific parameters of the remodelling process determine the rapidity of bone loss by trabecular perforation [20], and second that the increase in elastic modulus or the

increased activity of osteoclasts predisposes trabecular perforation in trabecular bone [21].

Recently we have re-evaluated the whole concept behind the current form of the bone remodelling equations and returned to the *on/off* concept of remodelling, first proposed by Harold Frost; he proposed that remodelling is not regulated in proportion to some deviation from a homeostatic strain but rather it is triggered to be *on* or *off* depending on the strain level – we have called this Boolean remodelling to distinguish it from theories that have derived from adaptive elasticity [22, 23]; in [23] we showed this to be able to explain bone loss in anatomical trabecular geometries. In paper [24], a PhD student under my supervision Patrick Wulliamoz computed that tissue level stimuli differ in normal and osteopenic bone for the same apparent level stimulus. Alex Lennon and I have recently authored a paper [25] on how Boolean remodelling may be implemented in a site-specific form for prediction of remodelling around prostheses. After some 20 years of thinking about this topic I am beginning to believe that, at last, we have a theoretical approach that incorporates both damage and strain and is a basis for a model with predictive capabilities.

An assessment of these bone remodelling papers can be made. The early set [1-13] established cogent arguments about how damage-adaptive remodelling could work. They played their small part in the later perfusion of ideas and experiments concerning the role of microdamage in bone physiology. However, in retrospect, the best that can be said about the bone remodelling concept presented in [1] is that it is ingenious – but ingeniously wrong. But I would still stand over the general argument that microdamage exists in bone and its quantity is regulated by remodelling and adaptation mechanisms in the tissue. The later set of papers [15-25] concludes with a theoretical approach that brings together experimental and theoretical approaches and can explain the bone remodelling cycle as a mechanoregulated phenomenon [21, 22, 23].

Modelling tissue differentiation

Modelling tissue differentiation was the subject of my Marie Curie Fellowship at the Orthopaedic Biomechanics Lab at Nijmegen University Hospital, The Netherlands from 1993 to 1995. Rik Huiskes ran this lab and we talked extensively about biomechanics. After floundering about for almost a year, I decided to use poroelasticity theory to investigate tissue differentiation at interfaces between bone

and implants (the title of my fellowship grant was "Structural Modelling of Bone/Implant Interfaces"). We first showed that we could compute the required parameters with available finite element codes [26]. Then we had the idea of simulating an experiment performed by Kjeld Søballe, an orthopaedic surgeon from Aarhus, Denmark. This experiment reported tissue differentiation around static and mobile implants put into the condyles of dogs. With our 'tissue differentiation' theory we hypothesised that combinations of strain and fluid flow 'mechano-regulated' tissue differentiation. I attended a conference in Riga in October 1995 (by this time I was back in Dublin as a Lecturer) to present some initial findings comparing our theory (based on both fluid flow and strain computed using a poroelastic representation of the tissue) with the dominant theory based on hydrostatic pressure and strain in a linear elastic model of the tissue [27]. Later we published a paper describing the theory in detail and proposing a new method for computer simulation of tissue differentiation, and I presented it as the European Society of Biomechanics Research Award paper in Leuven in August, 1996 [28]. Later a master's student in Nijmegen, Willem van Driel, performed a simulation of tissue differentiation by giving values to the various parameters and demonstrating that the theory could drive a simulation [29].

The next phase of my research on tissue differentiation algorithms could only begin when I got some money for it. This came eventually from grants from Trinity College and from the Hitachi Dublin Laboratory. Damien Lacroix, who had previously been an MSc student under my supervision, took up this research as his PhD project and we applied the tissue differentiation theory to fracture healing. We collaborated with David Marsh and Gang Li from the Department of Orthopaedic and Trauma Surgery at the Queen's University of Belfast and they advised us on the important features of fracture healing to include in the model: crucial was the source of cells – thus we extended the theory to include cell migration/proliferation as diffusive processes [30]. Later we analysed the effect of fracture gap size and loading and attempted to corroborate the results against a previously-published osteotomy experiment in sheep [31]. Furthermore Damien Lacroix performed the first tissue differentiation simulations in three-dimensions and we wrote a paper describing this [32]. It was clear by then that we were on the correct track with this research, not only as regards the biophysical stimuli most closely associated with stem cell fate (strain and fluid flow) but also in the importance of including the migration and proliferation of cells.

Daniel Kelly, who had previously been an MSc student under my supervision, took up this research for his PhD thesis. He analysed osteochondral defect healing within the framework of two European projects I had at the time. First we analysed an empty defect [33], and then a defect filled with a biomaterial scaffold [34]. This latter paper was the first to show how computational mechanobiology could be useful as a 'systems biology' tool and was widely presented at invited talks and conferences. Later, when Dr Kelly returned to Trinity College as a lecturer we collaborated on applying this model to healing in mandibular distraction, with the research being performed by a visiting student from the Politecnico di Bari, one Antonio Boccacio [35].

In the year 2001 I was on sabbatical at the Technical University of Delft and I shared an office with a young Ukrainian engineer Andriy Andreykiv, who was a PhD student under the supervision of Fred van Keulen. We developed further applications of the model but with much more sophisticated mathematical basis in that the differentiation algorithms were incorporated directly in the finite element solution scheme [36, 37]. In these papers we compared tissue differentiation and stabilization during fracture healing [36] and osseointegration into implant surfaces [37].

With time on my hands on sabbatical in Delft and Rotterdam, I had begun to think in terms of 'mechanoregulation algorithms'. Is mechanoregulaton in tissues executed automatically by cells in response to biophysical stimuli? I had thought about this before (paper [9]) in regard to tissue differentiation being a process of patterning that involves the setting up of boundaries, often remarkably distinct, between tissue phenotypes. Does a continuum model of cell distribution constrain against the emergence of such patterns? Maybe mechanoregulation is more correctly expressed in algorithmic form, "like rules governing a game of chess". Searching for a new approach, we investigated 'lattice modelling' based, generally speaking, on the concept of cellular automata. I wrote a paper exploring these concepts [38].

In 2004/2005 a Lecturer from the University of Zaragoza, Maria Angeles Pérez, came to Dublin on sabbatical and we worked on developing the lattice modelling approach. We used a lattice within each finite element to simulate the migration and proliferation of cell populations. We used the lattice approach to implement a random-walk model for cell migration and proliferation. We showed different solutions compared to our earlier mechanoregulation models based on

diffusion [39]. Damien Byrne started a PhD on this subject and developed the method in three dimensions and applied it to scaffolds used in tissue engineering [40, 41], and in a fully-three dimensional model of fracture healing [42]. (This work was a collaboration with Dr Damien Lacroix, by now working at the University Polytechnic of Catalonia in Barcelona.) My PhD student Hanifeh Khayyeri began work, together with Sara Checa a postdoctoral researcher, to attempt to better corroborate these experiments by comparing simulations done with experimental results in a bone chamber experiment performed by Magnus Tägil (from Lund University) and others there; we published our first paper showing a good comparison between experimental and computational results [43].

Dr Checa and I had earlier started to look at the problem of simulating mechanoregulation of angiogenesis. Using the capability of the lattice model to simulate angiogenesis would be essential if mechanoregulation models are to be applied in tissue engineering and regenerative medicine. Preliminary work showed that an algorithm to predict angiogenesis can be included in mechanoregulation simulations [44]. Next three papers were written applying the approach to the analysis of biomaterials for tissue engineering, developing the work of Byrne *et al.* [41]; first Sara Checa applied the tissue differentiation simulation including angiogenesis to a regular-shaped scaffold [45], next Hanifeh Khayyeri did simulations of how bone would regenerate in a loaded bone chamber by using lattice points to represent a real scaffold under development in Professor O'Brien's group at the Royal College of Surgeons in Ireland [46], and finally Clara Sandino, a PhD student from Damien Lacroix's group in Barcelona on a 4-month stay in Dublin, successfully applied the method to the analysis of a micro-CT generated scaffold geometry [47]. These three papers showed how the theory could be implemented in real applications and suggest serious potential for using it as a design tool in tissue engineering.

What of all this work on modelling tissue differentiation? First I believe the question of how mechanical forces regulate tissue phenotype to be one of the most fundamental in all of bioengineering, and central to solving many problems in implant mechanics and tissue engineering. Second the approach taken has been a balance of theoretical and experimental approaches – with experiments (reported below) being done in support of the theory. Thirdly the theoretical approach of using a biophysical stimulus combining strain and fluid flow in mechanoregulation algorithms seems to be a fruitful one, and it has

been taken up by other researchers. Fourthly, the work has undergone several phases and (in the words of the requirements for the ScD degree) "has been sustained over many years"; most recently we have begun to use a lattice to model mechano-regulated cell activity – this approach offers new possibilities in developing predictive simulations for tissue engineering applications.

Experimental mechanobiology and tissue engineering

Initially the research was performed to explore for ourselves how cells responded to mechanical stimulation. Later experiments were done as part of collaborative studies in tissue engineering. More recently we have been able to perform experiments directed towards corroboration of mechanobiological models.

The first set of papers [48-54] relate to the reaction of various cell types to environmental factors. Adriele Prina Mello, when he was a PhD student under my supervision, studied T-cell migration on different microtextured surfaces [48]; we collaborated with immunologists from St. James's Hospital who are co-authors on the paper [49]. Later an MSc student under my supervision, Matteo Moretti, showed that endothelial cells align perpendicular to the stretch direction on silicone substrates [50]; we were not the first to do this but we did show for the first time that it could occur on uncoated plasma-sprayed silicone substrates. Dr Prina Mello, by then a Research Fellow in the Centre for Research on Adaptive Nanomaterials and Nanodevices, performed experiments showing the effect of magnetic fields on neurons [51].

In a new line of research under a European project called "Biomechanical Interactions in Tissue Engineering and Bone Repair", my PhD student James McGarry and I tried to better understand cell reactions to mechanical stimuli by developing a finite element model of a single cell [52] – as far as I know such models had not been attempted by anyone else at that time. In collaboration with two scientists from the Faculty of Dentistry in Amsterdam, Jenneke Klein-Nulend and Margreit Mullender, we used these models to show how differently cells are mechano-stimulated as a result of fluid flow and strain [53]. This provided experimental corroboration for the idea of the theory papers [26-47] that strain and fluid flow are mechano-regulatory stimuli for tissue phenotype. Further experiments showed that the microtubule-actin cytoskeleton plays a central role in modulating cell mechanoresponsiveness [54].

Continuing this line of research, I started collaborating with several colleagues in other disciplines as follows: Suzi Jarvis from Physics (since moved to UCD), Veronica Campbell from Physiology, and Brian O'Connell from Dentistry. This team of researchers, together with a Research Fellow Dr Paula Maguire, co-supervised my PhD student James McGarry in performing atomic force microscopy (AFM) of single cells. These experiments showed the diverse set of responses that occur when single cells are subjected to stimulation – in fact a great many cells did not react at all to mechanical stimulation by the AFM indenter [55]. This result led to development of more sophisticated ideas about variability in cell responses; such observations could never, of course, have been made in the experiments with cells in confluent layers. During these experiments Dr Maguire and others noticed the development of regular structures in spreading mesenchymal cells (we called them geodesic structures); these looked similar to tensegrity structures and our team was the first to quantify the morphology and properties of these structures [56].

I was involved in collaborative work on mechanical testing of bone; the first paper was the PhD work of David Hardiman who was supervised by Professor Clive Lee and co-supervised by me. He performed hindlimb suspension experiments on rats and showed, among other things, that gene expression was changed as a result of the reduction in mechanical loading [57]. In a separate study my then PhD student Laoise McNamara (now working as a Lecturer in Biomedical Engineering at NUI, Galway) investigated the mechanical strength of single bone trabeculae. The tissue came from rats housed in Organon Laboratories in the Netherlands by Twan Ederveen. Garry Lyons, Senior Lecturer in Mechanical Engineering, advised on the design of the testing method that involved fixing the bone trabeculae in hypodermic needles. Harrie Weinans co-ordinated the European project funding the work – the project was called "Mechanical integrity and architecture of bone relative to osteoporosis, ageing, and drug treatment (MIAB)", and Christopher Price and Mitch Schaffler were collaborators from Mount Sinai Hospital, New York, who performed the mineralization analysis. The paper [58] gave the surprising result that osteoporosis stiffens trabecular tissue; further details of this were published in paper [59]. Later this data was used as a basis for computational simulations of bone loss in osteoporosis.

My interest in tissue engineering is mainly from the mechanobiological viewpoint – i.e., to answer the question 'how do

mechanical stimuli regulate stem cell differentiation in scaffolds?' Besides one theoretical paper [60] that showed how to determine mechanical properties of tissue-engineered cartilage in the presence of a degraded core, the work has been experimental [61-73]. The first set of papers describe cell-construct interactions [61-67]; paper [61] was the outcome of a European project with the experimental work performed by Drs Moretti, Wendt, Herberer, and Martin from the University Hospital in Basel, Switzerland, biochemical testing for collagens performed by Sally Dickinson and Anthony Hollander from the University of Bristol with Danny Kelly and myself performing the mechanical testing of the engineered cartilage. Later the Bristol and Dublin groups collaborated with other members of this research consortium (Aileen Crawford and Paul Hatton from the University of Sheffield) to show that biochemical and mechanical markers of quality in tissue-engineered cartilage could be correlated [62]. Paper [63] was a collaboration with Robert Brown and his PhD student Maurizio Marenzana from University College London; Danny Kelly and I computed the magnitude of stresses generated at the agrose gel interfaces.

The next set of papers [64-73] described tissue engineering work done at the Trinity Centre for Bioengineering. Our first paper [64] was from Eric Farrell's PhD work and it showed that a scaffold developed at MIT Boston by Yannas, and developed in Ireland by Fergal O'Brien from the Royal College of Surgeons in Ireland, could support tissue differentiation of rat mesenchymal stem cells along *both* the chondrogenic *and* osteogenic lineage; Messers Doyle and Price were students of Veronica Campbell who supervised Eric Farrell's PhD with myself as co-supervisor. Two further papers continued the work on this scaffold; the first was written mostly by Professor O'Brien reporting results found by our jointly-supervised MSc student Mary Waller and others reporting how permeability changes with strain for a soft-tissue scaffold [65], and the second by Dr Eric Farrell comparing tissue differentiation in 3D and on 2D surfaces [66]. The PhD work of Louise McMahon (supervised by myself and Professor Veronica Campbell) used this scaffold as a medium for applying cyclic strain in 3D environments; in her first paper [67] we reported how cyclic stretch in 3D can affect chondrogenic differentiation by reducing GAG-synthesis relative to unstretched controls – clamping also reduced chondrogenic differentiation. In a second paper [68] the contribution of stretch-activated ion channels was demonstrated. The signalling pathways active in chondrogenic differentiation were presented in [69]. In a

further study [70] we showed the effect of low oxygen concentration on the chondrogenic differentiation of mesenchymal stem cells and also signalling molecules mediating the process. In her PhD work Emma Kearney (supervised by Veronica Campbell and co-supervised by me) demonstrated the relationship between strain levels and programmed cell death in mesenchymal stem cells from rat bone marrow [71]. In a further paper, we quantified the effect of the magnitude of tensile strain on the rate of osteogenic differentiation in these cells [72]. In a final paper on this set of experiments, Elaine Byrne, a Research Fellow working closely with Brian O'Connell from the School of Dental Science, used real-time PCR to quantify expression of bone-related genes and showed that pore size, mechanical constraint, and cyclic loading affected gene expression [73].

Fundamental aspects of computational mechanobiology

Some scientists think writing review papers is a waste of time – if this is true I have wasted a lot of time. Paper [74] was co-authored with Marjolein van der Meulen of Cornell University. At the time we had a Wellcome Trust collaboration grant to fund visits between Trinity and Cornell and we used this to review and analyse current ideas in mechanobiology – the paper was invited for a special Millennium Issue of *Philosophical Transactions*, the world's oldest scientific journal. The next paper is a comprehensive review of tissue differentiation theories written mainly by myself but with contributions from Professor van der Meulen regarding fracture healing [75].

My *Meccanica* review paper [76] was written while living in Rotterdam during a sabbatical year. It is an attempt to elucidate the role of mechanics in the ontogeny and phylogeny of musculoskeletal tissues; the paper was presented as the opening plenary lecture to the annual meeting of the *Associazione Italiana di Meccanica Teorica e Applicata* in Taormina, Sicily, in the Summer of 2001. At this time I also wrote two chapters in books: the first describing current issues in computational mechanobiology [77], and the second on the relationship between computational mechanobiology and experiments [78]. The latter paper [78] was presented at the first joint symposium of the Trinity Centre for Bioengineering and the National Centre for Biomedical Engineering Science held in Coolbawn, Co Tipperary, in April 2004; it describes one of the most challenging issues in computational mechanobiology – that of relating apparent level stimuli (determined from computations) to cell level stimuli (acting in experiments). The PhD work of Adam Stops in Galway under the

supervision of Peter McHugh, and with contributions from myself and Louise McMahon in Dublin, gave us an opportunity to study this problem. In paper [79] we reported our result that strains in a scaffold were distributed about a level equal to approximately 10% of the apparent strain in a particular type of collagen-GAG scaffold.

In the *Meccanica* paper [76] referred to above, I had become interested in the idea that mechanoregulation 'rules' (later I preferred to call them algorithms) had evolved by natural selection and, in 2003, Niamh Nowlan began to work on this and we published a paper showing how evolution of mechanoregulation algorithms was possible – and what is more, evolution of such algorithms is no guarantee of optimal phenotypes [80]. Later we conducted an experimental analysis of mechanoregulation during embryogenesis in collaboration with Paula Murphy, Senior Lecturer in Zoology, who became co-supervisor for Niamh Nowlan's PhD thesis. First we wrote a detailed analysis of previous investigations on mechanoregulation of limb development [81] and then we performed a finite element analysis to show how mechanical forces due to muscle contractions may propagate ossification in the embryonic avian limb [82]. Later in this work we identified mechanosensitive gene expression in the avian limb with ColX and Ihh involved in mediating mechanoregulation of bone formation [83]. The PhD work of Karen Roddy, also supervised by Dr Murphy and myself, focused on mechanoregulation of joint formation in the avian limb, and the first part of her work describing, in high detail, the acquisition of shape in the joint has been published [84]. In 2007 the group was funded by the Wellcome Trust to continue this work in a mammalian model, and we began to collaborate with the group of Dr S. Tajbakhsh at the Pasteur Institute in Paris who were able to create mouse mutants with disrupted skeletal muscle development. With Dr Niamh Nowlan as postdoctoral researcher and Céline Bourdon as PhD student, data was gathered showing a pattern to rudiment development in muscleless limbs indicating a complex interplay between forces and location-specific gene expression in the developing limb [85].

Around this time a series of invited lectures allowed me to explore wider issues in computational mechanobiology: in a lecture to *The American Society for Gravitational and Space Biology* in Washington in November 2006 I described how mechanical forces may affect biological structures from their effects on single cells up to the phylogenetic influences over evolutionary time; in retrospect this may have been a bit over the top but the paper was published [86]. In an

invited lecture to the *International Conference in Computational Bioengineering* in Venezuela in September 2007 I described how bone remodelling algorithms and tissue differentiation algorithms could be combined for analysis of implant design [87]. In 2007 I was invited to write a review article for *Regenerative Medicine*, and Louise McMahon (then a postdoctoral researcher in Bioengineering), and Fergal O'Brien collaborated with me in an attempt to synthesise the state-of-the-art in biomechanics and mechanobiology of osteochondral tissues, particularly referring to the role of computational mechanobiology [88]. While on sabbatical leave in Barcelona in 2008 and living in Sitges, I wrote a chapter on the latest developments in computer simulation of tissue differentiation together with Damien Lacroix and Sara Checa [89]. I also collaborated on a review of how computer-aided design techniques can improve scaffold design for tissue engineering [90]. Next came the request for two book chapters that I would certainly have been unable to do for lack of time were it not for the input of Dr Checa: the first deals with integrating the various cell-activity algorithms to create a simulation of tissue differentiation [91] and the second reviews our work over many years in the area of simulation of tissue differentiation applied to problems in tissue engineering, particularly the optimal design of scaffolds [92].

Implant design and testing

The papers on implant design and testing [93-158] form the largest component of my published work to date. I believe our group made a useful contribution but I fear research on this subject is rather ephemeral; implant designs are engineered artefacts – they pass, often rapidly, into obscurity. I have divided the papers into six sections.

Hip prostheses and the lower extremity

My first scientific paper reported a three-dimensional finite element model of the artificial hip joint [93]. The model was very large for the time; it was created using the facilities at EOLAS (now Enterprise Ireland) in Glasnevin where I spent the first year of my PhD studies in 1987-1988. Accurate stresses in cemented hip replacement were computed. The co-authors were my PhD supervisor David Taylor and John Monaghan, an expert on finite element modelling who acted as an advisor for this part of my PhD work. Later I analysed the multi-axial stress state in that part of the femur where bone loss occurs [94,95] – this became the springboard for the papers on damage-adaptive bone remodelling already described above. Together with a fellow research

student Thomas Culleton we used the model to show that fatigue fracture occurred in retrieved cement mantles. It was the first paper proving what engineers had long suspected – the lack of strength of the cemented fixation of hip prostheses [96].

After the PhD I did a stint as a Research Fellow and Contract Lecturer in the Department of Mechanical and Manufacturing Engineering in Trinity College. One of my projects was the design of an external fixation device. This was done in collaboration with a Senior Experimental Officer Alan Reid, an orthopaedic surgeon John Corrigan, and a graduate student Simon Toland, who performed the experimental analysis. The paper demonstrates the biomechanical advantages of the device [97]. Unfortunately it never went into clinical service; in fact Mr Reid had second thoughts about the functionality of the device and did not appear as a co-author on the paper [97].

While a postdoc at the University of Nijmegen, I became external supervisor for Brendan McCormack who was registered as a PhD student at University College Dublin (UCD) where he was then a College Lecturer (since 2007 he has been Registrar at the Institute of Technology, Sligo). We collaborated on three papers testing the hypothesis that continuous damage accumulation occurs in cemented hip replacement under cyclic loading. We showed it to be true both in bending [98, 99] and in torsion [100]. The co-authors Donnachada Gallagher and Brian O'Dwyer were M.Eng.Sc. students in UCD who performed some of the measurements. These papers led to a clear understanding of the inadequate nature of polymethylmethacrylate as a fixation material in hip replacement. Later with Alex Lennon a more sophisticated apparatus to show that crack accumulation and growth depended on prosthesis design was developed [101]. Later these ideas were taken up by researchers in the University of Southampton and we collaborated with them on a paper which showed that damage accumulation could be successfully predicted in computational models [102].

Papers [103] and [104] represent work somewhat out of this sequence. Paper [103] is the only comparative analysis of bone plugs used in cemented hip replacement showing some are far more effective that others. Regarding co-authors, Paul Birthistle was a BAI student who performed initial experiments, Victor Waide was a postdoctoral researcher who worked with me for a brief period in 1999 and who repeated some of the experiments of Mr Birthistle, and Girish Kummar was an orthopaedic registrar working in Dublin at that time but who

subsequently returned to India. Paper [104] was written by Dutch orthopaedic surgeons who I met on a sabbatical year in Rotterdam in 2001 (they worked in the Erasmus University Medical Centre) – my contribution was to identify the fatigue failure of this prosthesis using scanning electron microscopy; this was the first documented fracture of this widely used Exeter design of hip prosthesis.

The next set of papers [105-110] report a sustained effort to develop a pre-clinical testing platform for cemented hip prostheses. The experimental research was funded by a consortium of research laboratories (from the universities of Nijmegen, Dublin, Berlin, Bologna, and Ulm) and industrial partners (Aesculap AG, Germany; Waldemar Link, Germany; Mitab, Sweden; Tecres, Italy; Sulzer, Switzerland). The experiments formed part of the PhD thesis of Suzanne Maher [105, 106, 107] and John Britton [108, 109, 110]. A machine for reproducible placement of prosthesis was developed [105], something never done before or since. Next a method was designed for measuring the motion of the prosthesis relative to the bone in a cyclic test – the design was done in collaboration with Garry Lyons, Senior Lecturer in Mechanical and Manufacturing Engineering [106]. This method was then shown capable of discriminating differences between two prostheses [107]. These papers were original because of the precision of the measurements, but we were strongly criticised at the time for excluding muscle loading. These were added in a re-design of the testing rig [108] which included contributions of my masters student Laura Walsh. The next paper quantified precisely the error in the measurement [109] and finally, in the culmination of this work, we showed how the testing method could successfully rank four cemented prostheses according to their clinical performance [110]. In conclusion, after several years of sustained research we developed a method for pre-clinical testing of hip prostheses – and we showed that it worked. Whether or not this will ever make much impact is an open question because such experiments are difficult to reproduce and required skills in fabrication and experimentation are increasingly hard to come by. Computation offers an alternative; commercial codes are becoming more reliable and less costly, and engineers are increasingly trained to use them. As part of the large European project mentioned above, we used finite element modelling of damage accumulation and migration of four hip prostheses in clinical use. We showed that we could rank prostheses in order of clinical performance; Jan Stolk performed the analysis as part of his PhD work under the supervision of Nico Verdonschot and Rik Huiskes

and our experimental work was used to corroborate the simulations [111].

Alex Lennon and I addressed the whole issue of computing the stresses in the cement in total hip replacements in 2001. In paper [112] we showed how best to represent the stress distribution, and how it is fundamentally different in polished surface versus matte surface stems. Also with Alex Lennon we conducted a rigorous analysis of heat generation and residual stress formation in cement [113] – this is technically very difficult and I expect the work of this paper may not be surpassed for some time.

A follow-on phase of this work commenced some years later in a project called "Patient-Specific Prosthesis Analysis" with Dr Lennon and Dr Britton (by then working as Research Fellows in the Trinity Centre for Bioengineering); we conducted a retrospective study demonstrating that computational modelling could be used as part of a pre-operative planning process to estimate, in a virtual way before the surgery, the longevity of a proposed reconstruction [114] – this was called a "breakthrough" by one of the paper's reviewers. A further paper compared different outcome measures [115]. However a limitation was the time taken to create the finite element models which prevented use of the method inter-operatively. Pavel Galibarov, under the supervision of Dr Lennon and myself, developed a method for automated mesh generation from radiographs and we published a preliminary paper on this [116]. We continue to work on a method for pre-clinical and/or inter-operative methods for predicting implant performance.

In evaluating this research it should first be said that the problems at stake are immense if we wish to have a hip prosthesis that will reliably function for the lifetime of the patient – even for young people undergoing surgery. So, despite orthopaedic implants being a mature technology there is much to be done to advance this subject. Our research was ambitious in trying to devise both experimental and computational pre-clinical tests for hip prostheses. Although the experimental challenges continue to be pursued by many researchers worldwide, we have recently focussed on computational methods for pre-clinical testing and pre-operative planning. The overall objective of our current work is to create a 'virtual environment' for surgery that will facilitate matching the implant to the needs of the individual patient. It is clear that such simulations are in their infancy in the medical device sector.

Prosthesis fixation with bone cement

These papers [117-130] deal with a specialised topic – the durability of the material used to fixate orthopaedic implants to bone. The successful performance of this material *in vivo* effectively determines the success or otherwise of a large class of orthopaedic implants.

First Brendan McCormack and I studied crack propagation paths from bone-cement/implant bi-material interfaces [117]. Next we did a statistical analysis of data (first presented in paper [99]) to show that both porosity and initial damage from shrinkage controlled crack accumulation rates [118]; the co-authors on this paper were Cathal Walsh and Simon Wilson who are statisticians from Trinity College. We found that the initial damage is correlated with eventual total damage. Alex Lennon attempted to quantify experimentally this shrinkage stress creating the initial damage [119] using the optical metrology equipment available at the European Commission Joint Research Centre (JRC) in Ispra, Italy where he collaborated with Maurice Whelan and C. Forno.

The next four papers [120-123] formed part of the PhD thesis of Bruce Murphy. We were the first to obtain data on S/N curves for *both* hand-mixed and vacuum-mixed bone cement quantifying variability [120]. Next we showed how microdamage accumulation rates could be measured experimentally [121]. We then applied this technique to establish a relationship between damage accumulation rates, stress, and porosity [122], and finally performed the first multi-axial fatigue damage accumulation study on bone cement [123]. These papers form, in my opinion, the most comprehensive and original contribution to the subject of the fatigue behaviour of bone cement. Later we published, together with David Taylor, a rebuke of other work that discards specimens with large pores during fatigue testing [124]. Paper [125] was a collaboration with the University of Nijmegen that used the non-linear damage accumulation data to predict damage accumulation in experimental specimens; Jan Stolk was the PhD student in Nijmegen, with Nico Verdonschot and Rik Huiskes as supervisors. This method was corroborated using our experimental data in paper [125]; it was then used in computer simulations to rank the performance of prostheses already discussed above (Paper [111]).

Paper [126] demonstrates how the fatigue data may be used to interpret stress analysis output from finite element modelling of orthopaedic implants. It was an invited contribution to a symposium on the *Functional Behaviour of Biomaterials* at the American Society of

Mechanical Engineers Winter meeting in Orlando, Florida in November 2000.

Paper [127] forms part of Alex Lennon's PhD thesis, written under my supervision. It is a theoretical paper showing how simulations can be done to predict the variability of response of bone cement; a numerical method was developed and corroborated against the experimental data obtained by Bruce Murphy as part of his PhD studies (i.e. paper [120]). It provides the methodology later used in a comparison between simulated and experimentally determined microcrack accumulation in an experimental model (published as paper [101] mentioned above).

Paper [128] was an invited contribution dealing with fixation methods in orthopaedics and paper [129] is a review of biomechanical and clinical research on cement-in-cement revision hip arthroplasty written by my MCh student Parnell Keeling and a consultant orthopaedic surgeon who uses the technique, Paddy Kenny. Paper [130] was written by Ruairí Mac Niocaill, an MCh student under my supervision: it presents an investigation of the technique of 'sucking' cement into the acetabular cancellous bone during total hip replacement showing that such sucking does indeed increase fixation strength.

Shoulder arthroplasty

The shoulder has proven to be one of the most difficult joints to replace because of the high forces in the upper extremity and the large range of motion required. In total shoulder arthroplasty, the humeral head is replaced with a humeral prosthesis and the shallow socket of the scapula (called the glenoid fossa) is replaced with a glenoid component. Our first study was relatively simple. A two dimensional model was created by Damien Lacroix when he was an Erasmus student under my supervision. It shows that metal backing of the glenoid component influences cement and bone stresses [131] – perhaps because of its simplicity this work has been reproduced by many others.

Work on shoulder arthroplasty was continued as an MSc project by Damien Lacroix. He created the first three-dimensional model of the scapula and we reported it in paper [132] – the co-authors on this paper were radiologists in St. Vincent's Hospital Dublin who assisted with CT scanning. The model was then used to predict which approach to shoulder implant fixation was best for both normal bone and rheumatoid arthritic bone and, together with another of my PhD students Linda Murphy, we published a paper showing that fixation

could be improved if prostheses were designed for various pathologies of bone degeneration [133]. Later for her PhD Linda Murphy showed that offsetting the 'keel' of the glenoid component could further improve the durability of the fixation [134]. This was done with an Austrian orthopaedic surgeon Herbert Resch, who conducted clinical trials on such a design. We also performed an analysis of an acromion-fixation glenoid component showing the structural effects of fixating the glenoid component to the acromion [134].

The next two papers on shoulder implants papers were work done while I was on sabbatical at the Technical University of Delft. The first was with two Polish engineers: Wojteck Święszkowski who worked as a postdoctoral researcher in Delft and Piotr Bednarz who worked at Erasmus University Rotterdam – in this paper we used both theoretical and finite element calculations to show that high contact stresses are generated in the glenoid component surface, and that these stresses can be minimized by the best choice of design parameters [136]. I co-supervised Andriy Andreykiv (as mentioned above) in a study of the effect of loading and porous material stiffness on ingrowth into an uncemented glenoid component. Essentially this study showed that the design of an uncemented surface for osseointegration of glenoid components was possible but success depends on the stiffness of the porous metal-backing [137].

Prosthesis design and musculoskeletal mechanics

Papers [138-145] deal with general issues relating to the design of implants and the behaviour of the musculoskeletal system.

Paper [138] is a review of finite element modeling in orthopaedic biomechanics up to the year 1997. It concludes with an opinion that the field of computational modeling will develop along three fronts: more advanced imaging, more sophisticated material modeling, and mechanoregulation algorithms – so far these predictions (though perhaps not difficult to make) have been borne out by current research. Next I wrote a substantive chapter for a widely-read Handbook describing the design and testing of bone replacement prostheses [139]. Paper [140] was presented at the *11th Conference of the Irish Manufacturing Committee* in Dublin City University and was selected for publication in the journal afterwards – it is one of the few papers dealing specifically with the issues surrounding preclinical testing of implants; it uses examples from Suzanne Maher's PhD thesis and therefore she is included as a co-author. Paper [141] was an invited

presentation to the *XXXII Convengo Nazionale dell'Associazione Italiana per l'Analisi delle Sollecitazioni* given in Salerno in September, 2001. It describes how both computational and experimental methods support each other in preclinical testing of orthopaedic implants.

I was invited to contribute this chapter to a very popular graduate textbook going into its third edition. Given the amount of work involved I probably should have refused. Instead I invited Frans Van der Helm from Delft and Georg Duda from Berlin to share the burden and we wrote a long and complex chapter that attempts to bring a graduate student from the basics ("What is a force?") to an understanding of the neuromusculoskeletal control system [142].

The next three papers [143-145] describe how finite element modelling may be used in bioengineering design. Paper [143] was an invited contribution to the *16th European Conference on Fracture* held in Alexandropolis, Greece in July 2006 – drawing on examples from former PhD students I attempted to show how finite element modelling can be used for decision-making in materials selection. Paper [144] is a textbook contribution co-authored with Mark Taylor of the University of Southampton – in it we present a comprehensive description of how finite element modelling contributes to practice in orthopaedics. Paper [145] was the introductory lecture at the *2nd Summer Workshop of the European Society of Biomechanics* held in Dublin in August 2007. Written together with Alex Lennon, this paper discussed issues of computational modelling in biomechanical engineering, including the thorny subject of model validation; it subsequently appeared in part as an editorial when the selected papers of the symposium were published as a special issue of *Medical Engineering & Physics* [146].

Vascular biomechanics

There are six papers on the mechanical behaviour of vascular tissue and of cardiovascular stents [147-152]. Funding was obtained from C.R. Bard Ltd, Galway (later Arterial Vascular Engineering (AVE) Ltd and later again Medtronic Inc). Our first paper [147] determined the hyperelastic properties of arterial tissue of pigs and human cadavers, and applied this to compute prolapse in the cells of several popular stent designs. The co-authors on this paper were Caitriona Lally, then a PhD student under my supervision and now a Lecturer in Biomedical Engineering in Dublin City University, Seosamh Daly, an MSc student under my supervision, Clive Lee, Professor of Anatomy at both the Royal College of Surgeons in Ireland and the Royal Hibernian Academy

who advised on the tissue for testing, and David Quinn and Finbar Dolan who worked for Medtronic at the time and who helped digitize stent geometries.

Later Caitriona Lally obtained more accurate hyperelastic properties using both uniaxial and biaxial tests, using a testing apparatus designed by Alan Reid, Senior Experimental Officer in Mechanical and Manufacturing Engineering [148]. This data was used to compare the stresses generated in a three dimensional model of the artery after two different stent designs were implanted [149]. Michael Early, a PhD student under the supervision of Daniel Kelly, wrote a paper dealing with stresses in stented peripheral arteries and my contribution related to study design and interpretation of results [150]. Furthermore we published a study attempting to predict restenosis in stented arteries [151]; this was the first attempt by anyone to simulate in-stent restenosis. Later Colin Boyle, a PhD student under my supervision, developed this work into a much more sophisticated model of restenosis using the lattice-modelling approach [152]. Paper [153] was a comprehensive review article on the biomechanics of stenting and stent designs; I was invited to write this paper and the work was shared between myself, Caitriona Lally and Daniel Kelly.

Middle-ear mechanics

Research on middle-ear mechanics began as a collaboration with Mr Alexander Blayney, Consultant Ear, Nose, and Throat Surgeon at the Mater Misericordiae Hospital, Dublin. Together with my colleague Henry Rice and an MSc student Peter Ferris, we modelled the outer and middle-ear using the finite element method [154]. Later Daniel Kelly, when he was an undergraduate student, modeled grommets in the tympanic membrane in an attempt to predict which design would perform best; Mark Rafferty was a Registrar working with Mr Blayney who contributed an evaluation of existing designs [155]. This paper won the Norman Gamble award from the Royal Society of Medicine in the UK. Later, Peter Ferris and I showed how placing ossicular replacement prostheses in the middle-ear changed the middle-ear's dynamic behaviour [156].

The next phase of this work used microCT data to better represent the ossicles, and improved the muscle and ligament modeling [157,158]; this work formed part of the MSc thesis of Daniel Kelly. This work remains the most comprehensive model of middle-ear mechanics. Some years later John Vard, a Research Fellow working under my

supervision, used this model to design grommets [159]. We used this work as the basis for a new design of middle-ear prosthesis, and a patent was drafted but was not proceeded with.

I have always been intrigued by the middle-ear mechanism. In these papers [76, 154-159] we have used a finite element model to test out many ideas about prosthesis design. We have also considered fundamental reasons for middle-ear morphology [76] concluding that it is not, as the text-books would have it, a lever, but rather it has evolved as a spring [76].

Historical, Educational, and Research Topics

History of biomechanics

Papers [160-162] examine the work of two Irish contributors to biomechanics. For these studies, it has been my pleasure to collaborate with Clive Lee, Professor of Anatomy at the Royal College of Surgeons in Ireland. The first paper [159] describes the work of Samuel Haughton; born in Carlow, he entered Trinity College at 17 years of age, and wrote extensively on animal mechanics; Haughton was one of Darwin's more vocal opponents. The second paper [160] described Haughton's work, and that of another Irish biomechanician Michael MacConaill; it was delivered as the opening lecture of the *12th Conference of the European Society of Biomechanics* held in Dublin in August, 2000. The third paper [162] presents our analysis of three biomechanical ideas of MacConaill setting them forth in the context of current biomechanical research.

Papers related to education and research in bioengineering

Papers [163–171] are an attempt to address some broader issues of bioengineering. In the late 1980s, David Taylor had set up the Bioengineering Design Forum as a venue for engineers and clinicians to exchange ideas about medical device designs. The forums were successful – for a while. I co-ordinated them for a period in the 1990s; the strengths and weaknesses of the forum concept were explored in paper [163]. Paper [164] is an exploration, together with some leading lights of bioengineering in Ireland at the time, of the nature of scientific collaboration between engineers and doctors, particularly the engineers' need to model the system (whether it be with computer models or with prototypes) and the clinicians' attempts to relate to these models, and to use them. Papers [165, 166] are about innovation and how it may

become part of the university enterprise. In particular they explore how the role of the university relates to innovation in society in general.

In January 2001, while on a study visit to the Institute of Fundamental Technological Research of the Polish Academy of Sciences in Warsaw, I began to consider the direction of research in theoretical mechanobiology (I had a lot of free time) and I wrote a critique published as paper [167]. I believe this is still the only real critique of modeling in biomechanics.

In an editorial accompanying the publication of the keynote papers from the *12th European Society of Biomechanics* conference, Brendan McCormack and I presented results of a survey conducted at the conference. The survey attempted to quantify the importance of current research questions in biomechanics [168]. So far as I know no one has tried this before or since.

Paper [169] was delivered in Sligo in January, 2008, as the 14th Samuel Haughton Lecture of the Royal Academy of Medicine in Ireland. It deals with the concept of the human body as a machine and the relevance of computer simulation in mechanobiology.

Papers [170] and [171] are the only papers in this thesis relating to education; the first was read at a joint *Royal Irish Academy/Science Foundation Ireland Workshop on Engineering at the 4th Level* held in the Chester Beaty Library, Dublin, in June 2006. It is an attempt to lay out a course for the development of graduate education in Biomedical Engineering in Ireland. The second was the opening lecture to the symposium held in honour of C.G. Lyons in Trinity College in October 2008; while introducing the theme of the symposium it also discusses some long-standing issues in the education of engineers.

Paper [172] was an invited contribution to a volume titled *What did you do today, Professor*? It was commissioned to encourage an interest in careers in science and engineering. It is included here as a conclusion to this thesis submission.

P.J. Prendergast

09 February 2009

Revised, 23 December 2009

II. LIST OF THE PAPERS

Mechanobiology and Tissue Engineering

Modelling bone adaptations

Modelling tissue differentiation

Experimental mechanobiology and tissue engineering

71 Mechanisms of strain-mediated mesenchymal stem cell apoptosis, *Journal of Biomechanical Engineering* **130**, 061004.1-061004.7 [EM Kearney, PJ Prendergast & VA Campbell] 693

72 Tensile strain as a regulator of mesenchymal stem cell osteogenesis, *Annals of Biomedical Engineering* (in review) [EM Kearney, E Farrell, PJ Prendergast and VA Campbell] 701

73 Gene expression by marrow stromal cells in a porous collagen-glycosaminoglycan scaffold is affected by pore size and mechanical stimulation, *Journal of Materials Science: Materials in Medicine* **19**, 3455-3463, 2008 [EM Byrne, E Farrell, LA McMahon, MG Haugh, FJ O'Brien, VA Campbell, PJ Prendergast, BC O'Connell] 721

Fundamental aspects of computational mechanobiology

74 Mechanics in skeletal development, adaptation and disease, *Philosophical Transactions of the Royal Society [Series A]* **358**, 565-78, 2000 [MCH van der Meulen & PJ Prendergast] 731

75 Mechanics of bone regeneration, In: *Bone Mechanics Handbook* (Editor: SC Cowin), CRC Press: Boca Raton, Chapter 32, pp. 32.1-32.13, 2001 [PJ Prendergast & MCH van der Meulen] 745

76 Mechanics applied to skeletal ontogeny and phylogeny, *Meccanica* **37**, 317-34, 2002 [PJ Prendergast] 759

77 Computational Mechanobiology, In: *Computational Bioengineering* (Editors: M Cerrolaza, M Doblaré, G Martínez, & B Calvo), Imperial College Press, pp. 117-33, 2004 [PJ Prendergast] 777

78 Mechanobiology: experiment and computation, In: *Topics in Bio-Mechanical Engineering* (Editors: PJ Prendergast & PE McHugh), Trinity Centre for Bioengineering & the National Centre for Biomedical Engineering Science: Dublin & Galway, pp. 41-57, 2004 [PJ Prendergast] 795

79 A finite element prediction of strain on cells in a highly porous collagen-glycosaminoglycan scaffold, *Journal of Biomechanical Engineering* **130**, 061001.1-061001.11 [AJF Stops, LA McMahon, D O'Mahoney, PJ Prendergast & PE McHugh] 813

80 Evolution of mechanoregulation of bone growth will lead to non-optimal bone phenotypes, *Journal of Theoretical Biology* **235**, 408-18, 2005 [NC Nowlan & PJ Prendergast] 825

81 Mechanobiology of embryonic limb development, *Annals of the New York Academy of Sciences* **1101**, 389-411, 2007 [NC Nowlan, P Murphy & PJ Prendergast] 837

82 A dynamic pattern of mechanical stimulation promotes ossification in embryonic long bones, *Journal of Biomechanics* **41**, 249-258, 2008 [NC Nowlan, P Murphy & PJ Prendergast] 861

83 Identification of mechanosensitive genes during embryonic bone formation, *PLoS Computational Biology* 4, e1000250, doi:10.1371/ journal.pcbi.100025 [NC Nowlan, PJ Prendergast & P Murphy] 871

84 3D representation of the developing chick knee joint: a novel approach integrating multiple components, *Journal of Anatomy* **214**, 374-87, 2009 [KA Roddy, NC Nowlan, PJ Prendergast & P Murphy] 881

85 Developing bones are differentially affected by compromised skeletal muscle formation, *Bone* (in press). doi:10.1016/j.bone.2009.11.026 [Nowlan NC, Bourdon C, Tajbakhsh S, Dumas G, Prendergast PJ & Murphy P] 895

86 Computational modelling of cell and tissue mechanoresponsiveness, *Gravitational and Space Biology* **20**, 43-9, 2007 [PJ Prendergast] 907

87 Combining mechanoregulation algorithms for bone remodelling and tissue differentiation, In: *Bioengineering Modeling and Computer Simulation* (Editors: Y González & M Cerrolaza), International Center for Numerical Methods in Engineering: Barcelona, pp. 238-48, 2007 [PJ Prendergast] 915

88 Biomechanics and mechanobiology in osteochondral tissues, *Regenerative Medicine* **3**, 743-759, 2008 [LA McMahon, FJ O'Brien & PJ Prendergast] 927

89 Computational models of tissue differentiation, In: *Computational Modeling in Biomechanics* (Editors: S De, F Guilak & RK Mofrad), Springer: New York, pp. 353-72, 2010, doi:10.1007/978-90-481-3575-2 [PJ Prendergast, S Checa & D Lacroix] 945

90 Computer-aided design and finite-element modelling of biomaterial scaffolds for bone tissue engineering, *Philosophical Transactions* **367**, 1993-2009, 2009, doi:10.1098/rsta.2009.0024 [D Lacroix, J Planell & PJ Prendergast] 965

91 Predictive modelling in mechanobiology: combining algorithms for cell activities in response to physical stimuli using a lattice-modelling approach, In: *Computer Methods in Mechanics* (Editors: M Kuczma, K Wilmanski), Springer-Verlag, Berlin Heidelberg, pp. 423-435, 2010 [S Checa, DP Byrne & PJ Prendergast] 983

92 Computational techniques for selection of biomaterial scaffolds for tissue engineering, In: *Advances on Modeling in Tissue Engineering* (Editors: PR Fernandes & P Bártolo), Springer: Leira, Portugal (in press) [S Checa, C Sandino, DP Byrne, DJ Kelly, D Lacroix & PJ Prendergast] 997

Implant design and testing

Hip prostheses and the lower extremity

93 Materials selection in the artificial hip joint using finite element stress analysis, *Clinical Materials* 4, 361-76, 1989 [PJ Prendergast, J Monaghan & D Taylor] 1015

94 Stress analysis of the proximo-medial femur after total hip replacement, *Journal of Biomedical Engineering* **12**, 379-82, 1990 [PJ Prendergast & D Taylor] 1031

Shoulder arthroplasty

131 Stress analysis of glenoid component designs for shoulder arthroplasty, *Journal of Engineering in Medicine, Proceedings of the Institution of Mechanical Engineers* **211H**, 467-74, 1997 [D Lacroix & PJ Prendergast] 1353

132 The use of quantitative computed tomography to generate a finite element model of the scapula bone, In: *Proceedings of the 14th Irish Manufacturing Conference: Sustainable Technology for Manufacturing Industries* (Editors: J Monaghan & CG Lyons), Trinity College Dublin, pp. 257-64, 1997 [D Lacroix, PJ Prendergast, R Murray, S McAlinden & E d'Arcy] 1361

133 Three-dimensional finite element analysis of glenoid replacement prostheses: a comparison of keeled and pegged anchorage systems, *Journal of Biomechanical Engineering: Transactions of the American Society of Mechanical Engineers* **122**, 430-36, 2000 [D Lacroix, LA Murphy & PJ Prendergast] 1369

134 Structural analysis of an offset-keel design glenoid component compared with a center-keel design, *Journal of Shoulder and Elbow Surgery* **10**, 568-579, 2001 [LA Murphy, PJ Prendergast & H Resch] 1377

135 Acromion-fixation of glenoid components in total shoulder arthroplasty, *Journal of Biomechanics* **38**, 1702-11, 2005 [LA Murphy & PJ Prendergast] 1389

136 Contact stresses in the glenoid component in total shoulder arthroplasty, *Journal of Engineering in Medicine: Proceedings of the Institution of Mechanical Engineers* **217H**, 49-57, 2003 [W Święszkowski, P Bednarz & PJ Prendergast] 1399

137 Bone ingrowth simulation for a concept glenoid component design, *Journal of Biomechanics* **38**, 1023-33, 2005 [A Andreykiv, PJ Prendergast, F van Keulen, W Święszkowski & PM Rozing] 1409

Prosthesis design and musculoskeletal mechanics

138 Finite element models in tissue mechanics and orthopaedic implant design, *Clinical Biomechanics* **12**, 343-66, 1997 [PJ Prendergast] 1421

139 Bone prostheses and implants, In: *Handbook of Bone Mechanics* (Editor: SC Cowin), CRC Press: Boca Raton, Chapter 35, pp. 35.1-35.29, 2001 [PJ Prendergast] 1445

140 Issues in pre-clinical testing of implants, *Journal of Materials Processing Technology* **118**, 337-342, 2001 [PJ Prendergast & SA Maher] 1475

141 Preclinical testing of prostheses and implants – the interplay of computational and experimental methods, *Associazione Italiana per l'Analisi delle Sollecitazioni*, September, 2003, 10 pp., published on CD-Rom [PJ Prendergast] 1481

142 Analysis of muscle and joint loads, In: *Basic Orthopaedic Biomechanics and Mechano-biology*, 3rd Edn. (Editors: VC Mow & R Huiskes), Lippincott Williams & Wilkins, pp. 29-89, 2005 [PJ Prendergast, FCT van der Helm & GN Duda] 1491

155 The effect of ventilation tubes on stresses and vibration motion in the tympanic membrane: a finite element analysis, *Clinical Otolaryngology* **24**, 542-48, 1999 [PJ Prendergast, DJ Kelly, M Rafferty & AW Blayney] 1675

156 Middle-ear dynamics before and after ossicular replacement, *Journal of Biomechanics* **33**, 581-90, 2000 [P Ferris & PJ Prendergast] 1683

157 The effect of prosthesis design on vibration of the reconstructed ossicular chain – a comparative finite element analysis of four prostheses, *Otology and Neurotology* **24**, 11-19, 2003 [DJ Kelly, PJ Prendergast & AW Blayney] 1693

158 Biomechanics of ossiculoplasty, *CME Bulletin Otorhinolaryngology Head and Neck Surgery* **7**, 64-6, 2003 [DJ Kelly, AW Blayney & PJ Prendergast] 1703

159 The influence of ventilation tube design on the magnitude of stress imposed at the implant/tympanic membrane interface, *Medical Engineering and Physics* **30**, 154-63, 2008 [JP Vard, DJ Kelly, AW Blayney & PJ Prendergast] 1707

Historical, Educational, and Research Topics

History of biomechanics

160 On a wing and a prayer: The biomechanics of the Rev. Dr. Samuel Haughton (1821-1897), *Journal of the Irish Colleges of Physicians and Surgeons* **28**, 38-43, 1999 [PJ Prendergast & TC Lee] 1717

161 Biomechanics in Ireland and Europe, In: *Proceedings of the 12th Conference of the European Society of Biomechanics* (Editors: PJ Prendergast, TC Lee & AJ Carr), Royal Academy of Medicine in Ireland: Dublin, pp. 1-4, 2000 [PJ Prendergast] 1723

162 Walking on water: The biomechanics of Michael A. MacConaill (1902-1987), *Irish Journal of Medical Science* **175**, 69-75, 2006 [PJ Prendergast & TC Lee] 1727

Papers related to education and research in bioengineering

163 The Bioengineering Design Forum: developing an innovation network, *Industry and Higher Education* **11**, 116-9, 1997 [PJ Prendergast] 1735

164 Modelling medical devices: The application of bioengineering in surgery, *Irish Journal of Medical Science* **168**, 3-7, 1999 [PJ Prendergast, DE Beverland, AW Blayney, NJ Dunne, TF Gorey, PA Grace, BAO McCormack, T McGloughlin, PR O'Connell, & JF Orr] 1739

165 Research programmes that promote novel, ambitious, unconventional, and high-risk research: an analysis, *Industry and Higher Education* **22**, 215-221, 2008 [PJ Prendergast, SH Brown & JR Britton] 1745

166 Innovation in the university: it is time, In: *Proceedings of the 26th International Manufacturing Conference* (Editors: G.E. O'Donnell & K Kelly), Dublin, pp. 3-6, 2009 [PJ Prendergast] 1753

167 An analysis of theories in biomechanics, *Engineering Transactions (Rozprawy Inżynierskie)* **49**, 117-33, 2001 [PJ Prendergast] 1757

* * * * * * * *