

**A NOVEL STRAIN-BASED
FRACTURE-HEALING ALGORITHM
FOR IN SILICO TRIALS –
APPLICATION TO FEMORAL
FRACTURE TREATMENT**

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degree of:**

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“The discovery of a good wine is increasingly better for mankind than the discovery of a new star.”

- Leonardo da Vinci (maybe)

Materials

- 3 kg frozen fruit of your choice
- 1 kg sugar
- 3 litres water
- 1 tsp yeast (KV-1116 or EC-1118)
- 1 tsp bread yeast
- 1 lemon
- 1 tbsp pectolase
- 1 Campden tablet
- 1 mesh bag
- 1 fermentation vessel (10 litre bucket)
- 1 aging vessel (demijohn)

Methods

- Mix fruit and sugar and leave to thaw and macerate
- Add to mesh bag in fermentation vessel, add water, add pectolase, wait 12 hrs
- Add crushed Campden tablet, wait 12 hrs
- Boil bread yeast for 5 minutes, then add to mesh bag, along with sugar, lemon juice, and yeast, and wait 10 days, submerging fruit once daily
- Remove mesh bag, wait until sediment settles, approx. 7-10 days
- Transfer to aging vessel, wait until wine clarifies, minimum 2-3 months

Result

- Approx. 6 bottles (4.5 litres total) of country wine, 14% ABV

ABSTRACT

Poor healing outcomes of bone fractures can result in revision surgeries, permanent mobility loss, or death. As research into optimal fracture treatments has progressed, rates of poor outcomes have decreased for many fracture types. Other fracture types continue to have high rates of morbidity and mortality, however, as traditional research methods have failed to identify optimal treatments. The aim of this work was to create a computational tool which is capable of predicting the fracture-healing sequence in response to the mechanical environment of a simple fracture.

A novel fracture-healing algorithm was developed which used minimum and maximum principal strains as its mechanical inputs. The limitations of previously published fracture-healing algorithms were addressed. The novel algorithm was validated against published experimental data of ovine fractures and was demonstrated to be independent of the initially-specified callus domain size. A sensitivity analysis of the algorithm demonstrated its robustness to its input parameters.

The algorithm was used to compare the effect of different rehabilitation-regimes on fracture healing in a model of a large-gap fracture stabilised with a fixed free-movement distance type fixator. This analysis indicated that a constant high stability rehabilitation-regime produces the shortest healing times for the tested fracture and fixator types. The algorithm was also expanded from an axisymmetric to a 3-D implementation in order to model a mid-shaft fracture of a realistic femur. Intramedullary nailing and lateral locking plate fixation were modelled and the fracture-healing algorithm accurately predicted the differences in callus development caused by the two fixation treatments.

The novel algorithm presented within this thesis allows for the *in silico* investigation of fracture-healing treatments and rehabilitation-regimes through its implementation in *in silico* trials.

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CHAPTER 1

INTRODUCTION

1.1 Scope of the chapter

This chapter introduces the clinical problem of fracture non-unions and reviews the challenges in researching solutions. A computational method is identified as a potential solution to address research gaps. The aims and objectives of this thesis are listed, and the thesis structure and chapter summaries are described.

1.2 Introduction

Bone fractures have historically been associated with significant morbidity and mortality rates. Minor fractures were treated conservatively with splints or plasters with some success, but severe fractures, including open fractures, were only treated with amputation of the effected limb and almost always led to death (Kakria, 2005). The use of surgical treatment options was limited by lack of anaesthetic and risk of infection (Bartoníček, 2010). Internal fixation was first detailed in the late 18th century, but screw and plate fixations were not widely performed until the late 19th century (Kakria, 2005). Development of novel fracture-fixation devices and techniques was advanced by the formation of the AO foundation, a group of orthopaedic surgeons and scientists, in 1958. Fixation devices eventually shifted their focus from purely mechanical stabilisation to a biological emphasis. This shift was led by the development of limited contact compression plates, which prevent disruption to underlying biological processes to promote healing (Perren, 1991). Further advancements in fracture treatment, which continue in the present, have reduced morbidity and mortality rates and have improved surgical outcomes.

Poor healing outcomes, however, persist for some fracture types and injury mechanisms. In particular, high-energy injury mechanisms, such as those seen in conflict, have led to fractures with a consistently high and unimproved rate of poor healing outcomes over the past century (Stewart *et al.*, 2020). Some fracture types, such as hip fractures, have had historically high morbidity and mortality rates, but research into treatments have been successful in improving outcomes (Smith *et al.*, 2015). Other fracture types, such as distal femoral fractures, have similarly high rates of morbidity and mortality and have received similar levels of research attention.

However, little progress has been made in their treatment because, despite high rates of poor healing outcomes (Smith *et al.*, 2015; Toro, 2015), these fractures are relatively uncommon. Therefore traditional research methods, such as large-scale randomised control trials (RCT's), fail to draw clinically relevant conclusions (Griffin *et al.*, 2019).

In silico trials have previously been used to successfully answer clinical questions using computational methods (Sarrami-Foroushani *et al.*, 2021). They allow for the modelling of broad virtual populations, including uncommon geometries and pathologies, as well as edge-case medical device configurations, which would be dangerous and immoral to test *in vivo*, but would provide valuable safety information. The greatest barrier to *in silico* trials is building sufficient model credibility through validation and uncertainty quantification such that the results of the trial are trustworthy ('Assessing credibility of computational modeling through verification and validation: application to medical devices: ASME V&V 40 - 2018', 2018).

The vision for this PhD is to develop and validate a computational tool which is capable of simulating a physiological sequence of fracture healing. This tool should be tested of its capability of comparing fracture treatments in order to demonstrate its suitability for application to a large-scale *in silico* trial. Such a tool could then be used to address clinical questions which have been left unanswered by traditional clinical trials, including rehabilitation-regime optimisation, fracture-fixator choice and configuration, and testing of novel fixation devices.

1.3 Aims

The aim of this PhD is to develop a computational tool which is capable of predicting the fracture-healing sequence in response to the mechanical environment of a simple fracture. The objectives of this PhD are:

- Review the epidemiology of fracture non-union and the available treatment types.
- Review existing fracture-healing algorithms and identify the key limitations preventing their further adoption.
- Develop a novel fracture-healing algorithm which overcomes the limitations of previous healing algorithms.
- Test the novel healing algorithm for validation against experimental data.
- Apply the novel healing algorithm to various fracture rehabilitation-regimes to identify the most effective regimes and demonstrate the use of the algorithm in rehabilitation-regime management.
- Apply the novel healing algorithm to compare different fixator types to demonstrate the potential for application of the algorithm to *in silico* trials of fractures to identify optimal treatments.

1.4 Thesis structure

Chapter 1 has introduced fracture non-unions and the challenges in the research of their prevention.

Chapter 2 reviews the anatomical and physiological background of fracture healing and non-union. Fracture types and currently available surgical treatment options and techniques are identified.

Chapter 3 reviews fracture-healing algorithms in literature and identifies the common features and parameters. Successful features and parameters are identified, as well as key limitations and errors in existing healing algorithms which have prevented their wider application.

Chapter 4 introduces a novel fracture-healing algorithm which uses minimum and maximum principal strains as its primary strain inputs. The novel algorithm is shown to overcome the limitations of previous healing algorithms. The algorithm is calibrated and then successfully tested for validation against experimental data. Mesh convergence and initial callus-domain independence of the healing algorithm are demonstrated.

Chapter 5 investigates the sensitivity of the novel healing algorithm to its parameter inputs to identify the robustness of the algorithm to these inputs. An over-sensitivity to key input parameters whose values are not reliably known was a key limitation of previous healing algorithms.

Chapter 6 applies the healing algorithm to an experimental fracture model with the largest fracture gap width, which was associated with the worst healing outcomes. A study on rehabilitation-regimes was performed by modifying the applied force magnitude and fixator stiffness, and regimes including dynamisation and inverse-dynamisation were investigated.

Chapter 7 expands the previously axisymmetric development and application of the fracture-healing algorithm to a 3-D model of a mid-shaft femoral fracture. Two

fixation models are simulated: one of an intramedullary nail, and one of a lateral locking plate, and the ability of the algorithm to capture the differences in callus development in the fracture models using the two fixators is investigated.

Chapter 8 summarises and discusses the key findings of this thesis and provides recommendations for future steps for effective application of the algorithm to an *in silico* trial for the treatment of distal femoral fractures.

CHAPTER 2

BACKGROUND OF FRACTURE HEALING AND CLINICAL TREATMENT

2.1 Scope

Fracture healing is a complex process which is strongly dependent on the mechanical environment in the fracture region. Failure of a fracture to heal properly is shown to be associated with significant morbidity and mortality. Advancements in treatment options and clinical decision making are reviewed, and significant remaining challenges are identified. This chapter presents the anatomy of long bones, epidemiology of long bone fractures, pathways of fracture healing, fracture treatment options, failed fracture healing, and clinical decision making. It concludes with describing the difficulties that remain in treatment.

2.2 Lower-limb skeletal anatomy

The lower limb experiences significant loads as a weight bearing structure, physiologically predominantly in the axial direction during standing or gait. This load-bearing requirement means that fractures in the lower-limb must heal thoroughly and structurally securely in order to resume normal physiological function post-healing. The largest bones comprising the lower-limb are the femur, tibia, and fibula (Figure 2.1). The femur joins the lower-limb to the body at the pelvis via a ball and socket joint, known as the hip joint. On the distal side, the femur joins to the tibia via a hinge-type joint, known as the knee joint, and to the fibula via a ligament. The knee joint acts primarily as a hinge joint, by flexing and extending, but also allows for a small degree of rotation during the so-called “screw home mechanism” in which the tibia externally rotates during final degrees of knee extension. This physiological screw home mechanism has been shown to play an important role in the healthy physiology of the knee joint, and is a barrier to implant longevity and patient satisfaction in total knee arthroplasty devices which fail to capture this behaviour (Collins *et al.*, 2015).

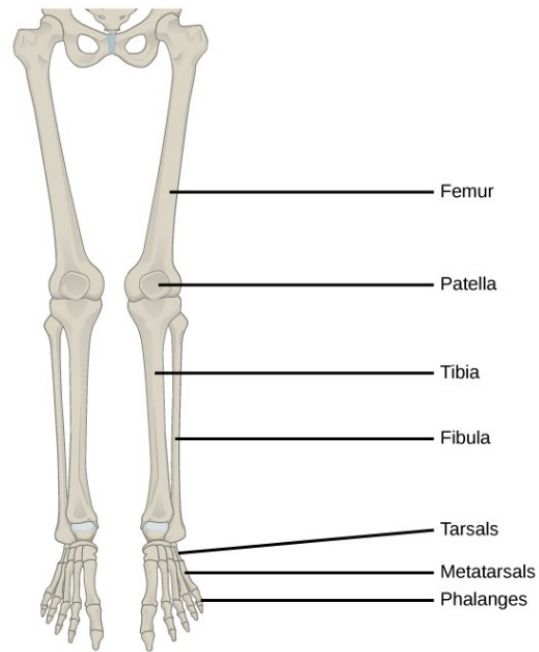


Figure 2.1: Skeletal anatomy of the human lower limb (Rye *et al.*, 2016). This image was reproduced from Wikimedia Commons and is licensed under the Creative Commons Attribution 4.0 International license.

2.3 Long bone morphology

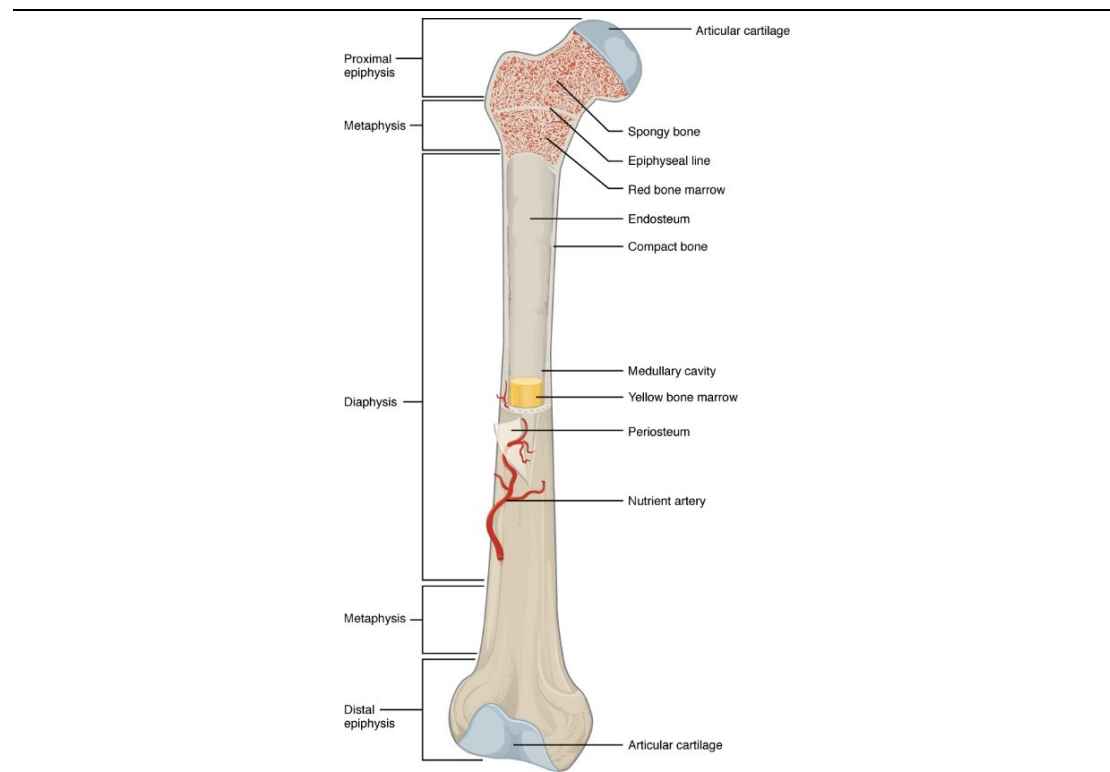


Figure 2.2: Sections of long bone, including epiphysis, diaphysis, and metaphysis (Betts *et al.*, 2017). This image was reproduced from Wikimedia Commons and is licensed under the Creative Commons Attribution 4.0 International license.

Long bones are made up of three sections: the epiphysis at the joints, the diaphysis at the long shaft section, and the metaphysis as a transition region between the epiphysis and diaphysis (Figure 2.2). There are two main types of bone tissue found in long bones: cancellous bone and cortical bone. Cancellous bone is made up of trabeculae, a highly porous honeycomb structure consisting of approximately 20% bone mass (Stewart, 2021). The orientation of the trabeculae create anisotropic material properties which allow for the optimisation of bone strength per bone mass (Parkinson and Fazzalari, 2013). Cancellous bone is therefore located in regions of high stress at the metaphysis and epiphysis (Little, Rogers and Flannery, 2011; Biggam-Sadegh and Oryan, 2015). Cortical bone is a dense bone type, with a porosity less than 5% (Clarke, 2008). It is found in the diaphysis, and surrounds the cancellous bone of long bones. Cortical bone is made up of cylindrical osteons, with innervation and blood perfusion provided by Haversian and Volkmann's canals, as shown in Figure 2.3.

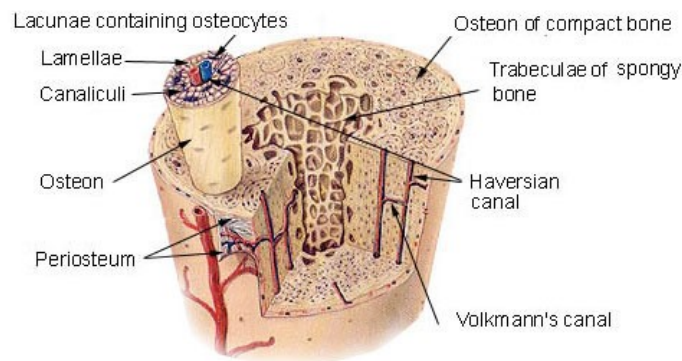
Compact Bone & Spongy (Cancellous Bone)

Figure 2.3: Make-up of cortical and cancellous, or trabecular, bone, showing osteons and perfusion with Haversian canals and Volkmann's canals (*Structure of Bone Tissue*, no date). This image is in the public domain and was reproduced from Wikimedia Commons.

Bone cells consist primarily of three types of cells: osteoblasts, osteocytes, and osteoclasts. Osteoblasts are differentiated mesenchymal stem cells (MSC's) and are responsible for forming bone. Osteocytes are the most common bone cell type and are derived from mature osteoblasts. They lie within the osteons and act as mechano-transducers for the surrounding bone matrix. Osteoclasts are responsible for bone resorption during bone remodelling and during the initial stages of fracture healing.

2.4 Fracture epidemiology

The global fracture incidence rate is estimated to be between 20.91 – 25.30 per thousand population per year (Wu *et al.*, 2021), while the UK rate is estimated at approximately 11.16 per thousand population per year (Court-Brown and Caesar, 2006). Fracture age distribution is weighted higher towards the elderly population due to fractures attributable to osteoporosis and osteopenia, which are conditions that affect bone quality and are found in elderly patients (Kannus *et al.*, 2001; Court-Brown and Caesar, 2006). A large increase in the incidence of osteopenic and osteoporotic fractures has begun and is anticipated in coming decades due to a rapidly aging population (Kannus *et al.*, 2001; Court-Brown and Caesar, 2006), and the current lifetime risk of an osteoporotic fracture is 40 – 50% in women and 13 – 22% in men (Johnell and Kanis, 2005; Court-Brown and Caesar, 2006). The overall age and gender distributions of fractures is shown in Figure 2.4. Along with the rising rate of osteoporotic fractures, the types of osteoporotic fractures encountered clinically are

changing. Typical osteoporotic fractures were considered to occur in the distal radius, proximal femur, and proximal humerus, but an increasing incidence of lower-limb osteoporotic fractures have been reported in the pelvis and knee, most apparently in the distal femur (Kannus *et al.*, 2001; Court-Brown and Caesar, 2006).

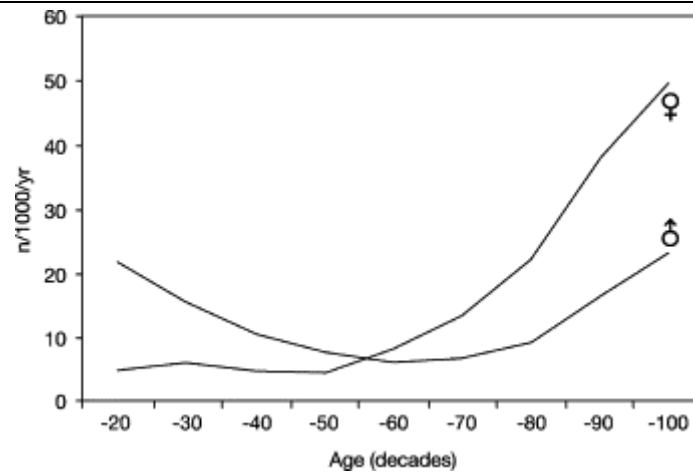


Figure 2.4: Overall fracture epidemiology age and gender distribution curves (Court-Brown and Caesar, 2006). Image reproduced with permission of the rights holder, Elsevier.

2.5 Long bone fracture classification

Fracture classifications consist of alpha-numeric codes which are used to group fractures into different types, categorised by location, severity, and likely mechanism of injury (Rüedi and Murphy, 2000). A standardised fracture classification system facilitates the accumulation and analysis of large fracture datasets, and therefore can be used to inform clinical fracture assessment and treatment options. The AO Foundation’s “Comprehensive classification of fractures of long bones” (Müller, 1990) has fulfilled this role of a standardised fracture classification system and has a citation frequency of over 2000 citations per year (Joeris *et al.*, 2019).

Localisation		Morphology	
Bone	Segment	Type	Group
1/2/3/4	1/2/3/4	A/B/C	1/2/3

Table 2.1: Classification code breakdown: Localisation and Morphology – Bone, Segment / Type, Group, Subgroup.

The AO long bone fracture classification consists of a two-digit numeric code to describe the fracture localisation, followed by a two character alphanumeric code to describe the fracture morphology (Table 2.1). The first localisation digit refers to the bone group of the fracture: 1, 2, 3, or 4 representing the humerus, radius/ulna, femur, and tibia/fibula, respectively. The second localisation digit refers to the segment of the bone group: 1, 2, or 3 representing proximal, diaphyseal, and distal, respectively, and 4 representing malleolar – only used for tibial/fibular fractures (Table 2.2). The significance of the type character, either A, B, or C, depends on the segment: if the segment is either proximal or distal, A, B, and C represent extra-articular, partial articular, and complete articular, respectively; if the segment is diaphyseal, A, B, and C represent simple, wedge, and complex fractures, respectively (Figure 2.5). The group is a digit, either 1, 2, or 3, which describes the likely mechanism of injury, such as bending or torsion, and varies for different fracture types (Müller, 1990).

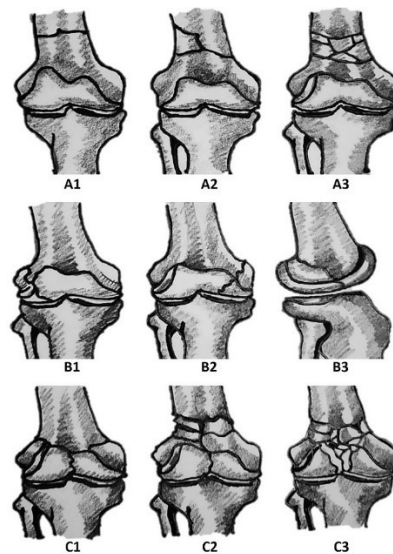


Figure 2.5: AO fracture morphology coding for distal femoral fractures (Jain *et al.*, 2023). ‘A’ represents extra-articular fracture, ‘B’ represents partial articular involvement, and ‘C’ represents full articular involvement. ‘1’ represents a simple fracture, ‘2’ represents a moderately complex fracture, and ‘3’ represents a comminuted fracture. Image reproduced with permission of the rights holder, Springer Nature Singapore.

Location	Humerus	Radius/Ulna	Femur	Tibia/Fibula
Proximal	11	21	31	41
Diaphyseal	12	22	32	42
Distal	13	23	33	43
Malleolar	-	-	-	44

Table 2.2: Numeric fracture localisation coding where the first digit represents the long bone and the second digit represents the section of the long bone.

2.6 Fracture healing

Bone fracture healing occurs as either primary (direct) healing, or secondary (indirect) healing. Primary healing consists of similar biological processes as bone remodelling (ElHawary *et al.*, 2021); osteoclasts create cavities on either side of the fracture line, which are then filled in by osteoblasts, forming osteons which bridge the fracture line, and the fracture is healed without the formation of a periosteal callus (Rüedi and Murphy, 2000; ElHawary *et al.*, 2021). Primary healing requires absolute stability of the fracture, with an interfragmentary gap of less than 0.01 mm and an interfragmentary strain (IFS) of less than 2% (Perren, 1978, 2002; Marsell and Einhorn, 2011). These biomechanical fracture conditions do not occur in untreated fractures, therefore primary healing can usually only be achieved by surgical fixation (Marsell and Einhorn, 2011).

Secondary healing consists of three main phases: inflammation, repair, and remodelling (Figure 2.6) (Claes, Recknagel and Ignatius, 2012). During the inflammatory phase, the damage to the vasculature and soft tissue surrounding the fracture leads to the formation of a fracture haematoma (Claes, Recknagel and Ignatius, 2012) – a soft fibrin scaffold populated with inflammatory cells and signalling factors resulting from blood clotting (Claes, Recknagel and Ignatius, 2012; Wang *et al.*, 2016). During the repair phase, a callus is formed using the fracture haematoma as a scaffold upon which to build bone (Claes, Recknagel and Ignatius, 2012). This phase involves many biological processes, but mainly consists of three processes: intramembranous ossification, chondrogenesis, and endochondral ossification (Figure 2.7) (Dimitriou, Tsiridis and Giannoudis, 2005; Claes, Recknagel and Ignatius, 2012). Intramembranous ossification occurs in the initial stages of the

repair phase (Claes, Recknagel and Ignatius, 2012). Bone is directly formed on the periosteal and endosteal sides of the cortex to create a protrusion which is referred to as the ‘hard callus’ (Marsell and Einhorn, 2011). Chondrogenesis is the process by which chondrocytes form cartilage between the proximal and distal ‘hard callus’ protrusions (Claes, Recknagel and Ignatius, 2012). This cartilage is referred to as the ‘soft callus’ (Marsell and Einhorn, 2011), and forms the initial bridging of the fracture gap and occurs periosteally to the interfragmentary gap (Epari *et al.*, 2006; Vetter *et al.*, 2010). Endochondral ossification is the processes where the gap-bridging cartilage is calcified and replaced by woven bone, stabilising the fracture (Dimitriou, Tsiridis and Giannoudis, 2005). During the remodelling phase, woven bone is remodelled into stronger lamellar bone and the callus is resorbed as its additional stability is no longer required, restoring the phenological bone shape (Vetter *et al.*, 2010; Claes, Recknagel and Ignatius, 2012).

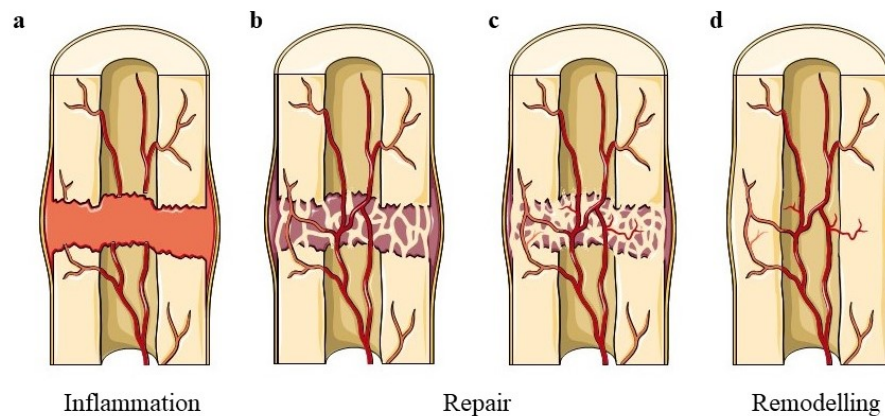


Figure 2.6: The stages of secondary fracture healing, classified into three phases: inflammation, repair, and remodelling; or classified into four sub-phases: (a) haematoma formation, (b) soft cartilage formation, (c) hard callus formation, (d) lamellar remodelling (<https://smart.servier.com>, no date). This figure was reproduced from Wikimedia Commons and was modified from the original image, which is licensed under a Creative Commons Attribution 3.0 Unported License, by adding text labels.

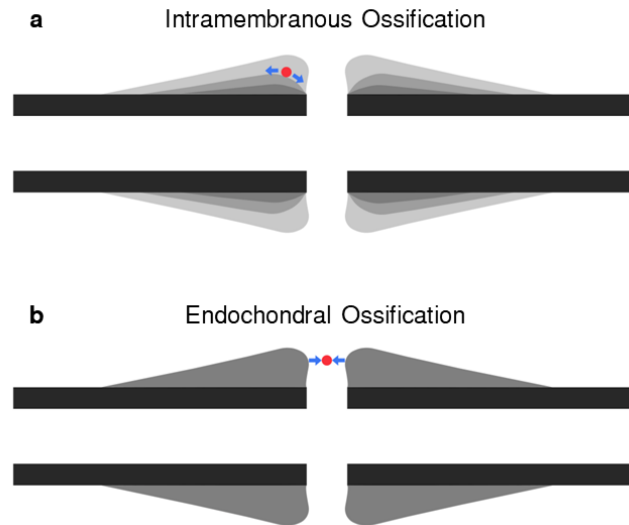


Figure 2.7: Diagram of (a) intramembranous ossification and (b) endochondral ossification pathways. In each panel, a representative ‘cell’ laying on the ossification pathway is shown in red. Intramembranous ossification begins periosteally and adjacent to the fracture site, while endochondral ossification begins in the fracture line, between the two periosteal ‘bulges’ formed by intramembranous ossification.

The surgical aim when primary healing is desired is simple: the fracture should be made as stable as possible with as small of a fracture gap as possible. This is achieved via full reduction of the fracture gap and rigid fixation, commonly using compression plates or lag screws to compress the two fragments together in order to prevent IFS (Rüedi and Murphy, 2000; Claes, Recknagel and Ignatius, 2012). Secondary fracture healing is aimed for in cases where anatomical reduction of fracture fragments or rigid fixation are not feasible. Moderate levels of movement at the fracture site are generally beneficial to secondary fracture healing, while excessive movement or overly rigid fixation inhibit healing (Marsell and Einhorn, 2011; Glatt, Evans and Tetsworth, 2017). An initial IFS of 2-10% is most commonly thought to be the ideal mechanical environment for secondary fracture healing (Perren, 2002; Elliott *et al.*, 2016). The greater number of parameters in the fixation of these fractures, including fracture gap size, fixation stability, and fixator type and configuration, means there are more unanswered questions in the treatment of fractures for secondary fracture healing. Therefore, this thesis focuses on secondary healing.

2.7 Treatment options

2.7.1 Principals of fracture treatment

The main principals of fracture treatment are:

- Anatomical reduction of articular surfaces, which is the reduction of any fracture gaps to ensure congruency of fracture surfaces on each fracture fragment and restoration of the undamaged surface geometry, generally leading to primary fracture healing.
- Restoration of the mechanical and anatomical axes of the fractured bone, which run through the centres of the two joints and the centre of the shaft, respectively, in order to facilitate joint load transmission and to prevent accelerated joint degeneration (Figure 2.8) (Davis and Moskowitz, 1973; McDevitt, Gilbertson and Muir, 1977). In the lower-limb, the mechanical axes of the femur and tibia are naturally at an angle in the coronal plane, and this physiological angle should be preserved (Yazdi *et al.*, 2018).
- Promotion of early mobilisation, especially for lower-limb fractures, to prevent non-union. Some amount of fixator compliance in the axial direction is desirable to promote mobilisation, but shear and torsional compliance should be minimised.

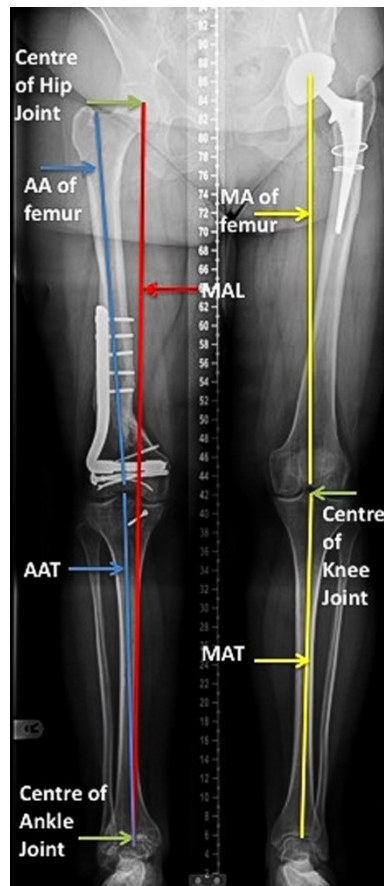


Figure 2.8: A lower-limb medical radiograph with various surgical fixations, demonstrating the restoration of the mechanical and anatomical axes of the fractured femur, designated ‘MA’ and ‘AA’, respectively, in the figure (Najefi, Malhotra and Goldberg, 2020). Image reproduced with permission of the rights holder, Churchill Livingstone.

2.7.2 Operative versus non-operative treatments

Fracture treatments can be broadly categorised into either non-operative treatments such as bracing and casting, or operative treatments such as internal or external surgical fixation. Non-operative treatments can be used for certain types of fracture such as for minimally displaced tibial fractures, but surgical fixation is strongly recommended for other types such as femoral shaft fractures (Rüedi and Murphy, 2000). Very generally, however, operative treatment leads to superior healing outcomes than non-operative treatment (Wallny *et al.*, 1998; Olson, Entezari and Vallier, 2020). Operative treatments are generally stiffer than non-operative treatments, specifically in shear and torsion. This high shear and torsional stiffness, combined with the predominantly axial loading of the lower-limb, means that operatively-treated lower-limb fractures experience mainly axial movement.

2.7.3 Shaft versus articular fracture treatment strategies

The choice of surgical fixation method depends on fracture location and classification, but lower-limb fractures can be broadly described as either diaphyseal, where the fracture is mainly on the shaft or metaphyseal bone, or articular, if the fracture has joint involvement. Diaphyseal fracture fixations generally aim for some amount of allowable movement in the fracture site, such as with intramedullary nails, in order to promote callus formation and bone union (Müller, 1990; Rüedi and Murphy, 2000). For fractures extending into the metaphyseal area, a combination of plates and screws are generally used as intramedullary nails are less equipped to stably attach to the smaller articular fragment (Rüedi and Murphy, 2000). For fractures with articular involvement, anatomical reduction is necessary to avoid incongruencies in the joint surfaces, which cause joint stiffness and pain, and therefore lag screws and compression plating are necessary treatments (Rüedi and Murphy, 2000).

2.7.4 Screws

Screws are commonly used in fracture fixations, either by themselves, or paired with other fixation devices. The threads of bone screws are matched to the type of bone in which they are used: cancellous bone screws have wider threads and pitches in order to better engage with metaphyseal and epiphyseal bone, while cortical bone screws have shallower threads and pitches for use in the dense cortices of diaphyseal bone (Rüedi and Murphy, 2000).

A lag screw is a screw which compressed two fracture fragments together as a result of its design: it consists of a threaded section to engage with the ‘distal’ fragment, an unthreaded section in the ‘proximal’ fragment which does not engage with the bone, and a screw head. As the screw mechanism is engaged, the screw threads actuate the ‘distal’ fragment towards the screw head and ‘proximal’ fragment. Since lag screws compress fracture fragments together, they are often used to target primary fracture healing, especially in articular fractures, and sometimes a single lag screw acting perpendicular to the fracture line is sufficient fixation for simple fractures (Koval *et al.*, 1996; Rüedi and Murphy, 2000), however, usually at least two

lag screws are required to stabilise the fracture in order to resist rotations about the axis of a lone screw (Rüedi and Murphy, 2000). A major drawback of lag screws is their lack of resilience to over-loading; since the screw threads are compressively engaged with the surrounding bone, over-loading can cause loosening, reducing the stability of the fixation (Rüedi and Murphy, 2000).

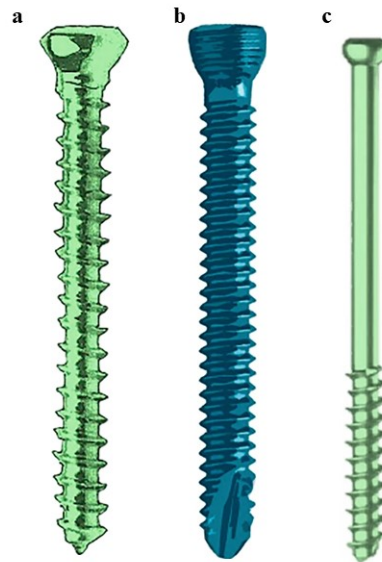


Figure 2.9: Examples of different types of screws used in fracture fixation (a) compression screw, (b) locking screw, (c) lag screw (Iyer and Samundeeswari, 2023). Images reproduced with permission of the rights holder, Springer Nature Singapore.

A conventional, or compression, screw has a typical screw design with a screw head and a fully threaded shaft. These screws are used to securely compress a fixation plate to a bone fragment and the design of some fixation plates compresses two bone fragments together as the compression screws are tightened. A downside of compression screws is the compression of the fixation plate to the bone fragment which can disrupt the biological fracture healing processes by damaging the periosteum of the bone (Rüedi and Murphy, 2000). In contrast, locking screws maintain a gap between the fixation plate and bone fragments. This is achieved by a threaded screw head which ‘locks’ into the fixation plate. Locking screws also give additional angular stability and apply less force to the screw shaft threads, which decreases their failure rate relative to conventional compression screws (Banovetz *et al.*, 1996; Rüedi and Murphy, 2000; Haas *et al.*, 2001). A compression screw, a locking screw, and a lag screw are shown in Figure 2.9.

2.7.5 Plates

Fixation plates have three fundamental functions: compression, neutralisation, and bridging. Compression plating, termed ‘dynamic compression plating’, compresses together two fracture fragments by utilising a screw head ‘gliding’ mechanism in opposing directions on either side of a fracture line (Figure 2.10a). As a conventional screw is inserted into a screw hole on a compression plate, it compresses the fixation plate to the fracture fragment, then after securing to the fracture fragment, the screw head is translated along the plate by the ‘gliding’ mechanism, moving the fragment relative to the plate. This compression between fracture fragments promotes anatomical reduction and primary fracture healing, but the contact between the plate and the periosteum can impair some of the biological processes involved in fracture repair (Rüedi and Murphy, 2000). Improved plates minimise the contact surface of the plate with the bone to reduce this impairment; these plates are termed ‘limited contact dynamic compression plates’.

Fixation plates can also be used to provide support to another fixation such as a lag screw (Figure 2.10c). This is achieved by ‘neutralising’ forces which the lag screw is poorly suited to resist, such as bending and torsion (*Plating: basic technique*, no date).

Bridge plating is typically used to stabilise comminuted fractures by spanning the fracture gap and promoting callus formation and secondary fracture healing. The amount of permitted motion in the fracture gap is controllable by varying parameters such as screw configuration (which holes in the plate have screws placed in them), screw type (conventional or locking), plate working length (the distance between the first screws on either side of the fracture gap), and plate material (generally titanium or steel) (Figure 2.10b). Bridge plating combined with locking screws is especially useful in treating fractures in osteoporotic bone as the use of locking screws reduces the risk of screw pull-out since the screw threads do not exert as much force on the surrounding bone, and the periosteum is (*Plating: basic technique*, no date).

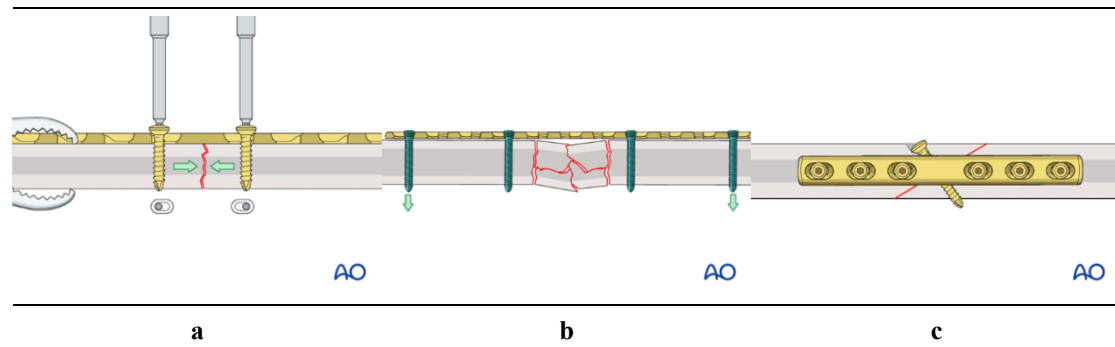


Figure 2.10: Illustrations of the three main functions of fixation plates: (a) compression plating, (b) bridge plating, (c) neutralisation plating (*Plating: basic technique*, no date). Images reproduced with permission. Copyright by AO Foundation, Switzerland.

2.7.6 Nails

Intramedullary nail fracture fixation is the standard treatment for simple diaphyseal fractures (Rüedi and Murphy, 2000). This surgical technique involves the insertion of a metal rod into the medullary canal of a fractured bone, aligning the bone fragments and stabilising the fracture. Prior to inserting the intramedullary nail, the medullary canal can either be reamed, or left un-reamed. Reaming is the removal of the contents and widening of the medullary canal, which allows for a thicker diameter intramedullary nail, and therefore a more rigid fixation. The nail is secured to the bone fragments distally and proximally using pins and screws (Figure 2.11). After nailing, a small amount of movement still occurs in the fracture gap due to the fit of pins in the nail (Dailey *et al.*, 2013; Ren and Dailey, 2020a). As the fracture site moves further from the mid-shaft towards the joints, the susceptibility of the fracture to instability due to the greater variability of loading due to muscular forces increases, and the surgical indications for plating versus nailing increase (Gwathmey *et al.*, 2010).

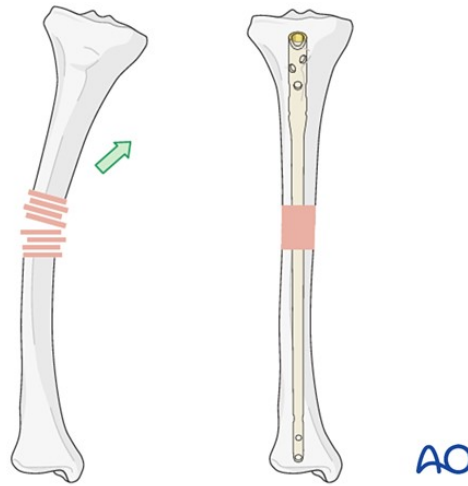


Figure 2.11: Diagram showing the ability of an intramedullary nail to maintain positions of the bone fragments, providing rigidity in the torsional, bending, and axial directions (*Intramedullary nailing: basic technique*, no date). Images reproduced with permission. Copyright by AO Foundation, Switzerland.

2.7.7 External fixation

External fixation involves using a fixator which is outside of the body. The fixator is secured to the bone fragments using a system of pins and wires which pass through the skin (Figure 2.12). This approach is predominantly employed for the temporary stabilisation of fractures, particularly in cases of open fractures where there is significant risk of exacerbating soft tissue damage (Rüedi and Murphy, 2000). External fixation is generally not suited for long-term fixation due to complications associated with the pins and wires traversing through the skin and soft tissues, which can lead to discomfort or infection. Additionally, external fixators have limited stiffnesses due to the larger moment arms on the fixator from being outside of the limb, which could hinder fracture healing, especially in lower-limb fractures (Rüedi and Murphy, 2000).

The Ilizarov fixator, or ring fixator, is a type of external fixator consisting of two pairs of rigid rings. These rings are secured to the proximal and distal fracture fragments using pins and screws, and the pairs are then connected with metal rods (*Ring fixator (Ilizarov)*, no date). Ring fixators are used for complex fractures due to their greater stability compared to standard external fixators.

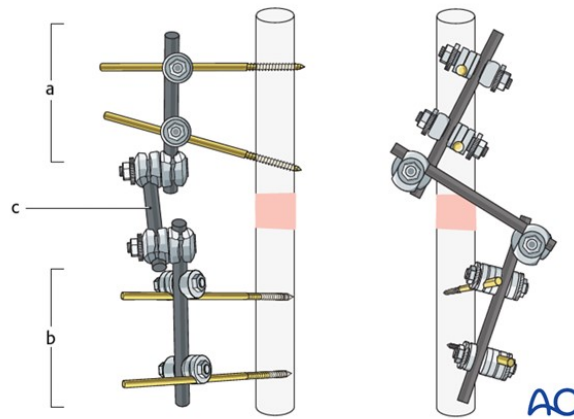


Figure 2.12: An external fixator securing two fracture fragments. The fixator consists of two partial frames (a and b) joined with a connecting rod (c) (*Modular external fixation: basic technique*, no date). Image reproduced with permission. Copyright by AO Foundation, Switzerland.

2.8 Fracture non-union

Despite best treatment efforts, some fractures do not heal completely. Delayed union and non-union are loosely defined terms, but fractures which fail to achieve a bony bridging within 6 months are classed as ‘delayed unions’, and fractures which fail to achieve bony bridging by 9-12 months are classed as ‘non-unions’ (Volpin and Shtarker, 2014). Non-unions have alternatively been defined as “a fracture that will not heal without further intervention” (Schmal *et al.*, 2020). Non-unions can be categorised by the amount of callus formation present: hypertrophic non-unions have significant callus formation, oligotrophic non-unions have minimal callus formation, and atrophic non-unions have no callus formation and some bone atrophy (Schmal *et al.*, 2020; Kloen *et al.*, 2022). Hypertrophic non-unions are considered to be caused by an inadequate mechanical environment, while atrophic non-unions are thought to be caused by inadequate biological factors, such as a lack of vascularisation (Elliott *et al.*, 2016). However, atrophic non-unions have been shown to have a similar degree of vascularisation as hypertrophic non-unions (Reed *et al.*, 2002, 2003). Non-unions have severe medical consequences; they cause pain while weight bearing due to the unhealed fracture (Schmal *et al.*, 2020) and their treatment can take years of painful interventions (Antonova *et al.*, 2013; Tay *et al.*, 2014) and possibly result in

permanent disability (Mills, Aitken and Simpson, 2017) or a false joint (Marsell and Einhorn, 2011).

Non-union rates are widely reported to be between 5% to 10% of fractures (Einhorn, 1995; Giannoudis and Tzioupis, 2005; Bhandari, Dijkman and Sprague, 2009; Schmal *et al.*, 2020). However, many cited figures derive from unreliable data sources (Brashear, 1965; Praemer, Furner and Rice, 1999; Schmal *et al.*, 2020). A more reliable source measured a non-union rate of 1.9% of fractures (Mills, Aitken and Simpson, 2017; Schmal *et al.*, 2020). Additionally, contrary to commonly held beliefs, osteoporosis and osteopenia have not been shown to independently increase non-union risks (Van Wunnik *et al.*, 2011; Schmal *et al.*, 2020).

While non-union rates are low in civilian non-combat, low-energy fracture, non-union rates in fractures sustained in combat environments or war zones have been shown to be as high as 50% (Penn-Barwell *et al.*, 2015; Stewart *et al.*, 2020). This increased rate of non-union is attributable to the higher-energy fracture mechanisms in conflicts, specifically blast injuries (Stewart *et al.*, 2020).

Non-unions are radiographically diagnosed using the RUST (Whelan *et al.*, 2010) or modified RUST (Litrenta *et al.*, 2015) scores, which quantify the degree of fracture healing at both cortices on both sides of the fracture line, as seen in a radiograph. In the modified RUST score, each cortex is scored between 1 – 4: 1 being no callus development, 2 being presence of a callus, 3 being a bridged callus, and 4 being a remodelled callus, for a minimum possible score of 4 and a maximum of 16. A summary of the RUST and mRUST scoring methods is shown in Table 2.3.

Scoring method	Callus	Fracture line	Score
RUST	Absent	Visible	1
	Present	Visible	2
	Present	Invisible	3
mRUST	Absent	Visible	1
	Present	Visible	2
	Bridging	Visible	3
	Remodelled	Invisible	4

Table 2.3: Descriptions of the RUST and modified-RUST scoring methods based on callus presence and healing stage, and visibility of the fracture line (Fiset *et al.*, 2018).

2.9 Clinical decision making

Clinical best practices in fracture treatment are generally informed through *in vitro* and *in vivo* testing. *In vitro* testing consists of benchtop mechanical tests of fracture fixation devices implanted on *ex vivo* bone or synthetic surrogate bone. The mechanical stability of devices can be quantified and the relative stabilities of different fixator configurations can be compared. *In vitro* studies have been performed on the stabilities of fracture fixation constructs using novel fracture fixation devices (Gaebler *et al.*, 2001; Duda *et al.*, 2002; Stoffel *et al.*, 2003; Augat *et al.*, 2008; Snow, Thompson and Turner, 2008; Uhl *et al.*, 2008; Gardner *et al.*, 2009, 2010; Bottlang *et al.*, 2010), screw types (Bottlang *et al.*, 2009), and fixator configurations (Field and Woodside, 1999; Ahmad *et al.*, 2007; Fitzpatrick *et al.*, 2009; Chao *et al.*, 2013). While *in vitro* testing can determine approximately fixator stiffness, the ranges of stiffness which promote fracture healing must first be determined with *in vivo* testing. Large-animal experiments, usually ovine, are used to compare the effect on fracture healing of various fixation parameters such as: shear stiffness (Augat *et al.*, 2003), axial and shear stiffness (Epari *et al.*, 2007), and non-linear axial stiffness (Han *et al.*, 2021). In these experiments, radiographs are taken throughout the healing process and the final-stage callus can be excised and mechanical tested to quantify the strength of the healed callus (Claes *et al.*, 1997). *In vivo* human trials are also used to answer clinical questions, such as the effect of dynamisation during rehabilitation (Fink *et al.*, 1996; Bottlang *et al.*, 2017) or the success of new treatments on specific fracture types, such as distal femoral fractures (Lujan *et al.*, 2010; Bottlang *et al.*, 2014).

While traditional testing methods have answered many clinical questions regarding fracture treatment best practices, there are significant limitations of *in vitro* and *in vivo* testing. *In vitro* testing can only determine the initial fixation stiffness of the fracture-fixator construct, and cannot determine the stiffness at other times in the healing process, as *in vitro* callus development is currently infeasible. Callus development is not only the primary aim of fracture treatment, but it also aids in reducing implant failure by sharing an increasing proportion of the load with the fixator, reducing the probabilities of implant failure due to fatigue failure (Vijayakumar *et al.*, 2006; Toro, 2015; MacLeod and Pankaj, 2018). And while stiffer fixators are better able to withstand cyclic loading (Stoffel *et al.*, 2003; Hoffmeier, Hofmann and Mückley, 2011; Chao *et al.*, 2013; Schmidt *et al.*, 2013; MacLeod and Pankaj, 2018), more flexible fixators lead to faster callus development, thereby reducing the loads experienced by the fixator (MacLeod and Pankaj, 2018). Optimal fixator stiffness is therefore a balance between compliance to promote callus development and stiffness to resist fixator damage. *In vitro* testing is unable to capture this balance, and inter-investigator variability in testing fixator stiffness exceeds two orders of magnitude (Grant, Schuetz and Epari, 2015; MacLeod, Simpson and Pankaj, 2018). While *in vivo* animal studies are able to capture callus development and its effects on fixator durability, these studies are also largely limited in the healing time-frame which can be investigated; accurate callus mechanical testing can only occur after animal sacrifice, therefore animal studies are often limited in scope due to the significant costs involved in large animal studies.

Conventional *in vivo* clinical trials also have significant limitations, despite being the current gold-standard clinical research tool to compare treatment options for a given affliction. Typically, a large cohort of patients is randomly assigned to one of the possible treatment options and patient outcomes are recorded. Statistical analyses are used to determine whether a particular treatment, on average, has superior patient outcomes. This approach can fail in trials addressing relatively uncommon, but severe clinical situations. Distal femoral fractures are associated with high morbidity and mortality rates, but do not yet have a conclusively determined optimal treatment strategy (Griffin *et al.*, 2015). A preliminary study was conducted to investigate the feasibility of a large-scale clinical trial to identify which of the two most common surgical fixation devices yields superior patient outcomes (Griffin *et al.*, 2019). This

preliminary study concluded that a full-scale clinical trial is unlikely to succeed due to limited patient and surgeon recruitment. Patient recruitment was limited due to the relative infrequency of this type of fracture and so a sufficiently large cohort for a clinical trial was unlikely to be obtained. Issues with surgeon recruitment was an unexpected finding of the feasibility study. Distal femoral fractures can differ from one another significantly, including in the degree of distal positioning, the degree of joint involvement, and bone quality. Therefore, some surgeons refused to perform randomly assigned treatments, likely because they believed one treatment was clearly superior for the particular fracture type, even if a clinical trial had not concluded this hypothesis. The variability, paired with the relative infrequency, of distal femoral fractures makes it infeasible to conduct a clinical trial for each type of fracture. Additionally, if the clinical trial had succeeded in identifying an overall superior treatment option, it is possible that the identified treatment would be sub-optimal for some specific fracture types, but a blanket recommendation for the identified treatment may have been prescribed.

In silico clinical trials can address these limitations of conventional clinical trials. *In silico* trials consist of performing a comparison of safety or efficacy of various treatment options, similar to conventional clinical trials, however, comparisons are performed using *in silico* models of the treatments applied to virtual patients. *In silico* trials can utilise different types of computational model, including artificial intelligence, finite element (FE) modelling, and computational fluid dynamics. For example, a recent *in silico* trial analysed the safety of a personalised high tibial osteotomy device to treat early knee osteoarthritis (MacLeod *et al.*, 2021). Computed tomography (CT) scans of prospective patients were used to create FE models of each tibia, one with a generic existing device and one with the novel personalised device, thereby creating a perfect-paired comparison. The study was able to conclude that the mechanical safety and stability of the personalised device are similar to those of the existing device. An *in vivo* trial of the novel device likely would have failed due to issues with patient recruitment, as the treatment is not widely performed. Additionally, the personalised nature of the novel device is better suited to an *in silico* trial in which a true comparison can be made for the individual circumstances by treating the same patient with both options, which would be impossible *in vivo*.

In silico trials are also able to investigate research questions which conventional trials are prevented from investigating due to ethical boundaries. Another recent *in silico* trial investigated the ability of flow-diverting stents to reduce flow to treat intracranial aneurysms (Sarrami-Foroushani *et al.*, 2021). In addition to replicating the results of previous conventional clinical trials, the *in silico* trial was able to investigate additional research topics, such as sub-populations of virtual patients with co-morbidities, such as hypertension, as well as associated failure mechanisms in treatments. The investigation of these sub-groups would likely not have been feasible using conventional clinical trials, as adequate sample sizes are difficult to obtain as patient populations are divided into sub-groups. Additionally, the investigation of device failure mechanisms would be unethical in an *in vivo* trial, however, gaining an understanding of failure mechanisms is crucial for designing against future device failures. This *in silico* trial enabled this difficult, but important, research question to be addressed.

2.10 Conclusion

Despite research and advancements in fracture treatment, traditional methods of clinical decision making have failed to identify optimal treatment practices for some fracture types, such as distal femoral fractures. There is a need for a tool to address the shortcomings of traditional *in vivo* and *in vitro* methods in fracture healing research. *In silico* methods have previously been applied successfully in other medical research areas which have been insufficiently addressed due to the limitations of *in vivo* and *in vitro* methods.

CHAPTER 3

REVIEW OF FRACTURE-HEALING

ALGORITHMS

3.1 Scope

In the previous chapter, remaining challenges in fracture treatment were explored and limitations of traditional *in vivo* and *in vitro* methods were identified. Specifically, these traditional methods have struggled to guide best clinical practices for fractures which are either relatively uncommon or are complex and varied. *In silico* methods were proposed to address these shortcomings, as they have been used previously to address similar gaps in clinical research. In this chapter, *in silico* tools for studying fracture healing are reviewed, and gaps in the literature are identified. The chapter concludes by selecting the most relevant existing tools and identifying the key limitations which must be addressed in order to develop a tool capable of addressing the unmet challenges in fracture treatment.

3.2 Background

Traditional methods of clinical research have failed to provide definitive solutions for some fracture types, such as distal femoral fractures, due to limitations in patient and surgeon recruitment, as well as the variability of fracture types (Griffin *et al.*, 2019). *In silico* methods, which utilise computational models to simulate clinical trials, offer a promising alternative. These methods can use FE modelling, artificial intelligence, and computational fluid dynamics to create virtual patients and perform precise, ethical, and detailed analyses of treatment options (Sarrami-Foroushani *et al.*, 2021). For instance, *in silico* trials could address fracture-healing research gaps by simulating various fracture types and treatment scenarios. An effective *in silico* tool for this purpose must be capable of predicting accurately both successful bony unions and non-unions, and must be appropriately sensitive to its parameters; i.e., the tool must be sensitive to physiologically relevant parameters such as fracture-gap size, but should be less sensitive to parameters such as diffusion rates. Such a tool would provide insights into optimal treatments for specific fracture types, and potentially lead to personalised and more effective clinical interventions.

Fracture-healing algorithms are a type of computational algorithm which model the various mechanobiological processes which occur during the fracture-

healing process. These models typically simulate the secondary fracture-healing process as primary fracture healing is sufficiently similar to bone remodelling, such that bone remodelling algorithms could be used to simulate primary fracture healing. Complex multi-fragment fractures can sometimes result in both primary and secondary healing, where one fracture line is treated with lag screw compression while the rest of the fracture is treated with bridge plating, however, fracture-healing algorithms have only focused on simple fracture cases in which only secondary fracture healing is present. A combined bone remodelling and fracture-healing algorithm could be used to simulate the complex case where both primary and secondary fracture healing are active. Fracture-healing algorithms aim to capture some, or all, of the stages of secondary fracture healing: inflammation, repair, and remodelling. The algorithms model the processes by which mesenchymal stem cells (MSC) differentiate into different osteocytes and form tissues in the callus. These processes are known to be affected and regulated by the mechanical environment in the callus (Perren, 2002), therefore, fracture-healing algorithms use the callus mechanical environment to guide, stimulate, or regulate the processes which they aim to model. For this reason, fracture-healing algorithms typically include an FE model of the fracture region and surgical fixation device. The FE model is used to calculate the local mechanical environment at each finite-element in the callus region. This information about the mechanical environment is then used by a ‘biological controller’ to model the various fracture-healing processes. As the outputs of the biological controller include tissue changes in the callus region, the material properties of the FE model must be updated to reflect these changes. Thus, as fracture healing progresses, the fracture-healing algorithm is able to capture the progressive ossification of the callus, and the eventual load-sharing with the fixator (MacLeod and Pankaj, 2018). This iterative process of an FE model calculating the callus region mechanical environment, a biological controller using the mechanical environment to update tissue concentrations, and the updated tissue concentrations altering the callus region mechanical properties in the FE model, is shown in a flowchart diagram in Figure 3.1.

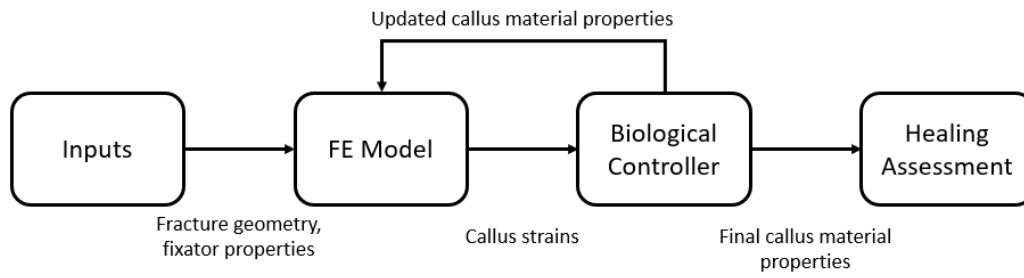


Figure 3.1: A flowchart diagram of a typical fracture-healing algorithm workflow.

Fracture-healing algorithms have potential as an *in silico* method to investigate fracture-healing treatments. Previous algorithms have been applied to various applications: optimising the stiffness of a particular fixator to minimise the time taken to heal a fracture (Steiner *et al.*, 2014b), investigating the impact of fracture type and geometry on healing outcomes (Ren and Dailey, 2020a), and investigating the long-term performance of bio-resorbable fixators (Quinn, Kopp and Vaughan, 2022). These applied studies use previously developed fracture-healing algorithms and feed in different inputs, such as fracture type and fixator properties, in order to compare outcome metrics.

Further potential applications which have not yet been explored include post-surgical rehabilitation-regime management and comparison between treatment types as an *in silico* clinical trial. Most fracture-healing algorithms apply a constant load for the entirety of the healing process, however, rehabilitation-regimes such as dynamisation or inverse-dynamisation (Egger *et al.*, 1993; Claes, 2022), where fixator stability is progressively decreased or increased, respectively, could also be investigated by altering the applied load in the fracture-healing algorithm. Most fracture-healing algorithms also only investigate a single type of fracture fixation device, rather than comparing between different device types. Comparisons between device types for the purpose of clinical recommendations are generally performed via randomised controlled trials (RCT) which compare healing outcomes of patients receiving different treatment options. RCT's are considered the gold-standard for determining optimal treatment, however, those investigating relatively uncommon fractures can suffer from under-recruitment of patients and surgeons, leading to under-powered or infeasible trials. This was the case for the prospective Trial of Acute Femoral Fracture Fixation (TrAFFix) RCT which aimed to investigate whether

lateral locking plates or intramedullary nails should be the recommended surgical fixation for distal femoral fractures (Griffin *et al.*, 2019). *In silico* methods do not suffer issues of patient or surgeon recruitment, and have previously been used to address clinical questions left unanswered by traditional clinical trials (Sarrami-Foroushani *et al.*, 2021). A fracture-healing algorithm could be used to perform an *in silico* clinical trial in place of the failed TrAFFix study.

3.3 Groups of fracture-healing algorithms

Fracture-healing algorithms generally operate under the principle of using a combination of state variables, such as local tissue type or presence of cells or vascularisation, and stimuli, such as mechanical strains or fluid flow, to update the tissue types in a callus region in an iterative manner, as shown in Figure 3.1. Fracture-healing algorithms typically differ in the state variables and stimuli used. Fracture-healing algorithms have developed along two main groups of algorithms: those which use a linear elastic model of the callus, and those which use a biphasic poroelastic model of the callus.

Carter *et. al.* developed the theory that the fracture-healing process is governed primarily by tensile strain and hydrostatic stress (Carter *et al.*, 1998) building on theoretical FE models (Carter, Blenman and Beaupré, 1988) and models of implant retrieval studies (Giori, Ryd and Carter, 1995). A linear elastic fracture-healing algorithm was first developed by Claes and Heigele (1999). Large animal experiments were used to identify ranges of strain and hydrostatic pressure which would lead to intramembranous ossification, endochondral ossification, and fibrocartilage formation. These identified ranges are shown in Figure 3.2, and were used to develop a model of fracture healing.

A biphasic fracture-healing theory was proposed by Prendergast and Huiskes *et al.* (Huiskes *et al.*, 1997; Prendergast, Huiskes and Søballe, 1997) which identified shear strain and interstitial fluid-velocity ranges to stimulate tissue differentiation. This theory was based on several studies which linked fluid flow with cellular differentiation in the fracture-healing process (El Haj and Cartmell, 2010; Davis *et al.*,

2015). This biphasic theory was developed into a fracture-healing algorithm by Lacroix et al. (2002) and was validated against corresponding experimental data (Claes *et al.*, 1997; Lacroix and Prendergast, 2002a). The combination of interstitial fluid flow and shear strain was used to determine tissue differentiation into bone, cartilage, or fibrocartilage. The ranges of fluid flow and shear strain that were used are shown in Figure 3.3.

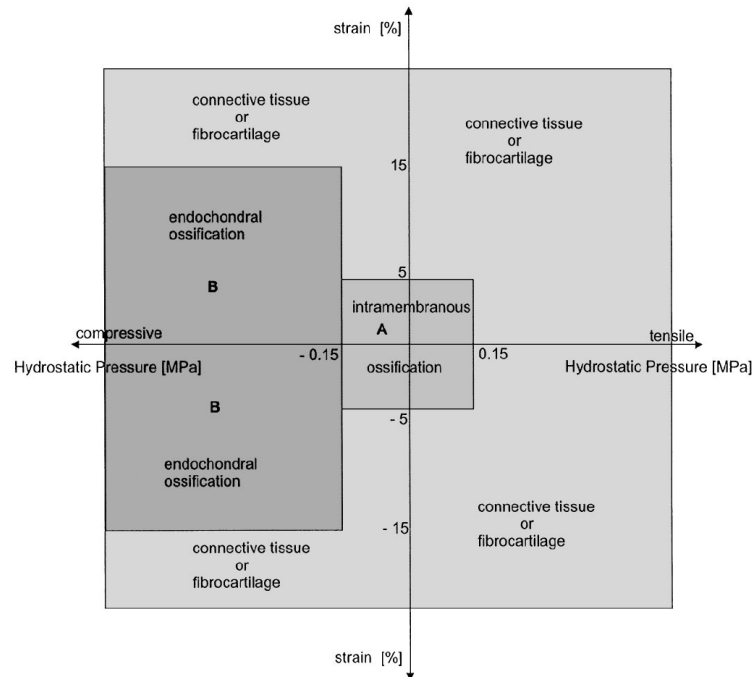


Figure 3.2: The Claes fracture-healing window, which predicts either intramembranous ossification, endochondral ossification, or fibrocartilage formation, based on the hydrostatic pressure and strain in the local tissue (Claes and Heigele, 1999). Image reproduced with permission of the rights holder, Pergamon.

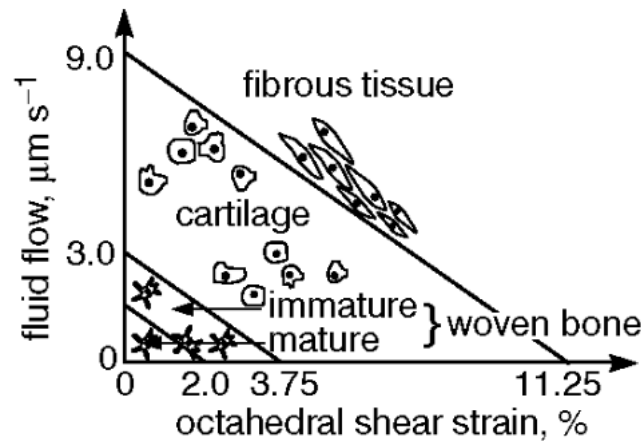


Figure 3.3: The Prendergast biophysical stimulus window, where the predicted tissue type formed in the local tissue area is based on fluid flow and shear strain (Lacroix *et al.*, 2002). Image reproduced with permission of the rights holder, Springer-Verlag.

3.3.1 Linear elastic fracture-healing algorithms

Ament and Hofer introduced the use of fuzzy-logic in fracture-healing algorithms (Ament and Hofer, 2000). Fuzzy-logic allows for the modelling of complex biological processes through the abstraction of inputs, outputs, and the processes themselves. Inputs are “fuzzified” by determining their membership to linguistic categorisations, such as “low” or “high,” using fuzzy membership functions. While in classical logic parameters would be categorised as either “low” or “high,” in fuzzy-logic partial membership to multiple categories is permitted. An example of a fuzzy membership function and a corresponding classical logic equivalent is shown in Figure 3.4. This partial membership also allows for partial activation of fuzzy rules, which better represents activation of biological processes. For example, with classical logic, a process may be activated with an input value of 0.49, but not activated at all with an input value of 0.51, whereas physiologically, the borders between activation and non-activation of processes is more “fuzzy”. Strain-energy density and bone-concentration gradient are the inputs used in this fracture-healing algorithm. The fracture healing of an ovine metatarsal was simulated and the interfragmentary movement (IFM) of the fracture gap over time was compared against corresponding animal experimental data.

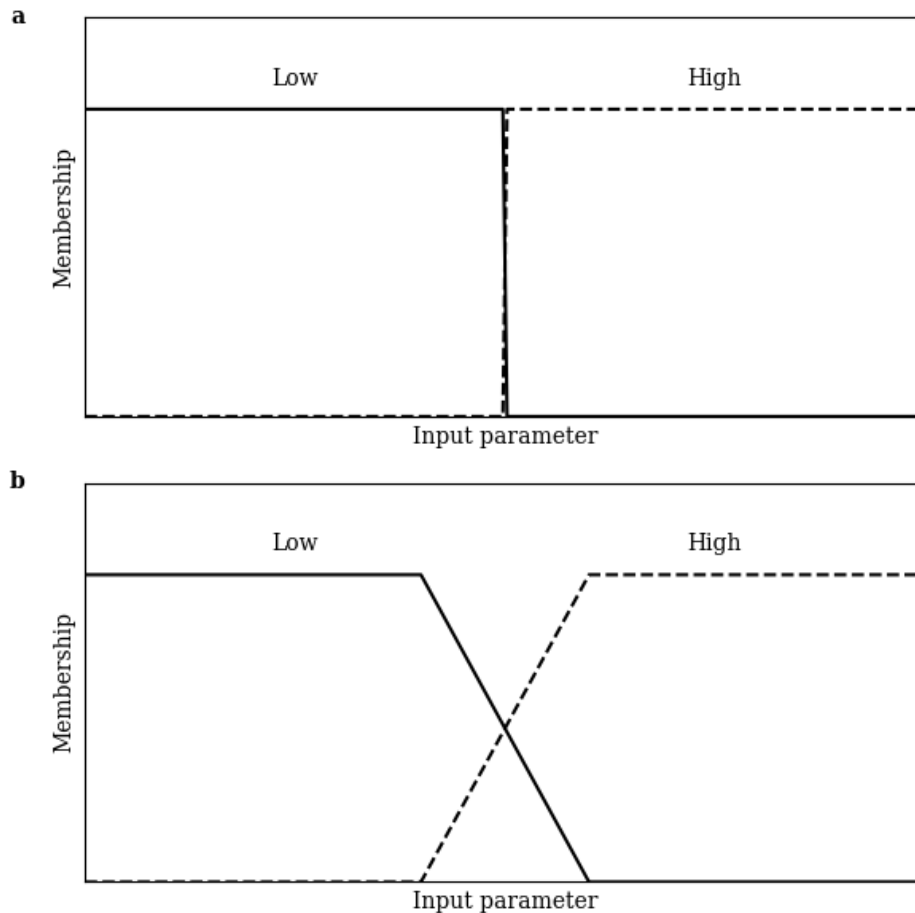


Figure 3.4: Comparison of (a) classical logic membership function with a ‘Low’ and ‘High’ function (b) fuzzy-logic equivalent membership function with ‘Low’ and ‘High’ functions.

The Ulm Fracture-Healing Algorithm is derived from the algorithm developed by Claes and Heigele (1999) and is perhaps the most widely applied fracture-healing algorithm. Shefelbine et al. (2005) implemented an algorithm with hydrostatic strain and octahedral shear strain as the mechanical stimuli which used fuzzy-logics to represent biological fracture-healing processes. Angiogenesis was additionally modelled as a fuzzy rule, with vascularity initialised at the callus external periphery, and the presence of local vascularity was a requirement for the fracture-healing fuzzy rules. Vascularisation and nutrient concentration were later modelled as diffusion processes (Chen *et al.*, 2009). The Ulm Fracture-Healing Algorithm was introduced by Simon et al. (2011) as a further iteration of the Shefelbine et al. model (2005). Ovine metatarsal fracture healing was simulated and the IFM of the fracture gap over time was compared against corresponding animal experimental data for two cases with different fixator rigidities (Claes *et al.*, 1995, 1997). A “separation” technique was applied, which separately calculated the linear callus model and the non-linear

axial stiffness fixator model, then combined the results in order to reduce computational expense. The Ulm Fracture-Healing Algorithm has been applied in many studies, having been used to investigate: the optimisation of fracture-fixation stiffness (Wehner *et al.*, 2010; Reina-Romo *et al.*, 2011; Steiner *et al.*, 2014b), the effects of different loading types (axial, shear, bending) on fracture healing (Steiner *et al.*, 2013, 2014a), the effect of implant degradation on fracture healing (Martin Pietsch *et al.*, 2018), fracture healing in metaphyseal bone (Engelhardt *et al.*, 2021), and simulating lateral distraction osteogenesis (M. Pietsch *et al.*, 2018; Niemeyer *et al.*, 2018).

Ren and Dailey (2020) implemented a derivative of the Ulm Fracture-Healing Algorithm to study ovine metatarsal fractures stabilised with intramedullary nails. Their model was applied to a parametric study, investigating the effect of fracture type and geometry on fracture healing. The nail was modelled as a non-linear axial spring, based on previous mechanical characterisations of similar intramedullary nail systems. The healing progress was quantified by measuring virtual torsional rigidity (Ren *et al.*, 2024). While the Ulm Fracture-Healing Algorithm models vascular perfusion from the external boundary of the callus inwards, perfusion was not included in the model by Ren and Dailey, leading to results of non-physiological early callus bridging in the direct inter-cortical gap. To address this, the next iteration of their fracture-healing algorithm incorporated a spatial proximity function to achieve callus-domain independence, wherein the results of the algorithm are unaffected by the initially specified callus domain, and to prevent early callus bridging in the direct inter-cortical gap (Schwarzenberg *et al.*, 2021). This proximity function was derived from curve-fitting bone-density distributions observed in radiographs of ovine fracture calluses (Ren *et al.*, 2022). The proximity function was successful in achieving a physiologically relevant callus geometry, however, the same callus geometry was reached in each case, as the geometry was prescribed by the proximity function, which acted simply as a growth-limiting function.

3.3.2 Biphasic poroelastic fracture-healing algorithms

Prendergast introduced the concept of using biphasic mechanical stimuli to regulate tissue differentiation around bone implants, described as a ‘mechano-

regulatory pathway’ (Prendergast, Huiskes and Søballe, 1997). The primary mechanical factors identified are distortional strain and interstitial fluid flow, which serve as biophysical regulators for MSC differentiation. These stimuli determine whether cells develop into fibrous tissue, fibrocartilage, or bone. FE modelling was utilised to simulate the mechanical environment at the implant site to predict tissue differentiation patterns. Distortional strain was calculated in the solid phase, and interstitial fluid flow was calculated in the poroelastic phase. This theory was later developed further with experimental corroboration by investigating the role of mechanical stimuli in tissue differentiation around bone implants (Huiskes *et al.*, 1997). Animal experiments were conducted to observe tissue responses to different mechanical environments (Søballe *et al.*, 1993). The experiments involved loading implanted bones and monitoring the resulting tissue differentiation. Subsequent analyses demonstrated a strong correlation between mechanical stimuli—such as distortional strain and fluid flow—and the types of tissue that formed around the implants (Prendergast and Huiskes, 1996; Prendergast, Huiskes and Søballe, 1997). These experimental data supported their theory by showing that specific mechanical conditions could induce predictably the formation of fibrous tissue, fibrocartilage, or bone.

Lacroix *et al.* (2002) introduced the first computational algorithm to simulate iteratively the fracture-healing process governed by the biphasic stimuli identified by Prendergast *et al.* (1997) and Huiskes *et al.* (1997), incorporating these stimuli into an FE model to predict tissue differentiation patterns during fracture healing. In a sensitivity study, Lacroix and Prendergast (2002a) analysed the impact of varying gap sizes and loading conditions on tissue differentiation, highlighting the critical role of mechanical environment in the healing process. This work was further expanded to three dimensions (Lacroix and Prendergast, 2002b), providing a more comprehensive simulation of the complex spatial dynamics of tissue differentiation and bone regeneration. Kelly and Prendergast (2005, 2006) applied these models to osteochondral defect healing, showing that the mechanical environment can be optimised to enhance cartilage repair and integration with subchondral bone. Geris *et al.* (2004) utilised a bone chamber in a rat tibia to study tissue differentiation, employing numerical simulations to predict how different mechanical and biological factors influence tissue development around loaded implants. Pérez and Prendergast

(2007) proposed an innovative approach using a random walk model instead of traditional diffusion equations to simulate cell migration, providing a new perspective on how cells navigate through the healing tissue matrix. Byrne et al. (2007) applied these theories to tissue differentiation within a scaffold, demonstrating how scaffold design and mechanical loading can be tailored to promote desired tissue outcomes in regenerative medicine.

Isaksson et al. (2006) compared various mechanical stimuli used in various fracture-healing algorithms (Carter *et al.*, 1998; Claes and Heigele, 1999; Lacroix and Prendergast, 2002a). While all models simulated accurately the general physiological process of fracture healing, deviatoric strain was the best single predictive stimulus, compared to dilatational strain and fluid velocity. In a follow-up study, Isaksson et al. (2006) compared these algorithms against *in vivo* experimental animal data (Bishop *et al.*, 2006) of ovine fractures treated with a customised external fixator (Bishop, Schneider and Ito, 2003), extending the comparison to torsional loading conditions as well. This study found that the model using deviatoric strain and interstitial fluid velocity (Lacroix and Prendergast, 2002a) best matched the experimental data from animal studies. Building on these comparisons, Isaksson et al. (2007) applied a model using octahedral shear strain and interstitial fluid velocity to a controlled distraction osteogenesis scenario, allowing for comparison against a more controlled experimental model (Brunner *et al.*, 1993, 1994). Multiple cell types, including MSC's, fibroblasts, chondrocytes, and osteoblasts, were then incorporated into the model, including different cellular processes such as proliferation, migration, differentiation, and apoptosis for each cell type (Isaksson *et al.*, 2008). This model was then tested for validation against experimental data (Gröngroft *et al.*, 2009) of murine fractures treated with lateral locking plates (Isaksson *et al.*, 2009), and it was found that the model predictions were consistent with the experimental observations, demonstrating similar remodelling patterns and callus morphologies over the healing period. A sensitivity study of the material properties included in the model showed a high sensitivity to the permeability of the tissue (Isaksson, Van Donkelaar and Ito, 2009).

3.3.3 Comparison of fracture-healing algorithms

The two main groups of healing algorithms, the Claes-derived group and the Prendergast-derived group, each have their strengths and weaknesses. The Claes-based algorithms are computationally simpler due to their single-phase approach, focusing solely on mechanical variables, making it particularly useful for studying the effects of different fixator types on healing outcomes. In contrast, Prendergast-based models attempt to capture more biological processes than the Claes-based models, which can be advantageous if the goal is to investigate the influence of biological factors, such as drug effects, on healing. However, this complexity may be a disadvantage when the primary interest is purely mechanical outcomes, as it introduces additional variables, along with increased uncertainty in their values, that may not be necessary for such studies.

Both algorithms predict a physiological course of healing, starting with initial bridging at the external callus. Despite their different approaches, the vascularisation in Claes' models and cellular diffusion in Prendergast's models serve a similar purpose: preventing early non-physiological inter-cortical bridging. This is illustrated by Ren and Dailey (2020a), who demonstrated that excluding the perfusion state variable in the Ulm Fracture-healing algorithm (Simon *et al.*, 2011), a Claes-based model, led to non-physiological results, which were later corrected by incorporating a spatial proximity function in Ren *et al.* (2022). This similarity highlights that both models depend on the callus domain and are highly sensitive to angiogenesis and diffusion rates, as the processes of vascularisation and cellular concentration begin at the callus boundary and move inward.

Validation of these algorithms has been limited, as most are tested against experimental data from successful unions only, reducing their predictive power for non-union risks. Isaksson *et al.* (2006) attempted to address this by validating against non-union scenarios but found that the algorithm predicted a steady-state non-union, whereas experimental data showed outcomes of either successful union or delayed union for the equivalent loading scenario. This indicates a need for further refinement in predictive models to account for the full spectrum of healing outcomes, especially for use as a predictor of non-union risk.

Another critical issue is the use of a pre-defined callus domain in most healing algorithms, which can lead to strain artefacts at the callus edges furthest from the fracture site, as noted by Wilson *et al.* (2015). This issue was further explored in a comparison of fracture-healing algorithms, which demonstrated the prevalence of callus domain 'flooding' (Wilson *et al.*, 2021). This phenomenon occurs when periosteal outgrowth begins at the callus edge with a strain artefact and then progresses inward. This periosteal outgrowth pathway is non-physiological, and is shown against the more physiological pathway in Figure 3.5 (Wilson *et al.*, 2021).

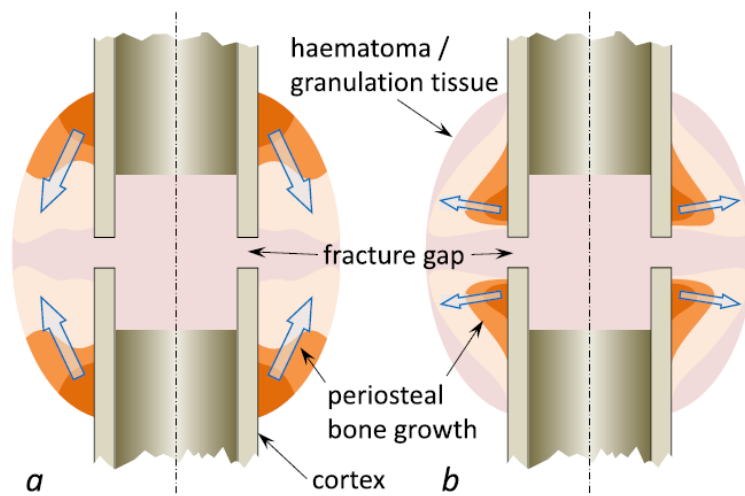


Figure 3.5: Diagram of a periosteal bone growth pathways (Wilson *et al.*, 2021). (a) The typical periosteal bone growth pattern predicted by fracture-healing algorithms. (b) The physiological periosteal bone growth pattern. Image reproduced with permission of the rights holder, Elsevier.

3.4 Ulm Fracture-Healing Model recreation

3.4.1 Methods

3.4.1.1 *FE Model*

An axisymmetric FE model was developed based on the model of Simon *et al.* (2011) of the fracture region and external fixator and is shown in Figure 3.6. The fracture modelled was a transverse ovine metatarsal osteotomy with two cylindrical

bone fragments with diameter and thickness of 16 mm and 2 mm, respectively, and a total construct length of 40 mm, including the fracture gap. The callus geometry was defined similarly to that of Claes and Heigele (1999) and Simon et al. (2011), however, the specific curvature of the callus is not defined. Here, the medullary and the peripheral surfaces of the callus were modelled with splines (Figure 3.6b). A fracture gap of either 2.1 mm or 3.1 mm was used, representing two cases, A and B, with different fixator free-movement regions. A mesh of either 4450 or 4576 quadrilateral elements for cases A and B, respectively, was used with an average element size of 0.25 mm, approximated from Simon et al.

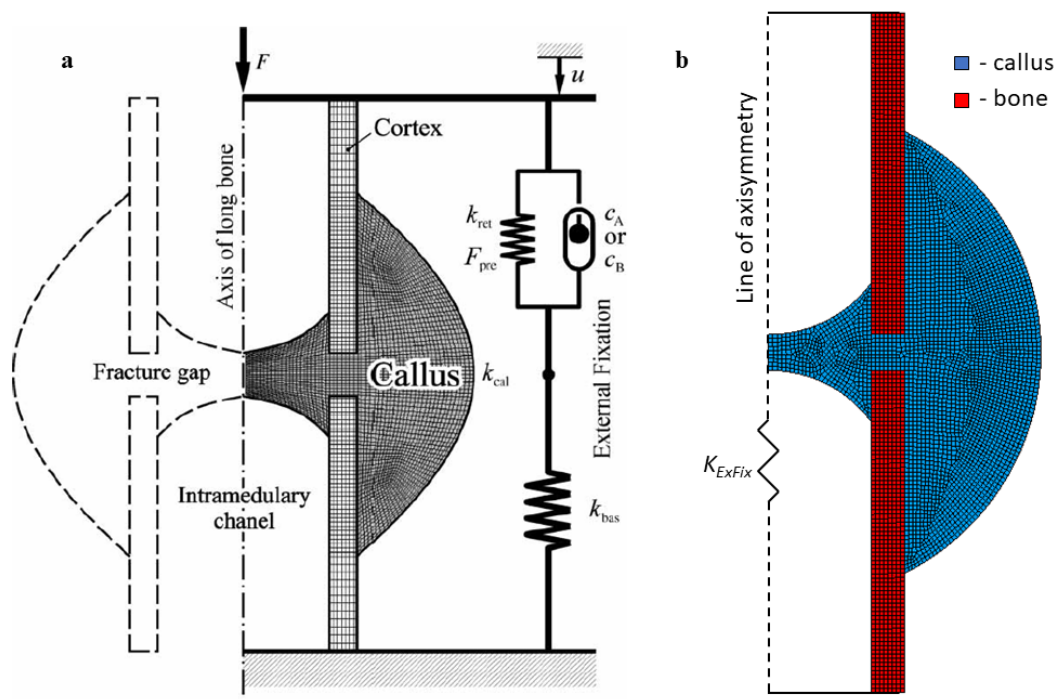


Figure 3.6: 2-D axisymmetric FE model of the callus and external fixator from (a) Simon et al. (Simon *et al.*, 2011). (b) Recreated FE model used in the present study. Image (a) reproduced with permission of the rights holder, Taylor & Francis.

All materials were modelled as linear elastic and are given in Table 3.1. Callus finite-element material properties were modelled as a mixture of woven bone, cartilage, and connective tissue based on the proportions of each tissue type within the element. A cubic rule of mixture, in which the material properties are calculated as the weighted sum of each tissue material property cubed, weighted by each tissue proportion, was used (Carter and Hayes, 1977; Simon *et al.*, 2011).

Material	Young's modulus (MPa)	Poisson's ratio
Soft tissue	3	0.3
Cartilage	200	0.45
Woven bone	400	0.36
Lamellar bone	10,000	0.36

Table 3.1: Material properties used in the healing algorithm, as used in Simon et al. (Simon *et al.*, 2011).

A “separation” technique, which separates the “linear” callus stiffness from the non-linear fixator stiffness, was used to solve for the callus-element strains without the computational expense of a non-linear analysis (Simon *et al.*, 2011). This technique is described by Simon et al., and is briefly summarised here. A 1 mm axial displacement was prescribed to one end of the construct while the other end was rigidly fixed, and an axisymmetric condition applied along the axis of symmetry. The axial reaction force at the fixed end was used to calculate the callus stiffness. This initial callus stiffness was used to create the non-linear fixator stiffness, described below (Figure 3.7), such that the combined stiffness would resist a force of 500 N at a displacement of 0.25 mm or 1.25 mm for cases A and B, respectively. This ensured that the initial IFM of the construct matched the initial free-movement ranges of the fixator.

The callus stiffness was calculated using the FE model at each iteration. The combined callus-fixator stiffness function was then used to determine the IFM at each time step, given an applied load of 500 N. A “stretch factor” was then used to calculate the ratio of the IFM to the applied unit displacement of 1 mm. The resultant callus-element strains from the FE model were then scaled by this factor. Hydrostatic, or dilatational, strain (equation 1) and octahedral shear, or distortional, strain (equation 2) were calculated at each finite-element, where ε_1 , ε_2 , and ε_3 are the principal strains.

$$\varepsilon_{dil} = \frac{1}{3}(\varepsilon_1 + \varepsilon_2 + \varepsilon_3) \quad (1)$$

$$\varepsilon_{dist} = \sqrt{\frac{1}{2}[(\varepsilon_1 - \varepsilon_2)^2 + (\varepsilon_2 - \varepsilon_3)^2 + (\varepsilon_3 - \varepsilon_1)^2]} \quad (2)$$

The fixator was modelled based on designs (Claes *et al.*, 1995) and experiments (Claes *et al.*, 1997) of an external fixator which allows for a pre-determined amount of free movement at the fracture gap, or IFM. The fixator was modelled as a non-linear axial spring with baseline stiffness, return stiffness, and pre-tensioning force of 4600 N/mm, 20 N/mm, and 100 N, respectively (Figure 3.7) (Simon *et al.*, 2011). Fixator stiffness in the pre-tensioning region is not reported by Simon *et al.*, so the baseline stiffness was used. The fixator is reported to be rigid in all bending and torsional planes (Claes *et al.*, 1995, 1997; Simon *et al.*, 2011).

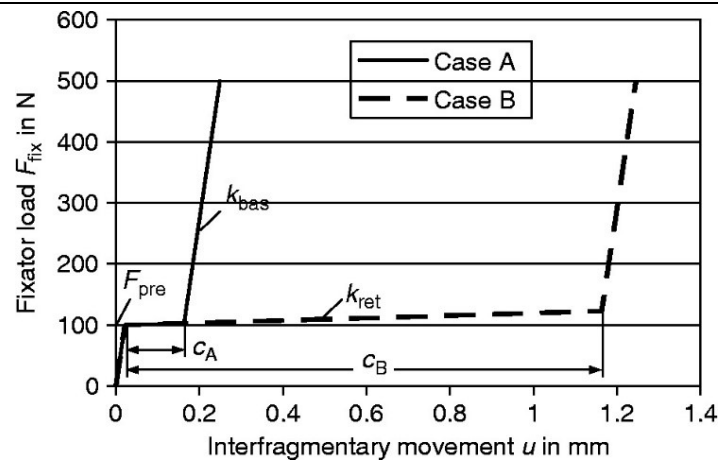


Figure 3.7: Spring stiffness, as a non-linear function of fixator load against IFM, of the external fixator used where k_{bas} , k_{ret} , F_{pre} , c_A , and c_B are the baseline stiffness, return stiffness, pre-tensioning force, and free-movement distances for cases A and B, respectively (Simon *et al.*, 2011). Image reproduced with permission of the rights holder, Taylor & Francis.

An alternative, non-separated, FE model was also developed not as described by Simon *et al.* This model directly applied the axial compressive force of 500 N rather than a unit displacement, and incorporated the fixator stiffness as a spring with stiffness defined exactly as in Figure 3.7 for both cases A and B. The spring stiffness is therefore in parallel with the callus stiffness. This means the initial IFM will not be exactly 0.25 mm and 1.25 mm for cases A and B, respectively, because there is also some initial callus stiffness contribution. This ‘non-separated’ method is the more standard method of modelling a non-linear spring in a mechanical system, uses non-linear FE, and does not require the use of the ‘stretch factor’ to calculate the callus element strains.

3.4.1.2 Fuzzy-logic System

Each callus finite-element was described using three state variables: blood perfusion, cartilage proportion, and woven bone proportion (Simon *et al.*, 2011). Perfusion ranged from 0 to 1 to represent no perfusion and full perfusion, respectively. Cartilage and woven bone proportion ranged from 0 to 1 and form the complement of soft tissue proportion, i.e., $c_{wb} + c_{cart} + c_{st} = 1$, where c_{wb} , c_{cart} , and c_{st} are the proportion of woven bone, cartilage, and soft tissue, respectively, therefore describing the tissue state of the elements.

The healing process was modelled as a series of timesteps, with each timestep representing one day. The FE model, described above, was run at each timestep and the distortional and dilatational strains at each callus element were calculated. Based on the strains calculated in the FE model, a fuzzy-logic system determines the updated state variables for each callus element at each timestep. This iterative process follows a similar pathway as that shown in Figure 3.1.

The fuzzy-logic system described in Simon *et al.* (2011) was developed using a modified Scikit-fuzzy library (v0.4.2) (Warner *et al.*, 2019) in Python (v3.6). The original model by Simon *et al.* (2011) was developed using the Matlab Fuzzy-logic Toolbox (v6.0 R12), however, both the present model and the Ulm model are implemented using the same Mamdani fuzzy-inference system. The fuzzy system used the dilatational and distortional strain values calculated in the FE model, along with the state variables of the current and adjacent elements to calculate the change in each state variable at the next iteration.

Fuzzy-system outputs were scaled using the relative area of the current element. The area scaling described in Simon *et al.* is based on a “reference area”, as shown in equation 3, where A_{ref} , $A_{element}$, and Δc_{fuzzy} are the reference area, the area of the current element, and the un-scaled change in tissue concentration determined by the fuzzy-system, respectively. The value of A_{ref} is not given in the paper. The present model scaled outputs based on the mean element area in the model, A_{avg} , as shown in equation 4.

$$\Delta c = \sqrt{\frac{A_{\text{ref}}}{A_{\text{element}}}} \cdot \Delta c_{\text{fuzzy}} \quad (3)$$

$$\Delta c = \sqrt{\frac{A_{\text{avg}}}{A_{\text{element}}}} \cdot \Delta c_{\text{fuzzy}} \quad (4)$$

Callus-element Young's modulus was calculated based on the updated state-variable proportions of each tissue type, and the material properties given in Table 3.1, using a cubic rule of mixture shown in equation 5, where E_{el} is the element Young's modulus, E_{tissue} is the tissue Young's modulus as defined in Table 3.1, $c_{el,\text{tissue}}$ is the concentration of the tissue type in the element with a value between 0 and 1, and Σ_{tissue} denotes the summation across all callus tissue types: soft tissue, cartilage, and woven bone. This cubic rule of mixture is based on the established cubic relationship between Young's modulus and bone density, and is commonly used in published fracture-healing algorithms (Carter and Hayes, 1977; Simon *et al.*, 2011). Callus-element Poisson's ratio was calculated using a linear rule of mixture shown in equation 6, where v_{el} is the element Poisson's ratio, v_{tissue} is the tissue Poisson's ratio as defined in Table 3.1, and $c_{el,\text{tissue}}$ and Σ_{tissue} are defined similarly as in equation 5. Callus-element material properties are updated in the FE model for the following iteration.

$$E_{el} = \sum_{\text{tissue}} E_{\text{tissue}} c_{el,\text{tissue}}^3 \quad (5)$$

$$v_{el} = \sum_{\text{tissue}} v_{\text{tissue}} c_{el,\text{tissue}} \quad (6)$$

The fuzzy rules and membership functions, as well as initial and boundary conditions, were implemented as described by Simon *et al.* and are given in Figure 3.8 and Table 3.2. Each of these rules is a phenomenological implementation of a corresponding biological process involved in secondary fracture healing: angiogenesis, intramembranous ossification, chondrogenesis, cartilage calcification, endochondral ossification, and atrophy. All callus elements were initialised as 100% soft tissue. Callus elements adjacent to the cortex and more than 5 mm from the fracture gap were prescribed 100% neighbour perfusion to represent the perfusion of

the intact cortex. The perfusion at the periphery of the callus was set to 30%. For the first 10 iterations, the callus elements adjacent to the medullary canal were prescribed a neighbour perfusion of 0%, and a neighbour perfusion of 30% thereafter.

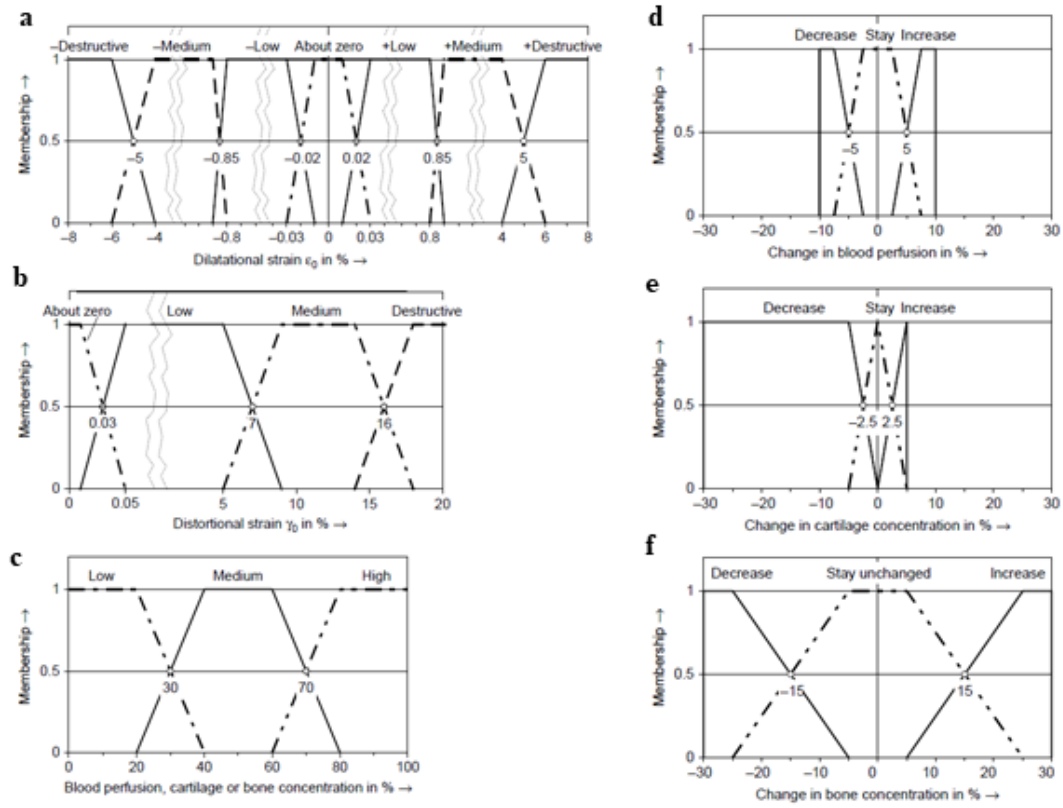


Figure 3.8: The fuzzy-membership functions used in the Ulm Fracture-Healing Model (Simon *et al.*, 2011). (a) Dilatational strain, (b) distortional strain, (c) tissue concentration, (d) change in perfusion, (e) change in cartilage concentration, (f) change in bone concentration.

Rule	Perf	nPerf	Bone	nBone	Cart	Dilatational strain	Distortional strain	Δ Perf	Δ Bone	Δ Cart
Angiogenesis	Low	Med or High	-	-	-	Neg. Med to Pos. High	Zero to Low	Increase	-	-
	Med or High	High	-	-	-	Neg. Med to Pos. High	Zero to Low	Increase	-	-
Intramembranous ossification	High	-	-	High	Low	Neg. Low or Pos. Low	Low	-	Increase	-
Chondrogenesis	-	-	-	-	-	Neg. Med to Neg. Low	Not Destructive	-	-	Increase
Cartilage calcification	-	-	-	Med or High	Med or High	Neg. Med to Pos. Low	Zero to Med.	-	Increase	Decrease
Endochondral ossification	Med or High	-	High	High	Low	Neg. Low or Pos. Low	Zero to Low	-	Increase	Decrease
Atrophy	-	-	-	-	-	Neg. or Pos. Destructive	-	Decrease	Decrease	Decrease
	-	-	-	-	-	-	Destructive	Decrease	Decrease	Decrease

Table 3.2: The fuzzy-logic rules implemented in the Ulm Fracture-Healing Model (Simon *et al.*, 2011). ‘Perf’ is the perfusion concentration of the element, ‘nPerf’ is the maximum neighbouring perfusion concentration, ‘Bone’ is the bone concentration of the element, ‘nBone’ is the maximum neighbouring bone concentration, ‘Cart’ is the cartilage concentration of the element. ‘ Δ Perf’, ‘ Δ Bone’, and ‘ Δ Cart’ are the outputs of the fuzzy-logic rules and are the changes in each tissue type concentration in the element.

3.4.2 Results

The Ulm healing algorithm simulations of IFM throughout the healing process for both case A and B (Simon *et al.*, 2011) are compared against ovine experimental data (Claes *et al.*, 1997) and are shown in Figure 3.9. The comparable results of the present replication study are shown in Figure 3.10, with simulations performed using both the separation technique, as described above and by Simon *et al.*, and with a non-separation technique.

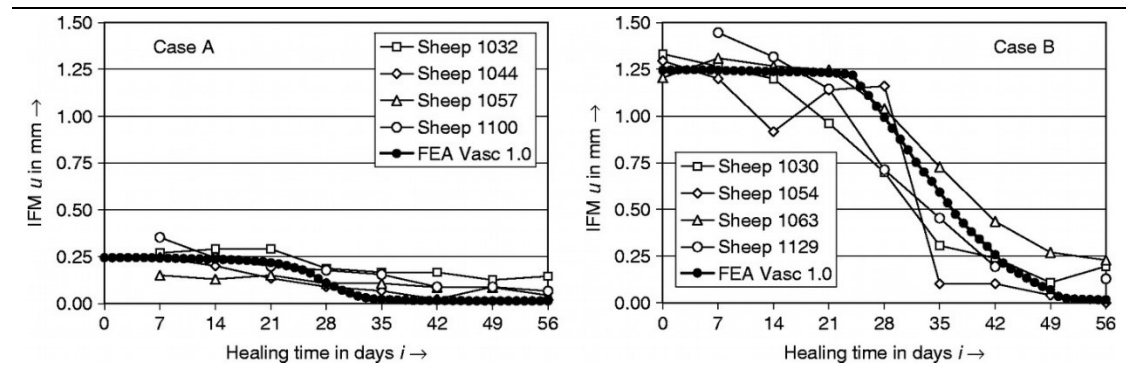


Figure 3.9: Healing algorithm predictions reported by Simon *et al.* of IFM throughout the healing process for two different fixator configurations (Case A and Case B) against experimental ovine data, where ‘FEA Vasc 1.0’ denotes a vascularisation parameter value of 1 was used (Claes *et al.*, 1997). Image reproduced with permission of the rights holder, Taylor & Francis.

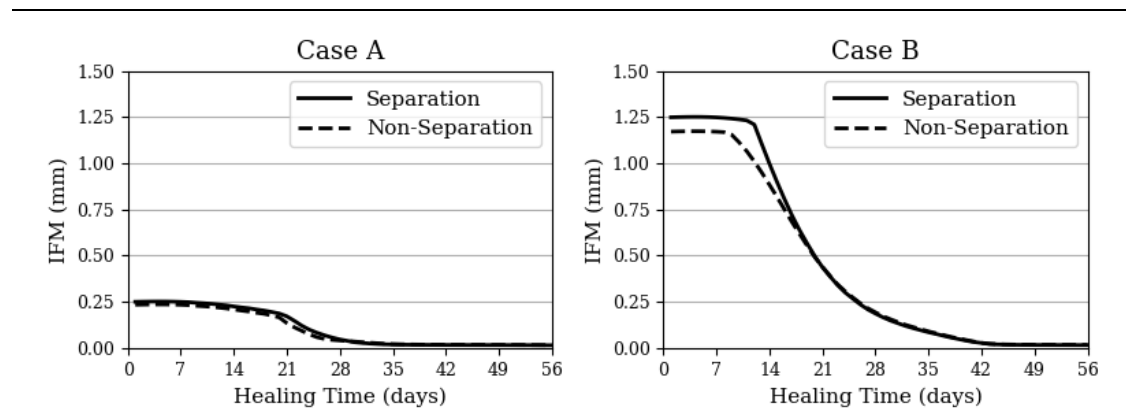


Figure 3.10: Recreated healing algorithm results of IFM throughout the healing process for two different fixator configurations (Case A and Case B), each simulated with both a separation method, as by Simon *et al.*, and with a non-separation method.

The time evolutions of perfusion, bone concentration, and cartilage are shown in Figure 3.11 for the Ulm Healing Algorithm and in Figure 3.12 for the recreated results for cases A and B using the separation technique. The same iterations (14, 28, 42, and 56) are shown for each figure.

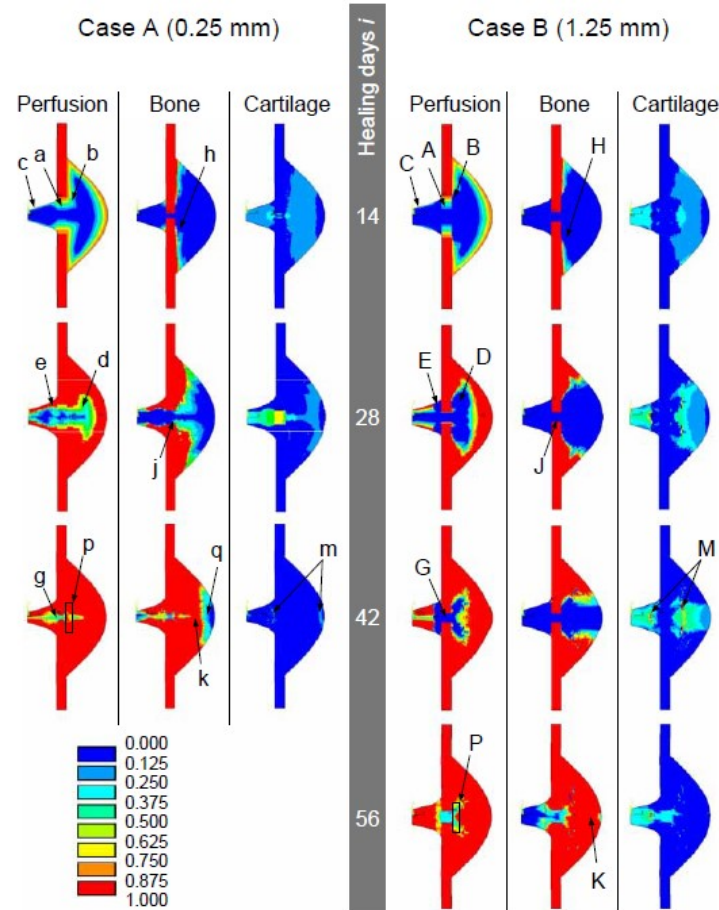


Figure 3.11: The perfusion, bone concentration, and cartilage concentration of the Ulm Fracture-healing algorithm (Simon *et al.*, 2011) for cases A and B at iterations 14, 28, 42, and 56. Image reproduced with permission of the rights holder, Taylor & Francis.

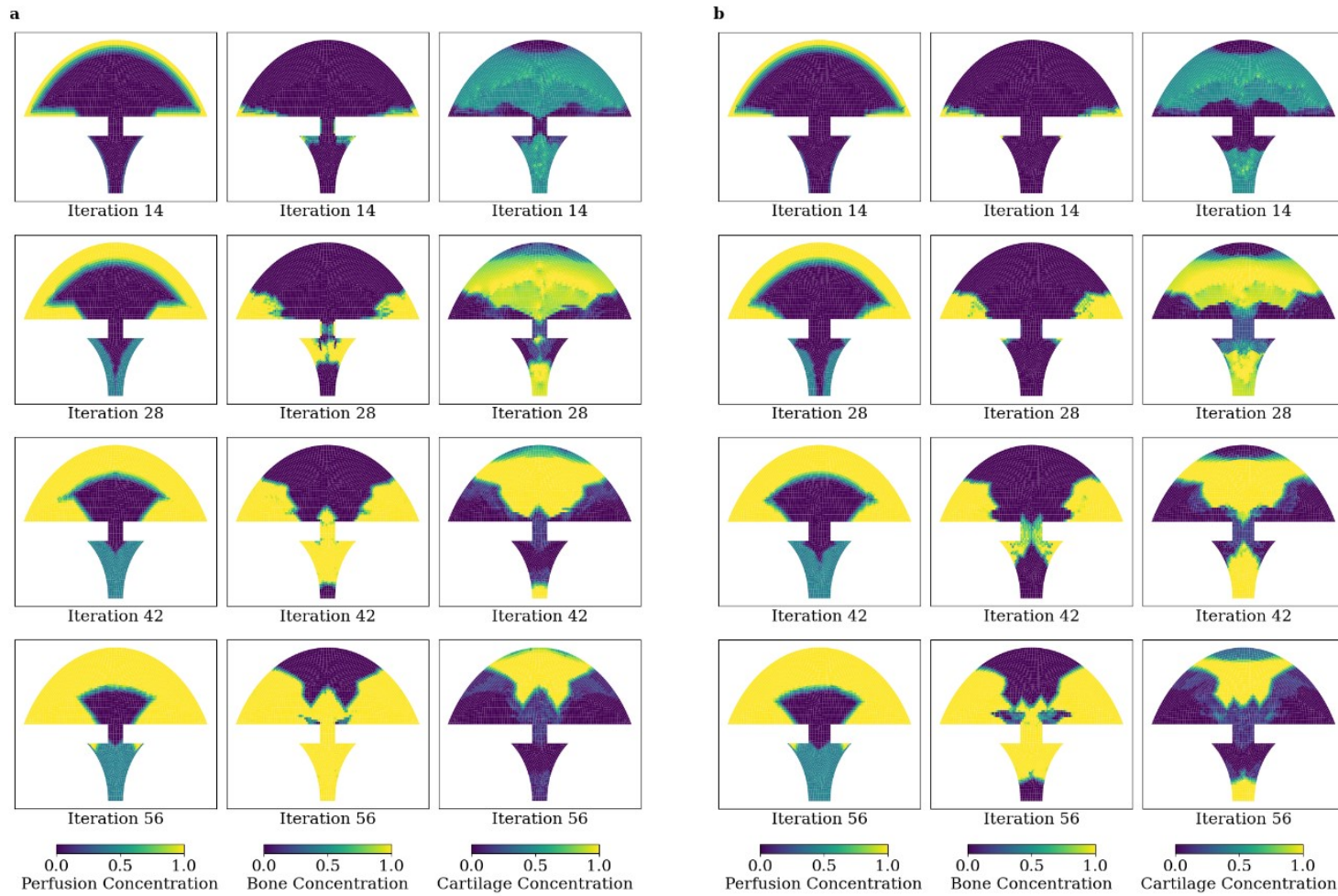


Figure 3.12: The perfusion, bone concentration, and cartilage concentration of the recreated healing algorithm at iterations 14, 28, 42, and 56 for (a) case A and (b) case B.

3.4.3 Discussion

3.4.3.1 Comparison of results

The resultant IFM progressions of cases A and B for the Ulm algorithm and the recreated algorithm agree fairly well, as shown in Figure 3.9 and Figure 3.10. In case B, the Ulm algorithm and the present model have a largely similar pattern of healing, however, the present model initiates the callus ossification process earlier in the process than the original Ulm algorithm. Despite the recreated model achieving similar IFM progressions as the Ulm model, the time evolutions of the perfusion, bone concentration, and cartilage concentration are significantly different from each other, as shown in Figure 3.11 and Figure 3.12. This failure to recreate the results of the Ulm model using the methods as described in the paper demonstrate likely errors in their described methods. These are described in more detail below. Additionally, the ability of the recreated model to relatively match the predicted IFM progression of the Ulm model, despite clearly having differing underlying model mechanics, demonstrates the inadequacy of IFM progression as a validation measure.

While the healing patterns reported in the Ulm algorithm and the present recreation of the algorithm differ, both are not physiological. In both cases, periosteal bone growth initiates at the ‘corners’ of the callus, at the locations furthest from the fracture site. Physiologically, periosteal bone growth begins adjacent to the fracture site (Figure 3.5).

3.4.3.2 Separation technique

Simon et. al. (2011) used a “separation” technique in order to linearise the FE model and reduce computational times of the algorithm. The “linear” callus was separated from the non-linear stiffness of the external fixator. The FE model was created with only the callus and cortex elements and an applied displacement boundary condition was used. The stiffness of the callus was determined from the reaction force generated by the displacement condition, and this callus stiffness was added to the non-linear stiffness of the external fixator. The inverse of this overall stiffness function was used to calculate the actual displacement, or IFM, of the system

for the true applied load of 500 N. The ratio of this actual displacement to the originally applied displacement was used as a linear scaling factor, and the element strains calculated in the FE model were scaled by this factor.

The aim of this separation technique is to reduce the complexity of the FE model by developing a linear model involving only the callus. However, the fracture gap sizes used are 2.1 mm and 3.1 mm for cases A and B, respectively, and the applied displacement is 1 mm. The IFS, therefore, can be approximated at 50% and 33%, respectively – far beyond the range of linear analysis.

Additionally, the fixator stiffness given in Figure 3.7 is poorly defined. The stiffness in the pre-tensioning region is not given. Furthermore, the displacement shown for the fixator at an applied load of 500 N is 0.25 mm and 1.25 mm for case A and B, respectively. When the fixator and callus are both modelled, the callus would have some stiffness contribution, and the IFM must therefore be less than 0.25 mm and 1.25 mm for the applied load of 500 N. However, the results shown in Figure 3.9 show an initial IFM of 0.25 mm and 1.25 mm. A possible explanation for this discrepancy is an inaccurate description of the non-linear stiffness shown in Figure 3.7 – this stiffness may refer to the overall system stiffness, as opposed to the fixator stiffness, as the figure labels would imply. In the present model, the fixator stiffness was constructed such that the overall initial system stiffness would lead to either a 0.25 mm or 1.25 mm IFM for a 500 N applied load.

The simulations in the present model were also run using a non-separated FE model in which the external fixator was represented as a fixed degree-of-freedom spring using the axial stiffness chart exactly as given in Figure 3.7. This resulted in different initial IFM results, as shown in Figure 3.10, as the callus provides an additional stiffness contribution. There are no major differences in the results of the non-separated simulation beyond the slight difference in initial IFM. This implies that the overall healing algorithm is relatively insensitive to the parameters of the FE model.

3.4.3.3 Callus shape

Callus shape and size has been shown to influence the results of other variations of the Ulm algorithm (Wehner *et al.*, 2010). The callus geometry used by Simon *et al.* is not well defined, only referencing the “standardised” callus geometry used by Claes and Heigele (1999). This geometry has been recreated in the present model using all available information, however, there are likely some discrepancies due to unreported methods by Simon *et al.* (2011). Cases A and B are described as two separate models with the same compressed IFM of 1.85 mm, and different uncompressed IFMs of 2.10 mm and 3.10 mm, respectively. However, Simon *et al.* only report one mesh size, which would imply both cases were simulated using the same mesh and geometry. Combined with the reported equal compressed IFM, this would possibly imply that the FE models were initialised in the compressed state, and a tensile, rather than compressive load, was applied. This would be inconsistent with the animal experiments which the study aimed to replicate, and the methodology reported is unclear. This is an additional possible cause of the discrepancy between the results of Simon *et al.* (Figure 3.9) and those of the present model (Figure 3.10).

Discrepancies in the element-size scaling methods used, as shown in equations 3 and 4, could also explain differences between the results obtained in the recreated model. Equation 3, as used in the Ulm algorithm, uses a “reference element area” to scale the outputs of the fuzzy system, however, this reference area is not reported. The present model uses the average element area as the reference element area. If a different reference area was used by Simon *et al.*, this could lead to different results.

3.4.3.4 Errors in reported methods

The methods described by Simon *et al.* have several definite errors in some areas and lack sufficient information in others. The fuzzy-logic rules describe angiogenesis as occurring with a dilatational strain of ‘Neg. Med to Pos. High’ (Table 3.2), however, the fuzzy-logic membership function for dilatational strain has no membership function for ‘Pos. High’, only a ‘Pos. Med’ and ‘Pos. Destructive’ (Figure 3.8a). The ‘Pos. High’ described in the fuzzy-logic rule cannot simply be another name for ‘Pos. Destructive’, as the destructive magnitude strains are reserved

for the atrophy rules, and therefore must be ‘Pos. Med’. This is the only verifiable error in the listed fuzzy-logic rules, but there are likely additional errors as the results reported by Simon et al. were not reproduced with either variation of the angiogenesis rule, nor with any other logical set of rules which may have been the actually implemented rule-set.

An additional definitive error in the methods described by Simon et al. is the perfusion concentration initial condition. The peripheral boundary of the callus was initialised with a perfusion of 30% (Simon *et al.*, 2011). Based on the fuzzy-logic membership function for perfusion (Figure 3.8c), these peripheral elements would have a perfusion of ‘Low’ and ‘Medium’. Angiogenesis has two fuzzy-rules: the first describes that an element with ‘Low’ perfusion must have a neighbouring element with ‘Med’ or ‘High’ perfusion; the second describes that an element with ‘Med’ or ‘High’ perfusion must have a neighbouring element with ‘High’ perfusion (Table 3.2). The first rule will occur, as the peripheral elements have ‘Low’ perfusion, and also have neighbours with ‘Med’ perfusion, since all peripheral elements are partially ‘Low’ and partially ‘Med’. Therefore, the first angiogenesis rule will occur in these elements until a perfusion concentration of 40% is reached, at which point the elements will no longer satisfy the ‘Low’ perfusion requirement for this rule. The second rule cannot be activated with a perfusion concentration of 40%, as it requires a neighbouring element with a ‘High’ perfusion of at least 60% (Figure 3.8c). Therefore, the initial condition described by Simon et al. results in all peripheral elements having a maximum perfusion concentration of 40%. An attempted recreation simulation using the initial conditions as described confirmed these findings. The results reported by Simon et al. in Figure 3.11 do not agree with the angiogenesis pathway described by their initial conditions. Therefore, the initial conditions reported by Simon et al. are incorrect. The angiogenesis pathway reported by Simon et al. in Figure 3.11 was partially replicated by modifying the second angiogenesis rule to require a neighbouring perfusion concentration of either ‘Med’ or ‘High’, but discrepancies remain, and other logical substitutions in the angiogenesis rules did not result in more similar angiogenesis pathways.

In addition to the definitive errors described above, some information required to recreate the model is lacking. Neighbouring elements are defined as ‘adjacent’

which implies a definition of two nodes shared between neighbouring quadrilateral elements. Simulations using this neighbouring element definition, however, resulted in drastically different simulated healing pathways. Neighbouring elements were likely actually defined as sharing one node in the model used by Simon et al., and this is the definition which was used in the present recreation.

The discrepancies between the methods reported and the methods which were likely actually used in the study by Simon et al. highlights the need for transparency in significantly code-based research studies. The algorithm presented in the study by Simon et al. was the only algorithm for which a recreation and replication effort was made in this work, however, no study presenting or using a fracture-healing algorithm has provided accompanying source code for their respective algorithms and there is a similar lack of methodological details. This lack of transparency in fracture-healing algorithms harms reproducibility efforts and weakens the credibility of these algorithms. The code used in the present replication effort is available at <https://github.com/GeorgeTMorgan/Ulm-Fracture-Healing-Algorithm-Recreation>.

3.4.3.5 *Distortional strain*

Distortional strain has been used as a primary input in each of the reviewed fracture-healing algorithms, and has been identified as the most comprehensive single mechanical input (Isaksson *et al.*, 2006). Distortional strain was chosen as it is basis-system invariant and quantifies shape change, which is widely understood to drive cellular mechanobiology. Distortional strain has been identified correctly as well-correlated with, and a good predictor of, both intramembranous ossification and endochondral ossification, the two main ossification processes involved with secondary fracture healing. However, distortional strain is unable to distinguish tensile-dominated shape change from compressive-dominated shape change due to its numerical formulation (equation 2). Therefore, if intramembranous ossification is more associated with tensile shape change and endochondral ossification is more associated with compressive shape change, then distortional strain is a poor predictive measure, as a given distortional strain conveys no differentiation between tensile and compressive shape change. Further description of the limitations of distortional strain as an

input for fracture-healing algorithms, as well as a proposed novel strain measure which address this limitation, are given in Chapter 4.

3.5 Conclusion

Published fracture-healing algorithms were reviewed and several key limitations were identified. The use of perfusion or cellular diffusion parameters makes these algorithms dependent on the initially-specified callus domain and highly sensitive to the perfusion or diffusion rate parameters, whose values are uncertain. Some studies perform mesh convergence analyses on the FE models used, but a mesh convergence analysis is never performed on the fracture-healing algorithm as whole, despite being a mesh-based algorithm. Experimental validation of published algorithms is performed only on successful healing cases and not on cases resulting in non-unions, which greatly limits the ability of these algorithms to be applied as predictive tools for non-union. Qualitatively, the algorithms reviewed predict non-physiological healing sequences, specifically in the pathways of periosteal bone growth. Additionally, poor methodological reporting in fracture-healing algorithms means work cannot be reproduced. A novel algorithm which addresses these limitations should be developed and any studies conducted with the algorithm should report the code used, in full, on open-source code platforms.

CHAPTER 4

VALIDATION OF A NOVEL FRACTURE- HEALING ALGORITHM

4.1 Scope

Chapter 3 reviewed existing fracture-healing algorithms and their applications. The style of model which is best suited to the structurally focused aims of this project was identified. The major limitations of the model, and of others, were identified. Specifically, non-physiological sequences of fracture healing are predicted, simulations are dependent on the initially specified callus domain and are overly sensitive to diffusion or perfusion-rate parameters, or the shape and healing sequence of the callus is prescribed with a spatial proximity function. This chapter develops a novel fracture-healing algorithm which is capable of overcoming these limitations by using principal strains as the mechanical signals. The algorithm is then tested for validation against experimental animal data.

Part of this chapter has published in the following journal article, with minor modifications:

Morgan, G.T., Low, L., Ramasamy, A., Masouros, S.D. (2024). A novel strain-based bone-fracture healing algorithm is able to predict a range of healing outcomes. *Frontiers in Bioengineering and Biotechnology*.

4.2 Introduction

Fracture healing is a complex process influenced by several mechanobiological parameters. In order to optimise fracture healing whilst taking into account these parameters, best treatment practices are determined typically by comparing treatments through *in vitro* benchtop testing and *in vivo* RCT's. However, the debate over optimal surgical treatments for certain fractures, such as distal femoral fractures, persists due to limitations of *in vitro* testing and *in vivo* RCT's (Megafu *et al.*, 2022; Wadhwa *et al.*, 2022). *In vitro* testing of fracture fixation is constrained by the scope of bioreactor ossification, which is limited to early stages of callus formation (Hoffmann, 2015) or bony ingrowth and remodelling of *ex vivo* bone (Kohli *et al.*, 2023). *In vitro* assessments are therefore limited to the initial fixation stiffness

and preclude evaluation of the effects of loading on the healing process itself. *In vivo* testing through RCT's can be limited by challenges in patient and surgeon recruitment, especially in less common fractures, as demonstrated by a feasibility study which concluded that an adequately powered RCT for distal femoral fracture fixation would not be viable due to limited patient and surgeon recruitment (Griffin *et al.*, 2019). Similar medical questions which have been left unanswered by traditional testing have recently been addressed effectively by *in silico* trials (Pappalardo *et al.*, 2019, 2022; Sarrami-Foroushani *et al.*, 2021; Viceconti *et al.*, 2021). Currently, there is no such *in silico* trial for fracture treatment as computational tools for fracture healing are under-developed.

Fracture-healing numerical algorithms have been developed that simulate fracture-healing progression in response to local mechanical environments in the callus region. These algorithms have previously been applied to the optimisation of fracture-fixator stiffness to improve healing outcomes (Steiner *et al.*, 2014b; Quinn, Kopp and Vaughan, 2022; Nayak *et al.*, 2024). Further potential applications of this technology include novel fracture-fixation device development, pre-surgical planning, and rehabilitation-regime optimisation. Previous fracture-healing algorithms, however, have limited abilities to explore such applications adequately. While some algorithms have been compared against *in vivo* experimental data, they have generally only been shown to replicate successful healing cases; they have not been shown to predict cases resulting in non-union. This limits these algorithms from being used as predictive tools for non-union risk assessment and therefore pre-clinical decision making and improvement of fracture treatment.

The ability of existing algorithms to demonstrate a physiological healing sequence is dependent upon, and highly sensitive to, the diffusion-rate parameter, which represents either a process of cellular diffusion (Lacroix and Prendergast, 2002a; Isaksson *et al.*, 2008; Ghiasi *et al.*, 2019; Quinn, Kopp and Vaughan, 2022) or angiogenesis (Shelfelbine *et al.*, 2005; Simon *et al.*, 2011). These processes require the presence of MSC's or vascularisation, respectively, in a specific region of the callus to allow ossification to occur. Diffusion is initialised from the external callus boundary, which prevents spurious bony union in the inter-cortical gap. This means that, in

addition to these algorithms being highly sensitive to the diffusion rate parameter, they are also highly sensitive to the initial callus region geometry. As callus geometry is highly variable between fracture types and the callus shape is unknown at the point of pre-surgical planning, this limitation further precludes these algorithms from several possible applications. To address this limitation, a recent algorithm did not include a diffusion process and instead used a spatial proximity function which specifically prevented early ossification in the inter-cortical gap (Schwarzenberg *et al.*, 2021). This attempt, however, had the same effect in prescribing the callus ossification pathway as the algorithms which used a diffusion process.

All fracture-healing algorithms which include strains as mechanical stimuli use the strain thresholds identified by Claes and Heigele (Claes and Heigele, 1999) for distortional and dilatational strain. Distortional strain has been identified as the more important strain input of the two in fracture-healing algorithms (Isaksson *et al.*, 2006). While distortional strain is highly correlated to both minimum and maximum principal strains based on its mathematical formulation, it is unable to distinguish between the two. For example, if a 5% maximum principal strain and zero minimum principal strain should predict intramembranous ossification, and a -5% minimum principal strain and zero maximum principal strain should predict endochondral ossification, then both situations would have a distortional strain of 5%, and distortional strain alone would be insufficient to distinguish between these situations. During secondary fracture healing, intramembranous ossification occurs on the growing bony bulges on the periosteum where shear dominates, however, the material directly external to the bulges experiences tension, which can be represented with maximum principal strain (Figure 4.1). Chondrogenesis and endochondral ossification occur in the region between the bulges where compression dominates, and this can be represented by the magnitude of minimum principal strain. This study presents a novel fracture-healing algorithm which uses principal strains as the mechanical stimuli.

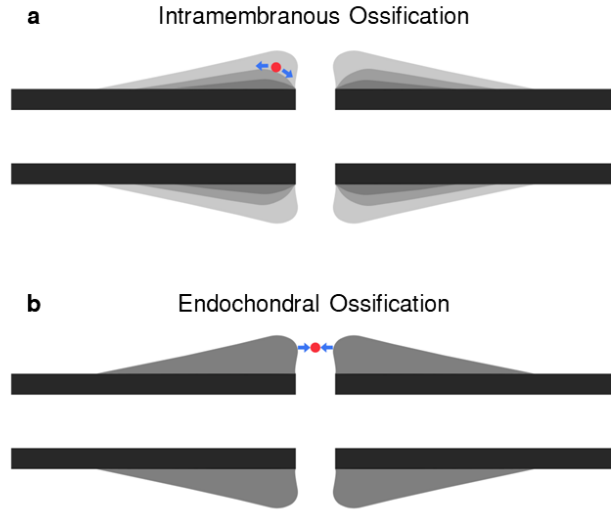


Figure 4.1: Diagram of (a) intramembranous ossification and (b) endochondral ossification pathways. In each panel, a representative ‘cell’ laying on the ossification pathway is shown in red. During axial compression, the ‘cell’ in panel (a) will experience shear, resulting in tensile strains, or high maximum principal strains, and in panel (b) will experience compressive strains, or high minimum principal strains.

4.3 Methods

4.3.1 Fracture-healing algorithm

The fracture-healing algorithm developed and used in the present study is described by the flowchart in Figure 4.2, where each of the boxes ‘FE Model’, ‘Biological Controller’, and ‘Healing Assessment’ are described in more detail below. An FE model was developed of the fracture site, the initial callus domain, and the fixator. Each callus finite-element was represented as a mixture of 3 tissue types: woven bone, cartilage, and soft tissue. Loading was applied and the resultant callus element strains were used as inputs to the biological controller, which determined updated tissue-type proportions, and in turn updated the callus element material properties in the FE model. This process was performed iteratively 150 times. The final FE model was then adapted to simulate a bending test to assess the bending stiffness of the final callus.

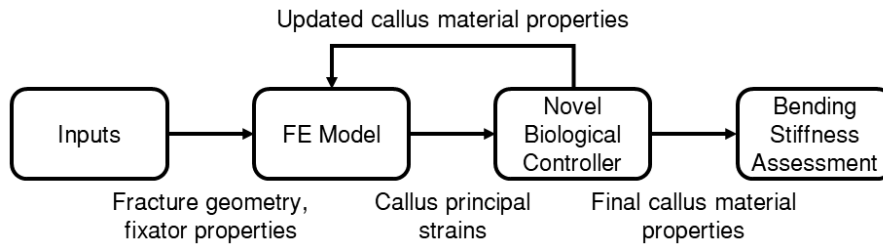


Figure 4.2: Flowchart of the novel fracture-healing algorithm, where the primary novelty is the biological controller using principal strains as its inputs.

Six different fracture cases were modelled with initial gap widths of 1 mm, 2 mm, and 6 mm, and initial IFS of 7% and 31%. Gap width is the distance between the two bone segments in the compressed state (Claes *et al.*, 1997). IFS is the amount of axial displacement of the bone segments relative to each other divided by the initial gap width. The combination of gap widths and initial IFS for each case is given in Table 4.1. These 6 models correspond to the groups used in an experimental study on ovine metatarsal osteotomies stabilised with a custom external fixator (Claes *et al.*, 1997), therefore allowing comparison between simulation results and experimental observations. The experimental groups included groups which resulted in successful unions and groups which resulted in non-unions.

Group	A	B	C	D	E	F
Gap width (mm)	1	1	2	2	6	6
IFS (%)	7	31	7	31	7	31

Table 4.1: Fracture gap width and initial IFS in each of the simulated groups, corresponding to the groups used in an experimental study by Claes *et al.* (Claes *et al.*, 1997).

4.3.2 FE model

An axisymmetric non-linear FE model was developed in MSC.Marc (v2021, MSC Software) of a simple transverse mid-diaphyseal metatarsal ovine osteotomy secured with an external fixator. The callus was modelled explicitly (Figure 4.3a). An 80 mm long section of the fracture region was modelled with the metatarsus represented as a hollow cylinder, with outer diameter and thickness of 16 mm and 2 mm, respectively. The callus domain was initialised with a diameter of 48 mm and a length of 52 mm, and shaped according to a standardised callus domain geometry in fracture-healing algorithms (Claes and Heigele, 1999; Shefelbine *et al.*, 2005; Simon

et al., 2011). The gap width of 1 mm, 2 mm, or 6 mm, references the gap width in the loaded state, as described in the experimental study by Claes *et al.* (Claes *et al.*, 1997). The geometry was meshed using linear triangular elements with an average element edge-length of 0.35 mm.

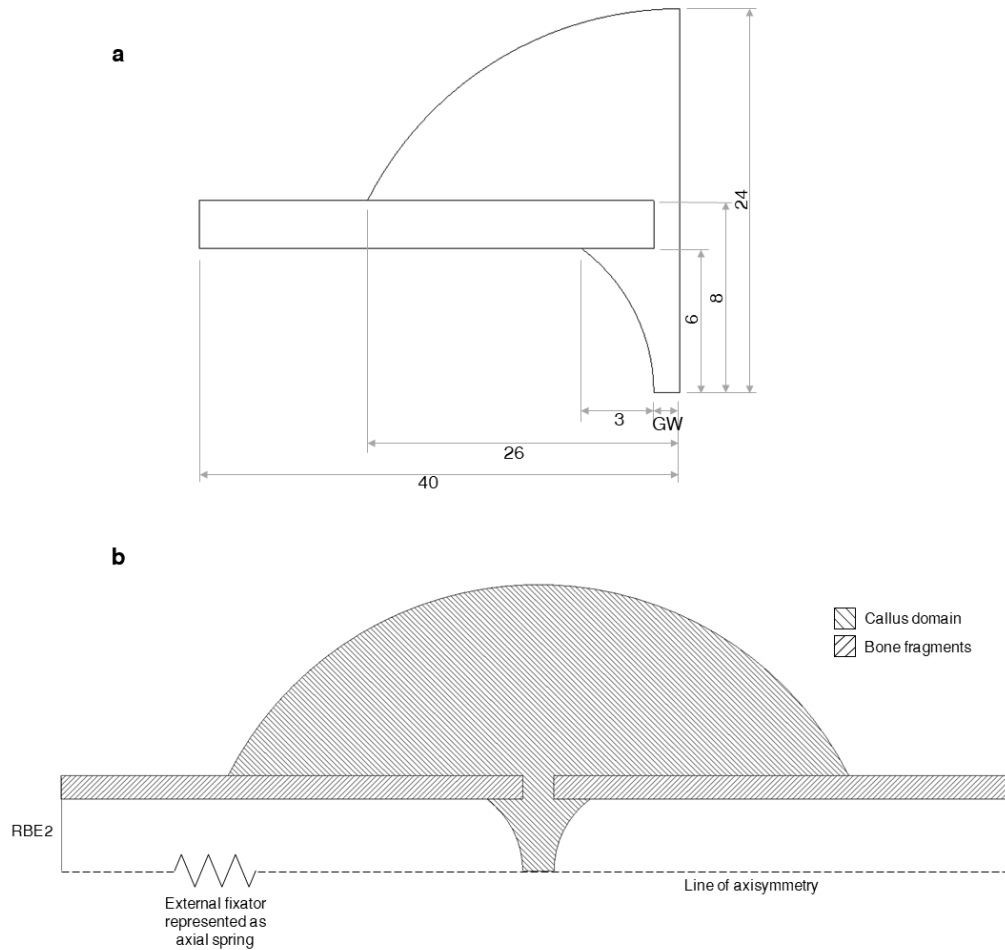


Figure 4.3: (a) Dimensions (in mm) of the bone fragments and callus region. GW denotes “gap width” in the uncompressed state and equals 1.07, 1.31, 2.14, 2.62, 6.42, and 7.86 mm for groups A-F, respectively. The gap widths of 1, 2, and 6 mm reported by Claes *et al.* were measured in the compressed state and must be scaled by the allowed initial IFS of 7% or 31% to determine the gap width in the uncompressed state. (b) Diagram of the axisymmetric FE model of a fracture, callus domain, and fixator. The external fixator is represented as a non-linear axial spring running from the far ends of both bone fragments. The securement of the fixator to each bone section is represented with rigid-body-elements (RBE2’s) connecting the far end of each bone fragment to a node located on the line of axisymmetry with all degrees of freedom linked.

The tissue types modelled were soft tissue, cartilage, woven bone, and lamellar bone. These were assigned Young’s moduli of 3, 200, 4000, and 10,000

MPa, respectively, and Poisson's ratios of 0.30, 0.45, 0.36, and 0.36, respectively. All materials were modelled as linearly elastic and isotropic (Simon *et al.*, 2011; Ren and Dailey, 2020a). All callus elements were assigned soft tissue material properties at the first iteration. After each iteration, the Young's modulus and Poisson's ratio of each callus element were calculated from the updated proportion of each tissue type within the element according to a cubic, and linear rule of mixture, respectively (Simon *et al.*, 2011), as described in equations 5 and 6 in Chapter 3.

The external fixator used in Claes *et al.* (Claes *et al.*, 1995) was designed to allow for a pre-determined amount of axial motion. The amount of free axial movement allowed was set to the desired distance while the fixated limb was in the loaded state (Claes *et al.*, 1997). In the present study, the fixator was modelled as a non-linear axial spring, with an initial stiffness of 4600 N mm^{-1} up to a force of 100 N, then a stiffness of 10 N mm^{-1} up to the desired free movement distance, and a stiffness of 4600 N mm^{-1} beyond (Claes *et al.*, 1997; Simon *et al.*, 2011).

Boundary conditions were applied at both ends of the bone construct (Figure 4.3b). Nodes on the distal cut-face were held in three translational directions and nodes on the proximal cut-face were held in two translational directions, allowing for relative axial movement. These conditions were applied in FE by using rigid-body-elements (RBE2's) with a control node for each face placed on the line of axisymmetry. The shear and torsional rigidities of the fixator are reported to be high (Claes *et al.*, 1995, 1997; Claes and Heigele, 1999), therefore shear and torsional loads were not modelled. The spring representing the external fixator connected the two retained nodes of the RBE2's at the bone ends. An axial load of 500 N was applied to the proximal retained node (Claes and Heigele, 1999; Simon *et al.*, 2011).

4.3.3 Strain calibration

The FE models of groups C and D were used to calibrate the strain thresholds of the biological controller. These models represent the initial stage of fracture healing when intramembranous ossification occurs. Reported final hard callus cross sectional areas from experimental data (Claes *et al.*, 1997) were used to develop FE models of

the final stages of fracture healing, after bony protrusions caused by intramembranous ossification had finished growing, and chondrogenesis was set to begin. The FE models of the final stages of fracture healing are shown in Figure 4.4.

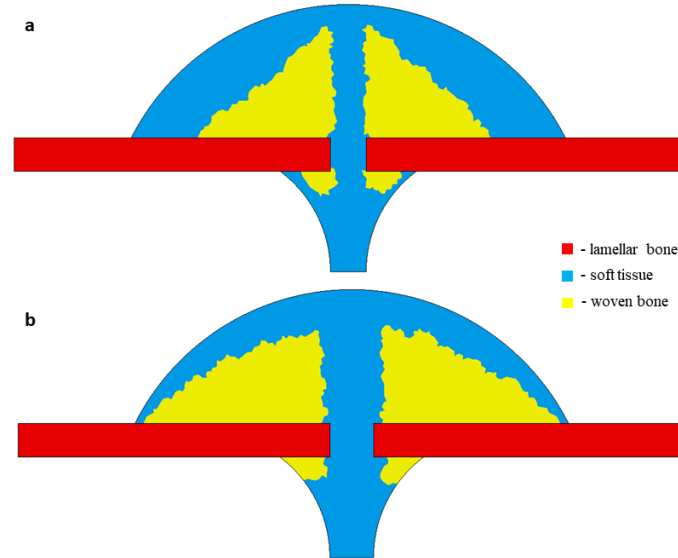


Figure 4.4: Material distributions in the FE models of the final stages of fracture healing, after bony outgrowths caused by intramembranous ossification have finished growing; (a) the model of group C (b) the model of group D.

Maximum principal strains at the initial stage of fracture healing are shown in Figure 4.5. Minimum principal strains in the callus at the final stages of fracture healing are shown in Figure 4.6. Distortional strains in the callus at the initial stage of fracture healing are shown in Figure 4.7.

The strain thresholds used in the biological controller were approximated based on these results. The maximum permissible distortional strains for biological processes to occur can be observed in Figure 4.7b, with fracture healing prevented in the intercortical fracture gap. The optimal range of minimum principal strain is shown on the strain contour plot shown in Figure 4.6, at the boundary of the periosteal bulges at the fracture gap.

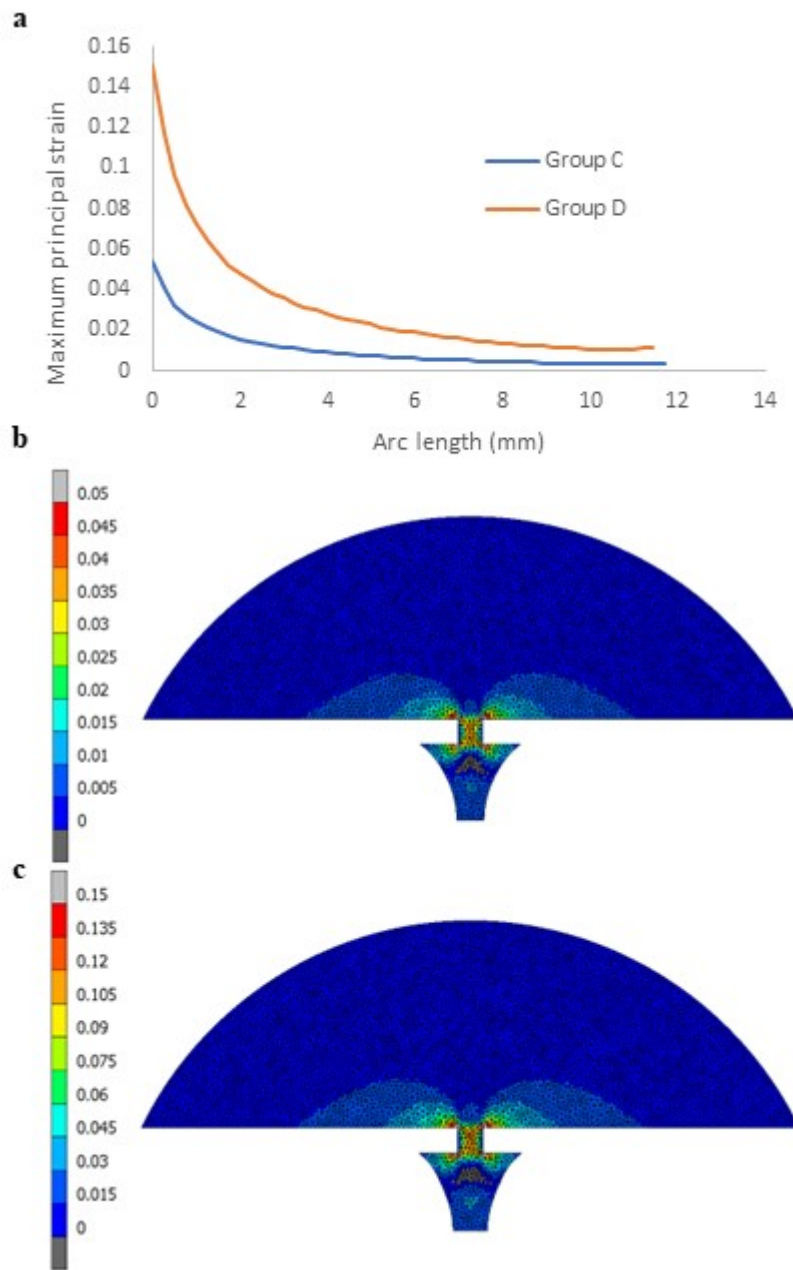


Figure 4.5: (a) The maximum principal strain along the periosteal surface where arc length represents the distance from the fracture line along the periosteal surface. These strains were extracted directly as a path plot from the FE post-processing software. Contour plots of maximum principal strain in the callus at the models of the initial stage of fracture healing for (b) group C and (c) group D. Element lines are shown and nodal averaging is off.

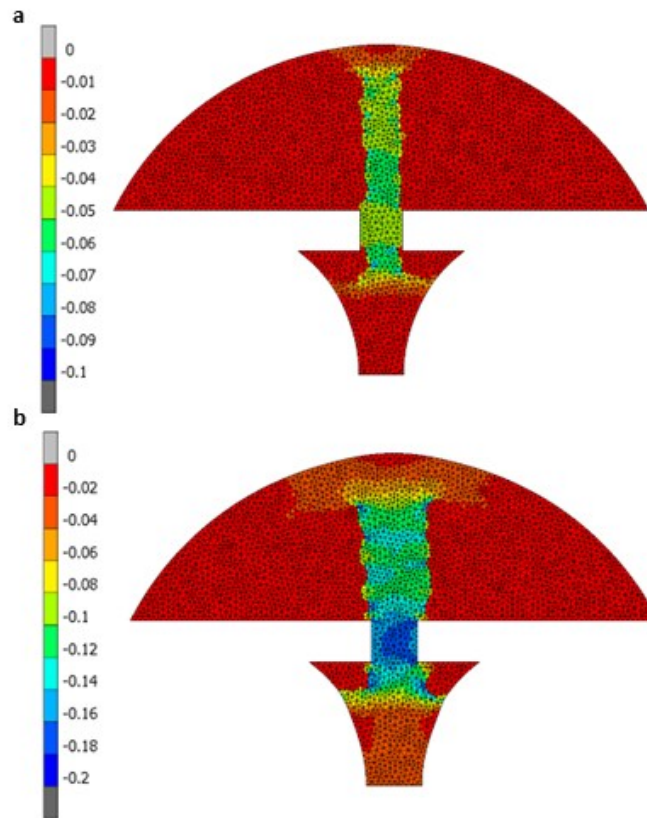


Figure 4.6: Contour plots of minimum principal strain in the callus at the models of the final stages of fracture healing for (a) group C and (b) group D. Element lines are shown and nodal averaging is off.

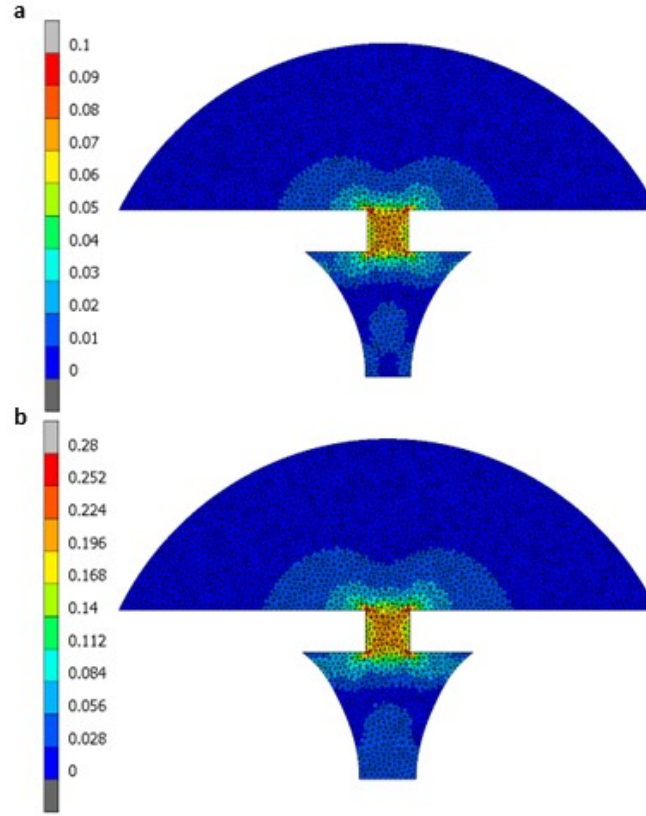


Figure 4.7: Contour plots of distortional strain in the callus at the models of the initial stages of fracture healing for (a) group C and (b) group D. Element lines are shown and nodal averaging is off.

4.3.4 Biological controller

A fuzzy logics approach was used to simulate some of the biological processes involved in secondary fracture healing based on previous fracture-healing algorithms (Ament and Hofer, 2000; Shefelbine *et al.*, 2005; Simon *et al.*, 2011; Schwarzenberg *et al.*, 2021). The present study is the first to use minimum and maximum principal strains as mechanical inputs. The biological fuzzy logic controller was developed using the Scikit-Fuzzy (v0.4.2) fuzzy logic toolbox (Warner *et al.*, 2019) in Python (v3.6, Python Software Foundation). The fuzzy logic controller determines the proportion of soft tissue, cartilage, and woven bone in each finite-element at the next iteration. The inputs to the fuzzy controller are the minimum principal, maximum principal, and distortional strains in each element in the current iteration, as well as the proportion of cartilage and woven bone in each element (c_{cart} and c_{bone}) and the maximum proportion of cartilage and bone of all neighbouring elements (c_{nCart} and

c_{nBone}). Neighbouring elements are defined as elements which share at least 1 node. The proportion of soft tissue in each element (c_{soft}) is determined from the relation given in equation 7, where c_{cart} and c_{bone} represent the proportion of cartilage and bone in the element, respectively.

$$c_{soft} = 1 - c_{cart} - c_{bone} \quad (7)$$

Inputs are “fuzzified” by determining their membership of linguistic categorisations in their corresponding membership functions. The degree of membership is calculated on a 0 to 1 scale. Fuzzy membership functions were defined for tissue proportions (Figure 4.8a), minimum principal strain (Figure 4.8b), maximum principal strain (Figure 4.8c), and distortional strain (Figure 4.8d).

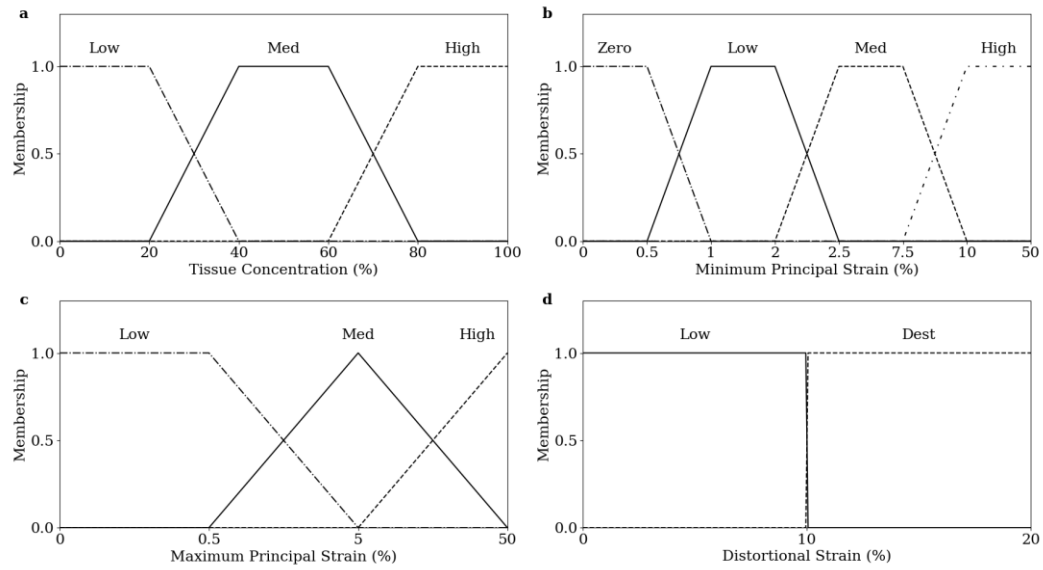


Figure 4.8: Fuzzy membership functions of inputs, (a) tissue prop, (b) minimum principal strain, (c) maximum principal strain, and (d) distortional strain.

Four of the biological processes involved in the fracture healing process were implemented: chondrogenesis, cartilage calcification, intramembranous ossification, and endochondral ossification. Chondrogenesis was disabled for the first 7 iterations to prevent non-physiological periosteal cartilage formation. Each biological process was modelled as a fuzzy logic rule; the set of rules is given in Table 4.2.

Rule	Bone	Cart	nBone	nCart	Minimum Principal Strain	Maximum Principal Strain	Distortional Strain	Δ Bone	Δ Cart
Intramembranous Ossification		Low	Med or High			Med	Low	1	0
Chondrogenesis	Low		Med or High		Med	Low	Low	0	1
Chondrogenesis	Low			Med or High	Med	Low	Low	0	1
Cartilage Calcification	High	Low	High					1	-1
Endochondral Ossification		Med or High	Med or High		Low			1	-1

Table 4.2: The four fuzzy logics rules implemented in the fracture-healing algorithm.

The calculation of the maximum proportion of cartilage and bone of neighbouring elements (c_{nCart} and c_{nBone}) requires each element to have a list of neighbouring elements through which to search for a maximum value. The construction of the lists of neighbouring elements for each element is prohibitively computationally expensive if a iterative looping algorithm is used, so a matrix-based neighbouring-element algorithm was developed. A connectivity matrix of dimensions $m \times n$ is constructed, where m is the number of global nodes and n is the number of global elements. The matrix is populated with booleans; for each row, representing an element in the mesh, the columns representing the nodes which belong to the element are populated with a 1, and all others with a 0. This matrix is multiplied with its transpose, yielding an $n \times n$ matrix, where each cell represents a pair of elements and is populated with the number of common nodes. A mask is then applied with the desired number of minimum common nodes to define a neighbour. A simple example is shown in Figure 4.9.

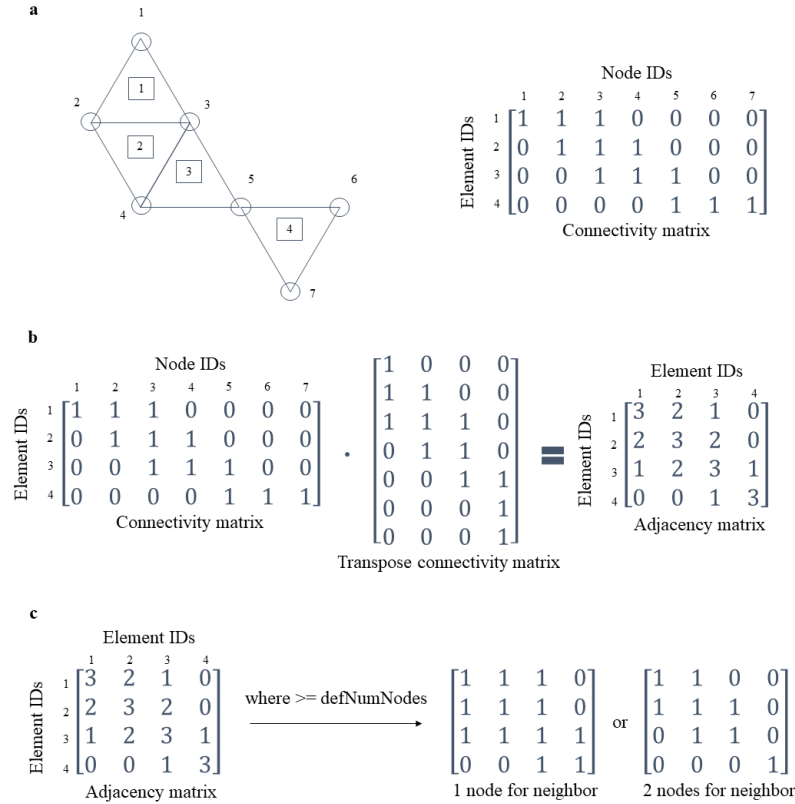


Figure 4.9: An example of the matrix-based adjacency algorithm. (a) A simple FE mesh consisting of triangular elements, with its corresponding connectivity matrix. (b) A demonstration of the multiplication of the connectivity matrix with its own transpose to yield the adjacency matrix. (c) Application of a mask to return a boolean matrix depending on the desired minimum number of shared nodes to define a neighbouring element.

The degree of activation of each rule was determined by interpreting the linguistic rule numerically. The membership of each individual statement was a value between 0 and 1, as determined by their input value and corresponding membership function. Each rule yields a single value between 0 and 1 which represents the degree of activation of that rule for the element. The effects on bone and cartilage concentration of all rules were summed for each element to determine the overall change in composition for the element.

A temporal smoothing function was applied in which the bone and cartilage concentrations in the current iteration were calculated as the mean un-smoothed concentrations calculated by the algorithm on the previous N iterations (Lacroix and Prendergast, 2002a). A parameter coefficient was used to scale the changes in bone

and cartilage concentrations according to the element size. The parameter coefficient was inversely proportional to the average callus element edge length, so a smaller element edge length means a larger parameter coefficient is used. The temporal smoothing parameter N was directly proportional to the average callus element edge length, and rounded to the nearest whole number. The parameter coefficient and temporal smoothing parameter for the callus mesh with an average element edge length of 0.35 mm were 0.57 and 7, respectively. A mesh convergence study was performed with average callus element edge lengths of 0.5 mm, 0.35 mm, 0.25 mm, and 0.2 mm.

A callus-domain independence study was performed by increasing the initial region of the callus in group B by 13% in radius and 20% in length. This study was performed to test the dependence of the algorithm on the size of the initialised callus domain.

The code for the biological controller and interfacing with FE software is available at <https://github.com/GeorgeTMorgan/fracture-healing-algorithm>.

4.3.5 Healing assessment

Bending stiffness of the fracture site was used as the healing assessment as IFM is a poor indicator of union (Ren and Dailey, 2020a) and the corresponding experimental data includes a final bending stiffness assessment (Claes *et al.*, 1997). Each axisymmetric FE model was converted to its corresponding 3-D FE model to assess the bending stiffness of the final construct and resultant callus. The bone fragments were extended axially to create a 150 mm long fracture region, as was used in the experimental bending stiffness assessment by Claes *et al.* (Claes *et al.*, 1997). The bone fragments and callus were meshed with linear tetrahedral elements with element sizes of 1 mm and 0.5 mm, respectively. Material properties for the callus elements were mapped from the 2-D callus by linearly interpolating values of Young's modulus and Poisson's ratio from the centroids of the 2-D callus elements, or by using a 'nearest' extrapolation for 3-D callus elements whose centroids fell outside of the interpolation window created by the 2-D callus element centroids. The

spring representing the external fixator was removed, as the fixator was explanted prior to experimental bending stiffness assessment (Claes *et al.*, 1997). A bending moment of 1500 N mm was applied through the retained node of the RBE2's at each bone fragment end. The distal retained node was fixed in all 5 other degrees of freedom, and the proximal retained node was fixed in 4 degrees of freedom, allowing for axial translation. Deflection was measured at the central-most node of the callus. Bending stiffness was calculated as the applied moment divided by the mid-span deflection.

4.4 Results

The temporal IFM progressions for the group B simulations with average callus element edge lengths of 0.5 mm, 0.35 mm, 0.25 mm, and 0.2 mm are shown in Figure 4.10. The mesh was considered to be converged with an average element edge length of 0.35 mm, and this mesh size was used for all subsequent simulations.

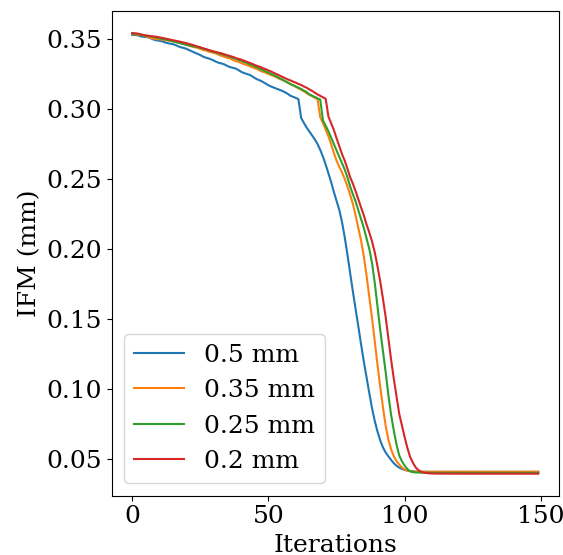


Figure 4.10: Temporal evolution of IFM for group B for four different callus average element edge lengths: 0.5 mm, 0.35 mm, 0.25 mm, and 0.2 mm.

No difference was observed on the qualitative progression on the simulated healing for group B when increasing the initial region of the callus by 13% in radius

and 20% in length, thereby demonstrating callus domain independence (Figure 4.11). The convergence of the healing simulation, defined by a change in IFM of less than 1% from the previous iteration, was delayed by 4 iterations in the simulation with a larger callus domain size.

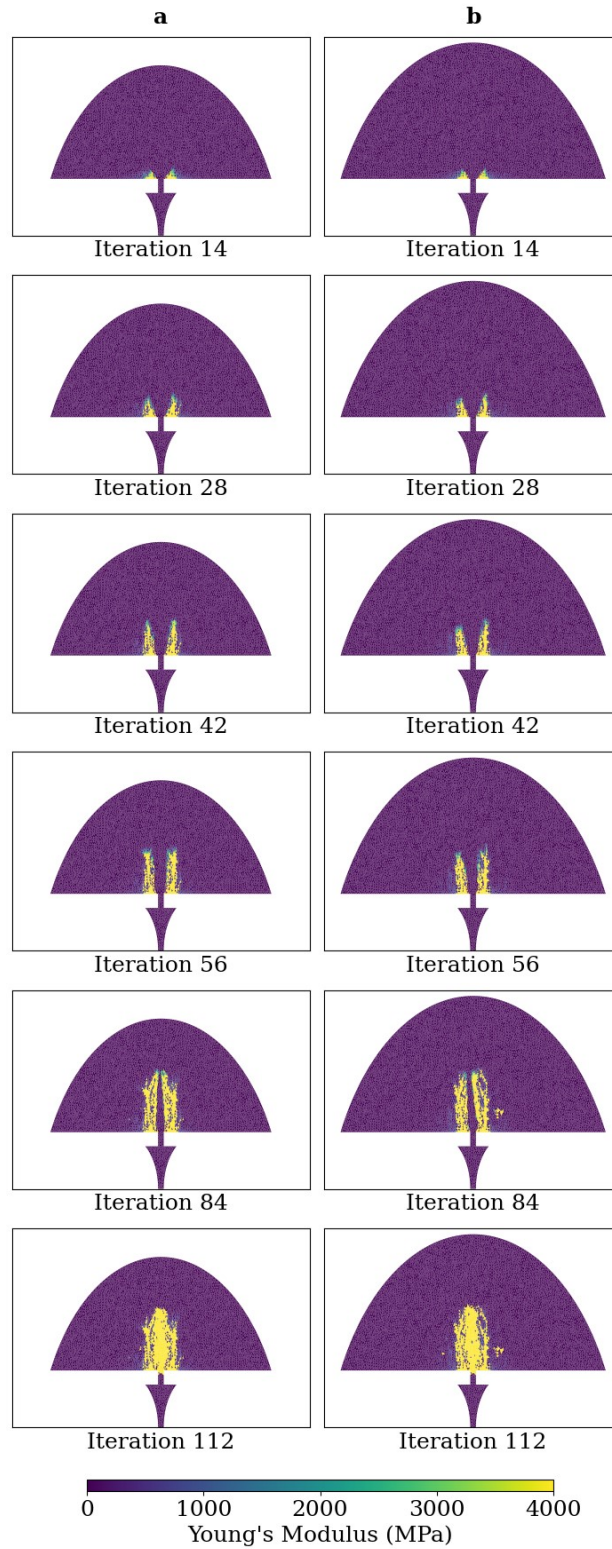


Figure 4.11: Young's modulus of each callus finite-element in simulations of group B at iterations: 14, 28, 42, 56, 84, and 112. (a) Callus domain geometry initialised as described in Figure 4.3a and (b) callus domain initialised with radius and length increased by 13% and 20%, respectively.

Figure 4.12 illustrates the Young's modulus, bone concentration, cartilage concentration, and intramembranous ossification activation level at each callus finite-element during iterations 28, 56, 84, 112, and 140 of the simulation of group D. Notably, the healing algorithm demonstrates physiological bony growth on the periosteum via intramembranous ossification, with bridging occurring at the outer callus, rather than in the direct inter-cortical gap. The bridging process involves cartilage formation via chondrogenesis, and subsequent ossification through endochondral ossification, rather than intramembranous ossification.

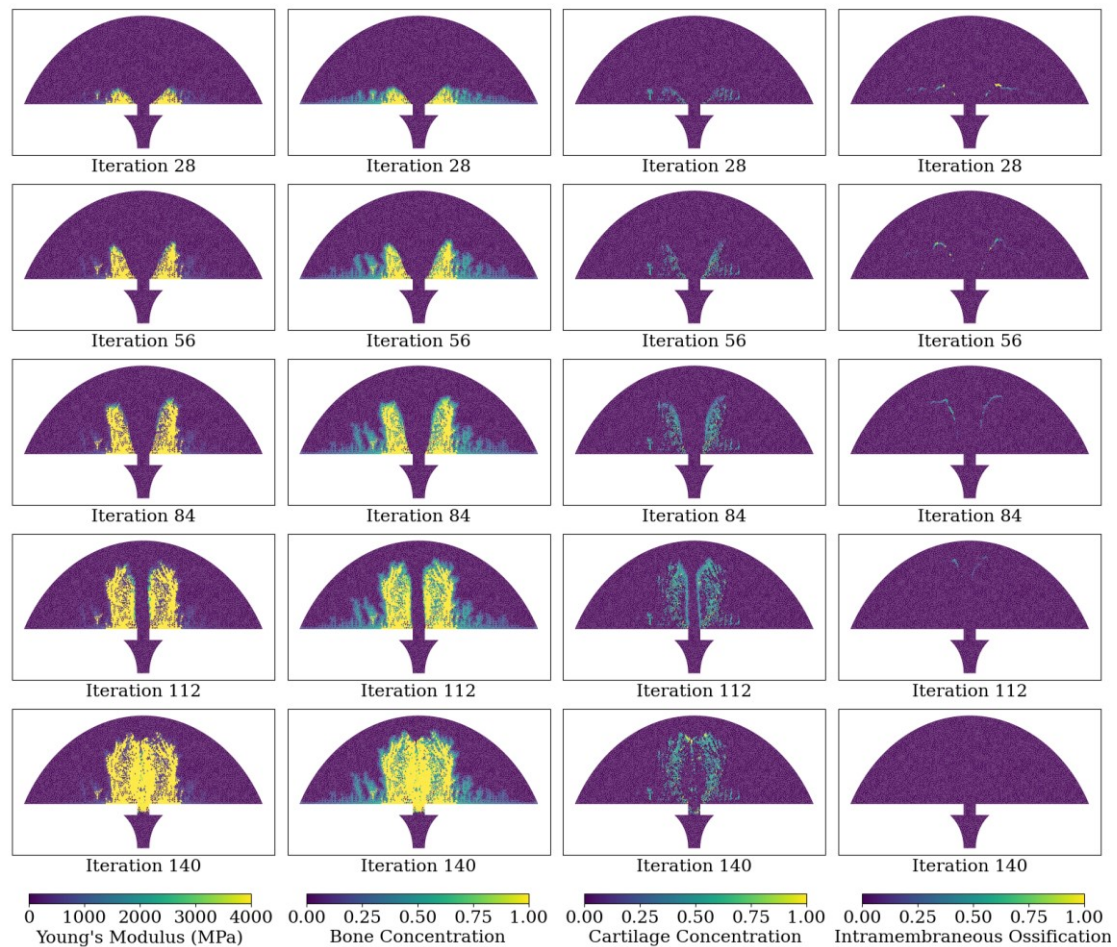


Figure 4.12: Simulated healing dynamics of Group D at iterations: 28, 56, 84, 112, and 140. The plotted variables for each callus finite-element span from the leftmost to the rightmost column: Young's modulus, bone concentration, cartilage concentration, and intramembraneous ossification activation. Bone and cartilage concentrations are depicted as tissue proportions within the finite-element, with a bone concentration of 1.0 indicating full ossification. Intramembraneous ossification is quantified as an activation proportion, with a value of 1.0 denoting complete biological rule activation.

Simulations of groups A-E converged at iterations 55, 102, 73, 136, and 120, respectively. The simulation of group F failed to converge within 150 iterations. The IFM progressions of each group are visually represented in Figure 4.13a, while the mean IFM progressions for each corresponding experimental group are displayed in Figure 4.13b (Claes *et al.*, 1997). Notably, the IFM progressions in the simulated groups closely mirror those observed in the experimental groups, and indicate that one healing day in the experimental data corresponds approximately to three simulation iterations.

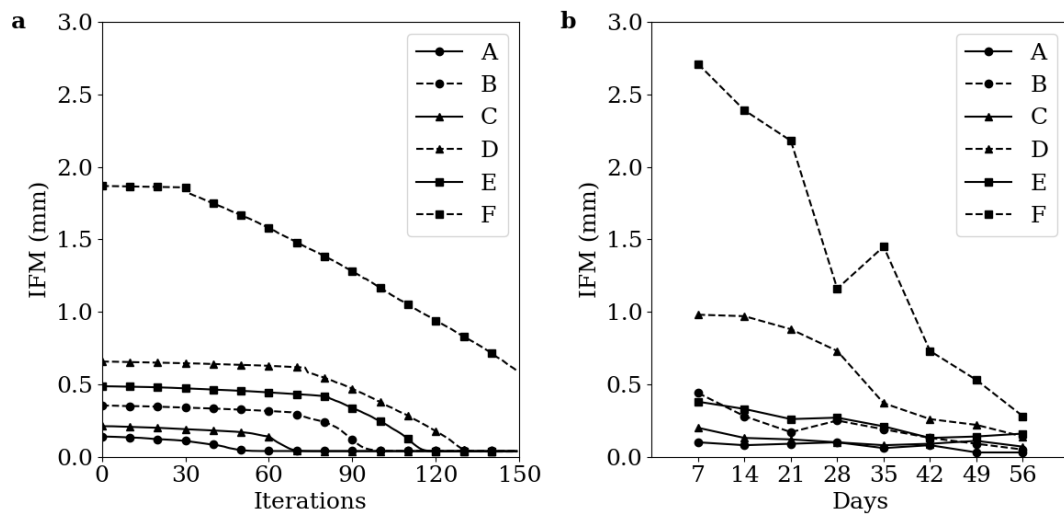


Figure 4.13: Temporal evolution of IFM across the healing process for groups A-F. (a) Simulation data. (b) Corresponding experimental data. Groups A-F are as defined by Claes *et al.* (Claes *et al.*, 1997). The low strain groups A, C, and E are denoted with solid lines and the high strain groups B, D, and F are denoted with dashed lines. The 1 mm, 2 mm, and 6 mm initial gap size groups are denoted with circle, triangle, and square markers, respectively. Markers in the simulation data are denoted every 10 iterations.

Virtual mechanical testing, conducted at the conclusion of the 150 iterations on the corresponding 3-D FE model, measured bending stiffnesses of 6.9, 7.3, 7.2, 8.4, 7.8, and 1.8 N m mm⁻¹ for groups A through F, respectively. The corresponding experimental bending stiffnesses were 24.3 ± 7.6 , 35.6 ± 23.1 , 26.6 ± 18.6 , 15.8 ± 14.6 , 8.9 ± 7.0 , and 1.6 ± 0.9 N m mm⁻¹, respectively (Claes *et al.*, 1997).

Figure 4.14 shows the Young's modulus at each callus finite-element during iterations 14, 28, 42, 56, 84, and 112 for groups A-F. The higher strain groups B, D, and F exhibited more extensive bony callus development compared to the lower strain

groups A, C, and E. However, bony bridging in the higher strain groups was delayed compared to their lower strain counterparts.

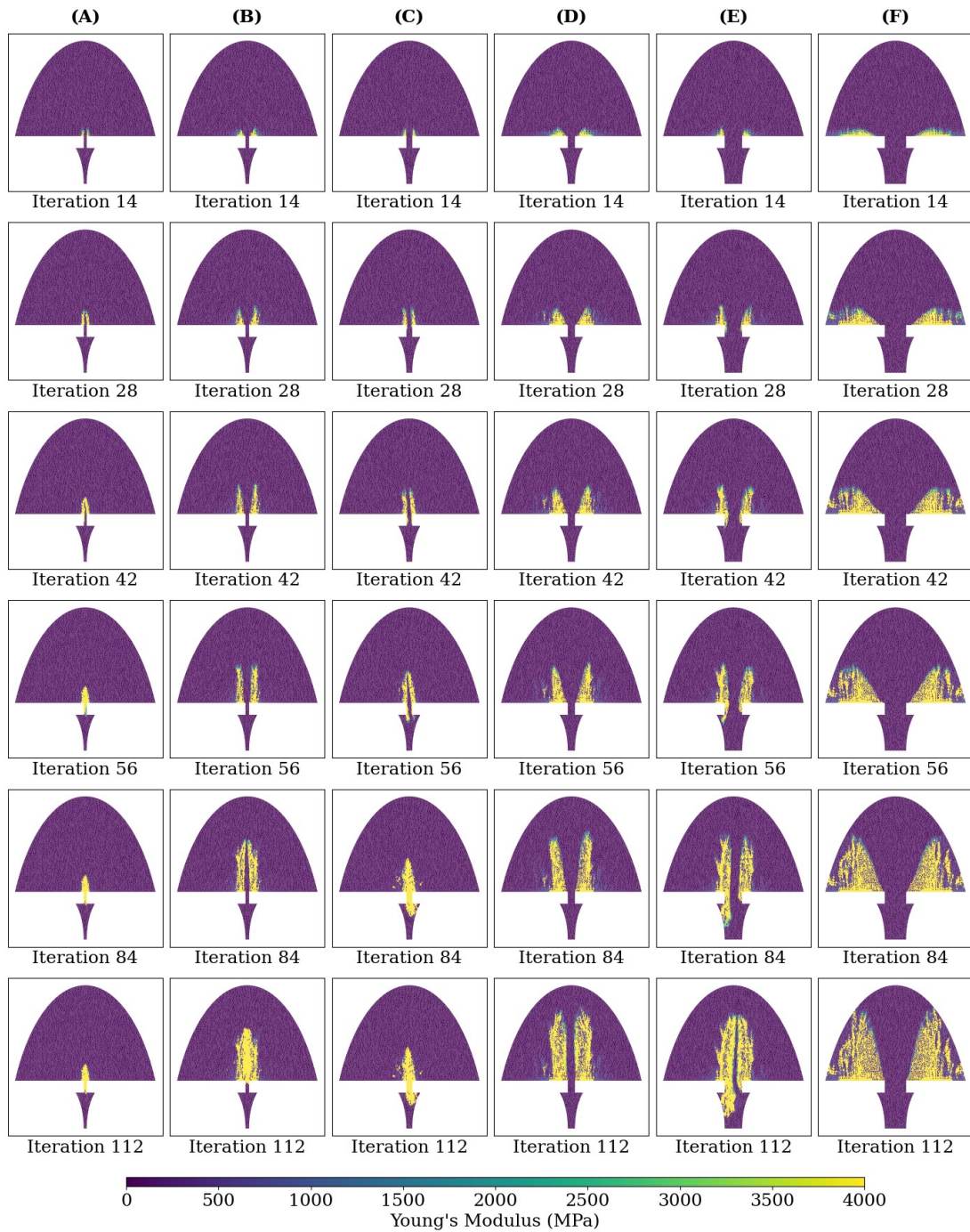


Figure 4.14: Young's modulus of each callus finite-element at iterations: 14, 28, 42, 56, 84, and 112 of the simulated healing process for groups A-F.

4.5 Discussion

This study introduced a novel fracture-healing algorithm based on principal strains as the primary mechanical stimuli. The algorithm was able to match closely experimental observations across different fixation stabilities and initial fracture-gap widths. Notably, this algorithm is the first of its kind capable of predicting cases not only of fracture union, but also non-union. The ability to distinguish between scenarios which are likely to result in union versus non-union is a primary application of fracture-healing algorithms.

4.5.1 Principal strains as mechanical stimuli

Intramembranous ossification is stimulated by shearing between the periosteum of the bone fragments and the soft callus region, with areas closer to the fracture experiencing higher shear forces and greater bony outgrowth. These characteristics of intramembranous ossification are effectively captured by maximum principal strain, as used in this fracture-healing algorithm. Chondrogenesis and endochondral ossification occur between the bony protrusions where compression, represented by minimum principal strain, dominates. Previous fracture-healing algorithms utilised porous flow (Isaksson *et al.*, 2008; Ghiasi *et al.*, 2019), dilatational strain, and distortional strain (Shefelbine *et al.*, 2005; Isaksson *et al.*, 2006; Simon *et al.*, 2011), with distortional strain identified as the dominant mechanical stimulus (Isaksson *et al.*, 2006). Although distortional strain is closely correlated with both minimum and maximum principal strains, it cannot distinguish between the two. The use of principal strains as mechanical stimuli in this healing algorithm enabled a physiological fracture-healing process. Furthermore, the threshold values of principal strains used in the fracture-healing algorithm were not tuned to the experimental data against which the algorithm was compared for the large and small gap groups. Despite the lack of tuning of the algorithm parameters to different fracture scenarios in the large and small gap groups, the algorithm still had good agreement with experimental data. This lack of requirement for tuning is testament to the robustness of the algorithm and gives confidence in its wide applicability.

4.5.2 IFM progressions

The patterns of IFM progression across the six groups align well with the corresponding experimental data (Figure 4.13). The healing algorithm was not temporally calibrated prior to the analyses conducted in this study, but the IFM progression patterns in Figure 4.13 and Figure 4.14 suggest that three simulated healing iterations correspond approximately to one day of healing. While the ability of the healing algorithm to predict similar IFM progression patterns as experimental data is encouraging, the IFM itself is not an accurate measure of fracture healing. This inaccuracy is exemplified by Group F in both the simulated and experimental results of Claes *et al.* (1997), where IFM decreases significantly over the course of healing, yet union is not achieved. Instead, more informative measures of successful fracture union should be used, such as bending stiffness or torsional rigidity (Ren and Dailey, 2020a).

4.5.3 Bending stiffness assessments

The bending stiffness assessments of simulated healing cases using this healing algorithm revealed that the healing algorithm could distinguish between groups that clearly healed (groups A-D) and those that did not (group F), mirroring the trends in bending stiffness among the corresponding groups in experimental data (Claes *et al.*, 1997). Although the trend in bending stiffness between the different groups was similar in the healing algorithm and the experimental data, a limitation of the current study is the discrepancy in the magnitudes of bending stiffness. For instance, the bending stiffness of group A was greater than that of group F in both the healing algorithm and experimental results, but the magnitudes of bending stiffness for group A were 6.9 and 24.3 N m mm⁻¹ for simulation and experiment, respectively. This discrepancy is likely due to the absence of bone remodelling in the healing algorithm; woven bone does not get replaced with stiffer lamellar bone, in a process that physiologically occurs from early-on in the secondary fracture-healing process (Ren and Dailey, 2020a). Incorporating a remodelling process into the fracture-healing algorithm would likely further ossify the periosteally formed bone, which is further from the fracture, and in the current model does not achieve a bone

concentration greater than approximately 30% (Figure 4.12). Another limitation of the current healing algorithm is its deterministic nature in simulating ‘borderline’ healing cases; the algorithm predicted successful fracture union in group E, whereas experimental data showed group E to have a mean bending stiffness between those of successful healing groups A-D and the unsuccessful healing group F. The large variance in the experimental bending stiffnesses, with a standard deviation of 7.0 N m mm⁻¹ and a mean of 8.9 N m mm⁻¹ in group E, suggests that rather than all of the sheep healing partially, likely some of the sheep in the group healed successfully while others experienced non-unions. This group represents an ambiguous healing case in which the specifics of loading, fracture geometry, and fixator stiffness are likely required to predict accurately the healing outcome, rather than the idealised parameters which were used in this study.

4.5.4 Initial callus-domain independence and mesh convergence

A significant advantage of the fracture-healing algorithm presented in this study is its independence from the initial callus domain and the absence of a pre-defined hard callus geometry, while exhibiting physiologically accurate stages of secondary fracture healing. The simulations for all successful healing groups began with periosteal bony outgrowth followed by cartilaginous, and later bony, initial bridging of the fracture gap at the external callus, and importantly, not in the intercortical gap. These qualitative stages of secondary fracture healing are in agreement with established literature (Iwaki *et al.*, 1997; Vetter *et al.*, 2010; Claes, Recknagel and Ignatius, 2012). Previous fracture-healing algorithms have either shown inter-cortical bridging (Ament and Hofer, 2000; Ren and Dailey, 2020a) or enforced external callus bridging using a pre-defined spatial proximity function which inhibits bone formation in the intercortical gap (Schwarzenberg *et al.*, 2021). Other algorithms prevent inter-cortical bridging through a ‘cellular diffusion’ (Lacroix and Prendergast, 2002a; Isaksson *et al.*, 2006) or ‘vascular perfusion’ (Shefelbine *et al.*, 2005; Simon *et al.*, 2011) parameter, which begins at the outer surface of the callus and diffuses inwards, only allowing bone formation where this parameter is active. Algorithms which use this diffusion parameter are therefore highly sensitive to the initial callus domain and diffusion rate (Isaksson, Van Donkelaar and Ito, 2009). Given that callus geometry is

highly variable between fracture types, and that the callus does not form until after surgical intervention, a fracture-healing algorithm that relies on accurate prescribed callus geometry may be useful for post-surgical rehabilitation management and early diagnosis of non-union, but is less suited for pre-operative planning, novel device development, or *in silico* clinical trials. The fracture-healing algorithm presented in this study, demonstrating callus domain independence, is better suited for these applications. Additionally, studies of previous fracture-healing algorithms either fail to perform a mesh convergence study, or only perform a mesh convergence study on the FE model and not the biological controller. The biological controllers are mesh-based algorithms, just as FE models are, and therefore a mesh convergence study should be performed for each biological controller. The present fracture-healing algorithm is the first to perform a mesh convergence study.

4.5.5 Limitations

Although the fracture-healing algorithm in this study aligns qualitatively with established literature and quantitatively with corresponding experimental data, the fracture scenario modelled is quite basic: it simulates an ovine metatarsal, which predominantly experiences axial loading (Duda *et al.*, 1997), and the high reported bending and torsional stiffness of the external fixator (Claes *et al.*, 1995) allows for an axisymmetric approximation to reduce computational expense. Additionally, the fixator type modelled here, which is one that allows some free movement axially, is an accurate model of the fixator used in the corresponding experiments, but is not widely used clinically. Intramedullary nails have a smaller amount of free axial movement (Dailey, Daly and Glass-Hardenbergh, 2015; Ren and Dailey, 2020a), and novel devices which are purposefully designed to target an allowable free-movement distance to promote fracture healing (Han *et al.*, 2021) are not widely used clinically. Realistic clinical fracture scenarios and fixators will require the ability to model non-axisymmetric loading. Therefore, this fracture-healing algorithm should be expanded into a 3-D representation to accommodate these expected loads. Modelling in 3-D would also enable patient-specific simulations, where bone fragment geometries are identified using CT imaging, and loads are derived from gait analysis and musculoskeletal modelling (Orth *et al.*, 2023). Furthermore, the use of minimum and

maximum principal strains as mechanical stimuli for biological fracture-repair processes warrants experimental investigation. A previous study has explored various strain measures, including maximum principal strain, in different tissue types during secondary fracture healing, but did not measure both minimum and maximum principal strains to investigate their individual effects on separate ossification processes (Morgan *et al.*, 2010).

4.6 Conclusion

This study presents a novel fracture-healing algorithm which uses minimum and maximum principal strains as the mechanical inputs. The use of these strains allowed for the callus-domain independence of the algorithm, without the need to prescribe the temporal-spatial ossification pathway of the callus. Validation was performed against published data from experimental animal studies for cases resulting in both union and, importantly, non-union. The capabilities demonstrated by this algorithm allow for its practical application to pre-surgical planning, novel fracture-fixation device development, rehabilitation-regime management, and non-union risk assessment. Previous fracture-healing algorithms have been shown to be highly sensitive to input parameters whose values are relatively unknown. A sensitivity study of the present fracture-healing algorithm will quantify its robustness to input parameter values. Further steps in the development of this algorithm will focus on its expansion to 3-D simulation to capture a wider variety of fracture geometries and fixator types. This will allow the comparison between treatments for fracture types which have been insufficiently addressed by traditional clinical trials.

CHAPTER 5

SENSITIVITY ANALYSIS OF A FRACTURE- HEALING ALGORITHM

5.1 Scope

In Chapter 3, published fracture-healing algorithms were reviewed, and a key limitation was identified as a high sensitivity to a cellular diffusion or vascular perfusion rate parameter, whose value is associated with a high degree of uncertainty. In Chapter 4, a novel fracture-healing algorithm was introduced which does not use a cellular diffusion or vascular perfusion parameter, and was able to demonstrate independence from the size of the initial callus domain. In this chapter, a sensitivity analysis of various parameter values is performed on three baseline models developed in Chapter 4, with the aim to quantify the robustness of the fracture-healing algorithm to parameter inputs. The chapter concludes with identifying key parameters discussing implications when using the fracture-healing algorithm in clinical applications.

5.2 Introduction

Previous fracture-healing algorithms have demonstrated a high sensitivity to parameters whose values are associated with a high degree of uncertainty. Over-sensitivity in *in silico* models has long been a source of distrust in modelling results. Recognising the significant role of *in silico* models in the initial and later stages of medical device development, such as regulatory submission, the American Society of Mechanical Engineers (ASME) has recently established a set of standards for the verification, validation (‘Assessing credibility of computational modeling through verification and validation: application to medical devices: ASME V&V 40 - 2018’, 2018), and uncertainty quantification (‘The Role of Uncertainty Quantification in Verification and Validation of Computational Solid Mechanics Models’, 2022) of these models. In addition, the U.S. Food and Drug Administration (FDA) has acknowledged the growing breadth of use-cases of *in silico* models in medical device development and has released guidelines for reporting (Morrison, 2016) and evaluating the credibility (Pathmanathan, 2021) of these models for regulatory submission. These publications demonstrate the expanding role of *in silico* models in device development and encourage their increased use by providing a clear framework for their application.

The parameter values used in the present algorithm are not experimentally-derived, and are therefore associated with a lower level of confidence in their values. A full uncertainty quantification following the standards outlined by the ASME and the FDA is outside the scope of this thesis, as this level of evidence is intended for regulatory submission of models. The aim of this chapter is to assess the robustness of the fracture-healing algorithm to the uncertainty of the parameter values and will identify the key parameters of the algorithm.

5.3 Methods

The fracture-healing algorithm described in Chapter 4 was implemented. Specifically, the models of groups C, E, and F were used as baseline models, representing successful healing, borderline healing, and non-union, respectively. The initial interfragmentary gap widths and initial allowed IFS's of these groups are given in Table 5.1.

Group	C	E	F
Gap Width (mm)	2	6	6
IFS (%)	7	7	31

Table 5.1: Fracture gap width and initial IFS in each of the simulated groups C, E, and F.

The parameters included in the sensitivity analysis are the rate parameters for each biological rule, the applied axial force magnitude, and the fuzzy logic membership function boundary values. The rate parameters are the amounts by which the outputs of each fuzzy rule are scaled; these rate parameter values are all 1 in the baseline models. The axial force magnitude applied at each iteration of the model is 500 N in each of the baseline models. The fuzzy boundary parameters included in the sensitivity analysis, “Dist”, “Max1”, “Max2”, “Min1”, “Min2”, and “Min3”, are shown in Figure 5.1, and their values in the baseline models are given in Table 5.2.

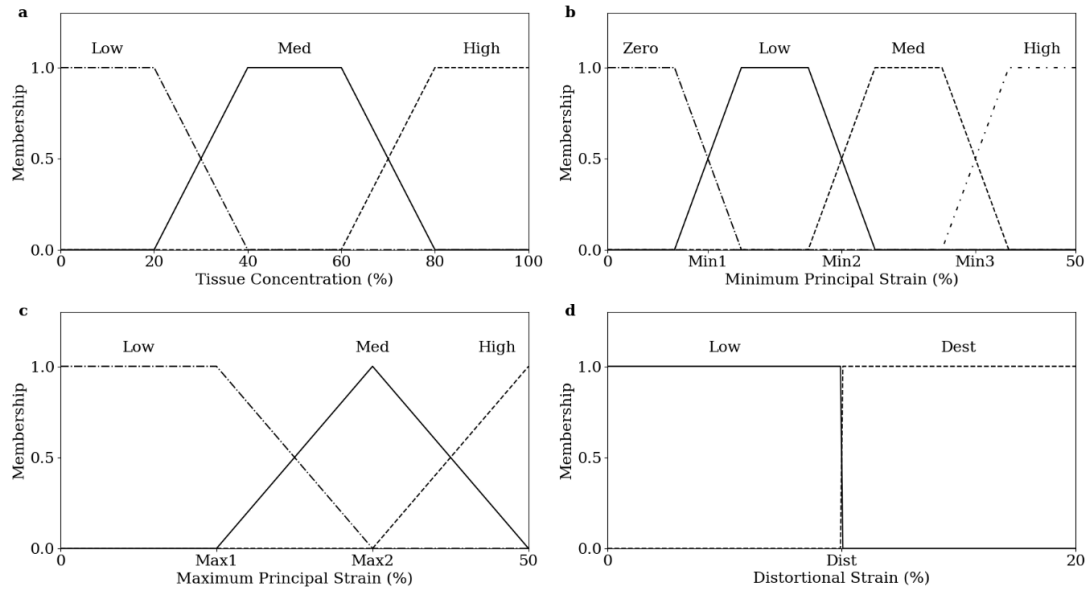


Figure 5.1: Fuzzy membership functions of inputs, (a) tissue prop, (b) minimum principal strain, (c) maximum principal strain, and (d) distortional strain, with the fuzzy boundary parameters ‘Dist’, ‘Max1’, ‘Max2’, ‘Min1’, ‘Min2’, ‘Min3’ indicated on the membership functions.

Fuzzy parameter	Baseline value (% strain)	Associated biological rules
Dist	10	IO, Chon
Max1	0.5	IO, Chon
Max2	5	IO, Chon
Min1	0.75	EO
Min2	2.25	Chon, EO
Min3	8.75	Chon

Table 5.2: The fuzzy logic membership function parameters which were included as parameters in the sensitivity analysis and their values in the baseline models, along with the biological fuzzy-logic rules which include the parameters (‘IO’ = intramembranous ossification, ‘Chon’ = chondrogenesis, ‘CC’ = cartilage calcification, ‘EO’ = endochondral ossification).

Parameter	Amount changed
IO Rate	$\pm 25\%$, $\pm 50\%$
Chon Rate	$\pm 25\%$, $\pm 50\%$
CC Rate	$\pm 25\%$, $\pm 50\%$
EO Rate	$\pm 25\%$, $\pm 50\%$
Dist	$\pm 25\%$,
Max1	$\pm 25\%$,
Max2	$\pm 25\%$,
Min1	$\pm 25\%$,
Min2	$\pm 25\%$,
Min3	$\pm 25\%$,
Force Magnitude	$\pm 10\%$,

Table 5.3: The parameters which were varied in the sensitivity analysis and the amount that each parameter was varied by. ‘IO’ = intramembranous ossification, ‘Chon’ = chondrogenesis, ‘CC’ = cartilage calcification, ‘EO’ = endochondral ossification.

Sensitivity analyses were performed by varying one parameter at a time, such that the sensitivity to each parameter was measured individually and independent of other parameters. Rate parameters and fuzzy boundary parameters were each raised and lowered by 25% and 50%. Multiple rate parameter levels were used to investigate the linearity of the model sensitivity. The minimum and maximum principal strain fuzzy logic membership functions were adjusted by shifting the parameters Min1, Min2, Min3, Max1, and Max2 by 25%, while maintaining the slopes of the surrounding membership functions. A larger magnitude change was not used for the membership function parameters as a larger change would result in ‘overlapping’ of adjacent membership functions. Axial force magnitude was raised and lowered by 10%. A smaller percentage change was used for the axial force magnitude sensitivity as the uncertainty of musculoskeletal-model-derived joint loads, which is the envisioned method of determining joint loads for the application of this model, are unlikely to exceed 10%. A “summary of effect” for each of the fuzzy boundary parameters, or the biological fuzzy-logic rules which include the parameter, is shown in Table 5.2. A table of each of the parameters varied and the amounts by which they were varied is shown in Table 5.3. 30 simulations were run for each of the three baseline models, for a total of 90 simulations, not including the baseline simulations.

The output metrics which were used to analyse the sensitivity of the model were the number of iterations taken to reach convergence, and bending stiffness at the final iteration. Convergence was defined as a decrease in IFM of less than 1% from the previous iteration. Bending stiffness was assessed using the same method as in Chapter 4.

5.4 Results

The sensitivity against the baseline of the number of iterations required to reach convergence of the models of groups C and E, not including rate parameter changes of 50%, are shown in Figure 5.2 and Figure 5.5, respectively. The sensitivity against the baseline of the final bending stiffness of the models of groups C and E, not including rate parameter changes of 50% are shown in Figure 5.3 and Figure 5.6, respectively. The sensitivity against the baseline of the rate parameters at change magnitudes of 25% and 50% of the models of groups C and E are shown in Figure 5.4 and Figure 5.7, respectively.

All of the changes in the final bending stiffness for the sensitivity analysis of the model of group C, not including rate parameter changes of 50%, were less than or equal to $\pm 1.5\%$ (Figure 5.3). Note that while the scales of the y-axis are consistent within figures, the scales of Figure 5.2 and Figure 5.5, and of Figure 5.3 and Figure 5.6, differ by a factor of two.

A sensitivity analysis of the model of group F showed no change in the convergence of the model; the baseline simulation, as well as all sensitivity simulations, failed to converge within 150 iterations. Changes in bending stiffnesses against the baseline value were large percentage-wise, however, the magnitude of all bending stiffnesses were small relative to the simulations of groups C and E as the model of group F consistently predicted non-union or delayed union.

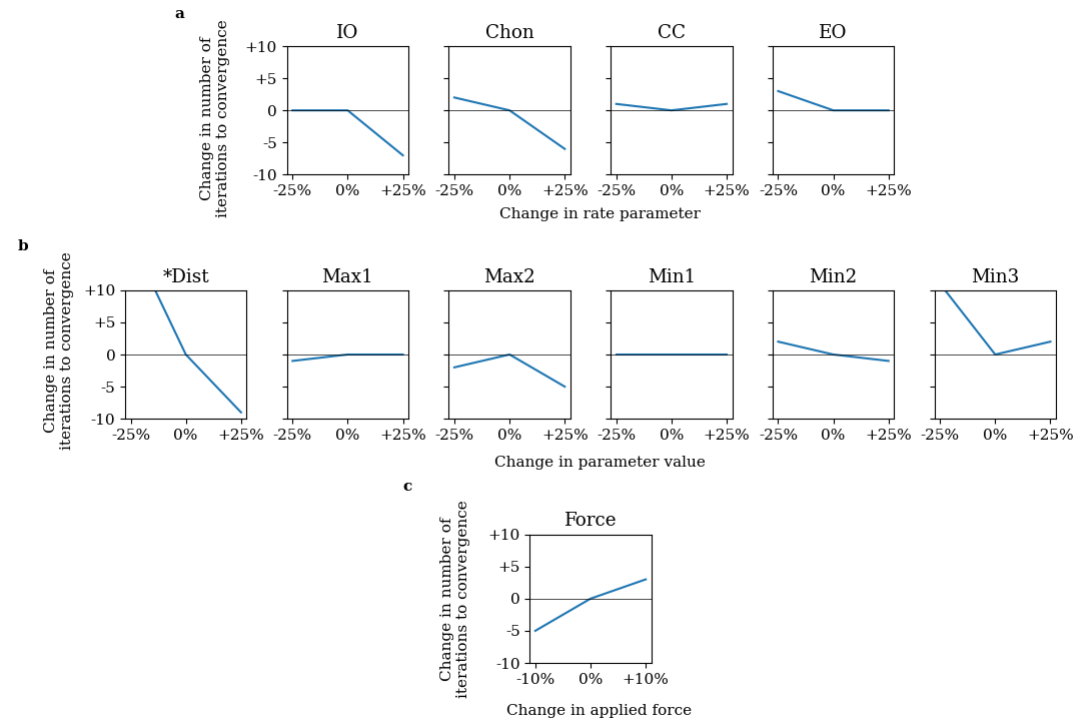


Figure 5.2: Sensitivity of the number of iterations taken to reach convergence for the model of the fracture group C to: (a) rate parameters for the four biological processes modelled ('IO' = intramembranous ossification, 'Chon' = chondrogenesis, 'CC' = cartilage calcification, 'EO' = endochondral ossification), (b) fuzzy boundary parameters, and (c) applied axial force. *The "-25% dist" simulation had a change in the number of iterations to convergence of +18 iterations.

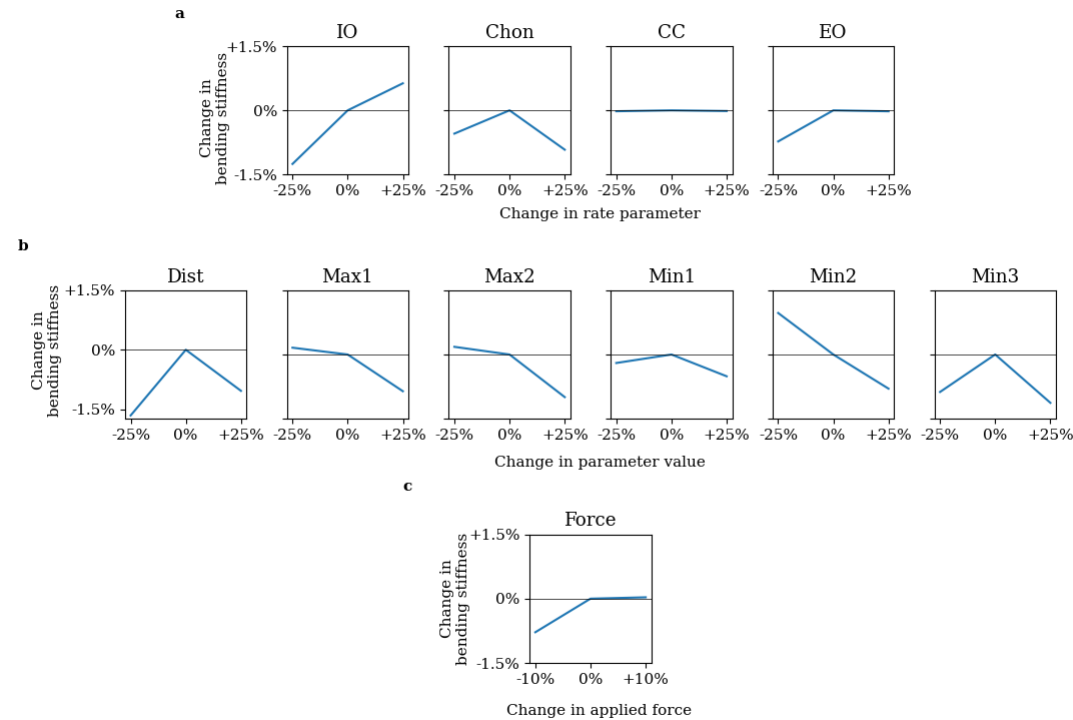


Figure 5.3: Sensitivity of the bending stiffness in the final iteration for the model of the fracture group C to: (a) rate parameters for the four biological processes modelled ('IO' = intramembranous ossification, 'Chon' = chondrogenesis, 'CC' = cartilage calcification, 'EO' = endochondral ossification), (b) fuzzy boundary parameters, and (c) applied axial force.

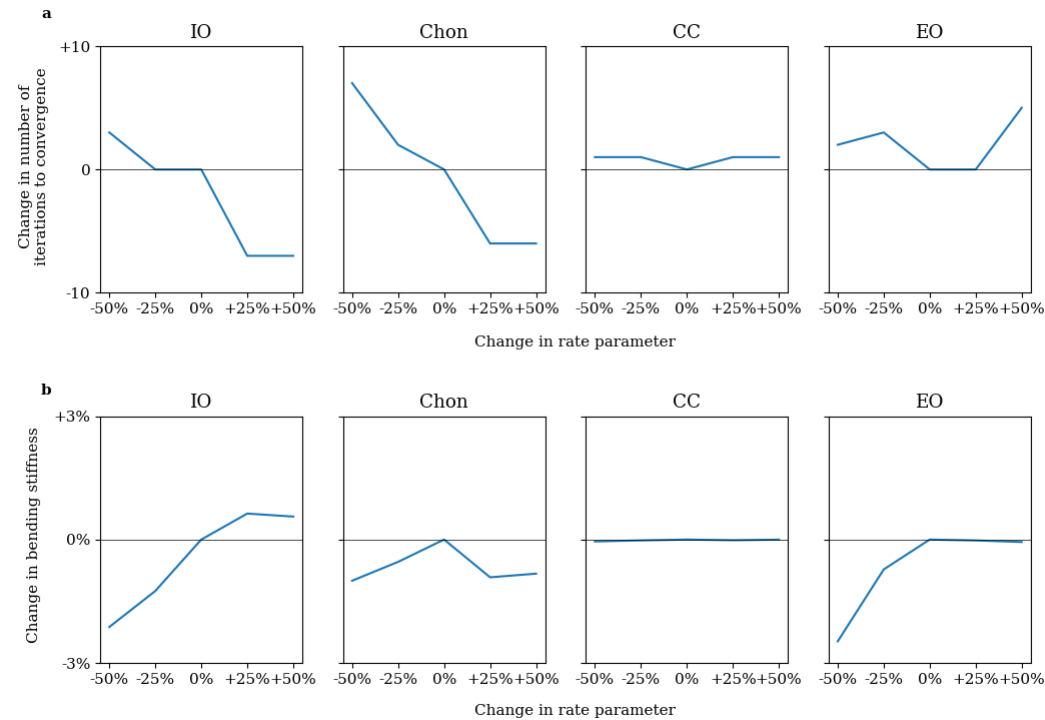


Figure 5.4: Sensitivity of the (a) number of iterations taken to reach convergence and of the (b) bending stiffness of the final iteration for the model of the fracture group C to rate parameters for the four biological processes modelled ('IO' = intramembranous ossification, 'Chon' = chondrogenesis, 'CC' = cartilage calcification, 'EO' = endochondral ossification).

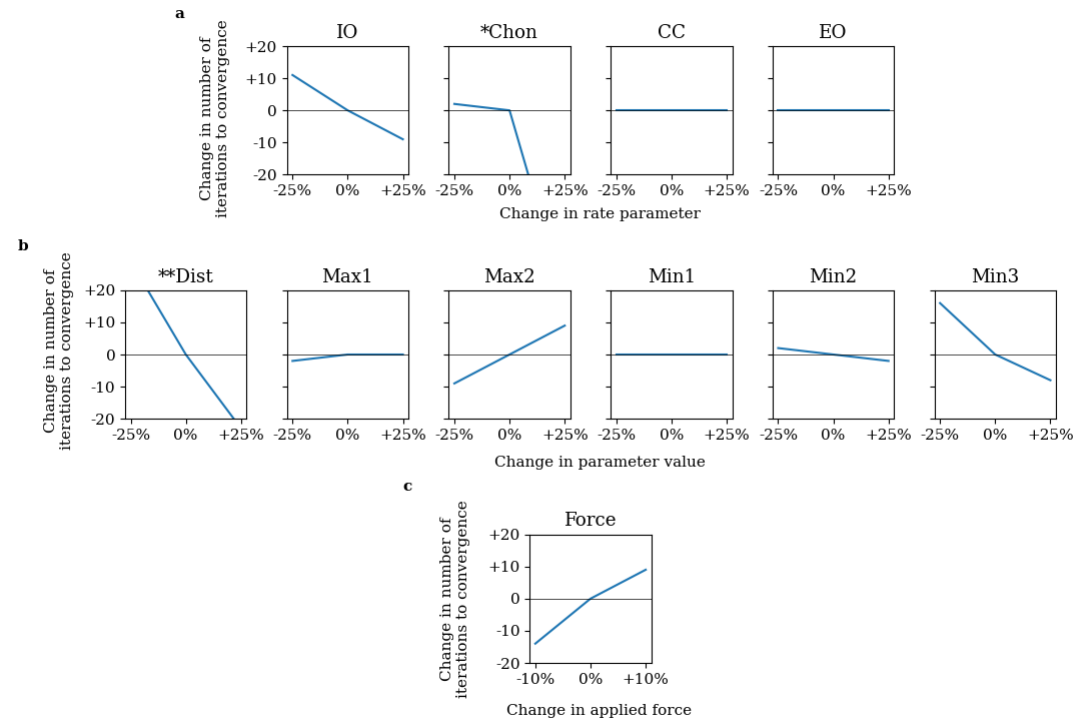


Figure 5.5: Sensitivity of the number of iterations taken to reach convergence for the model of the fracture group E to: (a) rate parameters for the four biological processes modelled ('IO' = intramembranous ossification, 'Chon' = chondrogenesis, 'CC' = cartilage calcification, 'EO' = endochondral ossification), (b) fuzzy boundary parameters, and (c) applied axial force. *The "+25% chon" simulation had a change in the number of iteration to convergence of -59 iterations. **The "-25% dist" simulation had a change in the number of iterations to convergence of +29 iterations.

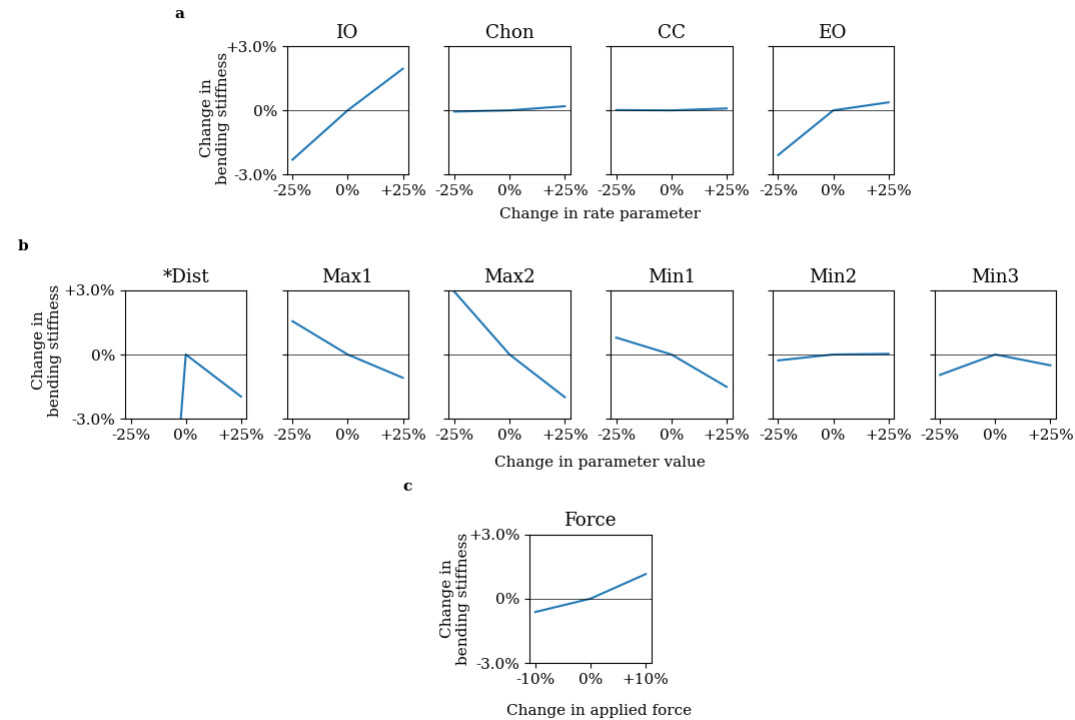


Figure 5.6: Sensitivity of the bending stiffness in the final iteration for the model of the fracture group C to: (a) rate parameters for the four biological processes modelled ('IO' = intramembranous ossification, 'Chon' = chondrogenesis, 'CC' = cartilage calcification, 'EO' = endochondral ossification), (b) fuzzy boundary parameters, and (c) applied axial force. *The "-25% dist" simulation had a change in the bending stiffness of the final iteration of -33%.

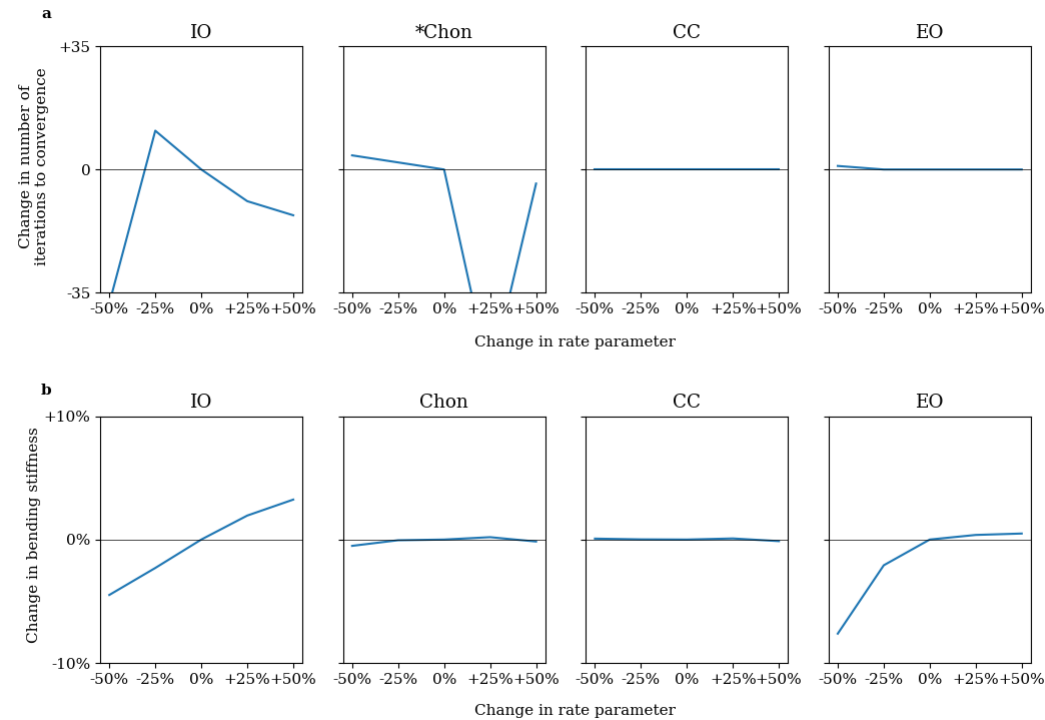


Figure 5.7: Sensitivity of the (a) number of iterations taken to reach convergence and of the (b) bending stiffness of the final iteration for the model of the fracture group E to rate parameters for the four biological processes modelled ('IO' = intramembranous ossification, 'Chon' = chondrogenesis, 'CC' = cartilage calcification, 'EO' = endochondral ossification). *The "+25% Chon" simulation had a change in the number of iterations to convergence of -59.

5.5 Discussion

5.5.1 Overall sensitivity as a confidence level in model predictions

The model of group E was more sensitive overall than the model of group C, as shown by comparing Figure 5.2 and Figure 5.5, and Figure 5.3 and Figure 5.6. The sensitivity analysis of group E also yielded the only change in predicted overall healing outcome from the baseline model, with the “-25% Dist” analysis predicting a non-union or delayed union, while the baseline model predicts a union. The sensitivity analysis of group F led to a prediction of non-union or delayed union in all cases, including the baseline case. In the experimental study by Claes et al. (Claes *et al.*, 1997) corresponding with the baseline models, the fractures in groups C and F resulted in unions and non-unions, respectively, while the fractures in group E resulted in a less consistent outcome, indicating that the fracture type of group E is a ‘borderline’ healing case.

While the baseline models of groups C and F predicted accurately healing outcomes of union and non-union, respectively, the baseline model of group E predicted successful union, while the corresponding experimental data was mixed. The models of groups C and F were both relatively less sensitive to parameter values than the model of group E. These findings suggest that a sensitivity analysis may be used to assess the confidence level in the healing algorithm predictions. The overall level of model sensitivity could be quantified using a standardised uncertainty quantification calculation (‘Assessing credibility of computational modeling through verification and validation: application to medical devices: ASME V&V 40 - 2018’, 2018). Since the sensitivity changes based on inputs, a generalised pre-hoc uncertainty quantification for the algorithm is not well suited for the algorithm. Rather, a post-hoc uncertainty quantification should be performed to assess the confidence in each of the algorithm’s predictions.

Figure 5.4 and Figure 5.7 demonstrate that sensitivity of the model does not vary linearly with the magnitude of change in parameter value. Figure 5.7a additionally demonstrates that a large change in parameter value can have the

opposite effect of a moderate change in parameter value on the number of iterations required to reach convergence, but Figure 5.7b shows that the change in overall healing outcome prediction is minimal. The changing of effect direction when moving from a moderate to a large change when looking at number of iterations taken to reach convergence indicates a possible change in the overall behaviour of the model; reducing the intramembranous ossification rate by 50% or increasing the chondrogenesis rate by 50% likely allows for chondrogenesis and endochondral ossification to dominate throughout the healing process, rather than intramembranous ossification occurring first, followed by chondrogenesis and endochondral ossification. While this change in overall model behaviour could be problematic, such large changes in the rate parameters are unlikely to be relevant, as the rate parameters are already effectively ‘normalised’ in the baseline model, to 100%, representing the full change of a callus element tissue type.

Overall predicted healing outcomes and final bending stiffnesses of the models were minimally changed in the sensitivity analysis. Final bending stiffnesses in groups C and E generally changed by less than 1.5% and 3%, respectively, when parameter values were changed by 10% or 25%. These overall findings demonstrate the robustness of the outputs of the algorithm to the uncertainty in the parameter values used.

5.5.2 Model sensitivity to individual parameters

Among the rate parameters for the biological processes, the model demonstrated the highest sensitivity to the intramembranous ossification rate parameter in terms of both the number of iterations required to reach convergence and the final bending stiffness of the models. An increased rate of intramembranous ossification led to faster healing times and higher final bending stiffnesses. This finding is to be expected, as intramembranous ossification dominates the early stages of secondary fracture healing. Changes to the chondrogenesis and endochondral ossification rate parameters caused moderate changes to the model outputs. Figure 5.5 and Figure 5.6 show that an increase in the chondrogenesis rate parameter leads to a drastic reduction in the number of iterations to reach convergence, but almost no change in the final bending stiffness. This demonstrates that chondrogenesis may act

as a “rate factor” in the healing algorithm, where changes to its value changes only the speed of healing, and not the final outcome. Changes to the cartilage calcification rate parameter had minimal impact. This suggests that the cartilage calcification rule has little role in the algorithm and could potentially be removed in order to simplify the algorithm. Alternatively, this rule rate could be removed from uncertainty quantifications to reduce computational expense.

Among the fuzzy membership function boundary parameters excluding Dist, the models were sensitive to the Max2 parameter. This parameter effects the intramembranous ossification and chondrogenesis rules, to which the healing algorithm was shown to be highly sensitive. Of the fuzzy boundary parameters for the minimum principal strain membership function, changes to Min3 had the greatest effect on the number of iterations required to reach convergence. Min3 affects chondrogenesis, which further supports the finding that chondrogenesis is a “rate factor” in the healing algorithm.

The magnitude of applied force parameter showed a moderate effect on the speed of healing, but had a relatively minor impact on the final bending stiffness. The range of force magnitudes simulated was intended to represent possible uncertainties in joint force estimations from musculoskeletal models, and was not intended to account for potential variations in post-surgical rehabilitation-regimes such as dynamisation or inverse-dynamisation.

5.5.3 Distortional strain fuzzy boundary parameter

Among all of the parameters investigated in the sensitivity analysis, the models were overall most sensitive to the Dist fuzzy boundary parameter. The Dist fuzzy boundary parameter was also the only parameter to cause a change in overall healing outcome from the baseline model; when the Dist parameter was reduced by 20% in the group E model, the healing algorithm predicted a non-union or delayed union, where all other simulations of the group E model, including the baseline model, predicted a successful union. This high sensitivity of the healing algorithm to the Dist parameter value is likely attributable to the dominance of intramembranous ossification in the initial stage of secondary fracture healing, and the “Low” Dist

requirement in the biological fuzzy logics rule for intramembranous ossification to occur during the simulation.

The sensitivity of the present fracture-healing algorithm to the Dist parameter was similarly demonstrated in a study of another fracture-healing algorithm; under a combined axial-torsional load, an increase in the Dist-equivalent in their model was shown to alter the model-predicted healing outcome from non-union to delayed union, which better agreed with their experimental validation data (Ren and Dailey, 2020b). Based on the findings of this other study, if the present healing algorithm is implemented in 3-D with a torsional or extreme bending load which causes high distortional strains, it may be necessary to increase the Dist fuzzy boundary parameter to ensure physiologically relevant predictions are made. In the present sensitivity analysis, an increase in the Dist parameter value led to a decrease in the number of iterations required to reach convergence, but a lower final bending stiffness. This faster, but poorer quality, healing is attributable to the geometry of the initial bony out-growth caused by intramembranous ossification; the bony protrusions extend to a smaller radial distance than in the baseline model, leading to a lower final bending stiffness. It should be noted, however, that the magnitude of the change in final bending stiffness from the baseline model was less than 3%, and any geometric differences were minor.

5.6 Conclusion

The sensitivity analysis demonstrated robustness of the fracture-healing algorithm with only minimal effect on prediction of healing outcome and final bending stiffness. This analysis shows promise as a method for uncertainty quantification, and as a measure of confidence in the healing outcomes predicted by the fracture-healing algorithm. The expansion of the algorithm to a 3-D model may necessitate adjusting the Dist fuzzy boundary parameter, as previous research indicates that under torsional loading, a higher Dist-equivalent parameter value is necessary to produce physiological healing outcome predictions. Although the healing algorithm showed some sensitivity to force, the tested magnitude ranges were intended only to account for uncertainties in musculoskeletal modelling-derived joint

loads. Application of the healing algorithm to study the effects of various rehabilitation-regimes on healing outcome, such as dynamisation and inverse-dynamisation, could provide valuable clinical information; a preliminary investigation of this is presented in the next chapter.

CHAPTER 6

INFLUENCE OF REHABILITATION-REGIME ON FRACTURE HEALING

6.1 Scope

Chapter 4 introduced a novel fracture-healing algorithm which was able to predict accurately union and non-union cases in physiological experimental data. Chapter 5 analysed the sensitivity of the algorithm to its parameter values. In this chapter, different rehabilitation-regimes, which prescribe applied loading and fixator free-movement distance over time, are investigated and their effects on the course of healing are determined. The regimes are applied to a fracture healing case which has experimental and computational healing outcomes bordering between union and non-union. The optimal rehabilitation-regime for the fracture and fixator modelled was found to be a constant level of high stability.

6.2 Introduction

Post-surgical rehabilitation is an important aspect of the fracture healing process. Some motion at the fracture gap is necessary to stimulate fracture healing, but too much is detrimental. Perren's strain theory, which states that an initial IFS between 2 and 10% leads to secondary fracture healing, is widely used as a general guideline for initial fracture stability, or fixator construct stiffness (Perren, 1978, 2002). However, more recent recommendations include changing of fracture stabilities over time: dynamisation, in which the fracture stability, or fixator stiffness, is reduced over time, and inverse-dynamisation, in which fracture stability, or fixator stiffness, is increased over time, have both been shown to be beneficial to fracture healing (Claes, Recknagel and Ignatius, 2012; Bottlang *et al.*, 2017).

A computational fracture-healing algorithm would allow for the direct comparison of rehabilitation-regimes while controlling for non-mechanical factors. Post-surgical rehabilitation-regimes are easier to influence than pre-surgical decision making and novel fixation-device development due to the lower regulatory barriers. As *in silico* clinical trials gain credibility but still lack the evidentiary weight of traditional clinical trials, an *in silico* trial on rehabilitation-regime optimisation could be sufficient evidence to influence clinical change.

This study analyses the model of group E, with a gap width of 6 mm and an initial IFS of 7%, from Chapter 4. The sensitivity analysis of this group in Chapter 5, as well as the corresponding experimental data (Claes *et al.*, 1997), indicated that this group is a ‘borderline’ healing case. This group was chosen to investigate the effect of various rehabilitation-regimes on fracture healing, and whether a regime is possible of achieving a conclusive ‘healed’ outcome, in an otherwise ‘borderline’ healing case. The models of groups E and F differ only in the stiffness profile of their fixators, therefore, this analysis also covers group F, as fixator stiffness is one of the rehabilitation parameters analysed.

6.3 Methods

Different rehabilitation-regimes were simulated by varying either the load applied or the stiffness profile of the fixator. The parameter used to vary the stiffness profile of the fixator was the allowable free-movement distance, d . The non-linear stiffness profile of the fixator used in the baseline model is shown in Figure 6.1. The fixator has an initial stiffness 4600 N mm^{-1} up to a force of 100 N, then a stiffness of 10 N mm^{-1} up to the desired free-movement distance, d , and a stiffness of 4600 N mm^{-1} beyond (Claes *et al.*, 1995, 1997). A ‘standard’ regime was also modelled to represent a more ‘standard-of-care’ fixator type, with a linear stiffness fixator with a stiffness of 1000 N mm^{-1} , corresponding to 0.5 mm displacement at 500 N load, approximately equal to the baseline non-linear stiffness fixator.

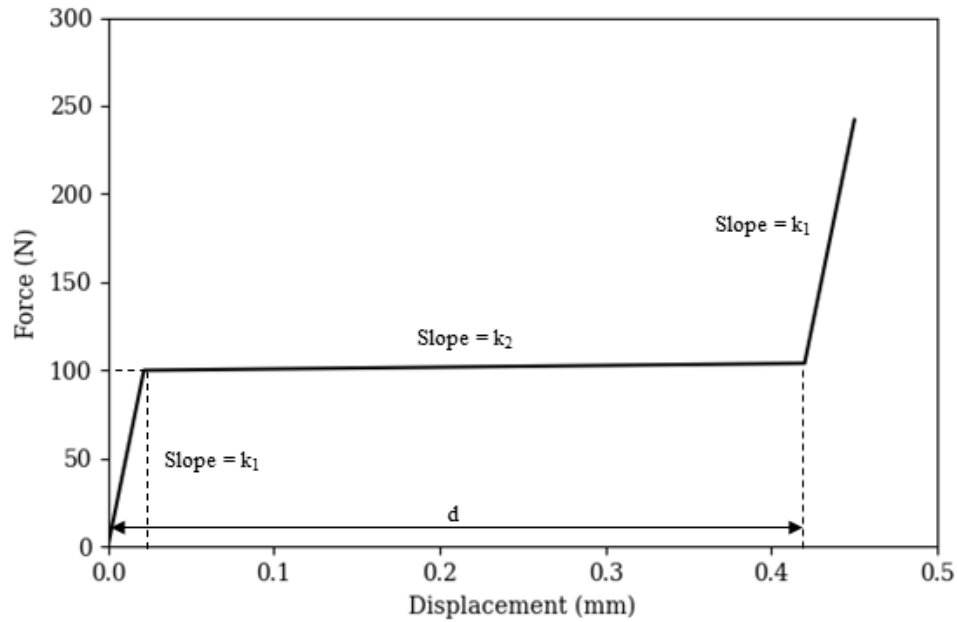


Figure 6.1: The non-linear axial stiffness function for the fixator used in the baseline model of group E. The fixator has an initial stiffness of k_1 up to a force of 100 N, then a stiffness k_2 up to the desired free-movement distance d , then a stiffness of k_1 thereafter, where $k_1 = 4600 \text{ N mm}^{-1}$, $k_2 = 10 \text{ N mm}^{-1}$, and $d = 0.42 \text{ mm}$ in the baseline case.

Fourteen different rehabilitation-regimes, including the baseline model, were simulated (Figure 6.2, Table 6.1). The ‘standard’ regime was modelled with a constant 500 N applied force. Constant-stability regimes, in which the stabilities were not changed over time, were simulated with high or low stability, with the stability represented as either force applied or fixator free-movement distance. The high and low stability values for force application used were 250 N and 750 N, respectively, corresponding to changes of 50% from the baseline value of 500 N. The high and low stability values for fixator free-movement distance used were 0.24 mm and 0.6 mm, respectively, corresponding to initial IFS’s of 4% and 10%, respectively, compared to a baseline initial IFS of 7%. Dynamisation, in which the stability is reduced over time from the high stability value to the baseline value, was modelled as either a linear change over the course of the simulation, or as a step change at iteration 75. Inverse-dynamisation, in which the stability is increased over time from the baseline value to the high stability value, was also modelled as either a linear change over the course of the simulation, or as a step change at iteration 75. At each iteration, the callus material properties were applied to the baseline FE model in order to simulate a force-stiffness-normalised IFM.

Stability parameter	General protocol	Protocol level	Values	Regime index
Force applied	Constant	High	750 N	R1
		Low	250 N	R2
	Dyanmisation	Step change	250 N to 500 N	R3
		Linear change		R4
	Inverse-dynamisation	Step change	500 N to 250 N	R5
		Linear change		R6
Free-movement distance	Constant	High	0.6 mm	R7
		Low	0.24 mm	R8
	Dynamisation	Step change	0.24 mm to 0.42 mm	R9
		Linear change		R10
	Inverse-dynamisation	Step change	0.42 mm to 0.24 mm	R11
		Linear change		R12

Table 6.1: The 12 rehabilitation-regimes simulated, not including the standard model nor the baseline model, which is equivalent to a constant protocol with a force of 500 N and a free-movement distance of 0.42 mm. The regimes which used applied force as the stability parameter (R1-R6) had a free-movement distance of 0.42 mm. The regimes which used free-movement distance as the stability parameter (R7-R12) had an applied force of 500 N.

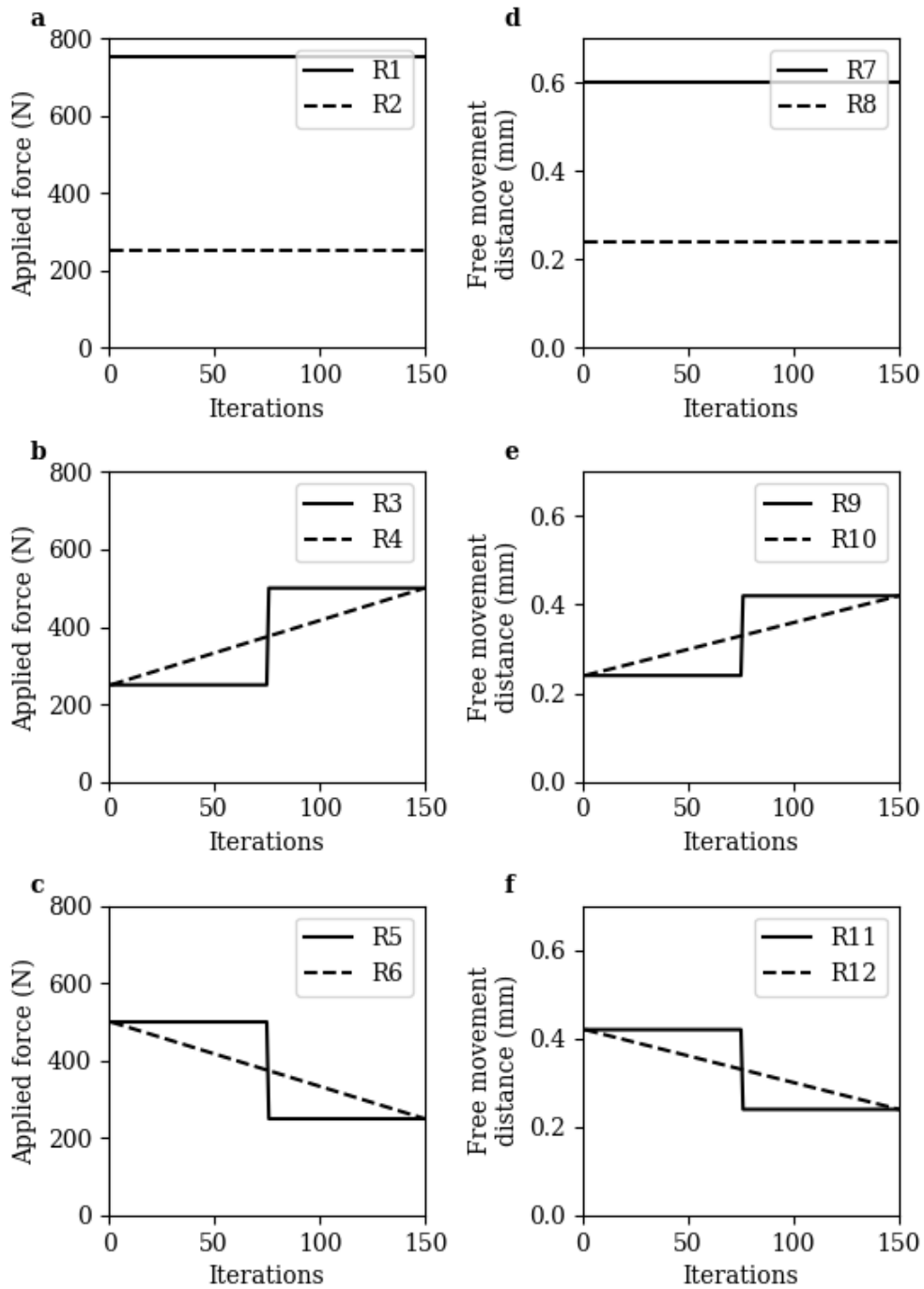


Figure 6.2: The 12 rehabilitation-regimes simulated plotted over 150 iterations, not including the baseline and standard regimes. (a) Constant applied force regimes R1 and R2, (b) dynamisation applied force regimes R3 and R4, (c) inverse dynamisation applied force regimes R5 and R6, (d) constant free-movement distance regimes R7 and R8, (e) dynamisation free-movement distance regimes R9 and R10, (f) inverse dynamisation free-movement distance regimes R11 and R12.

6.4 Results

The results of the simulations of the rehabilitation-regimes using applied force as the stability parameter, regimes R1-R6, are shown in Figure 6.3, against the baseline and standard simulations. The IFM progressions and the normalised IFM progressions of the regimes are shown in Figure 6.3a and b, respectively. The final bending stiffnesses of the simulations of regimes R1-R6 and the standard regime are shown in Figure 6.3c.

The results of the simulations of the rehabilitation-regimes using free-movement distance as the stability parameter, regimes R7-R12, are shown in Figure 6.4, against the baseline and standard simulations. The IFM progressions and the normalised IFM progressions of the regimes are shown in Figure 6.4a and b, respectively. The final bending stiffnesses of the simulations of regimes R7-R12 and the standard regime are shown in Figure 6.4c.

The highest stability regimes, R2, R3, R8, and R9, led to the fastest healing times. Inverse-dynamisation from the high stability state, demonstrated in regimes R3 and R9, had little effect on IFM progression when compared to the corresponding constant non-inverse-dynamisation regimes, R2 and R8, respectively. The constant low stability regimes, R1 and R7, yielded the slowest IFM progressions and regime R1 yielded the lowest final bending stiffnesses. The standard fixator led to the fastest healing time, except for regimes R2 and R3, but led to a lower final bending stiffness than the baseline model.

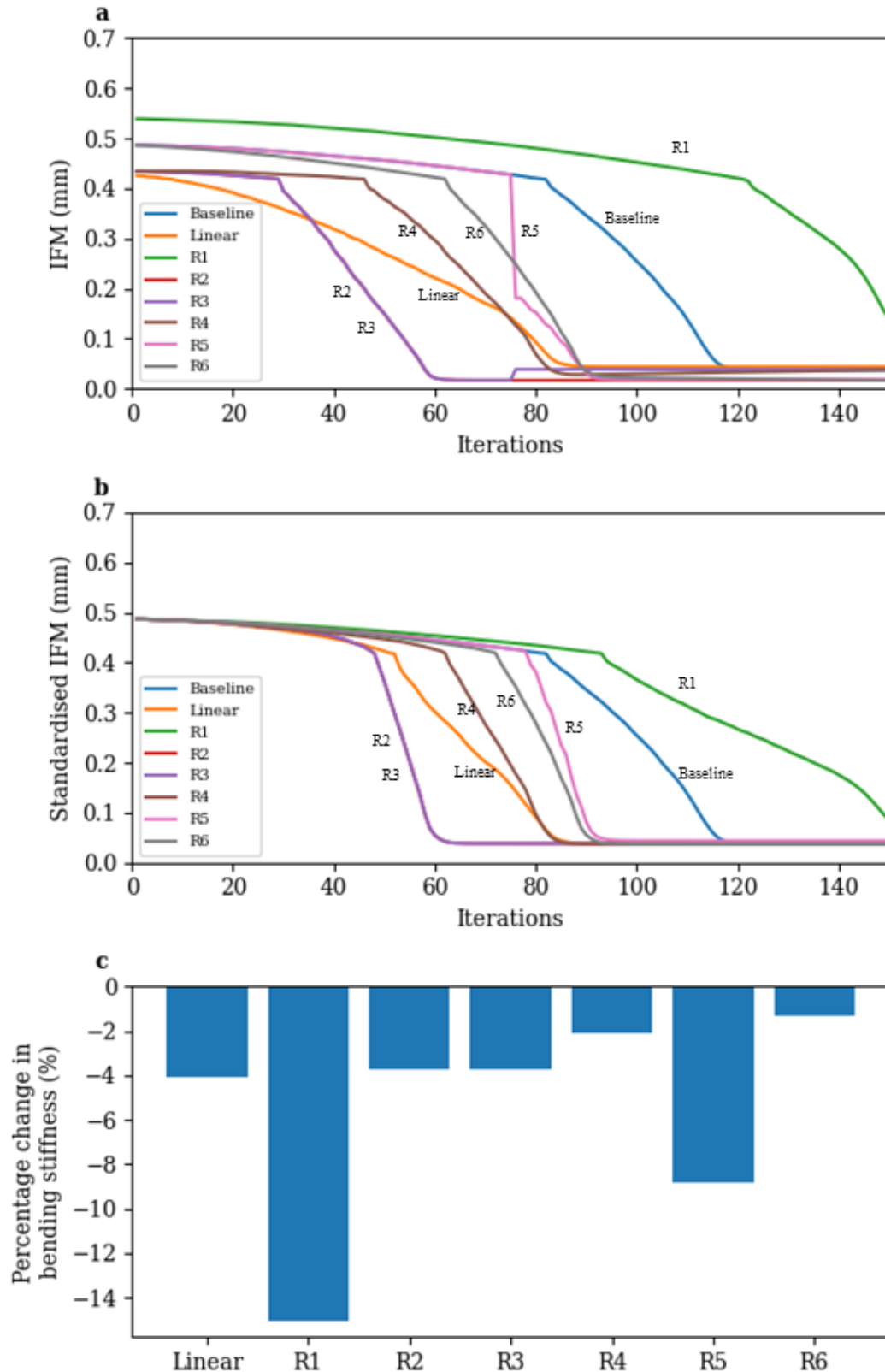


Figure 6.3: The results of the simulations of rehabilitation-regimes R1-R6 and the baseline and standard ‘linear’ models. (a) IFM progression, (b) normalised IFM progressions, (c) final bending stiffness. The normalised IFM progressions of R2 and R3 are overlaid in (b).

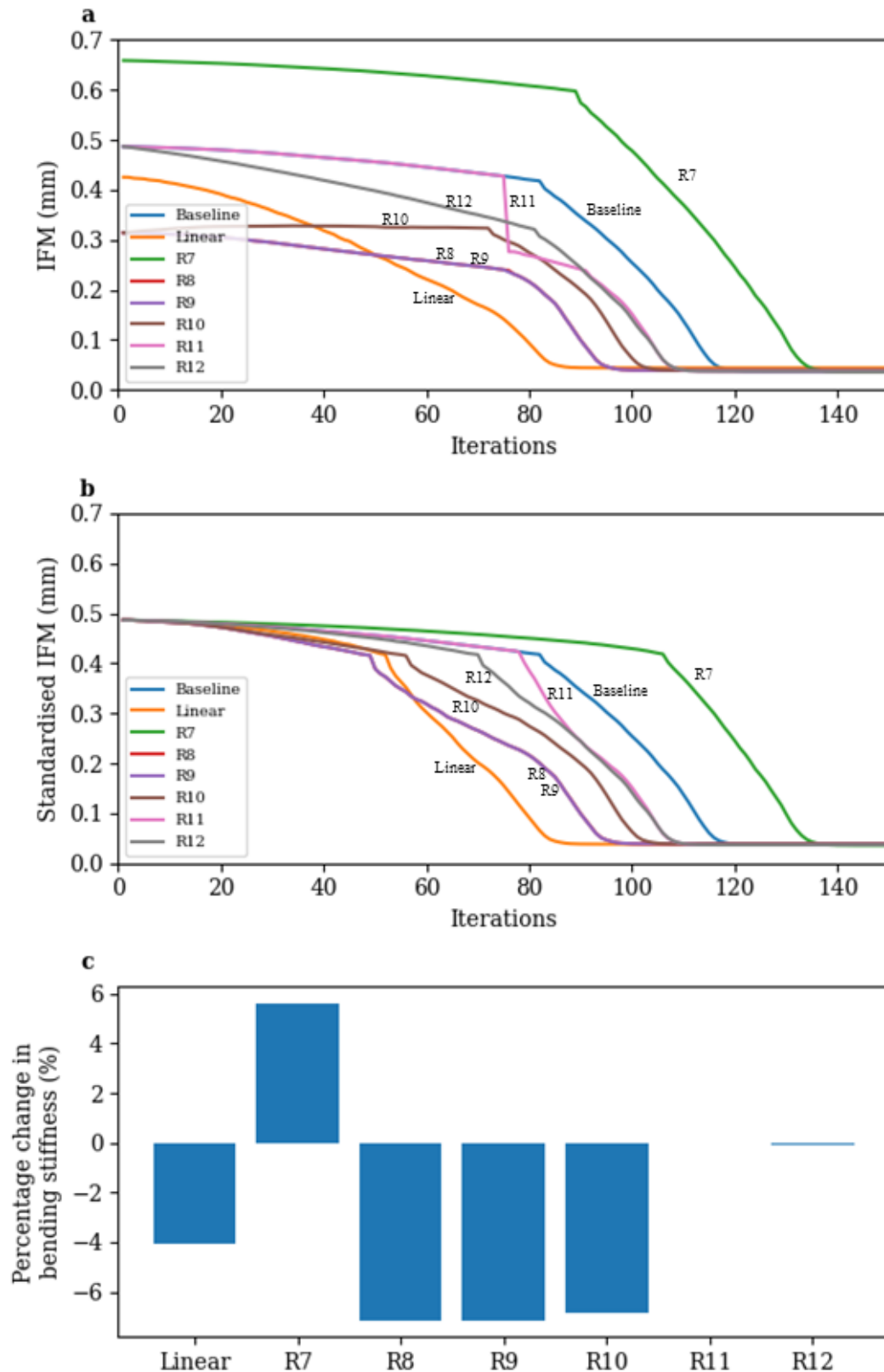


Figure 6.4: The results of the simulations of rehabilitation-regimes R7-R12 and the baseline and standard 'linear' models. (a) IFM progression, (b) normalised IFM progressions, (c) final bending stiffness. The normalised IFM progressions of R8 and R9 are overlaid in (a) and (b).

6.5 Discussion

The model developed in Chapter 4 for group E was used to examine 13 different rehabilitation-regimes, including the baseline model from Chapter 4. The model represented both groups E and F as both groups had an initial gap width of 6 mm and differed only in the free-movement distance of their fixators. Fixator free-movement distance was one of the parameters investigated in this study, therefore, the models can both be represented with the model of group E.

The primary factor negatively affecting the healing of model E was the large gap size. The results of Chapters 4 and 5 show that the models with smaller gap widths have superior fracture healing, which imply that the surgical goal should be to minimise the gap width. However, if a surgery results in a high gap width, such as the fracture model of group E, the results in this chapter demonstrate that stability, whether in terms of applied load or fixator stiffness, should be maximised to achieve the fastest healing times. This recommendation is contrary to current general concepts in fracture healing, which target an initial IFS of 2-10% to achieve secondary fracture healing (Perren, 1978, 2002), as the initial IFS in the model of group E was 7%, which falls within this recommended range. The results from this study suggest that recommendations of ideal initial IFS ranges may need to be adjusted based on gap width. Rehabilitation-regime management was not investigated for smaller gap widths, as rehabilitation likely has less influence in small gap fractures where successful fracture union is likely to occur with most current rehabilitation-regimes.

Dynamisation and inverse-dynamisation led to similar or worse healing times than a constant high stability rehabilitation-regime. The lack of effect of dynamisation and inverse-dynamisation predicted by the model may be attributed to the free-movement distance property of the non-linear stiffness fixator modelled in this study. Other fixators which have an allowable free-movement distance include a novel axial-micromotion locking plate (Han *et al.*, 2021) and intramedullary nails (Dailey, Daly and Glass-Hardenbergh, 2015; Ren and Dailey, 2020a). Dynamisation or inverse-dynamisation may have a greater effect on fracture healing in a model of a linear stiffness, non-adjustable fixator. The standard linear stiffness fixator led to faster healing times, but worse overall final bending stiffness than the baseline non-linear

stiffness fixator model. This indicates that fixators with an allowable free-movement distance are a promising treatment option compared to current standard-of-care linear stiffness fixators.

6.6 Conclusion

In this chapter, 14 different rehabilitation-regimes were applied to the model of group E from Chapter 4. Applied force and fixator free-movement distance were used as parameters to achieve the different rehabilitation-regimes; constant stability at high and low levels, dynamisation with step-change and linear change, and inverse-dynamisation with step-change and linear change. The results suggest that surgery should aim to minimise fracture-gap size for the best healing outcomes. For large fracture gap widths which have the worst outcomes, such as that of group E, the results from this study suggest that rehabilitation-regimes should focus on maximising stability by reducing axial load and fixator free-movement distance. Dynamisation and inverse-dynamisation were shown to be ineffective in this study, however, they may have more of an effect on models of different fixators. Other fixator types allow for mechanical behaviours other than pure axial movement, therefore 3-D modelling is required. In the next chapter, the fracture-healing algorithm is applied to 3-D models of a fracture treated with an intramedullary nail and a lateral locking plate.

CHAPTER 7

INTRAMEDULLARY NAILING AND LOCKING

PLATE FIXATION IN FEMORAL SHAFT

FRACTURE-HEALING SIMULATION

7.1 Scope

In Chapters 4 and 5, a novel fracture-healing algorithm was developed, validated against experimental data, and tested for sensitivity to its input parameters. In Chapter 6, the algorithm was used to compare the effect of different rehabilitation-regimes on fracture healing. In this chapter, the fracture-healing algorithm is expanded from a 2-D axisymmetric representation to a 3-D representation. A model is developed of a femoral shaft fracture and fixations of either an intramedullary nail or a lateral locking plate are applied. The fracture-healing algorithm is applied to these 3-D models and the fracture-healing patterns induced by the two fixators are compared.

7.2 Introduction

Distal femoral fractures represent 3-6% of femoral fractures (Martinet *et al.*, 2000; Court-Brown and Caesar, 2006) with an annual occurrence of 4.5 per 100,000 (Court-Brown and Caesar, 2006). While these fractures are approximately ten times less frequent than proximal femoral, or hip, fractures (Martinet *et al.*, 2000), they have similar morbidity and mortality rates. Proximal femoral fractures have received much attention recently with the introduction of the National Hip Fracture Database and inclusion of hip fracture management in the NHS Best Practices Tariff. This standardisation of care has led to decreased morbidity and mortality rates in these fractures (Smith *et al.*, 2015). There is no consensus on operative or post-operative management of distal femoral fractures (Smith *et al.*, 2015; Toro, 2015).

Locking plates generally have better angular stability than intramedullary nails due to the use of locking screws, which is particularly beneficial in intra-articular fractures. The lateral placement of locking plates, however, causes bending which creates an asymmetric mechanical environment in the fracture region which can lead to asymmetric callus development. Locking plates are increasingly popular and regarded as the preferred treatment option for distal femoral fractures (Ricci *et al.*, 2014; Rodriguez *et al.*, 2014). This increasing popularity is likely based on promising early results of locking plates (Schütz *et al.*, 2001; Kregor *et al.*, 2004; Weight and

Collinge, 2004; Kolb *et al.*, 2008), which have possibly led to over-application of this method leading to increased non-union rates (Ricci *et al.*, 2014; Rodriguez *et al.*, 2014). A review of trials comparing intervention options for distal femoral fractures found few relevant trials and little evidence to support locking plates as a standard treatment (Griffin *et al.*, 2015; Claireaux *et al.*, 2022) and many of the trials were performed on out-dated implants (Griffin *et al.*, 2017). Research into the effectiveness of locking plates is further complicated by the large choice in plate configurations and by the failure to control for mechanically relevant parameters when comparing across different configurations (MacLeod and Pankaj, 2018; MacLeod, Simpson and Pankaj, 2018).

A large-scale RCT to investigate whether locking plates or intramedullary nails lead to better outcomes in the treatment of distal femoral fractures was planned, but a feasibility study concluded that the study was unfeasible due to limitations in patient and surgeon recruitment (Griffin *et al.*, 2019). However, even if the trial was able to recruit sufficiently, the large number of parameters in distal femoral fractures, such as comminution or articular involvement, means that a generalised approach to distal femoral fracture pre-operative planning or best practices is unlikely to be effective. A large scale *in silico* trial could be used to provide a separate treatment recommendation for each classification of distal femoral fracture.

In modelling distal femoral fractures, capturing accurately the local effects of fixation methods presents significant computational challenges, particularly given the constraints of screw placement near the fracture site due to spatial constraints. Previous studies have demonstrated that while the method of screw modelling has a less pronounced impact on global mechanics, it influences significantly local mechanical outcomes (MacLeod, Pankaj and Simpson, 2012). Consequently, this chapter focuses on a mid-shaft femoral fracture model, allowing for certain modelling simplifications that reduce computational demands. The primary objective is to validate the ability of the fracture-healing algorithm to replicate the key mechanical differences between locking plates and intramedullary nails, such as the enhanced angular stability associated with locking plates and the more symmetric motion provided by intramedullary nails, and their respective effects on fracture healing. Notably, accurately simulating the fixation of locking plates and capturing angular

instabilities necessitates a 3-D modelling approach, which increases computational requirements.

7.3 Methods

7.3.1 FE Models

7.3.1.1 Bone and callus geometry and mesh

Two 3-D non-linear models were developed in MSC.Marc (v2021, MSC Software) of a femoral shaft fracture; one which was treated with an intramedullary nail, and one which was treated with a lateral locking plate. Femur geometry was taken from the Muscle Standardized Femur Model (Viceconti, 2017), which is based on a bone surrogate for *in vitro* testing. A simple transverse diaphyseal fracture was modelled as an osteotomy (Lewis *et al.*, 2021) which was created at the mid-shaft of the femur by removing a 5 mm section of bone. A callus region was created with a length and diameter of 56 mm and 64 mm, respectively, with no intramedullary portion. A diagram of the callus geometry is shown in Figure 7.1. The callus volume was created by revolving the 2-D sketch around the long-axis of the bone, then performing a Boolean subtract function on the volume to ensure the callus was flush to the bone sections. Trabecular bone was not included in the model geometry, but its exclusion is unlikely to affect the mechanical environment at the mid-shaft. The bone segments and callus were meshed with linear tetrahedral elements with average element edge lengths of 3 mm and 1 mm, respectively.

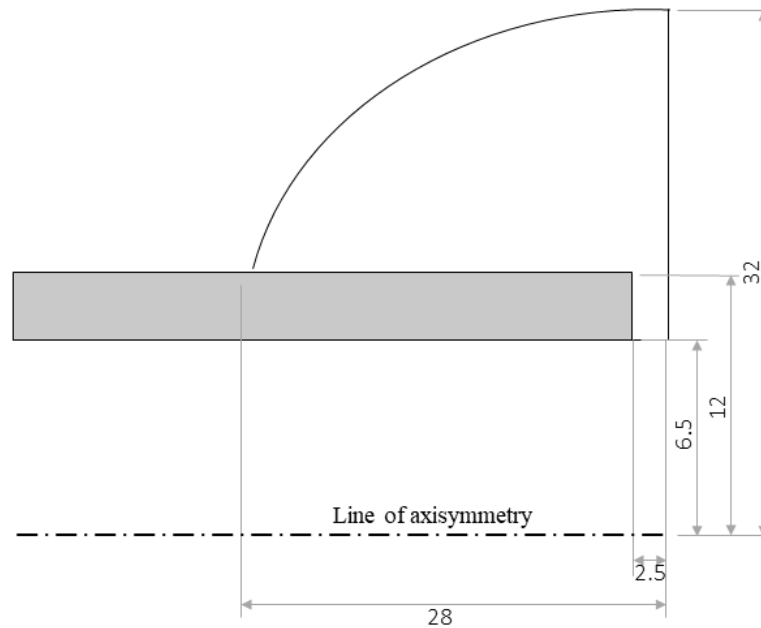


Figure 7.1: Dimensions of the initial callus domain. Shown is half of an axisymmetric profile of the callus region. The profile is revolved around the long axis of the bone to create the callus volume. An idealised bone segment of approximately the same inner and outer diameter of the bone segments is shown shaded.

7.3.1.2 Locking plate model

The locking plate was modelled with dimensions of 150 mm x 5 mm x 17.5 mm. 11 holes with an inter-hole spacing of 12.5 mm were created with diameters of 5 mm. Screws were modelled as 4.3 mm diameter beam elements connecting RBE2's at the plate, near-plate cortex, and far-plate cortex. The plate was located centrally over the mid-point of the callus on the lateral side. The central hole in the plate was located directly over the fracture gap. Screws were placed at the first, third, and fifth screw holes in the plate on both sides of the fracture gap. Through-holes of 4.3 mm diameter were created in both cortices of the bone segments at each screw location. Any plate and screw volume which overlapped with the callus region was removed from the callus region. The bone-plate offset varied between 2 mm to 5 mm along the length of the plate. The plate was meshed with an element edge length of 1.5 mm, and refinement to 0.75 mm in the region of the fracture, where bending stresses are highest. Linear tetrahedral elements were used with a strain-smoothing formulation, which are better suited for capturing bending behaviour than traditional tetrahedral elements (Dohrmann *et al.*, 2000).

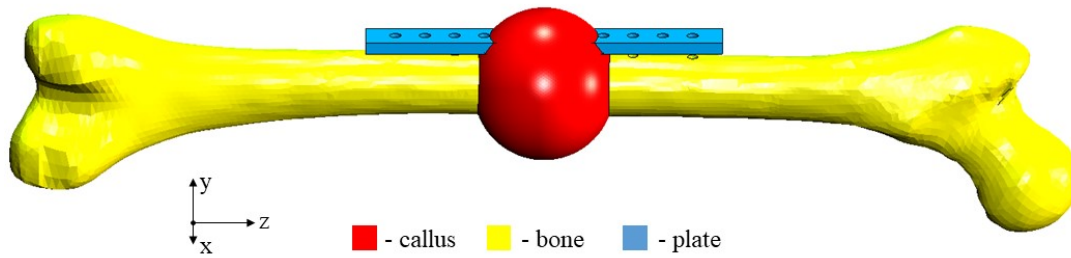


Figure 7.2: The locking plate FE model with the callus, bone segments, and locking plate shown in red, yellow, and blue, respectively. The locking screws are modelled as beam elements and are not pictured.

7.3.1.3 *Intramedullary nail model*

The intramedullary nail was modelled as 6 fixed-degree-of-freedom springs connecting the retained nodes of two RBE2's, which are located at a distance of 135 mm on each side of the callus centre, for a total nail length of 270 mm. At each nail end, two through-holes, orthogonal to each other, of diameter 4.3 mm were created in the bone segments, at distances of 130 mm and 135 mm from the callus centre. The interior nodes of each through-hole were tied to their nearest retained node, to attach the intramedullary nail to the bone segments. Axial and torsional stiffnesses were modelled as non-linear, with an initial free-movement range of 0.2 mm and 8°, respectively, followed by a linear stiffness of 2,650 N mm⁻¹ and 0.88 N m deg⁻¹, respectively, as shown in Figure 7.3 (Dailey, Daly and Glass-Hardenbergh, 2015; Ren and Dailey, 2020a). Bending stiffness, represented as two rotational degree-of-freedom springs, was 32 N m deg⁻¹ (Schandelmaier *et al.*, 2000). The intramedullary nail was modelled with a high shear stiffness of 20,000 N mm⁻¹, represented as two translational degree-of-freedom springs.

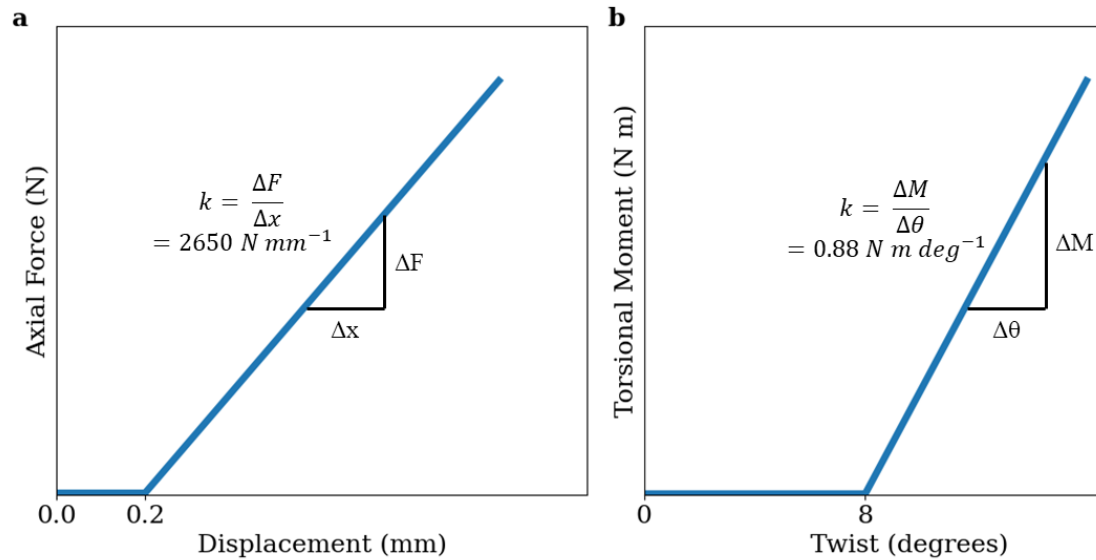


Figure 7.3: Non-linear stiffness plots used to represent the intramedullary nail, which include free-movement regions, for (a) axial and (b) torsional stiffness (Dailey, Daly and Glass-Hardenbergh, 2015; Ren and Dailey, 2020a).

7.3.1.4 *Material properties and boundary conditions*

Biological tissues were modelled as in Chapter 4, with linear elastic material properties. The locking plate and locking screws were considered to be made out of stainless steel. A summary of material properties used is given in Table 7.1.

Material	Young's modulus (MPa)	Poisson's ratio
Soft tissue	3	0.3
Cartilage	200	0.45
Woven bone	400	0.36
Lamellar bone	10,000	0.36
Stainless steel	200,000	0.3

Table 7.1: Young's modulus and Poisson's ratio of the materials used in the models. All materials were modelled as linear elastic isotropic.

The hip joint was modelled as an RBE2 with the retained node located at the centre of the femoral head and tied nodes located on the surface of the femoral head. The retained node was fixed in 2 translational degrees-of-freedom, allowing for axial translation. The knee joint was modelled with 2 RBE2's, one for each condyle, with the retained nodes located at the centre of each condyle and tied nodes located on the surface of each respective condyle. The medial condyle was fixed in all 3 translational

degrees of freedom, and the lateral condyle was fixed in 2 translational degrees of freedom, allowing for lateral translation (Nassiri, Macdonald and O’Byrne, 2013; MacLeod, 2015). Loading was applied at the hip as an axial force with a magnitude of 238% of body-weight, or 1,635 N (Bergmann *et al.*, 2001; Heller *et al.*, 2001; MacLeod, 2015). Glued contact was specified between all contacting bodies.

7.3.1.5 Interfragmentary movement measurement

IFM was measured at each iteration at the external surface of both the lateral and medial cortices to capture the bending dynamics of the locking plate model (MacLeod, Pankaj and Simpson, 2012). IFM was also measured at both cortices in the intramedullary nail model to confirm its predominantly axial behaviour.

7.3.2 Biological controller

The biological controller described in Chapter 4 was implemented. The only notable consideration when moving from the 2-D model used in Chapters 4, 5, and 6, to the 3-D model used here, is the number of nodes shared between two callus elements to define neighbouring elements. The number of nodes to define a neighbour was left unchanged at 1. The baseline parameters for the fuzzy rules and membership functions were used. Despite the callus-element edge-length of 0.35 mm in the models in Chapter 4 and the callus-element edge-length of 0.75 mm in the present models, the same mesh-parameter coefficient and temporal smoothing parameter of 0.57 and 7, respectively, were used, to reduce the required number of iterations. Therefore, the present model is not temporally calibrated, but temporal comparisons between the intramedullary nail model and the plate model can still be made.

7.3.3 Healing assessment

At the end of the 150 iterations, the fixator in each of the models was removed. Two RBE2’s were created, one at 100 mm distal and one at 100 mm proximal to the centre of the callus region, with a central retained node and tied nodes along the transverse cross-section of the femur. A bending moment of 5,000 N mm was applied at each of the retained nodes. The distal retained node was fixed in all 3

translational degrees of freedom, and the proximal retained node was fixed in 2 translational degrees of freedom, allowing axial translation. Deflection was measured at the centre of the callus. Bending stiffness was calculated as the applied moment divided by the mid-span deflection. Bending stiffness was measured in both directions across four planes: the sagittal plane, the coronal plane, and the two planes at 45° to the sagittal and coronal planes, where the sagittal and coronal planes are represented by the y-z and x-z planes, respectively, as defined in Figure 7.2.

7.4 Results

The simulations of the intramedullary nail and plate models both converged at iteration 50. The IFM progressions of each simulation, measured at both the medial and lateral cortices, are shown in Figure 7.4. The minimal difference between the medial and lateral IFM's in the intramedullary nail model simulation is attributable to the predominantly axial movement in the model, while the large difference between the medial and lateral IFM's in the plate model simulation is attributable to the predominantly bending behaviour of the plate model.

The Young's modulus, bone concentration, cartilage concentration, and intramembranous ossification activation level at each callus finite-element at iterations 7, 14, 21, 35, and 100 are shown for the coronal and sagittal callus cross-sections of the intramedullary nail model in Figures 7.5 and 7.6, respectively, and for the plate model in Figures 7.7 and 7.8, respectively. The intramedullary nail simulation shows axisymmetric callus development, with periosteal bulging, external callus bridging, and subsequent bridging at the cortices. In the sagittal plane of the plate simulation, the callus development on the anterior cortex is similar to that of the posterior cortex, with periosteal bulging, external callus bridging, and subsequent bridging at the cortices. In the coronal plane of the plate simulation, there is greater callus development at the medial, or 'far-plate', cortex than at the lateral, or 'near-plate', cortex. Bony bridging occurs at the lateral cortex before the medial cortex.

The bending stiffnesses of the final iteration of the simulations of the two models, with fixators removed, in 8 different bending directions, along with the

average and standard deviations of these directions, are shown in Table 7.2. The average bending stiffness of the intramedullary nail model is higher than that of the plate model. Within each model, bending stiffnesses are approximately equivalent in either direction of a given plane; for example, the bending stiffness of the nail model in the anterior-posterior plane is the same with bending in the anterior direction as in the posterior direction.

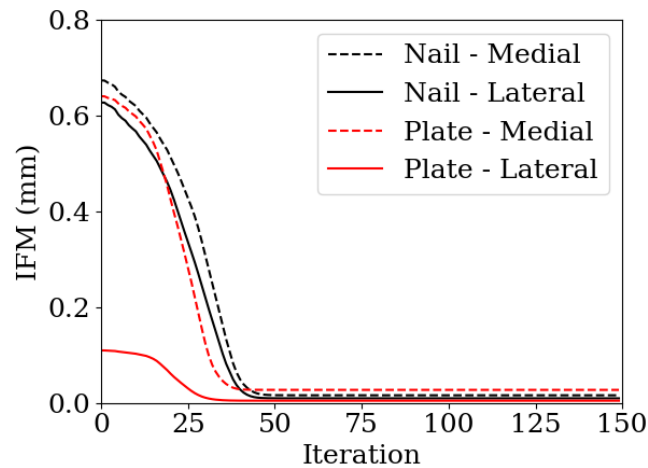


Figure 7.4: Temporal evolution of IFM in the intramedullary nail and plate model simulations, with IFM measured at both the lateral and medial cortices, representing the near and far-plate cortices in the plate model.

Bending plane	Bending stiffness (N m mm ⁻¹)	
	Intramedullary nail	Plate
AP-A	23.5	22.8
AP-A + ML-M	25.3	23.9
ML-M	23.7	21.6
AP-P + ML-M	22.0	20.7
AP-P	23.5	22.8
AP-P + ML-L	25.3	23.9
ML-L	23.7	21.6
AP-A + ML-L	22.0	20.7
Average ± Standard deviation	23.6 ± 1.2	22.2 ± 1.2

Table 7.2: Bending stiffnesses in 8 bending planes of the healed calluses of the model treated with an intramedullary nail and with a plate. ‘IM’ = intramedullary. Bending planes are coded by a two-letter plane followed by the direction of callus movement, ie: ‘AP-A’ = anterior-posterior (or sagittal) plane, with callus moving anteriorly. ‘ML-M’ = medial-lateral (or coronal) plane, with callus moving medially.

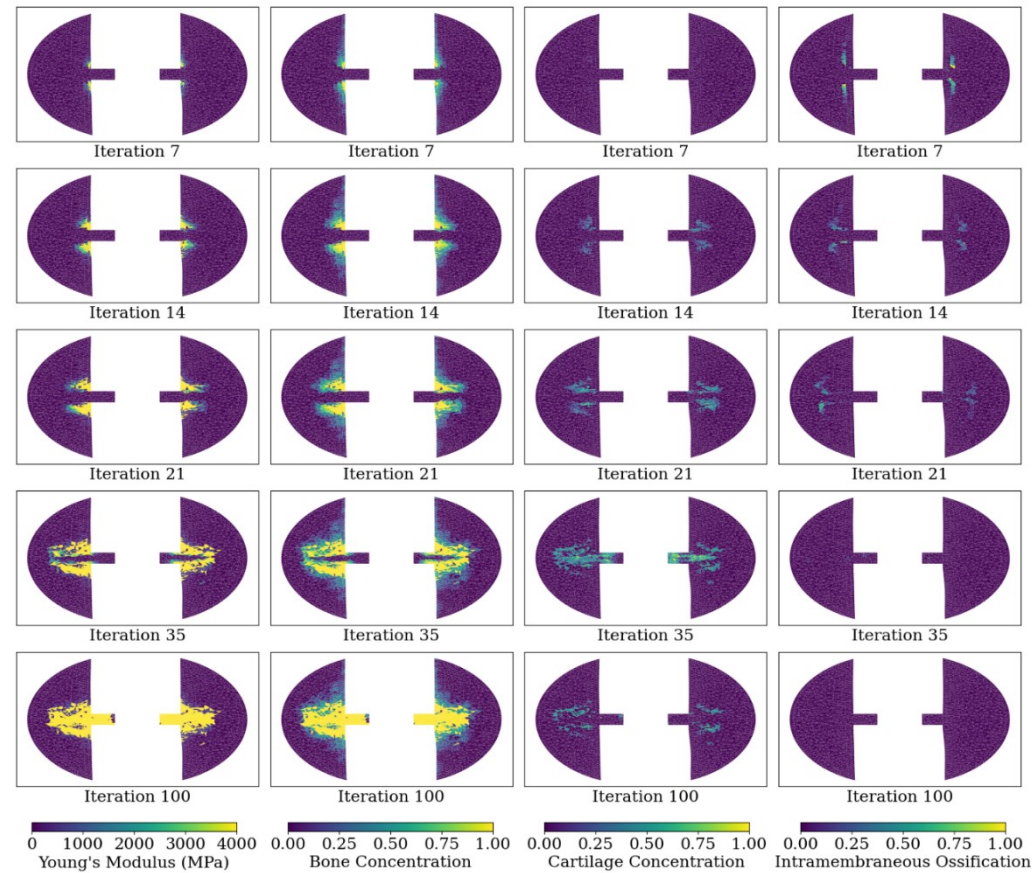


Figure 7.5: Coronal view of the callus cross-section of the intramedullary nail model simulation at iterations 7, 14, 21, 35, and 100. The plotted variables for each callus finite-element span from the leftmost to the rightmost column: Young's modulus, bone concentration, cartilage concentration, and intramembraneous ossification activation. Bone and cartilage concentrations are depicted as tissue proportions within the finite-element, with a bone concentration of 1.0 indicating full ossification. Intramembraneous ossification is quantified as an activation proportion, with a value of 1.0 denoting complete biological rule activation.

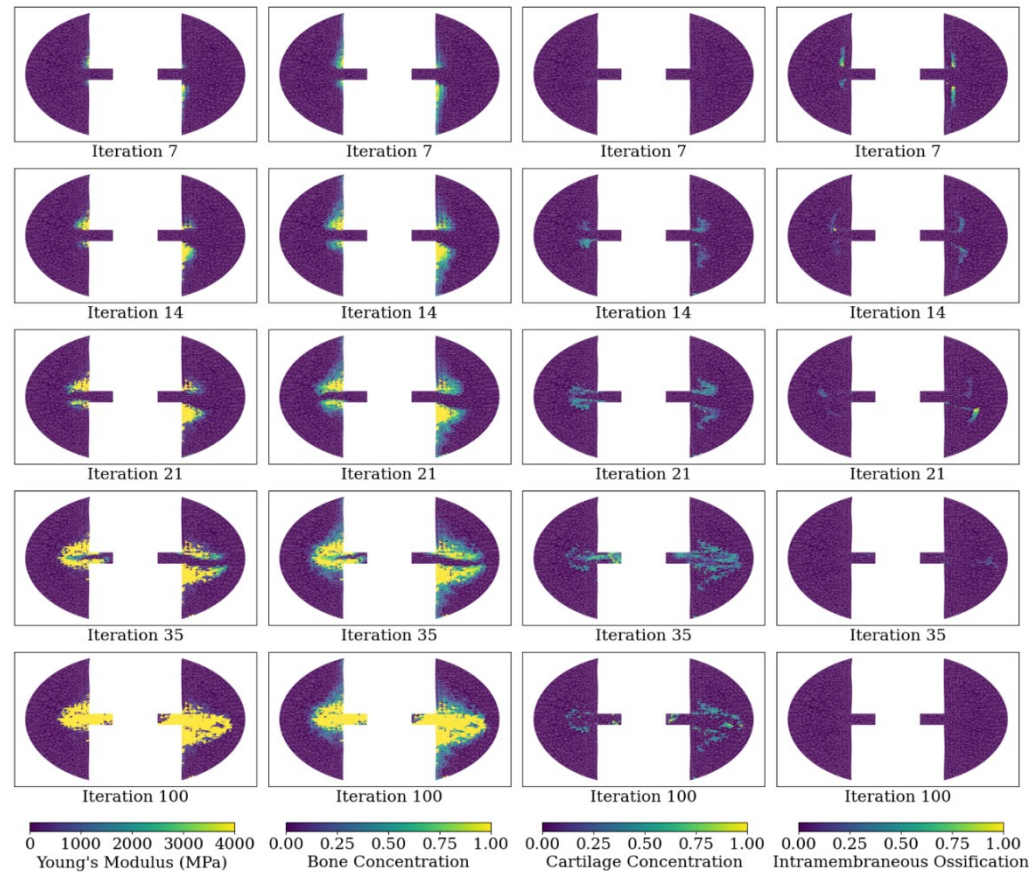


Figure 7.6: Sagittal view of the callus cross-section of the intramedullary nail model simulation at iterations 7, 14, 21, 35, and 100. The plotted variables for each callus finite-element span from the leftmost to the rightmost column: Young's modulus, bone concentration, cartilage concentration, and intramembraneous ossification activation. Bone and cartilage concentrations are depicted as tissue proportions within the finite-element, with a bone concentration of 1.0 indicating full ossification. Intramembraneous ossification is quantified as an activation proportion, with a value of 1.0 denoting complete biological rule activation.

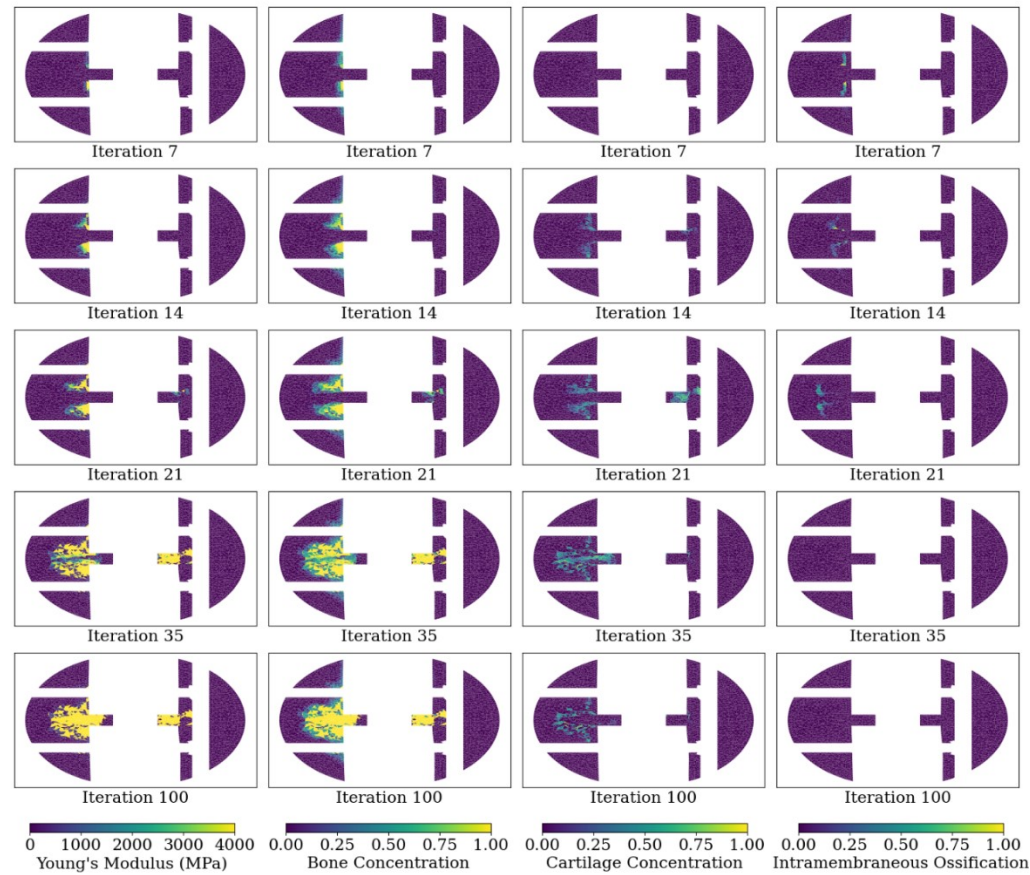


Figure 7.7: Coronal view of the callus cross-section of the plate model simulation at iterations 7, 14, 21, 35, and 100. Note the plate and two nails are visible in the outline of the callus. The plotted variables for each callus finite-element span from the leftmost to the rightmost column: Young's modulus, bone concentration, cartilage concentration, and intramembraneous ossification activation. Bone and cartilage concentrations are depicted as tissue proportions within the finite-element, with a bone concentration of 1.0 indicating full ossification. Intramembraneous ossification is quantified as an activation proportion, with a value of 1.0 denoting complete biological rule activation.

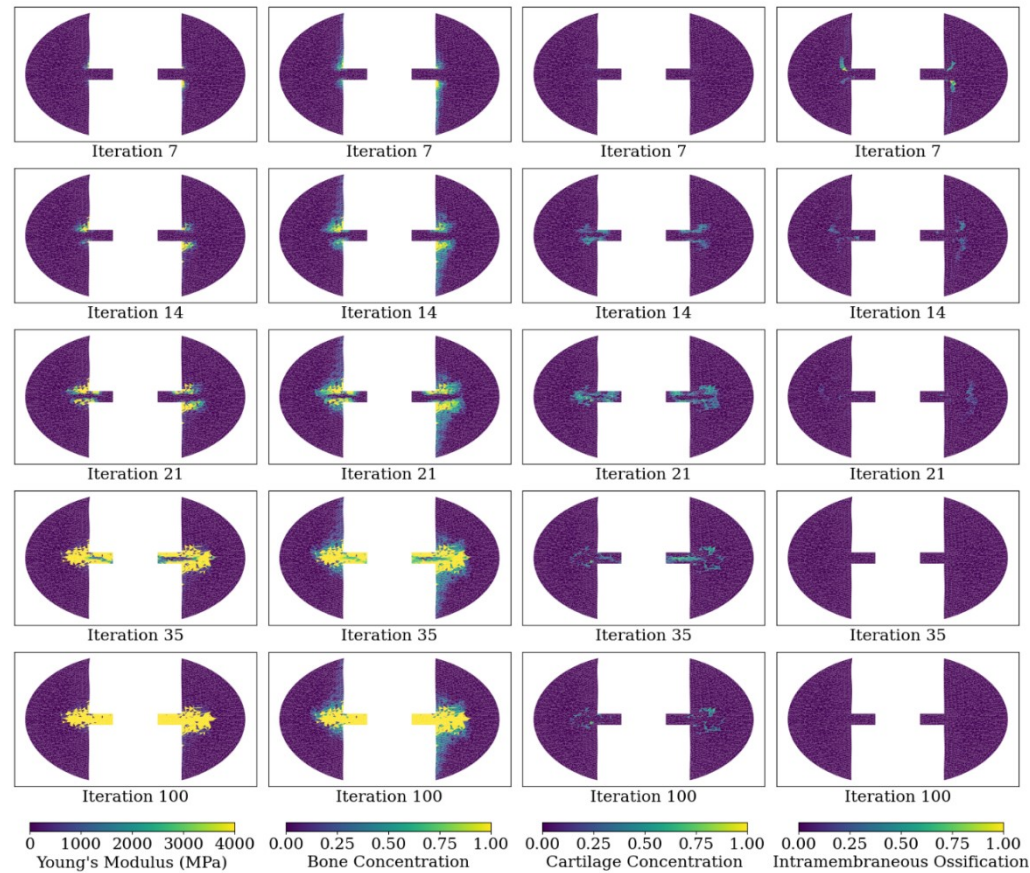


Figure 7.8: Sagittal view of the callus cross-section of the plate model simulation at iterations 7, 14, 21, 35, and 100. The plotted variables for each callus finite-element span from the leftmost to the rightmost column: Young's modulus, bone concentration, cartilage concentration, and intramembraneous ossification activation. Bone and cartilage concentrations are depicted as tissue proportions within the finite-element, with a bone concentration of 1.0 indicating full ossification. Intramembraneous ossification is quantified as an activation proportion, with a value of 1.0 denoting complete biological rule activation.

7.5 Discussion

The simulation of the model treated with an intramedullary nail had a symmetric IFM over the course of healing, with the medial and lateral IFM's closely matching, as shown in Figure 7.4. This led to mostly axisymmetric callus development, with some asymmetry in the sagittal plane, as shown in Figure 7.6. This asymmetry is likely attributable to slight bending of the intramedullary nail. The simulation of the model treated with a locking plate had an asymmetric IFM over the course of healing, with the medial, or far-plate, IFM greater than the lateral, or near-plate, IFM, as shown in Figure 7.4. The lateral IFM of the plate model converged before the medial IFM, highlighting the need to measure IFM's at multiple cortex locations for 3-D models, and the inadequacy of IFM as an indicator of fracture healing. The simulation of the model treated with a locking plate predictably had asymmetric callus formation in the coronal plane, as shown in Figure 7.7, with greater callus development at the medial cortex, matching with physiological observations in plate-treated fractures (Lujan *et al.*, 2010). The callus development in the sagittal plane, however, was mostly symmetric, as shown in Figure 7.8.

The fracture-healing algorithm previously demonstrated a physiological healing sequence in 2-D axisymmetric models, and continued to predict physiological healing sequences in the present 3-D models with both intramedullary nail and locking plate fixation. The simulations began with periosteal bulging, formed via intramembranous ossification, followed by cartilaginous bridging at the external callus, and bony bridging via endochondral ossification (Vetter *et al.*, 2010). In the locking plate model, the lateral, or near-plate, cortex exhibits inter-cortical bridging before the medial cortex, as shown in Figure 7.7. This is attributable to the lower overall strains in the near-plate region, specifically in the direct inter-cortical gap. Whether bony bridging occurring first at the near-plate cortex is physiological is unclear due to limited time-series radiograph studies and obstruction by the locking plate on images (Lujan *et al.*, 2010). This phenomenon warrants experimental investigation, as it could affect healing dynamics in locking plate treated fractures in the later stages of fracture healing, and could inform late-stage rehabilitation-regimes.

The bending stiffness assessments of the simulations of the two models were approximately equal, and interestingly demonstrated similar patterns in bending stiffness across the different bending planes tested, despite the asymmetric mechanical behaviour of the plate model; for example, both models had the highest bending stiffness in the ‘AP-A + ML-M’ and ‘AP-P + ML-L’ directions. The average bending stiffness of the intramedullary nail model was marginally greater than that of the plate model, which agrees with current clinical best practices for mid-shaft femoral fracture treatment (Gwathmey *et al.*, 2010). Based on the IFM traces at the medial cortex of the intramedullary nail and plate models, the plate treatment led to relatively faster healing, but IFM is a poor measure of healing outcome. An analysis of the bending stiffness at each iteration for the two models would yield insights into the relative healing timeframes of the two treatments, but this would significantly increase computational expense.

Previous *in silico* studies of femoral fracture fixation have used a gap width of 6 mm (MacLeod, 2015), but a 5 mm gap width was used in this study to reduce the callus volume, and therefore computational expense. The use of a smaller gap width would likely have little effect on the results of the study, as successful healing was achieved in both cases, and a reduction in gap width generally improves healing outcomes. The use of a larger gap width may amplify the differences in callus development between the two fixators; over a larger gap width, the effect of plate bending will lead to a greater difference in strain magnitudes at the far-plate cortex between the plate model and intramedullary nail model. This may lead to the fracture-healing algorithm predicting a non-union in the plate model and a successful union in the intramedullary nail mode, for a sufficiently large gap width.

A more simplified modelling approach was used to represent the intramedullary nail compared to the lateral locking plate; the locking plate was modelled explicitly, whereas the intramedullary nail was modelled as idealised springs. While the intramedullary nail spring stiffness values were obtained from experimental testing of similar fixators in literature, they may not be as well suited to the particular fracture case modelled in this study. However, the aim of the comparison between the fixator types was not to capture accurately the behaviour of both fixators, but to compare the overall differences in mechanical behaviour and how

these differences affect the predictions of the fracture-healing algorithm. The modelling methods used for the fixators are able to capture these main differences: the lateral locking plate behaviour is dominated by bending, while the intramedullary nail by axial movement.

A previous study which expanded a fracture-healing algorithm from a 2-D axisymmetric model to a 3-D model noted an over-sensitivity to distortional strain, with the model predicting non-unions where experimental data showed only a delayed union (Ren and Dailey, 2020a). In the present fracture-healing algorithm, no significant difference in overall algorithm output was observed between the healing predictions for 2-D axisymmetric models and 3-D models, however, no torsional loading was applied in the 3-D model. Physiological hip joint loading is predominantly axial (Bergmann *et al.*, 2001; Heller *et al.*, 2001), but some torsional loading can be present. The application of the present fracture-healing algorithm to a model using joint loads and muscle forces derived from musculoskeletal modelling of a patient during rehabilitation (Orth *et al.*, 2023) would yield better insights into the performance of the algorithm under physiological loading.

A mid-shaft femoral fracture rather than a distal femoral fracture was modelled in the present study to reduce computational expense. Modelling of a distal femoral fracture would likely require physical modelling of screws, along with their contact interaction with the bone fragments and plate (MacLeod, Pankaj and Simpson, 2012), since the screw locations would be closer to the fracture gap than in a mid-shaft fracture model. The use of a mid-shaft femoral model allowed for simplifications in the modelling of the screws in the fixations, as well as an abstraction of the intramedullary nail as 6 fixed-degree-of-freedom springs. A further simplification used in the present study was the use of joint reaction force, and no muscle forces. The inclusion of muscle forces and use of free boundary conditions have been shown to influence the bone strain predictions in FE models of the femur (Phillips, 2009; Viceconti, 2017), but whether the use of these more complex modelling methods would alter callus region strains in a femoral fracture model is unclear. A limitation of the models used in the present study is a lack of *in vitro* validation testing, however, the use of physiological boundary conditions, including

joint restraints, is challenging to model *in vitro*. The modelling of distal femoral fractures and the inclusion of muscle forces is discussed in Chapter 8.

7.6 Conclusion

In this chapter, the fracture-healing algorithm was applied to two 3-D models of femoral mid-diaphyseal fractures; one treated with an intramedullary nail, and one treated with a locking plate. While the fracture-healing algorithm had previously only been applied to 2-D axisymmetric models, the algorithm still predicted a physiological healing sequence in the 3-D models. The algorithm was capable of capturing accurately the effects of different fixator types on callus development; specifically, the algorithm predicted the asymmetric callus development caused by the bending motion in the locking plate model, and the symmetric callus development in the intramedullary nail model. Recommendations for future works to incorporate the fracture-healing algorithm into an *in silico* trial are given in Chapter 8.

CHAPTER 8

SUMMARY, DISCUSSION, AND FUTURE WORK

8.1 Scope

This chapter summarises the research conducted in this PhD and discusses its findings. Final steps to demonstrate the suitability of the novel fracture-healing algorithm for application to distal femoral fractures are prescribed. A large-scale *in silico* trial of distal femoral fracture treatment utilising the fracture-healing algorithm is outlined. Potential challenges in implementation are forecast and solutions are proposed.

8.2 Thesis summary

The aim of this work was to develop a computational tool for the simulation of the fracture healing progress in response to mechanical stimuli and demonstrate the capability of the tool for use in an *in silico* trial of fracture-fixation treatments.

The literature around fracture healing and fracture-fixation treatments was reviewed. Gaps in fracture fixation treatment recommendations were identified. Specifically, traditional methods of answering clinical questions, such as *in vivo* RCT's and *in vitro* testing, were found to have failed to deliver conclusive recommendations on distal femoral fracture treatment. An *in vivo* RCT was severely limited by patient recruitment, as distal femoral fractures are relatively uncommon. *In vitro* studies suffered from inconsistencies in methods used, such as boundary conditions, and are limited to capturing only the immediately post-surgical fracture-fixator construct stiffness, and not the stiffness throughout the healing sequence.

An alternative approach to addressing clinical questions was identified as *in silico* trials. Previous *in silico* trials were found to be capable of overcoming the limitations of *in vivo* and *in vitro* trials; *in silico* trials are not limited by low incidence rates, inter-study inconsistencies, or restrictions on invasive measurements. Furthermore, the ability of *in silico* trials to simulate devices and configurations which would be immoral to test *in vivo*, but would aid in novel fixation-device development and testing, was discussed.

Published fracture-healing algorithms were reviewed and categorised based on their main input parameters. Significant limitations in existing algorithms were identified as initial callus domain dependence and high sensitivity to the cellular diffusion rate, a parameter whose value is uncertain. Errors in methodology in a published fracture-healing algorithm were identified which prevented an attempted reproduction of published results.

A novel fracture-healing algorithm was proposed which uses principal strains as its primary strain inputs, rather than distortional and dilatational strain, or interstitial fluid flow. Minimum and maximum principal strains were used as continuum representations of compressive and tensile strains, respectively. Tensile and compressive strains were theorised to regulate intramembranous ossification and endochondral ossification, respectively, based on the known physiological stages of secondary fracture healing. The novel fracture-healing algorithm demonstrated mesh convergence and independence from the initial callus domain. Callus domain independence had not been previously demonstrated by a fracture-healing algorithm without the use of a spatial proximity function to prescribe callus shape.

The fracture-healing algorithm was tested for validation against 6 corresponding experimental models with varied fracture-gap widths and initial IFS's. The general healing outcomes of the experimental data of the 6 groups were predicted by the healing algorithm, but the overall magnitudes of bending stiffness, which were used to assess healing outcomes, were lower in the simulated data than in the experimental data. The healing outcome of group E was positive in the simulation, but was a 'borderline' healing case in the experimental data, with some cases healing successfully and others resulting in non-union. The trends of IFM over time for the 6 groups were similar for the experimental dataset and the simulated counterparts. Temporal calibration was not performed, but for the mesh size and fracture geometries used, 1 day corresponded approximately to 3 iterations in the healing algorithm.

The fracture-healing algorithm was analysed for its sensitivity to its input parameters. The models of groups C, E, and F were simulated. Biological rate parameters, fuzzy logic membership-function strain thresholds, and axial force

magnitudes were increased and decreased for each model in a one-parameter-at-a-time approach. The simulations of the models of groups C and F were found to have relatively lower overall sensitivities to the parameters tested, and the corresponding experimental groups had more consistent healing outcomes. The simulations of the model of group E were found to have a higher overall sensitivity and the corresponding experimental group had more variation in final healing outcomes. The results of this parametric study indicated that a post-hoc sensitivity analysis could be used to assess the degree of confidence in the model predictions.

The model of group E, which represented the ‘borderline’ healing outcome, was used to compare multiple rehabilitation-regimes in their effect on healing speed and outcome. The parameters used to change the stability of the fracture in order to simulate the rehabilitation-regime progressions were the free-movement distance of the fixator and the magnitude of applied axial load. Dynamisation and inverse-dynamisation were simulated, each with both a step change and linear change. Constant-stability regimes at high and low stabilities were also simulated. The study indicated that for large-gap fractures treated with fixed free-movement distance type fixators, a constant high stability rehabilitation-regime produces the shortest healing times.

The fracture-healing algorithm was expanded from an axisymmetric implementation to a 3-D implementation in order to model a mid-shaft osteotomy fracture of a realistic femur. Two fixation treatments were modelled: intramedullary nailing and lateral locking plate fixation. The fracture-healing algorithm was able to capture accurately the differences in callus development between the two fixator types; specifically, the effect of bending in the lateral locking plate on callus development asymmetry was predicted. This study was the first instance of a fracture-healing algorithm being applied to compare different fixator types, rather than different stiffnesses of the same fixator type.

8.3 Discussion

This thesis achieved its aim of developing a fracture-healing algorithm capable of predicting fracture non-union and borderline healing cases and capable of 3-D simulation, allowing for the comparison of different fracture-fixation devices and rehabilitation-regimes. The robustness of the algorithm to its parameters, and lack of tuning requirement when changing fracture scenarios, allows for more confidence in its predictions than in those of previous fracture-healing algorithms.

Overall healing outcomes, as determined by virtual bending stiffness assessment, in the simulations of the 6 experimental cases modelled were predicted accurately, however, the magnitudes of bending stiffness predicted by virtual mechanical testing were different than those measured in the experimental counterparts. This discrepancy in bending stiffness magnitude may be attributable to minor differences in testing method used; the virtual bending stiffness assessment was performed by applying a pure moment at the bone fragment ends, whereas the experimentally derived bending stiffnesses were determined using a 3-point bending test. Virtual 3-point bending tests were not performed to avoid computational difficulties in contact analysis of the 3-point bend pusher on callus soft tissues. The discrepancy in bending stiffnesses may also be attributable to small element-sized ‘gaps’ in the hard callus predicted by the fracture-healing algorithm which never ossified and remained as soft tissue. The incorporation of a bone remodelling fuzzy-logic rule to the fracture-healing algorithm, as has been incorporated by some previous algorithms, may address this limitation by ossifying these gaps and increasing the overall magnitudes of bending stiffness in the calluses. A bone remodelling rule could also allow for the modelling of primary fracture healing, and the healing of complex fracture cases where both primary and secondary fracture healing can occur.

A limitation of the methods used in this thesis is the assumption of linearly elastic and isotropic material properties. Previous fracture-healing algorithms have all used linearly elastic and isotropic material properties, however, biological tissues exhibit often nonlinear behaviours and have varying degrees of anisotropy. The tissues modelled in this thesis have all been shown experimentally to exhibit

nonlinearity, anisotropy, or both nonlinearity and anisotropy. This anisotropy may have a particular effect on the magnitudes of the minimum and maximum principal strains calculated, as the tissues may exhibit a high degree of anisotropy. The fracture-healing algorithm and FE models could be modified to model the anisotropic behaviour of the biological tissues. However, while this additional computational complexity may be able to capture more accurately the physiological strains occurring in the callus, the primary application of the healing algorithm is to be used as a predictive tool of fracture union rather than an exact representation of the underlying biological processes involved in fracture healing; therefore, simplifying assumptions are justified at this stage of algorithm development and intended use.

A limitation of the fracture-healing algorithm used is the lack of a temporal calibration. The time-series IFM progressions in the simulations were compared to the corresponding experimental data and 1 healing day was observed to correlate approximately to 3 iterations in the healing algorithm. However, this temporal calibration may be applicable only to the specific experimental model simulated or finite-element mesh size used. The relevance of this temporal calibration should be tested further by comparing the predictions of the healing algorithm on another fracture case with corresponding experimental data, while maintaining the same mesh-size coefficient and temporal smoothing parameter values. If the temporal calibration is found to not be applicable to other fracture models, then a partially generalised temporal calibration could still be performed for each fracture type. For example, if a temporal calibration is performed on a distal femoral fracture with a moderate gap width, this temporal calibration is likely applicable to models of similar fractures with similar mesh sizes. If no temporal calibration is possible, the fracture-healing algorithm can still be used for relative comparisons; while the algorithm may not be able to specify exactly how many days a given fracture will take to heal, it will be able to predict whether the fracture would heal faster with one type of fixation (such as an intramedullary nail fixation) or another (such as a lateral locking plate fixation).

Several simplifications were made in order to reduce the complexity of the models simulated: bone geometry was assumed perfectly axisymmetric in Chapters 4, 5, and 6; fracture geometry was idealised as a gap osteotomy in all cases; the effect of

muscle forces was neglected in all cases; and constant force application and fixator stability were used in Chapters 4, 5, and 7. These simplifications were necessary during the development of the fracture-healing algorithm in order to reduce computational expense, however, these simplifications can be addressed now that the algorithm has been developed and validated. Steps to address these simplifications are described in Section 8.4.

8.4 Future work

A large proportion of femoral fractures are classified as fragility fractures which are associated with low bone mineral density. The fracture-healing algorithm could be modified to simulate fracture healing in a patient with low bone mineral density. Screw-bone contact modelling will likely be affected, as the low bone mineral density will ‘loosen’ the contact between the screw and bone; this relationship will require *in vitro* validation. The algorithm could then be used to investigate whether an underlying biological condition causing the low bone-mineral density, such as osteoporosis or osteopenia, also affects fracture healing. If so, those effects could be incorporated into the healing algorithm; for example, by reducing the value of the biological rate parameters. The algorithm could then be used to investigate whether optimal surgical treatments and rehabilitation-regimes are different for patients with a normal bone mineral density versus patients with osteoporosis or osteopenia.

An FE model of a distal femoral fracture should be developed and compared against *in vitro* testing data, with surgical fixations of lateral locking plating or intramedullary nailing used. Difficulties in *in vitro* testing will lie in the restraint conditions of the femur, especially due to the proximity of the restraints to the fracture gap, the region of interest. The incorporation of muscle forces in the model of the femur could be of interest, as muscle forces have been shown to affect bone strains in intact models of the femur. An alternative approach for the incorporation of muscle forces is a free-boundary approach, in which the femur is restrained primarily by muscles, which are modelled as springs. Models which incorporate muscle forces will allow for the investigation of the effect of muscle forces on fracture healing, and

possibly generate novel treatment methods such as muscle stimulation to generate rehabilitative strains in bed-bound fracture patients. Models which incorporate muscle forces are difficult to validate experimentally, however. The fracture-healing algorithm could then be applied to the model of the distal femoral fracture, and an analysis similar to that performed in Chapter 7 could be performed to determine whether intramedullary nailing or lateral locking plate fixation leads to better healing outcomes in distal femoral fractures. The robustness of the fracture-healing algorithm means tuning of parameter threshold values will not be necessary when modelling more physiological scenarios such as the incorporation of muscle forces.

Further modelling simplifications which could be addressed with a model of increased complexity are bone geometry, fracture geometry, and loading conditions. Simulation of a patient-specific model could address these simplifications and serve as an opportunity for further validation of the algorithm in a patient-specific case. A previous study utilised CT data to develop a geometrically-accurate FE model of fracture and fixator, and used early post-operative inertial-measurement-unit (IMU) motion data along with musculoskeletal modelling to determine physiological loading conditions (Orth *et al.*, 2023). The patient-specific FE model was used to calculate callus strains and determine which callus regions would experience ossification based on strain thresholds for ossification identified by previous fracture-healing algorithms, but did not simulate any fracture-healing processes. A similar modelling approach could be used in conjunction with the fracture-healing algorithm presented in this thesis in order to simulate accurately patient-specific fracture healing. Specifically, musculoskeletal modelling could provide more physiological joint loads to use as boundary conditions for the FE model. The robustness of this novel fracture-healing algorithm should allow for the implementation of these more physiological loads without further algorithm development.

The algorithm presented in this thesis may be applicable not only to long bones in the lower-limb, but also to other bone types and locations. A previous fracture-healing algorithm was applied successfully to a metaphyseal fracture of the distal radius (Engelhardt *et al.*, 2021), but validation of the original algorithm (Simon *et al.*, 2011) was not adequately demonstrated, as discussed in Chapter 3. Applications of the present algorithm to other bone types should be prefaced by additional

validation testing of the algorithm to the bone type being investigated. For example, physiological loading conditions in other locations or types of bone may involve significant shear or torsional components.

8.5 Long-term vision

Large scale *in silico* trials have previously been used to demonstrate the efficacy and safety of novel medical devices, including orthopaedic implants such as TOKA fixation plates for high tibial osteotomy procedures. A similarly large-scale trial could be performed using the fracture-healing algorithm described in this thesis. Where the randomised control trial TrAFFix failed to conclude whether intramedullary nailing or lateral locking plate fixation leads to better healing outcomes in distal femoral fractures, an *in silico* trial of the same clinical question could be performed. The *in silico* trial will not be limited by injury scarcity and each of the fracture geometries can be used for both fixators, leading to perfect paired testing. Separate sub-trials could be performed for each of the AO classified types of distal femoral fracture, which would address concerns about providing a single treatment recommendation for all distal femoral fractures.

The fracture-healing algorithm presented in this thesis has been validated against experimental data, however, the threshold for credibility of *in silico* methods with direct clinical application is higher than has been met by the validation performed in this thesis. In order for the findings of an *in silico* trial using this fracture-healing algorithm to be considered credible, further *in vivo* validation is likely necessary. A prospective study should be conducted in which the progress of a patient with an instrumented fixation device is compared against the predictions of the fracture-healing algorithm using patient-specific input parameters, such as bone and fracture geometry. Device measurements, such as strain, can be compared against equivalent *in silico* measurements at multiple time points. Additionally, virtual mechanical testing of FE models developed from patient scan data can be compared against virtual mechanical testing of the algorithm-predicted callus. Successful validation following these steps would likely provide sufficient credibility for the

findings of an *in silico* trial utilising the fracture-healing algorithm to steer clinical decision making,

A significant challenge in implementing a large scale *in silico* trial is computational expense. This challenge is magnified in the application of fracture-healing algorithms as each simulation requires the solution of many iterations of a finite-element algorithm. The code of the biological controller presented in this thesis has been vectorised where possible, such as in the neighbouring element connectivity matrix calculation described in Chapter 4, and constitutes a negligible portion of the overall computational expense of the healing algorithm. The computational time of the healing algorithm is split approximately evenly between the FE model-data input and the FE model solution, both of which are controlled within the FE software. The 3-D simulations performed in Chapter 7 took approximately 7 days to run, in parallel, including post-processing (Intel Xeon W7-3465X 28 core CPU). While the FE model solution is an expected computational expense, the FE model data input is a less typical computational expense in *in silico* studies. The framework of the fracture-healing algorithm requires each callus finite-element to have a unique material property. Although commercial FE software is capable of processing large numbers of elements, large numbers of material properties are atypical and therefore considerably slow down the data-input stage. This input-output data flow restriction could possibly be addressed by utilising a Python-based FE solver such as FEniCS so that the material-property data can remain within the Python environment to remove the FE model-data input step. An alternative solution is to limit the total number of material properties used in the model to a pre-defined set of properties and assign each callus element to the material property which most closely matches its intended material properties.

8.6 Conclusion

This thesis proposed, developed, validated, and applied a novel fracture-healing algorithm which successfully predicted both fully healed and non-union outcomes. The algorithm was demonstrated to be independent of its initial callus domain and insensitive to its parameter inputs. The healing algorithm was used to

determine that for large gap-width fractures fixated with a free-movement distance type fixator, a constantly high stability rehabilitation-regime delivers the shortest healing times. The healing algorithm was applied to 3-D models of femoral fractures and predicted accurately the differences in callus development between models treated with different fixators, demonstrating the suitability of the algorithm for application to *in silico* trials of fracture healing.

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PUBLICATIONS AND CONFERENCE ABSTRACTS

Journal article

Morgan, G., Low, L., Ramasamy, A., Masouros, S. (2024) A novel strain-based bone-fracture healing algorithm is able to predict a range of healing outcomes. *Frontiers in Bioengineering and Biotechnology*.

Conference presentations

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Morgan, G., Fox, H., Low, L., Ramasamy, A., Masouros S. (2022) Prediction of fracture healing in long bones. *Summer Biomechanics Bioengineering Biotransport Conference*.

Morgan, G., Fox, H., Low, L., Ramasamy, A., Masouros S. (2021) Comparison of distortional strain definitions in a fracture healing algorithm. *Orthopaedic Research Society.*

Morgan, G., Fox, H., Low, L., Ramasamy, A., Masouros S. (2021) Finite element screw-bone interface modelling in locking plate fixated femoral fractures. *International Symposium on Computer Methods in Biomechanics and Biomedical Engineering.*

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Publication Title	Injury	Rightsholder	Elsevier Science & Technology Journals
Article Title	Epidemiology of adult fractures: A review.	Publication Type	Journal
Author / Editor	INSTITUTE OF ACCIDENT SURGERY.	Start Page	691
Date	01/01/1969	End Page	697
Language	English	Issue	8
Country	United Kingdom of Great Britain and Northern Ireland	Volume	37

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Title	A novel strain-based fracture-healing algorithm for in silico trials - application to femoral fracture treatment	Institution Name	Imperial College London
Instructor Name	Dr Spyros Masouros	Expected Presentation Date	2024-09-23

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Title, Description or Numeric Reference of the Portion(s)	Figure 1	Title of the Article / Chapter the Portion Is From	Epidemiology of adult fractures: A review.
Editor of Portion(s)	Court-Brown, Charles M.; Caesar, Ben	Author of Portion(s)	Court-Brown, Charles M.; Caesar, Ben
Volume / Edition	37	Issue, if Republishing an Article From a Serial	8
Page or Page Range of Portion	691-697	Publication Date of Portion	2006-08-01

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ISBN-13	9789811975394		Chart/graph/table/figure

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Publication Title	Handbook of Orthopaedic Trauma Implantology	Rightsholder	Springer Nature BV
Article Title	Importance of Orthopaedic Screws, Chapter 31, Other Implants Used in Orthopaedic Implantology	Publication Type	Book
		Start Page	545
		End Page	556
Date	04/06/2024		
Language	English		
Country	Singapore		

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NEW WORK DETAILS

Title	A novel strain-based fracture-healing algorithm for in silico trials - application to femoral fracture treatment	Institution Name	Imperial College London
		Expected Presentation Date	2024-09-23
Instructor Name	Dr Spyros Masouros		

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Title, Description or Numeric Reference of the Portion(s)	Figures 3 and 4	Title of the Article / Chapter the Portion Is From	Importance of Orthopaedic Screws, Chapter 31, Other Implants Used in Orthopaedic Implantology
Editor of Portion(s)	Iyer, Rajagopalan; Samundeeswari, S.	Author of Portion(s)	Iyer, Rajagopalan; Samundeeswari, S.
Volume / Edition	1st ed. 2024	Publication Date of Portion	2023-11-01
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ISSN	0958-2592		Chart/graph/table/figure

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Publication Title	The Foot	Rightsholder	Elsevier Science & Technology Journals
Article Title	Mechanical and anatomical axis of the lower limb in total ankle arthroplasty.	Publication Type	Journal
Date	01/01/1991	Start Page	101666
Language	English	Volume	44
Country	United Kingdom of Great Britain and Northern Ireland		

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NEW WORK DETAILS

Title	A novel strain-based fracture-healing algorithm for in silico trials - application to femoral fracture treatment	Institution Name	Imperial College London
Instructor Name	Dr Spyros Masourous	Expected Presentation Date	2024-09-23

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Title, Description or Numeric Reference of the Portion(s)	Figure 1A	Title of the Article / Chapter the Portion Is From	Mechanical and anatomical axis of the lower limb in total ankle arthroplasty.
Editor of Portion(s)	Najefi, Ali-Asgar; Malhotra, Karan; Goldberg, Andy	Author of Portion(s)	Najefi, Ali-Asgar; Malhotra, Karan; Goldberg, Andy
Volume / Edition	44	Issue, if Republishing an Article From a Serial	N/A
Page or Page Range of Portion	101666	Publication Date of Portion	2020-09-01

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ISBN-13	9789811975400	Portion	Chart/graph/table/figure

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Date	04/06/2024	Rightsholder	Springer Nature BV
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NEW WORK DETAILS

Title	A novel strain-based fracture-healing algorithm for in silico trials - application to femoral fracture treatment	Institution Name	Imperial College London
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Volume / Edition	1st ed. 2023	Author of Portion(s)	Jain, A., Samundeeswari, S., Shanmugasundaram, S., Kumar, D.
Page or Page Range of Portion	pp.1011-1038	Publication Date of Portion	2024-04-06

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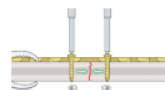
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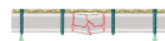
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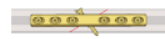
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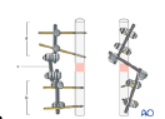
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ISSN	0021-9290		Chart/graph/table/figure

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Publication Title	Journal of biomechanics	Rightsholder	Elsevier Science & Technology Journals
Article Title	Magnitudes of local stress and strain along bony surfaces predict the course and type of fracture healing.	Publication Type	Journal
		Start Page	255
		End Page	266
Author / Editor	UNIVERSITY OF MICHIGAN, AMERICAN SOCIETY OF BIOMECHANICS, EUROPEAN SOCIETY OF BIOMECHANICS.	Issue	3
		Volume	32
Date	01/01/1968		
Language	English		
Country	United Kingdom of Great Britain and Northern Ireland		

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Title	A novel strain-based fracture-healing algorithm for in silico trials - application to femoral fracture treatment	Institution Name	Imperial College London
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Editor of Portion(s)	Claes, L.E.; Heigele, C.A.	Author of Portion(s)	Claes, L.E.; Heigele, C.A.
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Title, Description or Numeric Reference of the Portion(s)	Figure 2	Title of the Article / Chapter the Portion Is From	Biomechanical model to simulate tissue differentiation and bone regeneration; application to fracture healing
Editor of Portion(s)	D., Lacroix; Prof., P., J., Prendergast; G., Li; D., Marsh	Author of Portion(s)	D., Lacroix; Prof., P., J., Prendergast; G., Li; D., Marsh
Volume / Edition	40		
Page or Page Range of Portion	14-21	Publication Date of Portion	2002-01-01

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Publication Title	Medical & biological engineering & computing	Rightsholder	Springer Nature BV
Article Title	Biomechanical model to simulate tissue differentiation and bone regeneration; application to fracture healing	Publication Type	Journal
		Start Page	14
		End Page	21
		Issue	1
		Volume	40
Author / Editor	INTERNATIONAL FEDERATION FOR MEDICAL AND BIOLOGICAL		
Date	01/01/1977		
Language	English, French, German, German		
Country	Germany		

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NEW WORK DETAILS

Title	A novel strain-based fracture-healing algorithm for in silico trials - application to femoral fracture treatment	Institution Name	Imperial College London
		Expected Presentation Date	2024-09-23
Instructor Name	Dr Spyros Masouros		

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Publication Title	Injury	Rightsholder	Elsevier Science & Technology Journals
Article Title	Morphology of bony callus growth in healing of a sheep tibial osteotomy	Publication Type	Journal
Author / Editor	INSTITUTE OF ACCIDENT SURGERY.	Start Page	66
Date	01/01/1969	End Page	70
Language	English	Issue	1
Country	United Kingdom of Great Britain and Northern Ireland	Volume	52

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Instructor Name	Dr Spyros Masouros	Expected Presentation Date	2024-09-23

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Editor of Portion(s)	Wilson, Cameron J.; Epari, Devakara R.; Ernst, Manuela; Arens, Daniel; Zelter, Stephan; Windolf, Markus	Author of Portion(s)	Wilson, Cameron J.; Epari, Devakara R.; Ernst, Manuela; Arens, Daniel; Zelter, Stephan; Windolf, Markus
Volume / Edition	52	Issue, If Republishing an Article From a Serial	1
Page or Page Range of Portion	66-70	Publication Date of Portion	2021-01-01

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A numerical model of the fracture healing process that describes tissue development and revascularisation

Author: U. Simon, M. Utz, P. Augat, et al

Publication: Computer Methods in Biomechanics & Biomedical Engineering

Publisher: Taylor & Francis

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