

## Mechanics of soft tissue damage

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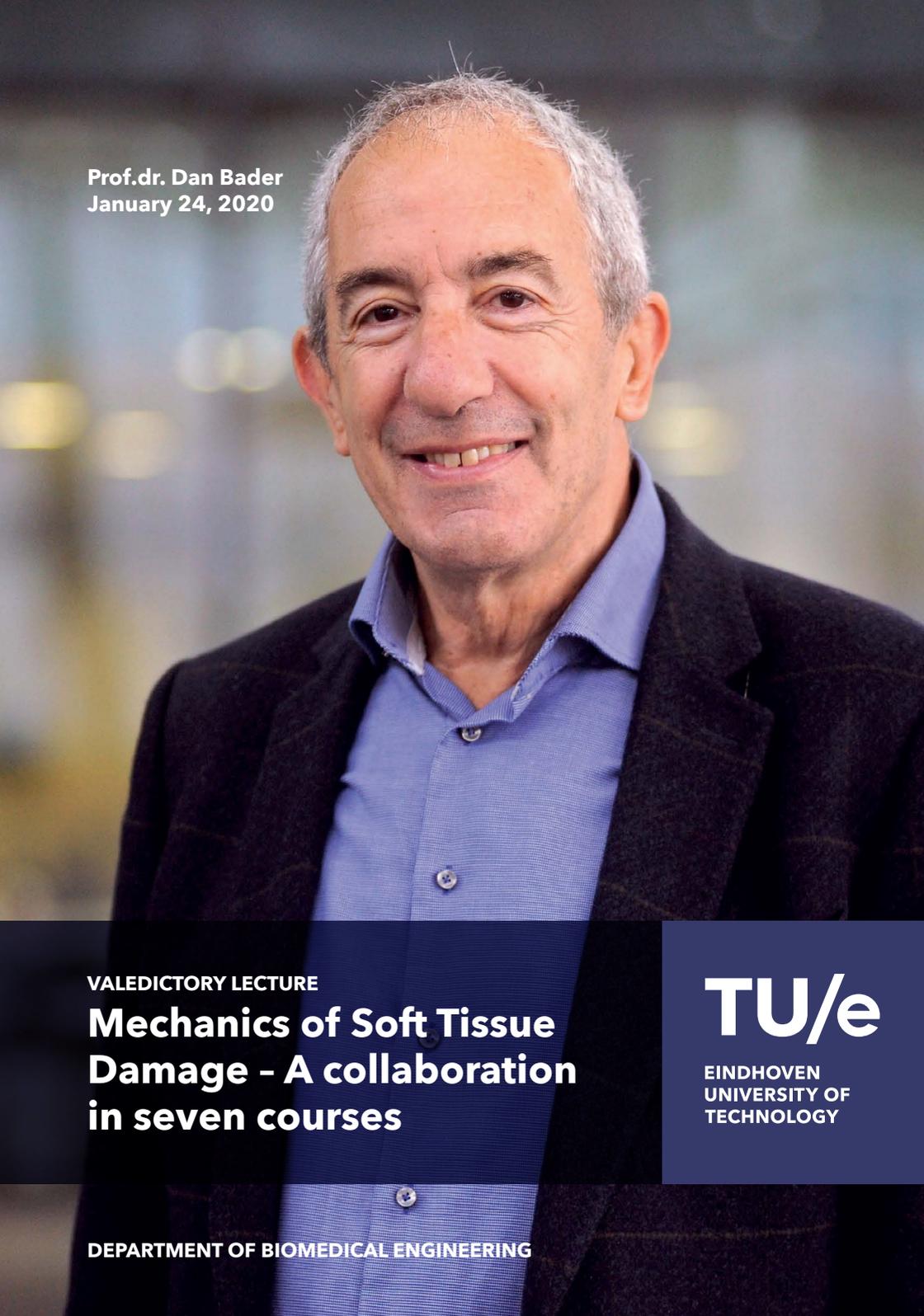
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A portrait of Prof. dr. Dan Bader, an older man with grey hair, smiling. He is wearing a blue button-down shirt and a dark jacket. The background is blurred, showing some lights.

Prof.dr. Dan Bader  
January 24, 2020

VALEDICTORY LECTURE

**Mechanics of Soft Tissue  
Damage - A collaboration  
in seven courses**

**TU/e**

EINDHOVEN  
UNIVERSITY OF  
TECHNOLOGY

DEPARTMENT OF BIOMEDICAL ENGINEERING

VALEDICTORY LECTURE PROF.DR. DAN BADER

# **Mechanics of Soft Tissue Damage - A collaboration in seven courses**

Presented on January 24, 2020  
at Eindhoven University of Technology

## Canapes

In preparing this presentation, I tried to recollect where my first association with Eindhoven began. Ironically, it started in the none-too glamorous surroundings of Stoke-on-Trent at a Gait Biomechanics event circa 1995. I met up with the then-postdoc Dr. Carlijn Bouten, who suggested that she needed to spend a period in a research laboratory outside of the Netherlands to progress her career. I was delighted to offer her the opportunity to come to my group in London, and we next met her and Dr. Cees Oomens at Queen Mary University of London (QMUL) in the East End of London. I proposed the choice of working on either a project associated with cell mechanics or one involving biomarker analysis of sweat collected in an environmental-controlled chamber based in the Medical School. She wisely chose the former and I think we can agree that this decision has served her well over the years, in which she has made advances in tissue engineering research associated with cardiovascular tissues. During her period in London, as will come as no surprise to anyone who knows her, Carlijn worked exceptionally hard in our new cell engineering labs and her achievement put most of my other research groups to shame. Indeed, the research yielded some seminal papers demonstrating that compression alone could damage the structural integrity of muscle-like cells (Bouten et al. 2001; 2003).

My next encounter with the team was when I was invited to visit TU/e and found myself sandwiched between Professors Jan Janssen and Frank Baaijens at a dinner somewhere in the city center, where they asked my opinion about the merits of setting up a Cell Laboratory in the new Biomedical Engineering Department. If I recollect correctly, I said something like, "if you want to provide realistic mathematical models to predict biological processes, you need accurate and robust experimental data." Well, the experimental work started modestly in three relatively small rooms in Gemini South but, soon after, new facilities were created which (much to my great envy) were approximately FIVE times larger than my equivalent labs in London.

## Soup

In 2000, I was appointed as a part-time professor in Soft Tissues Remodeling, initially for a three-year period. At the time, there was a convenient KLM Flight from London Stansted (a 35-minute drive from my London home) directly to Eindhoven Airport. At the time, this was nothing more elaborate than an enlarged shed. A few years later, the airfare increased dramatically and KLM redirected their flight to London Heathrow, nearly a two-hour journey from home. This inevitably put a great financial strain on my continued appointment at TU/e. However, Michael O'Leary, the owner of Ryanair, came to the rescue by selecting Eindhoven as a hub for all flights to the Netherlands and the southwest region of Germany. Their fares were about 15% of the KLM flights and have remained fairly acceptable since then. Accordingly, I declare myself one of the few fans of this budget airline. It has certainly helped to ensure the longevity of my 18-year appointment at TU/e.

So, what research was I involved with during those early years?

At the time, Cees and Carlijn had started their collaboration with Klaas Nicolay, who was working in the National MRI Facility in Utrecht. Klaas subsequently moved to Eindhoven as a full-time professor in Biomedical Engineering and built an MRI facility based on a Philips whole body scanner. This was adapted for small animal work in the Applied Physics building. He was joined by Gustav Strijkers and, in 2012, the entire group moved to the High Tech Campus at the joint facility with Philips.

The direction of this MRI-based research really excited me. Many years before, when I had worked in Oxford, I had been attracted to the work of Professor George Radda on using MR technologies (specifically spectroscopy) to assess metabolites in muscle damage related to degenerative diseases such as Duchenne Muscular Dystrophy. I saw the potential of adapting the MR approach for use in pressure ulcer research. This was pursued by Marielle Bosboom, whose work involved loading the tibialis anterior muscle of rats with an indenter for two hours outside the scanner and subsequently transferring the animal inside it, where T2-weighted images were recorded. What followed was a laborious process of creating histological sections of the indented muscle tissue and comparing the structural evidence of damage with that predicted from the T2 weighted images. Marielle's

thesis also introduced some numerical modeling to predict the internal mechanical strains required to induce muscle damage (Bosboom, 2001). The findings revealed large differences in the location and degree of muscle damage between the animals, partly due to the inability to reproduce the loading conditions between experiments.

Following on from Carlijn's work in London, the work on single cells continued and was extended in TU/e to examine the mechanical behavior of both single muscle cells and tissue-engineered constructs in the form of bioartificial muscles, so-called BAMs. This yielded a series of successful PhD projects, including those by Dr. Roel Breuls (2003), Dr. Emiel Peeters (2004) and, notably, Dr. Debby Gawlitta (2007). The latter's work using tissue-engineered models was the first to demonstrate - contrary to existing wisdom, which had focused on pressure-induced ischemia - that deformation alone can cause the development of cell death and muscle damage within 22 hours. By contrast, hypoxia evoked responses in the form of a change from aerobic to anaerobic metabolism, leading to an up-regulation of glucose and lactate concentrations within 24 hours, but cell viability was only reduced after 48 hours (Figure 1). In addition, lactic acidification was found to down-regulate tissue metabolism up to an acid concentration of approximately 23 mM, where metabolism was arrested and cell death enhanced (Gawlitta et al., 2007a). A similar tissue response was observed during glucose deprivation, which (at negligible concentrations) resulted in both a cessation of metabolic activity and a reduction in cell viability.

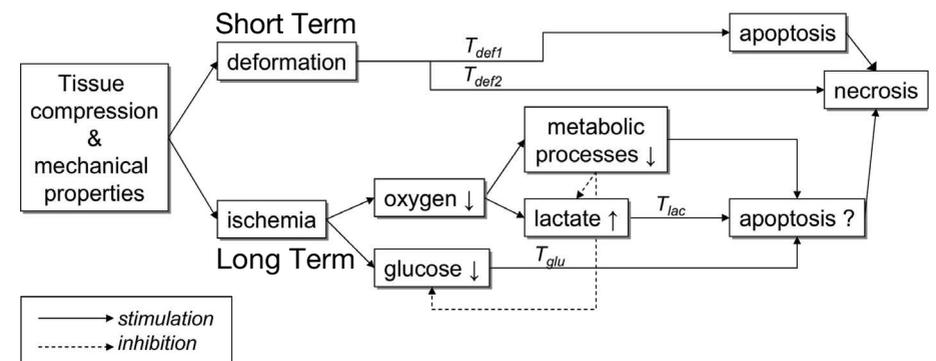


Figure 1. The distinct pathways of deformation and ischaemia, both of which can lead to muscle cell death (based on Stekelenburg 2005; Gawlitta 2007; Loerakker 2011).

The combination of results suggests that in the short-term (less than 24 hours), deformation, extreme acidification and glucose deprivation increased the level of cell death (Gawlitta et al., 2007b). These data provide more insight into how compression-induced factors can lead to the onset of deep tissue injury.

Subsequent progress was pursued by our colleague from Israel, Professor Amit Gefen, during his one-year sabbatical in Eindhoven. He used a new experimental method involving a half-spherical indenter to induce a non-uniform, concentric distribution of strains in the planar tissue-engineered construct. From the radius of the damaged region in the construct, the determination of the time-dependent critical compressive strains for necrotic cell death was possible. Analysis of the parameters of this sigmoid function indicated a 95% likelihood that cells could tolerate engineering strains below 65% for one hour, whereas the cells could endure strains below 40% for over four hours. The decrease in tolerance of the cells to compressive strains occurred within one to three hours post-loading. The specific strain-time curve is necessary for extrapolating biological damage from muscle-strain data in biomechanical studies of pressure ulcers, particularly deep tissue injury (DTI). (Gefen et al. 2008).

## Fish course

The association with Eindhoven enabled me to pursue my other great passion in research involving cartilage biomechanics. This interest had blossomed with my PhD work, where I used enzymes to break down human samples of articular cartilage in order to examine the relationship between the structure and function of this important load-bearing tissue.

At the start of the millennium, there was considerable research impetus for the development of tissue engineering cartilage and so, with the complementary expertise in experimental and computational mechanics, Queen Mary and Eindhoven led a successful European EU-5<sup>th</sup> framework grant 'IMBIOTOR', designed to develop "an Intelligent Mini Bioreactor" (Figure 2). This included enthusiastic contributions from your current Rector Magnificus, Professor Frank Baijens.

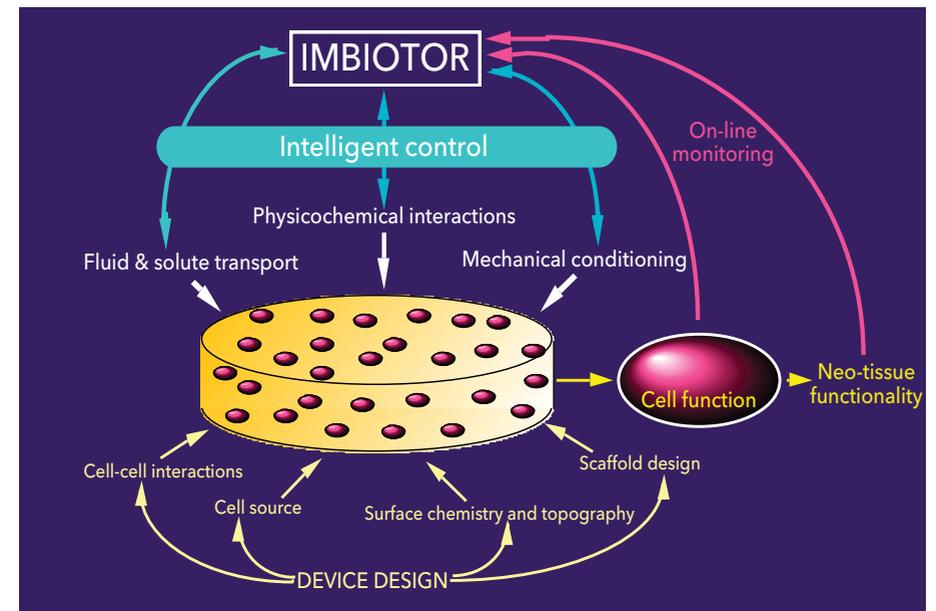


Figure 2. The concept of IMBIOTOR

We were very careful in selecting our partners, with significant consideration given to both scientific excellence and geographical locations and specific attention to culinary reputation. I think that Cees and Frank will attest to the excellent meals afforded by our hosts, particularly when we arranged meetings in Lyons and Capri.

In particular, I will never forget the lunch in a watermill just north of Lyons, where we enjoyed charcuterie as part of a delightful lunch washed down with a bottle of white Beaujolais which was sourced from a field 100 meters away from the restaurant. In regard to the science of the project, we progressed our understanding of what factors were required to up-regulate extracellular matrix from chondrocyte-seeded agarose constructs using biomechanical stimulation regimens (Chowdhury et al. 2003; Sengers et al., 2005; 2006). The introduction of the computational models enabled us to reduce the number of experiments which we needed to perform - it also belatedly introduced the partners to the Taguchi methods. In addition, this program nurtured the careers of future academics, including Eindhoven's Dr. Rene van Donkelaar, Professor Hazel Screen and Dr. Tina Chowdhury of QMUL, Dr. Bram Senger (who moved to Southampton) and Dr. Ronnie Schultz, who is now based in the Department of Cell Techniques and Applied Stem Cell Biology in Leipzig, Germany.

In 2003, the first review of my appointment recommended an extension for another three years. I won't bore you with the details of subsequent reviews but will just mention that they always concluded by saying "OK, just for another four years."

## Meat course

Cees' work in collaboration with Klaas Nicolay had now progressed to the utilization of a higher performance MRI system, which resulted in improvements to both the acuity of the real-time MR images and the corresponding FE models. Several PhD projects followed, yielding a number of seminal findings related to the aetiology of mechanical-induced damage to muscle tissue.

The first project involved the development of an MR-compatible loading device to improve reproducibility by controlling the indentation depth, resulting in smaller differences in the degree of muscle damage (Stekelenburg et al. 2007). It also enabled the opportunity to measure the moment of damage initiation and its subsequent temporal progression using T2-weighted MRI. This approach revealed, for the first time, that soft tissue damage due to large deformations was evident within ten minutes of indentation (Figure 3), considerably earlier than the damage evident at a more modest indentation resulting from pressure-induced ischaemia. This was evident two to four hours after indentation (Stekelenburg et al, 2008).

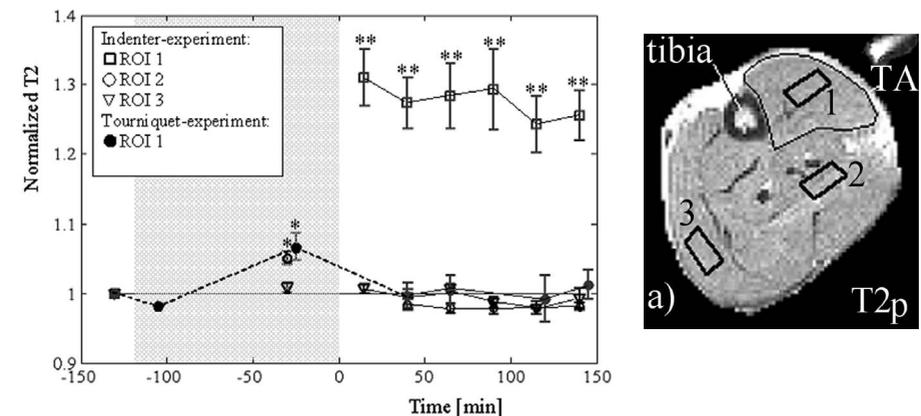


Figure 3. (left) The temporal profile of normalized T2 values prior to, during (shaded area) and after loading for indenter and tourniquet experiments for (right) three separate ROIs, as indicated on the MR images of a cross-section of the rat tibia (based on Stekelenburg 2005).

You will recall that these conclusions were similar to those involving tissue-engineering models, namely that the mechanisms associated with damage were important at different periods following loading. The former fast-occurring process was termed direct deformation damage, and although the exact processes have still not been fully clarified, they probably involve damage to the cell membrane and reorganization of internal cell structures, including the cytoskeleton. In addition, the importance of deformation was further confirmed by correlation between regions of high shear strain, calculated by tagging MR data and damage location. We discovered that by combining the animal model of DTI with numerical modeling, this type of damage was only apparent when a certain strain threshold was exceeded. It was later found that the amount of cell damage was linearly correlated to the magnitude of applied strain (Loerakker et al., 2010).

The PhD thesis of Dr. Anke Stekelenburg (2005), who contributed to the event today, represented my first and only appointment as a Primary Promoter/ Supervisor in Eindhoven. Unfortunately, the regulations forced me to present the official result to Anke in Dutch - an experience I am delighted that I have never been asked to repeat - although I was permitted to present the Laudatio in English.

Despite the significant progress in Anke's project, considerable differences between the animals still existed, which we considered to be a direct result of intra-animal variations with respect to the local internal deformations. Accordingly, animal-specific FE models were developed in the subsequent PhD project of Dr. Karlien Ceelen (2009) to simulate these MRI experiments with enhanced image resolution and estimations of the internal strain distribution in the muscle tissue during loading. By using a dedicated approach, differences between animals could be accommodated in terms of the geometry of the loading conditions in relation to the leg. Although this work highlighted the differences between the strains estimated by the FE models and strains derived from MR tagging experiments, the models could be used to demonstrate that regions of muscle damage clearly correlated with the presence of high deformations (Ceelen et al. 2008). The work also represented the first of its kind for comparing local tissue status in an attempt to identify a material property that reflects sensitivity to strain. In particular, it suggested that damage could be demonstrated when a threshold value of maximum shear strain or strain energy is exceeded. This is illustrated with three animal models in Figure 4.

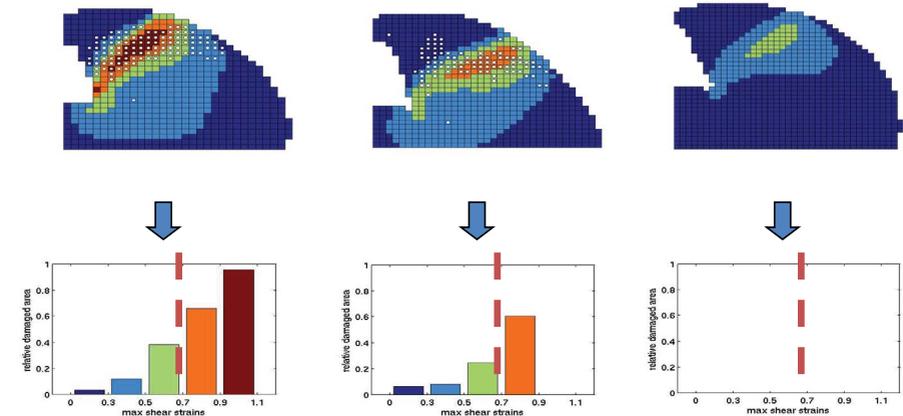


Figure 4. Maximum shear strain distributions in (top) colored maps and (bottom) histogram form for three separate animals, resulting from indentation over the tibialis anterior muscle. This indicates different strain magnitudes associated with damage. The dashed line represents a threshold value for estimated maximum shear strain.

Using a number of MRI parameters, including dynamic contrast-enhanced MRI, further studies revealed that reperfusion after a prolonged period of ischaemia may not be complete in specific areas of the tibialis anterior muscle, thereby extending the ischaemic conditions and aggravating tissue damage locally (Loerakker et al, 2011). It also confirmed that the effects of reperfusion must be fully considered when designing appropriate repositioning strategies for individuals at risk of developing pressure ulcers.

In the aforementioned experimental animal studies, an oblong-shaped indenter was employed to ensure that the muscle deformation could be simulated with a 2D FE analysis. In more recent studies, an indenter with a spherical head was designed and applied to the lower leg of rats and damage development was analyzed using different MR-imaging techniques. In these cases, analysis using a 3D FE model included regions of the leg that were not directly deformed under the indenter (Nelissen et al., 2018). These findings demonstrated, for the first time, that damage was not limited to the site of indentation but extended throughout the entire muscle tissue. The 3D approach thus resulted in a more accurate evaluation of both the spatial and temporal relationships between internal strains and damage.

As most of you will be aware, the collaboration with the Imaging Facilities came to a poignant conclusion with the closing down of the animal facilities at the High Tech Campus. Apart from focusing the mind, this deadline put considerable pressure on the final PhD projects focused on Deep Tissue Injury (DTI) (Nelissen et al., 2018, Traa, 2019). Nonetheless, there was significant progress associated with the change from 2D to 3D FE models to predict the internal mechanical conditions following indentation of muscle tissues (Traa et al. 2019). Unlike previous studies, this approach suggested that there was no distinct damage threshold evident at a well-determined strain or strain energy value, but rather a transition zone between a 'safe' region and a 'danger' region with a high probability of tissue damage. In addition, once damage has occurred, it propagates away from the loaded area to a much larger area of muscle than that which is associated with the highest strains. The 3D analysis showed that there is a subject-specific tolerance to mechanical loading and that the amount of tissue damage is not dictated by tissue deformations alone. Our work therefore stresses the importance of the appropriate modeling of physiological damage processes and of the assessment of individual susceptibility in future investigations into the aetiology of DTI (Traa et al., 2019).

At the present time, research involving MRI represents the 'gold standard' for imaging the soft tissue composite overlying bony prominences. However, it necessarily represents a complex and expensive modality and, as such, could not be considered for routine use in assessing the risk of developing pressure ulcers (PUs) in a clinical setting. This led to a recent investigation into whether ultrasound may provide the appropriate resolution of images of the deformed soft tissues in order to create robust computational models. This has been pursued in collaboration with a therapist colleague in Western Australia, Jillian Swaine. Her work showed that experienced sonographers have demonstrated good within- and between-operator reliability in the real-time ultrasound measurement of three soft tissue layers overlying the inferior curvature of the ischial tuberosities in a range of able-bodied and vulnerable individuals. Replicating this protocol in simulated sitting in a supine or a lateral recumbent position would eliminate the need for a specially-designed ultrasound chair and establish the reliability of the three-layer soft tissue US protocol that uses a preferred position of spinal cord-injured (SCI) participants and puts less ergonomic demands on the sonographer. The current sitting three-layer model can be used in 2D FEM to calculate internal strains in these soft tissues as a potential new risk factor for the development of PUs in the SCI population (Swaine et al., 2018).

## Vegetarian option

In 2011, I moved from a Bioengineering Department at QMU to a School of Health Sciences, based in a hospital but part of the University of Southampton. There was always the real possibility that this move would limit our collaboration but, in effect, this was strengthened. Indeed, the move enhanced our ability to translate some of our bioengineering activities to human models - the holy grail of 'from bench to bedside'. It also enabled me to appoint excellent, clinically-trained colleagues to Southampton, notably Professor Lisette Schoonhoven and Dr. Peter Worsley. In addition, the move enabled me to discover a completely new but related area after it was reported that medical devices were the cause of approximately 33% of hospital-acquired cases of pressure ulcers (Black et al., 2010). These functional devices are commonly used by individuals of a range of ages, from pre-term infants to amputees or patients in intensive care units. As a result of some generous UK funding to create a Network of academics, clinicians and industrialists, we were able to examine the performance of functional medical devices that were attached for prolonged periods to unconditioned skin areas. The focus in Southampton was to utilize a range of biomechanical, biophysical tools and biomarkers which reflected the status or health of vulnerable skin tissues. The complementary approach in Eindhoven was to predict the internal tissue stresses/strains as a result of the external boundary conditions. We thus examined the performance of a range of existing designs of devices, such as spine boards and respiratory masks (Oomens et al., 2013; Hemmes et al. 2017).

I have previously mentioned my interest in the potential of biomarkers as a means of interrogating skin status through the collection of local biofluids from loaded tissues. We proposed the use of sweat biomarkers, but then, in about 2005, two Eindhoven PhD students - Debbie Bronneberg (2007) and Lisette Cornelissen (2008) - adopted a multiscale approach to examine the release of inflammatory cytokines. In a tissue-engineered model subjected to increasing pressure, they demonstrated up-regulation of a selection of cytokines into the culture medium. They also proposed the use of a commercial tape, Sebutape, to collect sebum from loaded and damaged skin and thereby analyzed a selected number of extracted cytokines (Figure 5). Of particular interest was a small cohort study of patients in the Catharina Hospital in Eindhoven, which demonstrated a significant up-regulation over Grade 1 ulcers at the surface of sacral tissues (Bader and Oomens,

2018). The potential for the local detection of early signs of damage in vulnerable individuals is currently being pursued in a European project.

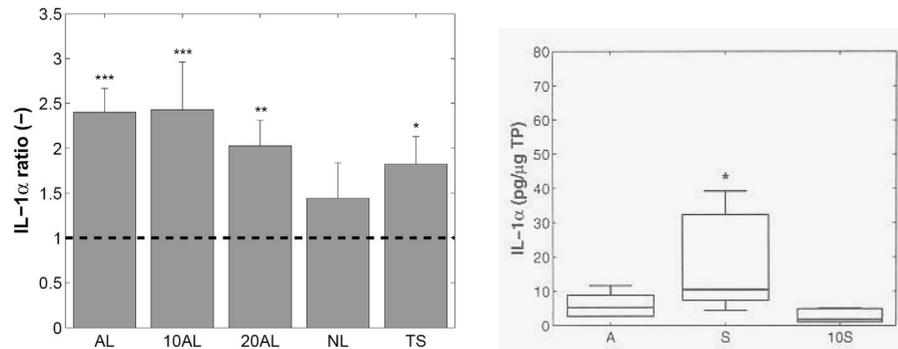
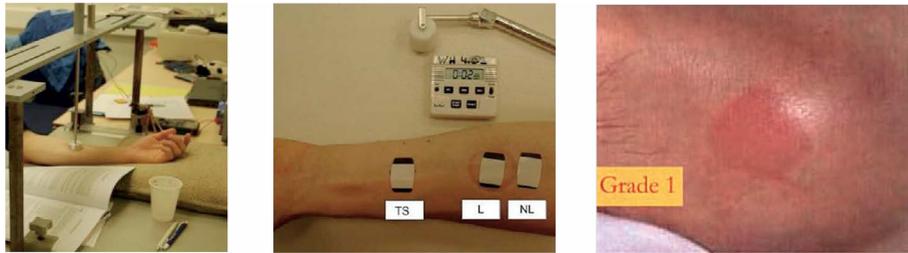


Figure 5. The collection of biomarkers in sebum using Sebutape from (top left) the loaded forearm of able-bodied volunteers and (top right) over Grade 1 ulcers at the sacrum of hospitalized patients. The corresponding up-regulation of IL-1a is indicated in the histograms.

The other long-held dream was to develop monitoring techniques designed for specific sub-groups of individuals at a high risk of developing pressure ulcers. As a first step, the outstanding PhD research of Dr. Sandra Loerakker (2011) included the analysis of blood biomarkers from both the animal model and a sub-group of SCI individuals at high risk due to their inherent immobility and lack of sensation (Loerakker et al., 2012). The study revealed the complexities of both sampling and the analysis of a selected number of muscle biomarkers, including creatine kinases and C-Reactive protein. The results highlighted the importance of co-factors – including level, severity, time since spinal injury and activity level of the individual – in determining the concentrations of muscle biomarkers in blood. It confirmed the importance of using an individual as his/her own control, i.e. using longitudinal test protocols involving repeated measures of an individual over a time period.

We revisited this approach in an extended cohort study performed in conjunction with Q Care Medical Services. It involved ten chronic SCI participants, two of whom developed pressure ulcers during the course of the 24-month study. The study highlighted differences between the biomarker levels in able-bodied and SCI groups. In the latter, two groups were identified, namely those with measurable baseline levels of myoglobin (which necessitates further evaluation) and those with negligible amounts of urinary Mb, for whom a dipstick method might be sufficient for evaluating Mb excretion due to DTI formation (Traa et al., 2019).

## Dessert

About five years ago, after visiting many critical scientific meetings (notably the EPUAP Scientific Annual Conference), it became apparent to both Cees and I that the messages being delivered to the clinical community (particularly those related to etiology) were strongly biased towards the conditions in which muscle tissue was initially damaged (Figure 6). They were thus associated with deep tissue injury. There is no doubting the seriousness of this condition with a variable prognosis – indeed, pressure ulcers can prove fatal. However, it must be recognized that DTI only represents approximately 5% of the total number of reported pressure ulcers. There was thus a pressing need to redress the balance towards attention on pressure ulcers which were initiated in the skin, as reflected in the majority of pressure ulcers found in both hospital and community settings. This particularly concerned research examining the tolerance of skin to mechanical-induced

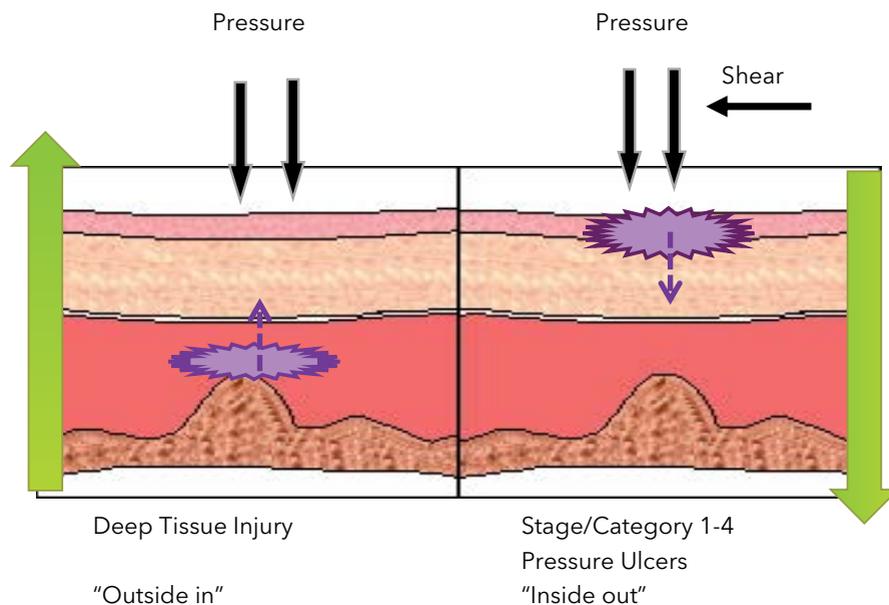


Figure 6. Schematic representation of the initiation sites and their direction of damage progression for (left) deep tissue injury and (right) pressure ulcers.

damage. It was certainly a return to the focus of Cees' PhD and other later projects in Eindhoven completed by Dr. Falke Hendriks (2005) and Dr. Marion Geerlings (2009). It also meant that I could return to the work of my Master's project in Aberdeen, which involved the mechanical loading of human skin.

Our focus on skin damage also coincided with successful awards from what was then the STW in the Netherlands, collaborating with the universities of Amsterdam, Twente and Leiden. These projects proved an exciting encounter with related research fields, typically tribology and drug delivery. The latter led to an experimental and numerical prediction of biomolecular transport to simulate vaccines injected into the outer layers of the skin using coated microneedles. The PhD project undertaken by Dr. Anne Römgens (2016) revealed the influence of geometric parameters, such as microneedle length and array spacing, on the efficacy of delivery in terms of activating antigen-presenting cells in the epidermis and dermis (Römgens et al., 2015; 2016).

The most recent PhD project was completed last year by Dr. Jibbe Soetens (2019). He adopted both computational and experimental approaches to both tissue and human models to examine skin behavior when exposed to a range of mechanical perturbations. The experimental study on human volunteers was largely conducted in our Environmental Chamber in the University Hospital in Southampton. It revisited our interests in sweat biomarkers and, in concert, examined the simultaneous up-regulation of inflammatory biomarkers when skin was exposed to diverse loading conditions. We developed a complex experimental protocol in which samples were collected at adjacent sites on the sacrum and subsequently analyzed while being loaded in either continuous or intermittent phases. Of several important findings, the work revealed that a small proportion of individuals within each of the able-bodied cohorts responded in a distinct manner to the loading regimens (Soetens et al. 2019). From this cluster analysis, certain individuals could be identified who might be at a higher-than-normal risk of skin breakdown (Figure 7). Such individuals would have to be monitored regularly, particularly if they were subsequently affected by co-morbidities such as diabetes, cardiovascular conditions, etc. To translate this early screening method using biomarkers into a clinical setting requires the further development of point-of-care sensors, which will be pursued in a new EU project.

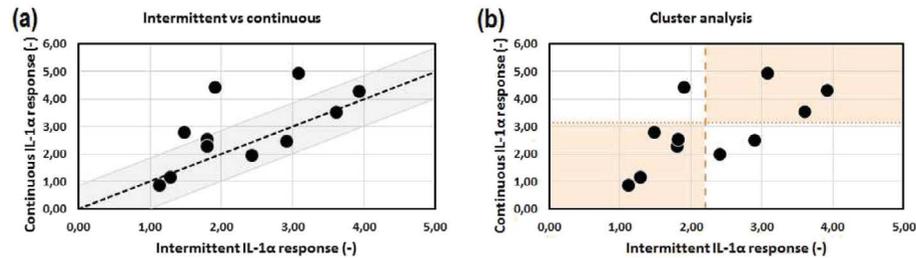


Figure 7. (right) The relative increase in IL-1 $\alpha$  response from 11 healthy participants subjected to continuous and intermittent pressures of 100 mmHg for a total of two hours and (left) two-step cluster analysis revealing that the responses to both loading regimens can be divided into two distinct sub-groups (based on Soetens et al., 2019).

## Cheese board

### INTERNATIONAL DISSEMINATION

In 2005, Cees, Carlijn and I, alongside Denis Colin from France, edited a book representing the state-of-the-art knowledge on Pressure Ulcer Research (Bader et al. 2005). It promoted a range of bioengineering tools to analyze the effects of loading using the hierarchical approach that we adopted. This involves a range of models, from cells to human studies. We were slightly surprised, however, when the publishers informed us a decade later that it had been translated into Chinese by a trio of austere individuals in full military uniform (Bader et al. 2016). Cees and I have also been involved in an international consensus to develop a new pressure ulcer conceptual framework (Coleman et al. 2014), as well as in a number of scientific advisory groups for international healthcare organizations.

My experiences with Eindhoven also involved a number of memorable and extreme trips with Cees and colleagues. These included a visit to present at the 8th National Wound Management Conference in Perth, Australia, hosted by our colleague Jillian Swaine. This trip coincided with a monumental hailstorm, which represented the first rain they had experienced in Western Australia for 100 days!!! The night after the storm, both Cees and I were introduced to conference delegates as "the Rain Makers." By contrast, a visit to Professor Vivian Mushawar's group in Canada in mid-winter was memorable in that we both lost our luggage at Vancouver Airport. We met our host in Calgary, where there was an outside temperature of -25o C, in a Greek restaurant, where we encountered a belly dancer performing around the tables - the less said about this, the better!

### TEACHING AND LEARNING EXPERIENCES

I have also enjoyed my teaching experiences in Eindhoven. My main responsibility was to develop a new module, 'Tissue Engineering', to cover both research and industrial aspects of a field that was undoubtedly new and exciting (Figure 8).



Figure 8. The emergence of tissue engineering as a top position for graduates, as recognized in the US's Time Magazine in 2000.

Top jobs	Time Magazine Europe May 29 <sup>th</sup> 2000
1	<b>Tissue engineers</b>
2	Gene programmers
3	Pharmas
4	Frankenfood monitors
5	Data miners
6	Hotline handymen
7	Virtual-reality actors
8	Narrowcasters
9	Turing testers
10	Knowledge engineers

During the ensuing period, my lectures had to keep abreast of the prevailing experiences in this dynamic area. Indeed, the highs and lows were documented by the late Michael Lysaght in a series of papers in the Journal Tissue Engineering. The module was originally delivered to a small cohort of 15 students but, as its popularity increased, it was included in a number of programs for Bachelor's and Master's students in Biomedical Engineering, as well as from other departments at TU/e. I adapted the module from one I had introduced at QMUL. Assessing the module proved interesting as pass marks in London were prescribed at 40%, which was effectively equivalent to a pass mark of 6 in Eindhoven. Interestingly, a number of Dutch students came to question their marks after the exam. However, by the time I had explained the reasoning for the limitations in their answers, they were happy to leave my office with an unchanged mark! Nonetheless, I have every confidence that the module has been suitably refreshed under the capable hands of its new coordinator, Dr. Sandra Hoffman Boss.

It has been a great joy to work with the cohort of PhD students in Eindhoven, many of whose work I have previously referred to. As would be expected, we often had heated debates about the design of experiments or the interpretation of data, which was all part of our experiences. However, they were generally sufficiently kind to accept my pedantic desire to use appropriate English in technical content, despite the fact that my endless corrections must have infuriated them. The value of the research from these PhD students was regularly acknowledged at international conferences. As an example, Sandra Loerakker was awarded Best PhD Thesis in the 2012 European Society of Biomechanics and the 2012 European

Pressure Ulcer Advisory Panel Meeting. More recently, Jibbe Soetens was awarded the Journal of Tissue Viability Prize at the EPUAP Annual Conference in Belfast.

Our collaboration has also benefited from the opportunity to host a series of TU/e students as interns to carry out research in my facilities at both QMU and, more recently, Southampton. They have provided me with the opportunity to develop research ideas using the skills developed by the interns at TU/e. I can confirm that they fully engaged in the activities, as can be seen with the two students - Man-Teng Fung and Dries Roover - who presented at a sandpit meeting organized by our 'Medical Devices and Vulnerable Skin Network' in Southampton (Figure 9). More recently, Hanneke Crielaard presented her internship research project very competently at the European Pressure Ulcer Advisory Annual Meeting in Lyons, France. She detailed the effects of repetitive loading on characteristic features of lymphatic flow in the skin, as monitored with a near IR imaging system. I have been impressed by how these students have performed and how they are proving great ambassadors for TU/e at international meetings.



Figure 9. Eindhoven interns (left) Man-Teng Fung and (right) Dries Roover presenting their project work at a 'Medical Devices and Vulnerable Skin Network' meeting in Southampton.

## Petit fours

So, what of future collaboration?

At the third time of asking, we were relieved that Eindhoven and Southampton were successful as key partners in a European Integrated Training Network (ITN) project 'Skin Tissue Integrity under Shear - STINTS'. With regards to UK partners, we got in just in time before the fateful, never-ending Brexit debacle. Both Cees and I are delighted to be active at the start of the program, but will be happy to hand over the reins to younger colleagues with fresh and exciting ideas. As an example, Dr. Richard Lopata will use ultrasound to determine the mechanical properties of skin and identify US parameters indicative of the initial loss of its integrity. To complete the circle of research, I am reminded of what my old PhD supervisor, Dr. Geoffrey Kempson, said to me: "once you start with the biomechanics of articular cartilage, you will never be able to leave it." This has proved prophetic; currently, Dr. Rene van Donkelaar and I are acting as guest editors of a cartilage biomechanics special issue of the Journal of Clinical Biomechanics.

In conclusion, the words of 'My Way' by Frank Sinatra come to mind:

"Regrets, I've had a few  
But then again, too few to mention"

On second thought, perhaps I should mention three small regrets, namely:

1. Having to publish with Dutch authors, with their associated everlasting number of initials representing their middle names.
2. I never did get to use MRS to identify biomarkers in the early stages of soft tissue damage.
3. I am not 20 years younger.

Obviously, I cannot end this presentation without mentioning some key individuals who have ensured that my time in Eindhoven proved both insightful and valuable to my academic career, as well as being great fun! Some of them were engraved in glass many years ago (Figure 10). In particular, Frank - who, alongside Jan Jansen, appointed me in 2000 - and Yvon Biemans, who has constantly provided a source of assistance to me, particularly when I struggled to arrange my life in the Netherlands. For that, I am eternally grateful. Other notables include Professor

Carlijn Bouten and my friend and fellow physicist, Professor Oomens. Dear Cees, we have shared so many great times together, including talking about music - even though I would like to state, in public, that you are 'tad stuck' in the rock culture of 1960/70s and need to become more au fait with modern bands.



Figure 10. Profiles of luminaries in the Soft Tissue Biomechanics and Tissue Engineering research group circa 2005.

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## Curriculum Vitae

Prof.dr. Dan Bader was appointed part-time professor in Soft Tissue Remodelling in the Department of Biomedical Engineering at Eindhoven University of Technology (TU/e) on January 1, 2001, a position he held for 18 years.

Dan Bader studied Physics at Liverpool University, followed by an MSc in Medical Physics at Aberdeen and a PhD in Cartilage Biomechanics at Southampton University (1985). He moved to the University of Oxford, where his research focused on bioengineering aspects of pressure ulcer prevention. He later joined the Interdisciplinary Research Centre in Biomedical Materials at Queen Mary, University of London (QMUL) to lecture in biomaterials. In 1999, he was appointed the first Professor of Medical Engineering at QMUL. Since 2000, he has been part-time professor in Soft Tissue Remodelling at Eindhoven University of Technology. In 2011, he moved to the University of Southampton to lead the Skin Health research group. Since 2014 he has led the UK EPSRC-NIHR Network and Network<sup>Plus</sup> on Medical Devices and Vulnerable Skin [www.southampton.ac.uk/mdvsn](http://www.southampton.ac.uk/mdvsn). He is currently one of the collaborative academic partners with TU/e in the EU ITN Skin Tissue INTEGRITY under Shear (STINTS) project.

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