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Identification of the Mechanical Properties of Living Skin

An Instrumentation and Modelling Study

Matthew David Parker

Supervisors: Poul M.F. Nielsen, Andrew J. Taberner, & Martyn P. Nash

A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

in Bioengineering

The University of Auckland

2016
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Funding Agencies

I was personally supported by the skin New Economies Research Fund (NERF) 9077/3608892 administered by the Foundation for Research, Science & Technolog), the Auckland Bioengineering Institute breast philanthropic fund, and the Medical Technologies Centre of Research Excellence (MedTech CoRE), administered by the Tertiary Education Commission of New Zealand.

Auckland Bioengineering Institute  
The University of Auckland  

2016
Abstract

The characterisation of soft tissue mechanics has the potential to benefit patients across a variety of medical conditions and procedures. Mechanical models of soft tissues may be used to predict surgical outcomes, identify lesions, assess the efficacy of treatments, and to optimise patient-specific treatment strategies. Characterisation of soft tissues that benefits individual patients requires the collection of force and displacement data, which should be gathered non-invasively, in vivo. Interpretation of mechanical data requires numerical models, due to the complex nonlinear, viscoelastic, anisotropic, and heterogeneous behaviour of skin.

In this thesis, experimental-modelling frameworks are presented, utilising both lumped-parameter, and finite-element, models. A six-axis force-displacement microrobot was modified to reliably apply dynamic forces (up to 200 Hz), in vivo, in indentation and extension experiments, while a 4-camera stereoscope was developed and validated to measure the resulting surface deformation field. A surface profiling algorithm was developed to identify the geometry of skin placed in an experimental setup, and to identify the position of the microrobot’s indenter tip.

Lumped parameter models were used to characterise the dynamic force-displacement behaviour of glabrous (on the palm) and hairy (on the anterior forearm) skin of ten volunteers. Individual directions were characterised by a Wiener model, identified through stochastic system identification, with variance accounted for ranging 94 % to 97 %. The use of stochastic system identification techniques provided a rapid means of characterising skin properties. Parameters were identified from 5-second samples, and the whole test procedure for full-scale perturbations lasted under 2 minutes per direction. The within-subject coefficients of variation (CV) of the Wiener static nonlinearity parameters provide insight into the reliability of the device. With normal indentation, the microrobot produced CVs ranging between 2 % and 11 %. The performance for extension tests was less reliable, with CVs ranging from 2 % to 19 %. However, the CV within individuals under extension is still within the ranges reported for commercial devices, such as the Cutometer and Reviscometer. Linear dynamic models were also found using stochastic system identification, at incremental loads. Linear models reported a Young’s modulus of 63 kPa at small indentation depths and 460 kPa at greater depths on the forearm, and 170 kPa to 1090 kPa for the palm. These values suggest that, at small indentations, perturbations were mostly made to the more compliant superficial layers in the skin, such as the hypodermis, before the stiffer layers were progressively recruited, such as the dermis and underlying tissues, such as muscle. The
microrobot and associated analytic techniques provide a unique system to mechanically analyse the nonlinear, anisotropic, viscoelastic, and heterogeneous properties of skin. It is the first device to employ stochastic system identification approaches in multiple directions without the need to reconfigure or reposition the probe relative to the skin. The results demonstrate its ability to measure skin properties in an efficient and reliable manner.

Lumped parameter models are difficult to relate to the underlying structure of skin. Finite element (FE) models were developed, which utilised constitutive relationships, to recreate skin geometry and predict surface displacements resulting from applied forces. FE meshes were fit to surface geometry data recorded from the stereoscope. Force boundary conditions were applied to FE nodes that were in contact with the indenter. The workflow was validated using controlled phantom studies. A single layer silicone gel phantom, and a composite silicone gel/rubber membrane phantom, were indented to 2.8 mm and 2.1 mm, respectively, and modelled in a finite element modelling package. Neo-Hookean models were selected for each material. Predictions of the surface deformation field were generated and compared to stereoscopic measurements. A least-squares nonlinear optimisation procedure was implemented, which minimised the difference between the model predictions and stereoscopic measurements. The identified parameter for the single-layer and two layer gel phantoms lay between the ranges of parameters found by independent measurements, and reproduced the surface deformations with an RMSE of 143 µm and RMSE of 138 µm, respectively. These findings demonstrate that a composite model can accurately predict the behaviour of a thin skin layer, tightly coupled to a thick bulk layer.

The FE modelling approach was applied to the forearm skin of a healthy volunteer, using a set of 1.5 mm displacement, in-plane and out-of-plane, experiments. A layered, 3D, quadratic Lagrange, FE mesh was used to model the experimental geometry. A Gasser-Ogden-Holzapfel constitutive model was used to calculate the surface deformations resulting from the application of boundary forces. A displacement-weighted mean-square error objective function was constructed for the deformation field. The FE model was able to recreate the nonlinear, anisotropic, viscoelastic, and heterogeneous behaviour with a RMSE of 211 µm. The use of stereoscopic data offered improved identifiability over traditional single-displacement measurement approaches, as demonstrated by Hessian identifiability metrics. However, the model was insufficient to capture skin's mechanical behaviour over the full force-displacement curve. The model may be improved by adding anisotropic pre-stress, and/or using a different constitutive equation. Improved constitutive models may be used in this workflow to predict surgical outcomes, identify lesions, assess the efficacy of treatments, and to optimise patient-specific treatment strategies.
Dedication

To my Poppa, Clarence Chadwick Chibnall
Acknowledgments

A project of this nature is not possible without contribution from a group of significant skilled people, who I would like acknowledge:

I am very grateful for the guidance, support, and encouragement, provided by my supervisors, Professor Poul Nielsen, Associate Professor Andrew Taberner, and Professor Martyn Nash. I have thoroughly enjoyed working with you all, through my bachelor and masters degrees, and to this day. Thank you for putting so much time and energy into providing ideas, feedback on presentations and manuscripts, and care for my sanity/wellbeing. I will fondly remember seeking the counsel of the three wise men, both at weekly meetings and trips abroad.

I would like to thank my colleagues at the Auckland Bioengineering Institute, especially:

- Dr Prasad Babarenda Gamage and Mr Amir HajiRassouliha. You two have been a huge help throughout my PhD. Your guidance with modelling, optimisation, and computer vision has been immense, and I have thoroughly enjoyed working with you.
- Dr Cormac Flynn, thank you for your ever-patient support when handing over your microrobot, designing experiments, and solving mysterious modelling bugs.
- The soft tissue instrumentation group, especially Messrs Sam Richardson and Alex Dixon. It has been a pleasure bouncing ideas, helping each other out at all times of the day and night, and keeping science fun.
- Dr Jess Jor, for your friendly guidance on skin modelling, and encouraging me to contribute to your review paper and book chapter. Your input gave me direction and focus at an early stage of my PhD.
- Dr Bryan Ruddy, for your enthusiasm and expertise in so many areas. I am sure I will be picking your brain many times in the future.
- Mr Steve Olding, thank you for your patience when teaching me CNC machining and how to catch a kingfish. I have had a great time working with you.
- To the level 5 instrumentation group, you have all made my postgraduate studies an enjoyable experience, having shared many skills, cakes, and stories. Special mention to the originals: Alex Anderson, Paul Roberts, Tom Lintern, Callum Johnston, and Mark Finch. I am lucky to have you all as friends.
- Finally, to Ellyce - Thank you for your support, especially through the last 18 months, and the 9 years before them. You did not sign up for over a year of living on opposite sides of the world, and I am so thankful you stuck with me in spite of my ever-
extending finishing date. I promise I will not do any more PhDs. Thank you to the Stehlins, my second family, who have made it easier for Ellyce and me while we’ve been apart, providing us both with love and support. Thank you to my parents, John and Lynley Parker, my siblings, Andrew and Jane, and my grandparents, Beverley and Chad Chibnall, who have provided many years of encouragement, love, and care. Mum and Dad also edited this thesis, so once again, all typos are on them.
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**Chapter 4**


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**Chapter 6, section 6.4, Constitutive parameter identifiability and the design of experiments for applications in breast biomechanics (2015) PhD Thesis**

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<td>development of the instrumentation, Design of experiments</td>
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Chapter 5, section 5.2.3 and Chapter 6

To form a journal publication on stereoscopic tracking validation, and a journal publication on skin characterisation

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### Chapter 1

## Abbreviations

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<th>Description</th>
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<tbody>
<tr>
<td>2D</td>
<td>Two-Dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three-Dimensional</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CCD</td>
<td>Charge-coupled device</td>
</tr>
<tr>
<td>CMOS</td>
<td>Complementary metal–oxide–semiconductor</td>
</tr>
<tr>
<td>CNC</td>
<td>Computer numeric control</td>
</tr>
<tr>
<td>cRIO</td>
<td>Compact, real-time input/output</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>D-SUB</td>
<td>D-Subminiature connector type</td>
</tr>
<tr>
<td>DAQ</td>
<td>Data acquisition</td>
</tr>
<tr>
<td>DC</td>
<td>Direct current</td>
</tr>
<tr>
<td>DIC</td>
<td>Digital image correlation</td>
</tr>
<tr>
<td>DOF</td>
<td>Degrees of freedom</td>
</tr>
<tr>
<td>FE</td>
<td>Finite element</td>
</tr>
<tr>
<td>FEA</td>
<td>Finite element analysis</td>
</tr>
<tr>
<td>FEM</td>
<td>Finite element model/mesh</td>
</tr>
<tr>
<td>FPGA</td>
<td>Field-programmable gate array</td>
</tr>
<tr>
<td>ID</td>
<td>Identification</td>
</tr>
<tr>
<td>ISU</td>
<td>Integer shift uncertainty</td>
</tr>
<tr>
<td>LED</td>
<td>Light emitting diode</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NCC</td>
<td>Normalised cross-correlation</td>
</tr>
<tr>
<td>OCT</td>
<td>Optical coherence tomography</td>
</tr>
<tr>
<td>PC</td>
<td>Personal computer</td>
</tr>
<tr>
<td>PCB</td>
<td>Printed circuit board</td>
</tr>
<tr>
<td>PCC</td>
<td>Phase-based cross-correlation</td>
</tr>
<tr>
<td>PCI</td>
<td>Peripheral component interconnect</td>
</tr>
<tr>
<td>PID</td>
<td>Proportional-integral-derivative</td>
</tr>
<tr>
<td>RMS</td>
<td>Root-mean-square</td>
</tr>
<tr>
<td>RMSE</td>
<td>Root-mean-square error</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>RRT</td>
<td>Resonant running time</td>
</tr>
<tr>
<td>RSTL</td>
<td>Resting skin tension lines</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra-violet</td>
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<td>VAF</td>
<td>Variance accounted for</td>
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1 Introduction

The characterisation of soft tissue mechanics has the potential to benefit patients across a variety of medical conditions and procedures. Mechanical models of soft tissues may be used to predict surgical outcomes, identify lesions, assess the efficacy of treatments, and optimise patient-specific treatment strategies. Characterisation of the soft tissues of individual patients requires the collection of force and displacement data, which should be gathered non-invasively, in vivo. This thesis focuses on the development of a measurement and modelling workflow for discovering and describing skin mechanics.

Skin provides a multi-purpose barrier between the human body and its surroundings. It insulates the body from ambient temperatures, controls inflow and outflow of many molecules, prevents pathogens from entering the body, and resists mechanical loads imparted on the body. Each of these roles helps to maintain homeostasis within the body.

Disease can affect the skin’s ability to achieve homeostasis. Measurable changes to the mechanical response of skin may indicate diminished barrier function, or be associated with disease in other organs. For these reasons, a significant field of research has been undertaken in an attempt to characterise the mechanical response of both healthy and diseased skin. Measurements have revealed the complex characteristics of skin, such as anisotropy, heterogeneity, nonlinearity, and viscoelasticity. These properties can be attributed to the complex, layered structure of the skin, and the varying constituents found in each layer. The mechanical response of tissue, and its underlying structure, is sufficiently complex that relating the two requires a mathematical representation of the system. It is anticipated that, with the use of a suitable model, characterisation of the mechanical behaviour of skin will lead to greater understanding and improved outcomes in areas such as wound healing, surgical planning, tissue engineering, transdermal drug delivery, and cosmetics development.

Characterisation of the mechanical response of skin may be used to predict the deformations that result from the application of a force, or vice versa. The skin’s response to deformation or force is dependent on the geometries of the interacting materials, the properties of their constituents, and the nature of the applied perturbation. Characterisation thus involves gathering data and interpreting them with the use of mathematical models. Stress-strain data from well-controlled deformation tests can be described by appropriate constitutive
Chapter 1 Introduction

models. For biological applications, constitutive models are implemented in numerical representations, such as finite element models, of anatomical systems to simulate physiological function.

1.1.1 Measuring the Mechanical Behaviour of Skin

Accurate parameterisation of constitutive relations requires careful experimental measurements. Data regarding the mechanical properties of skin are typically gathered by applying a force and measuring the resulting deformation. These data are then used with a computational model to discover and parameterise constitutive equations that adequately describe the observed behaviour.

The accuracy of computational models relies on the detailed consideration of deformation protocols and their associated boundary conditions. Mechanical experiments on skin have historically been performed on cadavers or excised tissues (Langer, 1861; Tong and Fung, 1976; Lanir, 1979). However, many features of skin, such as those that are dependent upon vascularisation, are altered by excision, and it is currently not possible to completely recreate in vivo boundary and environmental conditions in an in vitro environment. For complete characterisation of living skin, we thus rely on in vivo experimentation.

Forces are generally applied to in vivo skin by one or more of four techniques: suction, torsion, extension, or indentation. Other techniques are rarely used, but described in Chapter 2. Deformation measurements are typically made at a single point on the skin surface, at, or near, the site of force application. Recent studies have examined the parameterisation of constitutive relationships, and concluded that the identifiability of model parameters suffers from the sparsity of deformation modes and data (Holzapfel and Ogden, 2008; Moerman et al., 2009; Flynn, Taberner and Nielsen, 2011c). It is expected that reliable identification of model parameters may be aided by collecting rich data sets, via measurement of surface or volume deformation fields in a variety of deformation modes.

The first goal of this thesis is to develop suitable instrumentation to impart well-controlled forces on in vivo skin, and to measure the resulting deformation field.

1.1.2 Modelling the Mechanical Behaviour of Skin

Constitutive relations provide the connection between strain and stress and can be implemented in finite element models, which provide insight into stress- and strain-distribution throughout a complex geometry, such as skin. These models also provide a means of quantifying properties of the skin in areas where direct measures cannot be made, such as within the tissue.
Finite element models have proven useful in a range of applications, such as investigations of wound healing (Actis et al., 2006) and tissue damage (Hadid et al., 2012), producing facial animations for the film industry (Hung et al., 2009), determining characteristics for engineered tissue (Flynn and McCormack, 2009), driving virtual surgeries (Lapeer, Gasson and Karri, 2010), and to gain better understanding of physiology or constitutive models (Flynn, Taberner and Nielsen, 2011c). A more complete discussion of existing finite element applications is provided in Chapter 2.

The second goal of this thesis is to develop a characterisation workflow to identify the mechanics of skin, where the data describing nonlinear, anisotropic, heterogeneous, and viscoelastic behaviour is reproduced in a 3D geometric mathematical model. It is anticipated that this model will lead to an increased understanding of skin mechanics and encourage development of future skin models.

1.2 Objective & Scope

The overall objective of this PhD project is to:

Integrate modelling, mechanical instrumentation and image processing to characterise the mechanical properties of in vivo skin. Existing instrumentation will be refined to increase repeatability and robustness of measurements, and experimentation will be developed to improve the parameterisation of numerical models.

This thesis focuses on the combination of mechanical and imaging instrumentation, which is used to drive the choice of experimental protocols used to extract properties of a number of numerical models. This involves:

- improving and merging existing instrumentation, principally a force-sensitive microrobot with a three-camera stereoscope, to induce and measure three-dimensional deformations;
- ensuring that the instrumentation is capable of imparting and measuring deformations to characterise the mechanical properties of in vivo skin;
- designing and performing experiments on in vivo tissue to capture the anisotropic, nonlinear, viscoelastic, and heterogeneous behaviour of skin;
- modelling the mechanical behaviour using structural and/or phenomenological constitutive relationships which describe the deformation seen through the layers of skin; and
- validating the experimental and modelling approach with well-defined soft material phantoms.
Chapter 1 Introduction

This project focuses on identifying the mechanical behaviour of living skin in vivo. Studies on soft, layered phantoms are used to determine the problems, and their solutions, involved with identifying the constitutive parameters that characterise mechanical properties, such as anisotropy, heterogeneity, nonlinearity, viscoelasticity, and coupling between layers.

The techniques learned from studies on controlled phantoms are applied to living skin in vivo. In vivo studies provide quantitative descriptions of the mechanical behaviour of living skin. Beyond this project, in vivo measurements will be made: at various sites on an individual; on various individuals of different age, sex, and ethnicity; and about heterogeneous regions, such as around wrinkles, moles, scarred, or diseased skin. This information will be useful for biomechanical modelling, and may be of clinical value when diagnosing and/or ascertaining the effectiveness of treatments of diseases of the skin.

Three-dimensional surface deformation is evaluated using a stereoscopic camera rig. This rig is integrated with the microrobot to track surface changes throughout the time-course of various deformation profiles. Surface patterning is achieved through an airbrushed speckle-pattern, which allows a dense data set to be recovered through 3D cross-correlation methods. In order to identify the dynamic (viscoelastic) properties of materials, these techniques require a high level of synchronisation between the cameras and linear actuators of the microrobot.

1.3 Thesis Overview and Novel Contributions

Chapter 2 discusses background information for this thesis, such as skin anatomy, instrumentation used to perturb in vivo skin, and mechanical models used for skin characterisation. Chapter 3 details the developments made to the microrobot that were necessary to address the aims of this thesis. Chapter 4 presents a dynamic characterisation study on in vivo skin of 10 subjects, which was made possible through the instrumentation developments detailed in Chapter 3. Chapter 5 presents the development and validation of a four-camera stereoscope which provided accurate measurements of three-dimensional surface deformation. Chapter 6 presents a mechanical characterisation workflow, and a validation of the approach using soft material phantoms. Chapter 7 extends the modelling framework to an in vivo characterisation of skin on the forearm. Finally, the overall conclusions and future work stemming from this thesis are presented in Chapter 8.
1.3.1 Individual Author Contributions to the Work Presented in this Thesis

Like many projects, the research presented in this thesis was conducted as part of a larger research group. It leveraged work from past and present contributors of the Auckland Bioengineering Institute “Skin Mechanics” group, some of which is necessarily discussed in this thesis to form a more complete body of work. However, the author’s contributions must be clearly separated from collaborators, for the benefit of the assessors of this thesis. Primary collaborators, and their work that features in this thesis is listed below:

Mr. Amir HajiRassouliha: Improvement to the accuracy of a two-dimensional, phase-based cross-correlation method for feature tracking in digital images, improvement to the accuracy of a camera calibration algorithm, and the development of a generalised surface profiling algorithm (see section 2.6.4). There was a number of modifications made to these algorithms, which are presented throughout this thesis, and are the author’s own work.

Doctor Prasad Babarenda Gamage: Construction and optimisation of a 2-layer finite element model for validation of the skin modelling approach, using gel phantom phantoms. See section 6.4. This modelling work was an important addition to the validation experiments presented in this thesis, and forms a self-contained subsection. Other models presented in this thesis are the author’s own work.
Chapter 1 Introduction
2 Background

The following chapter outlines important literature pertaining to the goals of this thesis. This includes the instrumentation used to apply and measure deformations, as well as the constitutive and finite element models currently used to interpret the data. A discussion of current finite element applications is provided to motivate the goals of this thesis.

2.1 Skin Anatomy

Skin is organised into a distinctly stratified structure. At a basic level, skin can be divided into the epidermis, dermis, and hypodermis layers. Both the dermis and epidermis contain their own layered structures, but skin is often considered as comprising three layers, as they represent the most obvious features that are observable with low power microscopy.

The epidermis provides the body with a physical barrier to its environment. It resists day-to-day abrasion, impacts, and harsh temperatures, and limits the entry of chemicals and pathogens. The entire layer is approximately 150 µm thick, lacks vascularisation, and
consists mostly of epithelial cells. These cells are characterised by their high keratin content, with increasing keratinisation towards the outer surface of the skin. Cells are produced at the basal layer, situated at the epidermal and dermal interface, where the level of keratin is lower than the outer surface. As basal cells age, they migrate towards the epidermal surface, gradually keratinising and flattening. The keratinisation gradient can be demarcated into a viable epidermal layer and the non-viable stratum corneum. The stratum corneum consists of 15 to 20 cell layers (10 µm to 40 µm thick), which have been degraded to the point where they lack nuclei and are effectively saturated with keratin. It is the high level of keratin that provides the very stiff mechanical response and limited permeability of the epidermis. Further barrier properties of skin are provided in this layer by the secretion of cholesterol, fatty acids, lipids, and ceramides, which act to bond cells together.

Intertwined with the viable epidermis is the dermis; the layer that provides the bulk of skin’s load bearing properties. Like the epidermis, the dermis is also divided into further layers: the papillary and reticular dermis. This separation does not reflect a difference in constituent structure, but is defined by the physical appearance of the dermis, in which the superficial papillary layer extends into the epidermis. 75% of the dermis dry weight is provided by collagen fibres, arranged roughly in sheets parallel to the skin surface. These fibres restrict excessive stretch of the skin and exhibit a non-linear relationship between stress and strain.

Elastin fibres are found throughout the collagen network of the dermis, and act to return stretched collagen to its resting state. Small amounts of reticulin fibres are also present in the dermis, and appear to keep the collagen and elastin fibres in place. Fibres are supported by a proteoglycan-rich ground substance, which is thought to provide the viscoelastic response of the skin.

Located beneath the dermis is the hypodermis, an adipose cell-rich layer which acts as the main thermal insulation layer of the body. Its thickness is related to the body mass index (BMI) of a subject, as adipose cells store fat. This subcutaneous fat layer exhibits compliant behaviour in comparison to the dermal and epidermal layers, and can act to tether the skin to the underlying tissues. Connections may be a tight, no slip connection to underlying bone or muscle, or coupled to a membrane to provide a sliding mechanism over the underlying tissues.

### 2.2 Skin Mechanics

The mechanobiology of skin is complex. Skin exhibits a number of properties that prevent the use of simple models used for engineering materials. Engineering material models, such
as those used for metal and ceramics, typically assume a linear elastic relationship between stress and strain. In contrast, skin has been shown to be nonlinear, anisotropic, heterogeneous, viscoelastic, and under non-uniform pretension in vivo. The complexities of representing all of these features in computational models have often led researchers to select only a subset of these properties to represent. The following section describes the various mechanical characteristics, and the biology understood to be associated with them.

2.2.1 Anisotropy

It is unclear how much of the apparent skin anisotropy is due to pretension, and how much is due to the distribution and direction of constituent fibres in the skin. Pretension is relieved when tissue is excised, but samples have been shown to retain anisotropic behaviour (Lanir & Fung, 1974; Ridge & Wright, 1966). Lanir & Fung (1974) stated that anisotropy is “associated with the preferred orientation of the collagen fibers in the skin.” This relationship has formed the basis of many structurally-based constitutive models such as Lanir (1983).

The preferred direction of dermal collagen fibres was described in an in-depth study by Gibson, Kenedi, and Craik (1965). The authors performed a histological study of the dermis, excising tissue at sites across the body. They noted that a clear preferred direction of collagen fibres existed in 60% of sites that they tested.

Kumar et al. (2012) examined collagen and elastin content in two different directions, at various sites across the body. They imaged histological slides of samples, quantifying collagen and elastin content by their respective areas in photomicrograph images. The authors reported on areas in the body where collagen content differed by up to 10% and elastin content by 8%, but made no effort to align these axes with tension lines in the tissue, so no direct comparisons to force can be made.

2.2.2 Nonlinearity

As a whole, skin exhibits strongly nonlinear behaviour. This behaviour has been attributed to the recruitment of various fibres throughout the skin. Figure 2-2 presents a schematic stress strain plot, with the individual recruitment of fibres shown.
Chapter 2 Background

The recruitment of fibres has been elegantly described by Gibson et al. (1965). They write:

“In the relaxed state, the collagen fibres are unorientated, convoluted structures, separated from each other by tissue fluid and amorphous dermis. This arrangement allows continual movements of the individual fibres to absorb the minor stresses of normal activity, and relies on the ultimate strength of collagen to resist severe stretch. There is in the dermis an intertwined meshwork of collagen fibres so patterned that, in whatever direction it is stretched, all of the fibres eventually become parallel.”

Up to 30% strain, the stress response is due to the stretch of elastin fibres. This phase is often approximated as linear (see the first region in Figure 2-3). A nonlinear slope arises
Skin Mechanics

(figure 2-3) as collagen fibres are gradually recruited in the direction of strain. During this phase, the crimped ultrastructure of collagen provides a relatively compliant response. A second linear phase is seen when all collagen fibres in the skin are aligned with the direction of strain and sufficient strain has removed the crimp of collagen. This slope represents the material response of collagen uniaxially stretched. Above 60 % strain, collagen tends to defibrillate, causing failure in the tissue.

2.2.3 Viscoelasticity

The stress-strain response described above is also time dependent. Other than the initial low-modulus stretch region, when elastin fibres dominate the stress response, the elicited stress for a given strain depends on the strain rate. Strain-rate dependence reflects the relative proportions of stored and dissipated energy in the skin. When skin is stretched, some energy is stored in the elastic fibres, while some is dissipated through the tissue. The stored portion is referred to as the elastic portion, while the released energy is termed viscous. Both collagen and elastin fibres efficiently store energy under load, allowing tissue to recoil once the load is removed. However, a considerable portion of the energy introduced to skin is dissipated. The viscous energy loss is probably due to collagen fibres sliding through the proteoglycan-rich ground substance, as they align with the direction of force (Dunn and Silver, 1983). The fraction of stored energy relative to dissipated energy increases with strain rate, as collagen fibres do not have sufficient time to move throughout the semi-fluid ground substance.

Viscoelastic materials demonstrate the dissipation of energy through the difference in loading and unloading curves, which is termed hysteresis. Hysteresis decreases through progressive loading cycles, as the collagen fibres align with the direction of force. The change in the mechanical response through progressive loading is known as preconditioning, and is used by many researchers when trying to fit a constitutive model to the response. Preconditioning increases the consistency of various properties between successive tests. For example, the maximum strain for a given stress is known to creep in unconditioned tests, but approaches a constant value after a certain number of cycles. This provides a more predictable framework on which to base a constitutive model. However, each form of preconditioning stretch will produce a different mechanical state (Lokshin and Lanir, 2009a), which will cause parameterised models to be highly dependent on the preconditioning used. Studies such as Coutts, Bamber, & Miller (2013) have attempted to identify sufficient preconditioning routines for measuring a steady-state skin response, but there is still a lack of understanding of the effect of preconditioning protocols.
2.2.4 Skin Pretension

Skin is under varying levels of pretention when in vivo. This varies in direction at a single site, and across different sites on the body. Karl Langer identified both the existence of tension inherent in skin, as well as its non-uniform distribution across the body (Langer, 1862), (translated into English in Langer (1978b)). Through a series of excisions performed on cadavers, Langer observed a disparity between the sizes of a circular excision and its associated site on the body. When a sample of tissue was excised, the surrounding tissue gaped to a larger area, while the excised sample deceased in area. This result indicated that when skin is attached to the body it is in a state of tension. He also recognised that both the excised piece of tissue and its surrounding tissue would take on elliptical shapes. He proposed that the long axis of the wound showed the direction of greater tension in the skin. By repeating the excisions over the entire body of a cadaver, Langer recognised that the relative levels of tension inherent in the skin changed, with some regions showing equi-biaxial tension (resulting in a circular wound and excised sample) and occasionally areas with one axis in compression, in which case the smaller axis of the wound was smaller than the original incision diameter.

![Figure 2-4: Schematic of Langer's lines showing the dominant axis of tension. Adapted from Langer (1862).](image)

Bush et al. argued that skin might also be in a state of biaxial compression, a state on which Langer did not comment (Bush et al., 2008). Like Langer, Bush et al. performed circular
Skin Mechanics

biopsies, but varied the diameter of the excisions. Diameters ranged from 3 mm to 8 mm, and were performed using a circular punch biopsy tool. Biopsies from the neck and face were taken from living patients, removing benign tumours in the process. The authors stated a decrease in both axes in 40.6% of punch biopsies, indicating a state of biaxial compression.

Bush found that the smaller diameter punches were more likely to produce wound shrinkage. The authors attributed this effect to Ridge & Wright’s functional collagen lattice theory (Ridge and Wright, 1966). This theory assumes that the diamond-shaped arrangement of collagen, parallel to the skin surface (Flint, 1976), are functional units of a collagen lattice in skin. If the holes are smaller than the lattice element, and placed within the element, the compressive nature of the collagen bundles will cause wound shrinkage. In larger excisions, a break in the collagen bundles is more likely. This would act to disrupt the lattice’s compressive stress, and the wound would instead demonstrate the overall skin tension.

2.2.5 Heterogeneity

Heterogeneity describes the variation of the mechanical response between samples. This encompasses the previously described features such as pretension, anisotropy, nonlinearity and viscoelasticity. Significant heterogeneity exists between samples taken from a single subject. This effect may be due to the variation in skin constituents across the body, or their state of health. For example, both the palms and soles show a markedly thicker stratum corneum when compared to the rest of the body. In this example, a thicker stratum corneum causes a much stiffer response. Also, as described earlier the degree of preferred fibre direction in the dermis changes with body location (Gibson, Kenedi and Craik, 1965), which could influence the anisotropy of skin.

Viatour, Henry, & Piérard (1995) assessed the variations in properties evident at different skin sites under different levels of pretension. Suction, indentation and surface roughness measurements (see section titled Test Protocols for Characterisation of Skin Mechanics, page 14) were made on both arms of subjects. Heterogeneity was assessed at the elbow, wrist, and forearm in both flexion and extension. The authors described a great difference in surface roughness at the elbow between flexion and extension, but little change at the forearm, and none at the wrist. Viscoelastic measurements of the elbow were much lower than the other sites, and the difference in total skin extension under suction were minimal between tests. The forearm showed the least sensitivity to pre-stretch. The only significant change seen on the forearm, between extension and flexion was with the smallest indentation probe. Interestingly, the authors noted that little heterogeneity exists between mirrored sites on the
Chapter 2 Background

body. This may be useful in characterising healthy versus diseased skin in a subject with lesions on one side of the body.

Heterogeneity between people has also been extensively examined, investigating age, ethnicity, BMI and gender (Leveque et al., 1984; Salter et al., 1993; Wu, 1995; Silver et al., 2002; Boyer et al., 2009, 2012; Gerhardt et al., 2009; Krueger et al., 2011).

Each reported difference indicates that parameterised models need to be subject-specific. Furthermore, models used for one part of the body are unlikely to reproduce mechanical properties elsewhere. This demonstrates the need for versatile instrumentation capable of measuring skin at different sites, as well as body types.

2.3 Test Protocols for Characterisation of Skin Mechanics

The accurate parameterisation of constitutive relations requires precise mechanical experimentation. Data regarding the mechanical properties of skin are typically gathered by introducing some force and measuring the resulting deformation. The accuracy of computational models relies on the careful consideration of deformation protocols and their associated boundary conditions. It is currently not possible to completely recreate in vivo boundary and environmental conditions in an in vitro environment. Many mechanical properties of skin, such as vascularisation are altered by tissue excision, thus we must still rely on in vivo experimentation for a complete characterisation of skin. Forces are generally applied to in vivo skin by one or more of four techniques: suction, torsion, extension or indentation. Other techniques are rarely used, but have also been detailed in the following section. In vitro experimentation has been ignored in this review, unless it can be readily applied to in vivo skin.

2.3.1 Suction

It seems that methods utilising suction dominate the skin mechanics literature. Suction devices certainly dominate in clinical studies, due to their commercial availability and their relatively easy interpretation. Devices currently exist on the market, such as the Cutometer® (Figure 2-5, Courage+Khazaka electronic GmbH, Koln, Germany) or Dermaflex® (Cortex Technology, Hadsund, Denmark), and do not require complex mechanical models for analysis.
Suction studies are often used to assess the efficacy of topical agents on skin properties. Authors in these areas tend to look for a handful of parameters that show changes when applying a cosmetic product, or are interested in identifying any parameters that differ between different populations, such as old and young volunteers (Jachowicz et al. 2008; Gerhardt et al. 2009). Current suction experiments alone cannot characterise the anisotropic response of skin, which makes their use in parameterising constitutive models less common. However, a number of authors build finite element models around isotropic models, allowing the use of suction (Viatour, Henry and Piérard, 1995; Hendriks et al., 2003, 2006; Delalleau, G Josse, et al., 2008; Schiavone et al., 2008; Sutradhar and Miller, 2013; Luebberding, Krueger and Kerscher, 2014; Houcine et al., 2015). Anisotropy may be measurable under suction if multiple displacement measurements are made across the deformed tissue, however this property seems to be currently overlooked in the literature.

An interesting study was performed by Hendriks et al. (2006), where suction cups of different sizes were used. The authors hypothesised that using smaller suction cups would reduce the depth of skin affected by the test. Using optical coherence tomography (for a description of OCT see the section 2.5.3), Hendricks et al. showed that the smallest cup did indeed only deform the epidermis, while larger cups additionally recruited the dermis.

2.3.2 Extensometry

When constructing constitutive relations for soft tissues, researchers have historically favoured extensometry tests. The prevalence of this method was probably due to its similarity to the pioneering tests of elastomers (Rivlin and Saunders, 1951; Treloar et al., 1976) and in vitro tissues (Lanir and Fung, 1974). These early methods performed uniaxial and/or biaxial stretches on samples with simple geometry, producing readily interpretable results.

Extensometry protocols can capture the stress-strain anisotropy that exists in the direction of the skin surface. Lanir and Fung suggested that as skin can be regarded as incompressible, a 3D model of the skin can be fully characterised with biaxial tests, since its change in the third dimension can be fully described by the changes in the other two dimensions (Lanir and
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Fung, 1974). This concept has been adopted by a large number of researchers (Gunner, Hutton and Burlin, 1979; Delalleau, G. Josse, et al., 2008; Lim et al., 2008; Gahagnon et al., 2012). However, Holzapfel and Ogden showed with the use of invariants that biaxial testing alone is not enough to characterise the 3D response of an orthotropic material (Holzapfel and Ogden, 2008). This does not discount the use of extensometry devices, but requires the addition of further deformation protocols for full characterisation.

Lim et al. (2008) designed an extensometer that used a guard ring around the stretching apparatus and load cell. The aim of the guard ring was to shield the testing site from the resistive effects imposed by surrounding tissue, thus reducing the discrepancy between in vivo and excised tissue. The authors attempted to validate the test by performing tests on a rubber membrane and building a shell finite element simulation of the test. An “in vitro” test was performed with traditional uniaxial tension test on a dumbbell-shaped sample of rubber. “In vivo” tests were performed by applying the traditional and shielded extensometers to a square section of rubber which had each side fixed to a square base. The finite element model used a fixed Young’s modulus for the constitutive equation. Models with and without shields were compared to experimental data, using the Young’s modulus determined from the “in vitro” test. The model that included their modified extensometer matched the “in vitro” experimental results with an error of 13.7%. The unshielded extensometer model produced an error of fit of 91%. However, the model did not create a biofidelic phantom of skin, as it did not consider any out of plane attachments to the underlying tissues.

A similar design was presented by Jacquet et al. where follower tabs shielded the measurement probes from the tension developing in the surrounding tissues in response to compression (Jacquet et al., 2008). The authors tested the ability of the follower tabs to shield tension by varying the pretension of forearm skin. If the follower tabs were to properly shield the test area, no observable difference in apparent stiffness should be present whether the elbow was bent or straight. This was not the case, but the apparatus did reduce the difference in apparent stiffness when compared to a system without the shields.

Kvistedal and Nielsen (2009) presented an experimental setup where biaxial stretches were imposed in vivo, using a modified biaxial rig. 16 motors were arranged equi-spaced in a circle around the area of skin to be stretched, forming 8 separate axes. Each motor was attached to a strain gauge arm and double-sided taped to the skin. Each axis was drawn back to stretch the skin and measure the resulting force. A CCD camera captured surface strain, using a phase-based cross-correlation tracking method of a high-spatial frequency speckle pattern applied to the skin. This method provided very good control over the stretches imposed in the tissue.
2.3.3 Indentation

Indentation experiments also frequently appear in the literature, whereby a probe is extended into the skin, usually in a direction normal to the skin surface. This method was used for clinical studies as early as 1912 (Schade, 1912), where the author demonstrated his indenter’s ability to differentiate healthy and diseased skin in cases where clinicians failed to. Schade noted his elastometer’s abilities in detecting oedemas associated with kidney and heart failure, through increased viscous return of skin shape after indentation. The same device was revisited in 1949, where Kirk and Kvorning identified higher compliance, as well as elastic recoil of younger skin when compared to old skin (Kirk and Kvorning, 1949).
Chapter 2 Background

Indentation was first used for identifying engineering properties in biological tissues by Hayes, Keer, Herrmann, & Mockros (1972), where a linear elastic model was fitted to cartilage under spherical indentation.

Indentometry has been a standard test to identify engineering properties of thick rubbers, which was extended by Waters (1965), to identify the relationship between Young’s modulus and indentation of thin rubber sheets. Bader & Bowker (1983) applied Waters’ method to skin, assuming skin would behave in an analogous way to thin elastomers. Bader & Bowker’s indentation tests showed significant creep in the displacement-time curve, which the authors suggested may be due to sub-cutaneous sliding motion, relative to the dermis.

Zahouani et al. (2009) constructed an indenter that could move in two degrees of freedom. A spherical probe could be dragged across the skin in one axis (measuring friction), or indented normal to the skin (measuring the normal indentation force). This system was used to quantify the skin in terms of Young’s Modulus. The authors were interested in determining the contribution of the dermis to the overall mechanical properties of skin. They compared dermal substrates grown from isolated fibroblasts from a subject, to the subject’s own in vivo skin. These tests showed statistically insignificant differences between the Young’s moduli of dermal substrates and living skin, demonstrating the dominance of the dermis in the mechanical response. The authors also found significant viscoelastic responses to indentation in both dermal substrates and in vivo tests.

Boyer et al. (2009) stated that skin acts as a monolayer, and can therefore be considered homogeneous. With this assumption, they conducted pure normal indentation tests, and used these to inform simple mechanical models for the skin. The authors modelled the skin using Kelvin-Voight architecture (spring & dashpot models), and drew conclusions based on average values of stiffness and damping across age groups. The authors suggested that by indenting the skin at frequencies between 10 Hz and 60 Hz, this protocol could be used to distinguish between aged and young skin. They argued that the small amplitude of the indentations meant that they could attribute the measured mechanical properties to the skin alone, and avoid contributions from underlying tissues. However, the authors noted a correlation between BMI and Young’s modulus, indicating an effect from the relatively compliant subcutaneous fat. In a rheological model of the skin, this would be represented as a spring in series with the rest of the parameters, and would be the first to displace under load.

Bischoff et al. (2004) presented an indentation scheme that could measure the anisotropic properties of skin. The authors suggested using an axially asymmetric indenter to extract anisotropy measures from normal indentation procedures. By varying the position of the
indenter about its axis, this method could be used to extract in-plane anisotropies. When the long axis of an indenter is aligned with the stiffest axis of the skin, the resulting loads for a given displacement are smaller, while aligning the long axis with the most compliant axis results in maximum loads for the same displacement. However, increasing the size of the indenter in order to create a well-defined aspect ratio increases the effects of boundary conditions, surface curvature and heterogeneity of bulk samples.

A parallel-axis microrobot indentation device was presented by Flynn et al. (Flynn, Taberner and Nielsen, 2011a, 2011b). The microrobot, shown in Figure 2-8 consists of 3 voice coil motors, each of which drives an apex of a moving platform. This allows a probe situated on the top of the platform to indent in a roughly tetrahedral volume, producing indentations in directions other than normal to the skin surface. This robot has been used to measure nonlinear, anisotropic, viscoelastic mechanical properties of the forearm (Flynn, Taberner and Nielsen, 2011a), upper arm (Flynn, Taberner and Nielsen, 2011b) and face (Flynn et al., 2013).

Figure 2-8: Auckland Bioengineering Institute microrobot. Reproduced with permission from Flynn, Taberner & Nielsen (2011b).

2.3.4 Torsion

Some research, spanning the 1960s to the 1990s attempted to use torsion tests to measure properties of skin (Duggan, 1967; Finlay, 1970; Leveque et al., 1984; Escoffier et al., 1989; Salter et al., 1993). Like the extensometry tests of Lim et al. and Jacquet et al. (Jacquet et al., 2008; Lim et al., 2008), a non-moving guard ring is typically used to separate an area of
skin of interest from the surrounding tissue. Elasticity parameters are measured while the probe is twisted, much like those found with suction tests. Torsion is insensitive to anisotropy, so further discussion of this method is unnecessary.

### 2.3.5 Shear Wave Measures

A small field of work has been performed with shear wave measurements. The Reviscometer® (Figure 2-9, Courage+Khazaka electronic GmbH, Kölner, Germany), is an off-the-shelf tool used to measure anisotropy by inducing shear waves at the surface of skin. The device introduces a shear wave to the surface of the skin and measures the time taken for the wave to propagate to a sensor. The time taken for the wave to propagate (referred here as the Resonant Running Time (RRT)) is inversely proportional to tissue density and stiffness. From the RRT, a degree of fibre alignment can be deduced, as collagen fibres are stiffest along their axes.

![Reviscometer® shear wave device (Courage+ Khazaka electronic GmbH, Kölner, Germany).](image-removed-from-electronic-copy-of-thesis-due-to-copyright)

Figure 2-9: Reviscometer® shear wave device (Courage+ Khazaka electronic GmbH, Köln, Germany).

Verhaegen et al. (Verhaegen et al., 2010) investigated the Reviscometer’s use in determining scarred from healthy tissue, in an aim to reveal the collagen arrangement in vivo scars. The authors tested 50 subjects with normal skin and 50 subjects with scarred skin in various places on the body. They found the device identified significant differences in RRT as the angle changed on the arm (where skin anisotropy is often said to be linked to preferential collagen alignment), while finding smaller variations in RRT on belly tissue, where a more isotropic response is expected.

Paye et al. (2007) also used the Reviscometer to differentiate between cosmetic treatments, as well as untreated skin. They reported increased sensitivity in measurements with this device when compared to the cutometer.

Zhang et al. (Zhang and Greenleaf, 2007; Zhang et al., 2008) also looked at the ability of surface wave measurements to quantify skin viscoelasticity. Building on the idea of
measuring elasticity of tissues by subjecting them to external force impulses, a surface wave is created, and the time taken for the wave to propagate to a sensor, as well as its decay is recorded.

A ball-tipped device was shaken at amplitudes imperceptible to the test subject (apart from a vibrating sensation felt when applied to the palm). Surface vibration was measured using a laser vibrometer at 2 mm increments away from the force source, to a distance of 12 mm. At each position, the frequency was increased in 100 Hz increments up to 400 Hz. This method used a Voight model for capturing shear elasticity and shear viscosity of the skin. The model simplifies skin into a spring and dashpot in parallel. Both coefficients are extracted from a nonlinear fit of wave dispersion with frequency. Wave dispersion is found by measuring the wave speed at different frequencies.

The usefulness of these devices is limited in that they do not impose large strains on the skin. Unless an external device imposes stretches, these devices are restricted to measuring the mechanical properties of skin under small strains.

2.3.6 Ballistometry

In similar fashion to shear wave experiments, ballistometry techniques impart force impulses on the skin. Fthenakis et al. (1991) presented a balanced weight-counter weight pendulum to strike the skin. Measures of the angle of the pendulum arm were taken as the pendulum hit the tissue, recoiled and settled. The amplitude of the first recoil, the number of bounces, the area under the curve of the first bounce and the fraction of amplitude returned on the first bounce were calculated. Each was attributed to the elastic versus viscous response of tissue. The authors investigated these responses in aged versus young skin, as well as responses of different body sites, and skin in response to a vitamin A-rich formulation. The authors found a significant decrease in elastic contributions with aging. The wrist, temple and cheek were tested for the device’s ability to discriminate between skin regions. The device was capable of discerning the wrist’s response from the cheek and temple, but could not distinguish between the latter two. The vitamin A-rich formulation provided a stronger elastic contribution to the response than a placebo treatment. When combined with ultrasound, this effect was attributed to the thickening of the dermis. The major drawback of this model is its inability to resolve anisotropy. In addition, this dynamic test may present different results at different ballistometry speeds.
Chapter 2 Background

Summary Table of Test Protocols

The current abilities of each skin perturbation method, described in section 2.3, to capture the anisotropic, nonlinear, heterogeneous, and viscoelastic properties of skin are summarised in the table below.

Table 1. Summary of current abilities of test protocols for capturing skin mechanical properties

<table>
<thead>
<tr>
<th>Method</th>
<th>Non-linearity</th>
<th>2D Anisotropy</th>
<th>3D Anisotropy</th>
<th>Heterogeneity</th>
<th>Visco-elasticity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suction</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Extensometry</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Indentation</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Torsion</td>
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<td>×</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Shear Wave</td>
<td>×</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ballistometry</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

2.4 Modelling Skin Mechanics

2.4.1 Constitutive Equations

Experiments which gather sufficient data to capture the anisotropy, nonlinearity, viscoelasticity and/or heterogeneity of skin become difficult to interpret without the help of a mathematical model. Constitutive equations relate the strain of a material subunit to the stress that is imposed on it, and can take many forms.

Traditionally, researchers have used phenomenological constitutive models, as they provide a black-box approach that often adequately matches the data. These can be useful in predicting material behaviour in simple deformation protocols, but generally do not provide insight into the underlying structure associated with the response. Previous models presented in the literature have used linear elasticity (Khatyr et al., 2004), or pseudo-nonlinear elasticity (Tran et al., 2007) to simulate in vivo skin mechanics under indentation or extension deformations, however the majority of recent skin mechanics studies have concluded that these approximations of skin behaviour are inadequate (Meijer, Douven and Oomens, 1999; Bischoff, Arruda and Grosh, 2000; Rubin and Bodner, 2002; Hendriks et al., 2003; Holzapfel and Ogden, 2008; Bischoff et al., 2009; Misra, Ramesh and Okamura, 2010; Flynn, Taberner and Nielsen, 2011b). Nonlinear finite deformation elasticity theory has been
applied in most cases to capture skin behaviour and is applied to the studies presented in this thesis.

Nonlinear phenomenological models often require a small number of parameters to describe the stress-strain behaviour, which makes their solving more straight-forward, and may reduce the probability of finding equally good fits with multiple parameter sets. However, the simplest models that capture nonlinearity, viscoelasticity, and anisotropy, such as the Tong and Fung, and a modified Ogden equation require in excess of 5 parameters, and have shown identifiability problems (Ogden, Saccomandi and Sgura, 2004; Flynn, Taberner and Nielsen, 2011c).

For these reasons, many researchers have attempted to develop structurally-based constitutive models. These models aim to tie each parameter to a physical or mechanical property, such as fibre density in the dermis, the degree of alignment of fibres, or elastin mobility through the ground substance. Structural models typically contain a high number of parameters, and often suffer from non-unique solutions. Minimisation approaches to parameter identification often fail to predict structurally accurate parameters, as they identify local minima instead of the global minimum. The effects of non-unique solutions become evident when trying to use the same parameters to predict the response of the tissue to a different deformation protocol. To combat this problem, researchers often employ global search approaches, such as genetic or simulated annealing algorithms. However, there is no guarantee that these methods will identify the global minimum, and are computationally expensive and time consuming. Instead, direct measurement of parameters may aide identifiability (Lokshin and Lanir, 2009b).

The following section highlights some of the most important constitutive relations applicable or designed for skin. This is not a comprehensive set of equations used in skin, as many authors produce slight variations on the some of the following models.

### 2.4.2 Empirical Models

**Neo-Hookean**

The simplest nonlinear (also known as pseudo-nonlinear) model used in skin mechanics is the neo-Hookean. It belongs to family of hyperelastic models known as strain energy density functions, which relate the stored energy in a material to a deformation gradient. This model, originally designed for constitutive modelling of elastomers, can capture a slightly nonlinear response of an isotropic, non-viscous and incompressible material. This has been used in skin under sufficient preconditioning which acts to reduce anisotropy and viscous effects, and
following only the loading section of the stress-strain curve. The strain energy density function is as follows

\[ W = \frac{\mu}{2} (\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3) \]  \hspace{1cm} (2.1)

Where \( \lambda_i \) are the principal stretches and \( \mu \) is the shear modulus. This can be expressed in terms of the first invariant of the left Cauchy-green deformation tensor, and generalised with \( C_1 = \frac{\mu}{2} \).

\[ W = C_1 (I_1 - 3) \]  \hspace{1cm} (2.2)

Example uses of this model include Hadid, Epstein, Shabshin, & Gefen, (2012) where the authors assumed skin, plus the underlying tissue acted as a neo-Hookean material as a bulk. However, many authors have shown that this model provides a poor fit of multidirectional experimental data, even after extensive preconditioning (Flynn, Taberner and Nielsen, 2011b), (Delalleau, G Josse, et al., 2008)

**Mooney-Rivlin**

The Mooney-Rivlin model is an extension of the neo-Hookean, and can also fit isotropic, nonlinear and incompressible materials. Its additional term allows it to maintain good nonlinear fits to data at higher strains than the neo-Hookean, and penalises shear strains. Like the neo-Hookean, it can account for neither viscous effects nor material anisotropy. Its strain energy form is as follows, and it should be noted that the first term is the neo-Hookean strain energy function:

\[ W = \frac{\mu_1}{2} (I_1 - 3) + \frac{\mu_2}{2} (I_2 - 3) \]  \hspace{1cm} (2.3)

where \( I_2 \) is the second invariant of the left Cauchy-Green deformation tensor and the shear modulus \( \mu = \mu_1 + \mu_2 \).

**Ogden**

The Ogden (1972) constitutive relation has a similar form to that of the neo-Hookean and Mooney-Rivlin strain energy functions. It is also limited to isotropic, non-viscous and incompressible materials.

\[ W = \sum_{i=1}^{N} \frac{\mu}{\alpha_i} \left( \lambda_1^{\alpha_i} + \lambda_2^{\alpha_i} + \lambda_3^{\alpha_i} - 3 \right) \]  \hspace{1cm} (2.4)

The neo-Hookean relationship is expressed with \( N = 1 \) and \( \alpha_1 = 2 \). This model provides a general description of the neo-Hookean families of constitutive models. It is adapted by
various authors (Evans and Holt, 2009; Flynn, Taberner and Nielsen, 2011a; Groves et al., 2012).

**Tong & Fung**
Tong and Fung (1976) presented a constitutive model that captured the nonlinearity of the skin with an exponential term. A pseudo-strain energy function is given in equation 2.5, where the bulk, isotropic term relies on a set of material parameters ($\alpha$) and the Green strain tensor ($e$). Similarly, the nonlinear, anisotropic term relies on a set of material parameters ($a$), a scaling constant, $c$, and the Green strain tensor. $\rho_0$ refers to the density of the material in its initial, undeformed state.

$$\rho_0 W = f(\alpha, e) + c \exp[F(a, e)]$$  \hspace{1cm} 2.5

The exponential term imposes the upper limits of collagen extension. This model relied on sufficient preconditioning to fit data of single-direction stress-strain curves. The authors showed a good fit to biaxial and uniaxial tests on rabbit skin, however the parameters of their model did not reproduce the results from other test protocols, where the same sample was exposed to different directional stretches and preconditioning protocols. This revealed that the parameters of this model do not represent underlying physiology. Flynn et al. showed some success in reproducing in-plane experiments with skin, but reduced performance in normal indentation (Flynn, Taberner and Nielsen, 2011c).

**Gent**
Gent (1996) also presented a constitutive model that included chain extensibility limits, represented by a logarithmic term. This model was built for rubbers, as were the bulk of models applied to skin. This simple model relies only on the first invariant as follows.

$$W = \frac{\mu}{2} J_m \ln \left(1 - \frac{I_1 - 3}{J_m}\right)$$  \hspace{1cm} 2.6

Where $J_m$ is the constant limiting value for $I_1 – 3$ (the case for chain extensibility limiting) and $\mu$ is the shear modulus. This model is restricted to incompressible, isotropic materials.

**Criscione**
Criscione et al. presented a strain energy function for isotropic materials based on three strain invariants ($K_1, K_2, K_3$). (Criscione et al., 2000). The generalised strain-energy function is presented in 2.7.

$$W = \sum_{i=1}^{\infty} \alpha_i K_1^i + K_2^3 \left( \mu + \sum_{i=1}^{\infty} \beta_i K_1^i \right) + \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \zeta_{ijk} K_1^i K_2^j K_3^k$$  \hspace{1cm} 2.7
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Where material parameters include the shear modulus ($\mu$), the strain energy at the reference configuration ($\alpha_0$), the pressure in the reference configuration ($-\alpha_1$). $\beta_i$, $\zeta_{ijk}$ and the remaining $\alpha_i$ are additional material parameters.

The three invariants are based on the natural strain ($\ln \lambda_1$, $\ln \lambda_2$, $\ln \lambda_3$) and reflect the dilatation, magnitude and mode of distortion of an isotropic material. As outlined by Ogden et al. (2004) “These invariants possess the property that they form an orthogonal invariant basis, so that the associated stress response terms are mutually orthogonal. The authors assert that this is advantageous since the orthogonal entities exhibit a minimum covariance and therefore maximal independence.” Like Ogden, this constitutive relation is presented in a generalised form, in which additional parameters can be added until the model sufficiently replicates data.

An important note on constitutive models was made by Ogden, Saccomandi and Sgura (2004), in which the authors investigated the stability of various hyperelastic models and their associated nonlinear solvers for parameter identification. The authors highlighted the vulnerability of Ogden’s own strain energy form at generating multiple optimal sets of parameters. These sets each generated good fits for the tests for which they were optimized, but would fail to model new experiments, suggesting local minima.

The authors also examined the strain energy functions of Pucci and Saccomandi (a variation on the Gent model), as well as Criscione’s function. Pucci and Saccomandi’s model provided better cross-protocol fits, where parameters generated from uniaxial tests qualitatively recreated biaxial tests and vice versa. However, the parameters from this model failed to recreate compressive strains. The authors noted that the performance of this model could be increased if anisotropic properties were considered.

Ogden criticized Criscione’s strain energy function for failing to predict the full-range simple tension data with the suggested five parameters. Ogden stated that a satisfactory fit was not found until the number of parameters was increased to 15. A good fit was possible using the suggested five parameters, but only over moderate stretches. Furthermore, the authors identified that increasing the number of parameters can cause ill-conditioned Vandermonde matrices, which are necessary for parameter identification.

2.4.3 Structural Models

**Lanir**

Lanir (1983) proposed a constitutive equation that considered heterogeneity of tissues, collagen/elastin fibre density, degree of collagen undulation and heterogeneous strains. This
model’s strain energy density function summed individual fibre type strain energy functions, and also modelled the pressure exerted on the ground substance as collagen fibres align and de-crimp in response to stresses.

**Arruda Boyce**

Arruda and Boyce (1993) developed a constitutive model for rubber materials, using eight chains to represent a unit volume’s constituent macromolecular network. The model used two parameters, being an initial “rubbery” modulus and a chain extensibility limit.

The length of the constituent chains was modelled using a non-Gaussian distribution, allowing the chains of the unit volume to reach full extension. This model expressed strain energy in terms of the molecular entropy of the constituent chains. In this model, the strain energy related with deforming each chain can be calculated from the entropy difference between deformed and undeformed lengths of constituent fibres.

**Bischoff**

Bischoff et al. built on the Arruda Boyce model over a number of publications (Bischoff, Arruda and Grosh, 2000, 2002, 2004). The authors built a constitutive model that allowed characterisation of nonlinear, orthotropic properties of composite tissues, such as skin. This physiological model used the entropy change associated with the deformation of macromolecules in the composite, as well as the strain energy change associated with the deformation of a representative orthotropic unit cell. This model ignored viscous effects, and could only replicate elastic responses, requiring significant preconditioning of samples.

Bischoff separated the strain energy function into two terms, representing individual contributions from anisotropic fibres as well as the isotropic ground substance. This model proposed that constitutive fibres could be modelled as a statistical representation over the unit cell, and that these fibres were connected in a network.

Orthotropy can be expressed by the unit cell as its aspect ratio can be altered, adjusting the initial state of entropy on each fibre. As the chosen lengths of the unit cell increase, the number of rigid links increases, adding entropy. It is important to note that the chains represent fibre *directions* rather than individual fibres, so the entropy associated with them depends on fibre density in that direction, as well as fibre length, and the number of possible configurations for collagen chains.

The model reliably captured the results obtained from some historic papers. Dunn, Silver, & Swann’s (1985) results at low strain in healthy and scarred skin were reconstructed well, but it failed to predict high strain results in healthy skin. Uniaxial results for Belkoff & Haut’s
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(1991) and Gunner et al.'s (1979) ex vivo rat skin and in vivo human skin studies, respectively, were reconstructed reliably as well.

Flynn, Rubin and Nielsen
Flynn, Rubin, et al. (2011) built a six-chain constitutive model to describe anisotropy in tissues, based on Elata & Rubin (1995), which had been devised to describe brittle materials. Each chain described bundles of collagen and elastin. Fibres were arranged such that they would pass through the opposite vertices of an icosahedron. It was assumed that each fibre bundle had identical material properties.

This model assumed elastic behaviour (i.e. no viscous effects). Elastin fibres were assumed neo-Hookean. The authors modelled the recruiting of collagen fibres to force loading (occurring at the uncoiling/straightening from undulation of the fibres) using two different functions; a step function, as well as a normal distribution. The step function provided an analytic solution that was simpler than using the numerical integration methods needed for statistical distributions.

The model fitted uniaxial and biaxial stretch data on pig skin with an error of fit of 7.8 % and 10 % respectively. This fit the data better than Bischoff's model, but did not examine other modes of deformation.

Gasser-Ogden-Holzapfel
Holzapfel et al. (Holzapfel, Gasser and Ogden, 2000; Holzapfel, 2001; Gasser, Ogden and Holzapfel, 2006) presented a general soft tissue model, based partly on histological parameters, which is able to reproduce the highly nonlinear and anisotropic properties of skin. The model behaves as a composite structure, reinforced by both collagen and elastin fibres. The strain energy density function is broken into isotropic and anisotropic terms, which reflect the ground substance and fibres respectively.

Holzapfel's strain energy function is expressed in terms of invariants. Under small strains, the model's response is dominated by the first strain invariant, to describe an isotropic bulk material response. Under larger deformations, the fourth and sixth invariants begin to dominate. These invariants reflect stretches in the preferred collagen fibre directions. An Ogden type strain energy function is used to model the ground substance, with Holzapfel suggesting a neo-Hookean as an appropriate function. The anisotropic term is an exponential type, and contains stiffness parameters, as well as dimensionless nonlinearity parameters.

Lokshin and Lanir
Lokshin and Lanir (2009a) produced what appears to be the first constitutive relation to account for anisotropy, viscoelasticity, preconditioning, and nonlinearity, all the while
relating each parameter to a well-defined structural or mechanical property of the skin. The model builds on Lanir (1983) and looks at the strain history of quasi-linear viscoelastic collagen and elastin fibre distributions, giving it the ability to capture pre-conditioning of the tissue. The model was fitted to one set of biaxial data, and the identified parameters were used to predict different biaxial protocols on the same tissue. Qualitatively good fits, of similar magnitude and shape, were produced.

The authors argued that the failure of previous models to predict different stretch scenarios with a single set of parameters stemmed from omitting certain rheological features, such as viscoelasticity or pre-conditioning. A parsimony test, in which parameters are omitted and the resulting change in squared error is tracked, revealed that the removal of viscoelasticity and preconditioning degraded the fit by over six-fold each.

The model relies on a high number of parameters; 13 parameters are used to describe elastin, and 17 for collagen. The authors argued that this is not at risk of ill-conditioning, as each parameter relates to an identifiable structural/mechanical property. Unlike phenomenological models, where models may fit a data set by virtue of the number of parameters, these structurally-based parameters showed little variation across biaxial protocols on the same piece of tissue.

The most important parameters found using the parsimony test were nonlinearity and waviness of collagen, viscoelastic properties of collagen and elastin, and ground substance pressure.

Preconditioning on both fibre types occurred under different mechanisms. Collagen preconditioning reflects the increasing reference length of collagen, which is strain and time dependent. Elastin does not undergo the increase in gauge length, and instead undergoes strain softening, known as the Mullin effect, which depends on the highest previous fibre’s strain.

It should be noted that in the literature, the parameters of this model could be experimentally measured, due to the removal of skin from the body. Current in vivo measurement devices are not capable of measuring these parameters. In addition, the Lokshin and Lanir model was designed for membranous tissues, and would require additional parameters for complete three-dimensional characterisation.

### 2.4.4 Summary Table of Skin Mechanics Models

The abilities of each model, described in section 2.4, to recreate the anisotropic, nonlinear, heterogeneous, and viscoelastic properties of skin are summarised in the table below. Note
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that while many models show incapability to reproduce viscoelastic behaviour, they can be paired with separate viscoelastic models, such as the quasilinear viscoelastic (QLV) model based on a Prony series suggested by Fung (1993).

Table 2. Summary of abilities of constitutive models to capture skin mechanical properties

<table>
<thead>
<tr>
<th>Model</th>
<th>Nonlinearity</th>
<th>Anisotropy</th>
<th>Heterogeneity</th>
<th>Viscoelasticity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neo-Hookean</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Mooney-Rivlin</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Ogden</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Tong and Fung</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Gent</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Criscione</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Lanir</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Arruda-Boyce</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Bischoff</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Flynn, Rubin &amp; Nielsen</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Holzapfel</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Lokshin &amp; Lanir</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
</tr>
</tbody>
</table>

2.5 Combining Mechanical Tests with Imaging

Parameterisation of constitutive models may be refined by capturing more information about the deformation behaviour of a material. The accurate recreation of 3D geometry in finite element meshes has shown improved characterisation of skin mechanics over 2D approximations of skin (Flynn and McCormack, 2009). In addition, using force-displacement data in finite element models has shown favourable errors of fit, but questions of parameter identifiability arise. It is possible that while the data is adequately fitted using the identified parameters, other sets of parameters will fit the data equally well. Providing richer sets of data in the optimisation of finite element models might aide the identifiability of parameters. The inclusion of three-dimensional geometric measurements in finite element formulations has been hypothesised to aide in the reliable identification of the optimal parameter set. This information includes measurements of surface geometry, as well as volumetric
measurements. The following section describes a number of geometric measurements that have been incorporated with mechanical tests, and have been used in finite element models of skin.

### 2.5.1 Undeformed Geometric Measurements

Multilayered models of skin have revealed the importance of dermal thickness in accurate representation of its stress-strain response (Delalleau et al., 2009; Flynn and McCormack, 2009). Lagarde et al. (Lagarde et al., 2005) presented a method for automatic registration of dermal thickness from ultrasound images.

There is wide variation in the coupling used between finite element layers of the skin and underlying tissues. Some models assume frictionless movement of skin against underlying structures (Yoshida et al., 2000; Evans and Holt, 2009; Flynn and McCormack, 2009), while others use a tight, nonslip conditioning (Koch et al., 1996; Hung et al., 2009). The degree of sliding between skin and underlying muscle or bone varies with location on the body, where fascia may or may not be present. Little work has been performed on mapping this heterogeneity in subcutaneous connections, even though its effect on the stress-strain response has been suggested since the early 1980s (Bader and Bowker, 1983).

To accurately represent the tethering of skin layers and underlying tissues, other imaging modalities may be necessary. 100 MHz ultrasound is capable of imaging the stratum corneum and viable epidermis (El Gammal et al., 1999). 20 MHz ultrasound can image full-thickness skin, but its penetration depth comes at the expense of axial and lateral resolution. As a result, it can clearly separate dermis from subcutaneous fat, but fails to image the epidermis in non-glabrous skin (Fornage et al., 1993).

When microstructure of the dermis/hypodermis is required, optical coherence tomography can resolve structures at a similar level of precision afforded by high frequency ultrasound in the epidermis. OCT differs mostly from ultrasound in that it measures optical rather than acoustic heterogeneity in tissues. OCT is less sensitive to the scattering effects of tissue, and its resolution is limited only by the coherence length of the light source used. OCT is an interferometric tool in which a beam of light is split into reference and measurement beams, which are reflected on a mirror and tissue respectively and then recombined. The interference pattern produced will depend on the reflectance of the area of the sample that is being imaged. Interference patterns are only produced in areas where the reflected light is inside the coherence length, creating a 2D image slice. The mirror in the reference arm is then moved over a scale of 2 mm to 3 mm to produce a 3D image volume, with resolution limited to the coherence length of light. Typical coherence lengths range from 10 µm to 20 µm.
(Gladkova et al., 2000). This is larger than most cell diameters, so OCT is incapable of imaging individual cells in the dermis. OCT imaging depth is limited by the optical scattering nature of skin.

Individual cells can instead be imaged using confocal microscopy. This technique uses shorter wavelength light than OCT, and an objective lens and pinhole to focus light to various depths within the tissue. Light is emitted by the excitation of a fluorophore that tags a type of structure in the skin, and is passed through an objective lens to focus at a depth in the tissue. Light reflected off the tissue is then passed back through the objective lens. A pinhole is placed before a light collector at the focal length of the objective lens, which rejects light reflected out of the imaging plane. Moving the light source creates a planar image parallel to the skin surface. Multiple slices are imaged by moving the focal plane in the tissue, creating a 3D volume. Confocal microscopy has been used to gain cell-level images of the entire epidermis and the most superficial cells of the dermis. The shorter wavelengths used in confocal microscopy produce axial resolution of 0.5 µm to 1.0 µm and lateral resolution of 3 µm to 5 µm (Rajadhyaksha et al., 1999), but are scattered more quickly than OCT, resulting in the reduced imaging depth.

By implementing some of these imaging techniques simultaneously, it would be possible to provide an accurate description of the geometry, and the relative movement of important layers of skin, as well as the attachment to underlying structures. This would reduce the number of parameters to be optimised in finite element models, but it remains to be seen if surface deformation measures can provide sufficient information of parameters affected by geometry and sliding.

2.5.2 Surface Deformation Measurements

Digital image correlation (DIC) methods have been used to track surface deformations on skin. Stalof and Reafailovitch (2008) presented a two dimensional DIC method for tracking the stretch in 2D of skin on the back of the hand. DIC uses cross-correlation of two small sub-images, taken at two different times, and identifies the pixel shift between them. More information on DIC can be found in section 2.6.3.

Malcolm et al. (2002) presented a 2D strain capture system that used phase-based cross-correlation to track the movement of a random speckle pattern on the surface of membranes. This method was reported to be accurate to a 20th of a pixel. In contrast, most DIC algorithms use only the magnitude component of the cross-correlation and are accurate to around 1 pixel. The technique was used on skin by Kvistedal & Nielsen (2009). This method produced measures of the heterogeneous strain field throughout a biaxial stretch of in vivo skin. The
technique was extended to 3D using stereoscopic techniques, and demonstrated on silicone gel phantoms (Azhar et al., 2011).

Evans and Holt (2009) used a similar technique for 3D surface tracking of skin in extension. This method did not use phase information in the cross-correlation method, and used a sub-pixel interpolation scheme instead. The method was validated in a controlled study on a Sylgard 527 silicone gel under indentation (Moerman et al., 2009).

2.5.3 Subsurface Deformation Measurements

Sub-surface measurements have been made in vivo using OCT, confocal microscopy, ultrasound and MR imaging, throughout a deformation experiment. OCT (Delalleau et al., 2006) and confocal microscopy (Rajadhyaksha et al., 1995, 1999) have been used to image sub-surface epidermis.

MR imaging (Sinkus et al., 2005), ultrasound (Sandrin et al., 2002; Mofid et al., 2004; Sinkus et al., 2005; Delalleau et al., 2009; Iagnocco et al., 2010; Gahagnon et al., 2012; Coutts, Bamber and Miller, 2013), and OCT (Li et al., 2012a; Es’haghian et al., 2015) have been used in elastographic studies of subsurface skin. In each study, small-scale, simple perturbations produced highly localised estimates of mechanical properties. Simple material models can adequately fit small-strain data, and Young’s modulus, shear modulus and shear viscosity are commonly reported. Such methods will inevitably use more complex mechanical models when the scale of perturbations is increased, and should lead to improved cross-sectional characterisation of skin.

2.6 Existing Laboratory Instrumentation & Techniques

The bioinstrumentation laboratory at the Auckland Bioengineering Institute has designed and built instrumentation for in vivo skin and soft tissue characterisation. The work in this thesis leveraged existing laboratory instrumentation and expertise, and further developed this toolset to achieve the thesis goals. In this section, the laboratory equipment at the commencement of this work is described.

2.6.1 A Six-Axis Force-Displacement Microrobot

A novel force-sensitive microrobot had been previously been designed and built within the laboratory. The reader is directed to Cormac Flynn’s publications for in-depth details of the microrobot as it appeared immediately prior to the commencement of the present work.
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(Flynn, Taberner and Nielsen, 2011b; Flynn et al., 2013). A microrobot schematic is shown in Figure 2-10.

![Microrobot Schematic](image)

Figure 2-10. Six axis force-displacement microrobot with labels of the most commonly referred to components, designed & built by Cormac Flynn.

The microrobot was designed to apply controlled deformations to in vivo skin, and was sufficiently compact to access most body sites. Three parallel axes of motion, each driven by a linear voice coil motor (LA10-12-027A, BEI Kimco, USA), produced three-dimensional movement of a probe tip. Each axis, referred to in Figure 2-10 as a motor arm, was coupled to a moving platform that housed three single-axis force transducers (FSS1500NC, Honeywell, USA). Atop the force transducers was a removable probe tip. The force transducers were magnetically preloaded to resolve both compressive and tensile loads.

Each motor axis was guided using precision linear slides (BSP 730SL, IKO, Japan) attached to a rigid chassis. A sapphire vee-jewel bearing (VJ-1244-05, Small Parts, USA) was embedded in the top of each motor axis, providing a coupling between the axis and a corner of the moving platform. A hardened pin was embedded in a sliding block, attached to the moving platform via a precision linear rolling guide (BWU 6-10, IKO, Japan). This configuration constrained the moving platform such that 3D movements of the probe tip could be prescribed by movements of the three motor axes. Retaining springs were placed under
tension between the sliding block and the motor arm, ensuring that the hardened pin remained seated in the bed of the vee-jewel bearing. The coupling assembly is shown in a close-up view in Figure 2-11.

The position of each motor axis was resolved through linear potentiometers (RDC1014, ALPS, USA), mounted on position signal amplification boards and attached to the microrobot chassis. A hole was drilled into each motor arm to house the lever of a given potentiometer. The lever was glued into the motor arm to minimise backlash in the position signal. Position transducers were reported to provide a repeatability of 63 µm and sensitivity of about 0.5 V/mm (Flynn, Taberner and Nielsen, 2011a). The position of the probe tip was resolved from the position of each motor axis, using the forward kinematics routine described in the appendix of the same paper by Flynn, Taberner, et al.

The microrobot control scheme was implemented in LabVIEW 2010 (National Instruments, USA), on Windows XP (Microsoft, USA), and utilised a Peripheral Component Interconnect (PCI) motor control card (NI 7358, National Instruments, USA). The resolution of the probe tip displacement was 50 µm, and the resolution of the force measured at the probe tip was 30 mN. Proportional-integral-derivative (PID) position control was applied to the motor axes, and deformation protocols were run at 0.1 Hz across multiple studies (Flynn, Taberner and Nielsen, 2011b, 2011c; Flynn et al., 2013).
2.6.2 Finite Element Modelling

The Auckland Bioengineering Institute has extensive experience in finite element simulations of biological systems. In particular, it has been a major contributor to the CMISS package (Nash & Hunter 2000; Bradley et al. 2011, www.cmiss.org) and OpenCMISS (www.opencmiss.org) finite element computational packages. Both packages provide a range of basis functions for finite element interpolation. While most finite element packages allow linear and quadratic Lagrangian basis to describe mesh geometries, CMISS and OpenCMISS allow users to define meshes using cubic Hermite elements. Cubic basis functions use cubic splines to describe the surface curvature, which reduces the number of nodes required to provide good surface descriptions when compared to linear basis functions. The Hermite aspect of the basis function refers to the derivative continuity of the interpolating variable across elements. This property ensures smooth surfaces, which typically reflects the geometry of biological systems, such as skin.

Figure 2-12. Three-camera stereoscope with major components labelled, designed & built by Darren Alvares.
2.6.3 A Three-Camera Stereoscopic Imaging System

A three-camera stereoscopic imaging system was designed and built by Darren Alvares for the purpose of soft tissue deformation measurements (Alvares, 2009). The Stereoscopic system, herein referred to as a stereoscope, consisted of three Complementary metal–oxide–semiconductor (CMOS) cameras (Photon Focus MVD1024E160CL), which provided $1024 \times 1024$ pixel resolution, coupled with machine vision lenses (Fujinon CF25HA-1). The cameras were mounted on aluminium blocks, oriented 55° to horizontal, and is illustrated in Figure 2-12.

Image acquisition was performed in LabVIEW 2010 (National Instruments, USA), over a CameraLink hardware interface. CameraLink affords hardware-synchronised acquisition across each camera of the stereoscope by providing a dedicated trigger-signal line. However, the implementation of the LabVIEW-programmed control code did not utilise synchronised image acquisition.

2.6.4 Existing Laboratory Expertise in Stereoscopy

Calibration
A number of algorithms were used to calibrate the stereoscope. Performance metrics must be assessed with the overall calibration error in mind. In Darren Alvares’ Master of Engineering thesis (Alvares, 2009), a checkerboard-based algorithm, developed at the University of Bonn (Kahlesz, Lilge and Klein, 2007), produced a calibration error of approximately 0.4 pixels. The algorithm finds corners of a checkerboard, placed in approximately 100 unique positions throughout the working volume of the stereoscope. Improvements in the open source image processing toolbox (OpenCV) provided more accurate corner finding algorithms, which has since reduced reprojection errors to approximately 0.2 pixel. An example checkerboard pattern can be found in appendix A.

Surface Deformation Tracking
A phase-based cross-correlation method has been developed for 2D membranes (Malcolm et al., 2002), extended to 3D (Azhar et al., 2011), and refined (HajiRassouliha et al., 2013a). The approach tracks feature-rich material points as they deform through time. Sub-images are tracked for a given camera view through a two-step cross-correlation process. In the first step, standard DIC approaches are used to find the integer pixel shift between sub-images before and after deformation. DIC approaches use cross-correlation to identify the pixel-level translations of two images. Cross-correlation of the two sub-images in the spatial domain is computationally expensive. A more computationally efficient method is to calculate the
translational translations in the frequency domain, where the multiplication of two signals is equivalent to convolution in the spatial domain.

The two-dimensional Fourier transform converts the sub-images from the spatial domain to the frequency domain. The Fourier transform creates real and imaginary components of the image signal in the frequency domain. These components can be used to calculate the frequency and phase spectrum of the image. Normalised cross-correlation (NCC) identifies the peak cross-correlation score in the amplitude spectrum, which is discretised by the sampling rate (i.e. pixels), and provides the integer pixel shift. This is the first step in the surface deformation tracking algorithm and is typically where most DIC methods stop. For estimating subpixel shifts, some methods attempt to interpolate the shape of the cross-correlation score function.

In the tracking algorithms developed at Auckland Bioengineering Institute, a different approach is used to calculate the subpixel shift. As mentioned earlier, the Fourier transform allows the signal to be expressed in the frequency domain by its amplitude and frequency spectrum. In the second step of the algorithm, called phase-based cross-correlation (PCC), the phase spectrum is used, where the slope of the phase spectrum of the cross-correlated signal is measured. A linear shift in the spatial domain corresponds to a linear change in the gradient of the phase spectrum in the frequency domain. Unlike amplitude spectrum estimates, phase slope calculations are not restricted by the resolution of the image. However, the phase spectrum wraps about negative pi and pi, so is restricted to sub-pixel shifts. It is due to phase wrapping that NCC is used to identify the integer level pixel shifts, and PCC is then performed on the images after they are shifted to the integer level pixel shifts. The procedure is outlined in Figure 2-13, where two sub-images \( f(x) \) and \( g(x) \) in the spatial domain are brought into the frequency domain (\( \omega \)) using the Fourier transform \( F \), to calculate

\[
[f * g](x) = \hat{F}^{-1}(F(\omega)G^*(\omega))
\]

\[
h(x) = g(x - x_1)
\]

\[
[f * h](x) = \hat{F}^{-1}(F(\omega)H^*(\omega))
\]

\[
x_{Total} = x_1 + x_2
\]

Figure 2-13. Schematic of phase-based cross-correlation (PCC) algorithm showing the two fundamental steps of finding the integer shift and subpixel shift.
the integer pixel shift $x_1$, before a new sub-image $h(x)$ is created, leading to the calculation of the subpixel shift $x_2$ and thus the total shift $x_{\text{Total}}$.

A random speckle pattern is applied to the surface of the gel phantom by an airbrush to provide the high spatial frequency content required for PCC. The random speckle pattern adds sufficient features for tracking the surface material with cross-correlation and is widely used in both 2D and 3D DIC.

Three dimensional tracking of material points is achieved by triangulating the tracked features found in each camera view. This procedure requires features of the imaged surface to be matched across the camera views. The feature matching algorithms and the initial reconstruction of the imaged object’s surface is known as surface profiling. In reality, surface profiling is performed before the tracking algorithms are applied to the material points, but utilises the same PCC code to perform the feature matching. An in-house surface profiling algorithm was also developed, and is detailed in the following section.

**Surface Profiling**

![Image registration between two camera views using an affine transformation. The coordinates shown in both images show those of approximately the same feature. (a) a transformed image, attempting to recreate the speckled surface of shown in (b).](image)

Surface profiling is the method of measuring the initial surface geometry of an object. The material point tracking detailed in the previous section applies to two-dimensional images. In order to reconstruct the 3D locations of 2D-tracked points, a feature matching procedure must be performed, mapping material points across the camera views.

Three-dimensional surface profiling is performed in three steps:

1. Manual identification of material points across the camera views;
Chapter 2 Background

2. Automated identification of material points through image registration;
3. Reconstruction of the 3D geometry from the identified material points

In the first step, the algorithm must be given a starting point to begin matching features. A graphical interface is provided whereby the user selects features using a mouse cursor. The user interface is shown in appendix B. In the second step, an affine transform is performed on an image in an attempt to register the images across camera views. The affine transformation stretches a given image and adjusts its plane so that the view matches that of another camera. The material points identified in the first step are used as control points to construct the affine transformation. The transformation is optimised to minimise the difference between the coordinates of the control points found in step 1 in a base camera view, and the transformed coordinates in a reference camera. An example transform has been applied in Figure 2-14 (a) where a camera view has been transformed to match Figure 2-14 (b).

After registering the images, the user is prompted to select a region of interest in one camera view. This grid defines the material points that will be found across the registered images. An example grid is shown in Figure 2-15. The points of the grid represent the material points that will be matched across camera views, and used to construct the surface profile. The sub-pixel localisation of these features is performed using PCC as detailed in the previous section. As PCC is sensitive to scaling and rotation, the imaged surface must be reasonably flat to be adequately captured by a single affine transformation. PCC is expected to sufficiently match

![Image](image_url)

Figure 2-15. Grid of points defined by region of interest, and used to construct material points used in stereoscopic deformation tracking.
features if the transformed coordinates of the reference image are within 10 pixel of the base image. The affine transformation is a linear mapping that maintains points, straight lines, and planes, thus allowing the transformed image coordinates to be readily mapped to the original camera coordinates. Upon calculation of the untransformed coordinates, the surface profile can be reconstructed using the matched feature coordinates and the camera calibration matrices.

2.7 Applications of Finite Element Models of Skin

Through basic experimentation, characterisation of the mechanical response of skin has provided meaningful benefits to healthcare. For example, the discovery of Langer’s lines (Langer, 1862) has reduced operative scarring. Langer identified lines of higher pretension in the skin, which were later shown to correlate with preferential alignment of collagen fibres. By cutting in the direction of collagen fibre alignment, surgical incisions result in less visible scars. Similarly, Borges & Alexander (1962) identified relaxed skin tension lines (RSTL). RSTL lines have been shown to be useful in reducing existing scars. The lines are identified by pinching the skin, causing it to wrinkle. The direction of the wrinkles determines the major axis of z-plasty incisions. Z-plasties are surgical procedures where tissue is excised and the resulting wound is zigzag shaped. The authors found that by equalising the length of the incision in the direction of the RSTLs with the length that deviated from the RSTL, significant reductions in scarring were achievable. These examples demonstrate real benefits to patients through improved physiological understanding. In the time since these discoveries were published, numerical modelling such as finite element analysis, has led to a deeper understanding of skin physiology, which has been applied to wide-reaching application in healthcare, consumer products, and animation.

The following section is also not an exhaustive description of the literature, but should provide a good representation of the significant studies previously published in skin mechanics.

2.7.1 Understanding Physiology

(Delalleau et al. (2009) combined a cutometer with ultrasound to image the deformation of different layers of skin under mechanical testing. The authors argued that the effects of the hypodermis on overall skin mechanics are negligible, and built a three-layer finite element model to present this. Their model comprised a 1 mm layer which grouped the epidermis and dermis, a 1mm hypodermis layer, and a simulated underlying bone layer in the form of no-deformation boundary conditions. The upper two layers had Young’s moduli assigned from
Chapter 2 Background

literature, and were modelled with a neo-Hookean stress-strain relationship. These models assume that the layers of the skin are homogeneous. The authors showed that the low Young’s Modulus of the hypodermis (10\(^{-2}\) kPa) relative to the dermis (30 kPa) and epidermis in a multi-layer model produced very similar predictions as a single layer model, rendering its contributions negligible. Instead, the authors identified the dermal thickness as a critical property of the skin leading to its mechanical parameters, supporting claims made by Lagarde et al. (2005). Delaljeau et al. described the influence of dermal Young’s modulus as restrained, demonstrating the need for three-dimensional models.

Multilayer models have been developed to examine wrinkling in skin. Wrinkling is an important feature of skin in that it allows uninhibited movement of joints as well as adding emphasis to facial expressions, and could therefore find applications in surgical planning and treatment strategies. Magnenat-Thalmann et al. (2002) presented a 2D layered mesh, comprising of the stratum, papillary dermis and reticular dermis. The authors demonstrated wrinkling in their model, but used linear elastic materials, and is therefore limited to small strains. Flynn and McCormack (2009) built a 3D three layered finite element model consisting of the stratum corneum, dermis, and hypodermis. The authors showed that in their in-plane compression simulation, a three layer model produced more accurate results over models with fewer layers.

### 2.7.2 Clinical Applications

Finite element models have also been developed to improve clinical outcomes. Patient-specific models have been used to inform surgical incisions to reduce scarring (Yoshida et al., 2000, 2001; Lott-Crumpler and Chaudhry, 2001) and to predict the outcomes of facial plastic surgery. Mechanical models have also been used in wound healing studies. Synthetic prostheses have been developed for burns victims that mimic the mechanical properties of skin (Flynn and Rubin, 2012). Mechanical models can also inform tissue engineers on traits of healthy skin which they can attempt to recreate. Current tissue engineering approaches can provide artificial skin to treat severe burns, giant nevi, and chronic ulcers (Wood, 2011).

DeHoff and Key (1981) produced the first feasibility study into finite element modelling for wound closure. A 2D finite element model was built and driven by an isotropic Ogden function. The finite element model was compared to a generalised tension field theory (the previously preferred numerical model from Danielson & Natarajan (1975)), and considered the tension of sutures required to close a wound. With both straight line incisions, as well as z-plasties, the finite element method produced very similar results to field theory. Experimental measures of tension required to close a z-plasty incision were plotted against
the finite element model, but a poor fit was found. The authors identified that this model was severely limited as it was isotropic and elastic, and that the constitutive model was fitted using uniaxial data. Therefore a 2D mesh was most likely unsuitable.

Figure 2-16: Finite element mesh of an elliptical wound from DeHoff and Key, 1981.

Lott-Crumpler & Chaudhry (2001) used the finite element method in a similar fashion, but extended the models to fusiform and triangular wounds. The triangular wound presented three separate modes of wound closure. This paper assumed skin is a linear incompressible orthotropic material, and stated that the third dimension deformations could be derived from the 2D deformation. Arguments against this notion were presented in the section 2.3.2. This system was described by the authors as providing useful information on principal stresses and stress distributions between different suturing profiles. The authors attempted to validate their findings against Chaudry's earlier paper, using an analytical solution for suture stresses (Chaudhry et al., 1998). They claimed that their results “almost agree qualitatively...and are quantitatively near the results”, regarding the average stress index of the minimal and maximal stresses. However, no measures for various numbers of sutures in Lott-Crumpler & Chaudhry (2001) matched both values shown in Chaudhry et al. (1998) to the same order of magnitude.

Yoshida et al. expanded finite element models of wound closure to three dimensions (Yoshida et al., 2000, 2001). The authors tried to find a parametric model that would predict the optimal length ratio of the major and minor axes of a wound and the height of the extrusion of both edges of sutured skin. The model framework was based on 4-node, 2mm thick shell elements, with Young's and Shear Moduli defined from literature. A second layer of gap elements was implemented under the skin, allowing each model to reproduce boundary and slip conditions between the skin and subcutaneous tissue. The model predicted that extrusion height would decrease with increasing aspect ratio. However a balance must be struck between extrusion height and length of incision.
Chapter 2 Background

Koch et al. (1996) used a finite element model to predict the effectiveness of facial plastic surgery. Patient-specific models were built from CT data; including individual layers for the skin, underlying soft tissue and bone. The models were used to simulate incisions and resulting stretch to gain a qualitative prediction of face deformation. Quantitative results lacked sufficient accuracy to be relied upon in a real application, but with increasing geometric and constitutive complexity, better predictions may be within reach. These papers suggest that finite element models could be used by surgeons to plan individual surgeries.

Surgical training environments may also benefit from improved skin characterisation. Constitutive models have been used to drive haptic feedback in virtual surgery devices (Vuskovic and Kauer, 2000). Surgical quality may also be improved by augmenting a surgeon’s own touch sensitivity with intra-operative information from a robot. For example, tips of a laparoscopic tool could measure force in real time. Such information could provide predictions of tissue damage thresholds (Famaey and Vander Sloten, 2008).

2.7.3 Consumer Applications

Mechanical properties are often used to provide quantitative measures of the performance of cosmetic and grooming products. A large number of clinical studies have been performed to assess skin tightness or elasticity in response to the application of polymer films, such as moisturising creams (Paye et al., 2007; Jachowicz, McMullen and Prettypaul, 2008; Boyer et al., 2009; Sandford et al., 2012). The design of backpack straps has used finite element models to analyse the weight distribution on soft tissue in the shoulder (Hadid et al., 2012). Similarly, Hendriks and Franklin investigated the effect of different engineering materials on skin friction, which they suggested could be useful for razor design (Hendriks and Franklin, 2009).

2.7.4 Animation

Recently, considerable research has been devoted into constitutive models in the animation industry. This field requires accurate simulation of soft tissue deformations to produce believable special effects. While a research sometimes focuses on deformations and sliding of the underlying muscle (Chen and Zeltzer, 1992; Hung et al., 2009), its attachment to the overlying skin is important, and a significant number of animation papers include or focus on skin (Wu, 1995; Zhang, Prakash and Sung, 2001; Barbarino et al., 2008; Yang, Southern and Zhang, 2009).
2.8 Background Summary

Each implementation described in section 2.7 has provided a view of the clinical uses that finite element models may find. Although these scenarios were not ready for large-scale use in clinical settings, improvements to the predictive power of models is readily achievable through more realistic modelling of geometry and mechanical behaviour.

This chapter outlined the procedures that have been used to extract material properties of skin in vivo. Different perturbation modes were examined (section 2.3), followed by a discussion of existing modelling frameworks that have been used to interpret the data gathered from perturbation experiments (section 2.4). The addition of imaging systems into characterisation studies was presented (section 2.5), and finally, applications of finite element studies were described (section 2.7)

The following chapters discuss developments made to the existing instrumentation that were necessary to complete the aims of this thesis.
3 Microrobot Development

3.1 Background

An existing three axis parallel microrobot was described in section 2.6.1. Data gathered from the robot have been reported in a number of research outputs, in which skin was perturbed in vivo at various body locations, such as the forearm, upper arm, and face (Flynn, Taberner and Nielsen, 2011a, 2011b; Flynn et al., 2013). These publications demonstrated anisotropic, nonlinear, and heterogeneous properties of skin. However, the perturbations that were employed were invariably low-frequency triangle-wave displacements, which limited the microrobot’s ability to examine dynamic, viscoelastic skin behaviour.

In order to achieve the goals of this thesis, additional functionality and considerably improved performance was required, including the ability to:

1. perform high-bandwidth stochastic, reversible position perturbations in 3D (the previous version of the microrobot was limited to perturbing the force-sensitive probe along a simple trajectory at relatively slow speeds);
2. be synchronised with a multi-camera stereoscopy system;
3. acquire robust low-hysteresis force, accompanied by measurement of three axes of torque;

In addition, the previous device suffered from a set of technical issues, which limited its reliability and flexibility, including:

4. occasional breaks in execution or temporary freezes of the program;
5. issues where motor commands sent to the microrobot could be ignored;
6. occasional hardware faults, most commonly fraying of wires or the formation of dry solder joints;
7. the size and architecture of data acquisition hardware limited the portability of the system, limiting its applicability in clinical practice;
8. the preload and offset of the force traces were not constant within or between test procedures.

In this chapter, the steps that were taken to address each of these issues are described. The issues were addressed by:
Chapter 3 Microrobot Development

- moving the microrobot control to LabVIEW RealTime software environment;
- moving data acquisition to a compactRIO hardware platform;
- improving the microrobot chassis;
- improving the microrobot sensors.

Issues 1 & 2 were addressed by moving the system from a Microsoft Windows Operating System, to LabVIEW RealTime, a deterministic operating system. Issue 3 was also partially addressed by the movement to LabVIEW RealTime, and by changing the force sensing mechanism from three one-dimensional force transducers to a single 6-axis force/torque transducer. The implementation of RealTime code also addressed the technical issues 4 & 5.

Issues 6 & 7 were addressed by a redesign of the microrobot chassis, the movement to hardware control via compactRIO, a reconfigurable automation controller that is compatible with LabVIEW RealTime, and changes to the system’s wiring. Issue 8 was addressed at the same time as Issue 3, by replacing the force transduction mechanism.

3.2 Improving system flexibility, reliability, and portability

The previous software developed for the microrobot provided trouble-free in vivo mechanical experimentation in most circumstances. However, Windows-based software builds do not execute in real time, which can lead to variation in computational execution rates when background processes divert computing resources away from the device software. The existing control software was known to occasionally slow down, freeze and/or ignore motion commands, though these could be due to the implementation of the code itself, and not its environment. In addition, stochastic system identification approaches used in dynamic skin studies require a deterministic control system. The data acquisition componentry consisted of large PCI boards, which only desktop PCs can house, and limited the possible modes of microrobot operation. While closed-loop control of the microrobot had been implemented, force-feedback or open-loop modes required for highly dynamic perturbations were not so readily implemented.

Data acquisition and control of the microrobot required several bench-top amplifier boards and input/output connection boxes, two benchtop power supplies, and six batteries, all of which severely limited the portability of the device, and resulted in a fixed experimental setup. If the robot is to be used in a clinic it will ideally require minimal space and set-up time. It is also feasible that it will need to be positioned to measure skin at many different sites of the body, so it should be readily moveable.
3.2.1 Migration to CompactRIO

The National Instruments CompactRIO device platform is a system which provides deterministic, real time computations in a relatively compact form factor. The programming environment is very similar to LabVIEW for Windows, and provides a user-interface that can operate in Windows. Such systems can provide stability, as the user interface can also be implemented in the deterministic environment. CompactRIO is also well-suited to prototyping applications, as the controllers provide slots for ready-built or custom instrumentation modules, and its Field Programmable Gate Array (FPGA) architecture provides re-configurable hardware-timed programming. Modules can be swapped in and out of the controller system as project goals change. These features offer versatility in programming control, and allowed the microrobot to transition from low-speed prescribed 3D probe tip profiles, similar to established indentation/extension protocols, to highly dynamic stochastic force profiles, and provide the possibility of providing force-feedback driven protocols if necessary in the future.

Figure 3-1: compactRIO used by microrobot, showing 3 standard modules (leftmost) and two custom modules.

A NI cRIO-9022 compactRIO Real-Time Controller was selected for the microrobot project, as pictured in Figure 3-1. This system included an 8-slot chassis, which enabled the potential for simultaneous control of up to three microrobots in one experimental setup. Modules were chosen that could provide sufficient input and output signals for each motor, position transducer, and force transducer on the robot. The individual transducer needs for a single
microrobot (prior to the modifications outlined in section 3.3.3) are summarized in the table below:

<table>
<thead>
<tr>
<th>Transducer</th>
<th>Inputs</th>
<th>Outputs</th>
<th>Supply Lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position Transducer</td>
<td>3</td>
<td>0</td>
<td>GND, +12V, -12V, +5V</td>
</tr>
<tr>
<td>Voice Coil</td>
<td>0</td>
<td>3</td>
<td>GND, +12V</td>
</tr>
<tr>
<td>Force Transducer</td>
<td>3</td>
<td>0</td>
<td>GND, +12V, -12V</td>
</tr>
</tbody>
</table>

The motor driver modules that are readily available in the CompactRIO format provide digital inputs for position feedback, and are designed to accommodate sensors such as optical encoders. These modules provide a compact pulse-width-modulating digital power amplifier, which, while compact, can inject considerable noise onto the power rails of the system. In this device, motor position was determined by linear analog potentiometers, and read in through an analog input module. An analog output module generated the motor force commands. A custom amplifier module was designed and constructed to produce sufficient current to drive the microrobot motors.

### 3.2.2 CompactRIO Programming

A proportional, integral and derivative (PID) control routine for a three-motor single microrobot was designed in a LabVIEW FPGA project. Each axis was controlled in its own loop, operating at 10 kHz. Position, force, and torque measurements were acquired at 100 kHz; position measures were filtered at 1 kHz; and force/torque measures were filtered with a 20 Hz low pass Butterworth filter.

“Host” code was written in LabVIEW, to provide an interface to the FPGA code on the compactRIO. Functions from the NI LabVIEW SoftMotion Toolbox were used for code design, as they allowed coordinated movements of multiple axes, as well as smooth contouring between user-defined position set points in 3D space. The host code was designed so that endpoints could be defined for the tip of the microrobot, and then used to generate individual motor displacement trajectories. The speeds of each motor axis were synchronised so that each motor would start and stop simultaneously.

Routines were designed to calculate the forward kinematics of motor displacement to tip displacement, as well as the force vector seen at the probe tip from force transducer. These were based on the algorithms presented in the appendices of Flynn et al. (2011b).
Improving system flexibility, reliability, and portability

Experimental deformation profiles for the probe tip were written. These included normal indentation, planar motion, and off-axis motion, thereby providing the capability to perform a rich set of deformation experiments. These changes culminated in the deformation profiles used in the in vivo studies presented in Chapter 4 and Chapter 7.

The host code also allowed open-loop commands to be presented to each axis, so that highly dynamic motor force input commands could be generated in real time, or generated offline. These features enabled stochastic system identification techniques to be employed to discover and model the dynamic properties of skin. A dynamic study that takes advantage of this capability is detailed in Chapter 4.

3.2.3 Amplifier Selection and Construction

The previously-used motor amplifier circuitry was contained in a benchtop box (Figure 3-2) and required both positive and negative voltage power supplies. As portability was an important requirement, it was desirable that the microrobot amplifier's footprint be reduced, and that the device could run from a single power supply, such as a battery. Thus, a configuration of two amplifiers, known as an amplifier bridge, was chosen to provide bipolar outputs from a single-sided supply. The bridge amp architecture outlined in Figure 3-3 was based on an application note (Cirrus Logic, 2012). This configuration was selected as it minimised the variations in output under the slow supply voltage decline that can be expected with battery operation. It does so by ensuring that positive terminals on both master and slave amps are always halfway between the supply and ground.

Figure 3-2. Original microrobot amplifier boards.
Chapter 3 Microrobot Development

Operational amplifiers for the above configuration were chosen based on their power outputs. The allowable peak forces of the 11 $\Omega$ linear motors were 13.3 N, generated at 25.1 V, 2.28 A, while the continuous stall force was 4.95 N. At peak force generation, each motor would thus consume 57.2 W. A PA74 (Cirrus Logic/Apex) amplifier chip was selected for its ability to provide 3 A continuously at 40 V (120 W). Additionally, the PA74 was designed specifically for bridge applications, and unlike a number of dual-amplifier packages, consists of two completely accessible amplifiers, minimising the footprint of the required circuitry.

Printed circuit board (PCB) designs for the bridge amplifiers were created in Altium Designer Summer 2009 (Altium Limited, USA). A double-sided PCB design was developed that accommodated amplifiers for all three axes on a single board double-sided copper board. The board was manufactured on a circuit-board routing machine (LPKF Laser & Electronics AG, USA).
Improving system flexibility, reliability, and portability

Germany). Figure 3-4 shows the constructed board, with a few accessory components left unpopulated for greater visibility. This design provided a compact solution that has remained reliable in its three years of operation. However, both the board and solder joints are vulnerable to oxidation and could be improved with the use of silk-screened and solder-masked circuit boards and reflow soldering.

The amplifiers and associated circuitry were housed in a compactRIO module shell (NI cRIO-9953), which provided portability and robustness to the system (see Figure 3-5). The use of a blank module shell meant that the necessary inputs and outputs for the entire microrobot could be housed on the same CompactRIO chassis. This configuration was expected to improve reliability, as fixing the modules relative to each other minimises unnecessary strain on the wires when the system is moved.

The housing of three power amplifiers in a closed module raised concerns about overheating. After fitting each amplifier with its own heatsink, and providing a fan and vent in to the module’s top, the board was examined during typical operation. A single motor was driven over 1 mm displacements at 0.5 Hz for ten minutes, while temperature was recorded with an infrared camera. Although the exact emissivity of the heatsinks is unknown, a conservative estimate of 0.80 was used. Throughout the 10 minute procedure, the heatsink temperatures stabilised and did not exceed 48 °C. According to the PA74 datasheet, these amplifiers have
a maximum operating temperature of 85 °C. Although this test does not represent worst-case operating conditions, overheating has not been observed in the three years of operation.

3.2.4 Re-routing Wires

The original microrobot’s sensors terminated to soldered leads, which then connected to amplifier circuitry. The non-detachable wires can be seen in Figure 3-6. Although this figure shows some strain relief at the base of the microrobot (green insulation tape), moving the microrobot could lead to broken connections. This possibility led to the decision to re-route the wires internally within the microrobot chassis, and use connectors at the base of the chassis, thus removing strain at the transducer-wire connections. The term chassis is used in this subsection to refer to the microrobot instrument excluding the control hardware. It comprises the aluminium frame, the actuators and position and force/torque sensors.

The base of the chassis was redesigned so that wires were fed into a cavity in the robot. A custom-made PCB was placed inside the cavity, housing screw terminals for simple replacement of sensors if one was to fail. A separate header was soldered between the PCB and two push-pull Lemo connectors (LEMO, Switzerland), for simple, robust disconnection from the compactRIO. Holes were drilled into a new microrobot chassis to allow the motor and position sensor wires entry into the cavity. These changes can be seen in Figure 3-7.
Figure 3-7. Redesigned microrobot base showing (left) the cavity housing a connection PCB, (right) the assembled arrangement with motor and position transducer leads routed through the chassis. Numbered items are (1) Copper PCB board, (2) Motor wire channel (3) Position transducer wire channel, (4) screw terminals that connect to internally-routed wires in adjacent channels, (5) solder pins of LEMO connectors that exchange signals to/from the PCB and compactRIO cables, (6) connection point of LEMO cables, (7) position transducer wire entry point, (8) motor wires entry point.

Figure 3-8. Original microrobot force and position I/O board, positioned adjacent to the original motor amplifier stack.
Chapter 3 Microrobot Development

Converting to a compactRIO system, and re-routing the wires through the microrobot, provided an opportunity to reduce the total size of the instrumentation, while improving the reliability of the hardware. In addition to the benchtop amplifiers seen in Figure 3-8, the original microrobot required a benchtop force and position input/output (I/O) connection box. The I/O connection box seen in Figure 3-8 was eliminated, and a new PCB was designed that connected directly on top of the compactRIO instrumentation modules, through their D-SUB style connectors. The new connection box and compactRIO system are presented in Figure 3-9. Motor position and command signals were passed between the circuit board and microrobot via Lemo connectors, matched to the microrobot connectors. The amplified signals from the probe tip were passed to the PCB through another D-SUB connector. Screw terminals were used to supply power to the entire system (microrobot and compactRIO). A rocker-type power button was included in the box, allowing the power supply for the microrobot motor amplifiers to be disconnected when desired. An auxiliary jack was also added, allowing a remote emergency cut-off button to be attached. It is anticipated that these changes should aid the microrobot’s acceptability in a clinical environment, where a system that offers fewer exposed cables, reliable componentry, readily detachable components for sterilisation purposes, and increased portability would be attractive.

![Figure 3-9. CompactRIO-Microrobot connection interface box. Items numbered are (1) Power supply input (2) Force-torque input/output (3) Motor amplifiers power switch (4) LEMO connectors for microrobot motor and position inputs/outputs (5) Remote emergency power button jack.](image)
3.3 Operational improvements to the Microrobot

The limitations outlined in the background section of this chapter necessitated some major changes to the operational design of the microrobot chassis. Detailed below are improvements to moving parts, that were required for high speed dynamic characterisation studies, followed by a description of a re-designed force sensing-mechanism, which enhanced the reliability of force measurements across test procedures and subjects, and indirectly led to improved noise characteristics of the position signals.

3.3.1 Reducing Friction

![Figure 3-10. Exploded view of a rack-and-pinion style linear slide used to guide a microrobot motor arm.](image)

Premature wear was seen on the original microrobot, whereby noticeable friction developed in a motor arm. An additional change to the robot was the replacement of the linear bearings in the motor arms with rack-and-pinion style linear guides. The new configuration uses a pinion gear on the bearing race, which engages with rack gears that are mounted on the guide table. This added complexity ensures that the race remains within the optimal working limits of the bearing’s table and bed, whereas in the previous design, the race was prone to drift towards the bottom of the guide, causing premature bearing wear and increased friction.
3.3.2 Position Transduction

The position transducers on the microrobot were retained from the previous design. In their new configuration, a 5 V excitation voltage was supplied to the potentiometer. The potentiometer was configured in a voltage divider circuit, with the wiper arm attached to the motor arm, providing a voltage at the output proportional to motor position. In the original configuration, the output voltage was fed into the amplifier, which aimed to spread the output signal over the full input range of the analog input device. Here the expected output range of the amplifier was ±12 V. In reality, a voltage swing of around 0.5 V to 4 V was seen on each amplifier output. The analog input channels can be configured to 16-bit resolution over 0-5 V. In order to increase measurement resolution, the original amplifier circuitry was removed, and the regulated 5 V was passed directly into the potentiometer.

Significant noise was present on the original position transducer signals. As seen in Figure 3-11, when under PID control with fixed load, the position sensors recorded approximately 100 µm noise. This level of noise was sufficient to cause the control routine to produce audible hum as the motors hunted around the set point.

In order to take advantage of the sub-pixel resolution of the stereoscope’s surface deformation measurements, the microrobot’s perturbation profiles should be controlled and measured at similar levels of resolution. Identifying the source of noise in a circuit is rarely straightforward, as noise can be introduced through many mechanisms. An elimination and reintroduction procedure was performed to isolate the source of the noise. The motor amplifiers were disconnected and power spectra were recorded for each position signal. An approximately white noise distribution was seen in each power spectrum. Position circuitry was supplied with benchtop power supplies, while remaining circuitry was removed from power sources, whereupon the noise floor was observed to decrease by 30 dB. Reconnecting the motor amplifiers provided PID control in the absence of hum. By stepwise reintroduction of the remaining circuitry components, and computing power spectra as each component was repowered, the force transducer amplification board was identified as the source of noise. The force transducers were disconnected from the amplifier board, and instead connected to a NI-9237 strain gauge module. While the method of force transduction later changed, no such problems have been evident since. Position measurements are now typically held with approximately 10 µm peak-to-peak noise.
Position Calibration

Position transducers were calibrated by attaching each motor axis to a Vernier micrometer head. The micrometer head had a position resolution of 1 µm and range of 25 mm. The motor arm was drawn upwards from its bottom position in 500 µm increments.

An example calibration is shown in Figure 3-12. Note that error bars, representing the standard uncertainty in the position transducer voltage are present in this plot. However, the standard deviation is particularly small and does not visualise well, the standard deviation in the voltage was 1.5 mV, which corresponded to approximately 3 µm. This result was typical of each motor axis. Results are significantly better than the previous microrobot’s measurements, due to the removal of the original force transducer amplifier.

An investigation into the backlash of each motor axis’s position measurements was also performed. With the motor axis still attached to the Vernier micrometer head, the motor arm was cycled numerous times 500 µm above and below a set point, and being brought to rest each time it passed through the set point. Less than 10 µm backlash was observed on each motor arm.
Figure 3-12. Example position transducer calibration created from a Vernier micrometer.

3.3.3 Force Transduction

The original microrobot force transducer design required an amplification board. This board required $\pm 12$ V lines to drive three instrumentation amplifiers for the three Honeywell loadcells. However, when trying to control the robot (see Figure 3-11) the force transducer board was found to be injecting significant noise on to the position transducer lines. The amplifier board was removed, and the outputs of each load cell were instead wired to a 24-bit strain gauge module (NI-9237, National Instruments). This step led to the improved position transduction performance detailed in the previous section.

The final change to the microrobot chassis was to use two new methods of force transduction: replacing the Honeywell force transducers with a single six-axis force-torque transducer; as well as measuring the force directly produced by the motors, in addition to the tip force.

The original probe-tip assembly was designed so that it was completely constrained with relation to the force transducers. This constraint was enabled by routing tracks into the three legs of the probe tip. Each track was designed to remain in contact with the small steel ball of the force transducer. In theory, each ball would contact the track in exactly two places, thereby disallowing relative motion between the probe tip and the force transducers. The
Operational improvements to the Microrobot

kinematic constraint of a single force transducer is illustrated in Figure 3-11. The original probe design housed a magnet to preload the force transducers, which was intended to allow the measurement of both tensile and compressive loads.

Figure 3-13. An illustration of the theoretical kinematic constraint of the probe tip on a force transducer.

During calibration and indentation experiments, unwanted behaviour was identified in each force trace. Three problems were identified in the force traces:

1. drift in offset over time;
2. step change in offset after exposure to any impulse loads; and
3. non-monotonic force trace when indenting a material with known monotonic force-displacement behaviour.

A series of tests were performed to identify the sources of the unwanted behaviour. To measure the drift in offset, force traces were recorded for approximately 30 seconds under a 3 N load, while the motors remained unpowered. In the first case the load was applied directly on top of the force transducers (see Figure 3-14), while in the second case, the load was applied on the probe tip, positioned on the force transducers. After 30 seconds, no drift in offset was observed in the force traces for case 1 (load applied directly to force transducers), while in case 2 (load applied to probe tip), up to 36 mN drift was observed. The force transducers were then shown to be sensitive to the magnet, simply by waving the probe tip near them, causing fluctuations in the force traces.
Figure 3-14. Direct loading of force transducers for drift experiments with standard weights.

To test if the preloaded probe tip was indeed completely constrained, the robot was used to indent a silicone gel phantom. Two cases were performed: in the first case, the normal robotic probe tip was placed above the force transducers; while in the second case, the probe tip was replaced with a small metal disk.

Figure 3-15. Force traces for three Honeywell transducers under indentation. Time axis units are samples, acquired at 80 Hz (A) Indentation with microrobot probe tip in situ, (B) Indentation with a coin replacing microrobot probe tip.

Figure 3-15 shows representative force traces for the three force transducers under (A) the probe tip and (B) the disk. It is apparent from the wandering traces with the probe tip that the head was contributing to the unwanted behaviour in the force traces.
Operational improvements to the Microrobot

In a third test, the step-change in offset was examined. With the probe tip in place, the microrobot head was gently tapped. The force trace was measured before, during, and after each tap. The force trace was also recorded as the steel ball of the force transducer was rolled in its place on the transducer. Gentle taps to the probe tip resulted in ~20 mN steps in force offset. Similar changes in offset were recorded when rolling the steel ball of each force transducer.

Further tests were performed, as it was unclear if the wandering force traces were due to the kinematic constraints of the probe tip, or the magnetic preloading. Indentation was repeated with and without the magnet. However, the non-monotonic traces characteristic of Figure 3-15 (A) remained. It was therefore concluded that the kinematic constraints of the probe tip did not match the theoretical assumptions. When inspecting the photograph in Figure 3-13 it is clear that the track of the probe tip is cylindrical, rather than wedge-shaped as it is depicted in the figure's theoretical illustration. If the radius of the track closely resembles the radius of the ball, it is possible that some slop could be present, which would lead to the non-monotonic force trace under indentation. From the combination of these tests, it was evident that the probe tip was under-constrained with the force transducer surfaces, and due to the magnetic sensitivity and the inherent position-sensitivity to the orientation of the steel ball, this under-constrained head contributed to the drift and step offset changes, as well as causing the non-monotonic force trace during indentation.

While the probe tip could be replaced with a more well-defined kinematic constraint, these issues could also be circumvented by replacing the probe with a small force-torque transducer. Thus, a Nano17 Titanium force-torque transducer (ATI industrial automation, USA) was selected to replace the Honeywell transducers. The Nano17 transducer also resolved torques, and was not significantly larger than the existing force transducer setup. Dimensions are presented in Table 4.

<table>
<thead>
<tr>
<th>Nano17 Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>10.1 g</td>
</tr>
<tr>
<td>Diameter</td>
<td>17 mm</td>
</tr>
<tr>
<td>Height</td>
<td>14.5 mm</td>
</tr>
</tbody>
</table>

The nano17 transducer was factory calibrated, did not exhibit significant drift, or step changes in offset, and simplified the wiring of the microrobot. A single wire bundle was fed
to the transducer, which provided more access to the microrobot position transducers. Factory calibration specifications for the transducer are given in Table 5.

Table 5. SI-32-0.2 Factory calibration of Nano17 Titanium force-torque transducer

<table>
<thead>
<tr>
<th>Calibration</th>
<th>Fx,Fy</th>
<th>Fz</th>
<th>Tx,Ty</th>
<th>Tz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum</td>
<td>32 N</td>
<td>56.4 N</td>
<td>200 Nmm</td>
<td>200 Nmm</td>
</tr>
<tr>
<td>Resolution</td>
<td>5.8 mN</td>
<td>5.8 mN</td>
<td>32.6 mN/mm</td>
<td>27.2 mN/mm</td>
</tr>
</tbody>
</table>

**Force Constant Calibration**

The stochastic system identification technique used in dynamic characterisation studies (Chapter 4) relates the input motor force to the resulting position of the probe. The force generated by a voice coil motor is linearly proportional to the current passing through it. In this iteration of the microrobot, the motor current was also measured from the voltage developed across a 0.4 Ω current-sense resistor, placed in series with each motor. Current-sense resistors provide an alternative measure of force to the force-torque transducer, with a significantly reduced moving mass. The resistance of each sensor was measured using the 4-wire ohmmeter. While the current through a linear motor is proportional to the force, the “force constant” that describes the relationship is not in fact constant, and varies with the motor position. The force “constant”, or sensitivity, of each motor was thus measured against motor displacement, so that the current sensed by the resistors could be converted accurately into motor force. A Nano17 force-torque transducer was used to measure the force of each motor arm as the current was increased. The force-torque transducer was moved to various heights above the motor arm and the current step was repeated. Force measurements in the highly dynamic stochastic system ID approaches were thus calculated using the force sensitivity at the given motor position. An example calibration curve of the force sensitivity is provided in Figure 3-16.
Operational improvements to the Microrobot

Dynamic Performance

After calibrating each motor’s force sensitivity, the robot’s ability to impose and measure highly dynamic perturbations was examined. Perturbations that are of large enough displacement to measure the nonlinear aspects of the stress-strain curve are practically limited in their frequency content before pain or discomfort is experienced. Chen and Hunter estimated that the upper frequency limit should be approximately 200 Hz (Chen and Hunter, 2009). For the purpose of this thesis, assessing the robot’s bandwidth beyond this limit was considered unnecessary. A stochastic force profile was generated with a Gaussian distribution, and filtered with a low-pass cut-off of 200 Hz. The commanded open-loop signal was fed to the motor amplifiers, performing a normal indentation on a silicone gel. Details of the silicone gel are given in section 5.2.2. The measured force generated by the motors, and the resulting tip position was recorded, and the power spectral density of both signals was calculated. A successful test should manifest in relatively uniform power density of the spectrum from 0 Hz -200 Hz.

The dynamic performance of the position transducers and current-sense resistors is demonstrated in Figure 3-17, where the power spectrum is given for both signals under stochastic normal indentation of a silicone gel. This figure was generated from the average of ten spectra, computed from samples ten seconds in length. As mentioned earlier, this does not show the upper limits of the device, and instead focuses on the range required in

Figure 3-16. Force sensitivity as it varies with position for one motor axis.
experiments without causing discomfort to the subject. The input and output signals both show high power components up to the cut-off frequency of the low-pass filter, followed by a steep drop off, demonstrating the device’s capability to impose and measure dynamic components of interest.

Figure 3-17. Power spectrum of the input force and resulting position output. The input force profile was a stochastic input with Gaussian distribution, passed through a 200 Hz low-pass filter.
3.4 Summary

A number of changes were made to the microrobot hardware and software to enable the types of deformation studies completed in this thesis. The sensing operation of the robot was improved by changing from a magnetically-preloaded three single-axis transducer arrangement to a six axis force-torque transducer. The operational performance of the robot was also improved by upgrading the linear slides, which reduced the robot’s sliding friction. The microrobot has been shown to be capable of perturbing soft materials using frequency-rich dynamic displacements, and measuring the force perturbations. The updated microrobot is presented in Figure 3-18, where the major changes to force transduction, removal of position transducer amplifiers, and re-routing of wires are visible. Perhaps the most important modification to the robot was its migration to the compactRIO platform. The move to this platform provided a robust interface between the user and the robot; allowed data to be acquired in a deterministic manner; allowed readily reconfigurable modes of operation, such as closed-loop position control and open-loop force control; brought the microrobot closer to a clinic-ready state; and allowed integration with a high frame-rate stereoscopic camera system.
Modelling of Skin Using Stochastic System Identification

This chapter is an adaptation of a paper accepted for publication in the Journal of Biomechanical Engineering.

Research tools that provide quantitative measures of the skin’s mechanical properties allow more reliable evaluation of its health, and provide a more standardised method of assessment, than visual examination and touch. However, research devices utilizing suction, torsion, indentation, extension or vibration have yet to achieve significant use in clinical environments, partly because they have not demonstrated the ability to elicit or measure a complete description of the nonlinear, anisotropic, viscoelastic and heterogeneous properties of skin (Jor et al., 2013). A microrobot has been shown to perform high bandwidth, three dimensional, large-scale deformations in Chapter 3, and could be applied to skin to improve the assessment of treatment regimens and skincare products, to assist in the diagnosis of skin and systemic conditions, and to help provide an understanding of the mechanics associated with artificial skin development.

Mechanical properties of skin reported in literature vary widely. Reported values for simple parameters, such as the Young’s modulus, have varied by over three orders of magnitude (Diridollou et al., 1998). Variations in such estimates may arise from the choice of spatial and frequency ranges over which the skin is perturbed. Many testing protocols of skin deformations are performed using a relatively small displacement that is intended to correspond to the normal physiological range, which may produce a locally-linear response. However, larger-scale displacements performed at the same location can give rise to strikingly different estimates of simple parameters. By perturbing the skin using higher strains, useful information may be revealed about its structure or underlying constituents which may be relevant in applications such as needle-free jet injection or reducing scarring, and may improve the predictive capabilities of mechanical models. In addition, very few deformation devices have attempted to characterise the dynamic properties of skin (Boyer et al., 2007, 2009; Kennedy et al., 2009; Chen and Hunter, 2012, 2013; Sandford et al., 2012). Instead, the majority of studies opt to minimize viscous effects by perturbing at quasi-static
Chapter 4 Modelling of Skin Using Stochastic System Identification

rates. A device that can perturb skin throughout its nonlinear stress-strain relationship, at a variety of rates, may provide the basis for standardised testing of skin.

Single modes of deformation fail to determine the anisotropic skin response in directions both planar and normal to the skin surface (Holzapfel and Ogden, 2008). Chen and Hunter (Chen and Hunter, 2009, 2012, 2013) and Sandford et al. (Sandford et al., 2012) fabricated a dynamic indenter that could be repositioned on the skin surface to record both normal indentation and tangential extension deformations over large displacements. Like the microrobot, the device used a voice coil to apply high-bandwidth deformations through a probe attached to the skin surface. The motor's force output was measured through a current sensing resistor, and the tip position recorded with a linear potentiometer attached to the motor. Characterisation of the dynamic response of skin was performed using stochastic system identification techniques, which permitted perturbations with multiple frequency components to be applied simultaneously. Frequency-rich stochastic signals reduced the test duration when compared to other dynamic protocols, such as swept sinusoid approaches (Sandford et al., 2012). This benefits both subjects and clinicians, and reduces the sensitivity to subject motion which is often problematic. Models of the system's responses, such as Wiener systems or Volterra kernels, described the linear dynamics and static nonlinearity of skin, and provided measures of the stiffness, damping, and perturbed mass of the bulk material.

The device used by Chen and Hunter, and Sandford et al. required repositioning on the skin if both normal and tangential deformations are imparted. However, relocating the probe tip introduces measurement delay between applying deformation modes and some positioning uncertainty at the skin site, which may lead to errors in the resulting parameterisation of the skin's response. Errors due to relocation can be avoided if the system does not require reconfiguration of the testing device. The microrobot is capable of performing dynamic perturbations in both normal and tangential directions, and therefore represents a major improvement over the existing state of art tools for dynamic skin characterisation.

In this chapter, the improved microrobot is used to dynamically perturb the skin in multiple directions, without repositioning the probe tip. Indentation and extension tests were conducted on the thenar eminence of the hand (the area containing the fleshy group of muscles at the base of the thumb) and on the volar forearm. These markedly different areas were chosen to test the experimental feasibility of the device. Extensive literature can be found on the dynamic properties of the hairy skin on the forearm, but relatively little research exists on the glabrous skin of the thenar eminence.
This chapter uses linear and Wiener stochastic system identification techniques, combined with the versatile microrobot, to characterise the anisotropic properties of skin on the volar forearm and thenar eminence of the hand. With the use of these tools, measures of the bulk properties of skin and underlying tissue can be obtained, including the high frequency dynamics and static nonlinearities in both glabrous and hairy skin. The short experiments (5 s each) are shown to yield accurate results in both indentation and extension. A study of the difference between full scale and incremental loading schemes, and the effect of preconditioning routines for system identification is also presented.

4.1 Materials and Methods

4.1.1 Stochastic System Identification Hardware

Dynamic system identification requires a deterministic control and measurement environment. The microrobot, described in Chapter 3, was equipped with a lightweight probe tip, and placed underneath an acrylic and aluminium support structure, as seen in Figure 4-1. Note that the lightweight probe tip replaced the force-torque transducer, as force was considered a system input at the motor, and measured using current-sense resistors.

![Figure 4-1](image.jpg)

(a) Close-up view of microrobot showing the lightweight head setup, (b) A test subject’s arm strapped to an acrylic resting plate.

The microrobot was operated in open-loop force generation mode. An overview of the system architecture is presented in Figure 4-2. The input to the system is a voltage signal, generated offline, and executed by the analog output module during the experiment. The voltage is passed through the linear amplifier(s) to the Lorentz force actuator(s) generating the force(s)
Chapter 4 Modelling of Skin Using Stochastic System Identification

$F^*(t)$ that, in turn, perturb(s) the probe on the skin at position $P^*(t)$. The current $I^*(t)$ delivered to the Lorentz force actuators is measured by current sense resistors, resulting in the force measurements $x(t)$, with associated error $e_1(t)$. Likewise, potentiometer estimates of position $y(t)$ contains error $e_2(t)$. Note that this schematic applies for both normal indentation and tangential extension.

4.1.2 Stochastic System Identification

Skin and its underlying tissue structures form a nonlinear dynamic system. Like many biological systems, skin can be modelled as the combination of a linear dynamic system and a static nonlinearity. Wiener cascade models have been shown to provide a good description of the response of skin, where a static nonlinearity follows a linear dynamic component (Chen and Hunter, 2012). Note that the reverse order, where the linear dynamics cascade on from the static nonlinearity, represents a Hammerstein system which does not capture skin behavior as effectively (Chen and Hunter, 2013). This model has been used to describe biological systems, such as dynamic tension-length studies in active frog muscle fibres, but is not suitable for skin (Chen & Hunter 2012). The Hammerstein and Wiener models are actually sub-set models based on the Volterra series, which describes nonlinear behaviour, and captures memory effects (i.e. the current output relies on a combination of all previous input). Each kernel in the Volterra series grows progressively larger, which adds computational burden and limits their use. However, a recent study by Chen and Hunter demonstrated that a second order Volterra kernel improved the VAF by 5-15% over Wiener models, depending on the memory length (Chen & Hunter, 2012).
The above models do not examine creep or stress relaxation behaviour, as the test duration is in the order of seconds. Linear dynamic models that examine these properties include the Maxwell, Voigt, and standard linear solid models, based on the combination of spring and dashpots. Khatyr and Imberdis (2004) modelled the long-scale creep in uniaxial extension test by chaining many spring-dashpot together. Kearney et al. (2015) examined the frequency dependence of the dynamic shear modulus, measured from OCT elastography. The Maxwell and Voigt models did not fit the dispersion of shear modulus measurements, while the standard linear model showed a good fit. Boyer et al. (2009) used a voigt model to describe dynamic indentation tests from 10 to 60 Hz. Spring and damping parameters matched experimental measurements over the range tested, and weakly correlated with elastic and viscoelastic-related parameters from a cutometer. However, these tests were performed over a relatively narrow frequency range, and the test duration was substantial (40 seconds per frequency tested).

In a linear dynamic system, the impulse response function (IRF) provides a linear map of the input to the output. Identification of the impulse response function requires the biased cross-correlation of a stochastic input signal with its resulting output signal, as well as the biased autocorrelation of the input signal. A detailed description of the method is presented in Chen and Hunter (2012). For brevity, the IRF, $h$, is calculated in Equation 4.1:

$$h = F_s (R^{-1} \phi_{xy})$$

where $\phi_{xy}$ is the cross correlation of the input $x$ and output $y$, and $R$ is the Toeplitz matrix of the autocorrelation function, sampled at frequency $F_s$. Note that a Toeplitz matrix’s elements are constant on each descending diagonal from left to right. Singular value decomposition was chosen to invert the Toeplitz matrix in order to avoid possible numerical instabilities seen in many other inversion methods.

The non-parameteric IRF of skin has been shown to be approximated by a second order low-pass under-damped sinusoid. The general form of a fitted damped sinusoid can be found from the inverse Laplace transfer function, $H(s)$:

$$H(s) = \frac{1}{Is^2 + Bs + K}$$

Where $I$ is the system’s inertia, $B$ is the system’s viscous damping and $K$ is the system’s stiffness. The transfer function can equivalently be expressed in terms of system compliance, Gain, natural frequency, $\omega_n$, and damping, $\zeta$. 
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\[ H(s) = \frac{Gain \cdot \omega_n}{s^2 + 2\zeta \omega_n s + \omega_n^2} \]  

4.3

The damped sinusoid can be parameterized using a nonlinear optimization, to find the parameters set \( A_1, A_2, A_3 \):

\[ h(t) = A_1 \sin(A_2 t)e^{A_3 t} \]  

4.4

Parameterisation of the damped sinusoid was performed using a Levenberg-Marquadt nonlinear optimisation. The parameters of the damped sinusoid can then be expressed in terms of mass, stiffness, and damping terms (Sandford et al., 2012). The parameterisation relates to the inertia (or inertial mass), \( I \), stiffness, \( K \), and damping, \( B \), by the following equations:

\[ K = \frac{A_3^2 + A_2^2}{A_2 A_1} \]  

4.5

\[ I = \frac{1}{A_2 A_1} \]  

4.6

\[ B = \frac{2A_3}{A_1 A_2} \]  

4.7

This parameter set is used to describe the system dynamics that are captured from linear stochastic system identification.

Optimisation of the IRF parameters allowed comparisons between the variance accounted for (VAF) by the nonparametric model and by the subsequent parametric model. VAF is represented as a percentage, and provides a measure of the how well the model fits the data:

\[ VAF = 1 - \frac{\sigma_{y-y^*}}{\sigma_y^2} \]  

4.8

Where \( \sigma_{y-y^*} \) is the standard deviation between the measurement signal and model output signal, and \( \sigma_y^2 \) is the standard deviation of the measurement signal.
The output of a truly linear system can be recreated by convolving the input signal with the impulse response function. As skin is nonlinear, its IRF cannot completely account for the variance in the output signal. The variance accounted for by the impulse response has been shown to increase when passing the predicted output of the linear system through a static nonlinearity (Chen and Hunter, 2009). A static scaling term can be moved between the linear dynamics and static nonlinearity. The DC compliance (mm/N) was chosen as the constant by which the linear impulse response function was divided; doing so produced a predicted linear output in Newtons. By comparing the output predicted by the linear impulse response with the measured output, a polynomial describing the disparity may be found. The inverse function is then applied to the linear IRF, creating a new, nonlinear estimate. This last step is iterated until the variance accounted for converges. The form of the nonlinearity was described by an empirical formula, presented by Chen and Hunter (2012). The formula is presented in this chapter in Equation 4.9:

\[ Y = C_1(1 - e^{-C_2x}) \]  

where, \( Y \) is the measured probe tip displacement, \( x \) is the linear model’s predicted output, \( C_1 \) is a measure of the total compressible thickness of the perturbed tissue and \( C_2 \) determines how the bulk material’s stiffness is affected as the indenter goes further into the skin. Note that, when incorporating the nonlinearity, the system is reduced from three to two degrees of freedom. When the impulse response function is divided by the DC compliance it folds the spring contribution into \( C_1 \) and \( C_2 \), giving rise to scaled inertia, \( I_s \) and scaled damping, \( B_s \) parameters.

### 4.1.3 Stochastic Signal Inputs

A stochastic force profile was generated offline in LabVIEW. The profile was scalable to produce up to 3.5 N force per motor, with a Gaussian probability distribution. The resulting signal was low-pass filtered at 200 Hz, as frequency components above this limit are likely to exceed the bandwidth limit of the system and/or cause pain (Chen and Hunter, 2012). Under normal indentation, forces up to 10.5 N could be applied, as the force produced by each motor was summed. Three approximately tangential surface extension directions could be defined by passing the stochastic input through a single motor, while providing sufficient current to lock the remaining motors in their base positions. Three force input protocols were created for skin characterisation: a full-scale input and two incremental inputs. Incremental inputs were created by scaling the full-scale input to 20 % and stepping its mean value across the full-scale range. Fifteen increments and decrements were performed sequentially to
investigate any hysteresis in the incremental response. The incremental protocols varied by their form of preconditioning before each increment. The first protocol (denoted “Protocol A”) began each increment with a zero-maximum-zero force triangle wave, while the second protocol (“Protocol B” and shown in Figure 4-3) held the mean input value from the subsequent increment. Overall preconditioning of the skin was performed by applying a 0.5 Hz sinusoidal ramp from zero to full force output for three periods, followed by 10 s at the maximum input force, and then applying the stochastic signal for 100 s at full force output. Performing this preconditioning routine produced repeatable indentation depths to approximately 20 µm.

Figure 4-3. Stochastic input with stepwise increase in mean, referred to as “Protocol B”. Preconditioning at each step was performed by holding the mean value. The first 10 s show a full-scale preconditioning step where the maximum output force is held for demonstrative purposes, and do not reflect exact test conditions presented in this study.

4.1.4 Calibration of Microrobot Parameters

To produce physiologically meaningful measurements of skin, the microrobot’s mass, stiffness, and damping parameters were removed from the system estimates. A series of calibration procedures were developed to extract these parameters. The calibration tests were performed under normal indentation, and in each tangential direction. A directional difference in parameters can be expected, as tangential stretches cause the moving platform springs to deform, and recruit the moving platform linear slides, both of which are inactive under normal indentation. These extra sources of friction and stiffness reduce the force observed at the probe tip, compared to normal indentation. The reduction in force will cause
a reduction in the effective force constant, and sideways motor tests should be performed to calculate the scaling factor that will allow repeatable measurements independent of test direction.

The stochastic input was applied to a series of springs with varying spring constants. It was assumed that using springs added a known stiffness to the system, without adding appreciable mass or damping. The spring constants were independently measured on an Instron testing device (Instron, USA). These tests revealed whether the microrobot’s sideways measurements should be scaled to match normal indentation measurements.

The slopes of the sideways measurements indicated slight over-estimates due to reduced effective force-constant in sideways motions. For a given motor, sideways-compensated measures of the force constant were found by multiplying the original force constant by the inverse of the gradient found between sideways estimates and Instron measurements. This step reconciled the difference between sideways and normal indentation values. Measured stiffness, damping, and moving mass constants could then be subtracted from the system estimates.

In a verification experiment, spring constants were measured at varying average motor positions, against two known stiffnesses. In this experiment, an Instron-calibrated cantilever was tested at two different lengths to produce the two stiffnesses. The cantilever was constructed from brass shim, producing a stiffness element with minimal mass and damping. This test served to verify that the stiffness and motor force constants were adequately calibrated for position, and that damping and mass measurements were independent of stiffness and position.
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The estimates of moving mass of the microrobot were also verified, where independently measured weights were added to the microrobot tip, and the same stochastic perturbations were employed. A spring was added to the system, as seen in Figure 4-5 to provide sufficient stiffness to prevent the added mass from moving relative to the microrobot tip.

Figure 4-5. Moving mass verification under normal indentation.
Materials and Methods

Figure 4-6. Microrobot measurements of moving mass derived from stochastic system identification, as mass is added to the probe tip.

\[ y = 1.0671x + 75.972 \]
\[ R^2 = 0.9973 \]

Figure 4-7. Microrobot estimates of spring constants against Instron measurements, for each motor performing a tangential perturbation, and under normal indentation. Note that the range

\[ y = 1.2454x + 440.89 \]
\[ y = 1.3656x + 372.05 \]
\[ y = 1.5423x + 314.45 \]
\[ y = 1.0532x + 208.47 \]
The microrobot’s raw measurements of stiffness are plotted against a set of Instron-measured spring stiffness values. The approximately 1:1 relationship of the normal indentation and Instron measurements shows adequate calibration of the microrobot, with approximately 7% error in the sensitivity. The higher slopes of the sideways perturbations show that additional stiffness is introduced to the system. When the inverse slope is applied to the force constant of the motor involved, the estimates obtained in sideways motions is improved. In Figure 4-8, the sideways stiffness measurements match Instron measurements of two cantilever stiffness values, while the RMS errors associated with each motor, calculated between the Instron and microrobot measurements, and across motor position, are presented in Table 6.

![Chart showing microrobot estimates of stiffness as the motor position is varied for two cantilever positions (C.P. 1 & 2). The cantilever stiffness was measured at 126 N/m at C.P. 1 and 220 N/m at C.P. 2.](chart.png)

**Figure 4-8.** Microrobot estimates of stiffness as the motor position is varied for two cantilever positions (C.P. 1 & 2). The cantilever stiffness was measured at 126 N/m at C.P. 1 and 220 N/m at C.P. 2.

**Table 6.** Root-mean-square error in measured stiffness for two cantilever positions (C.P. 1 & 2), associated with each motor of the microrobot.

<table>
<thead>
<tr>
<th>Motor 1</th>
<th>Motor 2</th>
<th>Motor 3</th>
<th>Motor 1</th>
<th>Motor 2</th>
<th>Motor 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.P. 1</td>
<td>11</td>
<td>11</td>
<td>8</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>C.P. 2</td>
<td>13</td>
<td>27</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

**RMSE (N/m)**

**RMSE (%)**
Figure 4-8 also demonstrates that the force sensitivity, or force constant, was adequately calibrated with motor position. The slope of the motor sensitivity versus motor position was calculated for cantilever position 1, on motors 1 and 2 as these configurations captured the highest range in motor position. The slopes indicated a change in estimated stiffness of 29 N/m and 7.54 N/m over the entire motor position range. These changes with position correspond to 13 % and 3 % of the actual stiffness measured. The calibrated cantilever broke during testing of the third motor in position 2, which prevented testing at motor positions below 3.5 mm. The slope in motor 3, over the recorded range, corresponded to a 1 N/m change in measured stiffness. Note that the lower stiffness of cantilever position 1 (circular data points) does not have data below 3.5 mm. The stiffness at this position was too low to accommodate system ID approaches without reaching the lower displacement limit of the motor under test.

Figure 4-9. Microrobot estimates of moving mass as the motor position is varied for two cantilever positions (C.P. 1 & 2).

Figure 4-9 demonstrates the microrobot’s insensitivity to position and stiffness, when measuring mass. The grouping of mass estimates at approximately 0.025 kg for cantilever positions 1 and 2 shows insensitivity to mass. The flatness of estimates across the bulk of the motor position range shows insensitivity to motor position. However, motor 1 was shown to deviate from an approximately constant value in the upper ranges of travel in cantilever position 1. This behavior is not evident in the higher stiffness data recorded at cantilever position 2. Similar behavior is demonstrated for measures of the damping, shown in Figure 4-10. Greater sensitivity is shown in damping estimates towards the upper and lower bounds.
of motor position. Fortunately, most system ID experiments were performed within the central bands of motor position, but some incremental studies did perturb skin at more extended motor positions. Lower accuracy in the separation of damping coefficients should therefore be noted when examining the results. The difference in damping coefficients measured between motors 1, 2, and 3 can be expected, as the linear potentiometers and linear guide all demonstrated varying degrees of friction. Importantly, no substantial difference is demonstrated between the two cantilever positions.

![Graph showing system ID-derived damping coefficient vs motor position](image)

Figure 4-10. Microrobot estimates of the damping coefficient as the motor positions are varied, for two cantilever positions (C.P. 1 & 2).

### 4.1.5 Participants

Ten male subjects, who ranged in age from 21 years to 43 years, participated in the experiments. Each subject signed an informed consent form, as required by the University of Auckland Ethics Committee.

### 4.1.6 Experimental Procedure

Tests were conducted in an air conditioned room, where temperature varied between 23 °C and 24 °C, and relative humidity varied between 44 % and 50 %.

Full-scale normal indentation and tangential stretches were applied to the left forearm and palm of the subjects. The forearm of each subject was strapped to an acrylic plate, which was suspended from an aluminum frame designed to overhang the microrobot. Subjects were
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asked to relax their hands so that their fingers were loosely flexed, and the hand extended beyond the acrylic plate. The subject's arm was essentially straight, with a natural resting angle of the elbow similar to that illustrated in Figure 4-1(b). A 40 mm diameter hole in the plate provided access to the skin. Double-sided adhesive tape surrounded the hole, isolating the test area from the surrounding skin, thereby limiting the mass of tissue providing the force-displacement response, and minimizing movement at the surface of the skin at the boundary of the hole. Liquid cyanoacrylate was used to attach the probe tip to the skin, in accordance with previous dynamic studies (Chen and Hunter, 2009; Sandford et al., 2012). Cyanoacrylate provided a firm bond between the skin and probe tip, and securely coupled the skin to the indenter. At the end of the test session, subjects applied tension to the tip to remove it from the skin. When testing the thenar eminence, straps were placed across the wrist and the fingers and thumb, with the fingers extended together across the acrylic plate.

Indentations were made at a position 100 mm from the elbow along the volar surface of the forearm, and in the center of the thenar eminence at the base of the thumb of each subject. The total force input was adjusted for each subject so that the response was limited to be within the maximum probe travel. Incremental normal indentation and tangential stretches were also applied to the same locations for five subjects. Each protocol was initiated immediately after the first protocol was completed.

Figure 4-11. Location, direction, and order of applied tangential stretches. Dashed line indicates approximate proximal-distal axis that intersects the test site.

Tangential extension stretches were applied along the surface of the forearm of the subject by actuating a single axis at a time. The same signal was then applied to another axis, stretching the skin at 120° relative to the first axis. Finally, the third axis was actuated, generating a stretch in a direction -120° relative to the first axis (refer to Figure 4-11).
4.1.7 Data Analyses

Two-way repeated measures ANOVAs were performed to test whether there was any significant effect of testing site (thenar eminence, forearm) and direction (indentation, extension) or interaction between these two factors for any of the nonlinear parameters calculated. One-way repeated measures ANOVAs were performed to test whether there was any statistically significant anisotropy in nonlinear parameters calculated from tangential stretches applied to the volar forearm. Due to difficulties in applying tangential stretches on the thenar eminence, its anisotropy could not be assessed.

Coefficients of variation (CV, i.e. the standard deviation of a parameter divided by its mean) were calculated for parameterised linear and Wiener models of skin. The CV of parameters for a single individual assesses the reliability of the measurements, whereas the CV of parameters across individuals may provide insights into physiological variability. The CV within individuals was calculated as $\frac{1}{N} \sum_{n=1}^{N} \frac{\sigma_n}{\mu_n}$ where $N$ is the total number of trials, and $\sigma_n$ and $\mu_n$ are the standard deviation and mean, respectively, for participant $n$, for a given parameter and test direction. The CV across individuals was calculated as $\frac{\sigma}{\mu}$ where $\sigma$ and $\mu$ are the standard deviation and mean, respectively, of every test and every participant, for a given parameter and test direction.
4.2 Results

4.2.1 Linear Dynamics and Static Nonlinearities

Figure 4-12. Representative experimental results from nonlinear stochastic system identification on the volar forearm. The measured input force (a) is used to generate the Linear Impulse Response Function (b), shown blue in measured form, and red in parameterized form. The linear dynamics are then passed through the Wiener nonlinearity, shown in blue in (c). The nonlinearity has been parameterized, shown by the red line. The output of the Wiener nonlinearity is shown in (d), where the Wiener-predicted output (red) is shown against the potentiometer-measured output (blue).

For each test procedure, a linear prediction of the impulse response function was made before the static nonlinearity was fitted between the linear-predicted output and the measured output.

Representative results for normal indentation on the volar forearm are shown in Figure 4-12. A sample section of the measured stochastic force input is shown in Figure 4-12(a).
Parameterization of the Toeplitz-inverted impulse response function typically showed a qualitatively good fit, but often deviated around the peaks of the sinusoid (as seen in Figure 4-12(b)). The impulse response function followed a typical under-damped sinusoidal system response, with memory length less than 0.25 s. The static nonlinearity (seen in Figure 4-12(c)) was found by comparing the measured output with the predicted linear output. A two-parameter curve, (see equation 2), was used to describe the nonlinearity. The change in compliance as the tissue is displaced can be assessed by calculating the slope at locations along the curve. In accordance with behaviour noted by Chen and Hunter (Chen and Hunter, 2012), the looping in the experimental data is a physiological phenomenon, likely due to the viscoelasticity of the tissue. The predicted output, resulting from the Wiener nonlinearity is compared to the actual output in Figure 4-12(d), which shows a qualitatively good fit over the length of the protocol, with some deviation seen during large changes in displacement.

4.2.2 Full-scale Perturbations

Group mean linear estimates of model parameters are presented in Table 7, where they are classified by the location and direction of perturbation. Linear estimates of the microrobot’s mass and damping were subtracted from system estimates to produce the bulk tissue parameters listed. Under normal indentation, the volar forearm showed an average stiffness of 1.45 kN/m, whilst the thenar eminence showed a stiffness of 2.75 kN/m. However, the range of thenar stiffness estimates spanned the upper limit of volar forearm estimates, and two subjects displayed higher stiffness on their forearm relative to their palm. Up to 35 g of effective tissue mass was perturbed on the forearm, compared to 10 g on the thenar eminence. Damping on the palm was also shown to be approximately double that of the volar forearm.

Table 7. Group mean parameter values and standard deviations for the linear dynamic model.

<table>
<thead>
<tr>
<th>Position/Direction</th>
<th>K (kN/m)</th>
<th>I(g)</th>
<th>B (N s/m)</th>
<th>VAF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm/Normal</td>
<td>1.45 ± 0.21</td>
<td>15.5 ± 7.1</td>
<td>4.76 ± 1.8</td>
<td>93.4 ± 2.1</td>
</tr>
<tr>
<td>Palm/Normal</td>
<td>2.75 ± 1.04</td>
<td>6.40 ± 3.0</td>
<td>8.27 ± 2.0</td>
<td>93.1 ± 1.6</td>
</tr>
<tr>
<td>Forearm/1</td>
<td>2.09 ± 0.42</td>
<td>7.81 ± 2.3</td>
<td>2.81 ± 1.24</td>
<td>92.4 ± 4.6</td>
</tr>
<tr>
<td>Forearm/2</td>
<td>1.56 ± 0.23</td>
<td>3.72 ± 2.3</td>
<td>2.98 ± 0.66</td>
<td>93.4 ± 2.0</td>
</tr>
</tbody>
</table>

For extension experiments, the thenar eminence again showed stiffer responses than the volar forearm, with a larger range of stiffness values across subjects. The much smaller tangential responses on the thenar eminence, presumably due to its higher stiffness, were
insufficient for system identification. Results could only be obtained from seven subjects in direction 3 on the palm. Significant anisotropy was evident amongst the different perturbation directions on the forearm. Stiffness measures were lowest in direction 2 (1.5 kPa) (see Figure 4-11), and were approximately 2 kPa in directions 1 and 3. Estimates of mass ranged from 4 g to 8 g, depending on the direction of stretch. There was little variation in the average damping across the perturbation directions and sites tested in extension, with values ranging from 2.75 Ns/m to 2.98 Ns/m on the volar forearm, and 4.7 Ns/m on the thenar eminence.

Table 8. Parameter means and standard deviations of the subjects for the Wiener static nonlinearity model. Directions are denoted N (Normal) 1:3 (Extension in directions illustrated in Figure 4-11).

<table>
<thead>
<tr>
<th>Position/Direction</th>
<th>( I_s ) (s²)</th>
<th>( B_s ) (s)</th>
<th>( C_1 ) (mm)</th>
<th>( C_2 ) (1/N)</th>
<th>VAF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm/N</td>
<td>0.0655 ± 0.009</td>
<td>8.94 ± 0.83</td>
<td>8.64 ± 2.00</td>
<td>0.510 ± 0.12</td>
<td>96.7 ± 1.0</td>
</tr>
<tr>
<td>Palm/N</td>
<td>0.0347 ± 0.012</td>
<td>6.52 ± 1.69</td>
<td>8.49 ± 0.85</td>
<td>0.506 ± 0.15</td>
<td>96.5 ± 1.4</td>
</tr>
<tr>
<td>Forearm/1</td>
<td>0.0078 ± 0.002</td>
<td>2.86 ± 0.54</td>
<td>1.51 ± 0.39</td>
<td>2.00 ± 1.02</td>
<td>95.2 ± 2.9</td>
</tr>
<tr>
<td>Forearm/2</td>
<td>0.0075 ± 0.002</td>
<td>3.38 ± 0.44</td>
<td>1.78 ± 0.28</td>
<td>2.02 ± 0.67</td>
<td>93.5 ± 3.2</td>
</tr>
<tr>
<td>Forearm/3</td>
<td>0.0111 ± 0.003</td>
<td>3.17 ± 0.72</td>
<td>1.92 ± 0.42</td>
<td>1.69 ± 0.70</td>
<td>95.8 ± 2.4</td>
</tr>
<tr>
<td>Palm/3</td>
<td>0.0044 ± 0.003</td>
<td>2.46 ± 0.72</td>
<td>1.49 ± 0.41</td>
<td>1.34 ± 0.67</td>
<td>94.5 ± 4.1</td>
</tr>
</tbody>
</table>

Whereas the linear model’s variance accounted for was 93.4 % for the forearm under normal indentation, Wiener models produced average increases in VAF of 3.3 %. For lateral stretches, linear VAF ranged from 92.4 % to 93.4 %, depending on direction, with Wiener models providing a further 0.1 % to 2.8 % average increase. Linear models of normal indentation of the thenar eminence had VAF between 87.5 % and 94.7 %, with Wiener model improvements of 2.6 % to 4.0 %. For the remaining thenar eminence extension experiments, linear VAFs averaged 93.7 %, with Wiener models increasing the VAF a further 0.8 %.

Wiener static nonlinearity parameters are presented in Table 8. The volar forearm shows greater scaled mass and scaled damping than the palm, whereas there is little to distinguish the compressible depth or degree of nonlinearity between the two sites. The anisotropy of forearm extension displayed in the nonlinear model is less apparent. The scaled mass, scaled damping, compressible length, and degree of nonlinearity are similar between directions 1 and 2, whereas direction 3 exhibited slightly higher scaled mass and compressible length, a slightly lower rate of change of stiffness, and a similar scaled damping.
Two-way repeated measures ANOVAs with site (forearm and thenar eminence) and direction (indentation and extension) as factors were conducted on each of the four parameters \((C_1, C_2, I_s, \text{ and } B_s)\). There was a main effect of site on \(I_s\), \((F(1,6) = 15.862, p < 0.01)\) and \(B_s\) \((F(1,6) = 8.934, p = 0.02)\), with the forearm having higher scaled mass and damping. There was no effect of site on either \(I_s\) or \(B_s\). For all parameters there was a significant effect of the direction of testing, with indentation resulting in higher estimates of \(C_1\), \((F(1,6) = 378, p < 0.01)\), \(I_s\) \((F(1,6) = 131.9, p < 0.01)\) and \(B_s\) \((F(1,6) = 180, p < 0.01)\) and extension resulting in higher estimates of \(C_2\) \((F(1,6) = 49.59, p < 0.01)\). None of the interactions were significant.

Results from the one-way repeated measures ANOVAs showed that there was a statistically significant difference between directions for \(I_s\) \((F(2,18) = 11.103, p = 0.001)\) and \(B_s\) \((F(2,18) = 9.165, p = 0.002)\), but no effect on \(C_1\) or \(C_2\). Pairwise comparisons showed significant differences in \(I_s\) for all directions (all p-values < 0.001) and in \(B_s\) for directions 1 and 2 \((p = 0.004)\) and 1 and 3 \((p = 0.032)\).

The average CVs within individuals and across individuals are listed for the nonlinear parameters in Table 9. Under normal indentation, the CVs within individuals were between 2 % and 11 %, whereas the range of CVs across individuals was higher (9 % to 37 %). Under extension, CVs of the model parameters within individuals varied between 3 % and 20 %, and across individuals ranged from 13 % to 63 %. Across both sites and perturbation types, \(I_s\) and \(B_s\) demonstrated the lowest CVs within individuals, which were between 3 and 20 times lower than CVs across individuals.

Table 9. Mean coefficients of variation within and between individuals. Directions of perturbation are denoted N (Normal) 1:3 (Extension in directions illustrated in Figure 4-11).

<table>
<thead>
<tr>
<th>Position/Direction</th>
<th>CV means for individuals (%)</th>
<th>CV means across individuals (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(C_1)</td>
<td>(C_2)</td>
</tr>
<tr>
<td>Forearm/N</td>
<td>4.6</td>
<td>10.1</td>
</tr>
<tr>
<td>Palm/N</td>
<td>3.9</td>
<td>11.2</td>
</tr>
<tr>
<td>Forearm/1</td>
<td>9.4</td>
<td>18.3</td>
</tr>
<tr>
<td>Forearm/2</td>
<td>9.9</td>
<td>19.3</td>
</tr>
</tbody>
</table>
4.2.3 Incremental Perturbations

Figure 4-13. Representative static nonlinearity plot for a volar forearm using incremental loading schemes, Protocols A and B under (A) normal indentation and (B) extension.

Representative experimental results for the perturbation schemes, “Protocol A” and “Protocol B”, applied to the volar forearm under normal indentation and extension are presented in Figure 4-13. Both perturbation schemes are separated into ascending and descending parts. The incremental loading curves appear to have flatter slopes than the full-scale loading curves, especially in normal indentation (Figure 4-13A). Hysteresis can be seen in the offsets of the groups, although individual increments showed little difference in gradient across directions or protocols. The difference in offset between the protocols, seen in both panels in Figure 4-13, was shown to depend on the order of perturbations. In other words, by performing Protocol B before Protocol A, the offsets that are displayed in Figure 4-13 were reversed, with the results from Protocol A located within the loop of Protocol B. This behaviour suggests that the output displacement is more sensitive to the level of preconditioning than it is to the type of preconditioning. The same general appearance of Figure 4-13 held across perturbation sites and preconditioning levels.

Linear parameter estimates of tissue stiffness, mass, damping and the VAF for the different incremental protocols are plotted against position for an incremental extension experiment on the forearm in Figure 4-14. The reported mass and damping parameters have had the constant estimates of the robot’s mass and damping removed. The stiffness and damping parameters show a monotonically increasing trend with increasing stretch of the skin, whereas the mass and VAF remain relatively constant. However, the VAF decreases towards the upper limits of extension.
Chapter 4 Modelling of Skin Using Stochastic System Identification

Figure 4-14. Representative experimental results from linear stochastic system identification on a forearm using incremental loading, under across-surface extension. (a) The tissue stiffness estimated at various stretches is shown. (b) The perturbed mass estimated as various stretches is shown, after the actuator mass is subtracted. (c) The tissue damping at various stretches is shown after the actuator damping is subtracted. (d) The VAF for each site is plotted against actuator tip position.

The linear estimates of stiffness, mass, damping, and VAF are presented for normal indentation of the forearm and palm, and an extension test on the forearm in Figure 4-15. Parameter estimates were made using protocol B (triangle wave preconditioning). The general trends seen in the mass, stiffness, damping, and VAF when plotted against position were consistent over all 5 subjects tested.
Discussion

This chapter presents a method for characterising in vivo the multi-directional dynamic properties of skin using one device in a single configuration. Development and modifications to the hardware, electronics, and software of an existing multi-axis microrobot are detailed. Linear dynamic and Wiener static nonlinear stochastic system identification protocols have been adapted to a device that is more versatile than those used in previous dynamic skin studies (Finlay, 1970; Khatyr and Imberdis, 2004; Boyer et al., 2009; Kennedy et al., 2009; Liang and Boppart, 2010; Chen and Hunter, 2013; Sandford et al., 2013; Kearney et al., 2015;
Chapter 4 Modelling of Skin Using Stochastic System Identification

Weickenmeier, Jabareen and Mazza, 2015). Stochastic system identification was applied to the volar forearm and thenar eminence, the latter being a location for which there was little dynamic data.

Identifying the nonlinear, viscoelastic, and anisotropic properties of skin in vivo is important for the diagnosis and treatment of conditions that affect its mechanical properties, and may allow for the precise delivery of drugs using needle-free devices. Linear models of skin are insufficient to describe the change in properties as a function of input depth, such as the nonlinear increase in stiffness.

Wiener systems have been shown to produce good fits to dynamic skin behaviour (Chen and Hunter, 2009, 2012). Although other nonlinear stochastic models, such as Hammerstein and Volterra kernels, have been applied to human tissue, Wiener models have demonstrated the highest VAF in skin (Chen and Hunter, 2013). In this study, linear models accounted for 85% to 93% of the variance. The incorporation of Wiener nonlinearities into the model increased the VAF to between 94% and 97%. Previous studies have reported linear VAF between 75% and 81%, and an increase in the VAF of around 5% when Wiener models were added. The relatively high VAF with linear models in the present experiment may be an artefact of the stroke length of the device used to perturb the skin. Although the current device did not produce deformations as large as those implemented by Chen and Hunter (Chen and Hunter, 2009) and Sandford et al. (Sandford et al., 2012), the increase in VAF with the Wiener model shows that nonlinearities in the parameters are nevertheless evident in the results.

The use of stochastic system identification techniques with the microrobot provided a rapid means of characterising the parameters of the effective skin model. Parameters were identified from 5-second samples, and the whole test procedure for full-scale perturbations lasted under 2 minutes per direction. Rapid testing procedures are of benefit in many applications such as assessing the efficacy of skin care products, or rapidly determining the condition of the skin in a dehydrated patient in a clinic.

A limitation of the current device was evident when attempting to perform extension tests in multiple directions. In most subjects, extensions on the palm in directions 1 and 2 could not be analysed, as the system applied sufficient force to deform the skin. Glabrous skin has previously been shown to be significantly stiffer than hairy skin (Sandford et al., 2012). In this study, the force was limited by the power supply and current amplifiers, which led to degradation in the stochastic input signal above the range of forces used. The power supply and amplifiers were originally chosen for lower frequency perturbations, and a purpose-built setup may allow future multi-directional characterisation of stiffer tissues such as those on the palm. Additionally, the relatively large estimates of perturbed mass in extension
Discussion

Directions raise concerns about the values reported. These values represent approximately 11% to 21% of the robot’s moving mass, and therefore may not be reliable. A lighter probe tip may facilitate more reliable measurements of mass in extension.

This chapter provides new measures of the dynamic properties of the skin of the thenar eminence. Previous studies of the mechanical properties of skin on the palm have used suction (Jemec et al., 2001), ballistometry (Jemec et al., 2001), and optical coherence elastography (Liang and Boppart, 2010; Li et al., 2012a). Liang and Boppart (Liang and Boppart, 2010) reported a Young’s modulus of 24.9 kPa for the thenar eminence, compared to 101.18 kPa for the volar forearm, and Li et al. reported separate Young’s moduli for the dermis (250 kPa) and subcutaneous fat (50 kPa) of the palm (Li et al., 2012a).

For a semi-infinite body under normal indentation, a linear elastic model provides an estimate of the Young’s modulus $E$ by

$$E = \frac{(1 - v^2)K}{2R_p},$$

where $v$ is the Poisson’s ratio, $K$ is the spring contribution (the stiffness parameter identified from linear system identification) and $R_p$ is the probe radius. The Poisson’s ratio for skin is approximately 0.45 (Raveh Tilleman, Tilleman and Neumann, 2004). From the incremental estimates in our study, this provides a Young’s modulus of 63 kPa at small indentation depths and 460 kPa at greater depths on the forearm, and 170 kPa to 1090 kPa for the palm. These values suggest that, at small indentations, perturbations were mostly made to the more compliant superficial layers within the skin, rather than underlying tissues. The initial response could be an isolated response from the hypodermis, as the early incremental estimates match reported moduli for subcutaneous fat (Li et al., 2012a), with the increasing stiffness caused by the gradual response of the living epidermis, dermis, stratum corneum, and eventually the underlying muscle. While it may be counterintuitive that underlying structures deform first, this is due to the highly nonlinear stiffness of the skin, which very quickly resists deformation as the imposed stress increases in comparison to the much more compliant hypodermis. In an extreme case, this situation may resemble a sheet of metal sitting on top of some foam. As force is applied to the metal sheet, it does not strain (much), but the underlying foam does. In the dermis, strains are quickly resisted due to the recruitment of collagen fibres, whereas the hypodermis lacks a fibrous structure and demonstrates a much more compliant and linear response. The much higher stiffness of the thenar eminence is likely due to its relatively thick epidermis, which has previously been
reported to be around 1 MPa (Geerligs et al., 2011). The stratum corneum in glabrous skin ranges from approximately 100 µm to 200 µm, compared to 10 µm to 40 µm in hairy skin. Identifying Wiener nonlinearities, or measuring the incremental moduli, may provide a means of characterising the thickness of skin layers. If the change in modulus with indenter depth is shown to correlate with the recruitment of various skin layers, this information could be useful in specifying a velocity profile for delivering a drug to a specific depth in the skin for site-specific action (Hatefi and Amsden, 2002). For example, many compounds are designed for subcutaneous delivery and must penetrate the dermis while avoiding underlying tissues. Accurate delivery requires knowledge of local mechanical properties and layer thickness. Thus, controlled delivery of such drugs will require rapid soft tissue characterisation immediately prior to injection.

The range of Young’s moduli found at full-scale characterization, and at different incremental loads fits well with existing literature, in both normal and tangential deformation modes. Whilst some indentation devices have reported much lower stiffness on the forearm (approximately 8 kPa) (Pailler-Mattéi, Bec and Zahouani, 2008; Zahouani et al., 2009), these estimates have been generated at much lower strains. Other deformation profiles report higher values. Estimates from torsion experiments have ranged from 20 kPa to 100 kPa (Sanders, 1973), to moduli over 1 MPa on the forearm (Escoffier et al., 1989). Suction tests have also resulted in considerable variability in Young’s moduli from as low as 130 kPa to as high as 57 MPa (Grahame and Holt, 1969). Although Young’s modulus provides a mechanism in which to compare results with existing literature, it should be acknowledged that the range in previously reported values decreases the value of comparisons. In addition, due to the nonlinearity in skin, it is only valid over shallow indentations, and is not appropriate to accurately characterise the behaviour of layered structures. However, if the device is to find clinical applications, simple parameters such as Young’s modulus can be favourable, as it provides a readily understandable and distinguishable description of skin that can be compared to measurements made with the same device and protocol.

Khatyr et al. (2004) reported extensometer-derived Young’s moduli values of 130 kPa to 660 kPa, depending on the direction of extension. These tests most closely resemble the lateral stretches in the present study. In the former study, it was found that the average elastic modulus along the axis of the arm was approximately five times higher than its modulus in the perpendicular direction, and twice as high as that at 135 ° from the axis (Khatyr et al., 2004). The present findings show a lower degree of anisotropy; the maximum stiffness and Young’s modulus seen in direction 1 (Fig. 4) aligns most closely with the long axis of the forearm. Flynn, Taberner, et al. (2011b) demonstrated that although the proximal-distal axis of the arm produced the stiffest response, the perpendicular direction did not
produce the least stiff response, which was found at 60° from the long axis. Likewise, we found the lowest modulus in direction 2, rather than the approximately perpendicular orientation of direction 3 relative to the long axis of the arm. These results are consistent with Langer’s lines on the anterior forearm (Langer, 1978a), where the lines in the test area deviate from the long axis of the arm, and align more closely with direction 1.

The within-subject CVs of the Wiener static nonlinearity parameters provide insight into the reliability of the device. With normal indentation, the microrobot produced CVs ranging between 2% and 11%. The performance for extension tests was less reliable, with CVs ranging from 2% to 19%. However, the CV within individuals under extension is still within the ranges reported for commercial devices, such as the Cutometer and Reviscometer (6% to 14% (Nizet, Piérard-Franchimont and Piérard, 2001)), Dermaflex (11% to 35% (Jemec et al., 2001)) and Dia-stron (2% to 17% (Jemec et al., 2001)). The CVs for scaled mass and scaled damping remained low across all experimental modes and locations (2% to 4% normal, 2% to 6% extension), and the CV for the compressible depth parameter was less than 11% across tests. Improvements in the CVs of measurements made during extension may occur by increasing the force input, thereby increasing the signal to noise ratio of the impulse response function. The microrobot compares favorably with existing commercial devices used to assess the skin’s properties. The reliability of the microrobot in measuring the skin’s mechanical properties in multiple directions suggests that it could be a useful measurement tool for assessing conditions such as skin hydration and wound healing. It also holds promise for testing the efficacy of skincare products, particularly those that contain high-molecular weight polymers used to induce skin tightness (Sandford et al., 2012).

This chapter presents a unique study of the effects of preconditioning modes on incremental system identification. The “incremental law” of skin was presented over 30 years ago (Fung, 1981), but has received relatively little attention since then. Under quasi-static loading, the stress-strain plots of skin have been shown to vary with the scale of the perturbation. Stress-strain plots taken from small perturbations with incrementing displacements have shown locally-linear responses, where the slope does not equate to the tangent of the loading, unloading, or mean curve of the entire stress-strain response. This study is unique in that it demonstrates that the effect holds under dynamic loading, in both indentation and extension experiments. It demonstrates that the depth- or stretch-dependent damping and stiffness that results from strain-hardening occurs in both glabrous and hairy skin, and indicates higher stiffness at local perturbations, as seen in the flatter slopes of the incremental loading curves. The selection of a triangular wave, or average incremental force preconditioning regime, made no clear difference to the estimation of skin parameters. What is more important is providing sufficient preconditioning throughout the entire test range. The
results suggest that large-scale preconditioning of the skin does not adequately condition the skin at the smaller scale, so incremental measures must be made with their own tailored preconditioning scheme. Although incremental measures use linear system identification to provide simpler mathematical means of characterising the nonlinear response of skin, they come at the cost of lengthy experiments, and the results are more difficult to compare across subjects.

The reduction in the VAF for increments at the upper limits is likely due to the reduced signal to noise ratio, as the increased stiffness at high extension reduces the resulting displacement. Outliers are seen in one set of results, at approximately 0.5 mm extension in the mass, stiffness, and damping terms. This may be due to the significantly shorter duration of tests at each increment in comparison to the full-scale tests.

The natural pre-tension of skin was not modelled in these characterisation studies. Pre-tension acts to push the skin response further up the stress-strain curve. While pre-tension affects the parameters reported in this chapter, a pragmatic approach was taken to minimise these effects. In both skin sites tested, the test subjects were asked to relax their arms and hands, and care was placed in the repeatable placement of the arm and hand. Incremental and fullscale perturbations were also employed in a single sitting, therefore minimising any differences in pre-tension between test protocols.

The microrobot and associated analytic techniques provide a unique system to mechanically analyse the nonlinear, anisotropic, viscoelastic, and heterogeneous properties of skin. It is the first device to employ stochastic system identification approaches in multiple directions without the need to reconfigure or reposition the probe relative to the skin. The results demonstrate its ability to measure skin properties in an efficient and reliable manner. The linear parameter values that were measured for skin lie within the ranges reported previously using a variety of techniques, and the Wiener parameters are comparable to those presented in previous studies using stochastic system identification. The versatility, reliability, and speed at which the microrobot device quantitatively measures the properties of skin underscore its potential usefulness in clinical research.
5 Stereoscope Development

Following the developments made to the microrobot in Chapter 3, Chapter 4 presented a set of dynamic perturbation experiments that demonstrated viscoelastic, non-linear, anisotropic and heterogeneous mechanical behaviour of skin. A lumped parameter dynamic model of skin was shown to reconstruct the behaviour of skin in single directions, however, a single parameter set from the chosen model would not be able to reconstruct the full 3D response.

Finite element methods have been used in an attempt to form mathematical models based on the physical representation of skin, as discussed in section 2.4. However, identifying the parameters of the constitutive equations has proved to be difficult. It is hypothesised that robust identification of the governing equation parameters will be assisted by measuring the surface geometry and deformation throughout a perturbation study.

An existing three-camera stereoscopic system had been designed and built to provide estimates of the initial surface geometry, and track its deformation. A description of the stereoscope was given in section 2.6.3. While the three-camera stereoscope was initially intended to be used in the work presented in this thesis, a number of limitations were identified during experimentation. These were:

1. low frame rates;
2. high spatial-frequency noise;
3. poor synchronisation between cameras; and
4. limited overlapping fields of view.

Digital camera technology has advanced significantly in the decade since the existing stereoscope was built. The low frame rate and high spatial-frequency noise limitations of this system could be readily overcome by replacing the cameras with modern technology. The poor synchronisation of the existing stereoscope was a limitation due to the software, rather than a hardware limitation. The limited overlap between camera views could be addressed by increasing the number of cameras. This chapter first details the changes implemented in the construction of a new four-camera stereoscope, before presenting a characterisation of the stereoscope’s deformation measurements and associated stereoscopic techniques, and finally the development of a stereo-tracking algorithm for indenter localisation.
5.1 Four-Camera Stereoscope

As outlined previously, a number of limitations of the existing stereoscope motivated the construction of a four camera stereoscope. Similar four-camera stereoscopes, using the same calibration (HajiRassouliha et al. Currently under review) and surface profiling algorithms (HajiRassouliha et al. Currently under review) detailed throughout this thesis, have been well characterised ((HajiRassouliha et al., 2013a)).

The stereoscope comprised four USB 3.0 CCD camera bodies (Flea3 FL3-U3-13Y3M, Point Grey Research Inc., Canada) with 6 mm lenses (Fujinon TV Lens DF6HA-1B, Fujifilm Corporation, Japan). The lenses were chosen to produce similar fields of view to the previous stereoscope when placed closely around the microrobot.

Circular polarisers (UV HMC Digital Silver 27 mm, Hoya Corporation, Japan) were attached to each lens to reduce specular reflections. Cameras were mounted on aluminium blocks, angled at 55° from horizontal. This angle was selected from the previous three-camera stereoscope, which was aimed to reach a balance between ideal depth reconstruction (which would be achieved by having cameras placed orthogonally to each other) and creating similar points of view (required for feature matching across views). Each camera was evenly spaced around an acrylic ring, placed concentrically with the microrobot, at a diameter of 125 mm. The placement of the cameras produced an approximately 40 mm × 40 mm field of view at the microrobot tip. The depth of field at maximum aperture was approximately 70 mm. An acrylic alignment plate was laser cut to ensure the stereoscope was placed concentrically about the microrobot. The alignment plate had an inner diameter matched to the microrobot diameter, and two protruding arms that were designed to run along the inner diameter of the stereoscope mounting ring when the plate was spun about the microrobot.

Software-triggered image acquisition was performed at rates up to 150 frames per second in LabVIEW 2011 (National Instruments, USA). A trigger was set from the compactRIO hostcode, which initiated image acquisition across the four cameras within 1 ms. Object illumination was supplied by an array of light emitting diodes (LEDs), positioned around the cameras. LEDs of various wavelengths were used in subsequent studies, which will be addressed in their associated chapters.

Camera calibration routinely recorded back-projection errors for each camera of around 0.2 pixels. The pixel error corresponded to approximately 20 µm error in 3D around the imaging volume.
5.2 3D Deformation Characterisation

Much research effort has focussed on developing sensitive measurement systems in order to resolve deformation distributions of deformable materials under mechanical perturbations (Luo et al., 1993; Jeffrey D. Helm, 1996; Lyons, Liu and Sutton, 1996; Tyson, Schmidt and Galanulis, 2002; Schreier, Garcia and Sutton, 2004; Stoyanov, Darzi and Yang, 2004; Stoyanov et al., 2005; Tiwari, Sutton and McNeill, 2007; Moerman et al., 2009; Ke et al., 2011; Hu et al., 2012). However, the accuracy of these systems typically receives little attention. While many systems claim the ability to track deformation throughout a test, studies often lack validation, or instead claim accuracy based on topological metrics (Ke et al., 2011). Topological accuracy is often assessed using planar objects, with relatively few methods tested on objects with curvature (Garcia and Orteu, 2001; Hu et al., 2013). Validation of deformation tracking is yet more sparse, and when addressed has been limited to rigid translations and/or rotations of simple geometries (Ke et al., 2011; Hu et al., 2012), with relatively few studies using heterogeneous deformations that can be expected with soft materials (Garcia and Orteu, 2001; Orteu, 2009). Those that include deformation tracking validation often relate their results to well-understood models of simple deformation, using steel cantilevers (Luo et al., 1993; Quan, Tay and Huang, 2004), thermal expansion (Lyons, Liu and Sutton, 1996), and/or uniaxial extension (Schreier, Garcia and Sutton, 2004). Ambitious approaches by Stoyanov et al used Computed Tomography (CT) to independently measure silicone phantoms of a soft tissue with a specular surface (Stoyanov, Darzi and Yang, 2004), and a whole heart under deformation (Stoyanov et al., 2005), producing a measured “reference” geometry. Relatively large discrepancies were observed between measurement protocols, which may be due to different environmental conditions between CT and stereoscopy. No method exists that relates two stereo-based independent measures of surface deformation. Such an approach would permit the assessment of tracking performance in the same environmental conditions and may provide more reliable measures.

Speckle-based tracking was performed using the techniques outlined in section 2.6.4. The present chapter describes a new method of assessing deformation tracking performance using an independent tracking system that can be applied to the surface of the deforming object. A feature of this validation approach is that it compares the measured deformation to a known deformation in the same stereoscopic measurement system, using the same cameras and stereoscopic calibration for both measures. While the stereoscope has its own measurement errors, its calibration error is well characterised (HajiRassouliha et al., 2013a), and comparing measurement systems within the same environment eliminates errors between imaging modalities and their associated variations in environments. Fluorescent
microspheres were used as an independent marker system that can be tracked using simple, robust circle finder algorithms. The microspheres were shown to produce insignificant signal on a speckle-based pattern that uses our tracking algorithm. The microsphere-derived deformation map was related to the speckle-derived map through a surface-fit finite element mesh.

5.2.1 Initial Tracking Validation

A traditional tracking validation was performed using the original three camera stereoscope, to validate the performance of the calibration, lens distortion model, and tracking algorithm in a simple translation study. A checkerboard (of different dimensions to the calibration checkerboard) was attached to a translation stage with 100 nm resolution (Parker Hannifin Corporation, USA) and moved in 2 mm through horizontal and vertical planes above the stereoscope. The experimental setup is shown for vertical and horizontal translations in Figure 5-2 and Figure 5-3, respectively.

Figure 5-1. Experimental setup for vertical translation tracking tests of a checkerboard.
Translation errors were within the calibration error of the stereoscope for vertical and horizontal translations up to 10 mm above and below the anticipated placement of skin when imaging.

5.2.2 Silicone Gel Phantoms

Silicone gels have previously been used as tissue phantoms, as their soft material response is well characterised, and they allow the construction of geometric shapes that simplify the application of boundary conditions. Two phantom architectures were designed to examine the stereoscope’s performance: a cube-shaped phantom; and a cylinder-shaped phantom. A two part Sylgard 527 composite was chosen for the phantom material, as it is a stable gel, with a long shelf life (Culjat et al., 2010), and its stiffness can be controlled by varying the ratios of a two-part mixture (parts A and B) to mimic skin and other soft tissues (Azar, Metaxas and Schnall, 2001; Augenstein et al., 2005; Rajagopal et al., 2007a; Chung et al., 2008). A 2:1 part A to part B ratio was chosen at it has previously been used to mimic skin and underlying soft tissues (Rajagopal, Nielsen and Nash, 2004). The two liquid components were mixed with a magnetic stirrer for 30 minutes, and poured into each phantom’s mould.

A 40 mm × 40 mm × 40 mm cube-shaped mould was constructed (Figure 5-3(a)). The mould was assembled from 5 sides of 3 mm thick laser-cut acrylic, leaving the top surface free. 3 mm acrylic provided sufficient rigidity to constrain deformations to the top surface of the gel. The sides of the box were welded and sealed with dichloromethane. The filled container was placed in a 90 kPa vacuum for 30 minutes to remove air bubbles, before being moved to a 40 °C oven for 24 hours.

A wide spatial frequency speckle pattern was applied to the free surface of the cured gel, providing the features on which cross-correlation could be performed. The speckle was achieved by airbrushing an acrylic-base spray paint on to the surface, where the airbrush
was adjusted to produce paint speckles of approximately 0.2 mm to 0.6 mm. These features were spanned from 2 pixel to 6 pixel on the stereoscope images.

A cylindrical phantom was designed and built to fit inside a microCT (Figure 5-3(b)), providing 3D volumetric measures of the gel. The cylindrical mould was machined from acetal on a CNC lathe, and incorporated an acetal cylindrical indenter, which was held in position on the phantom using a laser-cut acrylic clamp. The Sylgard 527 gel was cured in the well in a similar process outlined for the box-type phantom. A speckle pattern was applied to the surface using iron sand filings, providing a material tracking feature that would be visible in both stereoscope and CT images.

Figure 5-3. Phantoms constructed for characterisation studies. (a) cube phantom, (b) cylinder phantom.

5.2.3 Measuring the Reference Geometry Under Deformation

While this chapter presents a validation approach based entirely in the stereoscope environment, attempts were made to gain an independent measure of the surface geometry. The cube phantom was indented using a cylindrical indenter and imaged with a laser scanning FARO arm (Faro Technologies, USA). Laser scanning was previously used to assess the three-camera stereoscope’s accuracy in surface profiling (Alvares, 2009). However, the large size of the laser scanning head prohibited it from scanning near the site of indentation.

An alternative approach involved X-ray computed tomography (CT). Substantial thermal expansion was observed when imaging the well-type phantom under X-ray. The expansion of the gel created a significant discrepancy between the stereoscope and CT measures of the gel surface. While the gel could be left to equilibrate in the CT, an extended period of running
the X-ray source would be required, and the stereoscope would have to be operated in a similarly temperature-controlled environment. Since this would be costly, and the X-ray source was due for replacement, a third technique was used to assess the stereoscope’s 3D deformation tracking performance. This procedure is detailed in the following section.

### 5.2.4 Microsphere Tracking Validation

A novel validation approach was taken, where the measured deformations were compared to a known deformation in the same stereoscopic measurement system, using the same cameras and stereoscopic calibration for both measures. While the stereoscope has its own measurement uncertainty, comparing measurement systems within the same environment eliminates errors between imaging modalities and their associated variations in environments.

To validate the performance of the tracking algorithm, an independent set of surface markers were placed on the surface of a 35 mm × 35 mm × 35 mm box-type phantom. The phantom was constructed in the same manner described in section 5.2.2. The markers were formed from an array of 500 μm - 600 μm diameter fluorescent polyethylene microspheres (UVPMS-BG-1.00 500-600um, Cospheric LLC, USA). The size and fluorescence of the microspheres created readily distinguishable features on the surface. An advantage of spherical features is that their centres of mass are maintained across camera views, allowing reliable localisation of their position. The 505 nm green fluorescence, excited at 365 nm ultraviolet
(UV) illumination, provided a strong signal that could be imaged independently of the speckle signal. A polyethylene terephthalate ethylene film template containing $8 \times 8$ evenly spaced laser-cut holes was placed onto the gel surface. Microspheres were then rolled into the template holes before the template was removed, leaving an approximately uniform distribution of surface markers across the surface of the gel. The slight adhesive property of the speckled surface ensured that the microspheres stayed in their assigned positions throughout an indentation. The four microspheres closest to the centre of the gel were removed, in case they would interfere with the indenter-gel interface.

The four-camera stereoscope was calibrated and the gel’s surface was profiled using the techniques described in section 2.6.4. Multicamera calibration produced backprojection errors for each camera between 0.21 pixels and 0.25 pixels. The pixel error corresponded to approximately $20 \mu m$ error in 3D around the imaging volume.

**Indentation**

The gel was placed on a rigid frame and suspended approximately 3 mm above, and axially aligned with the microrobot, as seen in Figure 5-5. The microrobot control code was initialised and the probe was raised until it appeared to be less than 0.5 mm away from the gel surface. The tip was then raised in 10 $\mu m$ increments until an increase of approximately 10 mN was seen in the force trace. The indenter was retracted 10 $\mu m$ from this point, setting the zero position of the experiment. A normal indentation to 4.5 mm at 100 $\mu m$ increments was performed above the zero position, to ensure that robot and gel were bedded into position. The robot was returned to its zero position and the experiment was initiated. Image sets were taken at each under normal indentation, up to a total deformation of 4.5 mm above the zero position. Each image set consisted of two photographs per camera; speckle-dominated

Figure 5-5. Illumination schemes of the phantom showing (a) The speckle pattern under red light (b) The microsphere array under UV light.
illumination via red LEDs, and a microsphere-only illumination via UV LEDs, as shown in Figure 5-5. At each indentation step, probe tip position, force and torque were recorded for 3 seconds. On completion of the profile, the robot tip was removed, allowing uninterrupted views of the surface from each camera, and producing an image set used for surface profiling of the gel.

**Surface Profiling & Tracking**

Surface profiling of the gel was performed using the algorithm described in section 2.6.4. The inclusion of the microrobot indenter head in the stereoscopic images produced a square hole in the data of approximately 6 mm × 6 mm underneath and adjacent to the indenter, producing a 42,608-point surface profile. The surface profile was then tracked using phase-based cross-correlation, as described in section 2.6.4. Figure 5-6 provides a close up view of the tracked surface profile under indentation, showing the direction and scaled magnitude of the tracked features, while Figure 5-7 presents the full surface of tracked points, demonstrating (a) the relative magnitude of tracked features on a given image, and (b) a 3D-reconstruction.

![Figure 5-6. Close-up vectors of PCC-tracked pixel displacements in one camera. Note the vectors are scaled by 10.](image-url)
Microsphere Identification

At each indentation step, microsphere centroids were identified across camera views using three separate circle finder algorithms. LabVIEW 2014’s circle finder Virtual Instrument code (National Instruments, USA), cross-correlation of a synthetic microsphere image template, and a Svoboda-type (Svoboda, Martinec and Pajdla, 2005) circle finder were tested and assessed based on the reprojection error of identified coordinates. Reprojection error denotes the difference between the identified camera coordinates, and those that are found by triangulating the identified coordinates to 3D locations, and then tracing them back towards the cameras. Of these methods, LabVIEW’s circle finder code produced the lowest reprojection error. In the images of the undeformed gel, the microspheres were manually ordered so that their coordinates could be matched across camera views. These initial positions were then used as starting values in subsequent images. As was the case with tracking, some microspheres were blocked by the indenter in each camera view. A similar masking tool was used to identify when a reduced number of cameras were required for reconstruction.

Finite Element Framework

In order to validate the performance of the tracking algorithm, a mathematical framework was required to relate the locations of speckle-identified points to the locations of microspheres. It was assumed that the microspheres move with the deforming gel and could thus be considered constant material points. A finite element (FE) mesh preserves the relative position of material points as its nodal locations move to accommodate a shape change. By fitting an FE mesh to the speckle-identified points, and causing it to deform...
according to the tracked positions of the speckle, the locations of the microspheres could be resolved throughout the deformation.

A $12 \times 12 \times 1$ element cubic Hermite mesh was chosen to represent the volume of the gel. An alignment routine was created to merge the coordinate system of stereoscope-derived data cloud with that of the mesh geometry. The edges of the acrylic box were found using LabVIEW 2011’s IMAQ Find Edge algorithm. Eight edges were found for the top four corners of the box, and the intersections of these edges were used to define the box corners. Each corner was triangulated across the stereo-images, providing four points in the stereoscope coordinate system. Additional constraints tied the four corners to lie on a plane of best-fit to the acrylic edges surrounding the profiled surface. The four corners were then rigidly aligned with the corners of the finite element mesh.

Figure 5-8. Intercepts found from the identified box edges, and colour coded to show the corresponding corner across the four camera views. These corners were used to align the stereoscope and finite element coordinate systems.
Fitting was performed in CMISS, an FE computational package (Nash & Hunter 2000; Bradley et al. 2011, www.cmiss.org). Face fitting was applied to the top surface of the mesh using the surface profile during this procedure. Each node on the surface was restricted to 1 degree of freedom (DOF), in the direction normal to the surface, while nodes on all other surfaces were fixed. The surface profile fit produced an RMS error of 39 μm.

To maintain the material coordinates of the gel under deformation, the tracked positions of the speckle-tracked point cloud must be fitted to the same material locations on the mesh. The constraints on surface nodes were relaxed to 3 DOF, and at each indentation step the new data positions were surface-fitted to the original projections. By retaining the old data projections, the relationship between the speckle-informed mesh and microsphere positions was maintained, allowing their localisation at each step. Surface fitting in this manner produced an RMS error at full indentation depth of 61 μm.

Microsphere positions were “embedded” on the gel surface by orthogonally projecting their locations onto the gel and saving the local coordinates of the projection, along with the projection distance. Embedding of microsphere positions was performed in OpenCMISS (an open-source version of CMISS, www.opencmiss.org). At each step, the new position of a microsphere could be obtained by finding the surface normal vector, and reprojecting along the surface normal to the original projection distance. The updated reference position of the microsphere was then found by multiplying the surface normal by the projection distance. Doing so for all microspheres provided a speckle-informed measurement that could be directly compared to the stereo-reconstructions of each microsphere (considered the reference geometry).

Microspheres were grouped according to their positions on the gel; an inner, middle, and outer banding of spheres. The discrepancy between the manual reconstructions from stereoscopic images and model-generated predictions was assessed for the three separate groups. The relative error for each group was also calculated at the full indentation depth, by dividing the average discrepancy by the average displacement of the group’s microspheres, as measured from the stereoscopic images. The RMS error of fit between the speckle-tracked points surrounding a microsphere group and the mesh were also calculated.

**Independence of Marker Validation**

It is important that the microsphere markers do not interfere with the measurements made on the speckle. In order to validate feature independence, a speckle pattern was applied to a strip of double-sided tape laid flat on a sheet of 3 mm acrylic. The stereoscope was inverted so that its cameras pointed downwards, allowing images to be taken before and after microspheres were dropped onto the surface of the speckled tape. Microspheres were dropped,
rather than placed on the surface to minimise large-scale perturbations to the speckled tape, thus allowing a simpler comparison between surfaces with and without microspheres.

The cameras were recalibrated in their inverted positions. Surface profiles were constructed on the two image sets with and without microspheres. It was assumed that the tape was planar, and planes of best fit were found for both image sets. The RMS error between the original image set (no spheres) and the ideal plane was 6.47 µm, whilst the images that included the spheres created an increase in RMS error to 7.13 µm.

To investigate the local effect of microspheres on the speckle-identified surface geometry, the point clouds were rigidly transformed so that they lay in the $z = 0$ plane. The plots in Figure 5-9 use colour to show the absolute error between the ideal plane and each point. Errors were found to be greatest at the edges of the region of interest, thus a maximum error of 20 µm was chosen on the colour spectrum in an attempt to maximise the apparent differences within the central regions. From Figure 5-9 it was concluded that the presence of microspheres did not sufficiently affect the cross-correlation method for capturing surface geometry, as local measures of error looked to increase by less than 3 µm.

![Figure 5-9. Out-of-plane error for surface profiles (a) with, and (b) without microspheres. Note that the microsphere positions in both images (denoted with red circles) are superimposed from their reconstructed positions.](image)

**Microsphere Tracking**

The reconstructed surface profile, used to create the initial finite element mesh consisted of points spanning the gel and top acrylic edges. Surface fitting of the data cloud with acrylic edges removed produced an RMS error of 58 µm. Data clouds at each indentation step were fitted to the finite element, resulting in an RMS error of 61 µm at full indentation depth.
Chapter 5 Stereoscope Development

All 60 microspheres were reconstructed at each indentation step. The reconstructed positions of the microspheres were embedded in the finite element mesh at the initial state. Predictions of the microsphere locations were generated using the model at each indentation step. Microspheres were grouped according to their positions on the gel: an inner, middle, and outer banding of spheres. The discrepancy between the manual reconstructions from stereo

![Figure 5-11](image-url)  
Figure 5-11. Fitted FE mesh at 4.5 mm indentation depth, showing the locations of reconstructed microspheres. Groupings of microspheres are demarcated by colour.

![Figure 5-10](image-url)  
Figure 5-10. Discrepancy between stereo-reconstructions of microsphere positions and model-generated predictions of microsphere locations, grouped by their positions on the surface of the gel.
images and model-generated predictions was assessed for the three separate groups. The groups are demarcated using colour, shown in Figure 5-11.

The discrepancy between manual reconstructions and model-generated predictions are plotted against indentation depth, according to their grouping, in Figure 5-10. Outer and middle groups show the smallest error, and appear to slowly increase to approximately 20 µm at full indentation, while the inner group of microspheres show a steeper increase in error overall with indentation depth, peaking at approximately 55 µm at maximum indentation depth. The RMS displacements and relative error of each microsphere group at full indentation depth is listed in Table 10. Relative error is defined in this study as the discrepancy divided by the RMS displacement.

<table>
<thead>
<tr>
<th>Microsphere Group</th>
<th>RMS displacement (µm)</th>
<th>Relative error (%)</th>
<th>RMS mesh fit error (µ,)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner</td>
<td>569</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Middle</td>
<td>424</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Outer</td>
<td>162</td>
<td>3</td>
<td>51</td>
</tr>
</tbody>
</table>

Discussion

The results presented in Table 10 show that phase-based cross correlation of a speckle pattern is a viable tool for correctly measuring and tracking deformation. The validation of material tracking performance is a difficult problem, as no gold-standard system exists for imparting or measuring repeatable deformations. In this study, a method to validate tracking performance using a measurable independent marker system has been developed. Relatively small discrepancies were found between model-predicted positions of microspheres and their manual reconstructions from stereoscope images. Tracing the source of this error is difficult, as many factors contribute to uncertainty. While the inner ring of spheres shows significantly higher error than the other groups, its relative error was shown to be similar to the middle ring of spheres, and less than the outer ring. The middle and outer groups show approximately the same absolute error, but substantially different relative errors. The speckle data near the middle group showed the least fitting error, and the inner group showed approximately 55 % higher errors of fit, while the outer group showed almost three times the fit error of the middle group. The similarity of the absolute errors in the middle and outer groups suggests that their errors are primarily due to uncertainties of microsphere reconstruction, as the outer group showed very small displacements while producing the same absolute error. The inner ring of microspheres produced the highest absolute error, but a slightly lower relative error than the outer group. The error of fit for the FE mesh is not as
high as the outer group, suggesting that the errors that accumulate here arise from the errors associated with the tracking data in this region of high curvature, rather than from an inability of the mesh to adequately deform to the speckle data.

Unfortunately the nature of indentation experiments means that the areas of highest deformation are obscured by the indenter head. A hole in surface data approximately twice the footprint of the indenter was obscured from the view of the stereoscope, reducing the accuracy of the finite element mesh geometry. This may have led to the increase in relative error for the inner group of spheres when compared to the middle ring of spheres. Placing additional cameras at steeper angles to the surface may allow a smaller hole in the surface reconstruction near the indenter. Limitations on the control of the microrobot probe tip position were evident when looking through the stereoscope images, and in small force traces in the Y axis of the force-torque transducer (less than 25 mN). Some side-to-side motion could be seen as the tip progressed further into the gel. By using the indenter edges to define the location of the indenter, only the initial position could be defined. If the position of the indenter was tracked throughout indentation, out of plane motions could be included in the models. This side-to-side motion can be attributed to slop or backlash in the linear potentiometers used to measure the position of each motor axis. This motion could partially account for the non-smoothness of the microsphere discrepancies shown in Figure 5-10. With these limitations in mind, the presented validation approach has demonstrated that surface strain-tracking algorithm can track material points to within 5 % – 13 % of RMS displacements, even in areas of relatively high curvature. This study also led to the development of an indenter head tracking procedure, as outlined in section 5.3.

The planar imaging studies presented in Figure 5-9 indicate that the microspheres did not have a significant impact on the speckle-tracked data cloud, and provide an independent means of measuring 3D surface deformations. This technique may be applied to any deformable surface, and provides a straight-forward method of validating a system’s ability to measure surface deformations. In the present work we have shown that our stereoscope can accurately track surface deformations on a continuous, homogeneous, isotropic surface. Further studies may assess the stereoscope’s ability to measure heterogeneous and anisotropic materials, or those with surface discontinuities. It is reasonable to assume that the stereoscope will be unaffected by heterogeneity and anisotropy, as cross-correlation is a local method and makes no assumptions based on these conditions. Instead, heterogeneous and anisotropic materials are more likely to affect the constitutive modelling framework.
5.3 Indenter Head Tracking

While the location of the indenter tip can be estimated from the microrobot’s position transducers, a more reliable method may be developed using the stereoscope. If the tip position were to be resolved using the stereoscope, its measurements would also be in the same coordinate system as the surface deformation data, eliminating a step for data alignment and thus a step where errors may accumulate.

Previous attempts to resolve the microrobot tip position were described in Prasad Babarenda Gamage’s PhD Thesis (Babarenda Gamage, 2015) using a tracking plate sandwiched between the tip and the force-torque transducer. The tracking plate was printed with a speckle pattern and a series of circles that lay on a ring concentric to the probe, as shown in Figure 5-12. This approach was chosen to provide sufficient information to accurately locate the 3D coordinates of the patterned plate. From these coordinates and a-priori information on the distance between the plate and the probe tip, the position of the probe tip could be reconstructed. However, this approach suffered from two alignment issues: the plate was a separate part from the probe tip; and the pattern was printed on paper and later attached to the plate. Any misalignment between the printed pattern and the indenter tip would result in a fixed offset error.

![Figure 5-12. The template used for tracking the indenter position is shown in (a). The template attached to the indenter is shown in (b). Reproduced from (Babarenda Gamage, 2015).](image)

Alignment issues could be solved by applying a speckle pattern directly to the indenter, and relying only on geometric information about the indenter, rather than an aligned pattern. A new indenter design used a cone-shaped base to create a traceable feature. After speckling
the cone, its orientation and apex could be uniquely identified using a simple geometric fit to stereo-reconstructed data. A-priori knowledge of the length between the cone’s apex and the indenter tip allowed unique localisation of the indenter tip.

The point cloud describing the cone surface was created from a special implementation of the surface profiling algorithm described in section 2.6.4. In this application, the original algorithm could not reliably reconstruct the surface, due to the cone's size and high degree of curvature. A given area of the cone surface was only ever imaged by a maximum of two cameras, while the degree of curvature was sufficiently high that a single affine transform was suitable for a fraction of the overlapping area. In the special implementation, a small region of interest was defined around overlapping views of the cone, creating two sub-images between camera pairs. The affine transformation step was then applied to the sub-images. An example affine transform is demonstrated in Figure 5-14. Point correspondences were found on the sub-images, and then reconstructed using their full-size image coordinates. Eight surface profile sets were created (four camera pairs, where each pair constructed a surface profile for both cameras as the reference view), in order to remove the reference camera bias (see section 2.6.4). The eight surface profiles were then combined into a single point cloud, which described the shape of the cone.
Indenter Head Tracking

Figure 5-14. Registering camera views of the indenter for feature matching. In this implementation of surface profiling, sub-images were taken to find a single affine transform between views. Note the small area that the single affine transform creates a reasonable match across views (a) the registered image (b) the reference image.

Cone fitting was performed using the Least Squares Geometric Elements Library `lscone` function in MATLAB (Forbes, 1991), providing the cone origin and the vector describing the cone’s orientation. The length to the tip was then projected along the vector, producing the estimate of the cone tip.

Validation

A series of controlled experiments were performed in order to verify the tracking accuracy of the microrobot tip. The CNC-milled indenter head was attached to a Vernier micrometer and translated in three directions throughout the stereoscope’s working volume: two “tangential” directions that approximated the plane where skin would be positioned, and a direction

Figure 5-15. Tracked displacements of the indenter tip for 500 µm shifts.
normal to the tangential directions, denoted “normal”. Images were captured at 500 µm ± 10 µm increments, and used to track the indenter head up to a 5 mm displacement. The measured displacements are plotted for the three directions in Figure 5.15. Under tangential movements, the mean and standard deviation measurements were 495.7 µm ± 25.6 µm and 493.5 µm ± 20.9 µm. Under normal movements, the mean measured displacement and standard deviation was 499.8 µm ± 17.7 µm.

Discussion

The use of a conical indenter tip has produced smaller head tracking errors than previous studies. Flynn reported microrobot indenter resolution of 50 µm, although the accuracy was not verified independently (Flynn, Taberner and Nielsen, 2011a), while Babarendra Gamage’s stereoscopic approach suffered from approximately 100 µm alignment errors. In this new procedure, each measurement was within ±40 µm of the actual position, with a standard deviation less than ±30 µm in all directions.

The error in the stereoscope measurements of probe-tip movement was smaller than that measured using the microrobot’s encoders. The error may be further reduced by using more cameras to increase the surface that was profiled, or using an indenter with less height above the localisation cone, as any errors in the parameterisation of the cone’s orientation are multiplied by the projection to the probe tip. It should be noted that the mean estimates of the tip displacement were lower than expected, suggesting a systematic error in this approach. This may be due to incorrect scaling of the camera parameters, or to insufficient data points, used in the geometric fit, to identify the location of the cone. However, the indenter is unlikely to move more than 1.5 mm tangentially (which may have approximately 15 µm systematic error associated with it), and 8 mm normal to the skin surface (approximately 2 µm systematic error). Combined with the standard deviation, these errors are within the same order of magnitude as the stereoscope calibration error.

5.4 Surface Profiling Skin

Existing surface profiling techniques used in the laboratory were described in section 2.6.4. When profiling skin, a slight change to the method was necessary, due to the high degree of curvature of skin in the in vivo experimental setup. Using a single affine transform over the whole image could not sufficiently map two views to reliably match a feature between views, as seen in the noisy surface profile of skin generated from a single transform in Figure 5.16.
Image registration was performed over smaller regions of interest, where views could be registered sufficiently using a single affine transform, much like the implementation in section 5.3. Each smaller region was reconstructed separately and then pieced together. Figure 5-17 shows an example sub-region where the fiducial markers were selected across two views. Note in Figure 5-17 that the identified points are scattered towards the skin boundary. A feature of the control point selection GUI was auto-control point placement, based on the current estimate of the affine transform. If an auto-placed feature is further than a few pixels away from where the user has manually identified the feature, it is a clear
indication that the affine transform is not suitable in that region, and cross-correlation is likely to fail. This feature aids the user in selecting a suitably small region of control points. After applying the affine transform, the matched features were examined both qualitatively and quantitatively to determine if they were adequately matched. The identified features were visually examined, and a region of interest was selected that seemed to contain mostly well-matched features. The region of interest was selected on the transformed image, rather than the reference image, as it was easier to visually identify well-matched features. An example region of interest is highlighted around a set of PCC-identified matched features in Figure 5-18.

![Image](image.png)

Figure 5-18. Region of interest chosen by visual inspection for patchwork surface profile.

A cross-correlation metric was used to assess the performance of a registered region of interest. This second step of the selection procedure determined how many patches were necessary to adequately reconstruct the entire surface. An “integer-shift uncertainty” (ISU) metric was used, which is defined as the number of pixels that shared a cross-correlation score within 85 % of the peak cross-correlation score. This method describes the inverse of the confidence in the cross-correlation score. An integer shift uncertainty greater than 8 pixels was found to lead to significant numbers of erroneous point correspondences, and a new region of interest and/or sub-image was defined. While a threshold of 85 % is arbitrary, it has shown to provide a good starting point for the integer-shift uncertainty.

Each sub-region exists in the same stereoscope coordinate system, so patching them together was straightforward. An example of combined patches of matched features are given in Figure 5-19. The integer-shift uncertainty is plotted by colour, and a comparison can be made to the original algorithm. The average and standard deviation ISU is also provided. Although

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the sub-regions were created from as few as two cameras, no alignment of the patches was performed. This procedure gives confidence in the multi-camera calibration, as small errors in the camera parameters may lead to visually apparent discrepancies between the surfaces reconstructed from different camera pairs.

An example patchwork surface profile is presented in Figure 5-20. Note that some outliers (less than 50) were manually removed from the point cloud. Although changes in density are evident in the reconstructed surface profile, the areas of high density are the result of the reasonably flat region towards the centre of the skin region. The views are more similar between all cameras, and this area is the most likely to show high degrees of deformation.

Figure 5-19. Integer-shift uncertainty for (a) the original surface profiling algorithm (b) the patchwork surface profiling algorithm.
Figure 5-20. Four views of a reconstructed surface profile made from sub-image patchwork. The colour represents the height of the skin beyond the acrylic boundary.
Discussion

When comparing the new surface profile in Figure 5-20 to the original algorithm shown in Figure 5-16, it is apparent that the patchwork method captures the surface geometry more closely than using a single affine transform over the entire surface. A quantitative measure is provided in Figure 5-19, where the integer-shift uncertainty is presented. The mean and standard deviation of the integer-shift uncertainty was approximately halved when using the new patchwork procedure. Note that the new algorithm does not show matched features in every region of the skin. The remaining area of the skin was matched with this camera as the reference camera, and the ISU is associated with the points identified in the registered camera. Although the process is manually demanding, it is less labour-intensive than the extensive point cloud clean-up that would be required with the original surface profile.

The performance of the stereoscope is limited by its ability to identify features across camera views, and thus construct the surface profile. In the current algorithm, small patches of the surface was reconstructed using affine transforms. A more efficient process for surface profiling may be achieved with a model-based approach. A single affine transform could be used to create an initial geometric model of imaging object. A texture map may be used on the geometric model, and each camera view could be reconstructed through a ray tracing algorithm. An optimisation function could then be constructed which adjusted the geometric model to minimise the difference between the ray-tracing-generated prediction of a camera view and the acquired image. Such a process could be completely automated, saving considerable processing time, and has the potential to be more reliable than the patchwork approach.

5.5 Summary

This chapter presented a series of stereoscope-related developments that addressed the limitations of the previous stereoscope. The selection of Point Grey USB 3.0 cameras reduced the high spatial frequency noise, and the overall size of the stereoscope. Software developments allowed synchronised image capture across four cameras at up to 150 fps, and could be triggered from the microrobot control code. The use of four cameras increased the overlapping regions of interest across camera views. More cameras may lead to further improvements.

The ability of the stereoscope to track a real-world, heterogeneous deformation was examined using an independent marker system. As independently measuring the surface geometry and deformation is still a challenging research question, the validation approach was performed
within the stereoscopic environment. This technique has demonstrated that the surface strain-tracking algorithm can track material points to within 13% of RMS displacements, even in areas of relatively high curvature.

An indenter head tracking routine was created from a special adaptation of a surface profiling algorithm combined with geometric fitting of a novel head design. The head tracking algorithm was shown to identify the tip position to an accuracy in the order of the calibration error.

A new approach to surface profiling used a patchwork of affine transforms to match surface features across multiple views. The patchwork technique was shown to improve performance, both qualitatively and quantitatively, over the original surface profiling algorithm.

The developments of this chapter provide valuable geometric data that may be used to improve the identifiability of constitutive relationships, used in finite element models, to relate stress inputs to resulting strains. In the next chapter, a modelling framework will be presented that takes advantage of the rich surface deformation information.
6 Developing Stereo-driven Finite Element Models

Section 6.4 in this chapter was performed in collaboration with Thiranja Prasad Babarenda Gamage, who performed parameter estimation on a two-layer, deformable phantom (Babarenda Gamage, 2015).

Interpreting the complex deformation modes employed in skin characterisation studies requires the use of a computational framework, such as a finite element model. The mechanics of finite element models are driven by constitutive models, but can account for more complex geometry and deformation modes than can be achieved using traditional analytic formulations. Computational models also allow modelling of heterogeneous structures through the combination of layers of differing material properties or geometries that use different constitutive models (Evans and Holt, 2009).

At present, most finite element models of in vivo skin attempt to identify parameters of constitutive relations, based on limited deformation data (Jor et al., 2013). Deformations are often prescribed by point source boundary conditions, derived from the measured locations of a perturbation probe, such as an indenter or extensometer. Camera-based deformation tracking tools may provide detailed descriptions of deformation that could permit improved estimates of material parameters over the single-point measurements that are traditionally employed.

This chapter presents a modelling framework that uses surface deformation measurements to identify the constitutive parameters that describe the force-displacement relationship for a specific test subject. The technique is demonstrated using skin-mimicking gel phantoms, on which well-controlled mechanical experiments were performed. Moerman et al. (Moerman et al., 2009) presented a 3D DIC method which provided descriptions of surface deformations on a Sylgard 527 phantom. The authors were able to use the surface deformation description to extract material properties of the gel using a displacement-driven 2D finite element model. However, the 3D data was radially averaged and reduced to 2D, removing any ability to resolve anisotropy. In contrast, this chapter presents a novel FE implementation that uses phase-based cross-correlation deformation tracking to identify constitutive model
parameters in a 3D model, employing a silicone phantom under indentation using the microrobot described in Chapter 3.

This chapter provides details on each step of a characterisation workflow, which involved indenting a soft material, capturing surface deformations, and identifying the material parameters through a finite element model. The workflow was applied to homogeneous, layered elastic phantoms.

The implementation and optimisation of the finite element model is presented initially using a single layer, homogeneous Sylgard 527 phantom. The ability to extract material properties from multiple layers, via indentation and stereoscopic deformation measurements, is then demonstrated using a two-layer composite phantom. The composite, constructed from a Sylgard 527 gel attached to a dental dam membrane layer, was modelled using a similar computational workflow. The composite-identified parameters were then compared to parameter sets that were identified through experiments on the separate materials. The results of the single- and composite-layer phantoms are discussed in the context of finite element modelling of skin mechanics.

6.1 Modelling workflow

The modelling workflow is presented in Figure 6-1, which is colour-coded to indicate the software tools used at each step. Experiments were controlled using LabVIEW, while the stereoscopic and microrobotic data were recorded. The data from the microrobot were used to determine the force and displacement boundary conditions that were to be input the model. Stereoscopic images were processed using MATLAB, where the non-deformed surface profile was identified, and used to create material points for surface deformation tracking. The CMISS software package (www.cmiss.org) was used to fit the surface profile using a finite element model that represented the geometry of the phantom. OpenCMISS (www.opencmiss.org) was used to embed the surface profile in the FE mesh, creating the modelled material points that were to be compared to stereoscope-derived measurements. MATLAB was used to perform parameter identification, whereby a nonlinear least squares function made calls to CMISS and OpenCMISS. In this optimisation loop, an initial set of parameters was selected from the literature (where applicable) and the model was solved using CMISS. The deformed mesh geometry was loaded into OpenCMISS, and the new locations of the predicted material points were evaluated. These were compared to the measurements in the MATLAB optimisation code, and used to update the material parameters in an iterative sense until the discrepancy between model predictions and stereoscope measurements was deemed acceptably small.
Figure 6-1. Modelling and analysis workflow with colours representing the different computational tools.
6.2 Experimental Setup

6.2.1 Phantom Construction

The single layer Sylgard 527 gel phantom was reused from the stereoscope tracking validation experiment in section 5.2. This experiment was designed to examine the modelling framework using a soft object that was subjected to large strains under controlled conditions.

A two layer phantom was also designed, to mimic a membranous skin layer overlaying a bulk sub-cutaneous tissue. This composite phantom was used to test the method of extracting material parameters of the separate layers of a composite tissue.

A two-layer design was constructed, whereby a bulk Sylgard 527 layer was cured in situ over a dental dam rubber membrane. Like Sylgard 527, dental dams have been used and characterised in previous skin/membrane phantom experiments (Malcolm et al., 2002).

A clamping rig was designed to be placed over a section of dental dam that could be pre-stretched in a biaxial rig. While the validation experiments were performed under zero press-stress conditions, the clamping rig allowed the membrane to be pre-stretched to a desired level, and then have gel cured onto it. The rig consisted of a 3D-printed housing for the gel, which together with an acrylic sheet, would sandwich the dental dam in place. An exploded diagram of this device is provided in Figure 6-3. To ensure zero slip of the membrane, it was secured with pins, allowing it to be removed from the biaxial rig. Seepage of the uncured gel was minimised using an O-ring seal between the 3D printed box and the dental dam.
Figure 6-2. Exploded view and photographs of layered phantom rig reproduced from Babarenda Gamage (2015). (a) exploded view (b) photographed views.
6.2.2 Deformation Experiments

The single layer phantom indentation setup presented in section 5.2 was reused for these experiments. Normal indentations of up to 2.8 mm, were performed in 100 µm increments, and image sets were taken at each step.

In the two-layer case, indentation was performed on the dental dam surface, as well as on the back surface of the silicone gel. The two-layer setups are illustrated in Figure 6-3, showing the tip in contact with the gel and membrane surfaces. During these experiments, the probe presented in Figure 5-12 was used to register the probe tip position. Indentation was performed in 200 µm increments to a total displacement of 3.4 mm and 3.6 mm for the silicone and membrane surfaces, respectively.

![Figure 6-3](image)

Figure 6-3. The experimental setups for indenting the two layer phantom, showing indentation of (a) the gel, and (b) the dental dam and gel. Reproduced from Babarenda Gamage (2015).

The mechanical properties of both layers were independently measured, to assess how well the framework could parameterise each layer's properties in the composite phantom. Before construction of the composite phantom, a biaxial rig was used to impose an independent extensometric deformation on the dental dam; DIC was used to track the membrane's deformation; and force displacement traces were recorded at 8 tethering points around the edge of the membrane. After construction of the composite phantom, the setup shown in Figure 6-3(a) was used to derive an independent measurement of the Sylgard 527. An acrylic support plate (shown in Figure 6-2) was added to the boundary plate to provide a fixed boundary at the dental dam surface, forming the assembly denoted “①” in Figure 6-2. In this setup, only the gel was assumed to deform.
6.3 Parameter Estimation for a Single Layer, Homogeneous Gel

The speckle-tracked deformation data was used to identify the constitutive parameters of the gel by adjusting the model parameters to minimise the discrepancy between the mechanical model’s prediction and the strain-tracked data. The indentation experimental data from section 5.2 was used, but slight modifications were made to the finite element model.

Model construction

To relate the position of the microrobot tip to the stereoscope and finite element coordinate systems, the four corners of the probe tip were manually reconstructed in the stereoscope’s view. The LabVIEW 2014 image acquisition toolbox was used to fit lines to the square edges of the tip in each view, using the “Find edge” function. The intersections of these lines were assumed to represent the corners of the tip. The central element of the mesh was aligned with these corner points. Further adjustments were made to the mesh, whereby the element size was decreased, thus increasing the element density towards the centre of the gel. This discretisation was implemented as the change in element density reflected the increasing degree of deformation recorded towards the centre of the gel. Derivative continuity of the cubic Hermite elements was relaxed at the indenter-gel interface. Tight coupling boundary

![Figure 6-4. Convergence analysis plot showing the Euclidean differences for seven points within the FE mesh as a function of the mesh resolution (indicated as the number of geometric degrees of freedom).](image)
conditions between the indenter and the gel were applied, assuming a rigid adhesion between the surfaces.

![Figure 6-5. Force-displacement trace at the indenter tip for indentation of a Sylgard 527 gel.](image)

The force-displacement relationship of Sylgard 527 under indentation was approximately linear, and is shown in Figure 6-5. Neo-Hookean hyperelastic constitutive models have demonstrated good fits to deformations of Sylgard 527 gels (Babarenda Gamage et al., 2011), and thus were used as the underlying constitutive relation for the model. The FE model was solved with force boundary conditions at the four nodes of the tightly-coupled gel-indenter interface, whereby the normal force measured at the microrobot tip was divided across the nodes. Nodes at the gel-acrylic interface were fixed in all degrees of freedom, while all remaining nodes were free to move.

A mesh displacement convergence analysis was performed whereby 7 points were randomly generated to positioned within 5 mm from the gel surface and within a 10 mm radius of the indenter tip. An initial neo-Hookean stiffness parameter, and a Poisson’s ratio of 0.5, was selected from the literature for a 2:1 Sylgard 527 gel (Babarenda Gamage et al., 2011). The FE model was solved with force boundary conditions at the four nodes of the gel-indenter interface. For each mesh, the displacement of each of the seven points was calculated and compared between the mesh resolution levels. Results of this convergence analysis are illustrated in Figure 6-4, through the Euclidean difference between mesh refinements, whereby the displacement of each point was subtracted, at a given mesh resolution, from the displacement at the final mesh resolution. The Euclidean difference thus showed that convergence occurred with approximately 6,000 degrees of freedom (DOF), beyond which
Parameter Estimation for a Single Layer, Homogeneous Gel

Further mesh refinements produced less than 10 µm changes in the displacement of the 7 points. As such, a $7 \times 7 \times 3$ element mesh, with 256 nodes, (6,420 DOF) was chosen for simulating indentation.

**Material Parameterisation Estimation**

The constitutive model parameters, denoted $\theta$, of the phantom were identified using nonlinear optimisation. A least squares objective function, $\phi$, was minimised, as shown in equation 6.1:

$$\text{minimise} \quad \theta \in \mathbb{R}^n \quad \phi(\theta) = \|z(\theta)\|^2$$

6.1

where $z(\theta)$ is the residual vector defined as the difference between the experimental stereoscopically-tracked surface geometry data, $Y$, and the model predictions, $y(\theta)$, as shown in equation 6.2 (Bates and Watts, 1988).

$$z(\theta) = y(\theta) - Y$$

6.2

The optimisation procedure used the `lsqnonlin` solver function in Optimisation toolbox of MATLAB 2014b (MathWorks, USA), which uses a subspace trust-region method, based on the interior-reflective Newton method. The options of `lsqnonlin` were set as follows: `optimset('LargeScale','on','DiffMinChange',1e-3,'DiffMaxChange',9e-1,'TolFun',0.000001,'TolX',0.001). In the case of the single-layer homogenous phantom, $\theta$ contained only the neo-Hookean parameter, $\mu_0$. The initial value of this parameter was set to 2.5 kPa, and lower and upper bounds of 1.6 kPa and 6.0 kPa, respectively, were applied during the optimisation. While the optimisation procedure was initiated in MATLAB, the objective function was evaluated at each step by an external call to OpenCMISS, where the FE model was solved. Deformation was localised around the indenter tip, due to the compliance of the gel. The objective function that arose from the full data set was found to be approximately constant, and hence an optimal set of parameters could not be identified. By thresholding the data to select only tracked points that moved in excess of specified displacement used in the optimisation, a sufficiently convex objective function was produced (see Figure 6-6). Threshold displacement values were incremented in 100 µm, until 300 µm, whereby sufficient convexity was achieved. The measured root-mean-square displacements of the selected group of points was 662 µm, with a standard deviation of 236 µm.
Optimisation of the constitutive model produced a neo-Hookean stiffness parameter of $\mu_0 = 1.90$ kPa. The optimal root-mean-squared error (RMSE, the difference between stereo-tracked point cloud and the predicted point cloud) was 143 $\mu$m, with a standard deviation of
Parameter Estimation for the Two Layer Phantom

51 µm. Qualitatively, the shape of the predicted surface in the neighbourhood of the indenter was similar to the measured data, with a slight upwards-bulging ring, probably due to incompressibility, at approximately one third of the distance from the indenter towards the boundary of the gel container, as was seen in the stereoscope images. The deformed mesh geometry can is illustrated in Figure 6-7, and the Euclidean displacement error for each stereo-tracked point used in the optimisation is shown in Figure 6-8.

![Figure 6-8: Top view and side view of deformed mesh geometry, simulated using the optimal stiffness parameter, showing errors associated with the prediction against their tracked positions.](image)

**Identified Parameter Comparison**

The value of $\mu_0$ identified by stereoscopic deformation measurements closely matches a similarly-mixed Sylgard-527 phantom investigated by Babarenda Gamage et al. in a previous study (Babarenda Gamage et al., 2011). In that study, the parameter was identified in a two-layer cantilever that had been laser-scanned in a number of orientations. The authors identified a range of $\mu_0$ of 2.05 kPa – 2.18 kPa when using seven directions in a combined optimisation. Due to potential differences in the gel used in the cantilever phantom and the gel used in this study, such as the relative concentration in parts A and B, or quality control of the batches, the actual material properties cannot be assumed to be identical.

### 6.4 Parameter Estimation for the Two Layer Phantom

Parameter estimation using the two layer phantom was performed and described by Babarenda Gamage (2015), and thus will not be described in depth. The major outcomes of
Chapter 6 Developing Stereo-driven Finite Element Models

this estimation served as a validation of the modelling approach, and so it is appropriate to briefly present the results in this section.

The indentation studies of the two-layer phantom achieved maximum surface displacements of 1437 µm and 2110 µm for the gel and membrane surfaces, respectively. Force-displacement curves are plotted for the gel and membrane surfaces in Figure 6-9. Data from independent tension tests of the isolated membrane are shown in Figure 6-10. The linearity in the gel surface indentation and the isolated membrane biaxial stretch force-displacement curves showed that these materials are inherently linear over this range of displacements. Conversely, the force-displacement relationship for the indentation of the combined layers was distinctly nonlinear.

Figure 6-9. Indenter tip force vs indentation depth, as measured by the microrobot for the exposed surfaces of the 2 layer phantom, reproduced from Babarenda Gamage (2015).
6.4.1 Modelling the Isolated Materials

The validation of multi-layered models required independent modelling of the gel and isolated membrane, to identify their material parameters. Finite element models of these layers were implemented using CMISS and optimised using MATLAB. Similar procedures to that described in section 6.3 were performed for both the silicone gel and the membrane. These models were implemented in OpenCMISS, using large deformation volume and membrane theory for the gel and membrane, respectively. Meshes were constructed using 3D cubic Hermite elements.

6.4.2 Modelling the Composite Two-Layer Phantom

The two-layer phantom was modelled in OpenCMISS by combining the two separate 3D meshes. A no-slip condition was applied to the interface between the two meshes. Similar boundary conditions to those applied to the single layer gel phantom were used here, except that the gel surface was unconstrained due to the removal of the acrylic support plate.
6.4.3 Comparison of the Identified Parameters

The parameters that were identified using the isolated deformation experiments, and those from the layered phantom, are listed in Table 11. An RMSE is also given, which quantifies the error between the stereoscopically-tracked material points, and the two-layer FE model predictions when using the isolated and combined material parameters.

The condition number and the determinant of the Hessian matrix are also provided in Table 11 to indicate the identifiability of the model parameters. A contour plot of the objective function is provided in Figure 6-11. The line of the contour demonstrates the bounds in which all combinations of parameters produce an RMSE within 50 µm of the optimum.

Table 11. Composite surface indentation parameter identification results, adapted from Babarenda Gamage (2015)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$c_{\text{membrane}}$ (kPa)</th>
<th>$C_{\text{gel}}$ (kPa)</th>
<th>RMSE (µm)</th>
<th>Cond(H)</th>
<th>Det(H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated</td>
<td>135</td>
<td>1.92</td>
<td>138</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Combined</td>
<td>259</td>
<td>1.77</td>
<td>111</td>
<td>$1.0 \times 10^{-6}$</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Figure 6-11. Contour plot representing the combination of parameters ($c_{\text{gel}}$ and $c_{\text{membrane}}$) that produce an RMSE within 50 µm of the optimum RMSE. This illustrative contour line was chosen as it represents approximately 1 pixel. Reproduced from Babarenda Gamage (2015).

While the identified stiffness parameters for the gel were similar for the isolated and combined parameter sets, the optimal combined membrane parameter was approximately double that of the isolated parameter. However, the RMSE was shown to be similar in both cases and, by examining the objective function contour plot in Figure 6-11, it was clear that
the objective function was less sensitive to the membrane stiffness, as the aspect ratio of the uncertainty ellipse shows the significantly longer dimension approximately aligned with the membrane parameter. This was reflected in the small condition number of the Hessian shown in Table 11. The identifiability of these parameters may be improved by testing different modes of deformation, since normal indentation was unlikely to elicit much strain in the membrane.

6.5 Discussion

The neo-Hookean stiffness parameter that was identified in these studies shows close agreement to a previous study on a Sylgard 527 gel with the same mixture ratio (Babarenda Gamage et al., 2011). In that study, the parameter was identified from laser scans of a cantilever placed in a number of self-weight configurations. Finding similar parameter values across different deformation modes demonstrates repeatability in the measurements, however, the relatively large variation in mechanical properties between batches makes definitive comparisons difficult.

The two-layer experiments provided a validation of the modelling framework for heterogeneous materials, by allowing the identified parameters to be compared to those identified using more isolated identification approaches. The results showed that the FE model could predict surface deformations with an RMSE of 138 µm using stereoscope-data-identified material properties, which were in close agreement to independent measurements. These findings demonstrate that a composite model can accurately predict the behaviour of a thin “skin” layer, tightly coupled to a thick “bulk” underlying layer.

Creating an objective function from the stereoscopic measurements provides a rich data set, which may help to constrain the parameters of a given model when compared to previous simpler data sets generated from only the position of the force or deformation applicator. Using a wider variety of surface displacement measurements may lead to improved characterisation of the 3D behaviour of skin. Richer data sets generated by the combination of stereo vision and indentometry provide more rigorous tests for determining model parameters. Digital image correlation methods have been used to track the surface deformation of in vivo skin (Evans and Holt, 2009) and other tissues (Zhang, Eggleton and Arola, 2002; Jacquemoud, Bruyere-Garnier and Coret, 2007; Affagard, Feissel and Bensamoun, 2015). Recent studies have created rich data sets by coupling deformation instrumentation with various imaging devices that capture data throughout the thickness of skin. Ultrasound (Houcine et al., 2015; Kearney et al., 2015) and Optical Coherence Tomography (Es’haghian et al., 2015; Houcine et al., 2015; Li et al., 2015) images have been
Chapter 6 Developing Stereo-driven Finite Element Models

coupled with simple mechanical loading in elastographic studies, which provide measurements of layer thickness and highly localised estimates of simple mechanical properties, such as Young’s modulus, shear modulus, and shear viscosity, throughout the depth of soft tissues or soft tissue equivalents. Such methods will inevitably require more sophisticated constitutive models to provide significant improvements to three-dimensional characterisation of skin. Like these through-thickness measurements, those of surface displacements may provide more constraints to the model parameters, leading to more robust identification. From the limited overlap in each imaging modality, and the possibility of non-unique parameter identification, it is apparent that the combination of multiple imaging and mechanical testing protocols from the same in vivo sample offers the best way to fully characterise the structure–function relationships of skin.

After assessing the accuracy of the stereoscope’s tracking algorithm in section 5.2, this chapter has demonstrated its application to identify the material properties of layered, soft materials by creating a rich data set for identifying constitutive parameters. The development of an experimental and modelling framework has provided the ability to characterise the mechanical behaviour of soft materials. In the following chapter, these techniques are adapted to characterise the mechanical behaviour of in vivo skin.
7 Modelling of Skin Using Finite Element Models

This chapter discusses the application of the characterisation framework, previously outlined in Chapter 6, to in vivo human skin studies. A 3D, multilayer, finite element model was developed from an existing 2D skin model, an appropriate constitutive model was chosen, and a series of tests was conducted on the skin of a volunteer. A series of objective functions was tested to assess whether including stereo-tracked deformation increases the identifiability of the constitutive model parameters.

A large number of studies assume linear elastic (or nearly linear, hyperelastic) and isotropic behaviour of skin, so that simple constitutive models can be used, such as Young’s Modulus constitutive parameters, or neo-Hookean strain energy functions. While these models attempt to describe skin behaviour using one or two constitutive parameters, they produce poor fits to skin when trying to represent the mechanical behaviour over a typical range of in vivo strains (Jor et al., 2013). Other studies have used more complex strain energy functions, such as the Ogden (1972) constitutive model, but continue to assume isotropy (Evans and Holt, 2009; Flynn, Taberner and Nielsen, 2011c). While anisotropy has also been simulated in finite element models with isotropic constitutive behaviour by applying an anisotropic pretension on the skin (Flynn et al., 2013), there is evidence that skin is inherently anisotropic (Lanir, 1979). A model should be chosen that describes material nonlinearity, anisotropy and viscoelasticity. In this chapter, an existing finite element model is described in relation to previous microrobotic studies on the skin, before details of the model’s development are given. An experimental protocol is then outlined to examine the nonlinear, anisotropic, and viscoelastic behaviour, and results from parameter estimation of constitutive parameters are presented.

Numerous constitutive models have been presented in recent skin research, which exhibit nonlinear, anisotropic, and viscoelastic behaviour (Jor et al., 2013). While some models derive their mechanical behaviour from the underlying structural constituents, such as collagen fibres (Lanir, 1979, 1983; Lanir, Lichtenstein and Imanuel, 1996; Bischoff, 2006; Lokshin and Lanir, 2009a, 2009b; Flynn and Rubin, 2012), the large number of parameters required makes unique parameter identification challenging without invasive testing or imaging. Instead, most modelling approaches are phenomenological, whereby specific aspects of skin
Modelling of Skin Using Finite Element Models

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behaviour are captured with fewer parameters (Tong and Fung, 1976; Rubin, Bodner and Binur, 1998; Rubin and Bodner, 2002; Ogden, Saccomandi and Sgura, 2004). While these models capture the fundamental properties of skin under simple deformations, such as uniaxial or biaxial extension, the heterogeneous deformations found in in vivo skin measurements have not been as adequately reconstructed. Some phenomenological models derive parts of their constitutive equations from tissue structure to address these issues, such as the Holzapfel-Gasser-Ogden (Holzapfel, Gasser and Ogden, 2000) or Gasser-Ogden-Holzapfel model (Gasser, Ogden and Holzapfel, 2006), which contains distributions of fibres within an isotropic matrix.

7.1 Skin Mechanics Modelling Workflow

The skin mechanics modelling workflow is presented in Figure 7-1, which is colour-coded to indicate which software tools were used at each step.

Experiments were controlled using LabVIEW, and the stereoscopic and microrobotic data was recorded. The data from the microrobot were used to construct the force and displacement boundary conditions that affected the model. Stereoscopic images were processed using MATLAB, where the undeformed surface profile was identified, and used to create material points for surface deformation tracking.

A finite element model, representing the skin and underlying tissue geometry, was fitted to the surface profile using CMISS. OpenCMISS was used to embed the surface profile in the FE mesh, creating the modelled material points whose displacement was be compared to stereoscope-derived displacement measurements. MATLAB was used to perform constitutive parameter identification, wherein a nonlinear least squares function made program calls to Abaqus and OpenCMISS. In this optimisation loop, an initial set of parameters was selected from literature values (where applicable) and the model was solved using Abaqus. The deformed mesh geometry was read into OpenCMISS, and the new locations of the material points were evaluated. The material point locations were compared to the stereoscope-tracked measurements in the MATLAB optimisation code, and the material parameter were updated until either the discrepancy between model predictions and stereoscope measurements, or the objective function gradient, had reached their respective tolerances.

The approach of indenting a soft material, capturing surface deformations, and identifying the material parameters was validated using homogeneous silicone phantoms, and layered elastic phantoms in collaboration with Thiranja Prasad Babarenda Gamage, as described in Chapter 6. This chapter provides details on each step of the workflow. The experimental
protocol is described, the implementation and optimisation of the finite element model is explained, and the model results are presented and discussed.
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Figure 7-1. The skin mechanics modelling workflow, colour-coded by the software tools used to perform each step.
7.2 Experimental Procedure

7.2.1 In vivo Experiments

A 24 year old male volunteer was selected for a series of indentation tests on the volar surface of the left forearm. After applying a speckle pattern for deformation tracking, the subject’s arm was strapped to an acrylic plate. The experimental setup is presented in Figure 7-2, however, for this picture, the arm was not set in the position of the experiment.

![Experimental setup for in vivo experimentation, including the four-camera stereoscope, microrobot, and acrylic support plate. The arm is placed for demonstrative purposes, and does not represent the actual placement for the experiments detailed in this section.](image)

Surface profile images were taken while the microrobot probe tip was out of the field of view of the skin. Liquid cyanoacrylate adhesive was applied to the probe tip, which was then moved into contact with the skin surface. A zero-position was set on the experiments when approximately 10 mN was seen in the probe tip force trace. The probe was then extended to a 2 mm normal indentation for 30 seconds, allowing the adhesive to set, and the skin to be preconditioned. The probe was then returned to the zero-position.

A series of deformation protocols was then sequentially applied to the skin, following similar directions described by Flynn et al (Flynn, Taberner and Nielsen, 2011a). Each protocol consisted of a 1.5 mm peak-to-peak sinusoidal profile applied to the skin at 0.1 Hz, for three sinusoidal periods. A normal indentation profile was followed by 12 tangential profiles, a
tensile retraction in a normal direction, and three “out of plane” profiles. The tangential stretches were performed in 30° increments, starting from an initial alignment with the longitudinal axis of the arm. The out-of-plane profiles were oriented 45° from the skin surface normal direction, and in 45° increments within the tangential plane. The protocols are summarised in Table 12, where they are defined with respect to an angle, $\theta$, within the surface plane, and an angle, $\Phi$, which described the deviation from the surface plane. It is important to note that $\theta$ was defined in relation to the stiffest in-plane direction measured in the forearm, which was in keeping with the notation employed by Flynn et al. (Flynn, Taberner and Nielsen, 2011b, 2011c; Flynn et al., 2013). A sub-set of these protocols is demonstrated in Figure 7-3.

Table 12. Direction protocols performed in vivo.

<table>
<thead>
<tr>
<th>Direction Name</th>
<th>$\theta$ (°)</th>
<th>$\Phi$ (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>In-plane 000</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>In-plane 030</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>In-plane 060</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>In-plane 090</td>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>In-plane 120</td>
<td>120</td>
<td>0</td>
</tr>
<tr>
<td>In-plane 150</td>
<td>150</td>
<td>0</td>
</tr>
<tr>
<td>In-plane 180</td>
<td>180</td>
<td>0</td>
</tr>
<tr>
<td>In-plane -150</td>
<td>210</td>
<td>0</td>
</tr>
<tr>
<td>In-plane -120</td>
<td>240</td>
<td>0</td>
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<tr>
<td>In-plane -90</td>
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</tr>
<tr>
<td>In-plane -60</td>
<td>300</td>
<td>0</td>
</tr>
<tr>
<td>In-plane -30</td>
<td>330</td>
<td>0</td>
</tr>
<tr>
<td>Normal retraction</td>
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<td>90</td>
</tr>
<tr>
<td>Out-of-plane -30</td>
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<td>45</td>
</tr>
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<td>Out-of-plane -75</td>
<td>285</td>
<td>45</td>
</tr>
<tr>
<td>Out-of-plane -120</td>
<td>240</td>
<td>45</td>
</tr>
</tbody>
</table>
Experimental Procedure

During the deformation protocols, stereoscope images were captured at 1 Hz. Upon completion of the deformation protocols, the subject’s forearm was imaged across the test area with OCT and ultrasound.

7.2.2 Processing Stereoscope Images

Features for deformation tracking were created by airbrushing acrylic-based paint in a high spatial frequency speckle pattern onto the skin. Speckle size ranged from 0.2 mm to 0.6 mm, which resolved to 2 to 6 pixel on the stereoscope images. A surface profile was created of the initial skin geometry as the forearm rested on the experimental plate. The surface profile was constructed using the registration process presented by HajiRassouliha et al. (2013), with the modifications detailed in section 5.4. Using the “integer-shift uncertainty” metric led to the reconstruction of 13 patches. The reconstructed surface profile is shown in Figure 7-4 and is described in more depth in section 5.4.

The surface profile point-cloud was used to define the points to track. Cross-correlation was performed on image sets from a single camera, and reconstructed across the views at each deformation step. Regions of interest were defined in each camera view, for each deformation step.
direction, masking out the indenter from the tracking field of view. The region of interest masks were then used to remove any data points that were occluded by the indenter, and the remaining camera views were used to reconstruct the material points.

7.3 Modelling Implementation

The large-scale deformations observed in indentation experiments of gel phantoms (section 5.2 and Chapter 6) and in existing microrobot skin characterisation studies motivated the use of finite element models based on finite elasticity theory. This study builds on existing finite element formulations in CMISS, OpenCMISS, and Abaqus, which have been previously used to model complex soft tissue deformations, such as skin (Flynn, Taberner and Nielsen, 2011c), the heart (Nash and Hunter, 2000), and the breast (Chung et al., 2008). It is important that finite element packages are verified to ensure that finite elasticity governing equations are correctly implemented. Abaqus software packages are accepted across engineering industries, and contain verification studies in the installation files, while OpenCMISS and CMISS packages have been verified in a number of publications, where simulations were compared to analytic solutions (Rajagopal et al., 2007b; Bradley et al., 2011), and validated experimentally using gel phantoms (Rajagopal et al., 2007b; Chung et al., 2008; Babarenda Gamage et al., 2011).

7.4 Modelling Skin Geometry

7.4.1 Previous Mesh Geometry

A 2D linear mesh was developed for previous microrobot skin studies by Flynn et al (Flynn, Taberner and Nielsen, 2011c). The existing mesh consisted of a single layer of shell elements, 1.5 mm thick, and was shown to adequately reproduce in-plane force-displacement behaviour of skin on the forearm. However, the lack of an underlying tissue was proposed to account for the relatively large errors observed in out-of-plane test directions.

The mesh geometry consisted of a 4 mm circular central region, which represented the indenter region, a 20 mm diameter middle region, and a 40 mm outer region. The indenter region was meshed with a mixture of quadrilateral and triangular elements. The outer region was meshed from elements with radially increasing length, while the inner group was meshed from elements with uniform radial length. Two views of the mesh are given in Figure 7-5.
7.4.2 Extension to 3D

Similar 2D mesh geometries were created in Abaqus and extended to three dimensions. The shell mesh geometry was used to extrude both the dermal and sub-dermal layers through the extrusion feature in Abaqus CAE. An example mesh geometry is shown in Figure 7-6. In this example, 4 skin element layers and 3 subdermal element layers were created. Creating the skin and subdermal layer in this manner allowed them to be assigned different constitutive models, while also allowing the layers to be tightly coupled. While a greater number of element layers would improve the aspect ratio of some of the central elements, further refinements quickly increased the number of nodes in the mesh. The Abaqus license employed on the high performance computing system was limited to meshes containing fewer than 20,000 nodes. The coordinate system was aligned such that the skin surface lay in the XY plane, and Z axis was aligned normal to the surface.

Figure 7-6. Example 3D linear composite mesh generated in Abaqus.
7.4.3 Higher Order Elements

Care must be taken when using 3D linear elements. Full integration of a linear element risks shear locking, where the curvature of a deformed geometry is not captured. Reduced integration avoids shear locking, but risks hourglassing. In these elements, certain bending conditions on the element result in zero stress at the integration points, thus the element has no stiffness to this mode of deformation, and a zigzag appearance often manifests in the mesh. The reader is directed to the “Getting started with Abaqus” manual (Dasault Systemes, France) for more information.

These problems can be avoided by using higher order elements. Finite element implementations in CMISS and OpenCMISS typically avoid these problems by using cubic Hermite elements. This element type captures curved surfaces, but also ensures derivative continuity. At the time of this publication, cubic Hermite elements were not supported in Abaqus. Quadratic elements were supported in CMISS, OpenCMISS, and Abaqus environments, and capture the curvature of the surface geometry.

Minor differences exist between the native quadratic elements in Abaqus and CMISS/OpenCMISS. While CMISS/OpenCMISS use 27 node elements, the mesh tools in Abaqus CAE generate 20 node elements. Although 20 node elements are native, Abaqus can read 27 node quadratic elements generated elsewhere. A program was written in Morphic (available online from Duane Malcolm, New Zealand\textsuperscript{1}), to convert the linear mesh into 27 node quadratic elements.

7.4.4 Geometric Mesh Fitting

A MATLAB script was created to export the top layer of the composite mesh to CMISS for geometric fitting to a surface profile of the skin. Nodes where the indenter met the skin (referred to hereafter as indenter nodes) were moved to the height of the indenter, as estimated from stereoscopic imaging of the indenter (see section 5.3). Surface fitting was performed on the mesh in the same manner described in section 6.3. The \( z \) components of the top surface nodes were free to move, and adjusted to minimise the distance between the top surface of the mesh and the surface profile point cloud of the undeformed surface. Subsurface nodes, indenter nodes, and the surface nodes on the mesh boundary were fixed. A second script then translated the fitted mesh into an Abaqus input file form. In this script, nodes that lay on the element layers between the top and bottom surfaces were offset from the top

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\textsuperscript{1} Morphic mesh visualisation and manipulation program available from https://github.com/duanemalcolm/morphic/blob/master/doc/introduction.rst
surface nodes’ coordinates, so that the skin layer had a uniform thickness. The fitted mesh is shown in Figure 7-7, while a cross-section view is shown in Figure 7-8 to demonstrate the offset sub-surface layers.

Figure 7-7. Quadratic composite mesh after geometric fitting to the surface profile point cloud.

Figure 7-8. Example cross-sectional view of a fitted skin mesh, using quadratic Lagrange basis functions.

7.5 Modelling Mechanics

7.5.1 Constitutive Equation Selection

A constitutive model of the skin should be able to recreate its nonlinear, anisotropic, and viscoelastic behaviour. The original FE model described in section 7.4.1 was previously implemented with an Ogden model and a special-case 2D implementation of the Tong & Fung constitutive model (Flynn, Taberner and Nielsen, 2011c). The Ogden model is an isotropic constitutive model, but anisotropic behaviour was still captured in these implementations by applying an anisotropic prestress to the model. In reality, skin is intrinsically anisotropic, but is also exposed to anisotropic prestress. The implementation of the Tong and Fung model, which required a custom user-defined subroutine, written for 2D cases (Flynn, Taberner and
Nielsen, 2011c), and included material and prestress anisotropy, produced better fits to experimental data.

Initial attempts were made to use the Ogden model and to apply an anisotropic prestress, as described by Flynn, Taberner, et al. (2011c). In Abaqus, the calculation of *STRESS type initial conditions are solved in an initial step, before the perturbation step is performed. In the initial step, the stress field is applied to the mesh, and the model is solved to ensure all forces are in equilibrium. In the 2D case, the zero-displacement boundary condition placed along the model edges ensures that nodes inside the boundary do not have to move to achieve equilibrium. In the 3D case, these nodes do not constrain the surface nodes, as their coordinates are no longer within the plane of the constraints, and the mesh thus deforms to reach equilibrium. Therefore, anisotropy was modelled in this study through the constitutive model.

While a prestressed Tong & Fung model had also been previously used, its implementation was limited to 2D models. Abaqus has a built-in Tong & Fung implementation which does not include prestress. This model requires 21 parameters to recreate the anisotropic response of skin, and many of these parameters are poorly defined, which limits the practical use of this constitutive equation. Instead, the Holzapfel-Gasser-Ogden model (referred to as the Holzapfel model or GOH model in this chapter) was chosen, as it is also implemented in Abaqus, and can represent material anisotropy using just five parameters. The generalised Holzapfel model has been described in section 2.4.2, but reduces to 4 parameters when a single family of fibres is chosen and when a fibre distribution and incompressibility is assumed. The reduced strain energy function is given by:

$$W = C_{10}(\bar{I}_1 - 3) + \frac{1}{D} \left( \frac{\langle J^e \rangle - 1}{2} - \ln J^e \right) + \frac{k_1}{2k_2} \exp[k_2 \langle \bar{E}_\alpha \rangle^2] - 1$$

where $W$ is the strain energy function, $C_{10}, D, k_1, & k_2$ are material parameters, $\alpha$ is the family of fibres, $\bar{I}_1$ is the first invariant of the right Cauchy-Green tensor, $J^e$ is the elastic Jacobian, and $\bar{E}_\alpha$ is described as:

$$\bar{E}_\alpha = \kappa(\bar{I}_1 - 3) + (1 - 3\kappa)(\bar{I}_4 - 1)$$

where $\kappa, 0 \leq \kappa \leq \frac{1}{3}$ is a parameter that describes the distribution of the fibres, and $\bar{I}_4$ is the square of the stretches in the fibre direction. More information on $\kappa$ can be found in Gasser et al. (2006). If the skin is assumed incompressible, the second term drops out, to give:

$$W = C_{10}(\bar{I}_1 - 3) + \frac{k_1}{2k_2} \exp[k_2 \langle \bar{E}_\alpha \rangle^2] - 1$$
By assuming that there is not a distribution of fibres, and that they are instead completely aligned, \((\kappa = 0)\), \(E_\alpha\) reduces to:

\[
E_\alpha = (I_4 - 1)
\]

Thus the strain energy function can be written as

\[
W = C_{10}(I_1 - 3) + \frac{k_1}{2k_2} \exp[k_2(I_4 - 1)^2] - 1
\]

which requires three material parameters, \(C_{10}\), \(k_1\), and \(k_2\). Note that this formulation is not valid when a high degree of nonlinearity exists in two directions. Therefore, a \(\kappa\) value, which represents a fibre orientation distribution, must be included.

The Holzapfel (2006) model is a hyperelastic model, and therefore does not rely on strain history. Modelling viscoelasticity thus required a different constitutive model. A quasilinear viscoelastic (QLV) model based on a Prony series is one of the simplest approaches to model viscoelasticity. This architecture was initially suggested by Fung (1993). This model was chosen as only two parameters are needed to define the viscoelastic behaviour, which was aimed to provide improved identifiability over the alternative models. In a QLV model, the stress at time \(t\) is calculated as

\[
T(t) = T_e(t) + \int_0^t T_e(t - \tau) \frac{dg_R(t)}{d\tau} d\tau
\]

where \(T\) is the total Cauchy stress tensor, composed of the elastic Cauchy stress tensor, \(T_e\), and the viscous loss term, which contains the reduced relaxation function, \(g_R(t)\). The reduced relaxation function is calculated from a Prony series as

\[
g_R(t) = 1 - \bar{g}_1^p (1 - e^{-\frac{t}{\tau_1^q}})
\]

where \(\bar{g}_1^p\) and \(\tau_1^q\) are material parameters.

In the interests of identifiability, the subdermal layer was represented by an incompressible neo-Hookean constitutive equation, as it is described by two material parameters. The neo-Hookean strain energy function, \(W\), is given as

\[
W = C_{10}(I_1 - 3) + D(f - 1)^2
\]

Choosing values for the Poisson’s ratio, \(\nu\), from the literature reduces the optimisation problem to a single parameter, the Young’s modulus \(E\), as \(c_{10}^{Bulk}\) and \(D\) are derived from \(\nu\) and \(E\) as follows:
\[ D = \frac{6(1 - 2v)}{E} \]  \hfill (7.9)

\[ c_{10}^{\text{bulk}} = \frac{E}{4(1 + v)} \]  \hfill (7.10)

As skin is often modelled as incompressible or nearly incompressible, the Poisson’s ratio for the neo-Hookean model was set towards the higher end of reported literature values (0.48, Li et al., 2012b).

### 7.5.2 Boundary Conditions

Boundary conditions were chosen as an extension of the model from 2D to 3D. The ring of nodes at the model boundary was fixed in all degrees of freedom. This boundary condition was analogous to the gel phantom study in section 5.2. In this configuration, it was assumed that the compression of the arm as it strapped down on to the acrylic plate, and the double-sided adhesive that was used to attach the skin surface to the acrylic plate is sufficient to constrain all tissue movement to within the 40 mm diameter exposed surface. Tight coupling was assumed between the skin and underlying tissue. As the skin and underlying tissue now contained a bottom surface, the bottom nodes were also fixed in all degrees of freedom, representing a rigid floor to the model, where deeper tissue was assumed to stay rigid under the experimental protocol. A kinematic constraint was applied between the central indenter node and the remaining indenter nodes, which distributed the measured indenter tip forces onto the area of contact. All remaining nodes throughout the mesh were left unconstrained in three dimensions.

### 7.5.3 Convergence Analysis

A convergence analysis was performed to determine the number of elements required to reliably simulate the deforming surface. Mesh geometries were built where the number of elements was varied radially, axially, and circumferentially. The displacements were assessed at 8 points on the surface under a normal indentation and a tangential stretch at each refinement. The Euclidean distance between the starting- and end-points was calculated for each of the 8 points in each mesh. Results of this convergence analysis are illustrated in Figure 7-9., through the Euclidean difference between mesh refinements, whereby the displacement of each point was subtracted, at a given mesh resolution, from the displacement at the final mesh resolution. A mesh with approximately 10,000 degrees of freedom was shown to produce similar displacements within 70 µm of a mesh with over twice
the number of degrees of freedom. This discrepancy was of the same order as the calibration error, and smaller than the surface profile fitting error.

![Figure 7-9. Euclidean difference plots for 8 surface points as the finite element density was increased for (a) tangential stretch (b) normal indentation.]

### 7.6 Identifying Model Parameters

**Parameter Estimation**

The constitutive parameters of the skin and underlying tissue, denoted \( \theta \), were identified using nonlinear optimisation. A weighted least squares-type objective function, \( \phi \), was minimized, as shown by equation 7.11:

\[
\text{minimise } \theta \in \mathbb{R}^n \quad \phi(\theta) = \|w \cdot z(\theta)\|^2
\]

where \( z(\theta) \) is the residual vector defined as the difference between the experimental data, \( Y \), and the model predictions of the stereoscopically-tracked surface geometry, \( y(\theta) \), as shown in equation 7.12 (Bates and Watts, 1988) and \( w \) is the weighting vector in equation 7.11, defined from some chosen metric, such as the total measured displacement.

\[
z(\theta) = y(\theta) - Y
\]

The optimisation procedure was implemented in MATLAB, using a trust region reflective algorithm in the `lsqnonlin` function from the Optimisation toolbox. Upper and lower expected value vectors were passed to the optimisation algorithm to limit the range of each parameter in \( \theta \). Constitutive parameters were scaled using equation 7.13, to avoid identification issues caused by large discrepancies in parameter values (Fletcher, 1987).
\[
\theta_i = \frac{p_i - L_i}{U_i - L_i}
\]

\[
p_i = L_i + (U_i - L_i) \cdot \theta_i
\]

where \(p_i\) is the unscaled constitutive parameter, and \(\theta_i\) is the scaled parameter used in the optimisation. \(U_i\) and \(L_i\) are the upper and lower expected values for the unscaled parameter.

At each iteration of the algorithm, the objective function was evaluated through calls to Abaqus to solve the FE model, and OpenCMISS to evaluate the deformed locations of material points. The parameter set, \(\hat{\theta}\), represents the optimal set, and was determined when the change in the objective function error is less than \(10^{-6}\), or the norm of the change in scaled parameters was less than 0.001.

**Objective Function Selection**

When verifying the modelling methodology using silicone gel phantoms (such as the example given in section 6.3), the surface deformation was shown to be highly localised around the indenter. Computing the root-mean-square residual without weighting or using a minimum displacement cut-off led to flat objective functions. In these cases, the objective function was found to be sufficiently flat such that the objective function tolerance was achieved at the first optimization step, and the parameters were not changed from their initial values (Babarenda Gamage, 2015; Parker et al., 2015). When estimating parameters for skin, while the fibre constituents may act to spread deformation further across its surface, similar complications can be expected. For the studies on gel phantoms, a threshold displacement was used to avoid flatness in the objective function (see section 6.3). For the studies on skin, a more systematic approach was taken that aimed to retain all of the recorded deformation data. This involved testing three objective functions, which used different approaches to weighting the residual vector:

1. each point was weighted by 1 (i.e. no weighting);
2. each point was weighted by its maximum displacement;
3. only the indenter tip forces and its displacement were included.

When applying the first objective function, the RMSE of the predicted surface data was dominated by points that underwent minimal deformation. This resulted in a flat objective function where perturbations to the parameters did not result in sufficiently large changes in the objective function. In all cases tested, the optimiser exited with the initial parameter estimates. This finding was consistent with the observations of the studies on phantoms described in Chapter 6.
For the second approach, points that underwent small displacements contributed less to the objective function, whereas points that underwent large deformations had a comparatively greater influence on the objective function. It should be noted that the weighting applied to a stereoscopically-tracked point was equal at all stages throughout the experiment. This objective function proved sufficiently reliable for the remainder of this chapter.

The third objective function was tested as a comparison, where $z(\theta)$ contained the differences between the predictions and recordings of the microrobot tip displacement (the stereoscopic data were not used). This third objective function helped to compare the stereoscope’s contribution to skin characterization studies over a more traditional approach, using only the microrobot. Results from this test are given in section 7.6.1.

The parameters of the constitutive equation in Equation 7.1 are at risk of practical non-identifiability, due to coupling between $C_{10}$, $k_1$, and $k_2$. Coupling in $k_1$, and $k_2$ is due to their appearing in the same term. In addition, $C_{10}$ and $k_1$ are likely to be coupled, as the scaling of the isotropic, neo-Hookean term (representing the ground matrix) is likely to trade-off against the scaling of the exponential term (representing the collagen fibres). In order to reduce coupling issues, $C_{10}$ and $C_{10Bulk}$ were fitted independently over the initial linear region of the force-displacement curve. After independent identification of the $C_{10}$ and $C_{10Bulk}$ parameters, initial estimates were taken from the literature for the remaining parameters.

The coupling between $k_1$ and $k_2$ was examined by plotting the objective function for ranges of parameters. In this study, the remaining parameters were kept constant. The objective

![Figure 7-10. Objective function over a grid of values for $k_1$ and $k_2$, investigating correlation between the parameters. The red line shows an approximate valley floor to the error, demonstrating by the trade-off between $k_1$ and $k_2$.](image-url)
function is plotted as a function of the two parameters, in Figure 7-10. A flat-bottomed valley was found in the objective function, diagonally oriented between $k_1$ and $k_2$, and highlighted by red line. It is likely that the optimisation will settle anywhere along the valley floor, depending on the initial estimates. This implies that the identified parameter set is not uniquely identifiable. In this case, either $k_1$ or $k_2$ therefore should be set, and the remaining parameter should be optimised. As the objective function valley was more closely aligned with $k_2$, an arbitrary value was selected for this parameter.

**Parameter Selection**

The Akaike Information Criterion (AIC) is a common metric that can be used to assess how many parameters should be used to model a system (Akaike, 1974). In many cases, increasing the number of parameters decreases the objective function. The AIC assesses how well the addition of a parameter improves the fit to the data, while keeping the model as simple as possible. While a number of AIC formulations exist, based on different model assumptions, an AIC is calculated as suggested from Anderson, Burnham & White (2010) as:

$$AIC = N \ln \left( \frac{SS_{\text{error}}}{N} \right) + 2(M + 1)$$  \hspace{1cm} 7.14

where $N$ is the number of observations, $SS_{\text{error}}$ is the sum of squared errors, and $M$ is the number of model parameters.

The AIC was used to determine which parameters should be included in the model. The best model is revealed by the lowest AIC (including negative values). It is important to note that the AIC metric is a relative means to compare a set of given models, and the goodness of fit should complement the AIC to assess how well a model performs.

The choices of parameters used in each model were taken from equations 7.1, 7.7, and 7.10. The finite element model was run with various parameters removed, and the objective function’s normalised residual was calculated for each step. The parameter selection, RMSE surface projections, objective function normalised residual (resnorm), and AIC is summarised in Table 1.

<table>
<thead>
<tr>
<th>Parameter List</th>
<th>$M$</th>
<th>RMSE (µm)</th>
<th>Resnorm (µm$^2$)</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
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<td>$k_1$</td>
<td>4</td>
<td>224</td>
<td>7776</td>
<td>-17814318</td>
</tr>
<tr>
<td>$k_1, \kappa$</td>
<td>5</td>
<td>215</td>
<td>7600</td>
<td>-17894788</td>
</tr>
<tr>
<td>$k_1, \kappa, g_1^{-p}, r_1^{p}$</td>
<td>7</td>
<td>211</td>
<td>7078</td>
<td>-17931637</td>
</tr>
</tbody>
</table>

Table 13. AIC calculated using a displacement-weighted objective function, for various parameters sets.
While this table does not include every possible parameter combination, the number of parameters was chosen systematically. In the GOH model, the nonlinearity of the skin response is determined by the exponential term, which includes $k_1$ and $k_2$. If $k_1$ and $k_2$ are not present, the GOH model reduces to the neo-Hookean model, which is relatively linear. In this chapter, models are also described in terms of number of parameters to be estimated. For example, the model that included $k_1$ in the optimisation is referred to as a 1 parameter model, as the remaining parameters ($k_2, c_{10}, c_{10}^{Bulk}$) were fixed during optimisation. The output of the 1 parameter model is shown in Figure 7-11, where the microrobot tip force-displacement is plotted. The anisotropy parameter, $\kappa$ was added in a separate optimisation, before $\tau_1^p$ and $g_1^p$ were introduced in a third optimisation. While they contribute different aspects of the hysteresis, $\tau_1^p$ and $g_1^p$ were not tested independently, as they would not contribute any change to the objective function on their own, and would thus increase the AIC, due to an increase in $M$.

![Figure 7-11. Force vs. displacement plots for the optimal single-parameter model in (a) tangential and (b) out of plane deformation modes. The free model parameter was $k_1$.](image)

With the addition of $\kappa$, the force-displacement traces demonstrated good anisotropic fits to high-strain regions (Figure 7-12). The lower-strain regions for the stiffer directions were not fit as well as the 1 parameter model with the addition of $\kappa$, which is due to coupling between the exponential stiffness and the anisotropy parameters. The coupling between $\kappa$ and $k_1$ can be seen in Table 14, where the addition of $\kappa$ resulted in a roughly halving of the $k_1$ parameter, when compared to the optimal single-parameter model. In other words, as the material becomes more anisotropic, the same exponential stiffness parameter will result in an overall stiffer response along the material direction.
The addition of viscoelasticity reduced the RMSE by 4 µm, and showed considerable qualitative improvements in fitting (compare Figure 7-13 with Figure 7-12). By inspecting the AIC, as well as the models’ normalised residual and RMSE values, every parameter was determined to be appropriate for modelling the skin. In general, the out-of-plane force-displacement profile was well matched across the displacement range. However, the in-plane deformations were not as well characterised. An anisotropic, viscoelastic response was evident, but discrepancies remained between the model and experimental data, particularly in the directions with lower stiffness. The degree of nonlinearity was also underestimated, with poorer fits at lower displacements.

Figure 7-13. Force vs. displacement plots for the optimal 4 parameter optimisation in (a) tangential and (b) out of plane deformation modes. The free model parameters were $k_1$, $\kappa$, $g_1^{-p}$, and $\tau_1^p$. The addition of viscoelasticity reduced the RMSE by 4 µm, and showed considerable qualitative improvements in fitting (compare Figure 7-13 with Figure 7-12). By inspecting the AIC, as well as the models’ normalised residual and RMSE values, every parameter was determined to be appropriate for modelling the skin. In general, the out-of-plane force-displacement profile was well matched across the displacement range. However, the in-plane deformations were not as well characterised. An anisotropic, viscoelastic response was evident, but discrepancies remained between the model and experimental data, particularly in the directions with lower stiffness. The degree of nonlinearity was also underestimated, with poorer fits at lower displacements.
Table 14. Optimal parameters for various model selections. Note that $k_2$ was fixed at 10,000 in each optimisation.

<table>
<thead>
<tr>
<th>Parameter List</th>
<th>$k_1$ (kPa)</th>
<th>$\kappa$</th>
<th>$g_1^{-p}$</th>
<th>$\tau_1^{-p}$ (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_1$</td>
<td>5.28</td>
<td>1/3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$k_1,\kappa$</td>
<td>2.30</td>
<td>0.321</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$k_1,\kappa,g_1^{-p},\tau_1^{-p}$</td>
<td>2.2</td>
<td>0.323</td>
<td>0.402</td>
<td>0.44</td>
</tr>
</tbody>
</table>

The discrepancies between stereoscopic data points and their model predictions are plotted over the 4 parameter model in Figure 7-14 and Figure 7-15. The error in the predicted data point locations was under 800 µm across all perturbation directions, except for normal indentation. In this perturbation, a small number of points near the indenter produced large errors (up to 1100 µm). This may be due to a relatively small number of data contributing to the objective function, wherein normal indentation perturbed the skin surface in a relatively localised manner when compared with tangential stretches, thus fewer points underwent large deformations during normal indentation. A single purely-normal perturbation was used in the objective function, in comparison to four purely-tangential perturbations, which would also weight the objective function towards minimising in-plane errors.
Figure 7.14. Difference maps between stereoscopically-tracked surface points and model predictions, for out-of-plane perturbations, for a 4 parameter optimisation ($k_1, \kappa, g_0^{-1}, \tau_1^p$), at maximum force input. Arrows indicate in-plane motion of the indenter (not to scale). Magnitude of indenter motion was approximately 1500 $\mu$m in each direction. See Table 12 for description of perturbation direction.
Figure 7.15. Difference maps between stereoscopically-tracked surface points and model predictions, for in-plane deformations, for a 4-parameter optimisation \( (k_1, \kappa, g_p^{-1}, \tau_1^p) \), at maximum force input. Arrows indicate in-plane motion of the indenter (not to scale). Magnitude of indenter motion was approximately 1500 µm in each direction. See Table 12 for description of perturbation direction.

7.6.1 Comparison to Microrobot-only Objective Function

**Identifiability**

Parameter identifiability was assessed after the optimal set of parameters was identified, for the stereoscope data objective function and the microrobot-only objective function. Although the parameters of the full model were not uniquely identifiable, due to the correlation between \( k_1 \) and \( k_2 \), the identifiability of the remaining parameters were examined when \( k_2 \) was fixed.
Chapter 7 Modelling of Skin Using Finite Element Models

Three parameter-determinability metrics are typically used to assess the identifiability of model parameters. Recalling Equation 6.1, these metrics are calculated using linear approximations of the model predictions ($y$), for describing the neighbourhood surrounding the optimised parameter set ($\hat{\theta}$) (Bates and Watts, 1988).

The neighbourhood surrounding $\hat{\theta}$ is approximated by a second order series expansion of $\phi(\theta)$, as shown in Equation 7.15:

$$
\phi \approx \hat{\phi} + \frac{1}{2} (\theta - \hat{\theta})^T H_{\hat{\theta}} (\theta - \hat{\theta})
$$

where $\hat{\phi}$ and $H_{\hat{\theta}}$ are the objective function value and Hessian matrix, respectively, evaluated at $\hat{\theta}$. The Hessian matrix contains the second-derivatives of $\phi$ with respect to each model parameter, and is defined in Equation 7.16.

$$
H_{\hat{\theta}} = 
\begin{bmatrix}
\frac{\partial^2 \phi}{\partial \theta_1^2} & \frac{\partial^2 \phi}{\partial \theta_1 \partial \theta_2} & \cdots & \frac{\partial^2 \phi}{\partial \theta_1 \partial \theta_n} \\
\frac{\partial^2 \phi}{\partial \theta_2 \partial \theta_1} & \frac{\partial^2 \phi}{\partial \theta_2^2} & \cdots & \frac{\partial^2 \phi}{\partial \theta_2 \partial \theta_n} \\
\vdots & \vdots & \ddots & \vdots \\
\frac{\partial^2 \phi}{\partial \theta_n \partial \theta_1} & \frac{\partial^2 \phi}{\partial \theta_n \partial \theta_2} & \cdots & \frac{\partial^2 \phi}{\partial \theta_n^2}
\end{bmatrix}
$$

The Hessian is a quadratic approximation of the objective function, and is thus often only a reasonable approximation close to the objective function minimum, $\hat{\phi}$. When an objective function value, $\delta \phi$, is chosen close to the objective function minimum, an indifference region is created, wherein all sets of parameters produce objective function values equal or less than $\delta \phi$, as shown in Equation 7.17.

$$
\theta: (\theta - \hat{\theta})^T H_{\hat{\theta}}^{-1} (\theta - \hat{\theta}) \leq \delta \phi
$$

The indifference region is an $n$-parameter ellipsoid in the parameter space, where all parameter sets within the $n$-dimensional volume will produce a $\phi$ value less than or equal to $\delta \hat{\phi}$. For visualisation of 2D indifference ellipses, the reader is directed to Babarenda Gamage (2015).

The shape and size of the indifference region is determined by the curvature of the objective function, which is represented by the Hessian matrix. These descriptions of the indifference region can be efficiently calculated directly from the Hessian and are a standard approach to assess the identifiability of the model. The three metrics defined from the Hessian are as follows:

1. $\text{det}(H_{\hat{\theta}})$
The determinant of the Hessian is related to the volume of the indifference region. The larger the value of \( \text{det}(H_{\hat{\theta}}) \) the smaller the volume of the indifference region, which indicates less variance in the parameters.

2. \( \text{cond}(H_{\hat{\theta}}) \)

The condition number provides the ratio of the largest and smallest eigenvalues of the Hessian. A condition number close to 1 is desired, as it indicates equal variation in the neighbourhood of \( \hat{\theta} \). A condition number close to 0 or \( \infty \) (depending on which eigenvalue is used as the denominator) indicates a high level of anisotropy or eccentricity in the neighbourhood of \( \hat{\theta} \) which can indicate poor identifiability.

3. \( \text{det}(\tilde{H}_{\hat{\theta}}) \), where

\[
\tilde{H}_{ij} = \frac{H_{ij}}{\sqrt{H_{ii}H_{jj}}}
\]

The determinant of \( \tilde{H}_{\hat{\theta}} \) indicates the level of alignment of the indifference ellipse and the axes of \( \theta \). A value of 1 is also desired, as it indicates no correlation between parameters.

The identifiability metrics are summarised in Table 15 for the stereoscope-based objective function and the microrobot-based objective function.

<table>
<thead>
<tr>
<th>Objective Function</th>
<th>( \text{det}(H_{\hat{\theta}}) )</th>
<th>( \text{cond}(H_{\hat{\theta}}) )</th>
<th>( \text{det}(\tilde{H}_{\hat{\theta}}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereoscope data</td>
<td>( 1.279 \times 10^{20} )</td>
<td>0.03371</td>
<td>0.6570</td>
</tr>
<tr>
<td>Microrobot data</td>
<td>( 1.392 \times 10^{14} )</td>
<td>0.0160</td>
<td>0.3304</td>
</tr>
</tbody>
</table>

**Model Accuracy**

The optimal parameter sets that were identified using the stereoscope-based objective function and the microrobot-based objective function are provided in Table 16. The parameters were similar in both instances, and the force-displacement traces, generated from the optimal parameters from the microrobot objective function, presented in Figure 7-16, are qualitatively similar to the stereoscope-derived optimal parameters (compare with Figure 7-13). A stereoscopic point error plot for the deformation direction that showed the greatest difference between objective functions is provided in Figure 7-17, which demonstrates similar errors in the microrobot-based objective function and the stereoscope-based objective function.
Table 16. Optimal parameters identified from stereoscope- and microrobot-based objective functions.

<table>
<thead>
<tr>
<th>Model</th>
<th>$k_1$ (kPa)</th>
<th>$k_2$</th>
<th>$\kappa$</th>
<th>$g_1^p$</th>
<th>$\tau_1^p$ (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>stereoscope</td>
<td>2.2</td>
<td>10,000</td>
<td>0.323</td>
<td>0.402</td>
<td>0.44</td>
</tr>
<tr>
<td>microrobot</td>
<td>1.9</td>
<td>10,000</td>
<td>0.314</td>
<td>0.414</td>
<td>0.465</td>
</tr>
</tbody>
</table>

Figure 7-16. Force-displacement traces at the microrobot tip, using microrobot data only to construct the objective function. (a) in-plane deformations (b) out-of-plane deformations. These force-displacement traces can be compared to those generated from the stereoscope data in Figure 7-13.

Figure 7-17. Absolute error between stereoscope-measured surface deformation and model predictions for objective functions based on (a) stereoscope data (b) microrobot data.

The RMSE was approximately 10 $\mu$m lower in the microrobot objective function, and the observed differences between the two objective functions' difference maps were minimal.
These objective functions minimised displacement-weighted displacement errors, which may not correspond to the minimum of the un-weighted objective function. Therefore the RMSE may be larger for the stereoscope objective function compared with the microrobot objective function. The differences in the displacement error, are highlighted in Figure 7-18. The weighted stereoscope-data objective function behaved as expected, by penalising errors associated with large displacements, which is demonstrated in Figure 7-19. The error and weighted error graphs display the stereoscope and microrobot objective function contributions through blue and red scatter data, respectively. Both figures are separated into subplots to inspect the error and weighted error associated with (a) stereoscope data, and (b)

Figure 7-18. Displacement error as a function of tracked point displacement for (a) the stereoscope data and (b) the microrobot data, generated from the optimal parameters identified from the stereoscope objective function (blue points) and microrobot objective function (red points).

Figure 7-19. Weighted displacement error as a function of tracked point displacement for (a) the stereoscope data and (b) the microrobot data, generated from the optimal parameters identified from the stereoscope objective function (blue points) and microrobot objective function (red points).
microrobot data. Lower weighted error was evident in the stereoscope data above 0.9 mm displacements (Figure 7-19 (a)), which is reflected in lower absolute errors in Figure 7-18 (a). Slightly higher errors and weighted errors are visible in the microrobot data, in Figure 7-18 (b) and Figure 7-19 (b), respectively.

While the RMSE was dominated by points that underwent small displacements, a separate non-weighted stereoscope data optimisation was performed to compare the microrobot objective function to a similar scheme using stereoscope data. The stereoscope data was subject to a 200 µm threshold (similar to the procedures in Chapter 6). In this optimisation, the RMSE was reduced 12 µm over the displacement-weighted stereoscope-based objective function, approximately 1 µm lower than the microrobot-only objective function.

In the weighted stereoscope-based optimisation, the predicted z-axis (normal to the skin) deformations were substantially smaller than the measured response. Higher errors were seen in the z axis in the stereoscope measurements, while the x and y axes’ errors were substantially smaller. This possibly owes to the lower value of $\kappa$ identified with the microrobot data objective function, which acts to restrict anisotropy to an inplane response.
7.7 Validating Model Parameters

Validation of the model entails applying the optimal model parameters to a new dataset that was not used during parameter identification. In section 7.2.1, the deformations that were imposed on the skin were presented; however, only the out-of-plane deformations, and in-plane deformations between 0° and 180° were used in the model optimisation procedure. Owing to geometric asymmetry, the behaviour in the remaining 180° remains as a separate dataset that can be used to validate the model. Figure 7-20 shows the model predictions of these deformation directions and the measured data for the force and displacement under the microrobot tip. Figure 7-21 shows the error associated with model predictions of the stereoscopically tracked material points. The RMSE error in the validation directions was 245 µm, approximately 34 µm higher than the errors associated with the optimised directions.

![Figure 7-20](image_url)

Figure 7-20. Validation experiments and model predictions using the optimal parameter set based on stereoscope data.
7.8 Discussion

Finite element models have been used to predict or understand wound healing (Actis et al., 2006) and tissue damage (Hadid et al., 2012), to produce facial animations for the film industry (Hung et al., 2009), to determine characteristics for engineered tissue (Flynn and McCormack, 2009), to drive virtual surgeries (Lapeer, Gasson and Karri, 2010), to enable targeted delivery of drugs to skin or sub-dermal layers (Chen and Hunter, 2013), and to gain better understanding of physiology or constitutive models (Flynn, Taberner and Nielsen, 2011c).

Skin forms the interface between the human body and its environment. Owing to the importance of its barrier roles and appearance, skin has been studied in medicine,
biomechanics, cosmetics, consumer product development, animation, and forensics. Many of these applications require accurate models of skin that capture its complex mechanical behaviour (Flynn, Rubin and Nielsen, 2011). Therefore, nonlinear, viscoelastic, and anisotropic response of skin must be precisely quantified with in vivo perturbations, and carefully modelled with appropriate constitutive relationships, geometry, and boundary conditions (Jor et al., 2013).

In this chapter, the combination of microrobotic and stereoscopic instrumentation has been demonstrated in a novel characterisation study of in vivo skin. To the best of the author’s knowledge, this represents the first three-dimensional model of skin that utilises surface geometry and surface deformation tracking to identify the parameters of a constitutive model of skin. Moerman et al. (2009) produced a 2D model that used stereoscopic data to represent a normal indentation of a neo-Hookean gel. Evans and Holt (Evans and Holt, 2009), of the same research group, used stereoscopic deformation data in a 2D membrane model of skin. The authors used an Ogden constitutive equation to model in-plane deformations, thus ignoring anisotropy.

In this thesis, surface deformation data was fit to a 3D finite element model, and a displacement-weighted objective function was constructed to minimise the differences between model predictions and the measured deformation data for both normal indentation and in-plane perturbations. A Gasser-Ogden-Holzapfel constitutive equation was used to predict the deformations resulting from applied forces.

The finite element model reproduced anisotropic, nonlinear, viscoelastic and heterogeneous behaviour under normal indentation and in-plane deformation. However, the model implementation was unable to accurately reproduce the entire force-displacement relationship of skin as measured in these experiments. The degree of nonlinearity could not be adequately captured in all deformation directions. This may be due to the omission of skin tension from the model. Flynn et al. (2011b) showed reasonably good fits to anisotropic in-plane deformation data using a 2D formulation that included an anisotropic pre-stress. To do so, the authors created a user-defined material subroutine. Such a procedure would be beneficial to the 3D finite element formulation, and should be implemented in future studies.

The identified parameters were not unique, and multiple parameter sets that provide equivalently good fits to the data are likely to exist. The non-uniqueness of the parameters, and the lack of in vivo studies makes comparison to existing studies difficult. The bulk stiffness parameter, $c_{10}$, is similar to values reported by Koys & Nguyen, (2012), wherein samples of full-thickness skin from the human back were characterised by pressure-controlled inflation testing. The authors reported an average $c_{10}$ value of 0.0179 MPa over 6
samples. However, $c_{10}$ was optimised simultaneously with $k_1$, $k_2$, and $\kappa$. The values for $k_1$, $k_2$, and $\kappa$ average 9 MPa, 1244, and 0.25, respectively. It should be noted that two fibre families were modelled. A two-family model was not appropriate in the model presented in this thesis, as the current software implementation of this model shares parameters across each fibre family, which would create equal stress-strain responses along the $0^\circ$ in-plane and $90^\circ$ in-plane directions. In order to recreate an appropriate anisotropic response, a two-family in vivo model should include anisotropic pre-stresses on the skin. While a user-defined subroutine could alternatively implement unique properties for each fibre direction, increasing the number of parameters increases the chance of correlation, and the AIC would be required to determine whether the additional complexity was justified. Ní Annaidh, Bruyère, Destrade, Gilchrist, & Otténio (2012) used a 2-fibre family 2D Holzapfel model to describe the stress-strain response of excised back skin. The authors applied uniaxial extension to the skin, and histologically analysed the dermis to directly measure $\kappa$. Each reported parameter was significantly different from those identified in this thesis. The optimised $c_{10}$ and $k_1$ parameters from these uniaxial extension experiments were an order of magnitude larger than those identified in this chapter (0.1 MPa and 25.4 MPa, respectively), but this is likely due to the selection of a much larger fixed $k_2$ parameter in this chapter relative to identified parameter in the uniaxial extension study (0.1327). The measured $\kappa$ was 0.16, which is substantially more directionally dependant than the value determined from the studies in this thesis. Owing to the differences in deformation modes, the excision of skin, and the correlation between parameters, comparison of parameters with values reported in the literature did not provide a great deal of additional insight.

If the identifiability is to be improved, the design of experimental protocols should be informed by analyses of parameter identifiability. Recent work by Babarenda Gamage (2015) has demonstrated the potential of such an approach. Babarenda Gamage (2015) used model-based design of experiments to identify optimal experimental protocols for identifying the model parameters of tissues in the breast. The procedure was applied to determine the orientation of a patient that maximised the identifiability of material parameters based on experiments involving imaging the breast surface under gravity loading. Additional protocols may include more complex deformation profiles, wherein the indenter tip is moved through an arc; by using a series of different indenter geometries; or by introducing multiple microrobotic probes. An experimental setup could include multiple probe tips, such that one region of skin is perturbed by three or four microrobots, allowing more traditional extension or torsional protocols to be performed. An example setup of this type is illustrated in Figure 7-22.
The inclusion of stereoscopic data produced better displacement-weighted fits to the surface deformation measurements recorded by the stereoscope over single-point measurements, some better representations of the force-displacement curves under the indenter tip, and increased the identifiability, as demonstrated by the Hessian matrix metrics. While the parameters were not unique, this is likely due to modelling choices rather than the data set. Greater differences may be seen between the stereoscope-based objective function and microrobot-data objective function if a more appropriate model could be used, or when trying to characterise regions of high heterogeneity, such as tissues containing a lesion.

![3-microrobot setup](image)

Figure 7-22. 3-microrobot setup proposed to impose more complex deformations, such as biaxial extension and torsion.

A 3D implementation of pre-stress was not considered in this thesis. A user-defined subroutine could be developed to remove deformation caused by the application of the pre-stress, and an additional modelling workflow could be developed that accounts for the pre-stress caused by placing the arm into the experimental setup, as well is the resting tension that is inherent in the skin.

The Gasser-Ogden-Holzapfel constitutive equation was selected, due to its relatively few parameters, and its ability to reproduce anisotropic and nonlinear behavior in skin studies (Koys and Nguyen, 2012; Ní Annaidh et al., 2012). The use of exponential-based constitutive equations has been previously questioned owing to parameter correlation/identifiability issues (Ogden, Saccomandi and Sgura, 2004). A Tong and Fung anisotropic model could also have been used. However, this model requires a greater number of parameters, which are also known to be correlated (Flynn, Taberner and Nielsen, 2011c). More suitable relationships, which use either structural parameters, or more independent parameters may
be implemented in future, using a similar modelling workflow to that demonstrated here. Furthermore, a quasi-linear viscoelastic modelling approach has been used in this study. However, it has been criticised as being too simplistic to represent the true viscoelastic properties of skin, such as preconditioning (Flynn, Taberner, et al., 2011b), and may be replaced by a more complete model, such as that proposed by Lokshin & Lanir (2009a).

While a Holzapfel model was chosen to produce the anisotropic, nonlinear response of skin in vivo, several studies have employed alternative constitutive models. The experimental and modelling design of this study builds on the work of Flynn, et al. (2011b, 2011c). In that study, a shell-element mesh was driven by Ogden and Tong and Fung constitutive models. Both models were shown to replicate the nonlinear response of indentation and extension experiments on the forearms of 21 volunteers. Although the Ogden constitutive equation is isotropic, anisotropy was described through the identification of pre-stress in two directions. Viscoelasticity was also described through a quasi-linear viscoelastic approach, suggested by Fung (1993). Ogden models were examined with $N = 1$ and $N = 2$ (see Equation 2.4). With $N = 1$, the Ogden model could not describe out of plane responses. With $N = 2$, the Ogden model showed reasonably good fits to in-plane and out of plane responses, ranging 13 % to 21 %. However, the arrangement of collagen fibres in the dermis indicates that skin is inherently anisotropic (Jor et al., 2016). Slightly better fits were achieved with the anisotropic Tong and Fung model, but the authors noted that this may be due to the additional two parameters of this model. The Tong and Fung model used in this study was formulated for a membrane, and the extension to 3D materials would require additional parameters.

The Tong and Fung model was also used to replicate biaxial stretch experiments by Kvistedal and Nielsen (2009). Surface deformations were tracked in 2D, using a phase-based cross-correlation. The authors ignored viscoelasticity, and chose to separately fit to the loading and unloading curves, but reported being able to predict surface deformations with an rms error of 100 µm to 300 µm.

Evans and Holt, (2009) also used an Ogden constitutive equation (with $N = 1$) to recreate in-plane uniaxial stretch experiments in vivo. Digital image correlation was also used to track surface displacements. However, out of plane perturbations were not performed. The model was able to predict surface deformations with errors generally below 100 µm, except when close to the loading point (increasing to approximately 400 µm).

Groves et al. (2013) used a similar form of constitutive equation to describe uniaxial extension tests in excised human and mouse skin. The anisotropic, hyperelastic model consisting of 3 fibre-families embedded in an isotropic matrix was based on an earlier model, by Weiss et al.
The isotropic matrix used a Veronda and Westmann (1970) constitutive model. This model architecture uses two parameters (if incompressible) and undergoes exponential stiffening. Each fiber family also undergoes exponential stiffening, and has 4 parameters, including rate of uncrimping, and the degree of stretch. 14 parameters were thus used to reproduce the anisotropic, nonlinear behaviour in uniaxial tests. The authors noted that the identified parameters were highly dependent on the initial guess, but this was at least partly due to the optimisation method, which is susceptible to local minima. Fibre families were arranged parallel to the skin surface, which may not produce accurate predictions in normal indentation experiments, due to the complex out of plane arrangement of collagen fibres (Jor et al., 2016).

After implementing pre-stress, and perhaps choosing a different constitutive model, it may be useful to perform additional identifiability tests. For example, a practical sense of the identifiability can be gleaned from a series of optimisations using starting values for the parameter set. By assessing whether optimisations using different initial parameter values converge on the same set of optimal parameters, or produce differing sets, the model can be deemed practically identifiable or not identifiable.

The displacement-weighted objective function provided sufficient curvature to find an optimal parameter set. A weighting scheme was essential for this modelling implementation, as a traditional RMSE objective function was found to be too flat owing to the high volume of small-displacement data points. The displacement weighting is an important improvement over the thresholding approach employed in Chapter 6, as it does not discard any data. In future, the use of a strain-based weighting should be investigated, as the current approach may be erroneously weighted by points undergoing rigid translations. Doing so may improve the overall surface data RMSE when compared to microrobot-based objective functions. It should be noted that the deformation-weighted objective function that was used in this chapter tended to also weight the fitting towards the higher displacement region of the stress-strain curves. This behaviour is due to the generation of proportionally larger errors at the upper limits of applied force. This behavior is evident in the force-displacement plots that were generated under the indenter tip. An objective function that calculates the percentage error based on the current displacement may provide a means to even out the error across the stress-strain curve. However, this may result in a flat objective function, due to the domination of many points that undergo very small deformations, and may amplify noise.

A number of simplifying geometric assumptions were made during the construction of this model. It is likely that some geometric refinements will improve the characterisation of skin. In the presented model, the skin layer was assumed to be 1.5 mm thick and tightly coupled to the underlying subcutaneous tissue. Attempts were made to measure the dermal
thickness, using OCT and ultrasound. While OCT revealed the thickness of the epidermis, the instrument that was available lacked the imaging depth to resolve the dermis-subcutaneous tissue interface. Under ultrasound, while the penetration depth was adequate, the spatial resolution was not sufficient to identify the dermis-subcutaneous interface. Using higher resolution ultrasound, or an OCT with deeper penetration would provide geometrically-accurate measurements of the skin layers, which could be used to create more accurate numerical representation. Likewise, ultrasound may be useful in defining the dimensions of the subcutaneous tissue. The model may also be improved by representing the subcutaneous fat and underlying muscle as separate layers with distinct constitutive properties. Imaging studies may be used to reveal the nature of coupling between the skin and underlying tissue, which is unlikely to be completely coupled, and could be used to assess the influence of surrounding tissue. Relative movement between the layers may act to decouple in-plane and out-of-plane responses, and may allow a better fit to the in-plane data without sacrificing the quality of out-of-plane predictions.

7.9 Summary

This chapter presented a modelling workflow to reproduce nonlinear, anisotropic, viscoelastic and heterogeneous stress-strain behaviour of skin. A set of in-plane and out-of-plane experiments was performed to examine these properties of skin, using instrumentation developed in this thesis. The updated microrobot was used to perturb the skin, while the four camera stereoscope measured 3D surface deformations.

A layered, 3D, quadratic Lagrange, finite element mesh was used to model the individual-specific geometry, and was subjected to force boundary conditions, as measured by the microrobot. A Gasser-Ogden-Holzapfel constitutive relation was used with the finite element model to calculate the deformations resulting from the applied force boundary conditions. A stereoscopically-tracked 3D surface point cloud was embedded in the finite element mesh, and the deformed 3D coordinates of each surface point were evaluated at a number of time steps.

A displacement-weighted mean-square-error objective function was constructed, wherein the error was defined as the discrepancy between the stereoscopically-measured surface points and corresponding finite element model predictions. The finite element model was able to recreate the nonlinear, anisotropic, viscoelastic, and heterogeneous behaviour with an RMSE of 211 µm. The use of stereoscopic data offered improved identifiability over traditional single-displacement measurement approaches, as demonstrated by Hessian identifiability metrics. Although the model was insufficient to capture the mechanical behaviour of the skin
over the full force-displacement curve, the Akaike Information Criteria showed that each parameter of a single-fibre-family Holzapfel model was found to be important. The model may be improved by adding anisotropic pre-stress, and/or using a different constitutive equation. This modelling platform allows for future investigations into the use of structurally-based constitutive relations and associated parameter identifiability for simulating the mechanical behaviour of in vivo skin.
8 Conclusions and Future Work

This thesis presented an experimental and modelling framework to characterise the mechanical behaviour of human skin, in vivo, which may be used to inform surgical procedures, investigate effects of cosmetic products, and improve the functionality of laboratory-engineered skin. The aims of the research were to:

- improve and merge existing instrumentation, principally a force-sensitive microrobot with a three-camera stereoscope, to induce and measure three-dimensional deformations in soft materials, including skin;
- develop methods, based on the use of this instrumentation, to characterise the mechanical properties of in vivo skin;
- validate the experimental and modelling approach with well-defined soft material phantoms;
- design and perform experiments to capture the anisotropic, nonlinear, viscoelastic and heterogeneous behaviour of skin in vivo; and
- model the mechanical behaviour of human skin using structural and/or phenomenological constitutive relationships that describe the deformation seen through the layers of skin and underlying tissue.

8.1 Improvements to Skin Measurement Instrumentation

Chapters 3 & 5 discussed novel developments to existing laboratory instrumentation that aimed to:

1. reliably perturb in vivo skin using a versatile, portable, microrobotic indentation probe;
2. improve measurements of the indenter tip position and force, and resolve torques; and
3. implement a surface geometry deformation measurement system that could be integrated with the microrobotic probe.

8.1.1 Microrobot

The reliability, portability, and versatility of the microrobot was improved by implementing data acquisition and control on a LabVIEW RealTime/compactRIO software/hardware
Chapter 8 Conclusions and Future Work

LabVIEW RealTime control software provided easily-configured operation of the microrobot. For example, experiments could be performed using closed-loop position control, or open-loop force inputs, and synchronised with stereoscopic image acquisition. Benchtop motor amplifiers were replaced with a significantly smaller amplifier module that was housed in a compactRIO module.

A number of changes were implemented to improve the operational ability, portability, and reliability of the microrobot chassis. The linear sliders that guided each motor axis were upgraded to rack-and-pinion-type guides, which provided reliable movement of the bearing race by reducing backlash and thus improving the operational life of the bearings. Strain relief was applied to delicate transducer wires through internal routing and termination at push-pull connectors.

Changing the force transduction mechanism to a single 6-axis force-torque transducer improved the reliability of the force signals, reduced noise on the position transducers, and added more information, which could be used to enhance the characterisation of skin mechanics.

The addition of current-sense resistors provided an alternative means of force transduction and reduced the moving mass of an indenter tip that could be used for dynamic studies. A frequency analysis of the open-loop force input, and the resulting position measurement demonstrated the microrobot’s suitability for dynamic studies of in vivo skin.

In summary, changes to the microrobot system provided a robust interface between the user and the robot; allowed data to be acquired in a deterministic manner; allowed readily reconfigurable modes of operation, such as closed-loop position control and open-loop force control; improved portability; and allowed integration with a high frame-rate stereoscopic camera system.

8.1.2 Stereoscope

Chapter 5 presented a series of stereoscope-related developments that addressed the limitations of the previous stereoscope. The selection of Point Grey USB 3.0 cameras reduced the high spatial frequency noise, and the overall size of the stereoscope. Software developments allowed synchronised image capture across four cameras at rates of up to 150 fps, and could be triggered from the microrobot control code. An alignment procedure was created to transform the stereoscopically reconstructed point cloud into the microrobot coordinate system. The use of four cameras increased the overlap of the region of interest across camera views. More cameras may lead to further improvements.
The ability of the stereoscope to track a real-world, heterogeneous deformation was examined using an independent marker system. As independently measuring the surface geometry and deformation is still a challenging research task, the validation approach was performed within the stereoscopic environment. This technique has demonstrated that the surface strain-tracking algorithm can track material points to within 5% to 13% of root-mean-squared displacements, even in areas of relatively high curvature.

An indenter head tracking routine was created from a special adaptation of a surface profiling algorithm combined with geometric fitting of a novel design of the indenter head. The head tracking algorithm was shown to identify the tip position to a repeatability in the order of the calibration error.

A new approach to surface profiling used a patchwork of affine transforms to match surface features across multiple views. The patchwork technique was qualitatively and quantitatively shown to improve performance over the original surface profiling algorithm.

### 8.2 Extracting and Modelling Dynamic Behaviour of Skin

Chapter 4 introduced a dynamic study on in vivo human skin, and aimed to:

- ensure that the instrumentation is able to impose and measure large-scale, highly dynamic deformations to in vivo skin, in a variety of directions;
- demonstrate the anisotropic, nonlinear, viscoelastic, and heterogeneous behaviour of in vivo skin; and
- characterise the skin’s mechanical behaviour using a phenomenological model that describes the deformation seen through the layers of skin

This chapter presented a method for characterising in vivo the multi-directional dynamic properties of in vivo skin using one device in a single configuration. Linear dynamic and Wiener static nonlinear stochastic system identification protocols have been adapted to a device that is more versatile than those used in previous dynamic skin studies. This chapter provided new measures of the dynamic properties of the glabrous skin of the thenar eminence, which showed significantly different properties to the non-glabrous skin of the forearm.

The use of stochastic system identification techniques with the microrobot provided a means of rapidly characterising skin properties. Parameters were identified from 5-second samples, and the whole test procedure for full-scale perturbations could be achieved in under 2 minutes per direction. Rapid testing procedures are of benefit in many applications, such
Chapter 8 Conclusions and Future Work

as assessing the efficacy of skin care products, or rapidly determining the condition of the skin in a dehydrated patient in a clinic.

In this study, linear models accounted for 85 % to 93 % of the variance in the probe tip displacement profile, resulting from a stochastic force input. The incorporation of Wiener nonlinearities into the model increased the variance accounted for (VAF) to between 94 % and 97 %. Previous studies have reported VAF of linear models between 75 % and 81 %, and an increase in the VAF of around 5 % when Wiener models were added. The relatively high VAF with linear models in the present experiment may be an artefact of the relatively short stroke length of the device used to perturb the skin. Although the current device did not produce deformations as large as those implemented by Chen & Hunter (2013), or Sandford, Chen, Hunter, Hillebrand, & Jones (2013), the increase in VAF with the Wiener model demonstrated that nonlinearities in the parameters are nevertheless evident in the results.

Incremental identification protocols demonstrated depth-dependent stiffening estimates of Young's modulus that spanned values reported elsewhere in the literature. Young's moduli of 63 kPa and 460 kPa were identified at small and large, respectively, indentation depths on the forearm, and 170 kPa to 1090 kPa for the palm. The initial Young's modulus identified for the forearm is consistent with values of subcutaneous fat reported in the literature. The initial response could be an isolated response from the hypodermis, with the increasing stiffness caused by the gradual recruitment of the living epidermis, dermis, stratum corneum, and eventually the underlying muscle. The much greater stiffness of the thenar eminence, which has previously been reported to have stiffness of up to 1 MPa, is likely due to its relatively thick epidermis.

Identifying Wiener nonlinearities or measuring the incremental moduli may provide a means of characterising the thickness of skin layers. If the change in modulus with indenter depth is shown to correlate with the recruitment of various skin layers, this information could be useful in specifying a velocity profile for delivering a drug to a specific depth in the skin for site-specific action.

This chapter presents a unique study of the effects of preconditioning modes on incremental system identification. The “incremental law” of skin was presented over 30 years ago (Fung, 1981), but has received relatively little attention since then. Under quasi-static loading, the stress-strain behavior of skin has been shown to vary with the scale of the perturbation, whereby the skin exhibits different stiffness at localised perturbations when compared to large-scale perturbations. This study is unique in that it demonstrates that the effect holds under dynamic loading, in both indentation and extension experiments, and in hairy and glabrous skin.
The selection of a triangular wave or average incremental force preconditioning regime made no clear difference to the estimation of skin parameters. What is more important is providing sufficient preconditioning throughout the entire test range. The results suggest that large-scale perturbations that are designed to precondition skin do not adequately condition the skin at the smaller scale, so incremental measures must be made with their own tailored preconditioning scheme. Although incremental measures use linear system identification to provide simpler mathematical means of characterising the nonlinear response of skin, they come at the cost of lengthy experiments, and the results are more difficult to compare across subjects.

The microrobot and associated analytical techniques provide a unique system to mechanically analyse the nonlinear, anisotropic, viscoelastic, and heterogeneous properties of skin. It is the first device to employ stochastic system identification approaches in multiple directions without the need to reconfigure or reposition the probe relative to the skin. The results demonstrate the microrobot’s ability to measure skin properties in an efficient and reliable manner. The linear parameter values that were measured for skin lie within the ranges reported previously using a variety of techniques, and the Wiener parameters are comparable to those presented in previous studies using stochastic system identification. The versatility, reliability, and speed with which the microrobot device can quantify the properties of skin underscore its potential usefulness in clinical research.

## 8.3 Developing a Mechanical Characterisation Framework

Chapter 6 introduced an experimental and modelling framework, for characterising the mechanical behaviour of soft materials. This framework was presented with reference to soft material phantoms, and was used to validate the experimental and modelling approach. This goal was achieved by:

- designing and performing controlled experiments on well-understood soft phantoms; and
- modelling the mechanical behaviour using constitutive relationships that describe the deformations of multi-layered composites

A set of indentation experiments was performed on soft material phantoms, including a homogeneous silicone gel, and a heterogeneous, layered silicone gel-elastomer composite. A four-camera stereoscope was used to capture the surface geometry, and track the surface deformation throughout the indentation experiment. Finite element models were implemented in CMISS/OpenCMISS to predict the deformations resulting from the input
forces. Neo-Hookean constitutive relations were selected for each material, and an objective function was constructed to minimise the differences between model predictions of surface deformations and the stereoscopic measurements.

The neo-Hookean stiffness parameter that was identified for the single layer gel matched closely with existing experiments, which have used different deformation modes to characterise the material. Experiments on the two-layered phantom provided a validation of the modelling framework, for heterogeneous materials. The parameters that were identified from the composite phantom were compared to those identified by isolated identification approaches. The results showed that the FE model based on optimal material parameters could predict surface deformations with an RMSE of 111 µm, while independently-identified material properties could predict surface deformations with an RMSE of 138 µm. These findings demonstrate that a composite model can accurately predict the behaviour of a thin “skin” layer, tightly coupled to a thick “bulk” underlying layer.

Creating an objective function from the stereoscopic measurements provides a rich data set, which may help to constrain the parameters of a given model when compared to previous data sets that describe the force of position of a single material point on the surface. Using a wider variety of surface displacement measurements may lead to improved characterisation of the 3D behaviour of skin. Richer data sets generated by the combination of stereo vision and indentometry provide more rigorous tests for determining model parameters.

### 8.4 Application to Skin Mechanics

Chapter 7 presented a modelling workflow to reproduce nonlinear, anisotropic, viscoelastic and heterogeneous stress-strain behaviour of skin. The aims were to:

- design and perform experiments to capture the anisotropic, nonlinear, and viscoelastic behaviour of in vivo skin; and
- model the mechanical behaviour of skin using structural and/or phenomenological constitutive relationships, which describe the deformation seen through the layers of skin

A set of in-plane and out-of-plane perturbation experiments were performed to measure these properties of skin, using instrumentation developed in this thesis. The updated microrobot was used to perturb the skin, while the four camera stereoscope measured 3D surface deformations.

A layered, 3D, quadratic Lagrange, finite element mesh was used to model the experimental geometry, and was subjected to force boundary conditions, as measured by the microrobot.
Gasser-Ogden-Holzapfel constitutive model was used to calculate the deformation resulting from the boundary loads. A stereoscopically-tracked 3D surface point cloud was embedded in the finite element mesh, and the deformed 3D coordinates of each surface point were evaluated at a number of time steps.

A displacement-weighted mean-square error objective function was constructed, to quantify the difference between the stereoscopically-measured surface points and their finite element model predictions. The finite element model was able to recreate the nonlinear, anisotropic, viscoelastic, and heterogeneous behaviour with an RMSE of 211 \( \mu m \). Use of the stereoscopic data enabled improved identifiability over traditional single-point displacement measurement approaches, as indicated by Hessian identifiability metrics. Each parameter of a single-fiber-family Holzapfel constitutive model was found to be important, using the Akaike Information Criteria, although the model was insufficient to capture the mechanical behaviour of skin over the full force-displacement curve. The model may be improved by adding anisotropic pre-stress, and/or using a different constitutive equation.

8.5 Future Work

8.5.1 Improving the Experimental Apparatus

Additional changes are required to impose greater deformations and gather more information. These include:

- upgrading the motor arms of the microrobot to perform larger transverse movements (described in Section 4.3);
- adding multiple robots to induce more complex deformation modes (described in Section 7.8);
- improving the coverage of the stereoscope through additional cameras (described in Section 5.2); and
- improving the surface profiling algorithm using a model based approach (described in Section 5.4);

Additional information may be gathered through volumetric imaging modalities, such as OCT, MRI or ultrasound. By implementing some of these imaging techniques, it would be possible to provide an accurate description of the geometry, and the relative movement of important layers of skin, as well as the attachment to underlying structures. This would reduce the number of parameters to be optimised in finite element models. However, it
remains to be seen if surface deformation measures can provide sufficient information of properties that relate to sub-dermal layer sliding.

8.5.2 Improving the Skin Models

Additional features to the modelling approach may reduce the discrepancy between the model and experimental data. These features were discussed in section 7.8, and include:

- modelling anisotropic pre-stress;
- measuring and modelling the unloaded skin geometry, before strapping in to the experimental rig;
- measuring and modelling the force exerted on the skin by the support plate and straps;
- modelling the through-thickness geometry of the skin layers, measured through ultrasound, OCT, or MRI;
- modelling the epidermis, dermis, and hypodermis as separate layers;
- investigating inter-layer slippage;
- investigating model-based planning of experiments in order to improve parameter identifiability; and
- investigating more appropriate constitutive models.

8.5.3 Clinical Translation

The research presented in this thesis was concerned with prototyping methods to characterise skin mechanics. Validation of the experimental and modelling workflows, using healthy volunteers, demonstrated the abilities of both lumped parameter and finite element approaches to characterise the nonlinear, viscoelastic, heterogeneous, and anisotropic behaviour of skin. The techniques presented in this thesis should be extended to a larger number of subjects, allowing statistically meaningful conclusions to be drawn.

A number of practical challenges must be addressed before the characterisation workflow is assessed in the clinical setting. The user interface for data acquisition and control of the instrumentation was designed to be relatively user-friendly. However, post-processing of the data has not received the same consideration. In its current state, processing of the stereoscopic data is manually demanding, which is unlikely to be acceptable to clinicians. A robust hardware configuration is required whereby an occasional stereoscope calibration can be relied on for extended periods.

Also essential for clinical acceptance is the presentation of easily-interpreted and readily-visualised results. Modelling results should be displayed through a user-friendly interface,
with careful consideration of which parameters are clinically relevant, and how to communicate three-dimensional geometric results in an interactive environment. By creating readily visualised and interpreted results, mechanical models of soft tissues may be used to predict surgical outcomes, identify lesions, assess the efficacy of treatments, and optimise patient-specific treatment strategies.

8.6 Publications

The novel contributions of this thesis are summarised in Section 1.3. The publications that arose from this research are listed below:


Chapter 8 Conclusions and Future Work


APPENDICES

A Calibration

Figure 23. Checkerboard Pattern used in calibration. 1 square was printed at 3 mm, 1200 dpi
Control Point Selection GUI

B 1. Control Point Selection GUI, showing images of skin


Kirk, E. and Kvorning, S. a (1949) ‘Quantitative measurements of the elastic properties of the skin


