

**A combined computational and clinical
approach to investigating bone health in
lower-limb amputees**

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Abstract

A disproportionate number of lower-limb amputees are diagnosed with osteopenia and osteoporosis of the hip each year. The issue affects amputees of all ages, increasing their lifetime risk of hip fracture dramatically. Hip fracture compromises short and long-term prosthetic use and therefore has serious implications on mobility, physical dependency and morbidity. Through both clinical evaluation and computational modelling, this research aimed to determine the effect of lower-limb amputation on long-term bone remodelling in the hip and to understand the potential underpinning mechanisms for bone degradation in the younger amputee population.

The issue was investigated clinically with the aim of determining whether bone loss in amputees is systemic through the whole body or localised to the amputated limb. This was done by comparing bone-mineral density (BMD) in both hips and the lumbar spine of a young military population of 86 amputees and 82 control subjects. BMD in the femoral neck of amputee subjects was found to be significantly lower than in controls while BMD at the spine in each population was similar. In unilateral amputees, there was an additional degree of localisation between amputated and intact limbs where bone loss in the amputated limb was not reflected in the intact limb.

Patient specific musculoskeletal (MSK) and finite element (FE) models were developed for one unilateral, below-knee amputee, one bilateral, above-knee/through-knee amputee and one body-matched control subject. MSK modelling enabled comparison of muscle and joint reaction-forces throughout daily loading activities and provided the loading scenario implemented in FE. A strain driven bone adaptation algorithm applied in FE demonstrated the effect of loading on the femur structure of each subject.

Load placed on the femur and hip joint is lower in both amputee subjects than in the able-bodied control. In the unilateral below-knee amputee this is predominantly driven by functional compensation of the contralateral limb. In the bilateral, above-knee amputee the prosthetic appears to shield the amputated femur from the direct forces generated during weight-bearing. As a result of both, large areas of the bone no longer receive the stimulation they would have pre-amputation.

Overall, both clinical and computational findings suggest that changes in bone health could be predominantly mechanically driven where altered joint and muscle loading

causes altered mechanical stimulus in the femur; or *unloading osteopenia*. Then, over many cycles of remodelling, a net bone loss occurs. Importantly, this suggests the issue could be preventable, or even reversible, with the implementation of targeted loading regimes or changes to the design of the prosthetic socket. Moreover, there could be a benefit to distinguishing between bone loss in the young amputee population and systemic osteoporosis secondary to aging and endocrine changes.

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Chapter 1

Introduction

This chapter introduces the thesis. Context is given to the research highlighting: the state of lower-limb amputation worldwide; the implications of amputation on health and quality of life; and finally introducing the problem of reduced bone health in amputees. The reader is presented with the aims and objectives of the research at large; and how a clinical and computational engineering approach can be taken to further understanding bone loss in amputees. A summary of the chapters presents a breakdown of the work done in more detail.

1.1 Context of the research

Medical advances in the last two decades have seen unprecedented improvement in the survival rate following severe military injury and resulting traumatic amputation. As more amputees survive and re-assimilate into society we have learned more about the secondary mid-to-long term issues affecting the amputee population. One of these issues is a trend of reduced bone-mineral-density, particularly prevalent in the amputated femur and hip, which sees an increase in femoral fracture risk. Fragility fracture has serious implications on mobility, physical dependency and morbidity. In the amputee population, there is a disproportionate effect on functionality as it can compromise short and long-term prosthetic use. The prevalence of low bone-mineral density in traumatic military amputees is particularly alarming given the younger age of the population. Many young amputees are diagnosed with “osteoporosis” 10-15 years earlier than may be anticipated as a result of aging. Although research has highlighted the existence of the problem, the aetiology of this bone loss is poorly understood and often flippantly associated with bone deterioration in ageing and less active populations. As a result, similar treatment pathways and rehabilitation strategies are employed without full consideration of their suitability to a younger population with significantly longer to live. Before we can begin to safely prevent or reverse the onset of this issue we must first understand the potential underpinning mechanisms.

According to the World Health Organisation, there are an estimated 40 million amputees worldwide (Marino *et al.*, 2015). Increased life expectancy due to medical advances coupled with a higher incidence of diabetes and vascular disease means that this number is likely to grow in the civilian population (Paternò *et al.*, 2018). Ongoing conflicts in the Middle East and Africa will also contribute with increased traumatic amputations to military members and civilians living in conflict zones (Bertani *et al.*, 2015; Edwards *et al.*, 2015). Recent wars in Afghanistan and Iraq have been specifically associated with increased survival rates following highly complex military-related trauma (Edwards *et al.*, 2015). Improved personal protection equipment, advances in point-of-care treatment and rapid extraction of casualties contributed to a battlefield injury survival rate of over 90% (Edwards *et al.*, 2015; Singleton *et al.*, 2014). In turn, this has seen a rise in the number of military survivors with single and double lower-limb amputation. Moreover, extremity injuries are reported in over 45% of children within conflict zones. Increased incidence

of traumatic amputation can also be heavily attributed to use of improvised explosive devices (IEDs) and landmines (Bertani *et al.*, 2015; Henson *et al.*, 2020).

Lower-limb amputation has significant implications on mobility, morbidity and quality of life in every case and a wide array of medical issues associated with amputation has been well-documented. Short term issues include: a variety of skin disorders such as chronic ulceration, pressure sores and contact dermatitis (American Academy of Orthopedic Surgeons, 1992; Salawu *et al.*, 2006; Highsmith *et al.*, 2010; Robbins *et al.*, 2009); phantom limb pain and phantom limb syndrome (Jensen *et al.*, 1985; Ehde *et al.*, 2000; Esfandiari *et al.*, 2018; Robbins *et al.*, 2009); and a greatly increased risk of infection (Richards *et al.*, 2005; Berridge *et al.*, 1989). Secondary conditions such as lower-back pain, osteoarthritis, cardiovascular disease (secondary to general deconditioning) and finally bone loss (Butowicz *et al.*, 2017; Gailey *et al.*, 2008) are becoming more and more important to consider as lower-limb amputation is being seen in a younger population. All of these secondary conditions are directly related to changes in physical activity, physiological adaptations and movement compensations following amputation (Butowicz *et al.*, 2017). As such they manifest more prominently in the long term and present a significantly more important challenge in younger traumatic amputation (more often resulting from military conflict) than in civilian populations where the majority of amputations occur over the age of 50 (Butowicz *et al.*, 2017). Quite simply, younger amputees have more time for these issues to manifest and lead a more active lifestyle pre-amputation. Amputation is also very closely correlated with impaired mental health, particularly in victims of trauma (Talbot *et al.*, 2017; Sahu *et al.*, 2016; Durmus *et al.*, 2015; Holzer *et al.*, 2014). Overall, lower-limb amputation has been shown to have a significant negative impact on quality of life when assessed by a range of different metrics.

Lower-limb amputation also comes with a huge long-term economic burden. Edwards (2015) predicts the 40 year cost of repair, rehabilitation and prosthetic support for British soldiers wounded in Afghanistan to be as high as £288 million. Broken down this represents a cost of £0.87 million per unilateral transtibial amputee and £1.16 million per unilateral through-knee or transfemoral amputee. Those with double amputation incurred an additional cost of up to £0.45 million depending on amputation level in the other limb. Butowicz (2017) correctly suggests that most figures predicted in the literature are highly conservative, particularly as they do not account for the healthcare costs associated with the secondary conditions highlighted above. For example, the treatment cost of fragility

fracture as a result of reduced bone-mineral density is huge. In the UK alone, over 500,000 people present with fragility fractures each year, carrying an estimated cost to the NHS of £4.4 billion per annum (Vernon *et al.*, 2018).

Focusing specifically on the issue of bone loss, multiple studies have highlighted its prevalence in the amputee population (Flint *et al.*, 2014; Kulkarni *et al.*, 1998; Sherk *et al.*, 2008; Ramírez *et al.*, 2011; Leclercq *et al.*, 2003; Burke *et al.*, 1978; Rush *et al.*, 1994; Hungerford & Cockin, 1974; Shinchuk *et al.*, 2006; Bemben *et al.*, 2017; Smith *et al.*, 2011) (a more detailed account of these studies is provided in the background of Chapter 2). All highlight significant bone loss in the amputated limb, and perhaps more importantly, many identify the onset of bone loss at a younger age than is typically seen in the able-bodied population (Flint *et al.*, 2014; Sherk *et al.*, 2008; Ramírez *et al.*, 2011). The negative effect of such dramatic bone loss on lifetime risk of fragility fracture is disproportionately large in the amputee population as a result. Moreover, a study by Steinberg (2019) determined that lower-limb amputees are at increased risk of falling compared with able-bodied individuals due to impaired functional mobility. This further increases risk of fracture. Multiple case studies have highlighted additional procedural complications in hip fracture fixation (Rethnam *et al.*, 2008) and total hip arthroplasty (Masmoudi *et al.*, 2016; Lancer *et al.*, 2016) of amputee subjects. Rehabilitation following such procedures is exceedingly difficult in able-bodied individuals and even more challenging in amputees. Ultimately, the risk of young and previously active amputees being left wheelchair bound following hip fracture is far too high.

More research is needed to understand the causes and mechanisms behind bone loss following amputation. Then, educated steps can be taken to prevent or reverse the issue. There is some existing evidence to suggest that it could be localised, unlike bone loss resulting from age-related or postmenopausal osteoporosis, but this evidence is limited and inconclusive. More importantly, the implications of localised bone loss on rehabilitation outlook, treatment strategies and future solutions have not been considered. Diagnosing and treating it in the same way as bone loss in other populations could be detrimental in the long-term.

Currently the most commonly employed medical interventions for treatment of low bone mineral density and osteoporosis are: bisphosphonates, RANKL inhibitors (denosumab), hormone replacement and, more recently, anabolic therapies such as injection of parathyroid hormone. The efficacy of each has been proven, reducing fracture

risk in patients suffering with low bone-mineral density, age-related and postmenopausal osteoporosis. All have been shown to come with considerable side effects including: reduced renal function, gastro-intestinal problems, osteonecrosis, atypical femur fracture and hypocalcemia (Cosman *et al.*, 2014). Long-term safety in younger patients is also yet to be determined (Cosman *et al.*, 2014; Drake *et al.*, 2008; Hanley *et al.*, 2012; Golds *et al.*, 2017; Eviö *et al.*, 2004) and the impact of these treatments (particularly anti-resorptive therapies) on bone quality remains an important concern.

Bisphosphonates and denosumab can both be considered anti-resorptive drugs; they each suppress osteoclast activity in two different ways (Drake *et al.*, 2008; Hanley *et al.*, 2012). Bisphosphonates bind to bone mineral, are absorbed by osteoclasts and induce osteoclast apoptosis (Hanley *et al.*, 2012). Denosumab binds to the cytokine receptor activator of NF κ B ligand (RANKL) which inhibits the maturation, function and survival of osteoclasts (Hanley *et al.*, 2012). Both drugs additionally reduce the activation frequency of new remodeling units formed by osteoclasts and, as such, serve to reduce the rate of bone remodelling as a whole. This makes them particularly suitable in postmenopausal osteoporosis where osteoclast activity begins to outweigh osteoblast activity and remodelling rate can triple after the onset of menopause (Recker *et al.*, 2004). Left unchanged, increased remodelling coupled with an imbalance favouring bone resorption causes dramatic reductions in bone volume.

Hormone replacement therapy is a treatment used to relieve the symptoms of menopause. In terms of bone loss, it works in a fairly similar way to bisphosphonates and denosumab: decreasing the activity of osteoclasts and increasing their apoptosis (Eviö *et al.*, 2004; Recker *et al.*, 2004). Bone loss in aging men is characterised by decreased osteoblast activity (Compston, 2011) rather than increased osteoclast activity and increased rate of remodelling as in post-menopausal women. Increase in remodelling rate is not considered to play a major role (Compston, 2011). Therefore, although anti-resorptive drugs would slow/prevent loss of bone in this population too, such therapies would not be addressing the root cellular cause of the resorption-formation imbalance. In men, hormone replacement can be used to treat bone loss stemming from reduced testosterone (most often in those suffering with a condition such as hypogonadism). However, the potential risks associated with the treatment are well-documented (Golds *et al.*, 2017). Anabolic therapies, such as daily injection of parathyroid hormone, have been considered as one means of modulating (and increasing) bone formation, rather than

bone resorption. This provides potential in promoting bone regeneration as the injection stimulates osteoblast activity more than osteoclast (Russow *et al.*, 2019).

Considering the wide variety of treatment strategies available and the specific mechanisms of each one, it is important to determine the aetiology of bone loss in the lower-limb amputee population to ensure current treatments do not prove damaging in the long-term. Moreover, it could present the opportunity for alternative treatment strategies, perhaps less pharmaceutically focused ones without the risk of adverse side effects.

1.2 Thesis aims and objectives

This research investigates the established trend of reduced bone health in traumatic lower-limb amputees through the use of clinical data studies and development of multiple patient-specific computational models. More specifically, aims can be broken down as follows:

1. To determine whether bone loss manifests itself differently in lower-limb amputees to in the able-bodied population.
2. To determine how the loading environment within the joints of an amputee change post-amputation.
3. To determine to what extent bone loss could be driven by disuse or altered mechanical loading.

These aims will be met by:

1. Analysing bone mineral density at multiple diagnostic sites in a population of military amputees and age-matched controls.
2. Case study development of a patient-specific musculoskeletal model of a unilateral below-knee amputee subject used to analyse joint and muscle forces experienced during daily living.
3. Case study development of a patient-specific musculoskeletal model of a bilateral above-knee/through-knee amputee subject used to analyse joint and muscle forces experienced during daily living.
4. Development of a finite element model for each amputee to understand the effect of daily loading in terms of stress and strain at the hip joint of the below-knee and above-knee amputated limbs.

1.3 Summary of chapters

The thesis is divided into six chapters including the introduction. Each chapter begins with its own background section, including a review of relevant literature and builds upon findings in previous chapters. As the thesis involves both a clinical and computational approach, this is considered the clearest way to marry engineering, modelling and clinical background information throughout the thesis.

Chapter 2 presents a clinical study carried out using a subset of data from the ongoing ADVANCE study. The study compares the independent state of bone-mineral density at both hips and the lumbar spine of eighty-two traumatic military amputees and eighty-six healthy age-matched military controls. It tests the hypothesis that bone loss in the lower-limb amputee population is localised to the amputated limb and could be heavily driven by altered mechanical loading post-amputation.

Chapter 3 presents a predictive modelling framework for structural modelling of the femur. The framework interfaces experimental motion data, musculoskeletal and iterative finite element modelling using a strain-driven bone adaptation algorithm developed by Phillips (2015). The chapter introduces modelling concepts and components individually while applying the framework to create a healthy structural femur model which is used in future chapters to investigate hip loading post-amputation. The able-bodied subject is weight and height matched to both the unilateral below-knee and bilateral above-knee amputee subjects modelled in Chapters 4 and 5, respectively. Therefore, results presented in this chapter also provide the baseline for musculoskeletal and finite element modelling of amputation in future chapters.

In Chapter 4, the same modelling framework is applied to a unilateral below-knee amputee subject. First, the motion capture data acquisition process is presented followed by details on the development of a patient-specific amputee musculoskeletal model. Results from simulation with this musculoskeletal model provide the complete physiological loading scenario applied to a finite element model of the femur of the amputated limb. The chapter evaluates the effect of physiological loading on bone structure within the femur and how it differs compared to an able-bodied baseline. Minor alterations to Phillips' (2015) bone adaptation algorithm allow for simulation of bone deterioration within the first 5 years post-amputation.

Chapter 5 applies the framework to a bilateral above-knee/through-knee amputee subject. This requires the development of another patient-specific musculoskeletal model and additional adaptations to the computational modelling framework which are detailed throughout the chapter. Most importantly, it requires the inclusion of the prosthetic socket at the level of finite element analysis to determine what effect socket suspension and ischial weight-bearing could have on the loading of the femur in the above-knee amputated limb.

Throughout both Chapter 4 and 5, comparisons are made between results of musculoskeletal simulations and finite element simulations to identify key changes in amputee movement, loading and femur stimulation from control. Ultimately, predictive finite element modelling in each chapter lets us predict the effect of altered loading on bone remodelling and bone structure at the hip of each subject.

Finally, Chapter 6 concludes the thesis by comparing between results in each amputee subject and ties them to clinical findings in Chapter 2. It reflects on the work carried out, the accomplishments and future work that could and should follow this research.

Chapter 2

Clinical localisation study

2.1 Introduction

Chapter 2 outlines a clinical study into the localisation of bone loss in the lower-limb amputee population; completed using a subset of data from the Armed Services Trauma Rehabilitation Outcome Study (ADVANCE) ¹. Bone-mineral density in both hips and the lumbar spine of a young military population of 86 amputees and 82 age-matched control subjects were compared.

Results suggest that bone loss in the lower-limb amputee population is largely localised to the hip of the amputated limb and predominantly driven by a change in the mechanical loading environment post-amputation. Importantly, this would characterise a key difference between bone loss in amputees and systemic bone loss associated with age-related and post-menopausal osteoporosis. This suggests that there could be widespread benefit to distinguishing between the two in terms of diagnosis, rehabilitation pathway and patient outlook.

¹Armed Services Trauma Rehabilitation Outcome Study, www.advancestudydmrc.org.uk

2.2 Background

2.2.1 Bone function and remodelling

Bone is a metabolically active organ that undergoes continuous adaptation to meet the mechanical needs of the surrounding environment (Hadjidakis & Androulakis, 2006). Constant remodelling and renewal allows for substitution of primary bone, removal of microfractures and the establishment of calcium homeostasis (Rucci, 2008). This process relies on a balance between bone formation and bone resorption regulated and carried out by specialised cells: osteocytes, osteoblasts and osteoclasts (Caetano-Lopes *et al.*, 2007). Osteoclasts digest old or damaged bone leaving space for the osteoblasts to lay new bone until the resorbed bone is completely replaced (Hadjidakis & Androulakis, 2006). This occurs in four phases of remodelling: activation, resorption, reversal and formation (Rucci, 2008) as seen in Figure 2.1.

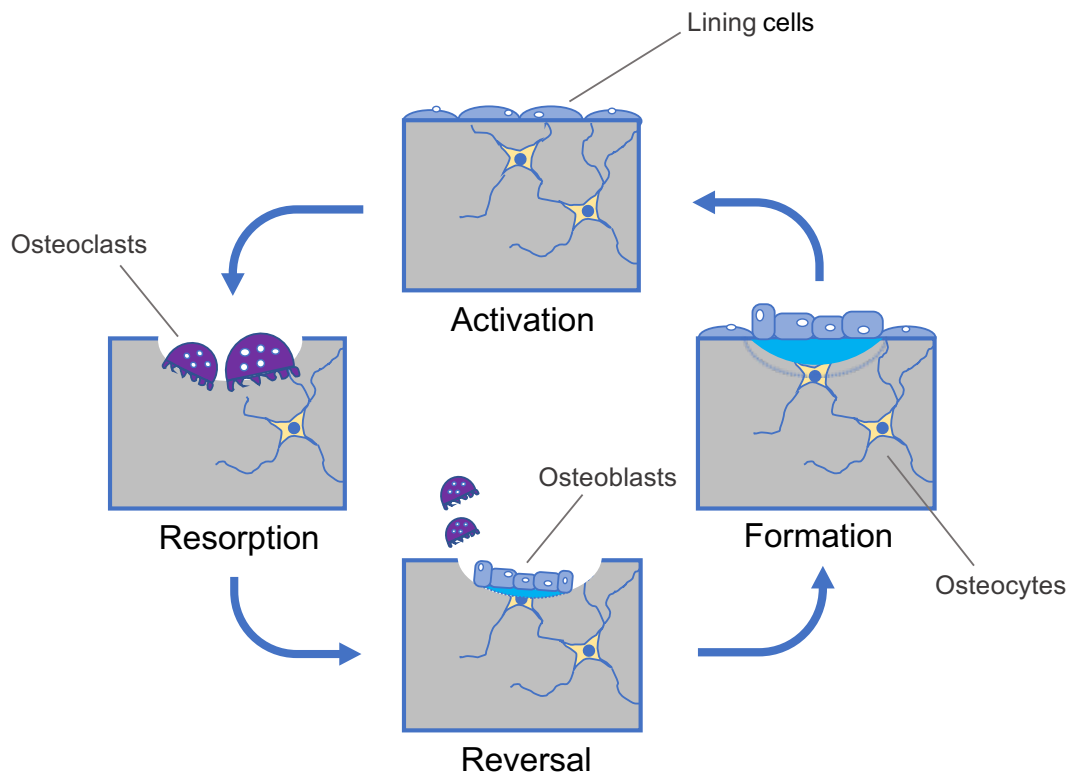


Figure 2.1: Schematic demonstrating four phases of bone remodelling: activation, resorption, reversal and formation. Adapted from a review series on bone remodelling by Peter Hill (Hill, 1998).

1. Activation: different inputs such as micro-fracture, a change in mechanical loading or chemical factors released within the bone activate bone lining cells and trigger pre-osteoclast differentiation into multinucleated osteoclasts.
2. Resorption: differentiated osteoclasts adhere to the surface of the bone and begin to dissolve it creating cavities or tunnels called resorption pits. Calcium is released into the bloodstream for use around the body. Once a pit is created, osteoclasts undergo apoptosis (cell death).
3. Reversal: reverse cells remove debris produced during the degradation of the matrix throughout the resorption phase. Mesenchymal stem cells proliferate and differentiate into pre-osteoblasts.
4. Formation: growth factors released during the resorption phase recruit osteoblasts to the resorption pit where they produce and mineralize new bone matrix.

The delicate balance of osteoblastic and osteoclastic activity is regulated by osteocytes which responds to both internal factors, such as age, and external factors, such as the imposed loading environment.

2.2.2 Systemic osteoporosis and the aetiology of bone loss in the aging population

Osteoporosis is defined as a “progressive systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture” (No authors listed, 1993). In the general aging population, it stems from a “systemic” imbalance of the remodelling process where osteoclast activity is higher than osteoblast activity. This results in more bone being resorbed than formed and bone-mineral density (BMD) drops over time (Tanaka *et al.*, 2005)(Figure 2.2).

Osteoporosis is diagnosed using criteria defined by the World Health Organisation (WHO) based on the T-score or Z-score (Kanis *et al.*, 2007) from measurement by dual-energy x-ray absorptiometry (DXA). The T-score is a measure of the difference in BMD from the average healthy white 30 year old, whereas the Z-score compares BMD to an age

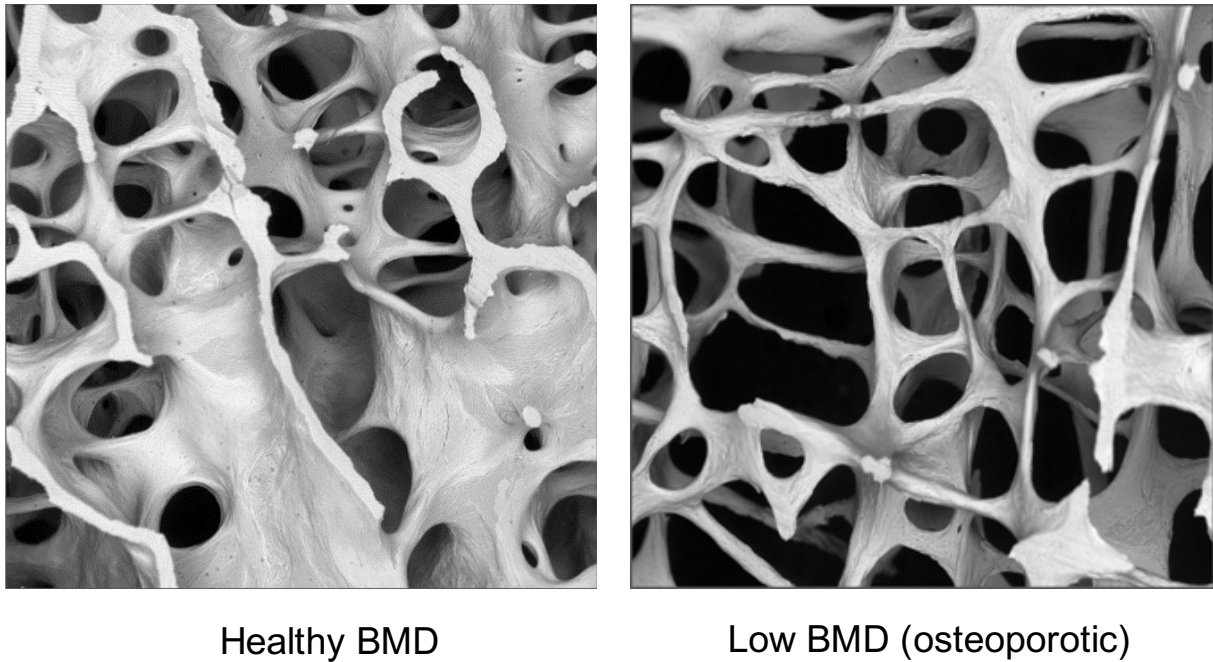


Figure 2.2: Comparison of normal and osteoporotic bone. Bone structure is highly degraded in osteoporotic bone making it more fragile and susceptible to fracture. Taken from the Bone Research Society’s Teaching Resources and included with the permission of Prof. Alan Boyde.

and gender matched population. Both metrics report BMD levels as standard deviation (SD) compared to the general population.

- Normal BMD = T-score/Z-score of -1 SD or above
- Osteopenia = T-score/Z-score of between -1 and -2.5 SD
- Osteoporosis = T-score/Z-score of -2.5 SD or below (Kanis *et al.*, 2007)

The International Osteoporosis Foundation ² highlights that osteoporosis is, typically, a later-life bone degenerative disease of which the prevalence increases substantially with age. The IOF estimates that around 7% of men and 22% of women over the age of 50 have osteoporosis. These figures increase to 25% of men and 45% of women over the age of 80 (Kanis *et al.*, 2007).

Women are at greater risk of osteoporosis beyond menopause, mainly due to a decrease in oestrogen production by the ovaries which can accelerate bone loss (Ji & Yu, 2015). Oestrogen lowers the body’s sensitivity to parathyroid hormone (the hormone responsible for breaking down bone and causing calcium release), increases calcitonin production

²International Osteoporosis Foundation, Facts and Statistics, <https://www.iofbonehealth.org/facts-statistics>

(the hormone responsible for regulating blood calcium and phosphate levels), accelerates calcium resorption by the intestine and reduces calcium excretion from the kidney. All of these serve to inhibit osteoclast activity and maintain calcium levels within the bone. Therefore, during menopause, when oestrogen is deficient, a weakened inhibition effect within the body causes a net loss of bone (mainly trabecular bone) characterised by increased resorptive activity (Ji & Yu, 2015).

The second phase of bone loss in the aging population affects both men and women. Unlike menopausal bone loss, it is characterised by a reduction of bone formation (or reduced osteoblast activity) mainly due to a shift in the bone marrow stem cells from osteoblastogenesis to adipogenesis (Demontiero *et al.*, 2011). This stage exhibits much slower, steadier bone loss from both trabecular and cortical bone (Ji & Yu, 2015).

It is, particularly, important to stress that both of these bone loss pathways are systemic, affecting the whole skeleton, although at different rates depending on which areas are most metabolically active (Firestein *et al.*, 2017; Metzger *et al.*, 2020). The higher active surface area in trabecular bone means that it is more metabolically active than cortical. As such, bone changes take place fastest in areas like the lumbar spine and proximal femur, two of the sites richest in trabecular bone (the spine typically even higher in trabecular density than the femur) (Nordin, 1979, republished in 2012). For this reason, DXA scans have always been carried out at these two sites. Bone deterioration will occur rapidly and dramatically in these two areas, although, in the aging population systemic changes to the endocrine system will affect the whole body.

2.2.3 General trends of decreased BMD in amputees

BMD loss in the hip and femur is considered a secondary complication of lower-limb amputation. Reduced BMD carries an increased fracture risk, with fractures occurring as a result of minimal trauma (Sozen *et al.*, 2016). The effect of a fracture can have serious implications on mobility, physical dependency and morbidity (Kerr *et al.*, 2017). For amputees this has a disproportionate effect on functionality compromising short and long-term prosthetic use.

Burke (1978) carried out one of the earliest reported studies on bone changes in lower-limb amputees where they began associating bone loss to osteoporosis. They

noted “osteoporosis” in the amputated limb of 37 out of 42 lower-limb amputees studied. Subsequently, a variety of cohort-studies have confirmed this trend of reduced BMD in both above-knee and below-knee amputees. Reports have comprised of both retrospective and prospective studies with population sizes varying from 7 to 200 amputees, including both below and above-knee. The majority measure BMD by DXA scan or peripheral quantitative computed tomography (pQCT) (Flint *et al.*, 2014; Leclercq *et al.*, 2003; Kulkarni *et al.*, 1998; Sherk *et al.*, 2008). In most, a T-score or Z-score is calculated at the amputated limb to diagnose subjects with osteopenia or osteoporosis. It has been reported that:

1. BMD is significantly lower in the amputated limb than in the average, non-amputated, limb of the healthy population (Kulkarni *et al.*, 1998; Sherk *et al.*, 2008).
2. BMD is lower in above-knee amputees than below and through-knee amputees (Flint *et al.*, 2014; Kulkarni *et al.*, 1998).
3. In unilateral amputees, BMD is lower on amputated than non-amputated sides although BMD in the non-amputated side is often lower than in the average healthy limb (Kulkarni *et al.*, 1998; Sherk *et al.*, 2008; Ramírez *et al.*, 2011).
4. The areas of lowest BMD occur at the femoral neck and the greater trochanter (Flint *et al.*, 2014; Kulkarni *et al.*, 1998; Sherk *et al.*, 2008; Ramírez *et al.*, 2011; Leclercq *et al.*, 2003).
5. By use of T-score or Z-score, high proportions (>50%) of amputees have been diagnosed with osteopenia and osteoporosis (Burke *et al.*, 1978; Rush *et al.*, 1994; Hungerford & Cockin, 1974; Shinchuk *et al.*, 2006).

2.2.4 How does this differ from systemic osteoporosis?

Comparatively, low BMD manifests itself quite differently in the young amputee population compared to the general population diagnosed with osteoporosis. The key differences are the age of onset and the localisation of bone loss. As previously discussed, studies investigating non-amputee populations have shown that bone loss begins in both men and women at around age 40, 10 years after peak bone mass has been attained

between the ages of 25-30 years old (Sambrook & Hunter, 2000). The loss of bone density beyond this point is a natural process with increasing age due to resorption exceeding formation. Significant bone loss has been recorded in a high proportion of amputees below the age of 40. This warrants further investigation due to the potential complications of long-term treatment of osteoporosis and the associated fracture risk. In 1974, Hungerford (1974) first reported characteristic findings of osteoporosis and osteopenia in the amputated femur of 90% of above-knee amputees. Since then, in more recent studies, this figure has dropped although the proportion remains significant (Burke *et al.*, 1978; Flint *et al.*, 2014; Shinchuk *et al.*, 2006). A study by Flint (2014) reported that out of 156 amputees tested, both unilateral and bilateral, the observed rate of low-BMD ($Z\text{-score} < -1.0$) was 68% in above-knee amputees and 37% in below-knee or through knee amputees. More importantly, the median subject age for the study was just 24 years old and 98% of participants were male. The majority of existing literature supports the same trend: low BMD affects a disproportionate percentage of the amputee population regardless of age.

Low-BMD in lower-limb amputees is also found to be more commonly localised to one particular area (the amputated limb) whereas in the general population the problem is systemic. One measure of this is T-score (or Z-score) discordance, which is far more common in the amputated than in the able-bodied (AB) population. Minor discordance is considered present when scores at two different measurement sites (such as the femoral neck and spine) are separated by one diagnostic class (ie. demonstrating normal BMD in one location and BMD consistent with a diagnosis of osteopenia in another). Major discordance is present when one site is osteoporotic and the other considered normal (Moayyeri *et al.*, 2007), therefore scores are separated by two diagnostic classes. A study by Moayyeri (2007) found diagnosis concordance (between T-score at the spine and the pelvis) in 2442 of 4188 (58%) non-amputee men and women scanned. It found major T-score discordance in only 2.8% of those studied and minor T-score discordance in a further 39%. By comparison, in a population of 16 unilateral amputees, Rush (1994) found normal BMD levels in the spine and contralateral limb but significantly lower bone loss in the amputated femur of all subjects. Femoral BMD was, on average, 28% lower in amputated than non-amputated sides which suggests major discordance between the two regions was common. Bemben (2017) and Smith (2011) found similar results.

Diagnosis discordance in amputees and the general population seem to occur inversely. Moayyeri (2007) found that of 1601 AB subjects who showed diagnosis discordance, 87% had lower BMD in the lumbar spine than in the femur. This finding is also supported in earlier AB studies by Woodson (2010) and Mounach (2012). Results from amputee studies (Sherk *et al.*, 2008; Bemben *et al.*, 2017; Smith *et al.*, 2011) suggest the opposite was found: where diagnosis discordance occurs, BMD in the femur is consistently lower than in the lumbar spine.

Comparing and contrasting the available amputee and non-amputee research into bone loss highlights a clear difference, bone loss in amputees seems localised rather than systemic. We believe that there is a need to address this difference conclusively. Data from a study by Sherk (2008) provides one example of the problem when comparing control and amputee BMD data at multiple diagnostic sites. However, the focus of their study and the conclusions it draws are in comparing bone loss between above and below-knee amputee populations rather than to the control population. Consistent use of the terms “osteoporosis” and “osteopenia” throughout the paper also suggest the authors were not concerned with differentiating between the aetiology of bone loss in the amputee and control populations. Moreover, given that amputee and controls subjects as old as 64 were recruited, it is not possible to fully neglect the effect of bone loss due to aging in the population studied.

2.2.5 The aetiology of bone loss in the younger amputee population

Based on the evidence available it seems that localised bone loss in younger amputees could be, in-part, a mechanical phenomenon. Changes in the loading environment post-amputation may reduce the stimulation experienced by certain regions of bone causing deterioration over the course of many remodelling cycles.

There are multiple theories describing how and why the loading environment changes post lower-limb amputation, however, there is very little conclusive evidence showing the direct effect of these changes on bone health and bone density. Some of the mechanical theories introduced in previous studies are outlined.

Ambulating and weight-bearing through a prosthetic socket results in vastly different loading through the femur and hip post above-knee amputation. Proximal load transfer, through ischial-weight bearing, is encouraged in order to deliberately offload the distal femur where the direct effects of surgery are most prominent (Pritham, 1990). Ramirez (2011) describe this effect as a form of stress-shielding where load is redirected through the stiff carbon fibre socket. Reduced loading through the distal end of the bone means consistently lower joint-contact forces through the femur and at the hip.

Bemben (2017) highlights the effect of dramatic unloading during bedrest immediately post-surgery. The study finds that the largest proportion of bone loss takes place in the first 6 months following amputation (up to 14.8% in the amputated hip) relative to the 6 months following where BMD stabilised or even increased slightly in some subjects. Flint (2014) demonstrated that amputees who begin ambulation within 2 months of amputation record significantly less bone loss than those who begin later. Reports of a positive correlation between prosthetic use and volumetric BMD in both studies suggest a lack of loading during bedrest could be responsible for substantial bone-loss in some amputees (Flint *et al.*, 2014; Bemben *et al.*, 2017). It also highlights the potential restorative effect that increased activity and loading, with a prosthesis, could have on bone loss.

Ambulation becomes much more difficult post-amputation. Sherman (2019) found mean daily step count among a population of military bilateral amputees as 2258 ± 192 during in-patient rehabilitation, decreasing to 1387 ± 363 at home away from rehabilitation, significantly less than the 10,000 steps prescribed to AB people by modern wearable technology campaigns (Miller *et al.*, 2001). Various studies suggest ill-fitting sockets and the prevalence of residual limb pain in long-term amputees as a potential reason for this (Smith *et al.*, 1999; Ehde *et al.*, 2000; Ephraim *et al.*, 2005). Moreover, most amputees simply do not possess the means and mobility to partake in activities such as running, jumping, stair-ascent and stair-descent. These activities are associated with some of the highest and most varied joint contact and muscle contractile forces (both in terms of range of loading direction and muscle recruitment) experienced by human beings, thus playing an important role in stimulating the skeleton (Villette, 2016; Cleather *et al.*, 2013; D'Lima *et al.*, 2012). This would suggest that many amputees are missing out on key loading profiles which have been identified as contributors to the structure of healthy bones.

General gait-changes post-amputation alter loading intensity and time during ambulation (Flint *et al.*, 2014). Research has shown that unilateral amputees spend less time on their amputated limb during gait (Jaegers *et al.*, 1995; Breakey, 1976). Linked to this is a suggestion by Burke (1978) that reduced loading on the amputated limb is a result of other conditions associated with amputation such as osteoarthritis.

Finally, a study by Tugcu (2009) suggested that lower muscle forces due to post-amputation muscle atrophy could contribute to reduced BMD in the amputated limb as post-amputation muscle contractile forces experienced by the bone are reduced. Their study finds a weak correlation between strength of the quadriceps muscle and total femur BMD. Overall, similar to the effect of resistance training on muscles, the levels of stimuli subjected to the human skeleton plays an important role on its physical structure (Villette *et al.*, 2019; Villette, 2016).

Reduced strain post-amputation, as a result of some or all of the theories highlighted above, could play a major role in the state of amputee bone health. Equally, this suggests that induced stimuli from targeted physiotherapy and external loading could have a role in preventing or restoring the bone lost in a young amputee population.

2.2.6 Micro-damage repair, bone signalling and bone wastage

On a local scale, bone remodelling is possible when driven by microdamage and osteocyte signalling. An increase or decrease in osteocyte signalling can have localised effects at specific bone sites (Shaffler & Kennedy, 2012). Osteocytes detect mechanical loading (and the resulting strain) in the bone and regulate bone formation accordingly. Simply put, increased mechanical stimuli can encourage an increase in osteoblastic activity while reduced stimuli can have the reverse effect (Shaffler & Kennedy, 2012).

Accumulation of microcracks within the bone has also been shown to lead to targeted bone resorption by osteoclasts at the site of microdamage. Osteocyte signalling is thought to play a role in this, however, osteocyte apoptosis is considered the more important driver (Rupler *et al.*, 2012). Osteocyte apoptosis has been shown to signal significant increases in osteoclast recruitment so that ‘dead’ bone can be removed (Plotkin, 2014). The subsequent increase in bone resorption naturally elicits a reaction from surrounding

osteoblasts by the release of growth factors so that removed bone can be replaced to complete the repair remodelling process (Rucci, 2008).

Many existing studies have demonstrated the potential for local bone loss due to reduced loading. These include investigations into cast-immobilisation (Ceroni *et al.*, 2012), spinal cord injury (Tan *et al.*, 2013), prolonged bedrest (Leblanc *et al.*, 1990; Berg *et al.*, 2007; Rittweger *et al.*, 2005) and reduced gravity environments (Orwoll *et al.*, 2013). Many others have presented the reverse scenario where local BMD gains occur after increased local loading due to unilateral resistance training (Kannus *et al.*, 1994) and sport-specific exercise (Sanchis-Moysi *et al.*, 2002; Sanchis-Moysi *et al.*, 2010).

2.3 Methods

In order to further explore the trends summarised above, a clinical study was carried out to investigate the localisation of bone loss in a population of young amputees and to identify what could be driving this problem.

It was hypothesised that BMD loss in the young amputee population would affect the amputated femur only and that other regions, such as the healthy femur and lumbar spine, would exhibit healthier BMD. This study proposes to investigate whether there is clinical data to support this hypothesis.

2.3.1 Study design and participants

This is a case-control study comparing bone loss in military lower-limb amputees and healthy age-matched military controls. It represents an exploration of a subset of data collected as part of the Armed Services Trauma Rehabilitation Outcome (ADVANCE) study.

“The ADVANCE study investigates the long-term physical and psychological outcomes of battlefield casualties from the UK Armed Forces following deployment to Iraq and Afghanistan between 2003 and 2014”³. Recruitment to ADVANCE started in March 2016 and follow-up will continue until 2036 (Bennett *et al.*, 2020). The study is a collaboration between the Academic Department of Military Rehabilitation (ADMR, Stanford Hall), Imperial College London and King’s College London. Full scientific protocol for this research has been approved by the Ministry of Defence Research Ethics Committee.

BMD is compared at two diagnostic sites: the spine and femoral neck (NOF). The amputee group consisted of eighty-six traumatic amputees, the breakdown of amputation level and type is shown in Table 2.2 and summarised below. Of eighty-six amputees, thirty-nine were unilaterally amputated and forty-seven were bilaterally amputated. This included amputations at a variety of levels: below-knee, through-knee, above-knee and hip disarticulation. For the purpose of this study, however, through-knee amputations, hip disarticulations and osseointegrated limbs were omitted. The subset constituted a random selection of the greater ADVANCE study cohort (of which there are approximately 180

³Armed Services Trauma Rehabilitation Outcome Study, www.advancestudydmrc.org.uk

lower-limb amputee subjects). The corresponding control group was selected from a list of non-injured men (n=2100) frequency matched to the injured group based on age, service, rank, role, regiment and deployment. While the author acknowledges the potential for bias in using a subset of a volunteer cohort, no evidence was found in the data.

By taking measurements at two sites, the study investigates the independent state of BMD at both to determine whether bone loss is localised to one region or systemic through both sites. Additionally, by comparing demographic and lifestyle data between control and amputee groups any potential contributors to differences in BMD can be identified.

2.3.2 Main outcome measures

DXA scans are used to measure BMD and Z-score at both the lumbar spine and femoral neck (NOF). Both the T-score and Z-score report BMD levels as compared to the general population, however, we believe Z-score is more suited to comparisons involving young amputees. Measurements at the spine represent the average state of bone in vertebrae L1-L4. Typically, in systemic osteoporosis or osteopenia bone loss at one site will be reflected at the other.

2.3.3 Demographic measurements

Extensive demographic and lifestyle information was collected for each amputee and control subject prior to DXA scanning. Additionally, two health-related questionnaires were completed per subject as part of the ADVANCE data collection protocol - one questionnaire is self-reported and the other researcher-administered. In-depth participant information allows for detailed comparison between both groups as we seek to determine what factors could account for differences between amputee and control subject BMD. Below is a summary of the information collected.

2.3.3.1 Age, height and weight

Age, height and weight of each subject was recorded at the time of DXA scan. For each amputee we included a healthy age-matched military control subject from the ADVANCE cohort.

2.3.3.2 Body composition

Body composition was measured by both body-mass index (BMI) and ratio of waist to hip circumference. BMI is a measure of body health and defined as a person's body mass divided by the square of the person's height (units: kg/m^2). For the amputee population, pre-injury height was used in calculations. The accuracy of BMI when comparing between amputees and control subjects has been called into question due to the effect of limb loss on calculations (Frost *et al.*, 2017). As such, a measurement of the waist-to-hip ratio provided a necessary a secondary comparison.

2.3.3.3 Gender and ethnicity

The gender and ethnicity of each subject was recorded. The cohort does not include any females. So few female subjects could be recruited that all were omitted to prevent any being easily identifiable and compromising anonymity. Comparisons could be made by proportions of each ethnicity across the control and amputee groups.

2.3.3.4 Prescription and recreational drug use

Recreational drug history was assessed for each subject. Subjects were first asked whether they have ever taken recreational drugs. Those who answered "yes" were further asked to specify which recreational drugs they have taken.

Prescription drugs were broken down into three sections. Subjects were asked whether they have, or are currently taking any anti-depressant, anxiolytic or opioid analgesic drugs. Those who answered "yes" were asked to record exactly which drugs they have, or were currently, taking. Subjects were further asked whether they had been prescribed any other form of drug not highlighted.

All drugs used could then be evaluated to determine whether they have any known deleterious effect on BMD or bone remodelling.

2.3.3.5 Smoking history

To evaluate past and present smoking history, subjects were first asked whether or not they had a history of smoking. Those who answered “yes” were asked further questions to determine whether they still currently smoke, how much they smoke (either currently or in the past) and whether they have previously used nicotine replacement therapy.

2.3.3.6 Alcohol consumption

Each subject’s relationship with alcohol was assessed by use of the Alcohol Use Disorders Identification Test (AUDIT). The AUDIT was developed by WHO as a tool to screen for excessive drinking and to assess alcohol consumption and drinking behaviours. The questionnaire includes ten items, each answer providing a weighted score from 0-4. The test can be either administered by a clinician or self-reported ⁴ (Babor *et al.*, 2001). In this study, the AUDIT was self-reported for all subjects.

The questions can be broken down into three broad sections assessing (1) consumption (2) dependence (3) alcohol-related problems. Scores can then be interpreted both combined and separately (Babor *et al.*, 2001). Comparisons made for this particular study looked at combined AUDIT score.

2.3.3.7 Activity levels

Activity levels in amputee and control subjects were assessed by the International Physical Activity Questionnaires (IPAQ). This consists of four sections which evaluate activity levels in four domains of daily living: work, travel, domestic and leisure. The main outcome measure is provided in minutes of vigorous activity, moderate activity and walking per week in each domain as well as a combined value across all of the domains. Moderate activity refers to any activity that takes “moderate physical effort and makes you

⁴AUDIT, <https://www.drugabuse.gov/sites/default/files/audit.pdf>

breathe somewhat harder than normal”. Vigorous physical activity refers to any activity that takes “hard physical effort and makes you breathe much harder than normal”.

Comparisons between amputee and control subjects have been made between total minutes of all activity, vigorous activity, moderate activity and walking per week combined across all four domains.

2.3.3.8 Functional mobility

Functional mobility was measured by 6 minute walk test (6MWT) in both amputee and control subjects on the day of DXA scanning. The test measures the furthest distance that a subject can walk quickly along a flat hard surface over the course of 6 minutes while shuttling between two markers spaced 100ft (30.48m) apart (Crapo *et al.*, 2002). In amputees, it serves as a good measure of functional mobility and exercise capacity as it tests both walking speed and efficiency of turning on a prosthesis (Lin & Bose, 2008).

2.3.4 Statistical approach

Statistical analysis was carried out using IBM SPSS version 26 (*IBM Corporation. 2018. IBM SPSS*). Descriptive statistics are presented as mean and standard deviation in Tables 2.1 and 2.3 and by maximum, minimum, median and interquartile ranges in Figures 2.3-2.5 as box plots. Independent T-tests were used to compare Z-scores and BMD differences between control and amputee groups. Paired T-tests were used to compare Z-scores and BMD differences at the NOF and lumbar spine within the same group.

Activity levels were compared between groups by independent T-test. As were continuous demographic variables such as age, weight, waist-to-hip ratio, amount smoked and AUDIT score. Binary demographic variables such as nicotine replacement therapy, recreational and prescription drug use were compared between control and amputee groups by χ^2 (chi-squared) test.

When analysing data, a threshold of $p < 0.01$ represents strong statistical significance.

2.4 Results

Results show significant differences between control and amputee BMD (Table 2.1 and Figures 2.3). The localisation of bone loss in amputees is demonstrated when comparing

Table 2.1: Bone-mineral density and Z-score in all lower-limb amputee limbs and control subjects (mean $\pm$ SD). Note: for control subjects, sound side measurements represent an average of both left and right NOF.

* $p < 0.01$ amputee compared to control at equivalent sites

[†] $p < 0.01$ spine and NOF compared intra-group

Subject	Measurement site	BMD (g/cm^2)	Z-score
Control	Spine		
	L1-L4	1.081 ± 0.015	-0.09 ± 0.13
	Femoral neck		
	Amputated side	—	—
BK amputee	Sound side	0.949 ± 0.010	0.38 ± 0.07
	Spine		
	L1-L4	$1.069 \pm 0.017^{\dagger}$	$-0.20 \pm 0.15^{\dagger}$
	Femoral neck		
AK amputee	Amputated side	$0.790 \pm 0.018^*$	$-0.71 \pm 0.14^*$
	Sound side	$0.864 \pm 0.022^*$	$-0.20 \pm 0.16^*$
	Spine		
	L1-L4	$1.032 \pm 0.016^{*\dagger}$	$-0.57 \pm 0.15^{*\dagger}$
	Femoral neck		
	Amputated side	$0.679 \pm 0.016^*$	$-1.63 \pm 0.12^*$
	Sound side	0.899 ± 0.016	0.08 ± 0.23

between bone at the spine and NOF of amputated limbs versus control limbs. Z score is significantly higher in the spine of amputees when compared to the NOF, while in controls there is no marked difference between Z-score at each site. Additionally, the demographic similarity between control and amputee groups, shown in Table 2.2, suggests difference in BMD levels can be narrowed down to the effect of amputation rather than demographic, lifestyle or weekly activity levels.

Figure 2.4 shows that the residual limb of AK amputees demonstrated significantly lower Z-score in the NOF than those of BK amputees. Figure 2.5 separates the population of amputees further (on a limb-by-limb basis) into unilateral below-knee, unilateral above-knee, bilateral below-knee and bilateral above-knee amputees. The subset of unilateral below-knee amputees exhibits the highest NOF BMD while above-knee amputated limbs

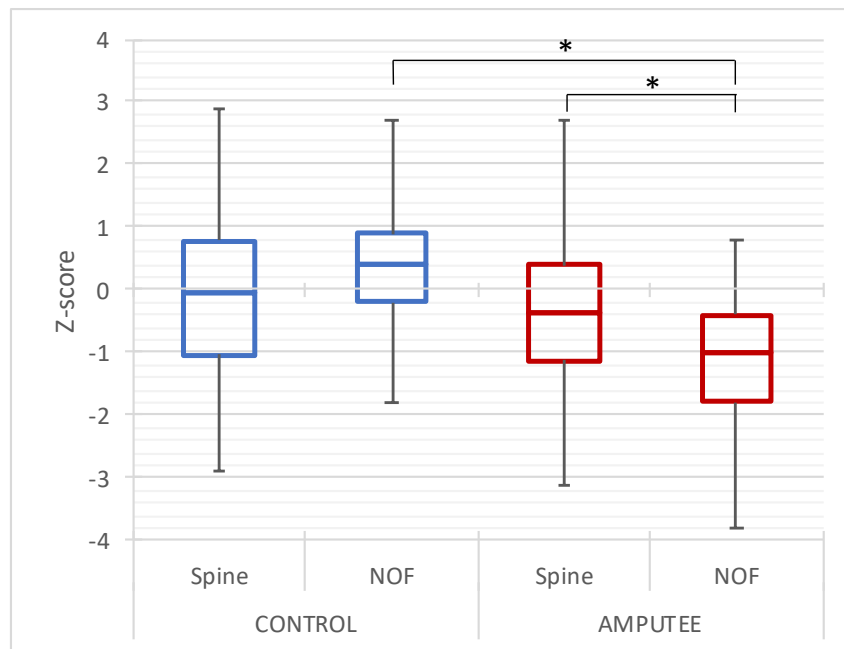


Figure 2.3: Comparison of Z-score between control subjects and combined amputee population at both the lumbar spine and femoral neck $*p < 0.01$

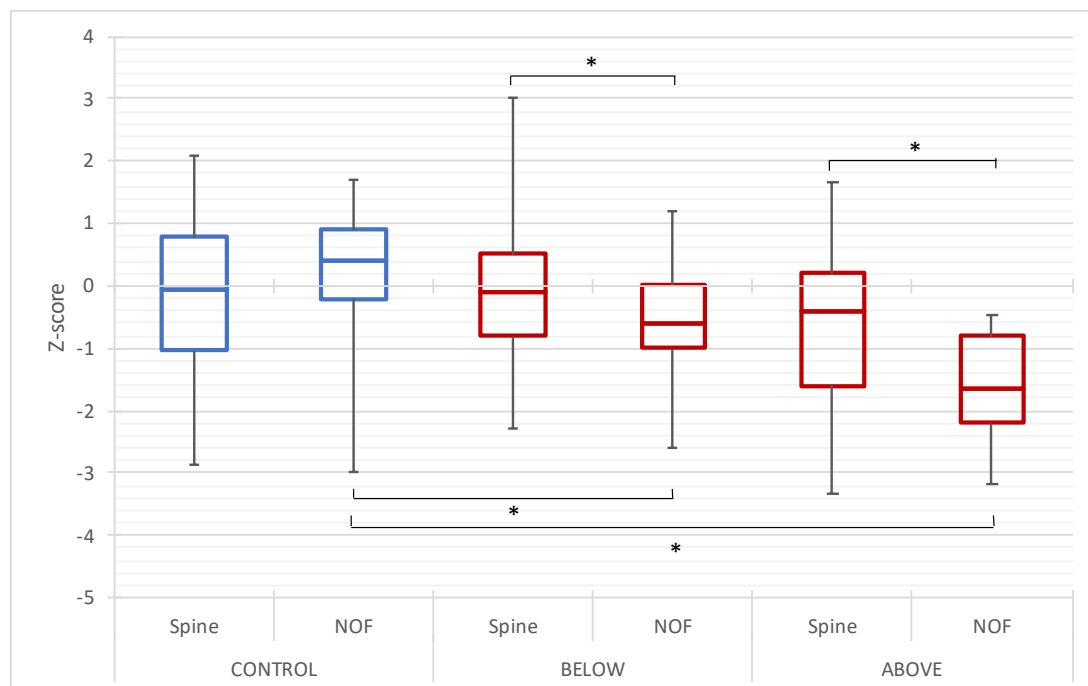


Figure 2.4: Comparison of Z-score between control subjects, below-knee amputee and above-knee amputee populations at both the lumbar spine and amputated femoral neck $*p < 0.01$

Table 2.2: Participant characteristics

	Control	Amputee	P-value
Ethnicity, n (%)			=0.619
White	76 (88.4)	73 (89.0)	
Black	3 (3.49)	5 (6.09)	
Asian	5 (5.81)	0 (0.00)	
Mixed	1 (1.16)	1 (1.21)	
Other	0 (0.00)	3 (3.66)	
Missing	1 (1.16)	0 (0.00)	
Age (years), mean (SD)	32.9 (4.60)	32.8 (4.54)	=0.809
Body mass index, mean (SD)	24.8 (4.19)	27.7 (3.81)	<0.001
Waist-to-hip ratio, mean (SD)	0.91 (0.071)	0.91 (0.059)	=0.876
Level of amputation, n (%)			
Unilateral below-knee	26 (30.2)	-	
Unilateral above-knee	7 (8.14)	-	
Bilateral below-knee	7 (8.14)	-	
Bilateral above-knee	23 (26.7)	-	
Below-knee/above-knee	7 (8.14)	-	
Other	16 (18.6)	-	
Smoking history, n (%)			=0.579
Never smoked	41 (47.7)	34 (41.5)	
Current smoker	14 (16.3)	18 (22.0)	
Ex-smokers	31 (36.0)	28 (34.1)	
Missing	2 (2.40)	0 (0.00)	
Amount smoked, mean (SD)			
Current smokers	11.5 (6.16)	12.2 (5.77)	=0.741
Ex-smokers	13.3 (7.11)	13.3 (7.53)	=0.979
AUDIT score, mean (SD)	5.4 (4.99)	7.1 (5.07)	=0.031
Recreational drug users, n (%)	27 (31.4)	22 (26.8)	=0.515
Prescription drug users, n (%)	90 (93.0)	34 (41.5)	<0.001
IPAQ results (mins/week), mean (SD)			
Walking	1214 (1652)	1280 (1580)	=0.579
Moderate activity	1452 (1487)	1022 (929)	<0.001
Vigorous activity	782 (936)	605 (856)	=0.089
Total activity	3449 (3425)	2908 (2855)	=0.073
6 minute walk distance (m), mean (SD)	421 (194)	623 (128)	<0.001
SIGAM mobility grade, n (%)			
A	5 (5.8)	-	
B	2 (2.3)	-	
C	1 (1.2)	-	
D	17 (19.8)	-	
E	17 (19.8)	-	
F	29 (33.7)	-	
Missing	15 (17.4)	-	

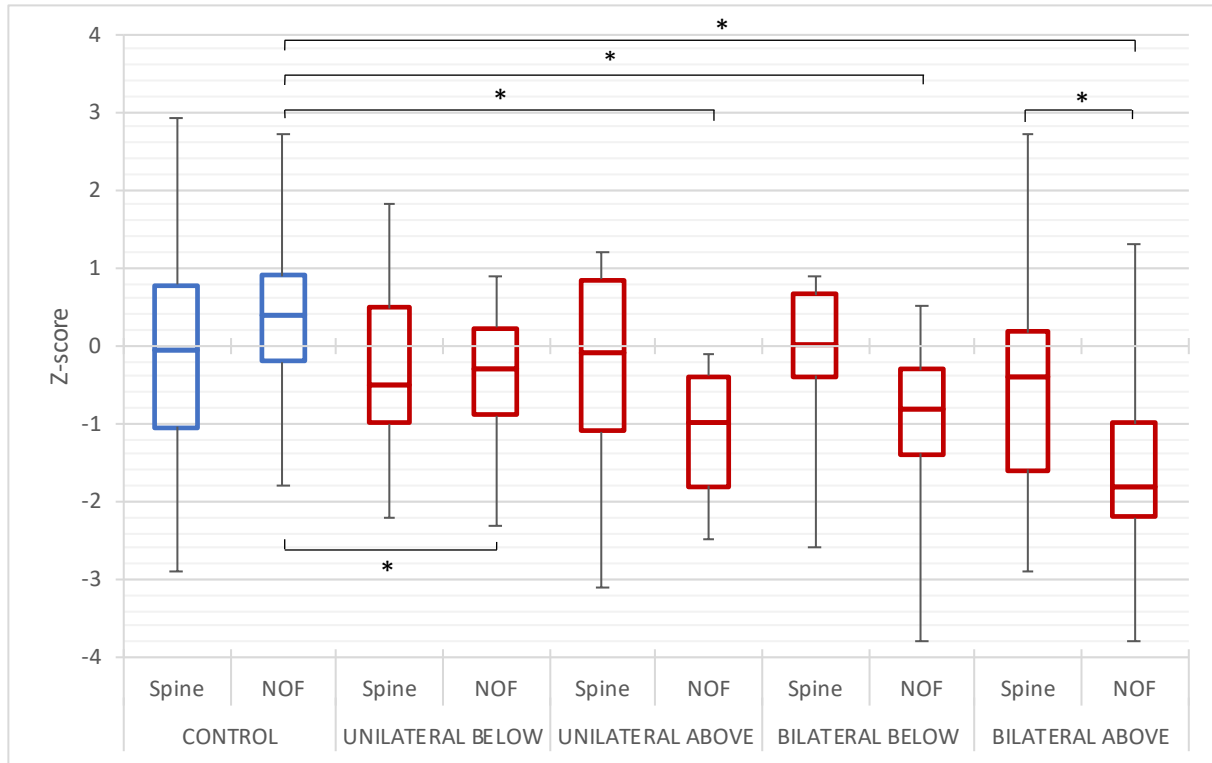


Figure 2.5: Comparison of Z-score between control subjects and limbs of varying amputation level at both the lumbar spine and femoral neck $*p < 0.01$

belonging to bilateral amputees exhibit the lowest. Spine BMD through all of these groups are statistically similar to controls.

BMD and Z-score also differ between the sound side and amputated NOF in unilateral amputees (Table 2.3). The amputated side exhibits lower BMD than the intact side in

Table 2.3: Bone-mineral density and Z-score in the amputated femur and sound side femur of unilateral amputee subjects (mean $\pm$ SD).

$*p < 0.01$ amputated NOF compared to sound side NOF in unilateral amputees

Measurement site	BK amputee		AK amputee	
	BMD (g/cm^2)	Z-score	BMD (g/cm^2)	Z-score
Femoral neck				
Amputated side	$0.785 \pm 0.041^*$	$-0.41 \pm 0.17^*$	$0.676 \pm 0.028^*$	$-1.54 \pm 0.23^*$
Sound side	0.864 ± 0.022	-0.20 ± 0.16	0.899 ± 0.033	0.08 ± 0.23

both AK and BK amputee populations. Figure 2.6 shows that for unilateral amputees, Z-score in the NOF of the residual limb is significantly lower than in the contralateral limb. This further demonstrates localisation of bone loss in the amputee population.

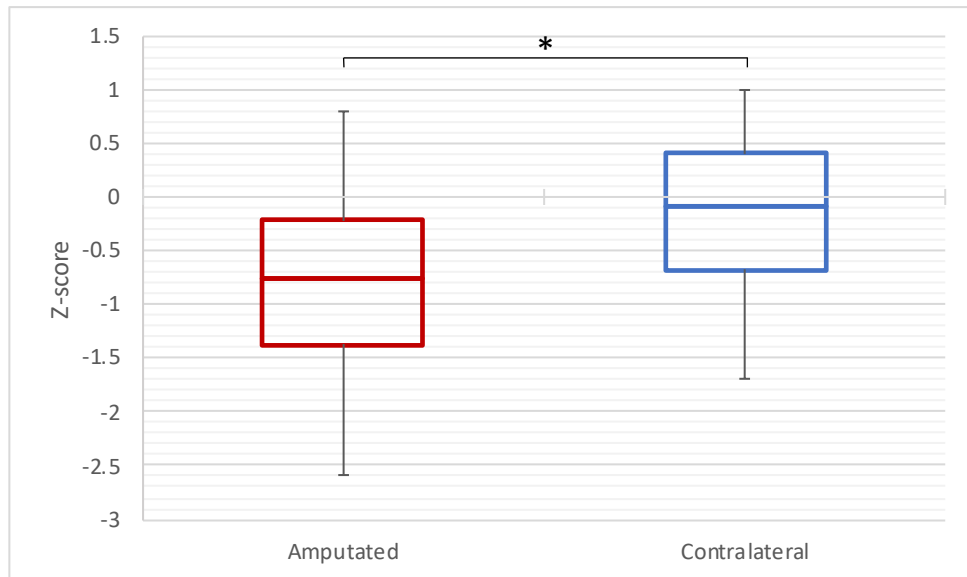


Figure 2.6: Comparison of Z-score at the femoral neck in amputated and contralateral limbs of unilateral amputee population $*p < 0.01$

2.5 Discussion

2.5.1 Demographic information

Differences in BMD could not be accounted for by age ($p=0.809$). Mean BMI was statistically higher ($p<0.001$) in control subjects than in amputees. However, as previously explained, the use of BMI has been shown to underestimate values when analysing lower-limb amputees (Frost *et al.*, 2017). Using waist-to-hip ratio as a proxy measurement for body composition we see no significant difference between groups ($p=0.876$). Both groups contained a similar distribution of ethnicities ($p=0.619$), the vast majority in each group being white British.

Analysing subjects' history of substance-use shows little difference again. Difference in alcohol consumption as defined by the AUDIT ($p=0.031$) shows weak statistical significance, unlikely a strong enough correlation to account for the scale of differences seen in BMD and Z-score. Lower scores in the control population are to be expected given that it is made up of active military members. It is also important to note that both active military members and military veterans exhibit a greater prevalence of moderate and heavy alcohol consumption than civilians of the same age (Waller *et al.*, 2015; Ames & Cunradi, 2004). Similar numbers in both groups have a history of smoking ($p=0.579$). Results show no significant difference in the amount smoked between control and amputee groups ($p=0.741$ in current smokers and $p=0.979$ in past smokers). A similar proportion of amputees and controls admitted to having used recreational drugs ($p=0.515$) and a similar proportion were currently taking anxiolytic prescription drugs at the time of DXA ($p=0.078$). The only strongly significant demographic differences show more amputees taking anti-depressants ($p=0.004$) and opioid analgesic ($p<0.001$) prescription drugs at the time of DXA scan. None of the opioid analgesics or anti-depressants taken by subjects have known deleterious effects on BMD, therefore their potential effect on bone loss can be deemed negligible.

Based on results of the IPAQ, control and amputee groups can be considered statistically similar in terms of weekly activity level. This suggests that global frequency of loading cannot explain reduced BMD in the amputee population but, rather, suggests that differences could be due to the effect of loading on a local scale.

There was minimal difference in between-group activity levels. Amputees completed slightly more moderate activity per week ($p < 0.001$) – 430 minutes more on average. Looking at the broader picture, difference in total minutes of activity per week between groups was not statistically significant ($p = 0.073$). Minutes of walking and minutes of vigorous activity per week were also similar ($p = 0.579$ and $p = 0.089$, respectively). Having said this, IPAQ defines different activity levels from a qualitative perspective of how heavily one is breathing during a certain task. Functional mobility within the amputee group is significantly impaired when compared to the control group of active military members. Evidence for this can be found in comparisons of 6MWT distance ($p < 0.001$) and the SIGAM functional mobility grades assigned to each amputee (88.6% of amputees scored a grade D or below). This suggests the IPAQ could be a poor discriminator of activity levels between groups considering how it is reported.

2.5.2 BMD and Z-score

The results strongly suggest that bone changes in the amputee population are localised to the amputated femur. Although frequency of loading is similar between groups, the direct effect of local loading on the amputated femur may be different to that of a healthy femur. This could be driving local BMD loss by reduced osteocyte signalling and warrants further investigation.

There was not a statistically significant difference between the lumbar spine BMD of amputee and control groups ($p = 0.195$) however, Figure 2.3 shows that BMD in the NOF was significantly less in amputees when compared with controls ($p < 0.001$). Unilateral amputees also had significantly improved BMD at the femur on their non-amputated side when compared with the amputated side ($p < 0.001$) (Figure 2.6). This evidence suggests that bone loss occurs at a higher rate in the femur of the amputated limb than in the spine and in the femur of the unamputated limb. Making intra-group comparisons, Z-score was significantly lower in the spine than in the femur of control subjects ($p < 0.001$), whereas in the amputee group, the opposite was found: Z-score was significantly lower in the femur than the spine ($p < 0.001$).

This all lends evidence to the argument that bone loss in the amputee population is local and is driven by abnormal loading in the amputated femur. Possibly due to intentional offloading through the design of the prosthetic socket (Pritham, 1990). This

is substantiated by the fact that NOF BMD is significantly higher in BK amputees when compared with AK amputees ($p < 0.001$). In AK amputation, the shielding effect of loading through a prosthetic socket is larger than in BK amputation where loading above the knee joint is closer to physiological loading in a healthy control. AK sockets commonly employ distal offloading and ischial locking (Pritham, 1990) which could encourage load to bypass the femur entirely. Additionally, spine BMD in unilateral and bilateral amputees is statistically similar ($p = 0.980$). Abnormal loading occurring at the femur seemingly does not affect loading at the spine to the same degree, further implicating the prosthetic socket as a key contributor.

Using the WHO clinical diagnostic criteria, we can compare our results to some of the larger, population-based studies investigating diagnosis discordance in the general ageing population (Table 2.4). By analysing subjects on an individual case-by-case basis we find

Table 2.4: Distribution of diagnostic discordance in control versus amputee cohorts by percentage

	Amputee	Control
Concordance	55.8	74.4
Major discordance		
higher in spine	5.4	0.0
higher in femur	0.9	0.0
Minor discordance		
higher in spine	31.6	1.2
higher in femur	6.3	24.4

major diagnosis discordance in 6% of amputees scanned and minor discordance in a further 35%. Unlike in the ageing population, however, this diagnosis discordance overwhelmingly favours a lower Z-score in the NOF than in the lumbar spine. Of all the amputee cases where discordance is present, 83% had a lower Z-score in the femur than in the lumbar spine. By comparison, Moayyeri (2007) found this in just 13% of a non-amputee, ageing, population where discordance occurred much more commonly in the reverse direction. These results suggest that rate of bone deterioration in the femur of young amputees is higher than the rate of deterioration in the lumbar spine and, possibly, the rest of the body. If the causes of bone loss were systemic (as in postmenopausal systemic osteoporosis) we would expect results to be in line with those found by (Moayyeri *et al.*, 2007). This is particularly pertinent given that the lumbar spine is typically more metabolically active (due to a higher proportion of trabecular bone) (Firestein *et al.*, 2017; Metzger *et al.*, 2020; Nordin, 1979, republished in 2012).

Most importantly, we believe that this study shows that bone loss in the young amputee population proceeds differently to bone loss in the general population. As such, there should be a distinction made between a clinical diagnosis of osteoporosis and one of low BMD in the younger amputee population. Reduced BMD might not be a sign of systemic osteoporosis but rather a sign of a bone's adaptation to a new mechanical loading environment post-amputation. The problem could potentially be halted or reversed with appropriate research into socket design, loading and bone stimulation.

In the majority of current available literature, reduced BMD levels in lower-limb amputees is used to diagnose osteoporosis or osteopenia (Burke *et al.*, 1978; Leclercq *et al.*, 2003; Kulkarni *et al.*, 1998; Rush *et al.*, 1994). More recently, a few researchers have begun to make subtle distinctions between bone loss in amputees and bone loss in the general population. Sherk (2008) first highlighted the possible similarities between bone loss post-amputation and bone loss as a result of periods of prolonged unloading from scuba diving (Pereira Silva *et al.*, 2004), bed rest (Leblanc *et al.*, 1990; Berg *et al.*, 2007; Rittweger *et al.*, 2005) and space travel studies (Orwoll *et al.*, 2013). Later studies by Bemben (2017), Flint (2014) and Ramirez (2011) made similar comparisons and do not equate amputee bone loss to osteoporosis or osteopenia but rather to physical phenomena such as bone stress shielding by the socket resulting in reduced load transmission through the skeleton. The author believes that a diagnosis of osteoporosis carries the implication that the problem is systemic and irreversible. This could have an important negative psychological impact and subsequently affect a person's outlook on rehabilitation. From a treatment perspective, the difference could also be vital. Osteoporosis is typically associated with endocrine changes in the older population. As a result, it is, most commonly, treated by hormone replacement therapy or bone-preserving medication such as bisphosphonates or denosumab. Both treatments have been shown to have adverse effects elsewhere in the body (Kennel & Drake, 2009; Tavani & La Vecchia, 1999) and could be inappropriate for treatment of younger amputees. It may be beneficial to avoid these treatment strategies altogether in a younger subject, for example an amputee, whose bone loss could be mainly attributed to unloading. A diagnosis of systemic osteoporosis could result in prescription of such drugs without proper consideration for the aetiology of the bone loss - leaving the issue of bone loading unaddressed. It could also prevent further research into the effect of end-loading, ischial weight-bearing and the design of future prosthetic sockets. Hence, in amputees, a more specific diagnosis of *unloading osteopenia* is presented as more appropriate.

2.5.3 Study limitations

All subjects evaluated in this study come from an active military background. As such, it could be suggested that results do not fully transfer to the broader general public. Active military members and veteran amputees could differ to civilian counterparts in terms of activity levels and demographics. This distinction, however, could also be used in future studies to determine the potential regenerative effect of a more active lifestyle on amputee bone health. Another potentially important characteristic of military amputations is the increased incidence of heterotopic ossification (HO). None of the subjects included in this study were known sufferers of HO, however, there is no evidence that those with HO were excluded from ADVANCE study recruitment (Bennett *et al.*, 2020). Having said that, the effect of HO on hip BMD measurements is likely to be negligible as it most commonly occurs distally towards the site of amputation; away from the femoral neck where hip BMD measurements were taken.

Looking ahead to future studies, it would be useful to evaluate progression of bone loss in both the short and long-term. For example, DXA measurements could be taken shortly after amputation and then repeated periodically in the years following. Understanding the rate of bone deterioration could give further insight into the aetiology of the problem; it would be interesting to determine how much bone loss can be attributed to the period of initial bedrest associated with intense trauma and recovery from surgery. A study by Bemben (2017) tracked the progression of bone-mineral density loss in amputees over the first year following amputation. A similar study with longer-term callback (5 or 10 years post-amputation) would have even more potential in isolating the immediate post-recovery changes in bone-mineral density from long-term progression of bone loss after normal daily activities are resumed.

The use of biological biomarkers is now commonplace in the diagnosis of systemic osteoporosis (Ji & Yu, 2015). Use of biomarkers could also be beneficial in determining the aetiology of bone loss in young amputees. Understanding if bone loss can be directly attributed to increased osteoclast activity or reduced osteoblast activity would be useful for comparison to bone changes in other populations. It is possible, however, that global biomarkers used in diagnosis of systemic osteoporosis fail to capture changes on a local level.

Chapter 3

Modelling Framework

3.1 Introduction

Chapter 3 outlines the main in-silico modelling framework used throughout this research. It interfaces musculoskeletal (MSK) and structural finite element (FE) modelling in order to generate and implement a full physiological loading scenario of joint and muscle forces on a specific region of bone. The process of bone remodelling and optimisation is simulated using a strain-based bone adaptation algorithm (Phillips *et al.*, 2015). The internal architecture adapts in order to optimally resist the loading placed upon it. This allows prediction of the long-term changes in structure that may occur as a result of altered loading. A visual representation of the modelling framework can be seen in Figure 3.1. The framework is used, firstly, to create an able-bodied (AB) structural femur model. This will become the starting point for further analyses into the effect of loading on the femur of below-knee (BK) and above-knee (AK) amputees. In this chapter the framework will be explained in the context of creating a control femur. Chapters 4 and 5 go into further detail on adapting the framework to model amputation of unilateral below-knee and bilateral above-knee amputees, respectively.

The framework is well-established within the Structural Biomechanics Group at Imperial College London, having already been used to predict the healthy internal structure of the femur, pelvis and vertebrae (Phillips *et al.*, 2015; Zaharie & Phillips,

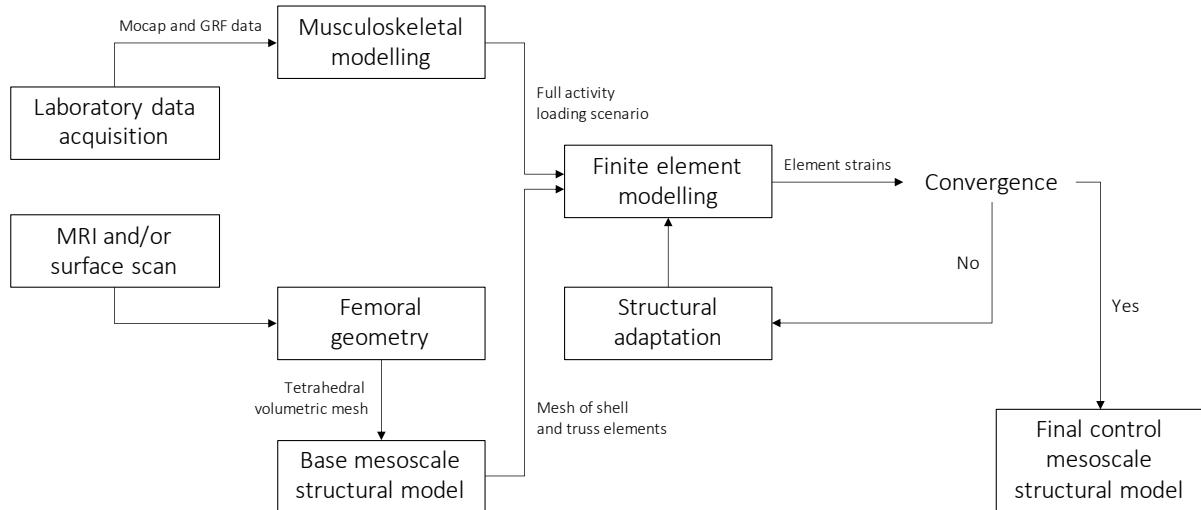


Figure 3.1: Musculoskeletal and finite element modelling framework for creation of the control femur. Adapted from Villette (2016).

2018; Favier, 2019). The amputee models represent the first time this novel approach has been applied to a compromised situation such as amputation. It also demonstrates the potential for using this framework in prediction of further bone remodelling from a healthy starting point.

Experimental data acquisition was completed for the control subject with the help of Dr Dan Zaharie, for the below-knee amputee subject with Dr David Henson and Biranavan Sivapuratharasu and for the above-knee amputee subject with Dr David Henson and Dr Ziyun Ding. No MRI data was required for the control subject as a generic MSK model was used. Full MRI data for the two amputee subjects was provided for me by Dr David Henson. In all three subjects, I carried out the MSK modelling, FE modelling and structural adaptation. The two amputee subjects required the development of novel patient-specific computational models at each stage and alterations to the existing structural adaptation scripts created by Phillips (2011; 2015).

3.2 Data acquisition

The control subject is male, 186cm in height and weighed 84.6kg at time of data acquisition. Importantly, his height and weight were approximately similar to both amputee subjects used in modelling in Chapters 4 and 5.

Kinematic data was collected in the Biodynamics Gait Lab at the Imperial College MSK Lab in Charing Cross Hospital. Thirty two spherical reflective markers were attached directly onto the lower-body of the control subject as recommended by the International Society of Biomechanics (ISB) (Wu, 2002) and demonstrated in Figure 3.2. A Vicon

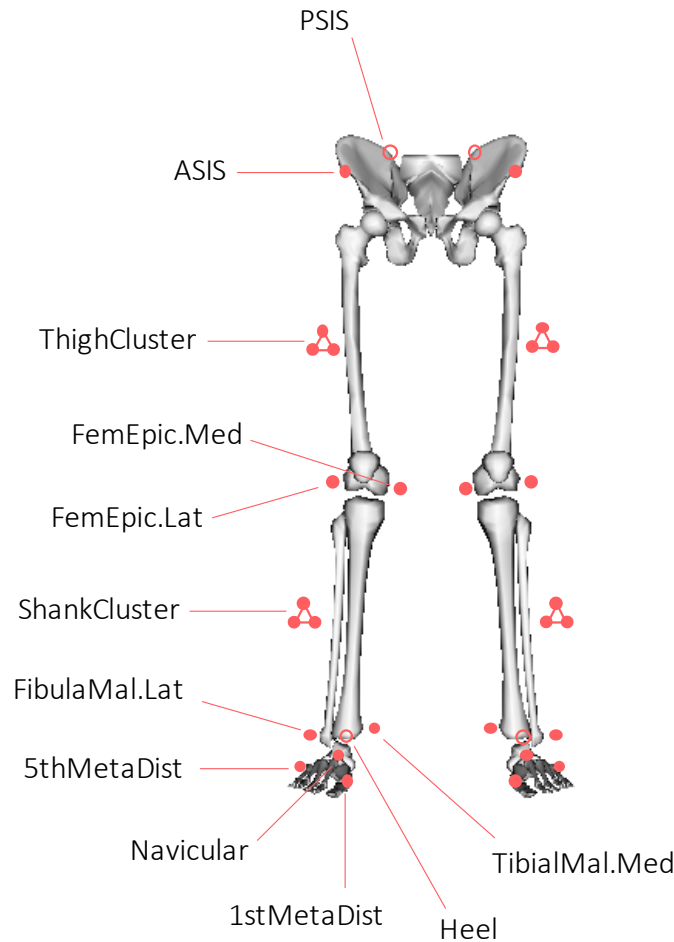


Figure 3.2: Schematic showing lower-body marker placement on the control subject during data acquisition.

system (*Oxford Metrics*, Oxford, UK) equipped with 10 infrared cameras was used to track the motion of the markers at a 100Hz sampling rate. Three Kistler force plates

(Type 9286BA, sampling rate 1000 Hz, Kistler Instruments Ltd, Hook, UK) were used to measure ground-reaction force.

Kinematic and loading data was collected for all six of the most common daily physical activities as recorded by Morlock (2001): walking, standing, stair-ascent/descent and sit-to-stand/stand-to-sit. These activities provide a full envelope of daily loading (Morlock *et al.*, 2001). Ten trials were collected for walking, stair ascent/descent and sit-to-stand/stand-to-sit activities. Five static pose standing trials were collected, these were also used in scaling the model. During gait data acquisition, force plates were appropriately placed midway along a 6m walkway to record consecutive steps at a self-selected, “natural” speed. Stair ascent/descent data was collected using an instrumented staircase (step height: 15cm and step depth: 25cm). Sit-to-stand/stand-to-sit data was collected using an instrumented seat. One force plate is placed on the seat itself, and the other two placed separately underneath the subject’s feet.

Each marker was labelled, trajectories marked, gap-filled and results filtered using a 4th order zero lag low-pass Butterworth filter (cut-off frequency of 6Hz) (Winter *et al.*, 1974) in Vicon Nexus (*Version 2.6.1*). Further data processing was carried out using the *Biomechanical Toolkit* (BTK) (Barre & Armand, 2014) in Matlab: first kinematic data checks were performed and gait events were identified using a 30N vertical force threshold. Additional filtering of force plate data was performed using a zero lag low-pass Butterworth filter (cut-off frequency 30Hz)(Eng & Winter, 1995). The BTK scripts also generated input *.trc and *.mot files compatible with use in OpenSim (*Version 3.0.1*).

3.3 Musculoskeletal modelling

Musculoskeletal modelling is a powerful tool used in this study to determine kinematic and kinetic loading data for each subject in OpenSim (*SimTK*) (Delp *et al.*, 2007). Modelling simulations are driven by experimental data. Kinematic and force plate data is combined for each subject and used to perform inverse dynamics, inverse kinematics and static optimisation in OpenSim and BTK. This allows for analysis of joint-angles, joint loading and muscle recruitment during activity on a frame-by-frame basis, as well as contributing to the physiological loading scenario used in FE simulations (van Arkel *et al.*, 2013a).

MSK modelling is governed by the Newton-Euler method (Loeb & Davoodi, 2016). Equations of motion are derived for each rigid body depending on its position, mass, moment of inertia and any external forces acting on the body segment. Constraint equations are then introduced to ensure that prescribed motion does not violate the degrees of freedom and constraints permitted at congruent joints. External forces include the effect of gravity, environmental forces (such as ground-reaction force) and muscle forces (modelled as strings acting around frictionless wrapping points to enhance muscle path and provide a more physiological representation of the muscle lines of action). Equations of motion can be solved in multiple steps to give forces, moments and accelerations at each joint and rigid body.

3.3.1 London Lower Limb Model

Control results were obtained using the London Lower-Limb Model (LLLM)(Modenese & Phillips, 2012). The model was also used as a starting point to create both bilateral and unilateral amputee models. The original LLLM was ipsilateral, implemented using an anatomical dataset (published by Horsman (2007)) and based on measurements from a single cadaveric specimen. The bilateral model was created by mirroring the right leg with respect to the sagittal plane. The bilateral LLLM consists of 13 rigid body segments: one pelvis (and fused sacrum) as well as right and left femur, patella, tibia, hindfoot, midfoot and phalanx sections. The segments are connected by nine joints: pelvis-ground (6 degrees of freedom), two hip joints (3 degrees of freedom each), two knee joints (1 degrees of freedom each), two patellofemoral joints (1 degrees of freedom each) and two ankle joints (1 degree of freedom each). Seventy six muscles are represented by

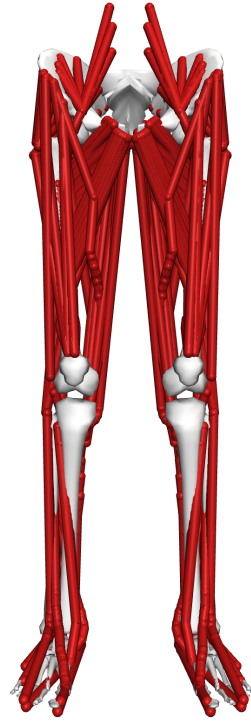


Figure 3.3: The bilateral London Lower Limb model used in MSK analysis of the control subject (Modenese & Phillips, 2012).

326 actuators which drive movement about each joint. Muscles are attached directly onto the rigid body segments outlined above. Muscle paths are enhanced by via points and frictionless wrapping surfaces where necessary.

Each muscle in the model is discretized into multiple actuators spanning across the full surface area of physiological insertion points. This has key benefits in finite element modelling: allowing for muscle forces to be properly spread across the surface of the bone rather than concentrated at just one point. Additionally, multiple papers have attempted to validate the LLLM against EMG data and hip joint contact force, concluding that the model is able to produce an appropriate balanced sets of muscle forces and joint contact forces when compared to experimental values (Modenese *et al.*, 2011; Modenese & Phillips, 2012; Modenese *et al.*, 2013).

3.3.2 Simulation

3.3.2.1 Scaling

When using a generic musculoskeletal model such as the LLLM, scaling is required to match size, weight and inertia properties to individual subjects. The OpenSim scaling tool alters the anthropometry of the model depending on certain user-defined parameters (Delp *et al.*, 2007). The tool compares experimental marker positions to the virtual marker positions on the generic model and scales accordingly. Accurate scaling relies most heavily on markers placed at anatomical landmarks to scale individual segments in 3D (Delp *et al.*, 2008). Inertial properties are adjusted according to regression equations by Dumas (2007). Each body segment in the control model was scaled linearly based on its length.

3.3.2.2 Inverse kinematics

Inverse kinematics are run to measure joint angles during each trial. The inverse kinematics tool matches coordinate data and experimental data on a frame by frame basis by solving for the “best match” pose where the sum of weighted squared errors of markers and coordinate data is at a minimum (Delp *et al.*, 2008).

3.3.2.3 Inverse dynamics

Inverse dynamics are run to determine the net joint moments during each trial. The inverse dynamics tool uses the previously calculated kinematics (giving generalised position of each segment) and the external loading applied to the model (force plate data) to solve the mass dependent relationship between force and acceleration with Newton-Euler equations of motion in a bottom-up approach (Delp *et al.*, 2008).

3.3.2.4 Body kinematics

The OpenSim body kinematics tool (Delp *et al.*, 2008) reports the spatial characteristics of a given body throughout analyses. This is important in the future calculations of inertial forces to be used during FE.

3.3.2.5 Muscle and joint force analysis

Static optimisation is used to estimate muscle forces. The static optimisation tool further resolves the net joint moments found during inverse dynamics into individual muscle forces. It attempts to minimise the sum of squared muscle activations at each step while minimising the objective function, J :

$$J = \sum_{m=1}^n (a_m)^p$$

where n is the number of muscles in the model; a_m is the activation level of muscle m at a discrete time step and p is a, typically, user-defined constant. In this study p is taken as 2 (Delp *et al.*, 2007; Delp *et al.*, 2008).

The MuscleForceDirection tool in OpenSim can then be used to output individual muscle lines of action and align them to a corresponding muscle force. It does this by outputting frame-by-frame muscle force data as vectors. This allows for the inclusion of muscle forces as force vectors from origin points in FE models of bone (van Arkel *et al.*, 2013b). The application of the MuscleForceDirection tool is explained in more depth in Phillips (2015).

Finally, hip and knee joint contact forces were calculated using the joint reaction tool. These forces correspond to all of the internal loads carried by the joint structure; also representing contributions of “un-modelled joint structures” such as cartilage and ligaments (Delp *et al.*, 2008).

3.4 Finite element modelling

The following section explains the development of the structural control femur using FE. Joint, muscle and inertial forces from MSK modelling are used to create the physiological loading scenario applied to FE analysis of the femur. This includes forces from all six activities trialled above. Starting from a ‘blank’ femur template with uniformly arranged shell (cortical) and truss (trabecular) elements, the model was run through many iterations of loading and each element adapted (varying thickness/cross-sectional area) towards a target strain. Ultimately the thickness and radius of cortical and trabecular elements, respectively, converge towards a final structure which is optimised to resist the loading placed upon it. This final converged femur provides us with an AB starting point for amputee analyses. The existence of all major proximal trabecular trajectories predicted by this adaptive FE model also provides some validation of the modelling framework.

3.4.1 Structural modelling of bone

The structural FE modelling approach uses idealised structural elements, trusses and shells, to represent trabecular and cortical bone, respectively. It lends itself to modelling in the mesoscale, part way between microscale and macroscale. Individual elements are larger than those found in-vivo but are still believed to capture the overall structure of bone, as demonstrated in the femur by Phillips (2015). Benefits of the structural modelling over continuum modelling approach include improved computational efficiency (van Lenthe *et al.*, 2006; Zaharie & Phillips, 2018; Pothuau *et al.*, 2004) as well as the ability to model material and structural directionality without requiring complex material properties as in an equivalent continuum FE model (Phillips *et al.*, 2015).

3.4.2 Base FE model

The base femur geometry was created from a CT scan of a Sawbones (*Pacific Research Laboratories Inc*, USA) fourth generation medium composite femur (#3403). The femur was processed in Mimics and 3-matic (*Materialise*, Belgium) to create a surface and volumetric continuum mesh of average edge length 3mm. The femur was uniformly scaled

to match the femoral length of the control subject used in data collection. The coordinate system of the femur was matched to ISB recommendations (Wu, 2002).

Using the nodal information from the base continuum model, an equivalent structural model was created in Matlab. Surface nodes were populated with linear triangular shell elements (S3) and assigned an arbitrary thickness of 0.1mm to represent the cortex of the femur. Each pre-existing node within the volume of the femur was connected to the sixteen nearest neighbouring nodes by two-noded truss elements (T3D2) to represent the trabecular bone architecture (as can be seen in Figure 3.4. Truss elements were assigned a uniform cross-sectional radius of 0.1mm. All elements were assigned linear material properties corresponding to that of cortical bone ($E=18\text{GPa}$, $\nu=0.3$) (Turner *et al.*, 1999).

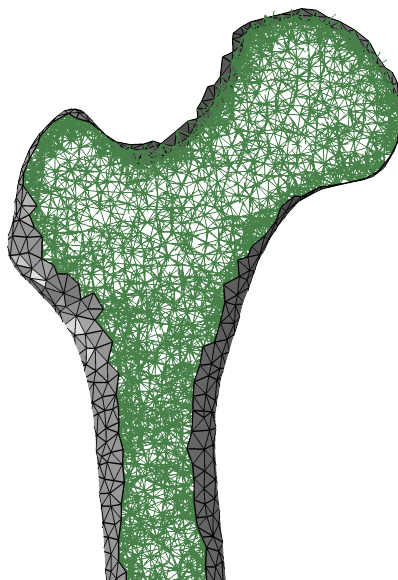


Figure 3.4: A 5mm slice of the base structural femur showing the arrangement of truss elements representing trabecular bone in green and shell elements representing cortical bone in gray.

3.4.3 Loading conditions

The model itself only contains the geometry of the femur. Loading and boundary conditions at the hip, knee and patellofemoral joints are applied using specifically designed load applicators and fixators. Joint contact forces are applied to the femoral head and distal condyles by use of load applicators; a concept developed by Villette (2016). They simulate loading through a joint, such as the hip, without modelling the congruent bone (the pelvis) and subsequently negate the need for contact modelling. They consist of 4

layers of continuum wedge elements (2mm thick) and when combined with the surface elements of the base femur model represent the bone-cartilage-cartilage-bone interfaces in a synovial joint (Villette, 2016). The applicators are created using Matlab by projecting each node on the surface of a joint outwards, in 2mm increments, along the direction defined by the original node and the joint centre. The wedge elements are superposed onto the regions of the base femur model where joint loading takes place (hip, tibio-femoral, patella-femoral joint). The material properties of the bottom two layers match that of articular cartilage ($E=10\text{MPa}$, $\nu=0.49$). The top two layers were assigned different properties of 10MPa ($\nu=0.3$) and 500MPa ($\nu=0.3$), respectively. The assigned material properties and thicknesses were chosen based on sensitivity studies carried out by Villette (2016) who found this particular combination recreated the most realistic distribution of pressure on the bone surface. The use of applicators provides a large reduction in computation time and power compared to the use of contact (Villette, 2016).

Joint contact forces were applied to a single node at the centre of each joint. This node was connected to the outermost surface of the load applicator by truss elements with $E=18\text{GPa}$, $\nu=0.3$ and a cross-sectional area of 2.5mm^2 . At the hip joint, forces were transferred but moments were not as the joint has 3 rotational degrees of freedom. At the knee joint only 1 rotational degree of freedom is present, therefore moments could be transferred. The knee contact force was split into two and applied at the centre of each femoral condyle, medial and lateral. Moments were applied via force couples at two points along the joint axis in order to facilitate the transfer of moments at the knee without introducing local moment transfer between the applicator and the bone underneath (Villette, 2016). At the knee, Kinematic restrictions replicate the effect of the patella ligament. An applicator at the patellofemoral joint applies the closing force of the patella on the femur during muscle contractions and knee joint motion. The patellofemoral joint was defined as a band passing between the two distal femoral condyles and part way up the anterior of the femoral shaft. This accounted for patella movement across the surface of the femur during knee flexion and extension.

Inertia applicators were also used (Villette, 2016) to evenly distribute the inertial force during activities over the whole surface of the femur. The inertia applicator uses soft truss elements ($E=5\text{MPa}$, $\nu=0.3$ and a cross-sectional area of 2.5mm^2) to link the thigh centre of mass to each of the femur surface nodes. Inertial force during activity could then be applied at the thigh centre of mass for each time step.

Loading comes directly from results obtained by musculoskeletal modelling. For each activity, forces were subsampled to increase computational efficiency. Eight frames each of: gait, sit-to-stand, stand-to-sit, stair ascent and stair descent were applied in FE as separate steps. Frames were selected based on an ‘integration limit error’ of the hip contact force. The difference between the integrated hip contact force for the complete sample of frames and the subsampled frames was within 5%. For each chosen frame, a full envelope of forces was created from the hip contact force, knee contact force, patella-femoral contact force, inertial forces and corresponding muscle forces. Muscle forces were applied as point loads at the position of each muscle origin or insertion on the surface of the femur.

3.4.4 Boundary conditions

The FE model employs ‘free’ boundary conditions which are directly matched to the degrees of freedom used in MSK modelling. This was done using boundary fixators at the acetabulofemoral and tibiofemoral joints. These fixators were based on a similar concept to the load applicators. The acetabulofemoral fixator links the external surface of the hip load applicator back to a node at the centre of the hip joint with softer trusses. As in MSK modelling, the hip joint does not allow for transfer of any moments. Although the node at the hip joint centre is restrained in the three translational degrees of freedom, truss connections to the surface of the joint are made by truss elements that do not resist bending moments. The tibiofemoral fixator links the external surface of both knee fixators - medial and lateral - back to the centre points of each condyle along the knee joint axis with the same trusses. The node in the medial condyle is restrained in the plane perpendicular to the knee joint axis. The node in the lateral condyle is restrained in the plane corresponding to the cross-product of the vectors defining the joint axis and the femoral x-axis (anterior-posterior) (Wu, 2002; Villette, 2016). This allows for moment transfer about the knee joint axis as in the MSK model and as applied using the force couple explained above. Truss elements used in the boundary fixators are softer than those used in the load applicators with $E=1\text{GPa}$ and $\nu=0.3$. The cross-sectional area of these trusses was 2.5mm^2 . A schematic showing the position of load applicators and boundary fixators is shown in Figure 3.5.

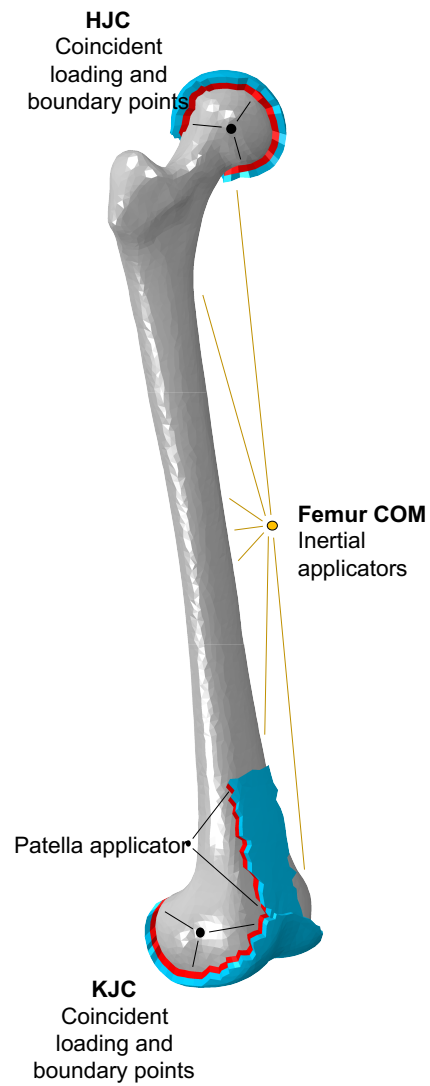


Figure 3.5: The control femur FE model, showing arrangement of load applicators and boundary fixators acting at the hip joint centre (HJC), knee joint centre (KJC) and patella-femoral joint.

3.4.5 Bone adaptation algorithm

Bone adaptation is carried out using ABAQUS (*Dassault Systemes S.A., France*) and Matlab. Successive FE models are run in the ABAQUS Standard solver, a Python (*Python Software Foundation*) script is used to extract results for import into Matlab. The driving algorithm is based on the Mechanostat principle (Frost, 2003; Phillips, 2011; Phillips *et al.*, 2015) where bone models towards a target strain. In the adaptive FE model, structural elements can either increase or decrease in size (thickness in shell elements and cross-sectional area in truss elements) based on the strain measured during each iteration of FE analysis. Strain above a certain threshold will cause element size to increase for the subsequent iteration of analysis and decrease for strain below a certain threshold.

At each iteration i , the absolute maximum strain value of the j^{th} truss and the j^{th} shell element for $\lambda = 1, \dots, n$ load cases was defined using Equations (3.1) and (3.2), respectively.

$$|\epsilon_{i,j}|_{max} = \max(|\epsilon_{11,j,\lambda}|) \quad (3.1)$$

where $\epsilon_{11,j,\lambda}$ is the axial strain in the j^{th} truss element for any load case λ .

$$|\epsilon_{i,j}|_{max} = \max(|\epsilon_{max,j,\lambda}^t|, |\epsilon_{min,j,\lambda}^t|, |\epsilon_{max,j,\lambda}^b|, |\epsilon_{min,j,\lambda}^b|) \quad (3.2)$$

where $\epsilon_{max,j,\lambda}^t$, $\epsilon_{min,j,\lambda}^t$, $\epsilon_{max,j,\lambda}^b$ and $\epsilon_{min,j,\lambda}^b$ are the maximum and minimum principal strains in the top and bottom surfaces of the j^{th} shell element, respectively, for any load case λ .

Equation (3.3) gives the target strain range (the lazy zone) as well as the strain ranges associated with bone resorption, bone apposition and the dead zone (Frost, 2003; Phillips, 2011).

$$\phi_{i,j} = \begin{cases} 1, & \text{for } 0 \leq |\epsilon_{i,j}|_{max} \leq 250\mu\epsilon & (\text{Dead zone}) \\ 1, & \text{for } 250 < |\epsilon_{i,j}|_{max} < 1000\mu\epsilon & (\text{Bone resorption}) \\ 0, & \text{for } 1000 \leq |\epsilon_{i,j}|_{max} \leq 1500\mu\epsilon & (\text{Lazy zone}) \\ 1, & \text{for } |\epsilon_{i,j}|_{max} > 1500\mu\epsilon & (\text{Bone apposition}) \end{cases} \quad (3.3)$$

For the subsequent $(i+1)^{th}$ iteration the cross-sectional area A or the j^{th} truss element and the thickness T of the j^{th} shell element were adjusted according to Equations (3.4)

and (3.5). The target strain ϵ_t was $1250\mu\epsilon$, the midpoint of the lazy zone.

$$\text{if } \phi_{i,j} = 1, A_{i+1,j} = A_{i,j} \frac{|\epsilon_{i,j}|_{max}}{\epsilon_t} \text{ else } A_{i+1,j} = A_{i,j} \quad (3.4)$$

$$\text{if } \phi_{i,j} = 1, T_{i+1,j} = \frac{T_{i,j}}{2} \left(1 + \frac{|\epsilon_{i,j}|_{max}}{\epsilon_t} \right) \text{ else } T_{i+1,j} = T_{i,j} \quad (3.5)$$

The algorithm favours adaptation in trabecular bone over cortical bone. This is important in the initial iterations to avoid oscillation of shell (cortical) element thicknesses. Truss elements experiencing a strain below $250\mu\epsilon$ were considered to be in the dead zone.

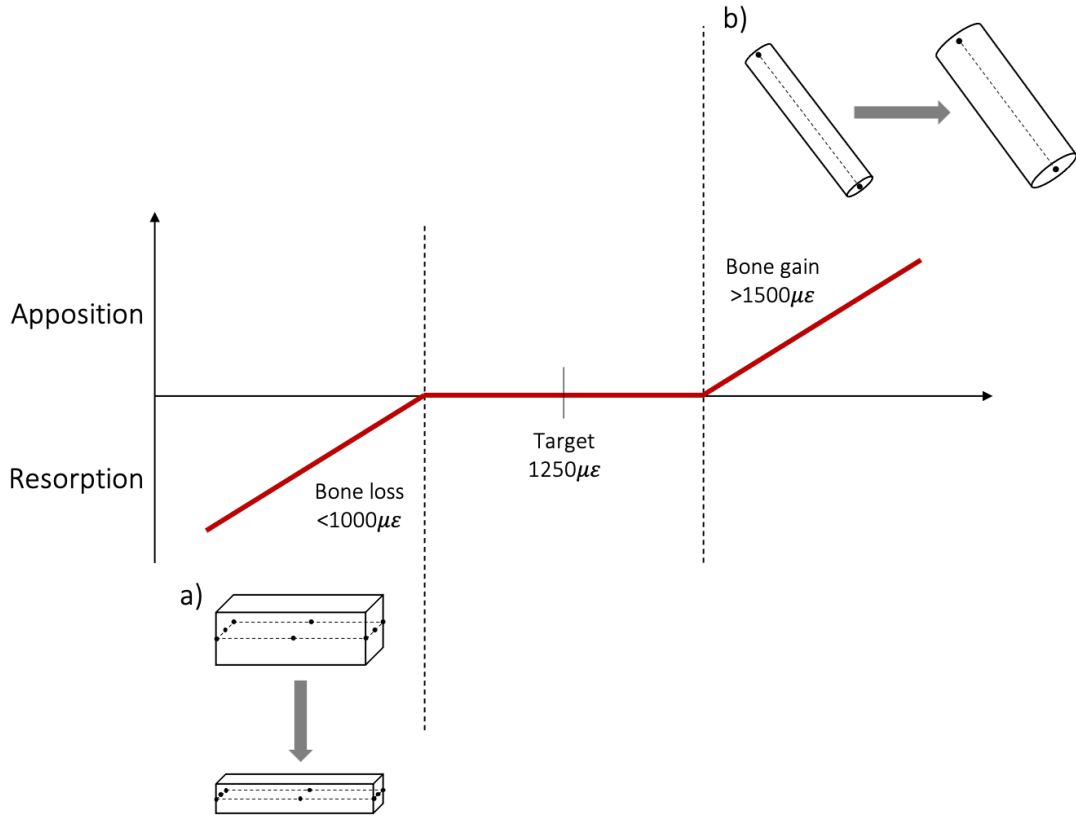


Figure 3.6: A graph showing the behaviour of elements during predictive modelling. Element thickness decreases if strain within the element falls below $1000\mu\epsilon$ (demonstrated on a shell element in (a)) and element thickness increases if strain within the element increases to above $1500\mu\epsilon$ (demonstrated on a truss element in (b)).

The cortical shell elements were linearly discretised into 256 sets according to their thickness. Sets ranged between the lower limit, 0.1mm, and the upper limit, 8mm (Stephenson & Seedhorn, 1999; Treece *et al.*, 2010). Each element was assigned to

the set corresponding to its thickness after rounding to the nearest discrete thickness value. The trabecular truss elements were linearly discretised into 255 sets according to element cross-sectional area. Sets ranged from cross-sectional areas corresponding to radii of between 0.1mm and 2mm (Nägele *et al.*, 2004). A 256th trabecular element set was also included for any element that fell into the dead zone. These elements were assigned a radius of 1 μ m allowing for effective removal of ‘dead’ elements from the model as their stiffness contribution was negligible while still maintaining numerical stability. Equally, this allowed regeneration of ‘dead’ elements wherever necessary as they could be re-assigned to one of the other 255 categories.

3.4.6 Additional FE analyses

Additional FE analyses were run on the complete adapted femur to determine how the structure worked to resist the loading placed upon it. Looking ahead to future chapters, where the control bone structure is used in simulations of compromised amputee scenarios, this step is important in providing context and comparison to a healthy control.

3.4.6.1 Isolating the effect of muscle and joint loading forces

In order to evaluate the effect of stimulation from both muscle and joint forces separately two additional models were recreated with altered loading scenarios - one modelling muscle forces only, the other hip joint reaction and knee joint reaction forces only. Different patterns of stress, strain and bone stimulation could be evaluated for each model to understand the independent contribution of muscle and joint loading to bone structure as well as the role of different structural features in resisting it.

3.5 Results

3.5.1 MSK

3.5.1.1 Ground reaction force

Experimental data captured three strides of AB gait over the course of 10 trials, Figure 3.7 shows the average of the first two steps. Ground reaction force data exhibits a typical double peak at early and late stance coinciding with the initial deceleration of the leading leg and then propulsion as the leg drives to push-off. Ground reaction force is symmetric across both legs, peaking at almost 1 times bodyweight during early and late stance.

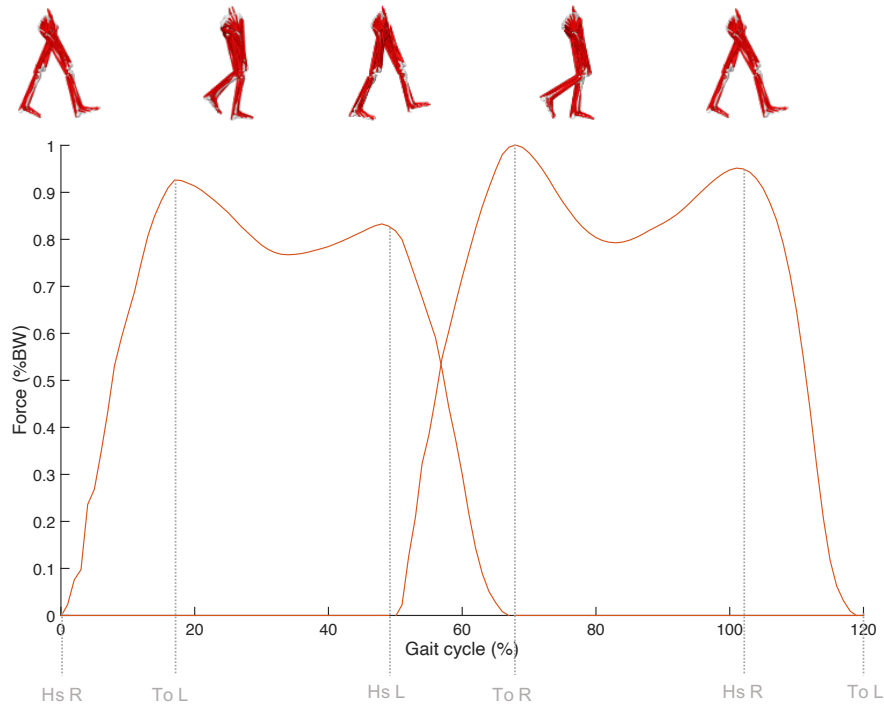


Figure 3.7: Average ground reaction force during gait in the able-bodied control subject.

3.5.1.2 Kinematics and kinetics

Inverse kinematics recorded for the AB control subject during gait are displayed in Figure 3.8 and inverse dynamics displayed in Figure 3.9. Both sets of results are in good

agreement with previously published data using the same model (Modenese *et al.*, 2013; Zaharie & Phillips, 2018).

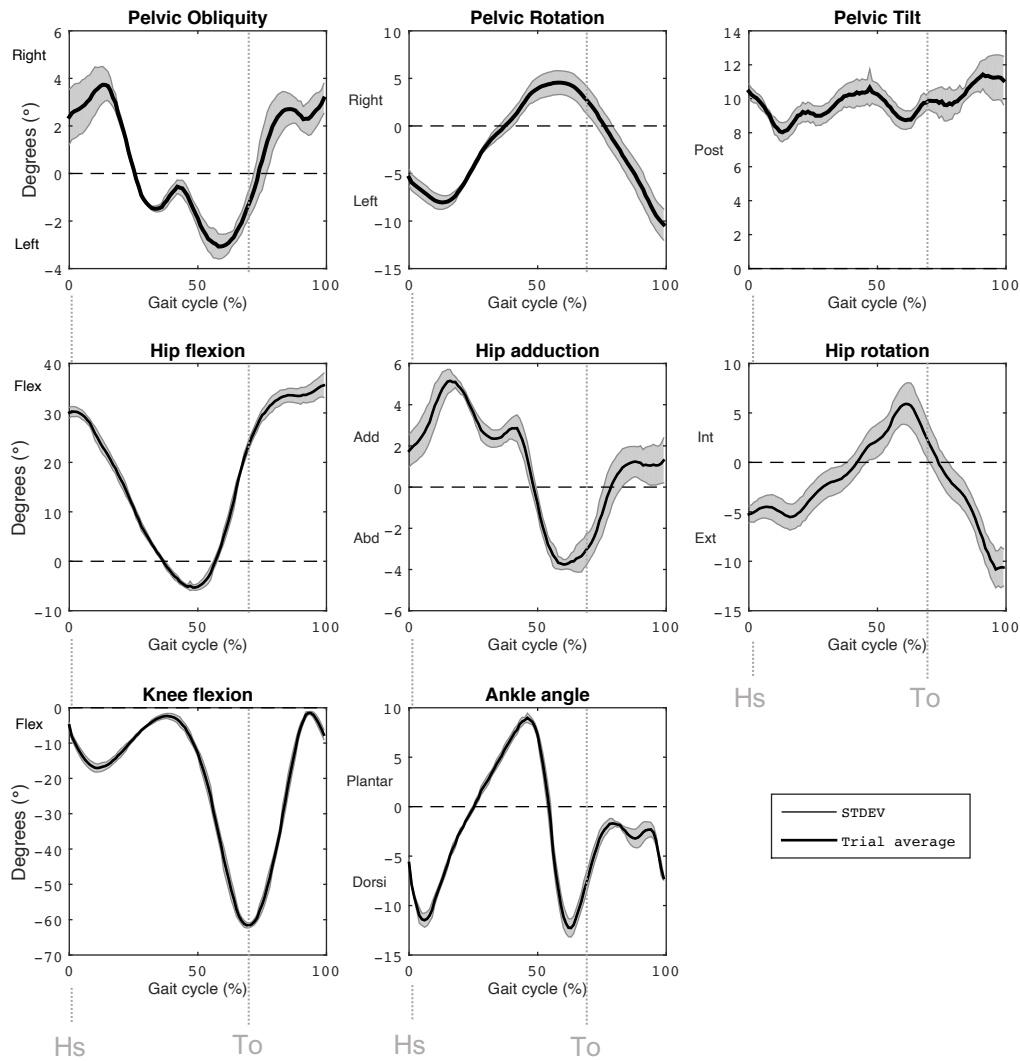


Figure 3.8: Average joint angles at the hip, knee and ankle during gait in the able-bodied control subject.

3.5.1.3 Muscle forces

Figure 3.10 presents the muscle forces predicted during gait for each major muscle group in the control subject: hip flexors, hip extensors, knee flexors, knee extensors, ankle dorsiflexors and plantarflexors.

The semimembranosus and semitendinosus contribute the most force to hip extension and knee flexion force during gait. Force production peaks at between 4-6N/kg from mid-

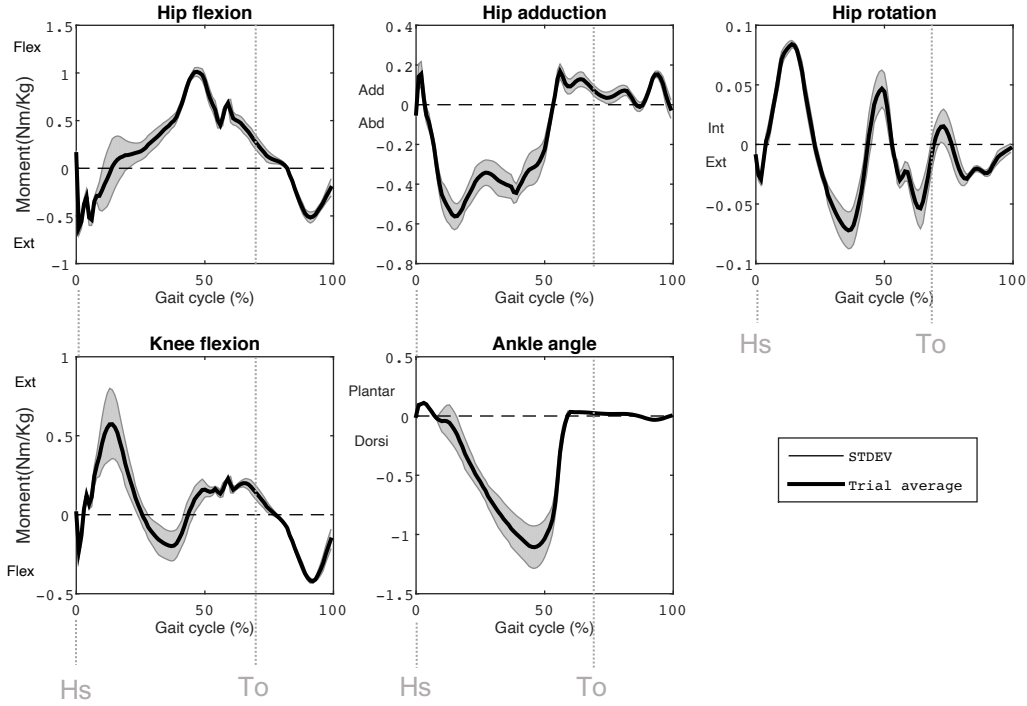


Figure 3.9: Average joint moments at the hip, knee and ankle during gait in the able-bodied control subject.

to-late swing as the muscles work to both flex the knee for clearance during mid-swing and to decelerate the leg in preparation for heel-strike. The biceps femoris, gluteus maximus and gracilis also activate but contribute relatively little towards hip extension and knee flexion compared to the semimembranosus and semitendinosus muscles.

The monoarticular hip flexors activate at pre-swing, to create forward swinging momentum at the hip, and continue to generate force until approximately mid-swing, where the majority of muscle activity ceases. The rectus femoris produces the most force of all hip flexors and knee extensors during control subject gait as it contributes to both functions. Lower activation (1.5N/kg force) seems to begin at first contact throughout the loading response before increasing to a peak force production (of around 4.5N/kg) at late stance where it contributes stability with isometric contraction at the knee and eccentric contraction at the hip. The rectus femoris maintains continued, low-level, contraction during pre and early swing like the rest of the hip flexors. The vastus muscles activate earliest of any knee extensors during the loading response to contribute to deceleration and shock-absorption at the knee. This only requires low levels of force production.

In the frontal plane, the hip abductors initiate activity in terminal swing and maintain contraction throughout the vast majority of the stance phase. The abductors work to resist

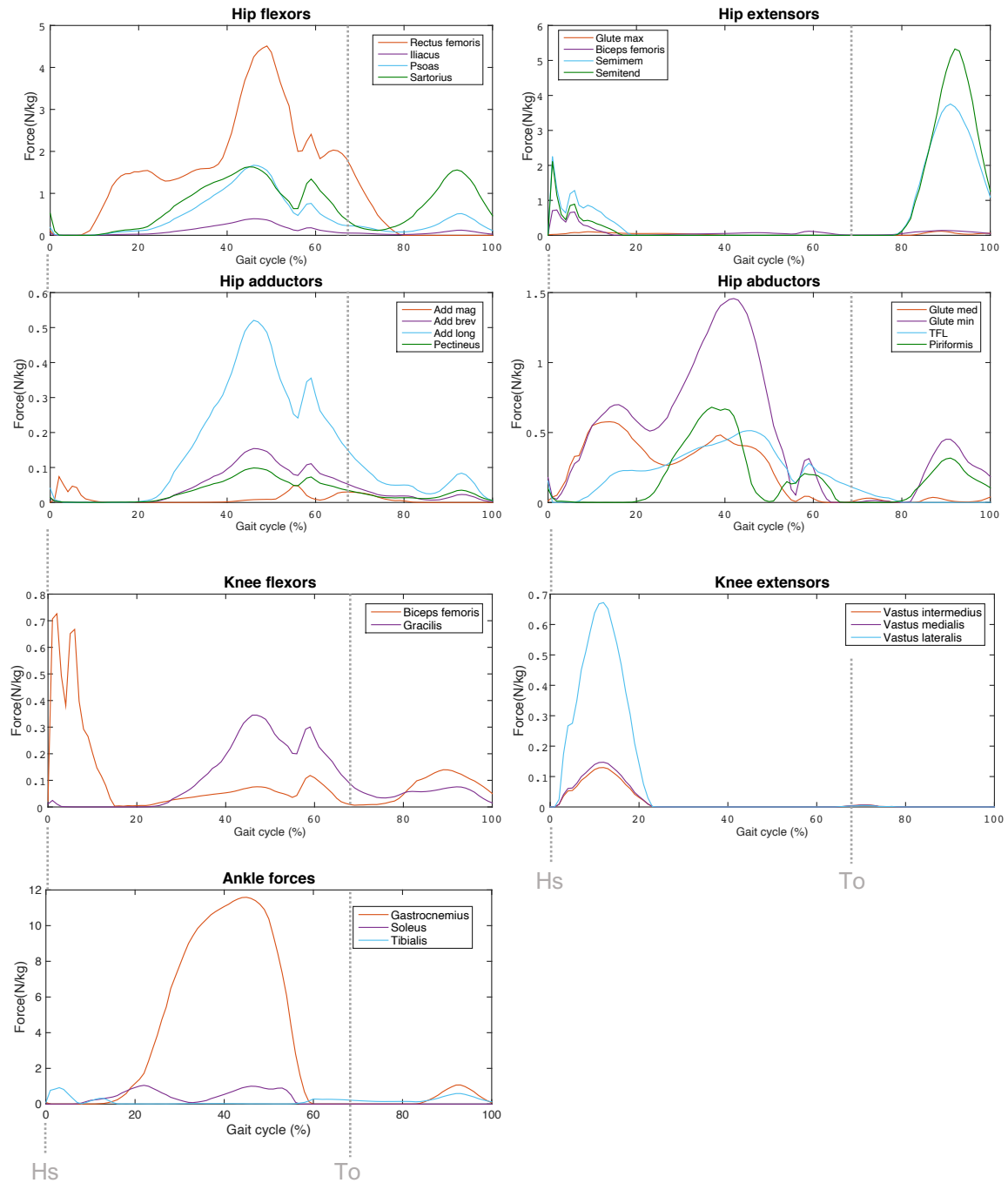


Figure 3.10: Predicted muscle forces required during gait in the able-bodied control subject.

contralateral hip-drop during single leg support phases of gait. The gluteus minimus is the major contributor in both legs, with a peak force production of 1.5N/kg occurring during push-off although the piriformis, gluteus medius and tensor fasciae latae also contribute substantial force. Hip adductor contraction begins in early-to-mid stance after toe-off of the contralateral leg. Force production continues to rise gradually to a peak force of just over 0.5N/kg at the beginning of push-off before dropping during toe-off and swing phase. The adductors of the control subject generate substantially less force during gait than the abductors.

The gastrocnemius muscles contribute significant power throughout the entirety of stance, rising steadily to a peak force of nearly 12N/kg during push-off to provide the majority of forward propulsion. The soleus muscles activate to stabilise the ankle joint during heel-strike before dropping to zero activation in midstance and rising again to contribute force to push-off. Peak soleus force generation during gait is 1N/kg. The tibialis muscles initiate low activation ($<0.5\text{N/kg}$ force) during the second half of swing to ensure slight dorsiflexion of the swinging foot and provide clearance from the ground. In general, it is important to note that the control subject demonstrates highly symmetric muscle activation between right and left legs during gait.

3.5.1.4 Total joint closing force

Figure 3.11 shows the variation of total joint closing force at the hip and knee during gait and Figure 3.12 during stair ascent/descent, sit-to-stand/stand-to-sit. During gait, total

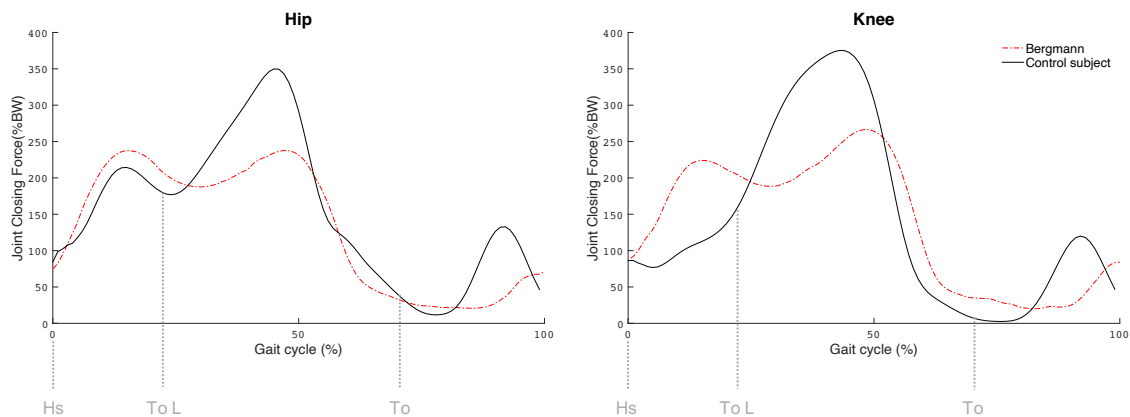


Figure 3.11: Total joint closing force experienced at the hip and knee of an able-bodied control subject during gait compared to results found by Bergmann (2016; 2014).

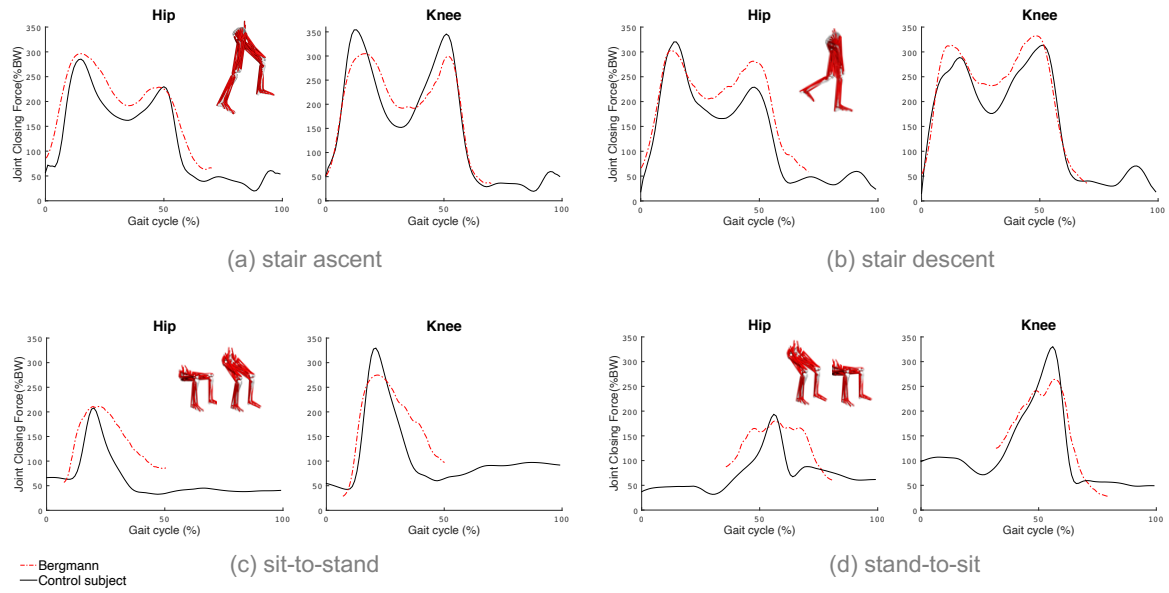


Figure 3.12: Total joint closing force experienced at the hip and knee of an able-bodied control subject during stair ascent/descent, sit-to-stand and stand-to-sit activities compared to results found by Bergmann (2016; 2014).

joint closing force is similar in both the knee and hip. Forces are highest during the stance phase with peak force occurring during push-off: a period of both high muscle activity and high joint reaction force. The total knee closing force peaks at an average of 3.76 times bodyweight while the total hip closing force at an average of 3.42 times bodyweight between both legs. Peak resultant joint closing forces are higher in gait than in any other activity, although from a loading perspective, the variety in shape and direction of force from other activities (demonstrated by Figure 4.12) will likely have a positive effect on joint loading. During gait, predicted forces represent a higher estimation than in studies by Bergmann (Bergmann *et al.*, 2016; Bergmann *et al.*, 2014) who used instrumented hip and knee implants to measure reaction force in each joint. Having said that, results are in good agreement with previously published data using the same in-silico model (Modenese *et al.*, 2013; Zaharie & Phillips, 2018). During other activities, predicted joint forces agree with those found by Bergmann more closely.

3.5.2 FE

Figure 3.14 shows a 5mm slice of the converged proximal femur adapted to a full 5 activity loading envelope. Figure 3.15 displays the same adapted femur while highlighting Ward's

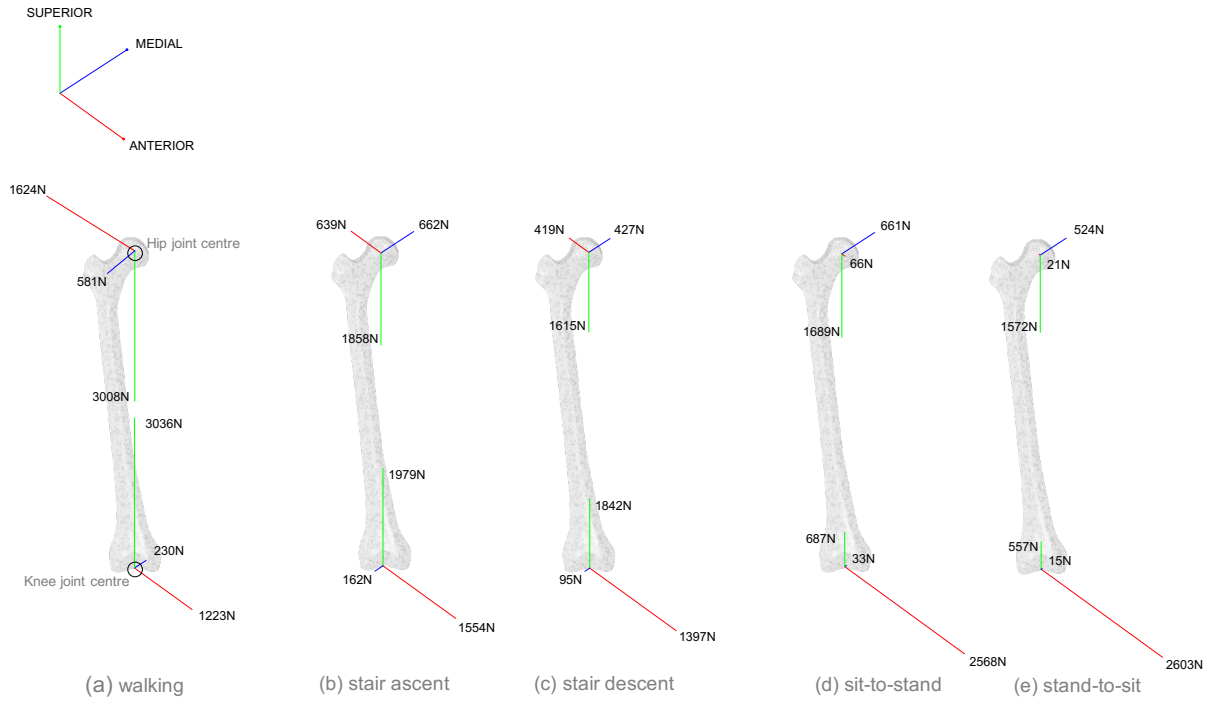


Figure 3.13: Total joint closing force experienced during select frames of walking, stair ascent/descent and sit-to-stand/stand-to-sit activities resolved into component forces to demonstrate the variation in loading direction from activity to activity.

triangle (Singh *et al.*, 2014; Kim *et al.*, 2009) and the five normal trajectories of trabecular bone identified by Singh (2014).

The converged proximal femur structure clearly demonstrates the presence of all five trabecular trajectories: principle tensile, principle compressive, secondary tensile, secondary compressive and the greater trochanter trajectory. The greater trochanter trajectory is marginally less prominent than others. Importantly, the model also correctly predicts the presence of Ward's triangle, an area of reduced BMD known to be present in the femoral neck (Kim *et al.*, 2009). The intermedullary canal is also represented, particularly by the absence of larger trabecular elements, and can be seen in transverse slices of the femoral shaft in Figure 3.14. In the distal femur, trabecular trajectories originate at the posterior aspect of each condyle (more densely populated in the lateral condyle than the medial), as well as from the surface of the patella-femoral joint. Smaller truss elements ($r \leq 0.1\text{mm}$) are also clustered around the hip and knee joint surfaces transferring load perpendicular to the thinner cortex in each joint.

The converged structures demonstrate cortical thickening in the inferior femoral neck and travelling down further into the medial and lateral aspects of the shaft. These areas of increased cortical thickness are also sparsely populated by thick trabecular elements

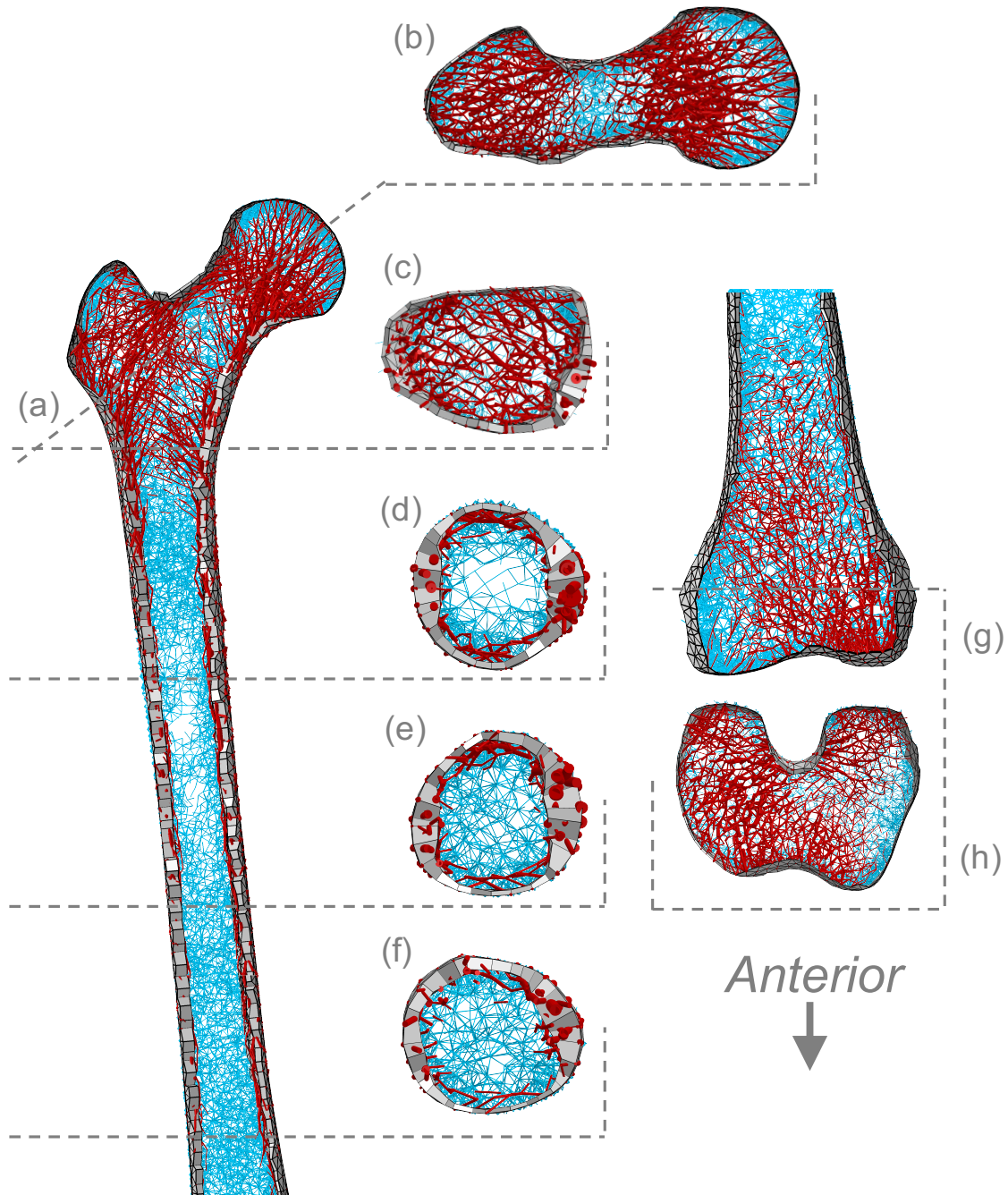


Figure 3.14: Selected 5mm thick slices of the converged control femur created when subjected to a full loading regime of six daily living activities. Cortical shell elements are shown in grey. Trabecular truss elements with a radius of 0.1 mm are shown in blue. Trabecular truss elements with a radius $>0.1\text{mm}$ are shown in red. Truss elements in the dead zone (with a radius of 1 μm) have been omitted for clarity.

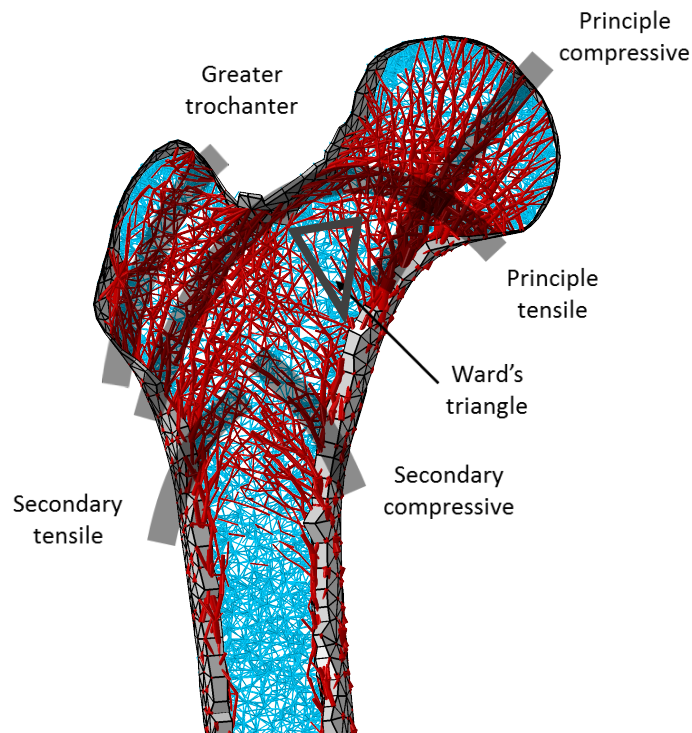


Figure 3.15: Frontal slice of the adapted proximal femur demonstrating the existence of the five normal trabecular trajectories in the predicted bone structure. Cortical shell elements are shown in grey. Trabecular truss elements with a radius of 0.1 mm are shown in blue. Trabecular truss elements with a radius $>0.1\text{mm}$ are shown in red. Truss elements in the dead zone (with a radius of $1\text{ }\mu\text{m}$) have been omitted for clarity.

running parallel to the length of the shaft while anterior-posterior aspects of the shaft contain thinner trabecular elements running perpendicularly. Cortical element thickness in the distal femur at the knee joint is consistently low. In areas of direct compression the load seems to be resisted by trabecular elements fanning - running perpendicular to a thinner cortex.

Figure 5.16 shows the cortical and trabecular structure of the femur model converged to a loading scenario of walking only. This is particularly important for comparisons in Chapter 5. Some key differences can be noted compared to the model that has been adapted to a full loading scenario. In the mediolateral direction, the femoral cortex is thicker. Trabecular structure in the distal femur is significantly sparser with far fewer thick trajectories shown in slices (g) and (h). Importantly, trabecular structure in the proximal femur is quite closely matched to that adapted from a full loading scenario. The main compressive and tensile trajectories are comparable in size and thickness, although a widening of Ward's triangle can be noted.

3.5.2.1 Effect of muscle versus joint loading forces

Figure 3.17 displays the independent effect of muscle and joint reaction forces to bone loading in the adapted control femur. Both scenarios contribute significantly to loading of trabecular and cortical bone. In general, the contribution of each seem to compliment each other effectively. In terms of the internal trabecular structure, muscle loading forces the greater trochanter trajectory, principle compressive trajectory, secondary compressive trajectory and large areas of the medial epicondyle compartment into significant tensile loading. Joint forces then seem to promote loading in all other areas: the principle tensile trajectory, the secondary tensile trajectory and the trabecular structure within the lateral epicondyle. In cortical bone, a similar complimentary pattern can be observed but both tensile and compressive loading is present.

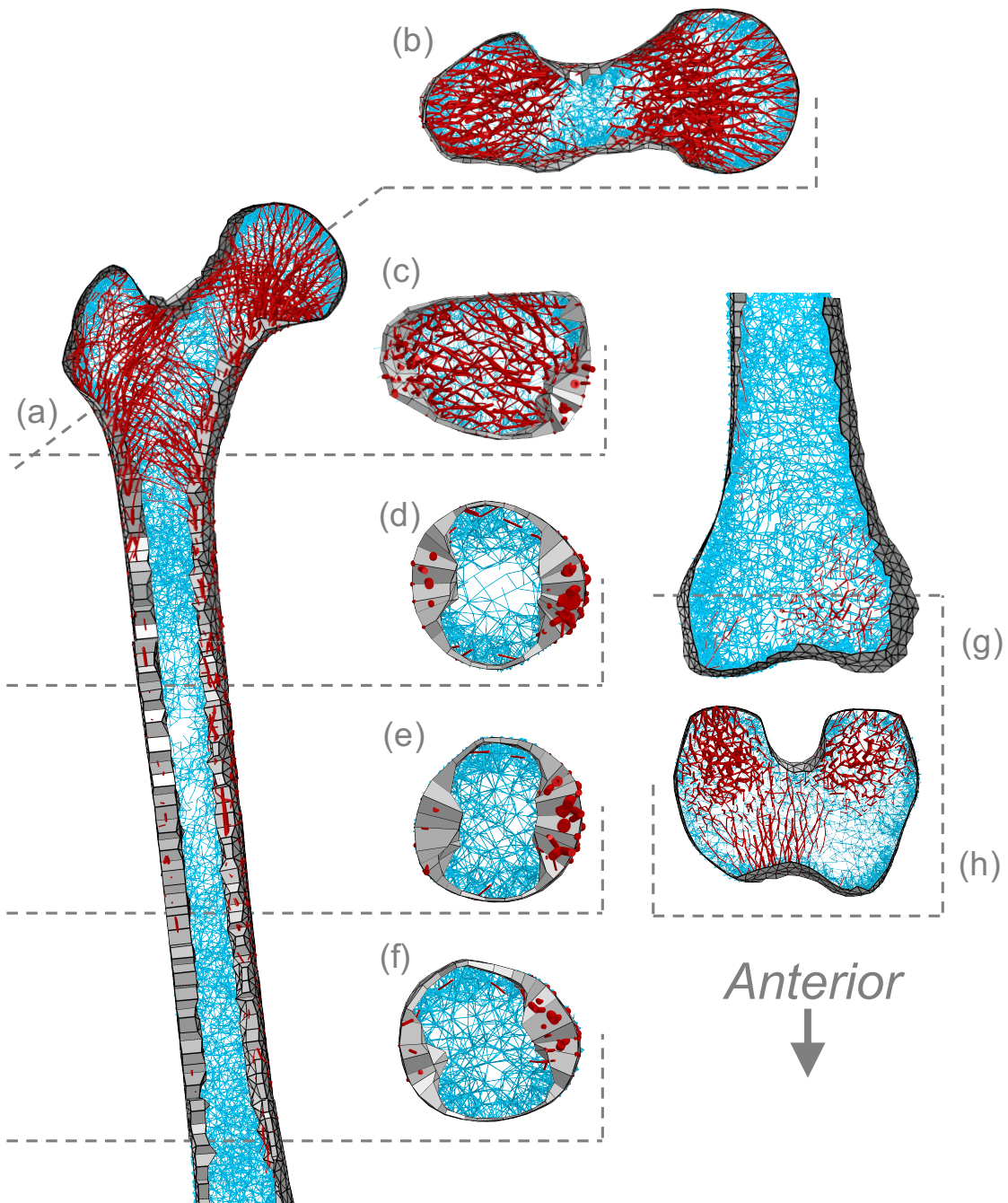


Figure 3.16: Selected 5mm thick slices of the converged control femur created when subjected to a loading regime of walking only. Cortical shell elements are shown in grey. Trabecular truss elements with a radius of 0.1 mm are shown in blue. Trabecular truss elements with a radius $>0.1\text{mm}$ are shown in red. Truss elements in the dead zone (with a radius of 1 μm) have been omitted for clarity.

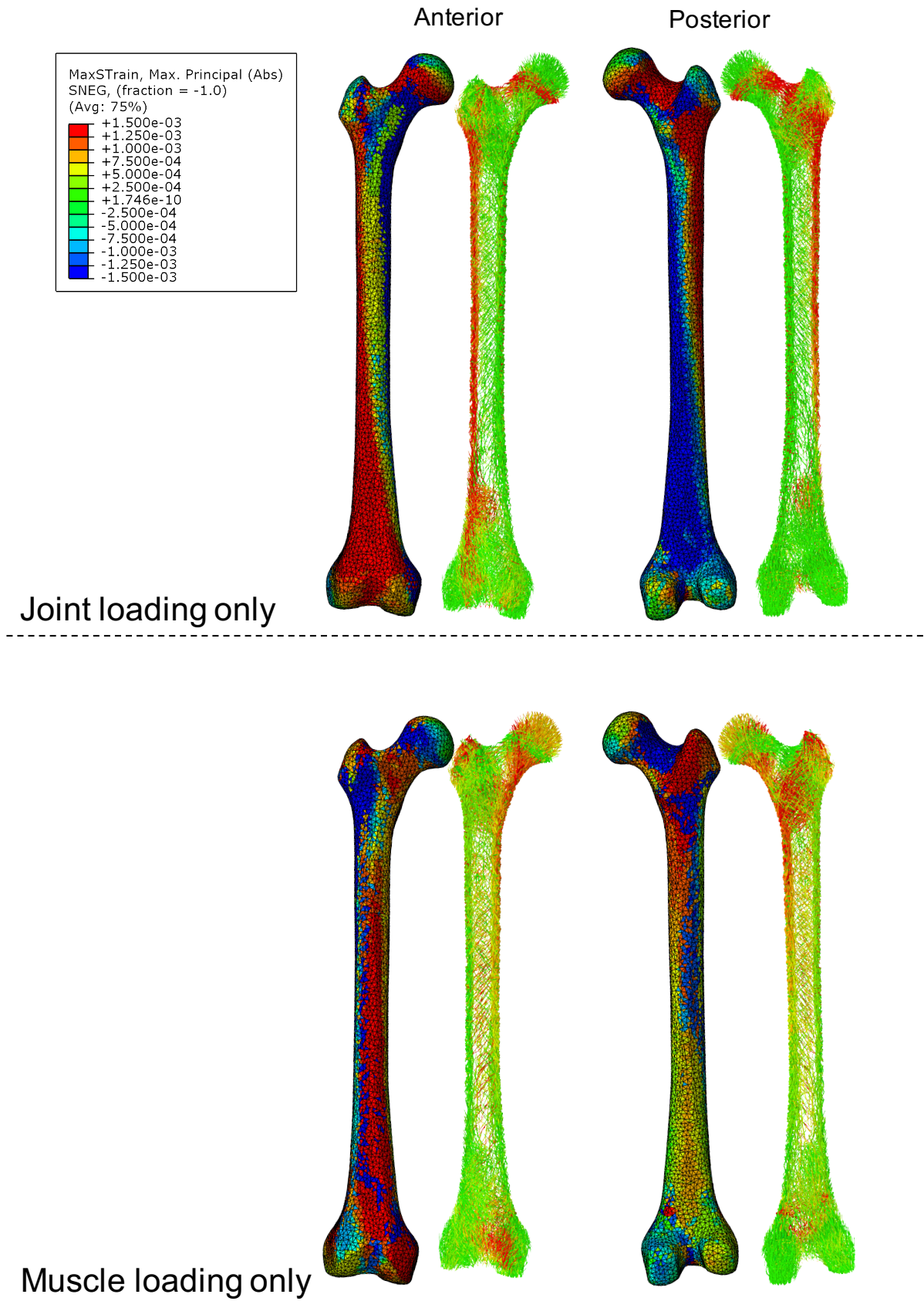


Figure 3.17: Plotting the maximum principle strain experienced at the femur of the control subject in separate loading scenarios, modelling the independent effect of muscle forces and joint reaction forces on the femur structure. Cortical and trabecular structure is shown from anterior and posterior views.

3.6 Discussion

Results of MSK simulation with the AB control subject are in good agreement with larger scale population studies in terms of kinematics and kinetics of gait (Riley *et al.*, 2007; Winiarski *et al.*, 2019; Bovi *et al.*, 2011; Slood & van der Krogt, 2018). More importantly, results are in very good agreement with previously published data using the LLLM (Modenese *et al.*, 2013; Zaharie & Phillips, 2018). The model demonstrates the large burden of power placed on the ankle joint during gait with the plantarflexors contributing considerably more force than any other muscle group during mid-stance to toe-off. This is a finding consistent with literature (Lee *et al.*, 2019; Slood & van der Krogt, 2018; DeLisa, 1998; Liu *et al.*, 2008). In general, the muscles of the calf carry the largest burden in centre-of-mass acceleration during gait (Liu *et al.*, 2008). Predicted hip and knee closing forces follow a very similar pattern to each other in terms of shape and magnitude during gait. The second peak, in each, is noticeably higher than in studies by Bergmann (Bergmann *et al.*, 2014; Bergmann *et al.*, 2016), however. This observation is also consistent with other studies using the same MSK model (Modenese *et al.*, 2013; Horsman *et al.*, 2007; Zaharie & Phillips, 2018). Zaharie (2018) identifies this as a consistent feature of joint force prediction using static optimisation; pointing to the similar relationship between in-vivo results from Bergmann (2016) and in-silico results from Heller (2001) despite using an identical dataset. Figures 3.12 and 4.12 demonstrate the loading profiles presented by stair ascent/descent and sit-to-stand/stand-to-sit activities. Although gait contributes the highest total joint force by some margin, the variety in directional loading from other activities is likely to effect bone stimulation, loading and subsequent structure significantly.

The predicted femur architecture achieved in this study is in close agreement with results found by Phillips (2015) and Villette (2019). In general, thickening of the cortical elements tends to take place in the areas required to resist bending and torsion such as the femoral neck and shaft (Hart *et al.*, 2017; Cole & van der Meulen, 2010). The surfaces of the hip and knee joints experience direct compressive load. This is resisted by fanning of trabecular elements in order to distribute the forces more evenly along the joint surface. The structure of the converged control proximal femur obtained in this study is compared to μ CT slices from Villette (2016) in Figure 3.18. Trabecular and cortical patterns in the proximal femur match those seen on μ CT scans quite closely but

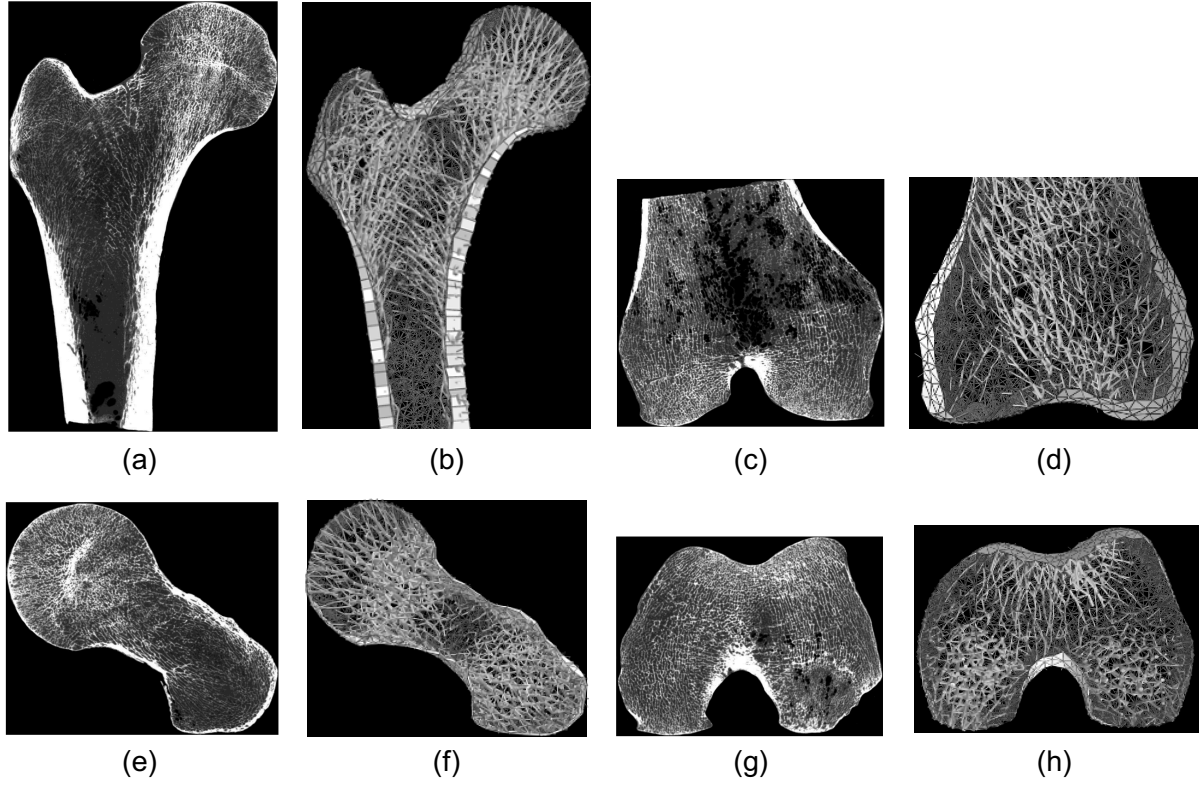


Figure 3.18: A comparison of slices from the converged control femur model created in this study to those of a real femur obtained by μ CT scan. μ CT slices were obtained from Villette (2016).

the predicted structure in the distal femur is not as closely matched. Although some key trabecular trajectories can be found (running antero-posteriorly from each condyle), they are less clearly distinguished from the noise of other differently aligned trabeculae. This is most clearly visible in the frontal slice. Additionally, the converged FE model predicts a substantially thinner cortex around either condyle while in the μ CT scans, the intercondylar notch contains an area of pronounced thickening. The trochlear groove of the in silico predicted femur is also more densely populated than in the real femur. This could be due to general shape differences that stem from using geometry derived from a Sawbones femur rather than a real one. Most of the curves on the distal aspects of the Sawbones geometry are less pronounced than the femur in the μ CT scans. This naturally lends itself to less-dramatic changes in structure as stress concentrations are likely to be lower. The absence of ligaments in both MSK and FE models could also play a role in altered loading and, subsequently, altered bone structure. This is expected to have a particularly large effect in the distal femur where the absence of the medial and lateral collateral ligaments mean load transfer from the patellar applicator is fully concentrated through the anterior surface of the distal femur. Inclusion of these ligaments

would likely see patellar force more evenly and physiologically distributed and subsequent bone structure more closely matched to CT scans. It should be noted, however, that although ligaments are not included at the knee joint, kinematic constraints are present to link patella movement to knee flexion/extension.

It is important to note that Phillips (2015), and others working in the Structural Biomechanics Group, have carried out a multitude of sensitivity studies and further analyses in developing the modelling framework. Similar predictions were carried out for the tibia, fibula, pelvis and vertebrae (Phillips *et al.*, 2015; Zaharie & Phillips, 2018; Villette, 2016; Favier, 2019). Each time the predicted structure compared favourably to radiographical scans and previous literature. Additionally, qualitative analysis carried out by Villette (2016) of the proximal femur demonstrates agreement with a variety of findings by Singh (2014), Kim (2009), Garden (1961) and Takechi (1977). Villette (2019) used the same modelling framework presented here to create a femur model that was later used in fracture prediction studies (Villette & Phillips, 2018). The converged model was found to appropriately predict the failure response of the femur in both longitudinal compression and sideways “falling” scenarios using a strain-driven fracture algorithm.

Figure 3.19 demonstrates the effect of a loading scenario complete with all six activities. Cortical and trabecular elements are colour mapped according to which activity is the most influential in determining its geometry. In general, walking is the most influential activity in terms of bone stimulation in the femur. This is to be expected given that it elicits the strongest absolute loading response in terms of resultant joint closing force of all activities measured (Figure 3.12). The majority of the proximal femur structure is heavily influenced by walking, as seen in Figures 3.19 and 5.16. It plays the key role in formation of both tensile trajectories (principle and secondary) and the primary compressive trajectory in the proximal femur. As a result, adaptation to walking alone creates a relatively well populated trabecular structure in the proximal femur. Walking, stair ascent and descent activities all contribute significantly to formation of the secondary compressive group. While Figure 3.19 suggests the greater trochanter trajectory is mainly stimulated by loading from stair descent, ascent and stand-to-sit, its prominence in Figure 5.16 shows that walking still contributes significantly to its structure.

Stair ascent and sit-to-stand activities become more influential on cortical geometry further down the shaft. This is highlighted in Figure 5.16 where distal trabecular structure is sparse compared to in the femur adapted with a full loading scenario. Sit-to-stand and

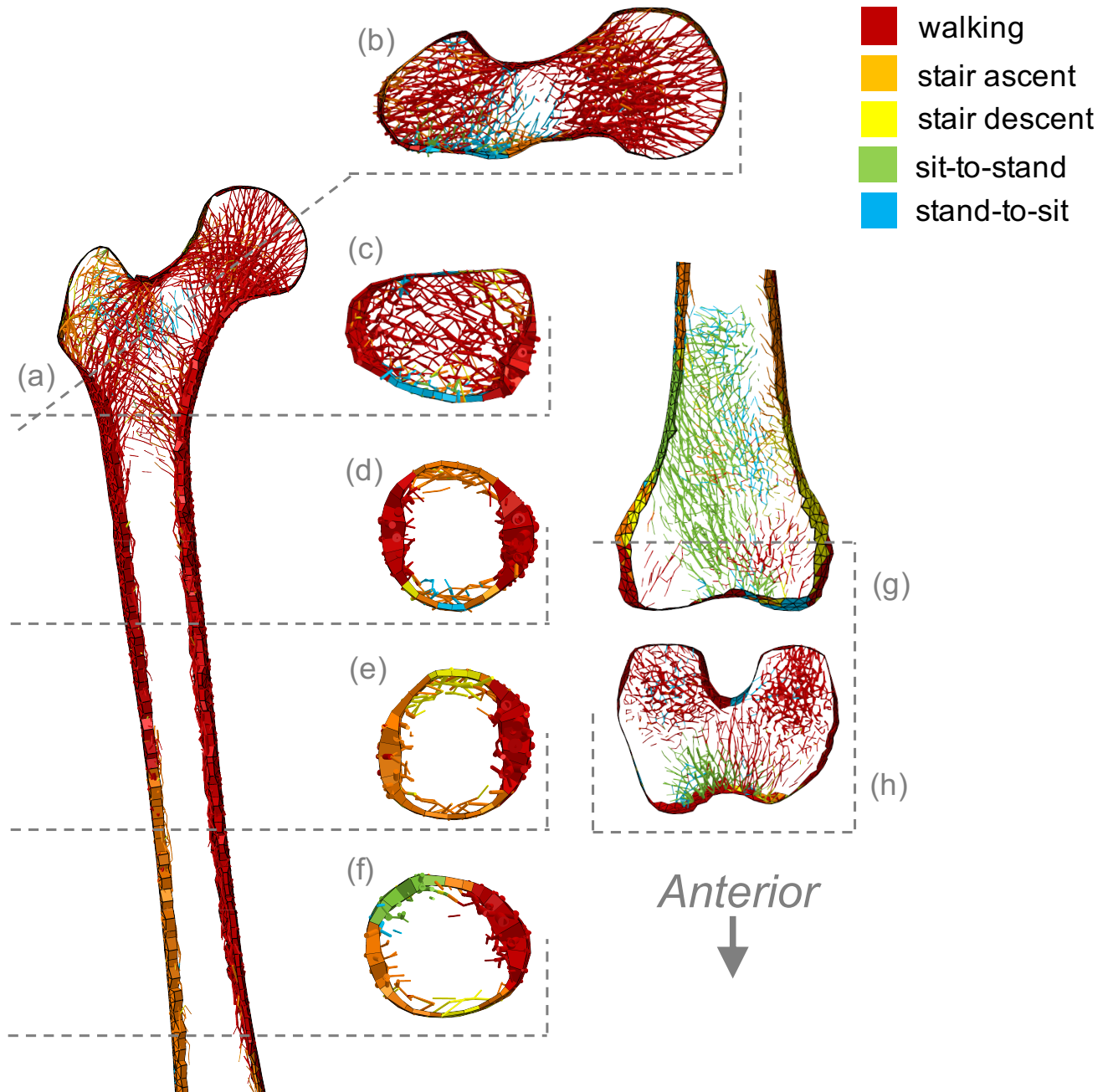


Figure 3.19: Shows adapted and activity-mapped version of the predicted control femur. Trabecular truss elements with a radius $>0.1\text{mm}$ are shown and colour-mapped according to which activity is most influential in determining geometry. Cortical shell elements are shown in grey.

stand-to-sit activities, in particular, provide the knee joint with more antero-posterior loading than walking. In turn, the addition of these activities seem to encourage a less pronounced bias towards mediolateral cortical thickness and a fuller distal trabecular structure. The stand-to-sit activity also has the most significant effect on smaller trabeculae within the femoral neck and Ward's triangle. Consequently, its absence in the walking only model can be noted by a slight widening of Ward's triangle. Looking ahead at future chapters modelling lower-limb amputation, this will be an important consideration as the AK amputee model will be driven with a single load-case: walking. This was, in one part, due to a lack of necessary equipment in the motion-capture labs and, in other part, due to the physical limitations of the amputee subject.

MSK results indicate that the actions of sit-to-stand, stand-to-sit and stair ascent elicit higher force generation in the vastus muscles and the gluteus maximus than during normal walking. Stair descent results show similarly increased vastus muscle force generation without the added gluteus maximus recruitment. In terms of total joint closing force, all four other activities also result in increased antero-posterior loading at the knee compared to during gait (seen in Figure 4.12). The variety in directional loading from other activities seems to have the most significant effect on bone loading, stimulation and subsequent structure in the distal femur. This is important when considering which loading profiles might be absent in amputees. Overall, Figures 3.19 and 5.16 suggest that while gait is a highly influential activity in terms of loading and bone structure at the proximal femur, the absence of other activities has a significant effect on anteroposterior cortical thickness and trabecular structure in the distal femur. Interestingly, while predictions for other activities see increased recruitment of specific muscles, the total muscle recruitment is similar through all 4 activities (shown in Figure 3.20). This was calculated by adding the peak force generated by every muscle throughout each activity individually and suggests that loading magnitude may not be the most important contributor to bone structure and healthy bone remodelling; loading variety is also pivotal.

3.6.1 Limitations

In a few ways this framework represents a simplification of physiological structures, loading and processes. One example can be found in structural modelling of trabecular bone using truss elements rather than beam (or a combination of beam and shell elements). The latter

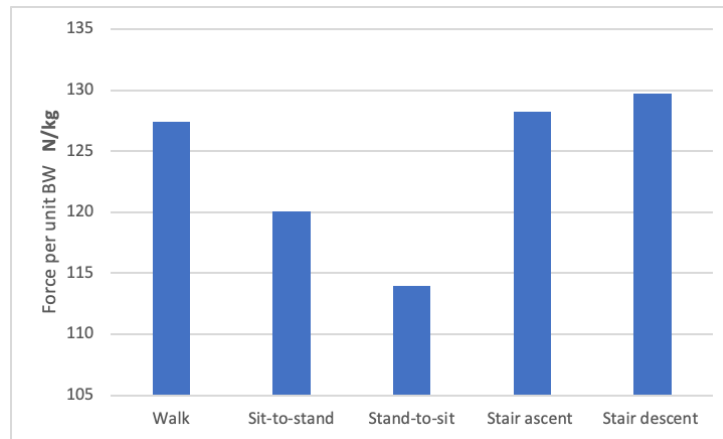


Figure 3.20: Cumulative peak muscle force generated during each activity per unit bodyweight.

would, likely, be more closely representative of trabecular bone’s natural ‘sponge-like’ lattice structure. Truss elements are idealised elements that only support modelling of axial loading, as such they do not resist bending moments or shear forces (Smith, 2009). Beam and shell elements do. However, a study by (Villette, 2016) found deformation in geometrically identical truss and beam models differed by just 1.4% at the expense of significant computational power and time. The beam model took between 3-5 times longer to complete equivalent static loading simulations. Moreover, under physiological loading, an optimised structure will naturally minimise bending moments and shear loading in lieu of axial compression and tension, as the former are less efficiently resisted through the cross section of structural elements (Villette, 2016).

The application of bone remodelling through an iterative FE model and bone adaptation algorithm is also highly simplified. Strain values corresponding to bone apposition, resorption and the target strain range differ considerably throughout literature (Frost, 2003; Sugiyama *et al.*, 2012; Jang *et al.*, 2009). It is also possible that prescribed ranges should differ depending on the location and type of bone being modelled (Villette, 2016). In reality, a multitude of various mechanical and biological markers drive bone changes in the human musculoskeletal system. In-silico simulation of bone remodelling due to microcracking, osteocyte signalling, osteoblastic and osteoclastic activity increases or decreases due to age, hormone and environmental loading changes would require the application of significantly more challenging concepts. Significant research would be required in quantifying the effect of each and their respective response to loading. Mechanistic approaches have been taken to adaptive FE in the past, such as using fluid induced shear stress as a remodelling driver (Riddle & Donahue, 2009; Adachi *et al.*,

2010; Pereira & Sheffeline, 2014), however, phenomenological approaches, as used in this study, are still more common and provide large advantages in terms of computational efficiency while still capturing the, generally accepted, “form follows function” nature of bone structure and remodelling.

Some of these limitations are specific to the modelling framework and how it was employed while others are applicable to the structural FE approach in general. However, this framework can be a powerful tool in future novel adaptive and predictive modelling applications. The remaining chapters present one such application: investigation of joint loading in lower-limb amputees and the effect of weight-bearing through a prosthetic socket.

Chapter 4

Unilateral below-knee subject

4.1 Introduction

Chapter 4 investigates femur and hip-joint loading in a unilateral below-knee amputee subject using patient-specific musculoskeletal (MSK) and finite element (FE) models informed by experimental motion data. The chapter outlines the development of each model before explaining how they were used to understand loading at the femur level and its potential effect on bone structure (or bone loss) in below-knee (BK) amputees. Predictive modelling of bone adaptation post-amputation is introduced. It is used to determine the direct effect of altered stimulus on the internal architecture of the amputated femur; further examining the clinical findings in Chapter 2 with in-silico modelling. At each stage, BK results are compared directly to those in Chapter 3 from the body-matched control subject.

Results from Chapter 2 suggest bone loss in the hip of unilateral BK amputees is significant, although, less prominent than in other amputee populations. The aim was to determine what effect altered loading played in this bone loss and, in turn to shed light on potential treatment strategies or future research directions.

4.2 Background

4.2.1 Characteristics of below-knee amputee gait

Unilateral below-knee amputee gait is frequently characterised by asymmetry between the amputated and intact limbs (Hurley *et al.*, 1990; Huang & Ferris, 2012; Nolan *et al.*, 2003; Bateni & Olney, 2002; Sanderson & Martin, 1996; Eshragi *et al.*, 2014; Jarvis *et al.*, 2020; Silverman *et al.*, 2008). The loss of the lower leg and anatomical ankle joint has a significant effect on spatiotemporal characteristics, kinematics and kinetics of gait. Gait progression is hindered greatly given that the plantarflexors are said to account for over 80% of mechanical power generated in able-bodied (AB) individuals (Eshragi *et al.*, 2014). Unilateral BK amputees spend more stance time on the sound limb during gait. Step length of the amputated leg is often significantly longer, perhaps logical when more time is spent in swing phase. The sound limb provides more stability during stance due to controlled plantar and dorsiflexion allowed at the anatomical ankle throughout heel-strike and midstance. Range of motion in the amputated ankle varies depending on prosthesis, but in all models it is found to be lower than on the sound limb. Very few prosthetic ankles can provide sufficient plantarflexion for stability during heel-strike. Similarly, few can offer power to plantarflexion once the prosthetic limb rises to replicate push-off. In general, almost all characteristic differences in kinematics and kinetics of amputee gait compared to AB gait can be attributed to compensation of the intact limb for the stability and power generation lost at the amputated limb.

4.2.1.1 Kinematics

Ankle range of motion is significantly higher in the sound limb than the amputated side. Dorsiflexion during swing phase helps to ensure clearance of the moving leg while greater plantarflexion during pushoff is required to generate compensatory power and aid progression in the intact leg. Ankle range of motion is also significantly higher in the intact leg of unilateral amputees than in AB control subjects (Eshragi *et al.*, 2014). At the hip, Bateni (2002), Ehsragi (2014), Ferreira (2014) report higher sagittal range of motion in both legs of unilateral amputees compared to controls, although Jarvis (2020) found no significant difference. Comparing leg to leg, Bateni (2002) and Eshragi (2014) both found

higher peak sagittal plane hip kinematics in the intact than amputated leg, once again, attributing it to the increased burden of progression. At the knee, unilateral amputees exhibit prominent knee flexion during the loading response of both legs but Eshragi (2014) and Sanderson (1996) report significantly higher flexion angle in the intact limb than the amputated. Over the course of the remaining gait cycle knee range of motion is higher on the prosthetic side; increased knee flexion during swing phase ensures clearance of the prosthetic foot over the ground (Eshragi *et al.*, 2014). Many different sources report a trend of increased anterior tilt of the pelvis in unilateral BK amputees. This may be linked to the fact that amputees walk with a slight forward bend of the torso to gain stability by bringing the centre of mass over the leading foot (Bateni & Olney, 2002). In terms of frontal plane mechanics, little direct comparison was found between unilateral amputees and control subjects in the literature.

4.2.1.2 Kinetics

Sagittal plane moments at the hip of the amputated limb vary greatly between studies. In some studies the hip of the sound limb experiences higher extensor moments during stance and higher flexor moments during swing than control counterparts (Bateni & Olney, 2002; Jarvis *et al.*, 2020). But this is not always the case (Sanderson & Martin, 1996). Both are thought to contribute to forward propulsion of the centre of mass. The support moment, is a term used in many studies to describe the sum of the hip extensor moment, knee extensor moment and ankle plantarflexor moment. Bateni (2002) suggest that the support moment in early stance comes entirely from the hip and knee during early stance of the intact limb.

At the knee of the amputated leg, unilateral BK amputees experience reduced knee extensor and flexor moments during early stance (Bateni & Olney, 2002; Winter & Sienko, 1988; Jarvis *et al.*, 2020). Bateni (2002) and Winter (1988) suggest the moment is near-zero in some subjects. Beyaert (2008) and Jarvis (2020) hypothesise that this could be a protective measure to reduce stress at the socket-residuum interface. The intact side, however, sees increased knee extensor moments compared to controls, attributed to the more pronounced flexion loading response of the knee. A higher flexion angle results in higher extension moment to maintain centre of mass height.

The intact ankle carries a significant burden of forward propulsion during unilateral amputee gait. Mid to late stance on the anatomical ankle sees increased plantarflexor moment compared to both the amputated leg and AB control legs. Previous studies all highlight a “longer and larger” (Bateni & Olney, 2002) dorsiflexion moment occurring during early stance of the amputated leg due to the reduced plantarflexion capabilities in the majority of prosthetic feet/ankles.

4.2.2 Musculoskeletal modelling of amputation

Musculoskeletal modelling is a powerful tool used to study the internal forces in a given musculoskeletal system. Joint moments, joint reaction forces and muscle forces can be determined for prescribed movements or full activities based on the theory of multibody dynamics. It has been used to study and understand the forces behind human movement, such as gait, for decades. More recently the modelling concepts have been applied to compromised scenarios to investigate the effect of injury, surgery or disability on movement and subsequent movement dysfunctions.

In creating or using any MSK model, a balance must be struck when weighing up model accuracy versus model complexity with careful consideration given to the specific use and outputs of the model. When modelling lower-limb amputation areas of particular interest include: post-amputation muscle origins and insertions, body segment parameters, modelling of the prosthetic socket interface and modelling of the prosthetic joints. To evaluate the previous approaches taken the following section focuses on three recent MSK studies by Fang (2007), Henson (2020) and LePre (2017) among a few others. Fang (2007) created a 2 degrees of freedom BK model with just 7 lower body muscles to investigate the effect of varying prosthetic alignment in the sagittal plane. The study demonstrates the efficacy of a highly simplified MSK model in returning useful muscle force predictions. Henson (2020) completed a small population study on six bilateral amputees, creating patient-specific MSK models to analyse gait kinematics, kinetics and muscle loading in each. LePre (2017) sought, specifically, to guide future work in modelling lower-limb amputation by presenting, and analysing, different approaches to residuum and socket dynamics and their subsequent effect on kinematic marker error.

Muscle origin and insertion points for any MSK model are most often acquired by MRI scan. 3D coordinates are marked out and transferred from segmented or digitised

muscle and bone geometries. In the case of patient-specific amputee models, such as those created in Henson (2020) and Bae (2007), scans of the subject are used to directly match post-operative muscle insertions (and pathways) to the positions located in MRI. Many open-sourced, non-amputee cadaveric datasets are also available and, in many studies, have been used to build more simplified MSK models (Kersting *et al.*, 2010; Fang *et al.*, 2007; LaPrè *et al.*, 2017). Adjustments to incorporate amputation are then made under the assumption that existing muscles are sutured to the distal residuum via a myodesis (Kersting *et al.*, 2010; Fang *et al.*, 2007; LaPrè *et al.*, 2017) and muscle function is relatively unchanged. Fang (2007) modified a cadaveric dataset by Hoy (1990), LePre (2017) modified a pre-existing generic model, developed by the creators of MSK software platform OpenSim, called Gait2354 (Delp *et al.*, 1990) and Kersting (2010) adapted the Twente Lower Extremity Model (Carbone *et al.*, 2015). These approximations, however, are not patient specific. Generic modelling can be a useful and efficient tool for modelling healthy individuals, however, the unpredictable nature of traumatic amputation leaves significant variation in residual limb musculature and structure between amputees. This is a major limiting factor in utilising generic models for amputee subjects.

Body segment parameters such as weight, centre of mass and inertial properties must also be adjusted for amputees. There are many of examples of studies using generic body segment parameters from pre-existing datasets or from anthropometric reference manuals such as those developed by Lohman (1988). These techniques, however, are less suitable for amputee subjects as accounting for the prosthesis and socket is difficult. In some studies, changes made to the amputated limb are not specified (Fang *et al.*, 2007; Kersting *et al.*, 2010). 3D scanning can also be used: anatomical landmarks can be defined, larger bodies split into smaller segments and inertial parameters calculated after assigning respective material properties in CAD software. This was performed by Henson (2020) on the amputee subject’s residuum and then the socket properties approximated and combined using the Huygens-Steiner parallel axis theorem (Haas, 1925; Henson *et al.*, 2020).

The prosthetic socket-residuum interface is greatly simplified in the most previous models of lower-limb amputation. In some the joint is ignored entirely, in most an additional joint is added but no additional degrees of freedom are permitted. This is in large part due to the potential for added complexity when including multiple degrees of freedom. Also, practical work to quantify movement at this interface in-vivo is

young and limited. Having said that, LePre (2017) investigated the effect of releasing different degrees of freedom at the socket-residuum interface on kinematic marker error. They identified that a 4 degree of freedom socket-residuum interface provides the best compromise of reduced marker error, complexity of model and realistic residuum-socket kinematics.

The prosthetic joints themselves can be spring loaded, fully locked, active, and passive, all with varying ranges of motion. In patient specific studies, MSK modelling of the prosthetic ankle joints (in the case of BK amputees) and prosthetic knee and ankle joints (in the case of above-knee (AK) amputees) is dependent on the prosthesis itself. Generic studies, such as those by Fang (2007) represent the knee joint as a single degree of freedom hinge joint and the ankle as passive – either fully locked or locked to a limited range of motion. Bae (2007) replicated a much more complex four-bar linkage mechanism consisting of 13 components and four joints at the prosthetic knee joint of their unilateral subject. In any case, musculoskeletal modelling of different prosthetic joints should be dependent on the actual prosthesis type and in-situ joint mechanics.

4.2.3 Finite element modelling of amputation - relevance to the below-knee model

§5.2 summarises the historical perspective on FE modelling of both BK and AK amputation. Key considerations such as the material properties, loading conditions, residuum-socket interface conditions and bone-residuum interface conditions are discussed and evaluated. In previous literature, the key difference between FE modelling of BK and AK amputation has been geometry. To the best of the author’s knowledge no work has been published modelling the effect BK patellar-weight-bearing or suspension loading on the femur or the hip. The historical research perspective, as highlighted in more detail in §5.2 has been focused on soft tissue damage at the skin.

Looking ahead to the BK model, the residuum, soft tissue and socket will not be included. Investigation of hip and femur loading can be done with identical (appropriately scaled) geometry to that used in Chapter 3. As such, many of the FE features discussed in § 5.2, although considered, are not as relevant to the design of BK model as they are the AK model.

4.3 Methodology

4.3.1 Data acquisition

4.3.1.1 Motion data

The unilateral amputee subject used in this study is male, 175cm in height and weighed 79.2kg at time of data acquisition (Figure 4.1). He suffered traumatic BK amputation

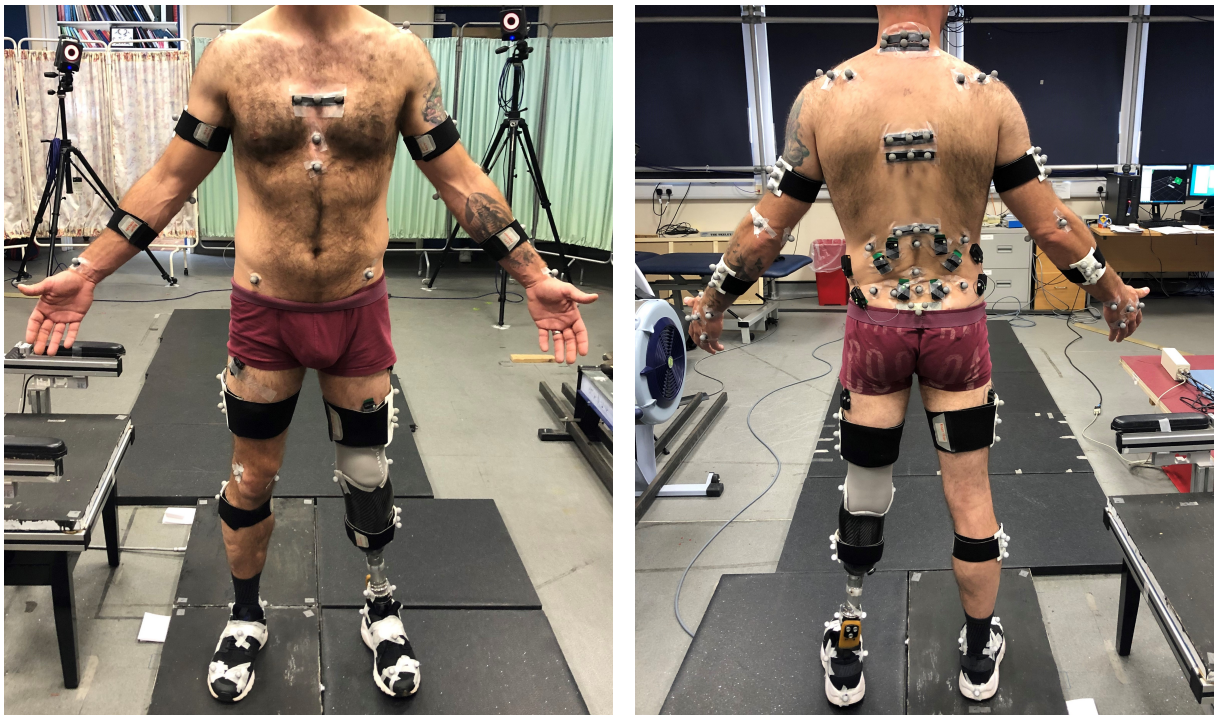


Figure 4.1: Image of the BK amputee subject during data acquisition. An increased, more expansive, upper and lower-body markerset was used for the BK amputee compared to control. Each marker location present in control was also present in the BK amputee subject.

in his left leg. At the time of data acquisition, it had been 8 years since the subject's last residual limb surgery. Motion data acquisition for this subject was carried out with Biranavan Sivapuratharasu and Dr. David Henson as part of a larger population-based study seeking to understand spinal loading in amputees, approved by the Imperial College Research Ethics Committee. The data acquisition process was similar to that used for the control subject (see §3.2). Kinematic and kinetic data was collected in the same lab with the same equipment. A more expansive upper and lower-body markerset was used in the unilateral BK amputee subject compared to in control (Wu, 2002). Minor

changes were made where needed on the amputated limb. Placement of markers on the prosthesis were kept as consistent as possible. Details of lower-body marker placement are outlined in Table 4.1 and displayed in Figure 4.2. The selection of both amputee subjects was opportunistic; reliant on which subjects were available, prepared to undergo MRI scanning and detailed motion capture. It should also be noted that although the DXA data for each subject is included in the larger population of amputees analysed in Chapter 2, ethical approval only permits anonymised use of this data. As such, no specific information will be given on the bone density of the amputee subjects used in Chapters 4 and 5.

Marker	Marker Name	Location
ASIS	L/R.ASIS	ASIS left and right side
PSIS	L/R.PSIS	PSIS left and right side
Thigh cluster	L/R.ThighCluster. Med/Lat/Up	Triangular cluster placed on lateral aspect of thigh
Lateral knee condyle	L/R.FemEpic.Lat	Lateral femoral epicondyle
Medial knee condyle	L/R.FemEpic.Med	Medial femoral epicondyle
Shank cluster	L/R.ShankCluster. Med/Lat/Up	Triangular cluster placed on anterior aspect of the shank, on the prosthetic socket
Lateral malleolus	L/R.TibialMal.Lat	Lateral tibial malleolus
Medial malleolus	L/R.TibialMal.Med	Medial tibial malleolus
Navicular	L/R.Navicular	Positioned on the superior aspect of the prosthetic foot
Calcaneus	L/R.Heel	Positioned on the heel of the prosthetic foot, roughly at the level of the navicular
Metatarsal 1	L/R.1stMeta.Dist	Positioned on the superior aspect of the prosthetic foot, above the 1st toe
Metatarsal 5	L/R.5thMeta.Dist	Positioned on the superior aspect of the prosthetic foot, above the 5th toe

Table 4.1: Marker locations for the unilateral BK amputee subject

Kinematic and loading data was collected for five trials of standing and ten trials of walking, stair ascent, sit-to-stand and stand-to-sit activities. The absence of stair descent data represented the only key difference between data acquisition in the BK amputee subject and the control subject. For each activity, an average of all trials was taken and processed for results.

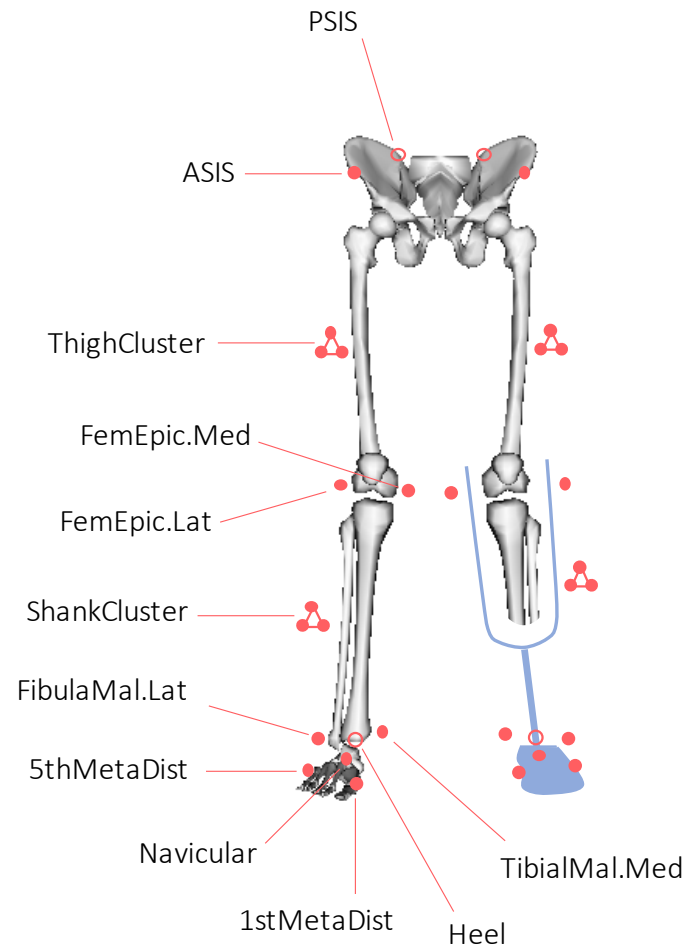


Figure 4.2: Schematic showing lower-body marker placement on the BK amputee subject during data acquisition.

4.3.1.2 MRI scanning

Full lower-body MRI data of both amputee subjects were provided by Dr. David Henson (Henson *et al.*, 2020). Scans were taken using a 3.0 T MRI scanner (*MAGNETOM Verio, Siemens, Germany*) between the iliac crest and the bottom of the unamputated foot. Field of view used = 450 x 450 mm, acquisition matrix = 320 x 320, axial plane resolution = 1.406 mm x 1.406 mm, slice thickness of 1mm with an approximate scan time of 45-60 minutes (Henson *et al.*, 2020). Therefore, in the BK amputee subject, scans captured the full length of as seen in Figure 4.3.



Figure 4.3: Figure displaying an example of MRI slices from the scans of the unilateral BK amputee subject.

MRI scans of the amputated limb were required to make post-amputation changes to the left leg in the unilateral MSK model. Scans were processed in Mimics (*Materialise, Belgium*). Manual segmentation of the scans allowed for recreation of 3D geometries of the skeleton and surrounding soft tissue on a slice by slice basis wherever needed. The wrapping and smoothing tools were then used to refine individual geometries where necessary. These geometries could be exported as a variety of file types and used in calculation of subjects' mass and inertia properties. Important anatomical information was also marked on the MRI scans. Individual muscle origins, insertions and known joint centres were marked as analysis objects. The coordinates of each could then be exactly identified and used in MSK model development.

The geometry of the prosthesis and socket were not needed for FE modelling in the case of the BK model as the model geometry extends only between hip and knee, not below to the socket-residuum interface.

4.3.2 Musculoskeletal modelling - building the unilateral model

4.3.2.1 Amputation

Both amputee MSK models were adapted from the existing bilateral LLLM used in Chapter 3. In the case of the unilateral BK amputee model, only the amputated leg was modified. Key features such as post-amputation muscle insertions, degrees of freedom, inertial properties and joint ranges of motion were matched as closely as possible to the BK subject's anatomy. A new joint was introduced at the level of amputation. Careful consideration was given to each change so that the MSK model would represent the most significant features of amputation while still ensuring conditions could be replicated in the FE stage of the modelling framework. The complete unilateral BK amputee model can be seen in Figure 4.4.

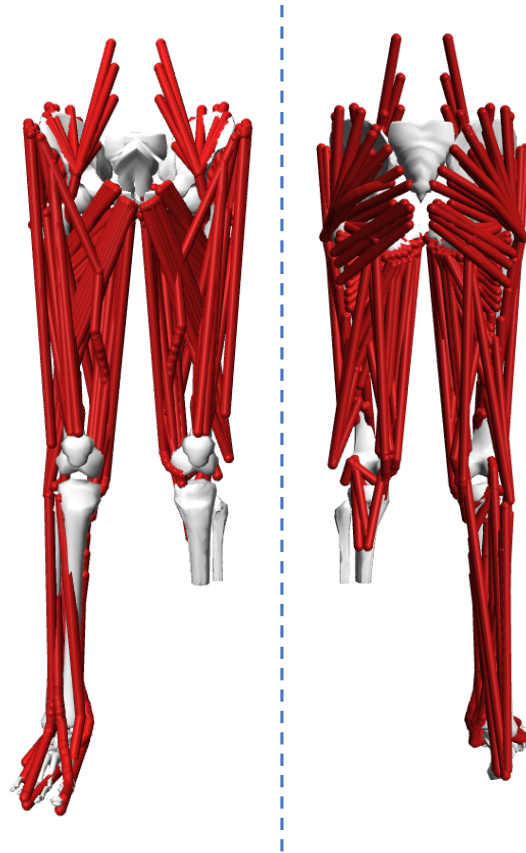


Figure 4.4: The complete unilateral BK amputee musculoskeletal model. The model is based on MRI scans of the same unilateral BK amputee subject used during data acquisition.

4.3.2.2 Muscle origins and insertions

Any muscle origins and insertions affected by amputation were altered to match the MRI scans taken of each subject. MRI scans were segmented in Mimics. Post-amputation muscle insertion points were identified with the visual guidance of various anatomical atlases. These insertions were matched in OpenSim. Muscles completely removed during amputation were removed from the MSK model. Wherever necessary, muscle paths and effective moment-arms were matched as closely as possible to in MRI scans.

4.3.2.3 Max isometric force

Muscle physiological cross-section area (PCSA) was not available for the individual BK amputee subject. Instead PCSA data from a larger population study of unilateral BK amputees completed by David Henson (Henson *et al.*, 2020) was used for both the amputated and contralateral limbs. A tetanic stress value of $55\text{N}/\text{cm}^2$ (O'Brien *et al.*, 2009) was used to then calculate the maximum isometric force of each muscle group and divided across corresponding actuators in the MSK model. Subjects analysed by Henson (2020) were of similar age and size to the subject used in this study.

4.3.2.4 Socket and prosthesis joint changes

A new body was added to represent the prosthetic socket and prosthesis of the amputated limb. The subject used a silicon suction suspension socket to encourage total surface bearing. The socket-residuum interface was modelled as an additional joint connecting the tibia to the prosthesis in MSK. Only pistoning (proximodistal translation) was permitted at this joint to capture any longitudinal slip or absorption at the socket. LePre (LaPrè *et al.*, 2017) studied the sensitivity of permitting various degrees of freedom at the socket-residuum interface in a BK amputee subject and while locking rotations in the frontal and coronal planes does represent some simplification, results were still in good agreement with the more complex joint models. Additionally, a more complex markerset would be required to properly quantify movements at this joint in all planes of motion.

The unilateral amputee subject used an Endolite Elite Blade prosthesis - a stiff carbon blade with rigid ankle joint. In the MSK model, the ankle and subtalar joints in the amputated leg were modelled as locked.

4.3.2.5 Mass and inertia properties

Centre of mass and inertia properties for each lower body segment were determined in Solidworks (*Dassault Systemes S.A.*, France) using the mass properties tool. Parts were divided into pelvis, right femur, left femur, right tibia and left tibia (amputated) by segmentation in Mimics. Segments were then imported into Solidworks as separate *.stl files. Each part was assigned a corresponding density value. Soft tissue (an approximation of muscle and fat) was assigned a density of 1.05g/cm^3 (White *et al.*, 1992) and bone a density of 1.5g/cm^3 (Favier, 2019). Solidworks could then calculate the new centre of mass and matrix of inertia for each body segment.

In this method, all materials were considered homogeneous. This is a simplistic assumption, particularly in the case of bone and soft tissue, however, for the purpose of calculating inertia and mass properties we believe this gave us an acceptable approximation of true values.

Unfortunately, in the case of the BK amputee, the 3D geometry of the socket and prosthesis could not be obtained. Mass properties for the prosthesis were taken from the product specifications ¹. Missing inertial properties were then taken from a study by LePre (2017).

4.3.2.6 Reserve actuation

Reserve actuators were included at every joint in the model. In OpenSim, these actuators augment the force generated at each joint when the force generated by muscle actuators is insufficient, thereby enabling simulations to run. These actuators are particularly important at amputated joints where no muscle actuators exist. Each one was given a low optimal force of 1N to ensure usage is heavily penalised, encouraging to model to find solutions based on muscle actuators primarily. Six residual actuators also exist at the pelvis. These provide the required actuation for pelvis motion in all 6 degrees of

¹Elite Blade, Blatchford, <https://www.blatchford.co.uk/products/elite-blade/>

freedom to compensate for the absence of upper body contribution to movement. They are unchanged from the original London Lower Limb Model (LLLM).

4.3.3 Finite element modelling - building the below-knee model

The following section explains how FE modelling is used to understand the effect of MSK loading at the hip of the bilateral amputee subject, thereby, seeking to further understand whether changes in the mechanical stimulation of bone could account for localised bone loss. MSK results must be interfaced or transformed into a complete loading scenario to be used in various FE models of the femur on the BK amputated side before we analyse the forces and subsequent stimulation occurring in the internal architecture of the femur.

4.3.3.1 Model geometry

As explained in Chapter 3, the fully converged femur model, generated by adaptation to a complete physiological AB loading scenario, is used as the starting point for bone adaptation in FE models of both amputee subjects. The BK amputee model requires less geometry manipulation than the AK model as amputation does not effect the geometry of the femur or the loading interface at the knee to the same extent. The converged femur is, however, scaled appropriately based on measurements taken between the hip and knee joint centre on MRI scans of the unilateral subject. This scaled femur makes up the main geometry of the BK amputee FE model. The same load applicators exist at the hip, knee and patello-femoral joint and the same fixators at the hip and knee joints as in the control model. The femur contains just over 200,000 linear trabecular truss elements (Abaqus element T3D2) and just over 10,000 linear triangular cortical shell elements (Abaqus element S3).

4.3.3.2 Loading conditions, boundary conditions and material properties

Loading and boundary conditions are applied in the same way as in the control model. Material properties used are also the same. They are displayed below in Table 4.2 for clarity.

Material	Young's Modulus/MPa	Poisson's ratio
Bone	18,000	0.3
Cartilage (applicator layer 2-3)	10	0.49
Congruent bone (applicator layer 3-4)	18,000	0.3

Table 4.2: Summary of material properties used in the BK amputee FE model

4.3.3.3 Predictive modelling

Predictive modelling differs from the adaptive modelling introduced in Chapter 3 in two main ways. Firstly, it separates each iteration of FE simulation into month-long remodelling periods, therefore, introducing a time dependence to any changes in bone structure. Secondly, the femur of the adapted control model is used as a starting point for adaptation rather than utilising a blank starting point allowing predictive models to focus on the rate of change of the femoral structure from an AB starting point.

Changes to the element cross-section geometry (area or thickness for truss and shell elements, respectively) take place according to the same principles as in adaptation of the control model. The same thresholds were assigned where overstrain drives bone apposition ($>1500\mu\epsilon$) and understrain drives bone resorption ($<1000\mu\epsilon$) according to Frost's Mechanostat (Frost, 2003). However, bone change was capped at a maximum value of 2% in trabecular bone and 1% in cortical bone per one-month remodelling period. These values were determined appropriate by background research into the maximal rate of bone loss in extreme loading conditions such as: during periods of prolonged bed rest (Rittweger & Felsenberg, 2009; LeBlanc *et al.*, 2007; Zerwekh *et al.*, 1998; Kramer *et al.*, 2017); following spinal cord injury (Hammond *et al.*, 2014; Wilmet *et al.*, 1995; Charmetant *et al.*, 2010; Fattal *et al.*, 2011), and prolonged exposure to reduced gravity conditions (Iwamoto *et al.*, 2005; Lau & Guo, 2011; LeBlanc *et al.*, 2007). However, values do differ throughout literature; a range of rate of change values could have been chosen for this study.

For each $(i + 1)^{th}$ iteration the cross sectional area A of the j^{th} truss element was adjusted according to Equations 4.1, 4.2 and 4.3 and the thickness T of the j^{th} shell element adjusted according to Equations 4.4, 4.5 and 4.6. $(M.\epsilon_{i,j} + c)$ represents the

appropriate linear multiplication factor for trabecular truss t and cortical shell c elements experiencing sub-maximal change in dimensions.

$$\text{if } \epsilon_{i,j} \leq 250\mu\epsilon, \quad A_{i+1,j} = A_{i,j} \times 0.97 \quad (4.1)$$

$$\begin{aligned} \text{if } 250\mu\epsilon < \epsilon_{i,j} \leq 1000\mu\epsilon \quad \text{or} \quad 1500\mu\epsilon \leq \epsilon_{i,j} < 2500\mu\epsilon, \\ A_{i+1,j} = A_{i,j} \times (M_t \cdot \epsilon_{i,j} + c_t); \end{aligned} \quad (4.2)$$

$$\text{if } \epsilon_{i,j} > 2500\mu\epsilon, \quad A_{i+1,j} = A_{i,j} \times 1.03 \quad (4.3)$$

$$\text{if } \epsilon_{i,j} \leq 250\mu\epsilon, \quad T_{i+1,j} = T_{i,j} \times 0.99 \quad (4.4)$$

$$\begin{aligned} \text{if } 250\mu\epsilon < \epsilon_{i,j} \leq 1000\mu\epsilon \quad \text{or} \quad 1500\mu\epsilon \leq \epsilon_{i,j} < 2500\mu\epsilon, \\ T_{i+1,j} = T_{i,j} \times (M_c \cdot \epsilon_{i,j} + c_c); \end{aligned} \quad (4.5)$$

$$\text{if } \epsilon_{i,j} > 2500\mu\epsilon, \quad T_{i+1,j} = T_{i,j} \times 1.01 \quad (4.6)$$

4.3.3.4 Isolating the effect of muscle and joint loading forces

As with the control subject, a separate analysis was performed splitting the complete BK amputee loading scenario into two new scenarios modelling (a) muscle forces and (b) joint forces only. While the structure of the bone remains the same as control, loading in the BK amputee subject will differ making comparison between the independent contribution of each set of forces important. This could also be of particular use in understanding the rehabilitation potential of each form of loading.

4.4 Results

4.4.1 Spatiotemporal characteristics

The BK amputee subject experiences higher acceleration and deceleration than the control subject during gait. This is the case in both the horizontal (in line with the direction of travel) and vertical planes. The pelvis of the BK amputee experiences a peak horizontal acceleration of 2.8m/s^2 and a peak horizontal deceleration of 2.9m/s^2 compared to values of 0.63m/s^2 and 0.93m/s^2 in the control subject. The same trend is present in vertical acceleration and deceleration (3.3m/s^2 peak acceleration and 2.8m/s^2 peak deceleration in the amputee subject versus 2.0m/s^2 and 1.3m/s^2 in the control subject, respectively). This is intrinsically linked to measured values of ground-reaction and joint-reaction force experienced at the knee and hip of each subject. Similar accelerations are measured on a local level at each femur by OpenSim.

4.4.2 Ground reaction force

Experimental data captured two full strides of unilateral amputee gait as displayed in Figure 4.5. One with the leading intact leg and another with the trailing amputated leg. Both exhibit the typical double-peak in ground-reaction force at heel-strike and toe-off. The amputated leg, however, experiences a much higher peak at heel-strike than the intact limb. The second peak at toe-off is similar in both legs. Compared to control, peak ground-reaction force is higher in both amputated and intact limbs of the BK amputee.

4.4.3 Kinematics

Figure 4.6 displays kinematic data at the amputated leg and the intact leg. Kinematics vary considerably between each leg. In the sagittal plane, the amputated limb reaches a lower peak hip flexion but a higher peak hip extension than the intact limb. Both legs demonstrate a prominent loading response at the knee during early stance with 15° of flexion occurring in the amputated and 30° of flexion occurring in the intact limb. The knee on the amputated side also reaches slight extension during terminal stance, unlike

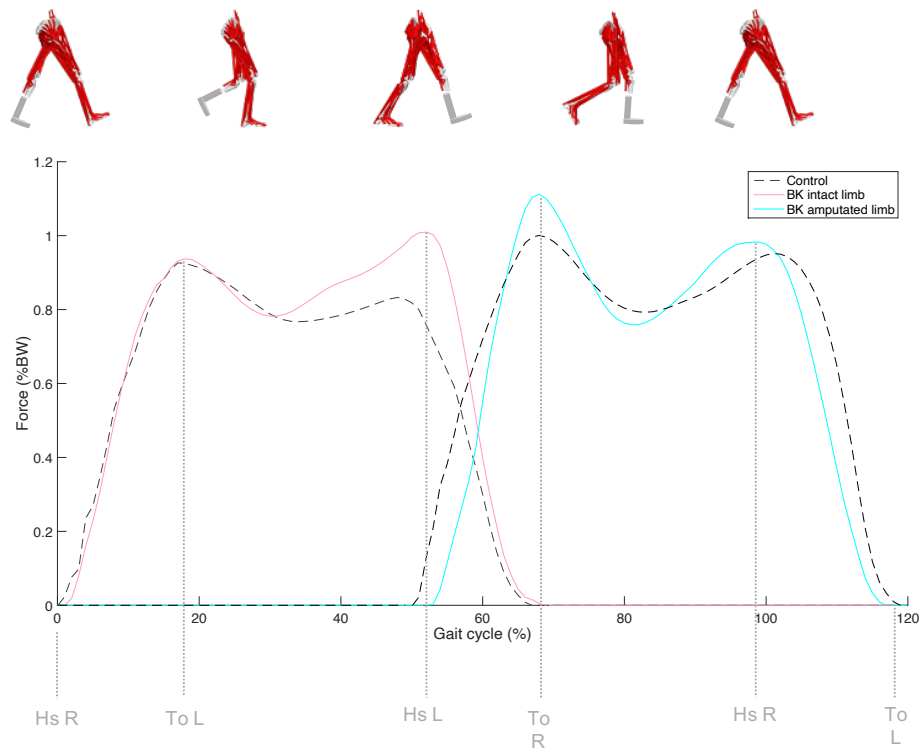


Figure 4.5: Ground reaction force comparison between the BK amputee and control subject.

the knee of the intact leg which maintains partial flexion throughout the full cycle. The intact ankle drifts from peak dorsiflexion during swing to 20° plantarflexion at push-off in order to aid forward propulsion. The amputee subject maintains an average anterior pelvic tilt of just over 10° throughout the gait cycle with peak values occurring at the beginning of each stride.

The intact leg demonstrates symmetric hip adduction/abduction during the gait cycle. Stance phase sees a double peak in hip adduction rising to 8° in early stance before dropping to below 4° during midstance but rising again to 6° adduction during push-off. A similar pattern is followed during swing of the intact leg where peak abduction of about 8° occurs at early swing before a smaller second peak at late swing. The amputated leg also demonstrates abduction during swing and adduction during stance. However, adduction during swing is about 2° more prominent (peaking at 10°) and abduction during stance about 2° less prominent (peaking at 6°). This slight bias towards adduction in the amputated leg is further represented in the pelvic obliquity plot where the unilateral subject shows a slight hip hike on the amputated side during intact leg support phases.

The pelvis rotates towards the leading intact leg at heel-strike before drifting into a neutral position at mid stance and finally a peak rotation in the opposite direction at

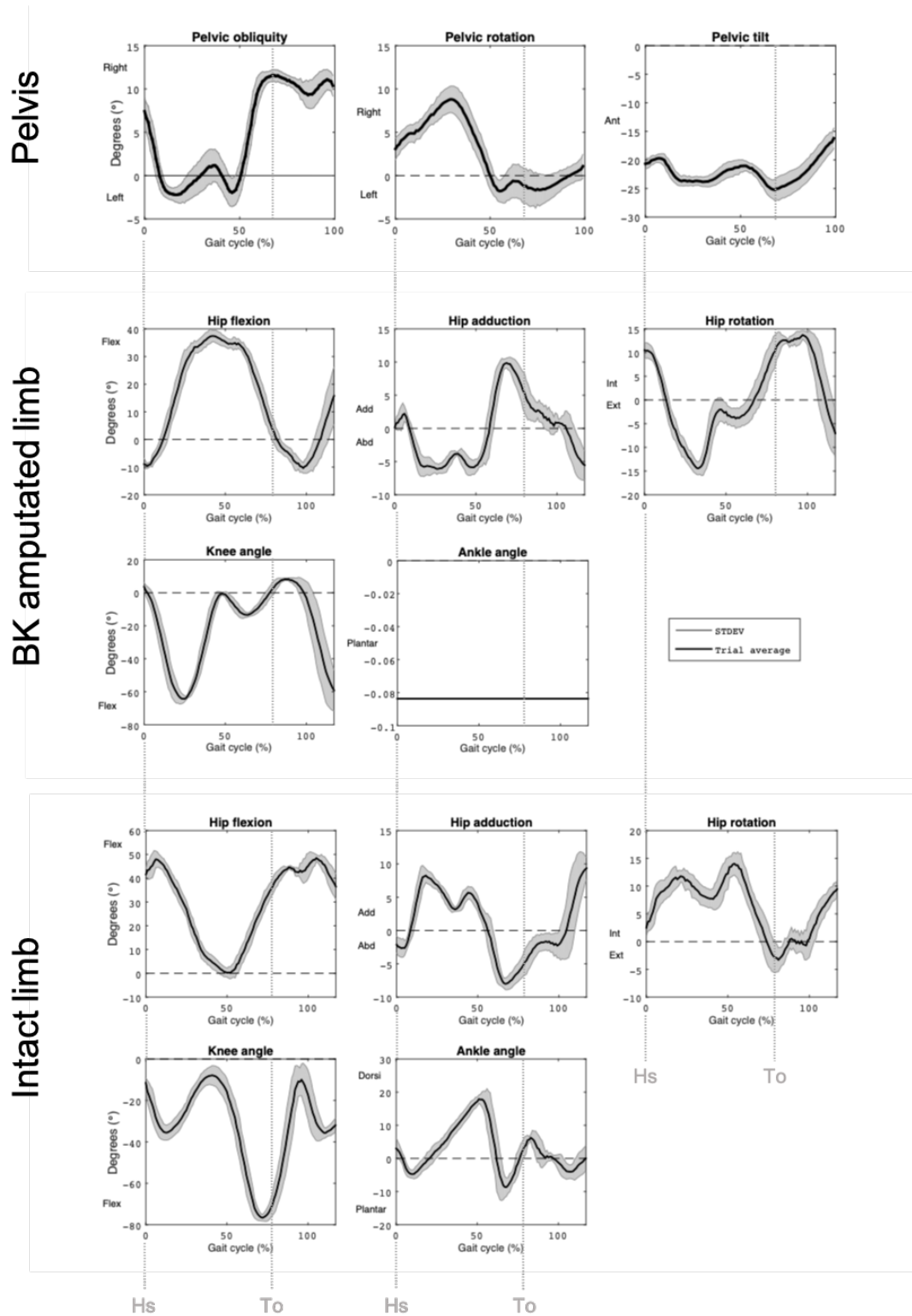


Figure 4.6: Inverse kinematics results from the amputated limb of the BK amputee subject during gait.

intact toe-off. Peak hip rotation is slightly higher at amputated heel-strike than intact (12° versus 9°). Hip rotation in both legs follow similar patterns: the hip is internally rotated during the majority of stance before drifting into external rotation during the majority of swing. The intact leg favours internal rotation of the hip with peak value of just under 15° compared to a peak external rotation of just 3° during swing. The hip on the amputated side is more symmetric moving between 15° of both internal and external rotation. In both legs, the transition is less smooth than might be typically expected with a slight double peak occurring in each phase. A small fluctuation in rotation occurs during push-off in each leg.

Some key differences between gait of the unilateral BK amputee subject and that of the AB control subject could have important implications on hip loading. Predictably, unilateral amputee gait is significantly less symmetric than control gait in terms of kinematics both in the frontal and sagittal planes. In general, range of motion in all three planes are higher during unilateral amputee gait. At the intact ankle, plantarflexion during push-off is almost double that in the control subject suggesting the intact ankle carries a particularly high burden of propulsion during gait. The amputee subject also maintains a consistent anterior pelvic tilt of just over 10° during the whole cycle while the control subject maintains an equivalent level of posterior pelvic tilt throughout.

4.4.4 Kinetics

Figures 4.7 displays joint moments experienced in the amputated and intact limb. As with the kinematic data, kinetic data in the unilateral amputee is highly asymmetric. In general, the magnitude of joint moments in the amputated limb is lower than those in the intact limb. The only exception to this is found in the hip sagittal moments where peak flexion and extension moments are nearly double those measured in the intact limb. Sagittal knee and ankle kinetics as well as frontal and coronal hip kinetics reach substantially higher peaks in the intact limb than the amputated which could have important implications on joint reaction forces and subsequently femur and hip loading.

Compared to the control subject, the joint moments predicted for the intact and amputated unilateral subject's legs roughly straddle those predicted for the control subject in terms of moment magnitude. Generally, moments experienced by the intact leg surpass those experienced by the control while in the amputated leg, joint moments fall below

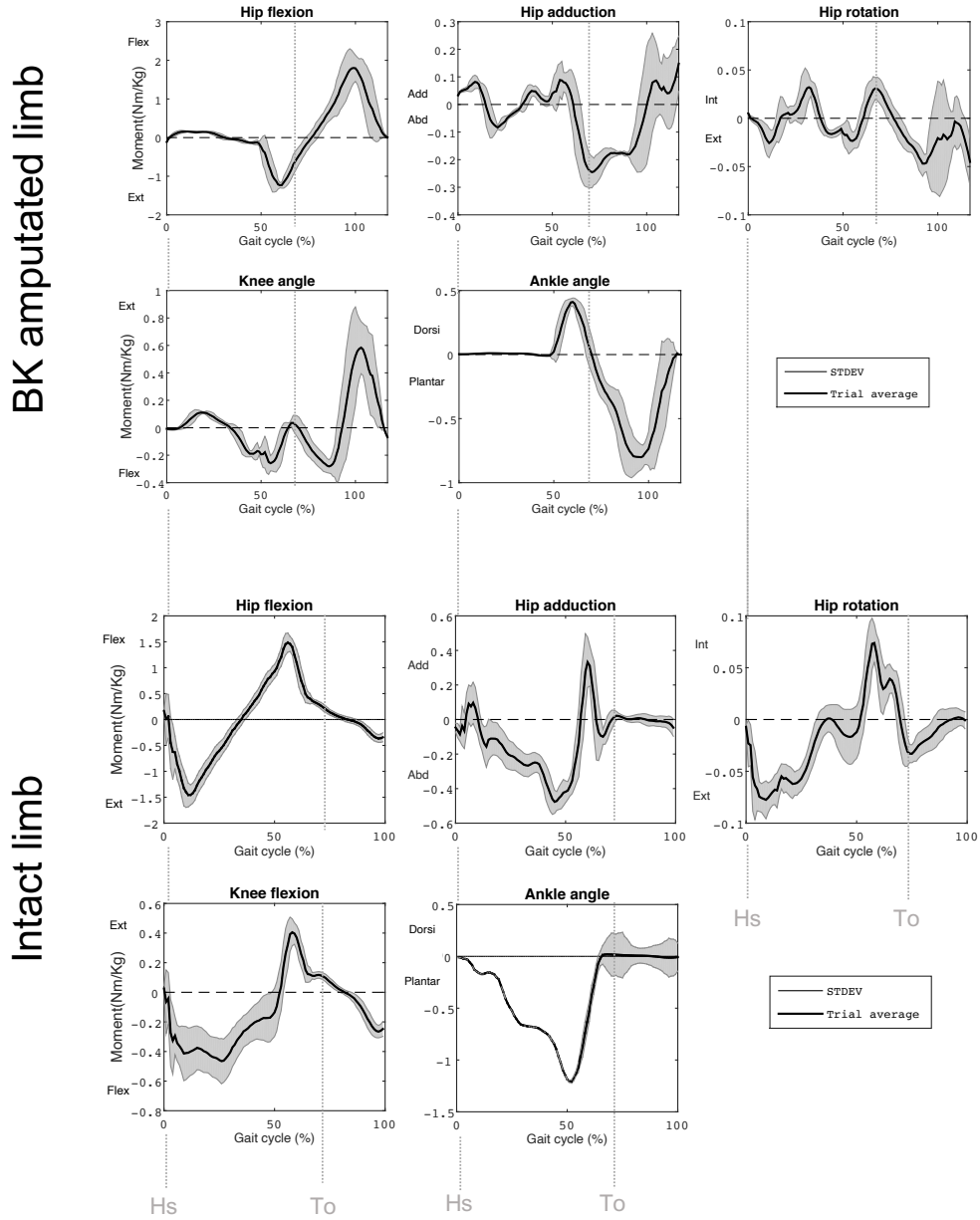


Figure 4.7: Inverse dynamics results from the amputated limb of the BK amputee subject during gait.

both at the knee, ankle and in the frontal plane of the hip. As previously eluded to, sagittal plane moments at the hip of the amputated leg are high.

4.4.5 Muscle forces

Muscle force predictions during gait of the BK amputee subject are displayed in Figures 4.8 and 4.9. The intact hip extensors begins contraction during late swing before peaking during the loading response and returning to zero contraction by mid-swing of the intact leg. At peak the semimembranosus contributes the majority of force generating a maximum of about 8N/kg to both hip extension and knee flexion. In the amputated leg, the semimembranosus and semitendinosus activate in a very different way. The amputated semitendinosus provides a low contraction during late swing, only, to decelerate the leg. The semimembranosus begins activating at a similar time but builds up to two more substantial peaks in force generation. The first (4N/kg force) occurs during the loading response and the second (over 10N/kg force) during the second half of stance (push-off into toe-off). In the BK amputated leg the hip extensors and knee flexors seem to contribute significant power to forward propulsion during gait, greater than observed in gait of the AB control subject.

Both intact and amputated leg hip abductors activate throughout the majority of single leg support phase. In both legs, the gluteus minimus provides the most force, peaking at just under 2N/kg in the intact leg and 2.75N/kg in the amputated. The intact leg sees a double peak in activation at early and late stance while gluteus minimus activation in the amputated leg builds continuously towards just one peak during midstance. The gluteus medius, piriformis and tensor fasciae latae provide lower supplementary activation during stance in both legs (less than 0.4N/kg force).

In both legs, the rectus femoris contributes the most force of all hip flexors and knee extensors. In the intact leg, it activates for a longer period, throughout early stance before peaking at just under 7N/kg of force production during push-off. In the amputated leg, activation only begins from midstance and peaks during push-off with a higher force production of 9.5N/kg. The rectus femoris contributes to the loading response at the knee in the intact limb along with support from the vastus muscles, though this is not the case in the amputated limb. The psoas major activates during mid-to-late stance in both

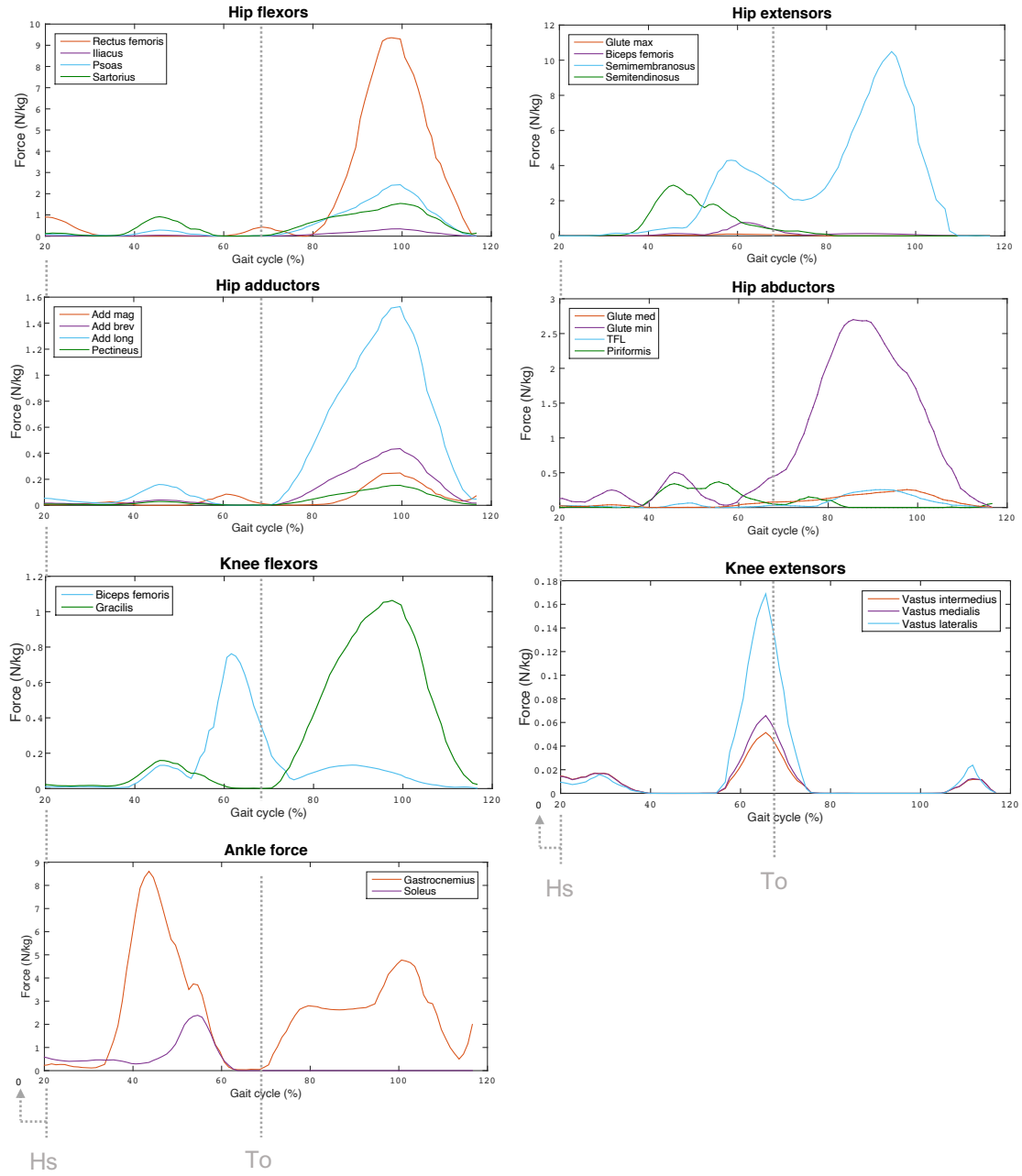


Figure 4.8: Predicted muscle forces experienced during unilateral BK amputee gait in the amputated limb. Separated into hip flexors, extensors, adductors, abductors, knee flexors and extensors for direct comparison to control results.

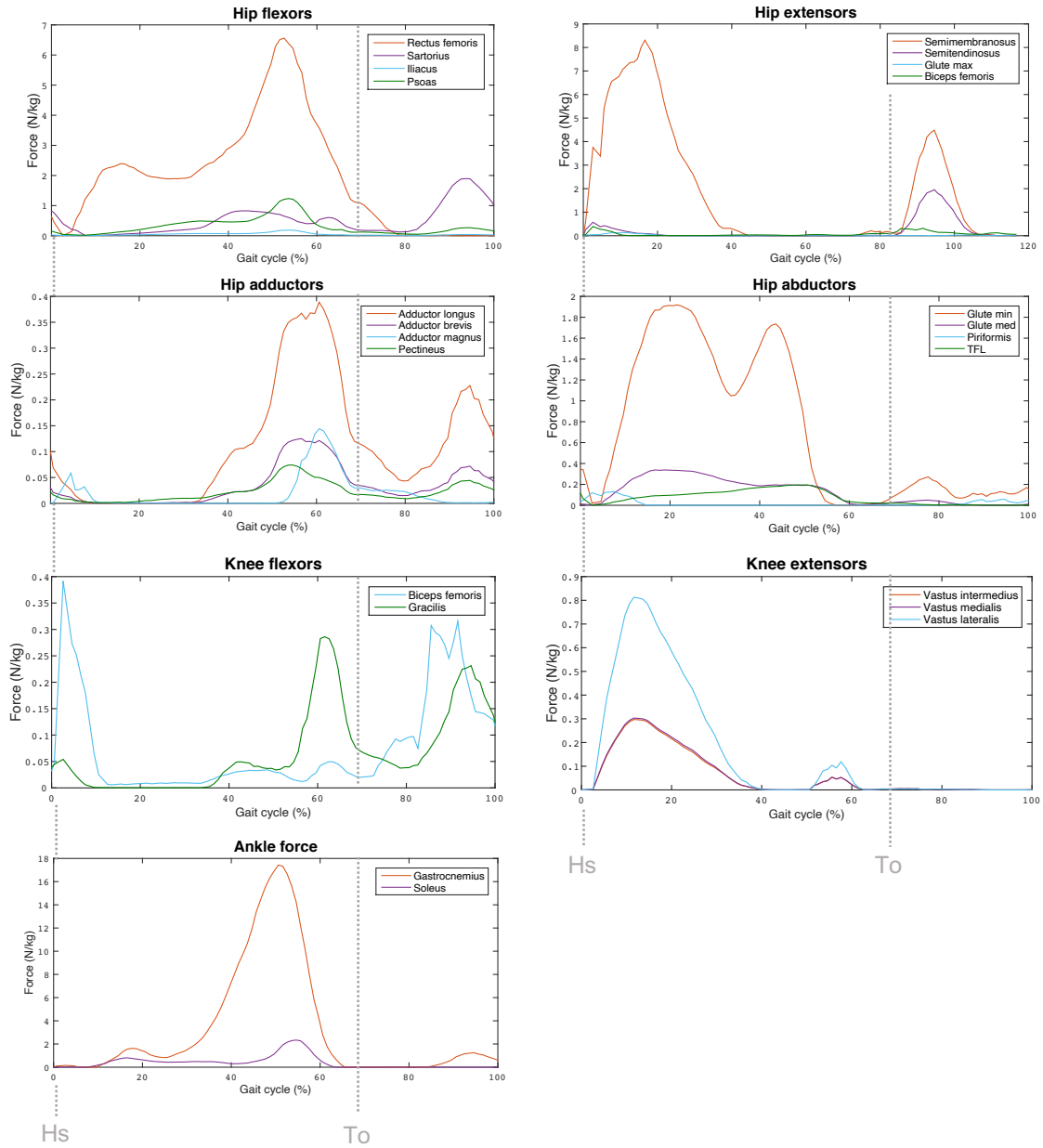


Figure 4.9: Predicted muscle forces experienced during unilateral BK amputee gait in the intact limb. Separated into hip flexors, extensors, adductors, abductors, knee flexors and extensors for direct comparison to control results.

legs. It works harder in the amputated leg than intact. Other hip flexors share similar activation profiles but contribute significantly less force.

The adductor muscles in the BK amputated leg work substantially harder than in the intact leg (peak force of 1.5N/kg versus 0.4N/kg in each adductor longus). In the amputated leg, adductor brevis, magnus and longus activation begins in early stance from toe-off of the opposing leg. It carries on to a peak during push-off, just prior to heel-strike of the opposing leg. The adductors of the intact leg follow a similar pattern but generate less force.

Generally speaking, active muscles in the amputated limb contribute higher peak force than equivalent muscles in the contralateral. Muscle activation pattern is similar in both limbs. Perhaps the only major (and most important) exception to this trend is in the gastrocnemius where the amputated ankle does not contribute any active power during plantarflexion. The gastrocnemius does, however, contribute to knee flexion during both stance and swing phases. In the intact limb, the gastrocnemius contributes significant power (over 17N/kg force) during midstance as a stabiliser and in late stance to forward propulsion. The intact gastrocnemius contributes substantially more force per kg than the any other muscle in the BK or control subjects. This suggests it plays an important role in compensation for the affected BK amputated leg in terms of movement creation and forward propulsion.

Comparing the muscle forces experienced in the contralateral limb to those experienced by the AB control subject we can further evaluate the effect amputation might have on femur and hip loading. Hip flexor, extensor, adductor and abductor muscles generate significantly more force in the BK amputee than in the AB control subject. The opposite is true for predicted force in the pure flexors and extensors of the knee. Additionally, the gastrocnemius on the BK amputated side generates less force than in either limb of the control subject. This is also significant in terms of femoral loading given its attachment at the medial and lateral condyles. Overall, from a loading perspective, the environment of muscle force generation is vastly different in the BK leg to the legs of the AB control subject. This could have potential in explaining altered bone structure in the mid-to-long term post-amputation.

4.4.6 Total joint closing force

Joint closing force at the hip and knee of both limbs during gait can be seen in Figure 4.10. In the amputated limb, hip joint closing force follows a very similar pattern to that

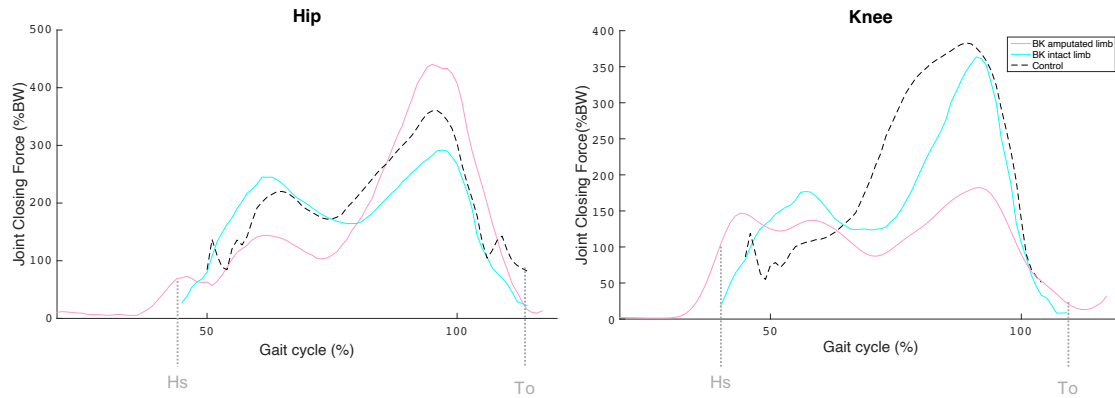


Figure 4.10: Total joint closing force at the hip and knee of the both limbs during unilateral BK amputee gait. Includes effect of typical joint reaction forces and the closing effect of muscle contraction acting across each joint.

seen in the control subject. A small primary peak occurs during the loading response and a second, of higher magnitude, during push-off. At the knee, primary and secondary peaks are similar in magnitude. The total force experienced in the hip is consistently higher than that experienced in the knee due to elevated muscle force generation in the rectus femoris and semimembranosus.

Peak hip force is higher in the BK amputated leg than in the AB control subject (4.5 BW compared to 3.5 BW in control). This can also be attributed to increased hip muscle activity. Peak knee force is lower in the BK amputated leg than in the AB control. Similarly, this can be attributed to muscle loading. Predicted force generation in the muscles crossing the knee are substantially lower in the BK amputee than in control (the most dramatic difference is seen in the gastrocnemius). This reduction is reflected in the total knee joint closing force (roughly 2 BW versus 4 BW in control). In the sound limb, hip and knee joint forces follow a more similar pattern to control.

Other activities provide little variation from gait in terms of joint loading profile in the amputated limb. Joint forces are shown in Figures 4.11 and 4.13. Stair ascent, sit-to-stand and stand-to-sit joint force predictions at the hip and knee fall below those values predicted during gait in all three planes. Magnitude of forces experienced in, particularly,

sit-to-stand and stand-to-sit activities are very low compared to the control subject. In general, loading from each of the accessory activities is largely focused vertically. Figure 4.12 has also been reproduced here for direct comparison between control and BK amputee scenarios.

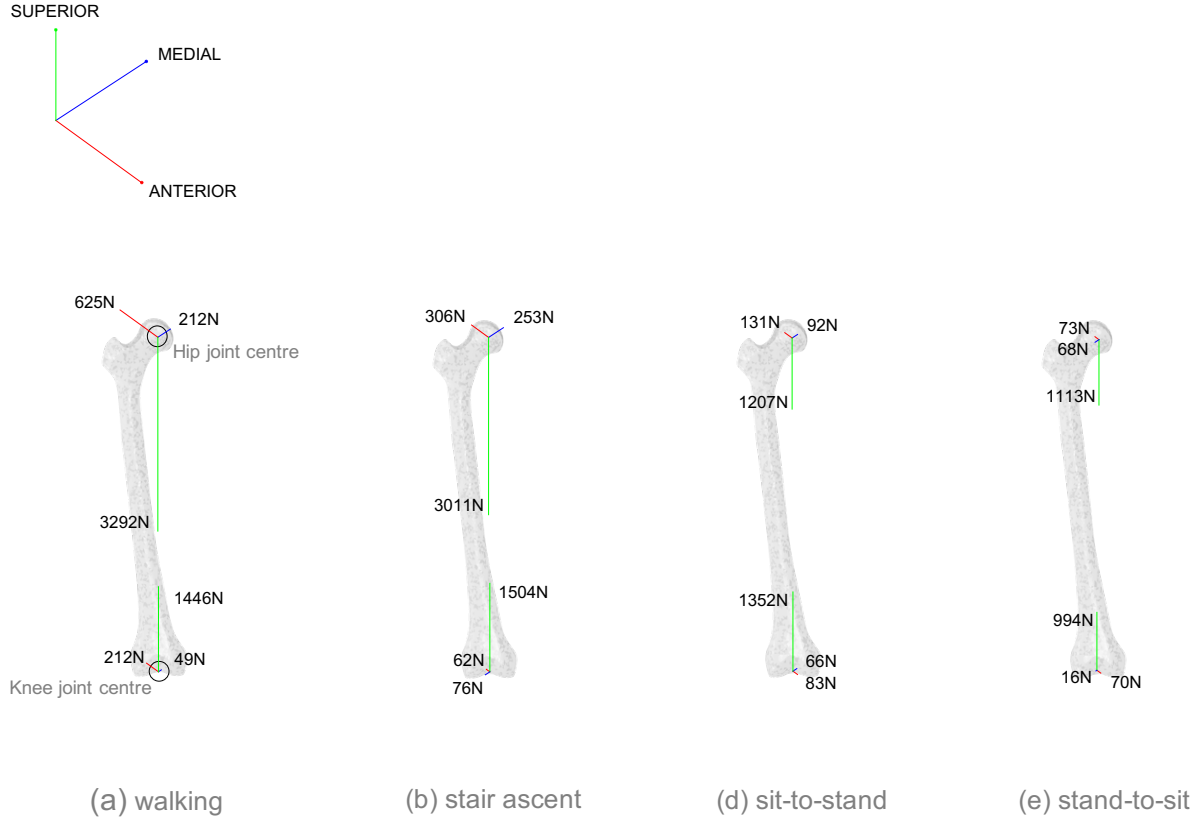


Figure 4.11: Total joint closing force experienced during select frames of walking, stair ascent and sit-to-stand/stand-to-sit activities in the BK amputee subject resolved into component forces to demonstrate the variation in loading direction from activity to activity.

4.4.7 Finite element modelling

4.4.8 Bone resorption risk

Figure 4.14 compares an envelope of strain experienced within the amputated femur to that experienced in the femur of the control subject. The maximum absolute strain experienced in each element, across all load cases, is compared as a proportion of the target strain ($1250\mu\epsilon$). It represents the bone resorption risk as a result of induced loading by comparing relative strain stimulation in every step of the loading scenario at once.

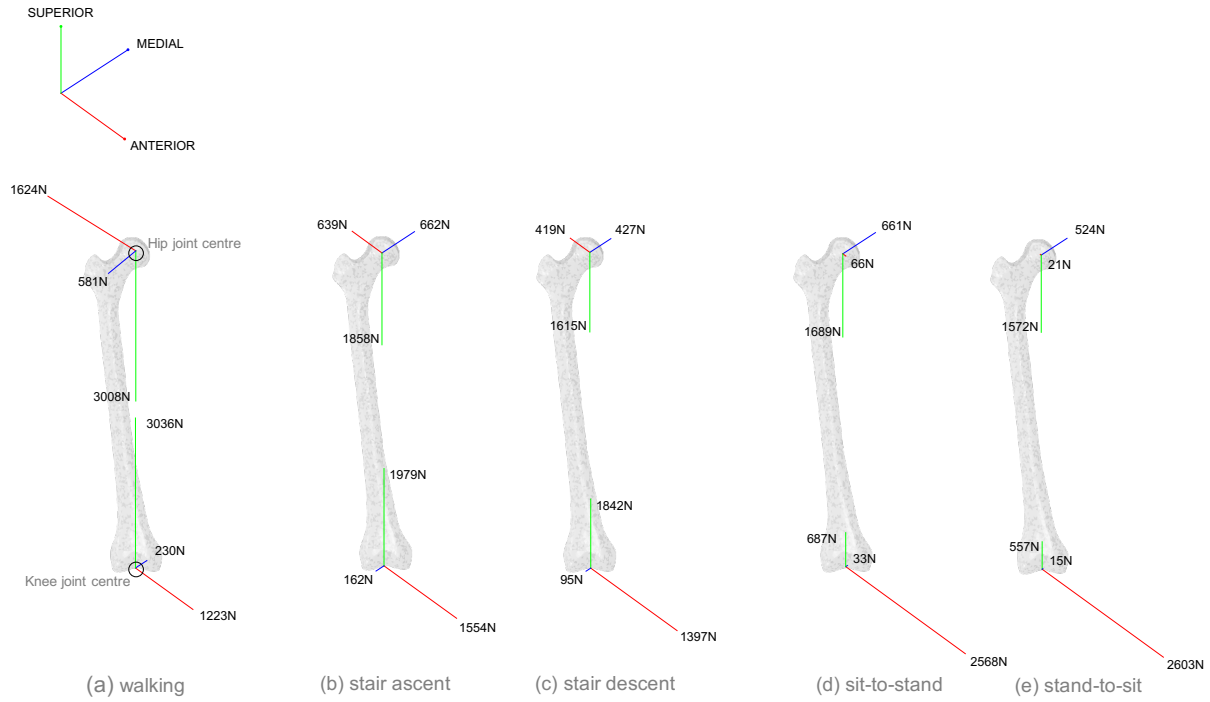


Figure 4.12: Total joint closing force experienced during select frames of walking, stair ascent/descent and sit-to-stand/stand-to-sit activities in the control subject resolved into component forces to demonstrate the variation in loading direction from activity to activity.

Generally, the majority of cortical bone is sufficiently stimulated and at low to no risk of bone resorption due to loading. Only 4% of cortical elements experience a maximum strain below the target strain across all load cases. In fact, the strain is high enough in certain areas that bone apposition could be expected. Bone resorption risk is more prominent in the trabecular elements with almost 40% experiencing strain below target. In the proximal femur, the thicker principle and secondary compressive trajectories seem to be at demonstrable risk of bone resorption. In general, loading is more pronounced on the posterior side of the proximal femur than on the anterior. Cortical and trabecular bone around common muscle insertions such as the lesser trochanter and linea aspera are predicted to be at low to no risk of bone deterioration. In the distal femur, loading slightly favours the medial condyle over the lateral. Significant sections of trabecular bone running perpendicular to the knee joint axis, between the two distal condyles, receives insufficient loading and is subsequently moderate to high risk of resorption is predicted. Finally, it is worth noting that the majority of elements are not pictured in Figure 4.14 as only elements with a radius of greater than 0.1mm are shown. In the BK amputee model, 44% of trabecular elements with a radius of less than 0.1mm experience strain below target.

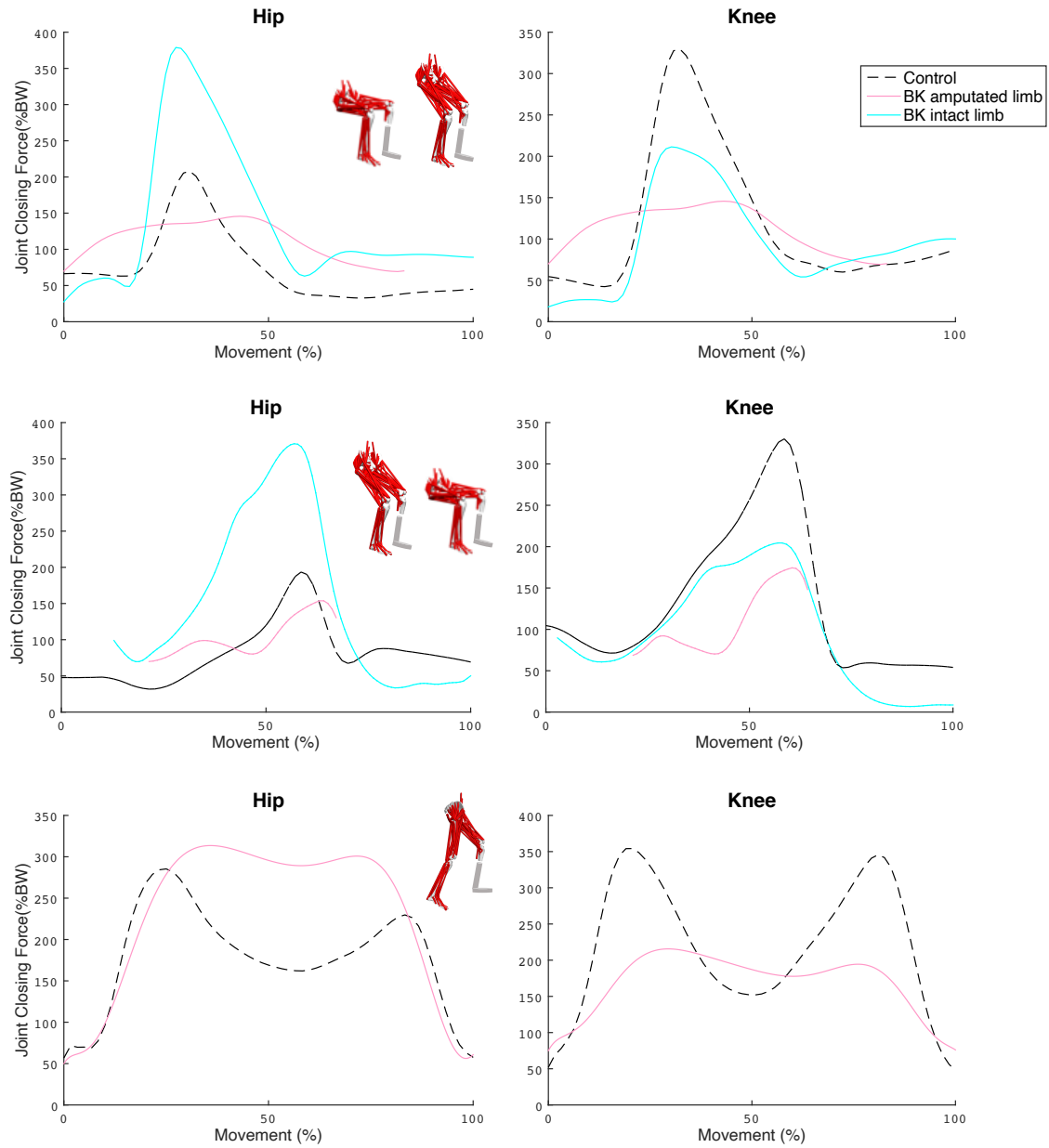


Figure 4.13: Total joint closing force experienced at the hip and knee in the BK amputee subject during (from top to bottom) sit-to-stand, stand-to-sit and stair ascent activities.

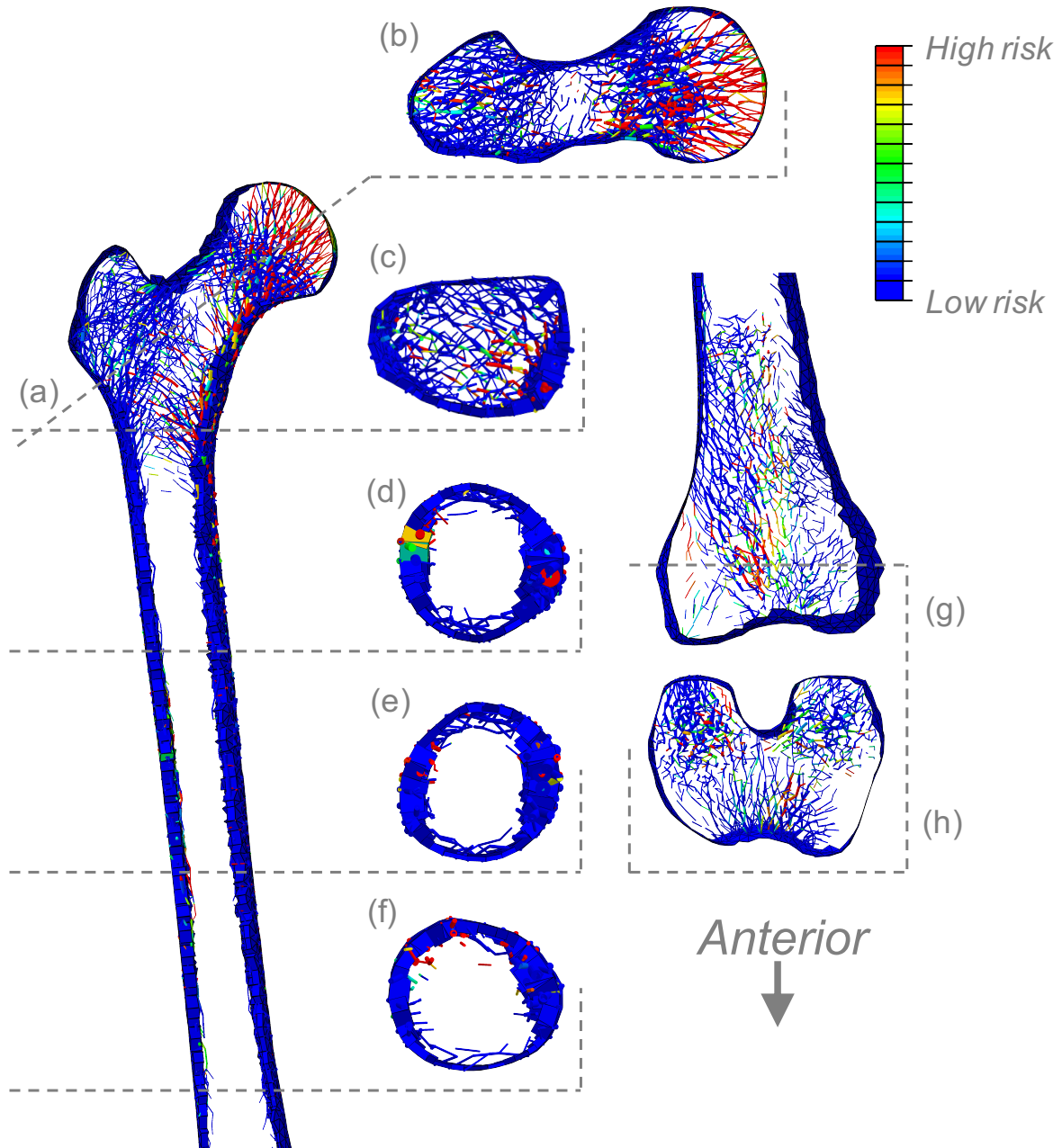


Figure 4.14: Plot showing the predicted bone resorption risk as a result of the BK amputee loading scenario. Each slice is 5mm thick and shows trabecular elements with a radius $> 0.1\text{mm}$.

4.4.9 Effect of muscle versus joint loading forces

Figure 4.15 demonstrates the bone loading effect when joint contact forces and muscle forces act separately on the femur. Direct joint loading, from the hip and knee contact forces only, contribute primarily to stimulation of the distal femur. The pattern of strain also highlights the relative bias towards sagittal plane loading as a result of joint contact forces in the femur of the BK amputated leg. Muscle forces place large portions of trabecular bone in tension throughout the internal structure of the femur in the amputated leg. Broadly speaking, tension is experienced along the posterior side of the cortical bone surface and compression along the anterior. The magnitude of principle strain recorded in the model demonstrating muscle loading only could be high enough to preserve bone density or even promote bone apposition in certain areas.

4.4.10 Predictive modelling of bone adaptation and remodelling

Predictive modelling demonstrates the significant potential for bone loss as a result of reduced loading post BK amputation. The internal architecture of the femur on the affected side is shown in Figure 4.16 and can be compared to the equivalent control femur in Figure 3.14. The BK model predicts a total trabecular bone volume loss of over 12% in over 60 months with most significant bone loss taking place in the distal femur. Comparing between slices (g) and (h) in Figures 4.16 and 3.14 demonstrates this effectively. The number and thickness of larger trabecular trajectories (highlighted in red) is greatly reduced between the control and BK amputee conditions (subjected to 5 years of amputee loading). The medial condyle, in particular, sees many large trajectories disappear entirely. In the proximal femur, the two compressive trajectories demonstrate significant thinning of trabecular elements. This also happens in the larger trabeculae of the greater trochanter and secondary tensile trajectories - however not as prominently as elsewhere. Within the femoral shaft, the quantity of smaller trabecular elements (radius=0.1mm, highlighted in both Figures in light blue) drops considerably around the level of slices (d) and (e).

However, the femur's adaptation is not only characterised by bone loss but also by redistribution of the pre-existing trajectories and cortical bone. Bone apposition is

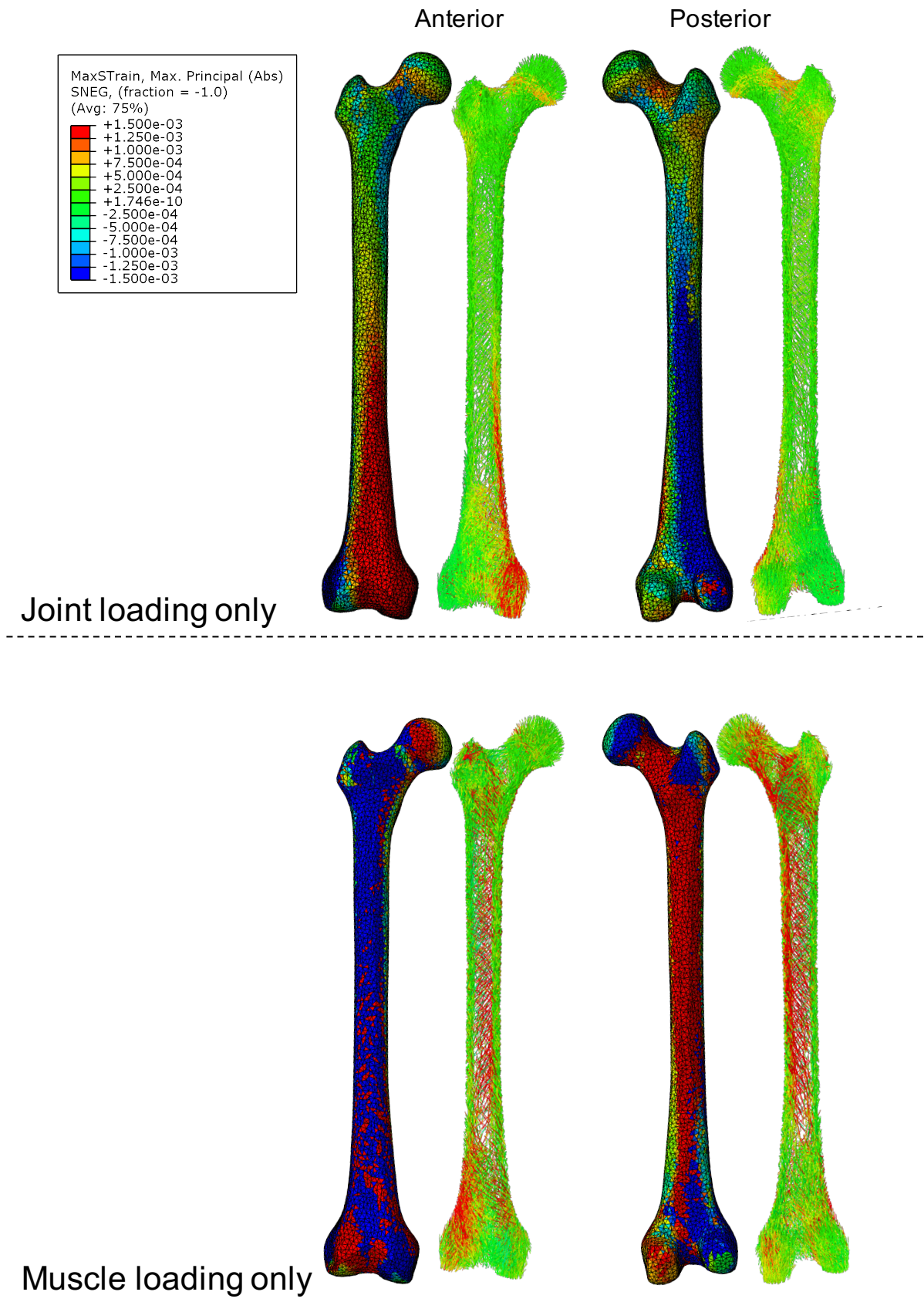


Figure 4.15: Plotting the maximum principle strain experienced at the femur of the BK amputee subject in separate loading scenarios, modelling the independent effect of muscle forces and joint reaction forces on the femur structure. Cortical and trabecular structure is shown from anterior and posterior views.

predicted in some areas of bone. While overall trabecular density drops considerably, cortical bone is actually completely preserved. Cortical thickening takes place in the lateral and anterior walls of the femoral shaft. Trabecular bone connected to major muscle attachment sites such as the lesser trochanter and linea aspera also thicken slightly.

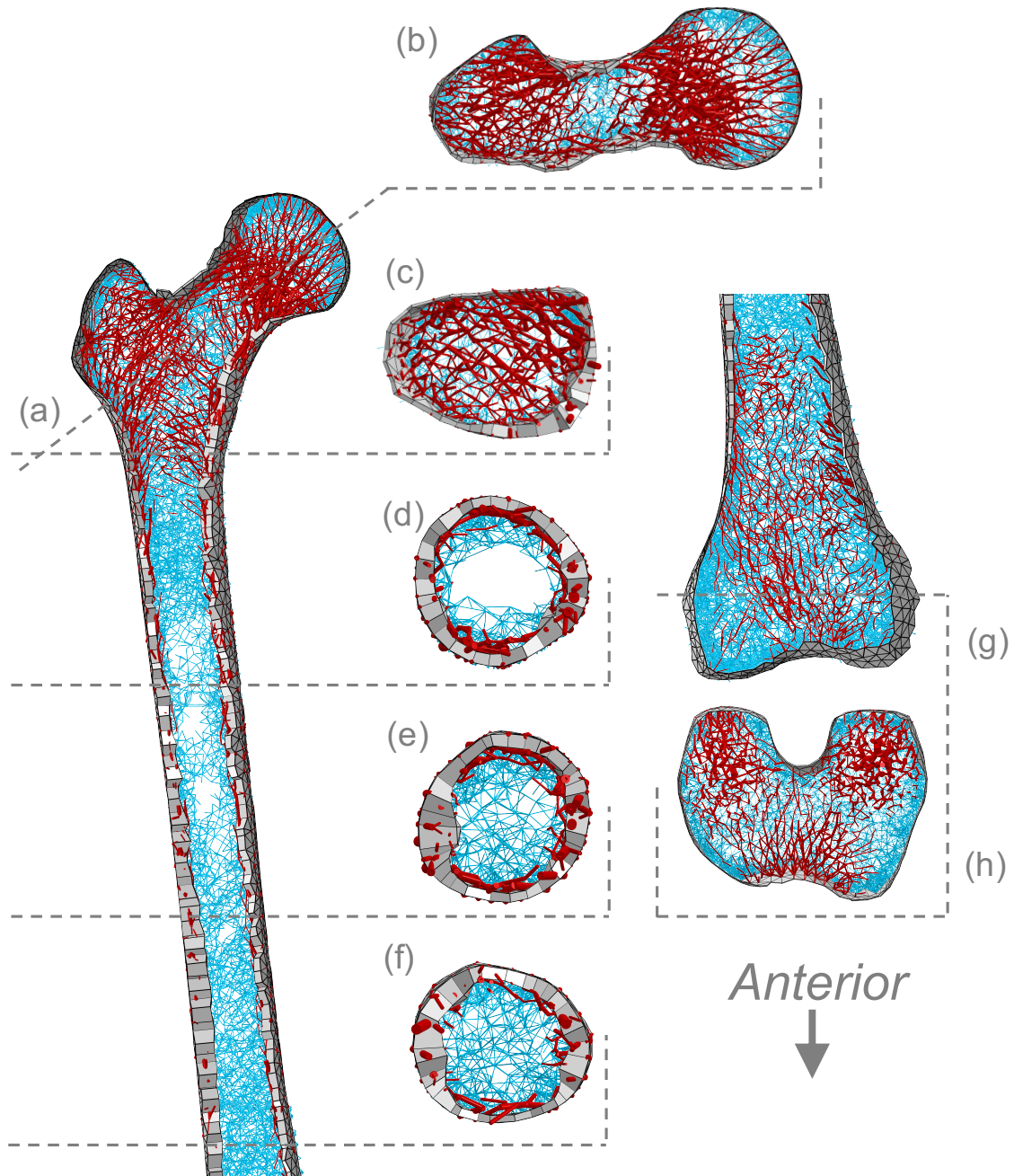


Figure 4.16: Selected 5mm thick slices of the BK amputee femur when subjected to a loading regime of 5 daily living activities: standing, walking, sit-to-stand, stand-to-sit and stair ascent. Cortical shell elements are shown in grey. Trabecular truss elements with a radius of 0.1 mm are shown in blue. Trabecular truss elements with a radius $>0.1\text{mm}$ are shown in red. Truss elements in the dead zone (with a radius of $1\text{ }\mu\text{m}$) have been omitted for clarity.

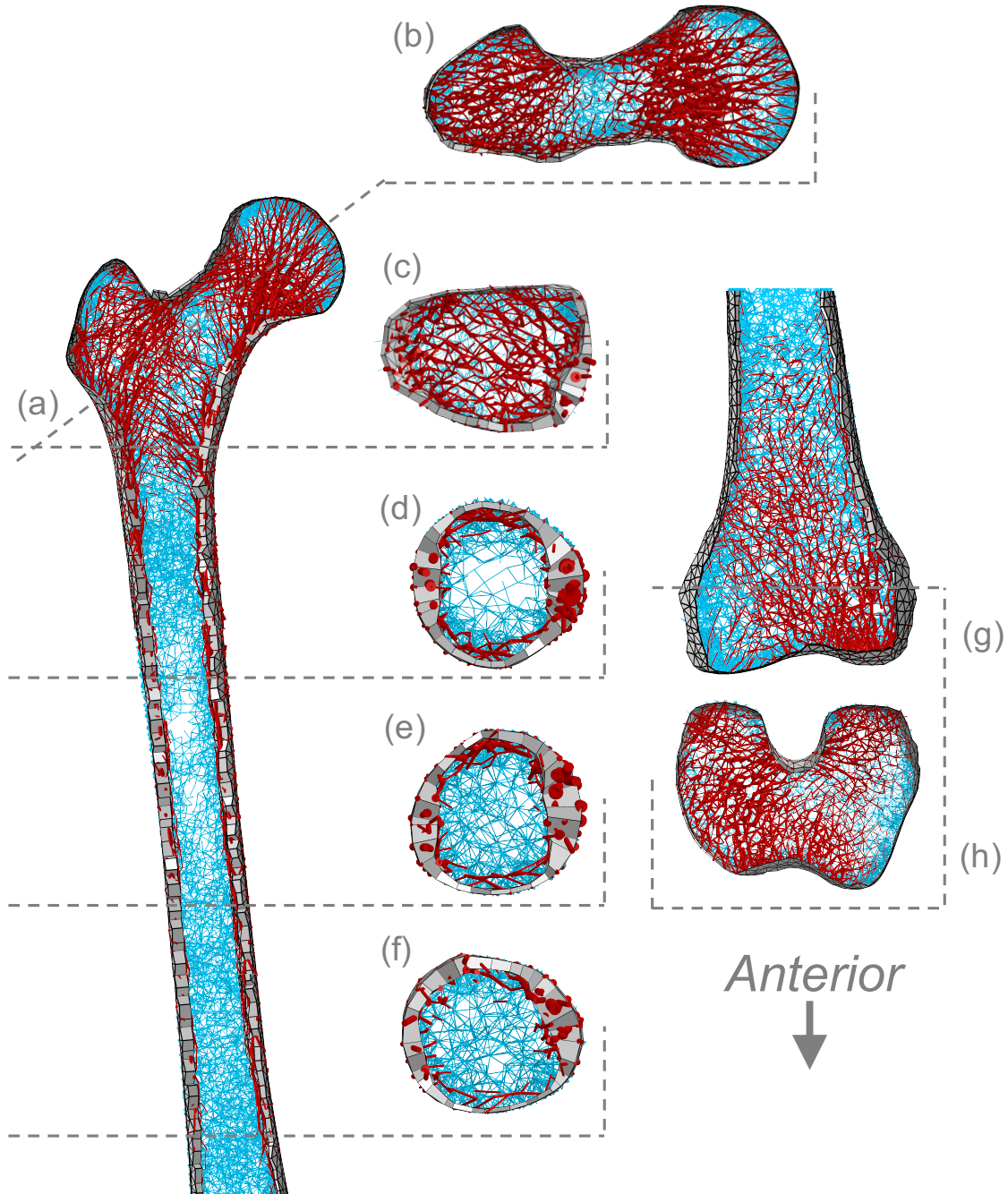


Figure 4.17: Converged femoral bone structure in the control femur. Optimised to an full able-bodied loading scenario. Recreated here from Chapter 3 for comparison to the BK amputee femur.

4.5 Discussion

4.5.1 Musculoskeletal modelling and amputee movement

MSK modelling results highlight some key differences between BK amputee and control movement. Altered loading could, in turn, affect bone density and structure over time. In general, results from MSK modelling are in good agreement with many of the trends identified in previous studies. Increased acceleration and deceleration associated with gait of the BK amputee translates to an increased ground-reaction force. Force is higher on steps with the amputated side where reduced control and proprioception lead to less-controlled movement. Functional compensation for the loss of an active ankle joint can be noted during all activities. During gait, it manifests most dramatically at the gastrocnemius and soleus of the intact ankle. The gastrocnemius is predicted to contribute more force to movement than any other muscle in the BK amputee or control subject. The hip muscles on the amputated side also work hard to control sagittal plane movement by providing power from the semimembranosus in early stance and controlled deceleration during contralateral heel-strike with the rectus femoris. As a result, hip closing force during gait in the amputated leg is larger than control, but knee closing force substantially lower. Stair ascent, sit-to-stand and stand-to-sit activities demonstrate very heavy reliance on the intact limb during movement - even more-so than in walking. As a result, none contribute significantly to the full loading envelope in the amputated limb. Substantially higher peak values occur during gait than in any other activity in both superoinferior and anteroposterior loading directions. Although sit-to-stand, stand-to-sit and stair ascent activities may provide some variety in loading profile locally at muscle insertions, the direction of total joint closing force varies far less from activity to activity in the BK amputee than it did in control which limits the overall contribution to bone loading and stimulation.

Generally, in terms of kinematics during gait, results found in this study can be considered in strong agreement with the trends identified in the previous literature despite being a single-subject case study. Results do exhibit some significant asymmetries between intact and amputated limbs during gait, as found in studies by Eshragi (2014), Jarvis (2020), Silverman (2008) and many more (Hurley *et al.*, 1990; Huang & Ferris, 2012; Nolan *et al.*, 2003; Bateni & Olney, 2002; Sanderson & Martin, 1996). The intact limb reaches

increased hip extension during push-off compared to the amputated limb. This is further demonstrated at the intact ankle joint where 20° of plantarflexion occurs, substantially more than in the amputated ankle and in the ankles of the body-matched control subject. The BK subject exhibits a prominent loading response at the knee joint with significant knee flexion occurring in both limbs. Though, in agreement with findings by Eshargi (2014) and Sanderson (1996), flexion angle is substantially higher on the sound side than on the amputated. The BK amputee subject maintains a high angle of anterior pelvic tilt as found in many other population-based studies into unilateral and bilateral amputee kinematics (Jarvis *et al.*, 2020; Devan *et al.*, 2015) and linked to the forward posture maintained by most amputees during gait employed to gain stability by bringing the centre of mass over the leading foot (Bateni & Olney, 2002).

Results from previous population-based studies highlight the considerable variation within unilateral BK amputee kinetics. Kinetic results from this study fall in line with some of the trends identified previously and disagree with others. However, this is to be expected when comparing a single-subject case study to the population at large. Unlike the majority of previous studies, hip extension and flexion moment in the BK amputee subject reach a higher peak in the amputated limb than in the intact. Typically, the opposite is expected as a higher extension moment during push-off and flexion moment during swing is thought to contribute to forward propulsion during gait. Peak hip abduction and adduction moment are double in the intact limb compared to amputated, suggesting the intact limb contributes significantly to balance in the frontal plane. At the amputated knee, the subject exhibits near-zero joint moment during early stance, significantly lower than the body-matched control. In the intact leg, early stance brings a pronounced knee extension moment, higher than in control. These trends have also been identified by Fey (2010), Bateni (2002) and Sanderson (1996) and speak to the compensatory burden carried by the intact leg in balance and controlled deceleration during early stance. The intact ankle joint provides major compensation in terms of forward propulsion during late stance in the BK amputee. Intact ankle plantarflexion moment peaks during push-off at over 1.5Nm/kg - approximately 50% higher than in the prosthetic side and in the able bodied control subject. The extent of compensation at the intact ankle could also go some way to explaining the atypically low hip flexor and extensor contribution of the hip of the intact leg. The BK amputee subject uses the ankle joint as the major driver in forward propulsion during gait. Moreover, the prosthetic ankle also demonstrates a characteristic “longer and larger” dorsiflexion moment (first identified

by Bateni (2002)) during early stance caused by the reduced plantarflexion capabilities of the prosthetic foot/ankle joint.

During gait ground reaction force is higher in steps with the amputated limb. Loss of the active ankle joint not only affects the ability of the leg to decelerate during heel-strike, but also means complete loss of proprioception and direct 'feel' for the ground during walking. These issues are less pertinent in the sound limb. This is illustrated by spatiotemporal results, which show lower accelerations and decelerations experienced during steps with the intact limb than the amputated. Additionally, both accelerations and decelerations experienced during BK amputee gait far outweigh those in control gait which demonstrates more smooth, consistent forward and vertical translation. Similar trends in acceleration and ground reaction force results were identified by others (Adamczyk & Kuo, 2015; Schaarschmidt *et al.*, 2012). Ground-reaction force during gait of both the amputated and sound limbs exhibit a double peak, similar to control. The second peak in the sound limb, however, exceeds that of the first. This is unusual when compared to control and when compared to the pattern of ground-reaction force experienced in the amputated limb, and arises due to the additional burden of forward propulsion carried by the intact limb in late stance to pushoff. Ground-reaction force during accessory activities (particularly during sit-to-stand and stand-to-sit) demonstrate very clear reliance on the intact limb in controlling the movement and position of the body centre of mass. Measured ground-reaction force was over 25% higher on the intact side during standing of the BK amputee and 20% higher during sitting illustrating the significantly increased burden placed on the intact limb during each activity.

In terms of muscle forces, the single largest force contribution to loading in the BK subject is the gastrocnemius in the intact leg during gait. It provides a peak value of almost 18N/kg of force during pushoff. This is more than double the contribution in the amputated limb and over 50% more than any other muscle contribution in either the BK or control subject. Significantly, this will take a significant burden of propulsion off the surrounding muscles in both the intact and amputated limbs. So many studies highlight the asymmetry of BK amputee gait, muscle activity and the over-reliance of unilateral amputees on the intact limb (Eshragi *et al.*, 2014; Jarvis *et al.*, 2020; Silverman *et al.*, 2008; Hurley *et al.*, 1990; Huang & Ferris, 2012; Nolan *et al.*, 2003; Bateni & Olney, 2002; Sanderson & Martin, 1996). At the knee joint, this will also contribute significant force to the overall joint closing force.

In the absence of an active ankle joint, the BK amputated limb seems to generate forward movement primarily through use of the semimembranosus during early stance to carry the body centre of mass over the foot. The rectus femoris also provides significant force contribution during late stance in decelerating the body centre of mass before heel-strike of the sound limb as found in Fey (2010). This illustrates another key difference between gait of the control subject and gait of the BK amputee. While control gait demonstrates complimentary cooperation between muscles to generate smooth movement, BK amputee gait seems to be characterised by a higher frequency of co-contraction (Isakov *et al.*, 2000) and, generally, less consistent muscle contractions working to either accelerate or decelerate the body centre of mass many times per step.

As previously eluded to, predicted muscle forces have important implications on bone loading and bone structure. Muscle loading pattern and magnitude are clearly very different in the amputated and sound limbs. Not only will independent muscle forces contribute to local bone loading at origin and insertion points, but they also contribute significantly to the total closing force of a joint which accounts for both the passive joint reaction force due to external forces (ground-reaction force) and also the active effect of muscles working across joints contributing to pressure within a given joint. Muscle force compensation by the intact leg during gait translates to a substantially reduced joint closing force at the amputated knee compared to control and compared to the intact limb, a finding in agreement with studies by Silverman (2014) and Miller (2017). This is also despite increased ground-reaction force due to reduced proprioception in the amputated limb. Lower contribution of the gastrocnemius and soleus during gait play a significant role in this. At the hip, however, significantly increased recruitment of the semimembranosus and the rectus femoris muscles see total hip joint closing force increased in the amputated limb compared to control which provides some positive bone-loading potential looking ahead to finite element modelling.

By comparison, knee joint closing force in the intact limb of the BK amputee peaks at a similar value to the control subject (Silverman & Neptune, 2014; Miller *et al.*, 2017) and hip joint closing force in the intact limb well-below both the control subject and the amputated limb. The latter prediction is particularly unexpected, contradicting measurements and predictions in a previous study by Fantozzi (2011). The BK subject seems to rely most heavily on, firstly, the gastrocnemius of the intact limb and, secondly,

the hip flexors and extensors of the amputated limb which is less common in the BK amputee population.

It is very important to note that the three most important accessory activities (sit-to-stand, stand-to-sit and stair ascent) also included in simulations contribute relatively little difference in terms of joint force at the knee and hip. In the control subject, these three activities (as well as stair descent) provided very important levels of anterior loading at the knee as well as posterior and medial loading at the hip joint that were not present during gait. In the BK subject, these activities provide very little pronounced loading in the anteroposterior and mediolateral planes, substantially less than during gait. The magnitude of vertical loading is also reduced in the cases of sit-to-stand/stand-to-sit activities. While in the control subject, each different activity contributes important variation in joint loading direction this is seemingly less the case in the BK subject due to heavy compensation of the intact limb during movements which see reduced ground-reaction force and muscle forces in certain key areas. Compensation by the intact limb is demonstrated by the discrepancy in ground-reaction force acting through each leg. This has a compounding effect on joint closing force as reduced weight-bearing also leads to reduced muscle contribution during the movement and seen in Figure 4.13.

4.5.2 Finite element modelling

FE results demonstrate the effect of altered loading post BK amputation on the femur of the amputated limb. Changes in loading scenario can have a considerable knock-on effect on bone stimulation and long-term bone remodelling. Risk resorption plots suggest direct compression of the femur is reduced compared to control. As a result the principle and secondary compressive trajectories in the proximal femur, and significant portions of the trabecular bone in the distal femur are at risk of bone resorption due to reduced loading. Predictive modelling confirms the potential for subsequent deterioration of bone architecture over time, predicting up to 12% trabecular bone loss within 5 years. Such substantial loss of bone structure would dramatically increase an amputee's lifetime risk of fragility fracture. Particularly, in the young amputee population this would have serious implications on long-term mobility, morbidity and quality of life.

Figure 4.14 predicts a few specific areas of bone to be at most immediate risk of bone resorption. The whole of the principle compressive trajectory and the largest

trabeculae in the secondary compressive trajectory demonstrate a high risk of bone resorption. Trabecular bone running longitudinally from the centre of the two distal femoral epicondyles is also at significant risk. As are certain trajectories running anteroposteriorly from the surface of the patellofemoral joint. This pattern of reduced loading can be directly attributed to altered loading at the knee joint of the BK amputee compared to control. Reduced vertical and anterior loading at the knee and patellofemoral joint (particularly prominent during sit-to-stand and stand-to-sit activities in the control subject) reduces the global bending affect of load on the femur substantially. Subsequently, the principle and secondary compressive trajectories transmit greatly reduced strain compared to control. This is similarly the case in the distal femur where reduced overall bending of the femur plays a role in reducing compression on the posterior trajectories of trabecular bone and reduced tension on anterior trajectroies. In the distal femur this effect is additionally compounded by the reduced direct effect of pressure acting on the bone surrounding the knee and patellofemoral joint. In general, increased longitudinal joint force acting at the hip of the BK amputee is not enough to counteract the effect of reduced anterior and longitudinal loading at the knee from a bone stimulation perspective.

The vast majority of cortical bone in the BK amputee is adequately loaded and at little to no risk of bone resorption. Only 4% of cortical elements experience a maximum principle strain below target strain. Having said that, bone resorption risk pattern does demonstrate slightly increased loading in the anteroposterior direction over the mediolateral. This is in large part due to the natural bend of the femur, but could also be indicative of reduced muscle loading in the frontal plane compared to the sagittal. Muscle forces predicted from MSK modeling support this, forces from the adductor/abductor muscles are far outweighed by the primary sagittal contractors of the hip such as the semimebranosus and rectus femoris.

Other specific pockets of resorption risk also exist in large part due to a reduced variety of loading directions present in the BK amputee subject. Despite including multiple different loading activities, compensation by the intact limb seems to limit loading in anteroposterior and mediolateral planes of the hip and knee of the amputated limb compared to control. The absence of the stair descent activity would, theoretically, contribute positively to the overall loading envelope, although the extent of its contribution is probably minimal. This is based on control results from stair descent which, at the knee, demonstrated a very similar loading profile to stair ascent.

Separating the BK amputated loading scenario into muscle forces and joint forces alone further highlights this lack of loading variety in the femur. Both joint and muscle forces contribute comparatively little in terms of stimulation in the frontal plane. This is in contrast to control where joint and muscle loading both played pivotal and complimentary roles in stimulating different parts of the femur structure in both the mediolateral and anteroposterior directions. Muscle loading in the BK amputee actually promotes significant strains, more than loading by the joint contact forces alone and in some areas of the femur even more than in control. Once again, these results suggest that the issue in bone stimulation for BK amputees is not necessarily the absence of loading magnitude but the absence of loading variety that could be attributed to functional compensation of the intact limb, particularly at the knee joint.

As a whole, muscle force contributes to significant bone loading in two different ways. On a local scale, individual muscle origin and insertion points are placed into tension by the muscle contractions pulling against the surface of the bone. The effect of this is well-demonstrated by both the risk resorption plot and the separated muscle force loading analysis. Increased hip muscle activity translates into areas of low/no risk of bone resorption at specific origins and insertions. For example, contractions of the adductor muscles and gluteus maximus will place cortical bone (and neighbouring trabeculae) on the posterior aspects of the femur, along the linea aspera, into tension. Similarly, the psoas and gluteus minimus muscles will promote stresses at the lesser and greater trochanter, respectively. Muscle forces can also have a wider global effect on the femur by effectively placing the whole structure into bending. In the case of the BK amputee, muscle force seemingly force the midpoint of the femur to arc posteriorly, promoting large-scale compression along the anterior surface and tension along the posterior (compounded by the local effect of muscle forces previously discussed). In the control subject, this effect is augmented by joint reaction forces and the natural curvature of the femur which promote a similar pattern of strain in the cortical bone of the femur.

Results of predictive modelling illustrate the potential long-term effect that differences in the BK amputee loading scenario could have on bone structure. Over the course of multiple remodeling cycles, areas of reduced stimulation are expected to experience thinning of trabecular and cortical elements as they adapt towards a target strain of $1250\mu\epsilon$. The bone resorption risk plot in Figure 4.14 proved to be a good indicator of where bone loss could be expected. Over the course of 60 month-long remodeling cycles

(approximately representative of 5 years) the femur structure lost a total of 12% trabecular density. Most prominent trabecular bone loss occurs in the distal femur. Almost all of the thicker trabecular trajectories (displayed in burgundy) thin considerably from the control scenario, many of them disappearing altogether (this can be most clearly seen in slice (h)). In particular, large areas of the medial epicondyle lose trabecular bone volume. This could be a result of reduced anterior loading at the knee joint compared to in control. The proximal femur experiences significant trabecular bone loss as well, though less than in the distal femur. The reduced overall global bending of the femur affects bone in the compressive trajectories most significantly. Trabecular bone fanning perpendicularly to the femoral head thins considerably. Larger trabecular elements in the secondary compressive trajectory, extending from the medial wall of the proximal femur across towards the greater trochanter, also deteriorate. Though, some slight bone loss also takes place in the tensile trajectories the difference is relatively small compared to elsewhere. It is also important to note that despite a net loss of trabecular bone, some trabecular thickening does actually occur in the BK amputated femur at posterior muscle insertion points of the lesser and greater trochanter. This speaks to the potential of muscle loading in long-term preservation or even strengthening of bone structure. It does however, also highlight the need for improved and varied direct joint loading as increased muscle contractions alone were not able to conserve trabecular bone across the whole femur.

Overall, the positive effect of muscle loading seemed to play a larger role in preservation of cortical element thickness. Net cortical bone volume is actually entirely preserved in the BK subject. Cortical thinning that takes place along the medial wall of the femoral shaft and down into the distal femur is counteracted (in terms of bone volume) by cortical thickening that occurs in the posterior and lateral walls of the shaft.

Considering both trabecular and cortical structural adaptation from predictive modelling, a significant net bone loss occurs in the BK amputated femur. The extent of deterioration experienced would, inevitably, lead to a greatly increased risk of lifetime fragility fracture. The amputee population have been shown (Chapter 2) to suffer these levels of bone deterioration from a much younger age than in the typical AB person making the issue particularly important.

4.5.3 Limitations

In the unilateral BK musculoskeletal model no damping effect from socket pistoning or residuum tissue deformation is included. Moreover, contact between the socket and upper shank is simplified for modelling purposes. The musculoskeletal model does not recreate socket suspension or patellar-tendon bearing which would require the addition of a new joint between the anterior aspect of the socket and the patello-femoral joint. The modelling of these features may result in further changes to the pattern of loading at the hip and knee joint. However, the direct loading effect of each of these design features has yet to be quantified and fully understood. Socket design and fit remains a highly subjective process. Therefore the added complexity in modelling each would not necessarily bring more representative results. Regardless of simplifications made in musculoskeletal modelling, results are in agreement with many trends identified in literature. Moreover, maximum marker errors and recorded root mean square errors were below 2cm throughout suggesting the model was able to track experimental data sufficiently well.

The absence of a stair descent activity in contribution to the total finite element loading scenario represents a noticeable difference between control and BK amputee modelling. However, the relatively small contribution of stair descent to loading in the control subject coupled with the limited contribution of stair ascent to loading in the amputee subject suggests the effect of its absence is negligible. Figure 3.19, recreated here from Chapter 3, demonstrates that stair descent contributes the least to overall bone structure in a healthy load case.

Predictive finite element modelling also presents some key simplifications. Changes made to the bone adaptation algorithm used in Chapter 3 to incorporate a time dependence in predictive modelling are highly simplified, namely, the assumption that cortical and trabecular bone should adapt at a maximum rate of 2% and 1% per remodelling cycle, respectively. These figures are in line with some of those quoted in previous studies of extreme bone loss, though, even between these studies, figures are highly variable. Additionally, the assumption that maximal bone deterioration and maximal bone apposition occur at a similar rate could be questioned. However, as a whole the model still presents good representation of how time dependent bone remodelling can be a powerful tool in the future. Fine-tuning of the rate of bone adaptation can be

adjusted with relative ease and linked more closely to particular populations, such as younger children (Specker *et al.*, 2010)), in more specific modelling scenarios.

Chapter 5

Bilateral above-knee amputee subject

5.1 Introduction

Chapter 5 investigates femur and hip-joint loading in the above-knee (AK) amputated limb of a bilateral above-knee/through-knee amputee subject. This was achieved using patient-specific musculoskeletal (MSK) and finite element (FE) models informed by imaging data and experimental motion capture data. The chapter outlines the development of each model in depth (noting essential modifications to the two previous subjects) and how each model has been applied to analyse hip-joint loading in an AK amputated femur. Predictive modelling, once again, determines the effect of altered loading on the internal architecture of the amputated femur in order to further examine the clinical findings in Chapter 2 with in-silico modelling. Comparisons are made between equivalent results in the bilateral amputee and able-bodied (AB) control subject throughout.

The chapter also presents an additional investigation carried out into the effect of ischial containment and the results of sensitivity studies performed to evaluate key modelling decisions and the robustness of the presented MSK and FE models. Results from Chapter 2 suggests that bone loss in the hip is more prominent in the bilateral AK population than any other amputee population. Major changes in loading patterns at

the amputated femur are expected as a result of both internal factors (joint and muscle forces) and external factors (the effect of the prosthetic socket).

5.2 Background

5.2.1 Characteristics of bilateral above-knee amputee gait

5.2.1.1 Kinematics

Above and through-knee amputations cause major compromises to the functionality of a limb. Unlike transtibial amputations, the functions of the healthy knee are lost completely. Equally, bilateral amputation can provide a more serious challenge to ambulation than unilateral. Direct proprioceptive contact with the floor is no longer present in either limb. As presented in Chapter 4, the contralateral limb in unilateral below-knee (BK) amputees also provides significant functional compensation (in terms of force generation and balance) for the deficiencies of the amputated limb (Adamczyk & Kuo, 2015; Rábago & Wilken, 2016; Breakey, 1976). Functional mobility data from Chapter 2 shows that the bilateral AK amputee population is the most physically impaired of all lower-limb amputation levels. This is supported by many other sources with both patient-reported and performance-based outcome measures (Linberg *et al.*, 2013; Gailey *et al.*, 2002; Akarsu *et al.*, 2012; Jarvis *et al.*, 2020; Henson *et al.*, 2020). As a result, bilateral AK amputee gait is expected to differ from the gait of other amputee populations, as well as from that of an AB control subject.

Functionality of any amputee can be directly related to the severity of injury/trauma as well as the extent, type and quality of surgical intervention. Subsequently, gait characteristics can differ greatly within the bilateral AK amputee population (McNealy & Gard, 2008; Cutti *et al.*, 2018). However, some key characteristics associated with bilateral AK amputee gait have been identified.

AK amputated subjects have been shown to exhibit less knee flexion at both heel-strike and weight acceptance than AB counterparts (Brandt *et al.*, 2017; Henson *et al.*, 2020; Taheri & Karimi, 2012). In passive prosthetic knee joints, maintaining a straighter knee avoids buckling and provides more stability to the amputee during stance despite resulting in more sudden deceleration of the centre of mass and an increased first peak in ground-reaction force (Broomhead *et al.*, 2012). Other microprocessor prosthetic knees possess the ability to flex on weight acceptance in an attempt to reduce this impact and

more closely mimic AB gait, however, evidence suggests that AK amputees do not always utilise this feature to its full potential (Henson *et al.*, 2020).

Both hip drop (Berger, 1992) and hip hike (Henson *et al.*, 2020; Sjö Dahl *et al.*, 2002; Michaud *et al.*, 2000; Segal *et al.*, 2006) of the swinging leg have been shown to occur in different studies. Although finding evidence of both is seemingly contradictory, both are ultimately a symptom of mechanical weakness in the hip abductors of the stance leg. Therefore, the two can be inherently linked. Weakness in the stance-leg hip abductor muscles (which work to maintain pelvic obliquity throughout single leg support) causes hip drop when not compensated by excessive torso lean in the frontal plane. Leaning of the torso naturally shifts the AK amputee's centre of mass over the standing leg and allows the opposing hip to raise up despite any abductor weakness (Henson *et al.*, 2020; Devan *et al.*, 2015; Michaud *et al.*, 2000). Hip hiking also ensures clearance of the amputated leg above the floor during swing (Hoffman *et al.*, 1997). In an AB person this can be achieved by dorsiflexion of the ankle. Hip drop during the loading response, specifically, has also been hypothesised to compensate for the lack of a clear weight acceptance phase at the knee by providing an alternative means of dampening impact (Michaud *et al.*, 2000).

Step width in the bilateral AK amputee gait is higher than in AB subjects (Highsmith *et al.*, 2010). Increased step width provides additional stability to compensate for reduced proprioception and the loss of all physiological knee and ankle joints in bilateral AK amputees (Highsmith *et al.*, 2010). Naturally, hip abduction angle is also higher on average in AK amputees than control subjects (Henson *et al.*, 2020; Jarvis *et al.*, 2020; Devan *et al.*, 2015). This stems from the increase step width as well as circumduction of the leg during swing phase. Circumduction works as another mechanism to provide clearance between the foot and the floor (Berger, 1992).

In the sagittal plane, reduced hip extension during AK amputee gait have been recorded compared to AB controls. This has been attributed to a few things: the mechanical obstruction of certain ischial containment sockets (Rabuffetti *et al.*, 2005; Hagberg *et al.*, 2005; Klotz *et al.*, 2011), hip contracture, tightness in the hip flexors (Berger, 1992) and excessive lumbar lordosis (Henson *et al.*, 2020; Berger, 1992; Goujon-Pilet *et al.*, 2008; Sjö Dahl *et al.*, 2002). The ischial brim of some prosthetic sockets can physically block excessive hip extension due to interference with the distal pelvis (Rabuffetti *et al.*, 2005). This can, in turn, encourage tightness in the hip flexors and lumbar lordosis, with each exaggerating the effect of the other (Klotz *et al.*, 2011; Jaegers

et al., 1995; Sagawa *et al.*, 2011). From a measurement perspective, when the pelvis is maintained in a position of significantly higher anterior tilt, less hip extension is required for the equivalent posterior foot position during toe-off.

5.2.1.2 Kinetics

Investigations into bilateral AK amputee joint kinetics are less abundant with only four relevant studies (Perry *et al.*, 2004; McNealy & Gard, 2008; Henson *et al.*, 2020; Jarvis *et al.*, 2020), one of which is a single case study into a subject with bilateral knee disarticulations (Perry *et al.*, 2004). Collectively, the studies present kinetic data for twenty-one bilateral amputees.

At the hip, Jarvis (2020), McNealy (2008) and Henson (2020) all find peak extension moment higher in amputees than controls. Henson (2020) and McNealy (2008) find the same for peak flexion moment, while Jarvis (2020) determines flexion moment in amputees and controls to be similar. All four studies highlight the increased power requirements at the hip of amputees to aid forward propulsion in absence of active ankle and knee joints. Results from two separate studies by Wentink (2013) and Jaegers (1995) confirm this finding by use of EMG. A further study by Visser (2011) concluded that peak hip strength correlated positively with bilateral amputee walking ability. In the frontal plane, predicted hip joint moments are lower than for controls (Henson *et al.*, 2020). At the knee, maximum extension moment was reduced during early stance and maximum flexion moment during late stance (McNealy & Gard, 2008; Jarvis *et al.*, 2020). Maximum ankle moments are largely dependent on the type of prosthesis used. McNealy (2008) and Jarvis (2020) find that plantarflexion moment to be slightly reduced during push-off compared to controls. Ankle power contribution to gait was significantly reduced compared to AB controls (McNealy & Gard, 2008; Jarvis *et al.*, 2020). Although some consistent trends can be identified, McNealy (2008) highlights a greatly increased inter-subject variability in bilateral amputee kinematics compared to controls; level of amputation, length of residual limb and prosthetic joint design will affect kinematics. This is particularly important to note in case-study analyses such as this one and that carried out by Perry (2004).

In terms of total joint contact force, Henson (2020) finds peak hip contact force is significantly higher in the AK amputee cohort than the AB controls. Additionally, he hypothesises that peak hip contact force during bilateral AK amputee gait is influenced

by increased muscle activation (correlating well with peak kinetic hip flexion moment) rather than external loading from ground-reaction force; which they find to be lower in AK amputees than AB subjects.

5.2.2 Finite element modelling of above-knee amputation

5.2.2.1 Previous FE models

FE analysis was first introduced to prosthetic socket design in the late 1980s (Zhang *et al.*, 1998). Zhang (1998) documented the first decade of models in a 1998 review paper which focused on the methods, assumptions, simplifications and efficacy of existing modelling techniques. The paper draws appropriate attention to some of the main hurdles in FE modelling of amputation. Namely, material properties, loading conditions, boundary conditions and the residuum-socket interface. Dickinson (2017) completed a review paper focusing on the current state of amputation modelling and all of these still remain important considerations today. Each model reviewed sought to evaluate the effect of prosthetic loading on either the residuum-socket interface (skin) or deeper soft tissue.

All models include the residuum soft tissue in analyses because the focus of almost all models is on the loading effect at the residual soft tissue or skin. Many earlier models approached representation of the prosthetic socket by use of rigid boundary conditions encasing the residuum (Brennan & Childress, 1991; Torres-Moreno, 1991; Mak *et al.*, 1992; Lee *et al.*, 1994). A similar technique was used by Krouskop (1987) to model the external surface of the femur within the residuum. More contemporary studies, however, have opted for explicit inclusion of these parts (as computational power and capacity has improved) (Dickinson *et al.*, 2017). The bone, residuum soft tissue and prosthetic socket make up the main parts of amputee FE models. The geometry of these parts is generally acquired through scans (most commonly CT scan, but also MRI and various types of surface-scanning techniques). These provide 3D geometry. The residuum soft tissue is most commonly represented as an amalgamation of skin, muscle and fat with only a few recent studies opting to separate these and utilise specific material properties for each (Ramasamy *et al.*, 2018; Henao *et al.*, 2020).

Material properties used have become more consistent since the first decade of modelling. Every study reviewed by Dickinson (2017) has given bone a Young's modulus

of between 10-16GPa and Poisson's ratio, ν , between 0.28-0.3. The majority of studies reviewed use linear elastic, isotropic, homogenous material properties for soft tissue (majority $E=100-1000\text{kPa}$, $\nu=0.45-0.49$). A small number use significantly more complex hyperelastic properties achieve similar results in terms of pressure and stress. However, Dickinson (2017)d does highlight the advantage of hyperelastic material models in predicting more realistic values of peak internal strain in the residuum.

There is variation in material modelling of the prosthetic socket. A few studies chose to model it as a fully rigid boundary due to its high relative stiffness compared to the residuum soft tissue. The others used a wide variety of Young's moduli and Poisson's ratio values depending on the socket build, type and material. Dickinson (2017) highlights the trend of artificially increased interface stresses when the socket is modelled as completely rigid.

Loading varies largely from study to study. In the oldest, and often most simplified studies, a single point load is applied to either the distal end of the assembly via the prosthetic socket or to the proximal end via the bone. The magnitude of this loading is assumed relative to subject body-weight. In a few, more complex loading magnitudes were determined by experimental pressure data (recorded within the socket). In more recent studies, loading has been broken down into various analysis steps where pre-stressing of the residuum is carried out during "fitting" and "donning" steps before multiple quasi-static loading steps are applied from experimental motion-capture data (Zhang *et al.*, 2013), socket pressure data (Torres-Moreno, 1991) or bone and socket displacement data from MRI scans during gait (Lacroix & Ramírez Patiño, 2011). Henao (2020) took this a step further by implementing dynamic loading at the distal prosthesis to simulate the full gait cycle using explicit dynamic loading in ABAQUS. The study recorded an increase of 23% in maximum pressure on the residuum when using dynamic loading (accounting for inertial and damping effects) compared to static. This study in particular, as well as guidance from Dickinson (2017), highlights the advantages of a physiological loading (and boundary) scenario over a simplified one.

There are two main interfaces to consider in FE modelling of amputation: the bone-residuum interface and the residuum-socket interface. Previously, the bone-residuum surface, when included, was tied or bonded (Henao *et al.*, 2020; Dickinson *et al.*, 2017; Zhang *et al.*, 1998). Dickinson (2017) further highlights that where bone is included, solid rigid bone models are most commonly employed. Having said that, none of the

cited studies have sought to investigate the effect of loading on bone, but rather the effect of loading on skin and residuum soft tissue. It is for this reason, that the residuum-socket interface has been researched in significantly more depth than the bone-residuum interface. Most recent models have opted to employ frictional contact (Dickinson *et al.*, 2017; Henao *et al.*, 2020). In fact, Dickinson (2017) presents seventeen examples of such studies. Frictional contact is considered the gold-standard for investigations into soft tissue and skin ulceration because it provides important advantages in understanding the shear stress that occurs at this interface as well as the normal stress. Although, contact modelling increases the computational cost of simulations significantly (Villette, 2016) and would have less effect at the depth of the residual bone.

5.2.2.2 Outputs and relevance

Beyond those highlighted here, there are many more examples of FE modelling of amputation. None, to the best of the author’s knowledge, seek to analyse the effect of prosthetic loading on bones of the residual limb (apart from studies into osseointegration). From 1987-1997, Zhang (1998) reported a large variety of modelling approaches but every model was focused on socket ‘fit’ and comfort. These terms were used as a proxy for describing the effect of the sockets on the skin and soft tissue of the residuum in terms of pressure, stresses and strains. This was similarly the case in the review by Dickinson (2017) where “published simulations of the causes and progression of adaptive bone remodeling were not found”. While these historical models provide useful insight into the approaches used for modelling materials, boundaries, loading and interfaces, when the focus of modelling decisions relates to replicating the in-vivo mechanical environment experienced by the femur, these decision will likely differ. In particular, complex residuum-socket interfaces carry more importance when evaluating forces on the residuum skin and soft tissue. The use of physiological loading and boundaries, however, becomes even more important. Studies have demonstrated the effect of over-constrained models on stress and strain in bone and the limitations of such rigid boundaries in predicting in-vivo scenarios. Additionally, recent work has shown the importance of a complete loading scenario in predicting the effects of daily living on bone (Phillips, 2011; Geraldles *et al.*, 2016; Zaharie & Phillips, 2018; Villette, 2016; Dickinson *et al.*, 2017; Henao *et al.*, 2020).

5.3 Methodology

5.3.1 Data acquisition

5.3.1.1 Motion data

The bilateral amputee subject tested in this study is male, 185cm in height (pre-injury) and weighing 85kg at time of data acquisition (seen in Figure 5.1). He suffered traumatic

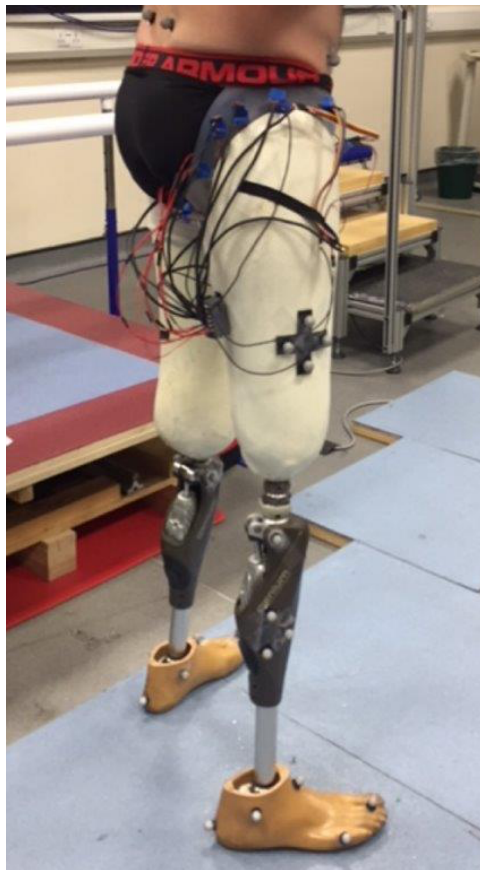


Figure 5.1: Image of the AK amputee subject during data acquisition.

AK amputation in his right leg and through-knee (TK) amputation in his left. At the time of data acquisition, it had been 7 years since the subject's last residual limb surgery. Data acquisition for this subject was carried out with Dr. David Henson and Dr. Ziyun Ding as part of a larger population-based study looking to understand the musculoskeletal function of bilateral above-knee and through-knee amputees. Ethical approval for this work was given by the Imperial College Research Ethics Committee and the NHS Research

Authority. The data acquisition process for this subject was the same as for the control subject (see Chapter 3 §3.2). Kinematic and kinetic data was collected in the same lab with the same equipment as control. The same lower-body markerset was used (Wu, 2002) with minor changes where needed on the amputated limbs. Placement of markers on the prosthesis are outlined in Table 5.1.

Marker	Marker Name	Location
ASIS	L/R.ASIS	ASIS left and right side
PSIS	L/R.PSIS	PSIS left and right side
Thigh cluster	L/R.ThighCluster. Med/Lat/Up	Triangular cluster placed on lateral aspect of thigh, on prosthetic socket
Lateral knee condyle	L/R.FemEpic.Lat	Lateral femoral epicondyle
Medial knee condyle	L/R.FemEpic.Med	Medial femoral epicondyle
Shank cluster	L/R.ShankCluster. Med/Lat/Up	Triangular cluster placed on anterior aspect of the shank, on the prosthetic limb
Lateral malleolus	L/R.TibialMal.Lat	Lateral tibial malleolus
Medial malleolus	L/R.TibialMal.Med	Medial tibial malleolus
Navicular	L/R.Navicular	Positioned on the superior aspect of the the prosthetic foot
Calcaneus	L/R.Heel	Positioned on the heel of the prosthetic foot, roughly at the level of the navicular
Metatarsal 1	L/R.1stMeta.Dist	Positioned on the superior aspect of the prosthetic foot, above the 1st toe
Metatarsal 5	L/R.5thMeta.Dist	Positioned on the superior aspect of the prosthetic foot, above the 5th toe

Table 5.1: Marker locations for the bilateral AK subject

It was, initially, our intention to collect kinematic and loading data for all six common daily physical activities (walking, standing, stair-ascent/descent and sit-to-stand/stand-to-sit) as suggested by Morlock (2001) and as done for the control subject. For the bilateral amputee subject significant impairment and the lack of active knee or ankle joints means stair ascent/descent and sit-to-stand/stand-to-sit activities could not be collected without significant recruitment of the upper body. This upper body involvement required major support by the chair handles and by the stair handrails. Without instrumenting both, meaningful muscle and joint reaction force data could not be obtained. Additionally, only a limited proportion of bilateral above-knee or through-knee amputee population are able to navigate the use of stairs independently (Narang *et al.*, 1984; Datta *et al.*, 1992), therefore, including the activity in a daily loading envelope would be inappropriate.

5.3.1.2 MRI scanning and subject geometry

3D geometry of the bone, soft tissue and prosthesis were required to build the MSK and FE models. The post-amputation location of muscle origins and insertions as well as mass and inertia properties are important in creating the adapted amputee MSK models. The geometry of the amputee residuum, femur and prosthetic socket are required in various stages of both MSK and FE model building.

Residuum geometry comes from MRI scans provided by Dr. David Henson (Henson *et al.*, 2020). In the AK amputee subject, the scans covered the area between the sacrum and the bottom of the residuum. Figure 5.2 shows one such slice of these scans. Scans were processed in Mimics (*Materialise*, Belgium) in the same way as done for the BK amputee subject in Chapter 4. Segmentation and identification of key muscles, origins and insertions allowed for proper modification of muscle insertions in the amputated MSK model as well as approximate inertial property calculations for each segment.

The geometry of the above-knee prosthetic socket was obtained by surface scanner. The scanner outputs a high resolution *.stl file which was imported into Rhino (*Robert McNeel & Associates*) and then 3-matic (*Materialise*, Belgium) for wrapping, smoothing and meshing.

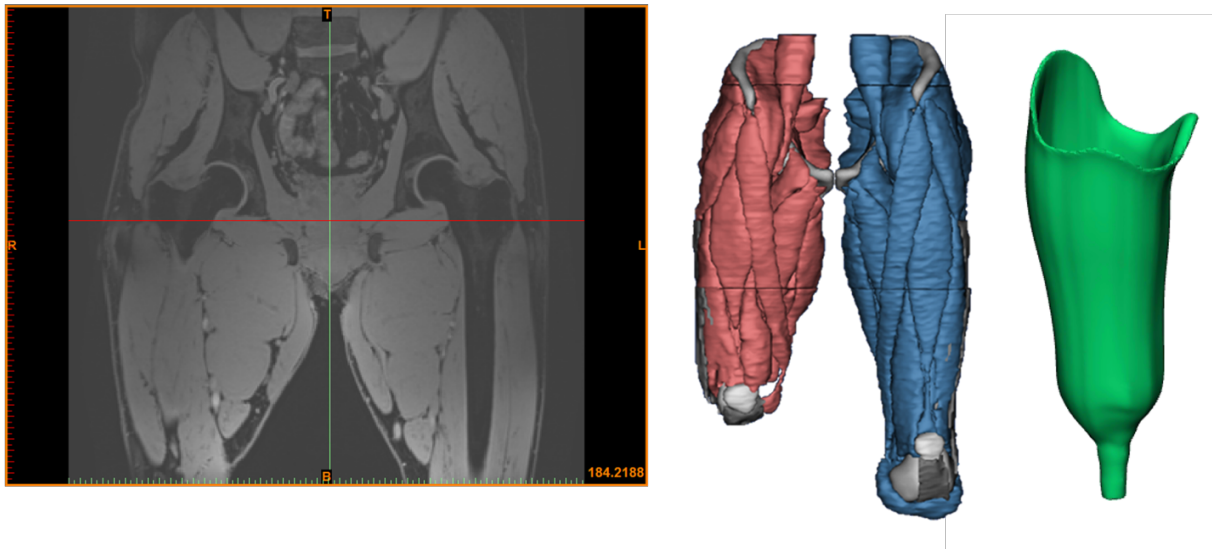


Figure 5.2: Figure displaying (from left to right) an example MRI slice from the scans of the bilateral AK subject, a 3D recreation of the subject geometry complete with key analysis objects marked on the right residual limb and the surface scanned prosthetic socket after import into 3-matic.

5.3.2 Musculoskeletal modelling - building the AK-TK model

5.3.2.1 Amputation

The AK-TK amputee model was approached with similar principles to the BK amputee model. The goal was to match key features of each model (muscle insertions post-amputation, degrees of freedom, inertial properties, joint ranges of motion) to each amputee subject. Like the BK model, the AK-TK amputee model was adapted from the London Lower Limb Model (LLLM)¹. Both amputee models were developed taking care to represent the most salient features of each amputee subject while ensuring conditions could be replicated in the FE stage of the modelling framework.

5.3.2.2 Muscle origins and insertions

As done for the BK model, muscle origins and insertions were matched to MRI scans taken of the amputee subject. Segmentation of key muscles in Mimics allowed for post-amputation insertion points to be identified in scans and altered accordingly on the MSK model in OpenSim. Muscles completely removed during amputation (for example many of those of the ankle, foot and lower leg) were removed from the MSK model altogether.

5.3.2.3 Maximum isometric force

Muscle physiological cross-section area (PCSA) data was available for the bilateral amputee subject, provided by Dr. David Henson (Henson *et al.*, 2020). As such the maximum isometric force of each muscle in the bilateral amputee model was subject-specific based on PCSA. The same tetanic stress used in the BK model was used in the AK-TK model: 55N/cm² in accordance with a study by O'Brien (2009).

¹SimTK: London Lower Limb Model, https://simtk.org/projects/lowlimb_london

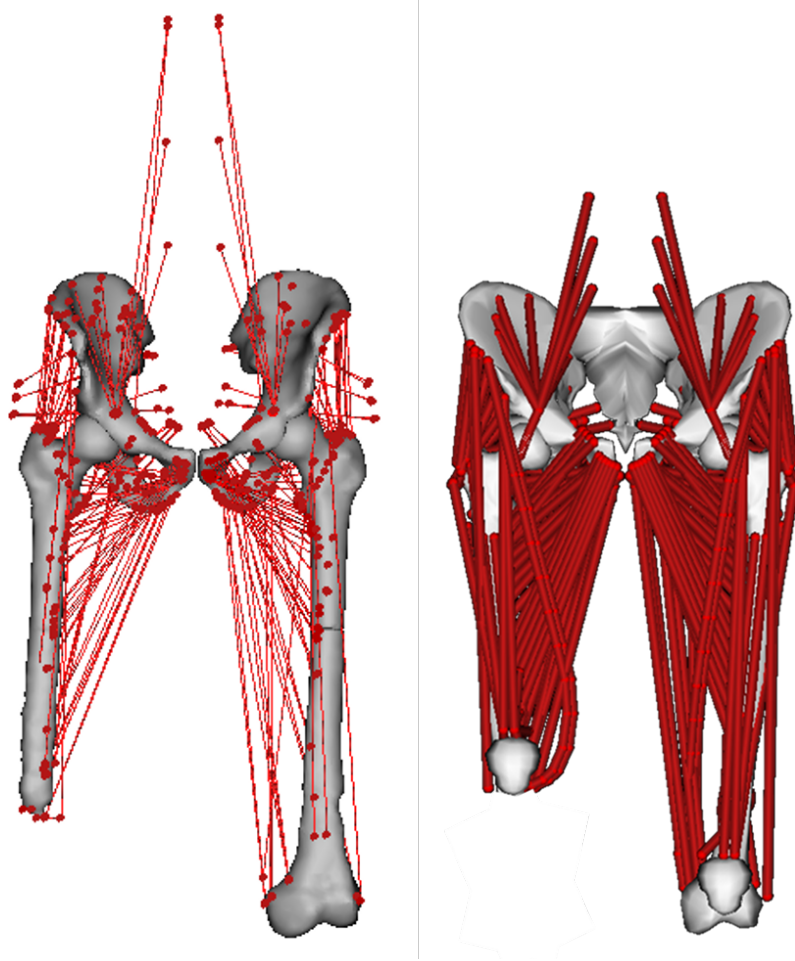


Figure 5.3: The AK-TK amputee musculoskeletal model compared to 3D visualisation segmented from MRI scans with muscle origins and insertions marked as analysis objects.

5.3.2.4 Socket and prosthesis joint changes

The bilateral amputee subject used Ottobock Genium X3² knee-joints in both amputated legs. These include single axis hinge joints with only 1 degree of freedom: flexion-extension. This matched the kinematics already permitted at the knee joint of the original LLLM. The knee joint axes were moved distally to match the new position in each limb when using a socket and prosthesis. The socket-residuum interface was modelled with an additional degree of freedom permitting socket pistoning, in line with recommendations by LePre (LaPrè *et al.*, 2017). It permitted small proximodistal translations of the socket relative to the residuum. On the above-knee amputated side these changes were introduced at a new femur-socket joint. On the through-knee amputated side the degree of freedom was released at the pre-existing knee joint.

The bilateral amputee subject used two passive Ottobock Triton low-profile feet³ with a rigid ankle joint on each leg. This was approximated by locking both foot and ankle joints in the MSK model.

5.3.2.5 Mass and inertia properties

Centre of mass and inertia properties for each lower body segment were determined in Solidworks (*Dassault Systemes S.A.*, France) using the mass properties tool. Parts were divided into separate body segments as shown in Figure 5.4. Amputee and prosthesis coordinate systems were matched in Mimics before body segments were imported into Solidworks as separate *.stl files. Each part was assigned a corresponding density value. Soft tissue (an approximation of muscle and fat) was assigned a density of 1.05g/cm³ (White *et al.*, 1992), bone a density of 1.5g/cm³ (Favier, 2019), the carbon fibre socket a density of 2.0g/cm³ (Minus & Kumar, 2005) and each prosthesis a density of 2.5g/cm³ (made up of a carbon frame and aluminium tube adapter²). Solidworks could then calculate the new centre of mass and matrix of inertia for each body segment.

²Ottobock, Genium X3: The world's most technologically advanced microprocessor knee, <https://www.ottobock.co.uk/prosthetics/lower-limb-prosthetics/prosthetic-product-systems/genium-x3/>

³Ottobock, 1C63 Triton Low Profile, <https://professionals.ottobock.com.au/Products/Prosthetics/Prosthetics-Lower-Limb/Feet/1C63-Triton-Low-Profile/p/1C63>

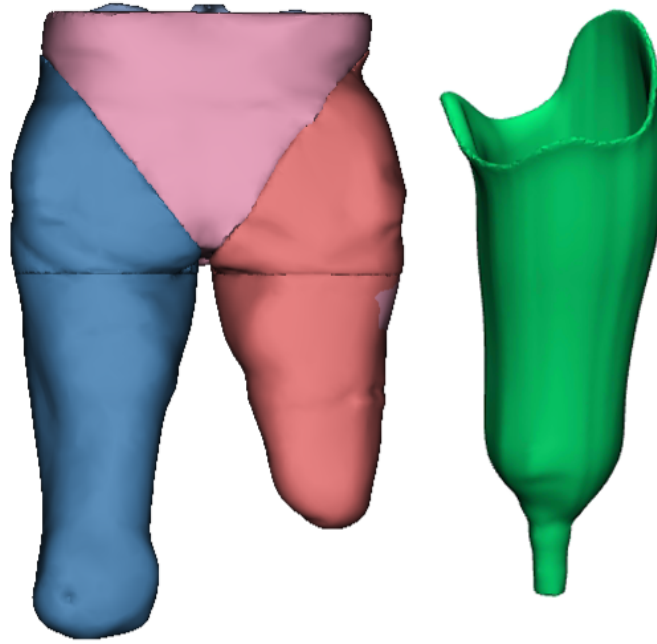


Figure 5.4: The right leg, left leg, pelvis and prosthetic socket parts, divided into segments for calculation of inertial properties using the mass properties tool in Solidworks.

5.3.2.6 Residual and reserve actuation

Residual and reserve actuation was introduced in the same way to as in the BK model. A reserve actuator was prescribed to each joint and given a low optimal force of 1N to ensure usage is heavily penalised, encouraging the model to find solutions based on muscle actuators primarily. Six residual actuators also exist at the pelvis to provide the required actuation for pelvis motion in all 6 degrees of freedom compensating for the absence of upper body contribution to movement. They are unchanged from the original London Lower Limb Model and the BK amputee model.

5.3.3 Finite element modelling - building the AK model

5.3.3.1 Model geometry and meshing

The AK FE model simulates loading in the AK amputated leg of the bilateral amputee subject only. It includes three parts: the amputated femur, soft tissue of the residuum and the prosthetic socket. As in the BK model, the adapted control femur was used in analysis of the bilateral amputee AK amputated leg. A virtual amputation was performed in Rhino to match the length of the sawbones femur to the length of the subject's amputated femur.

The level of amputation was calculated from the ratio of the length of subject's intact femur (knee disarticulation in left leg) to the subject's amputated femur. This leaves a scaled, amputated and adapted structural femur to be used in AK analyses. The amputated femur contains around 125,000 linear trabecular truss elements (T3D2) and around 7,000 linear cortical shell elements (S3).

Socket geometry is acquired by surface scanning the subject's ischial containment socket. This generates an *.stl file which was imported into 3-matic and meshed with around 34,000 S3 shell elements of 3 mm edge length. The external geometry of the residuum soft tissue is created to match the internal geometry of the prosthetic socket. The residuum is meshed with around 190,000 C3D4 tetrahedral continuum elements. The socket, residuum and femur parts are all aligned to the same coordinate system according to ISB recommendations (Wu, 2002).

5.3.3.2 Key design features

The inclusion of the prosthetic socket and residuum is pivotal in determining how force is transferred to bone through a prosthesis. The majority of this study focused on understanding the effect of prosthetic shielding (the dissipation of forces over the area of the prosthetic socket and residuum soft tissue) and the reduction in end loading (from use of suspension sockets). The latter was modeled with a small distal gap between the end of the residuum and the prosthetic socket. An additional, smaller, sub-study investigates the effect of ischial weight-bearing.

The residuum-socket interface used tie constraints. This interface has been represented with frictionless (Dickinson *et al.*, 2017; Zachariah & Sanders, 2000) and frictional (Dickinson *et al.*, 2017; Zachariah & Sanders, 2000; Henao *et al.*, 2020) contact in previous studies, however, the use of contact comes with a significant increase in computational demand. All previous studies were focused on investigating pressure and stress at the skin level, while this study is focused deeper at the mechanical environment within bone thus simplified constraint conditions were chosen at the residuum-skin interface to spare computational time and power. The bone-residuum interface was also connected by tie constraints, as has been done in all previous AK amputee studies using the FE method. This saved significant computational time and power considering the size of the model.

5.3.3.3 Loading and boundary conditions

As in the control model, loading and boundary conditions were matched to those used in the MSK model. At the hip joint, loading and ‘floating’ boundaries are transferred through identical applicators and fixators to the control model (Figure 5.5). The knee joint differs with the introduction of the residuum and socket. Unlike in the control model (where the force is distributed across medial and lateral condyles) the knee joint contact force is applied to the bottom stem of the prosthetic socket via a single point (at the new knee joint centre) and stiff beam elements. ‘Floating’ boundary conditions at the knee are applied to a different, but coincidental point by softer beam elements. Muscle forces are applied to the amputated femur as in the control and BK amputee models.

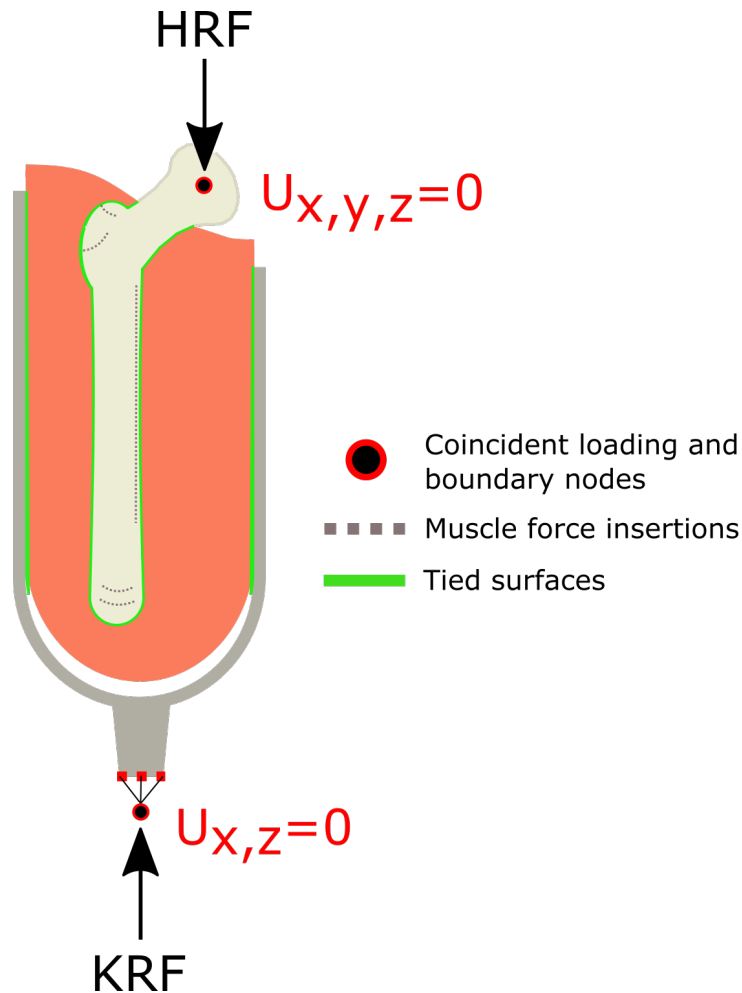


Figure 5.5: A schematic showing the boundary, loading and interface conditions used in FE modelling of the AK amputee femur, residuum and socket. Muscle forces were applied as point loads at the position of each muscle origin or insertion on the surface of the femur.

5.3.3.4 Material properties

Table 5.2 shows a full list of material properties used in the bilateral AK amputee model. All material properties are linear isotropic including a highly simplified residuum soft tissue model. Muscle, fat and skin are combined into a single set of material properties rather than each represented separately. Although previous studies have demonstrated the relative benefit of using more complex hyperelastic soft tissue properties on results at the socket-residuum interface, this brings with it an increased computational demand. The focus of this study lies at the mechanical environment within the bone, therefore simplified soft tissue properties were considered appropriate.

Table 5.2: Material properties used in bilateral AK amputee subject FE model.

Material	Young's Modulus/MPa	Poisson's ratio
Bone	18,000	0.3
Soft tissue	0.15	0.45
Carbon fibre	20,000	0.3
Cartilage (applicator layer 2-3)	10	0.49
Congruent bone (applicator layer 3-4)	18,000	0.3

5.3.3.5 Core FE analyses

Predictive modelling was carried out with the AK model in the same way as it was with the BK model in §4.3.3.3. The same principles of bone adaptation and remodelling were used with the same thresholds of strain used to guide bone resorption and bone apposition on an element by element basis.

Similarly, muscle and joint force analyses were carried out to investigate the independent effect of each on loading at the femur (as explained in §4.3.3.4). This analysis is made, perhaps, even more interesting in the case of the AK amputee given the additional effect of the prosthetic socket-residuum interface on direct joint loading.

5.3.3.6 Ischial weight-bearing mini-analysis

An additional study was carried out to model the concept of ischial weight bearing (a result of using ischial containment and quadrilateral sockets) and its subsequent effect

on bone loading. Theoretically, it allows for more comfortable ambulation by taking pressure off of the end of the amputated femur. Some of the load is, instead, guided into the ischium of the amputee via the medial brim of the socket. Ischial containment socket design is guided by the idea that approximately 50% of an amputee's weight should be supported at the ischium, although this is not measured or qualified quantitatively during the design process.

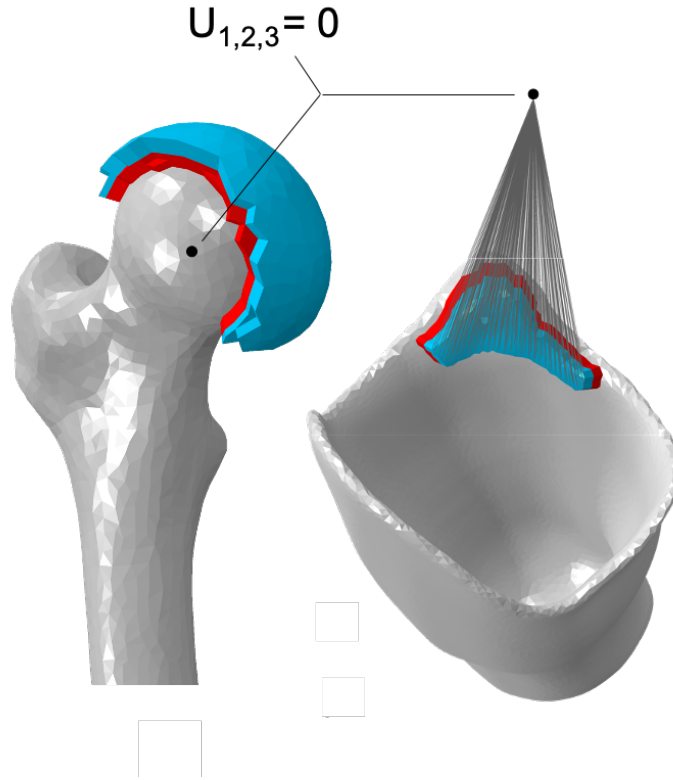


Figure 5.6: Both load applicators used to separate force between the medial brim of the ischial containment socket and the hip joint.

In FE, ischial containment was modelled using an additional load applicator placed on the ischial brim of the socket (Figure 5.6). The applicator was attached to a node located at the L5S1 joint by stiff beams. The stiffness of the applicator shell elements were varied to encourage different amounts of the load (up to 50% of the total force) through the ischial brim of the socket. For this study, a simplified loading scenario was also used. A single loading step with peak knee joint closing force (during gait) was applied to the bottom of the prosthesis at the knee joint centre. Boundary conditions were applied to respective nodes at the hip joint (attached to the femoral head) and at the L5S1 joint (attached to the socket).

5.4 Results

5.4.1 Spatiotemporal characteristics

The pattern of acceleration and deceleration at the pelvis throughout amputee and control gait was compared. The AK-TK amputee subject experiences substantially higher horizontal (1.9m/s^2 vs. 0.63m/s^2) and vertical (2.1m/s^2 vs. 2.0m/s^2) acceleration and substantially higher horizontal (4.9m/s^2 vs. 0.93m/s^2) and vertical deceleration (2.0m/s^2 vs. 1.3m/s^2) than the control subject during gait. This could be important in contextualising ground-reaction force results as well as joint-contact force experienced at the knee and hip. Similar trends are also reflected in accelerations measured at the femur on a local level.

5.4.2 Ground reaction force

Experimental data captured three strides of bilateral amputee gait – two strides with the leading AK amputated leg and one with the trailing TK amputated leg. Ground-reaction force during strides with each leg were similar in terms of shape and amplitude. Measured peak force was higher in the AK amputee subject than in the control subject as seen in Figure 5.7. Peak force occurred at heel-strike and toe-off (approximately 1.2 times BW compared to <1 BW for control) creating two prominent double peaks at the beginning and end of single-leg stance. A third, less-prominent peak appears during the loading response to mid-stance.

5.4.3 Kinematics

Figure 5.8 shows results of inverse kinematics in the AK amputated limb of the AK-TK amputee subject. In the sagittal plane, hip and knee range of motion during gait is similar in both limbs. Heel-strike occurs at just under 50° hip flexion and 5° knee flexion in both limbs. Unlike the AB subject, neither leg exhibits a particularly prominent loading response at the knee joint during the stance phase. Both knees extend towards mid-stance and maintain a neutral position (around 0° flexion/extension) throughout the remainder

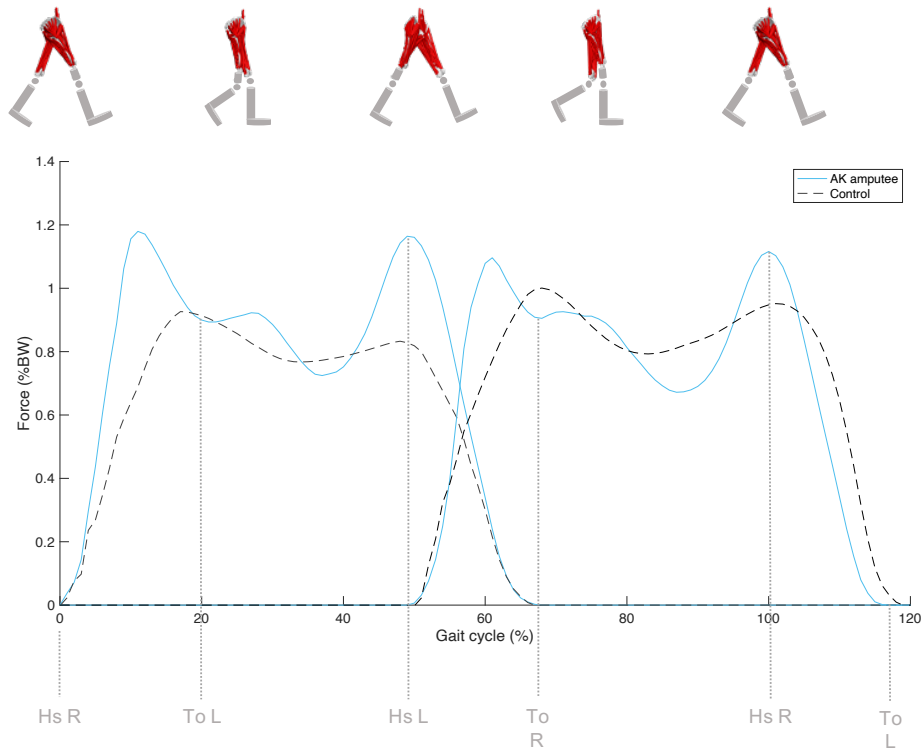


Figure 5.7: Ground reaction force comparison between the AK amputee and control subject.

of the single leg-stance phase. The extension of the knee at mid-stance corresponds to the middle peak in ground-reaction force. Both legs reach peak hip extension of 5° - 7° at toe-off. Knee flexion peaks at just under 70° in both legs during mid-swing before extending to heel-strike at 5° flexion. Peak hip flexion occurs just prior to heel-strike, nearly 55° in both legs - almost 20° higher than in the control subject. Hip range of motion during gait is substantially higher in the AK amputee than the control subject. The AK amputee also maintains a very high anterior pelvic tilt (over 15°) throughout the full duration of gait with peak AK anterior tilt, of over 20° , occurring at toe-off of the AK amputated leg. The pelvis of the control subject maintains a posterior tilt throughout.

In the frontal plane, kinematics are less symmetric than during control gait. This may stem from the tendency of the AK-TK subject's pelvic obliquity to favour a small drop towards the right AK amputated leg. This is most prominent during the contralateral stance phase of the TK amputated leg where hip drop peaks at just over 10° . During stance of the AK amputated leg, a lower peak pelvis obliquity of 4° occurs, once again, towards the swinging leg side. At the hip, the AK-TK amputee favours a higher degree of hip abduction (15° peak during early swing) than hip adduction (5° peak during push-off). The opposite is true in the left TK amputated leg where peak adduction (12°) is substantially higher than peak abduction (5°).

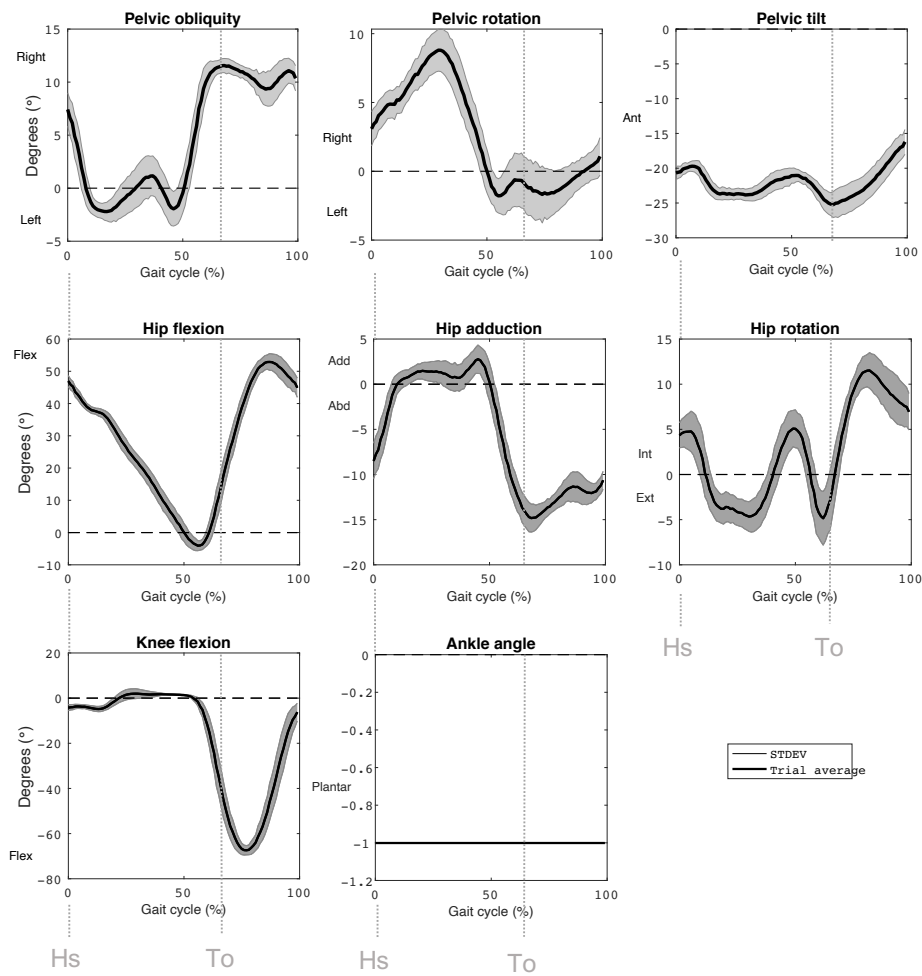


Figure 5.8: Inverse kinematic results from gait of the AK amputee subject.

The pelvis of the bilateral amputee subject rotates towards the lead leg during gait. It peaks at approximately 5° - 10° during early-mid stance. Hip rotation in both legs of the bilateral amputee subject favours a slight internal rotation throughout gait, oscillating between 5° external rotation and 10° - 15° internal rotation throughout the cycle.

AK-TK subject kinematics differ from that of the control subject in a number of ways. From a loading perspective, we can anticipate the key differences. Increased hip sagittal range of motion, abduction angle and anterior pelvic tilt may have significant impact on muscle force generation. The lack of a loading response at the knee and increased decelerations suggests potential for less shock absorption upon heel-strike and subsequently increased joint reaction forces generated from the ground up.

5.4.4 Kinetics

Sagittal joint moments outputted from inverse dynamics are symmetric across both legs in the AK-TK amputee subject. Kinetic data for the AK amputated limb are shown in Figure 5.9. Hip extension moment peaks at roughly 1.5Nm/kg during the loading response phase in each leg. Knee flexion moment increases to a peak of 0.5Nm/kg in early-mid stance, just after toe-off of the contralateral leg. Pelvic tilt moment varies between roughly 1Nm/kg of anterior and 1Nm/kg of posterior pelvic tilt. Peak anterior moment occurs during the loading response of the AK amputated limb. The moment then shifts towards a posterior pelvic tilt peak at terminal swing. The prosthetic ankles experience a sharp rise and fall in flexion moment throughout terminal stance and push-off. Peak moment at toe-off is slightly higher in the TK amputated leg than the AK (1Nm/kg versus 1.2Nm/kg). Neither ankle experiences any significant plantarflexion moment throughout gait.

The hip abduction moment peaks in both legs at terminal stance to toe-off. The AK amputated limb experiences a higher abduction joint moment throughout gait than the TK amputated limb (peaking at 0.6Nm/kg and 0.3Nm/kg , respectively). Following toe-off this moment rapidly shifts towards the peak adduction moment in both legs during early swing. Peak adduction moment in both hips falls between 0.3 - 0.4Nm/kg . The pelvis experiences significant obliquity moments that mirror its kinematic position. As the hip drops towards the swinging leg, a moment of between 0.5 - 1Nm/kg works to resist the motion.

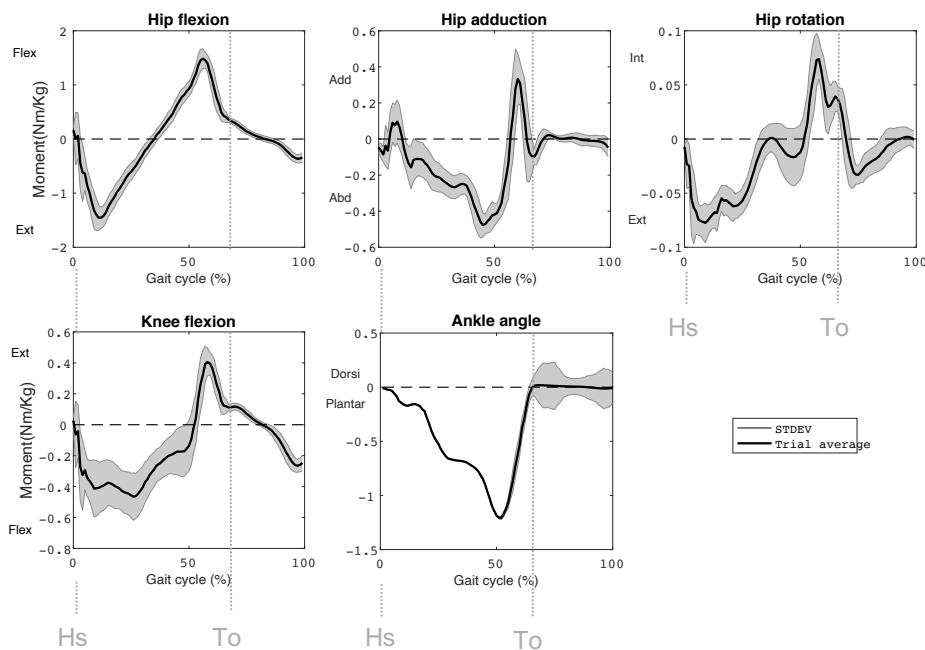


Figure 5.9: Inverse dynamics results from gait of the AK amputee subject.

Peak hip rotation moment in each leg is small 0.08-0.15Nm/kg in both external and internal rotation. The external rotation moment builds throughout the first half of stance before dropping to 0 by contralateral heel-strike. The swing phase in both legs sees a peak in internal rotation moment.

Some noteworthy differences arise in hip kinetics when compared to control. Higher sagittal hip range of motion is reflected by the substantially higher hip joint moments achieved at max flexion and extension. Similarly, adduction moment at the hip is also considerably higher in the AK subject than the control due to a consistently higher hip abduction angle. An extended knee flexion moment occurs during stance where the control subject experiences a knee extension moment - this is likely a compensatory response to reduced proprioception and less controlled deceleration occurring at the knee of the lead leg during loading response.

5.4.5 Muscle forces

Figure 5.10 shows muscle contraction force per unit weight for the AK amputated leg of the AK-TK amputee subject. As can be seen, the hip extensors in both legs begin force production during terminal swing before rising to a peak during the loading response in early stance. Force production is mainly driven by the semimembranosus and

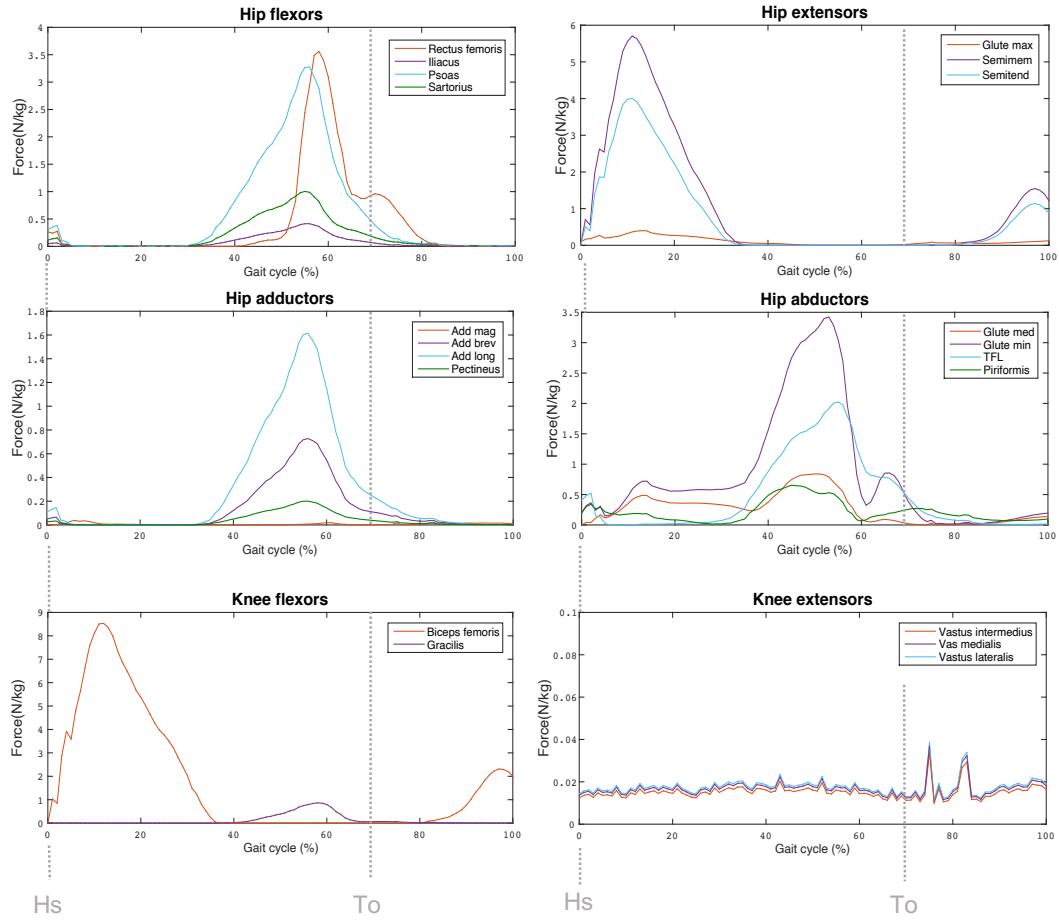


Figure 5.10: Predicted muscle forces experienced during AK amputee gait. Separated into (pre-amputation) hip flexors, extensors, adductors, abductors, knee flexors and extensors for direct comparison to control results.

semitendinosus, the gluteus maximus contributes less. Hip extensor contraction drops to zero by mid-stance. Force production is substantially higher in the TK amputated leg than in the AK amputated leg.

Low gluteus minimus force production begins at heel-strike and maintains throughout the loading response before increasing rapidly to a peak at push-off. During push-off the TFL, gluteus medius and piriformis contribution also increases. Both legs follow a similar pattern of force production in the hip abductors, however, the muscles of the AK amputated leg are required to contribute substantially more force.

The psoas major, sartorius and iliacus begin contractions after the loading response, gradually increasing towards peak contraction during push-off. Rectus femoris contribution begins only after contralateral heel-strike. The hip flexors continue to contract during pre-swing into early swing before falling to zero at mid-swing. Hip flexor muscles in both legs work symmetrically in terms of contraction time and amplitude.

The hip adductor muscles follow a very similar contraction pattern to the psoas major. In both legs, the force production increases gradually from mid-stance to a peak during push-off before falling to zero at mid-swing. More force is required in the AK amputated leg than the TK during gait; the adductor longus and brevis contribute the majority of force in both.

Given that both legs have been amputated above the knee joint, the contribution of any monoarticular muscles that previously crossed the knee (the vastus muscles) is zero. Previously biarticular knee flexors (such as the biceps femoris) and knee extensors (such as the semitendinosus, semimembranosus, rectus femoris and gracilis) contribute to movement as hip extensors and hip flexors, respectively.

In terms of the time and location of peak muscle activations, predicted muscle force plots for the AK-TK subject are quite similar to those predicted for the AB control subject. Perhaps the only specific difference can be found in activation time of the semimembranosus and semitendinosus. In the control subject, peak activation occurs in terminal swing whereas in the AK-TK subject this occurs firmly during early stance. However, we do find many noteworthy differences in terms of muscle activation magnitude. In general, muscle force is greatly increased in the amputated subject. Force generation in both the hip flexors and hip extensors is significantly increased. The increased flexion burden seems to be carried by the psoas and the extension burden by the re-attached

biceps femoris which would have contributed to both hip extension and knee flexion pre-injury. Hip abductor and adductor muscle force is also higher in the AK-TK subject, contributing about 2-3 times more force per kilogram than in the control case.

5.4.6 Total joint closing force

The total joint reaction force follows a similar shape in both the hip and knee of the AK-TK subject though forces of a significantly higher magnitude are experienced at the hip (as can be seen in Figure 5.11). Peak values occur during early and late stance as the joints contribute to deceleration during the loading response and acceleration during push-off, respectively. At both peaks, the joint reaction force at the hip is substantially higher than at the knee. The AK amputated leg experiences a maximum hip reaction force of approximately 5 times BW at push-off while knee-joint reaction force in the prosthesis peaks near 1 times BW. Peak hip closing force is about 1.5 times BW more in the AK subject than the control, while knee closing force peaks over 3 times BW higher in the control subject than the AK. Without any muscles crossing the knee joint of the AK-TK amputee the plot closely reflects the shape and magnitude of the ground reaction force. While the hip joint closing force accounts for both the joint contact force (from the ground up) and the contraction of all muscles crossing the hip joint.

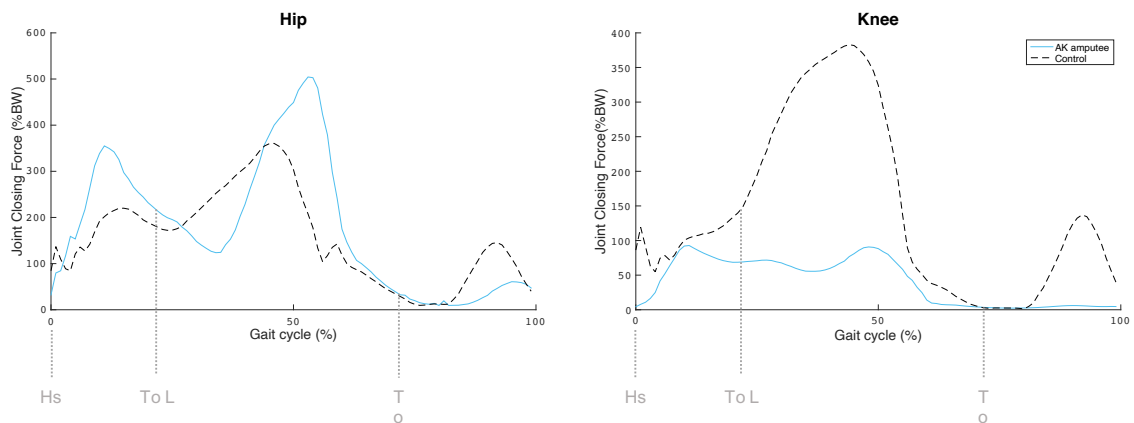


Figure 5.11: Total joint closing force at the hip and knee during AK amputee gait. Includes effect of typical joint reaction forces and the closing effect of muscle contraction acting across each joint.

5.4.7 Finite element modelling

5.4.8 Bone resorption risk

As done in the BK subject, Figure 5.12 compares an envelope of strain experienced within the amputated femur to that experienced in the femur of the control subject. This provides a representation of the bone resorption risk as a result of induced loading by comparing relative strain stimulation in every step of the loading scenario at once. In general, FE analysis shows a 32% reduction in bone stimulation within the proximal femur and an 81% reduction in the distal femoral shaft when compared to the AB control. The trabecular bone of the femoral neck and the cortical bone of the femoral shaft (with cortical strain dropping as you move distally) are at a particularly high risk of bone resorption due to reduced loading. Most significant reductions in strain seem to occur in the secondary tensile and compressive trajectories which demonstrates a high resorption risk due to insufficient loading. The principle compressive trajectory is also predicted to be at high risk, particularly trabeculae nearest the region of Ward's triangle. The principle tensile trajectory seems to be more sufficiently loaded than others as seen by elements running across the femoral head parallel to the principle compressive trajectory. The distal-most area of the greater trochanter trajectory is at high risk while the area where trochanter meets femoral neck is at lower. In general, cortical loading drops as you travel more distally down the femur. Transverse slices of the femoral shaft demonstrate that loading transfers most favourably in the antero-posterior direction of the femoral shaft compared to medio-laterally. At corresponding transverse slices, resorption risk is consistently higher in the medial and lateral cortices than the anterior and posterior cortices.

5.4.9 Effect of muscle versus joint loading forces

In the AK subject, the vast majority of bone loading seems to be driven by muscle forces (as demonstrated in Figure 5.13). On a local level, muscle origin and insertion points pull against the bone placing the cortex and nearby trabecular bone into tension. On a larger scale, the whole femur acts to resist the posterior bending effect created by the majority of muscle loading. Negligible force production by the vastus muscles means that the major contributions come from muscles acting upon the posterior surface of the femur: the greater and lesser trochanter, gluteal tuberosity and linea aspera. On the other hand,

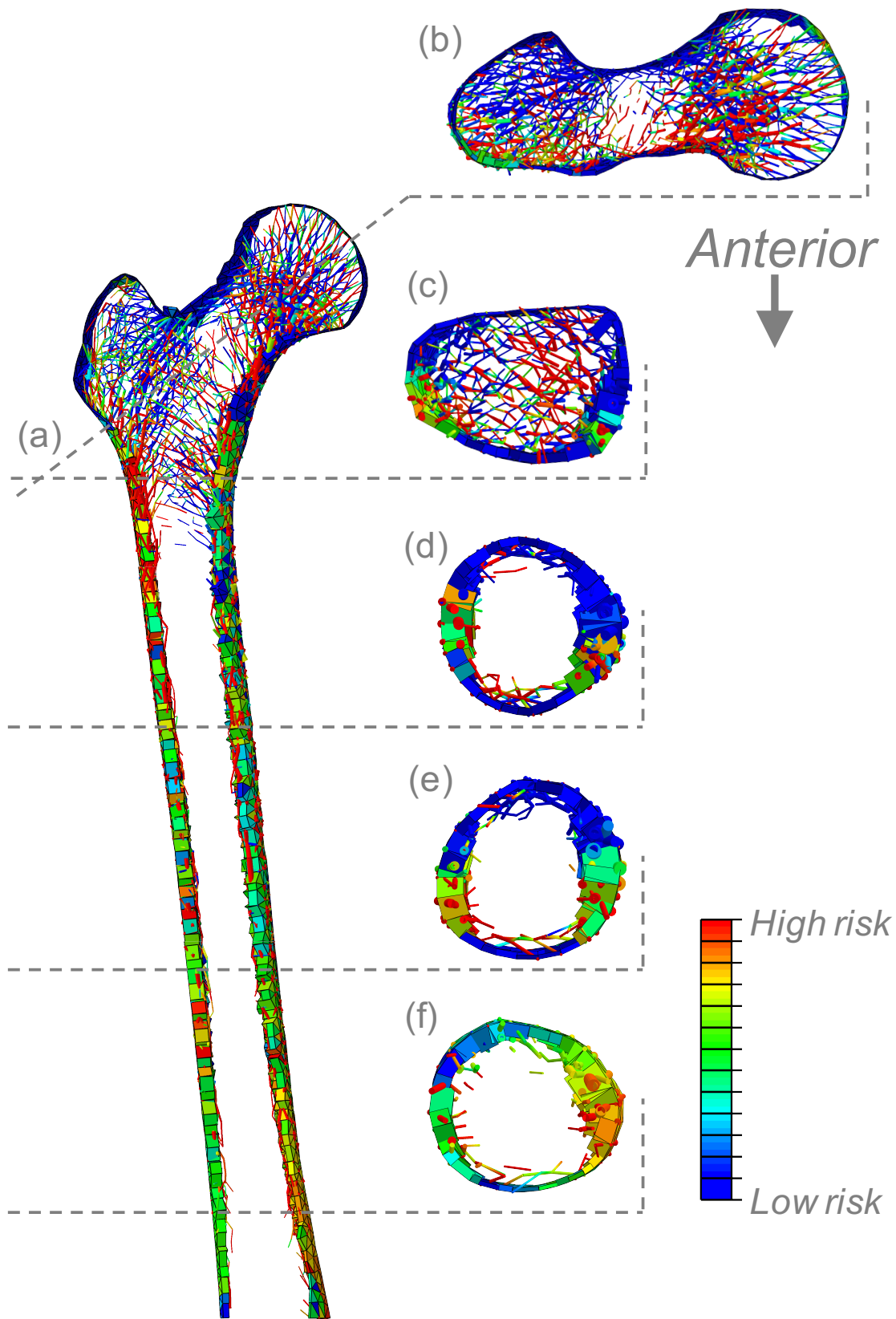


Figure 5.12: Plot showing the predicted bone resorption risk as a result of the AK amputee loading scenario. Each slice is 5mm thick and shows only trabecular elements with a radius $<0.1\text{mm}$.

joint loading contributes less to direct stimulation of the femur, in large part due to the shielding effect that the prosthetic socket has on the underlying bone. Load transmission takes place via the musculature of the residual limb rather than directly through the skeleton as in AB individuals.

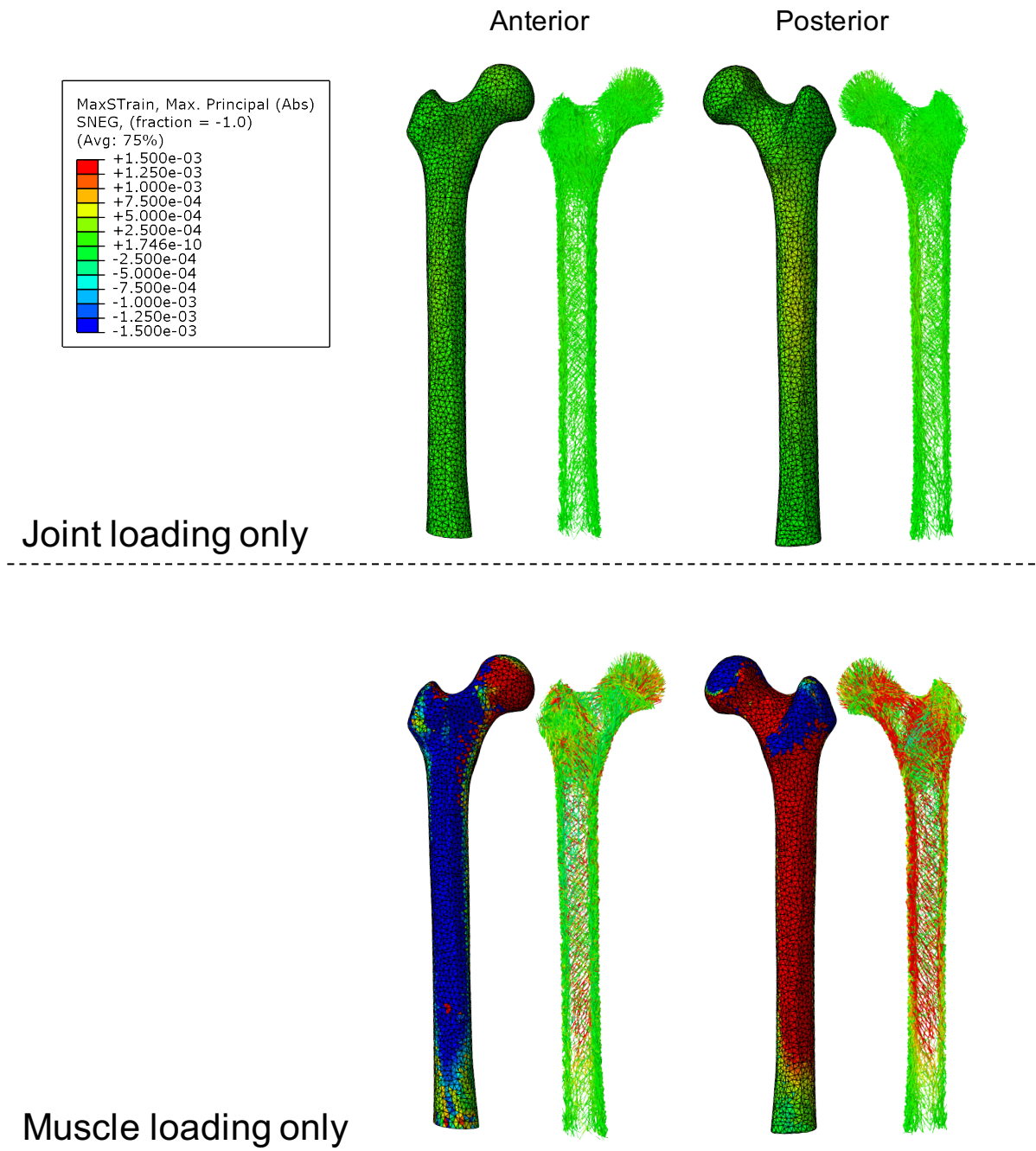


Figure 5.13: Plotting the maximum principle strain experienced at the femur of the AK amputee subject in separate loading scenarios, modelling the independent effect of muscle forces and joint reaction forces on the femur structure. Cortical and trabecular structure is shown from anterior and posterior views.

5.4.10 Predictive modelling of bone adaptation

The predictive model reports significant changes to the bone structure of the amputated femur as a result of altered loading. Results highlight the potential for a decrease in total bone volume of approximately 8% in 60 months (Figure 5.14).

Trabecular bone volume only drops a total of 20% in this time. Most substantial reductions in the average trabecular element thickness occur in the secondary tensile and compressive groups of the proximal femur. Ward's triangle also becomes more pronounced as further adaptation to the amputee loading scenario takes place. The principle compressive and tensile groups are less affected. Distally through the femoral shaft, the quantity of smaller trabecular elements (radius=0.1mm) drops considerably as demonstrated at the level of slices (d) and (e).

But as with the BK model, adaptation also demonstrates re-distribution of bone density with certain pre-existing trajectories and areas of cortical bone also experiencing increased thickness and volume. Key posterior aspects of the femur demonstrate trabecular and cortical thickening (the lesser trochanter, linea aspera and other muscle attachment areas). These results are most clearly demonstrated in Figure 5.14 slices (b), (c), (d) and (e). Total cortical bone mass is almost completely preserved in the AK amputee scenario, with only 1% decrease in cortical volume occurring. There is a noticeable shift from higher thickness on the mediolateral aspects of the cortex to thickness on the anteroposterior aspects of the cortex. The medial wall of the femoral shaft cortex gradually decreases in thickness further distally (as can be seen in slices (a), (d) and (e)). This is similarly the case for the lateral wall, although reduction in thickness is less dramatic. Small increases in cortical thickness occur in the posterior and anterior walls, however. The bottom portion of the amputated femoral shaft (from slice (f) downwards) experiences major bone loss in terms of trabecular density and cortical thickness in all four directions. Equivalent slices showing bone architecture in the AB control femur are included for direct visual comparison in Figure 5.15. Equivalent slices showing bone architecture in the AB control femur when adapted to walkign only are also reproduced here in 5.16. The latter provides an important secondary comparison point given AK adaptation took place with only loading from gait.

5.4.11 Ischial containment

Figure 5.17 outlines the effect of ischial containment on bone resorption risk - where 50% of load is transmitted through the medial brim of the prosthetic socket into the ischium of the amputee. It highlights the effect of ischial loading on stimulation of the bone while also demonstrating loading on the socket. A significant reduction in stimulation of the amputated femur can be seen when modelling ischial containment as increasing load is taken by the medial brim of the prosthetic socket. This corresponds with very large regions of the femur demonstrating a high resorption risk. Load being transferred through the socket seems to effectively bypass the hip joint altogether.

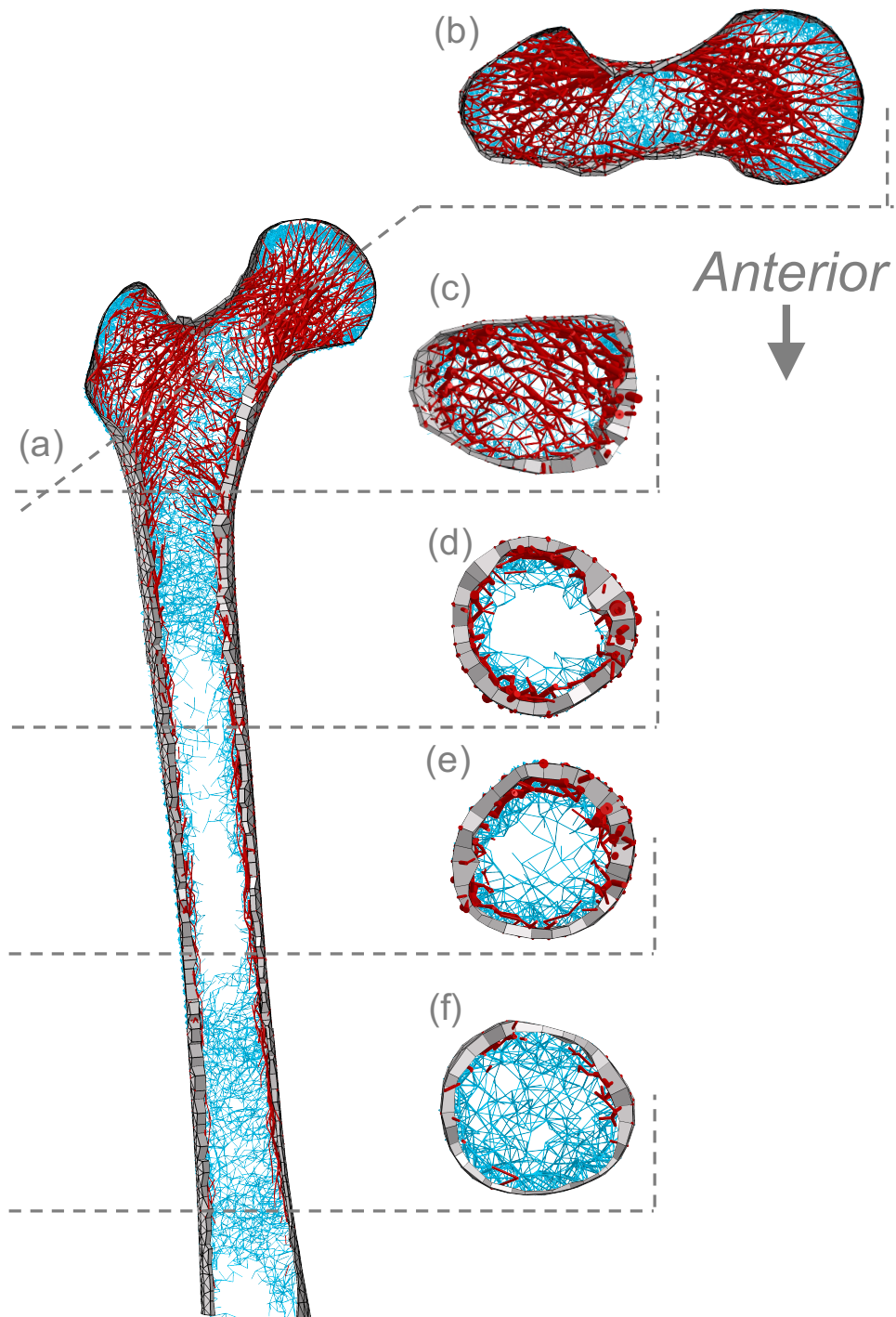


Figure 5.14: Selected 5mm thick slices of the femoral bone structure in the amputated femur after being subjected to 60 months of the AK amputee loading scenario. Cortical shell elements are shown in grey. Trabecular truss elements with a radius of 0.1 mm are shown in blue. Trabecular truss elements with a radius $>0.1\text{mm}$ are shown in red. Truss elements in the dead zone (with a radius of $1\text{ }\mu\text{m}$) have been omitted for clarity.

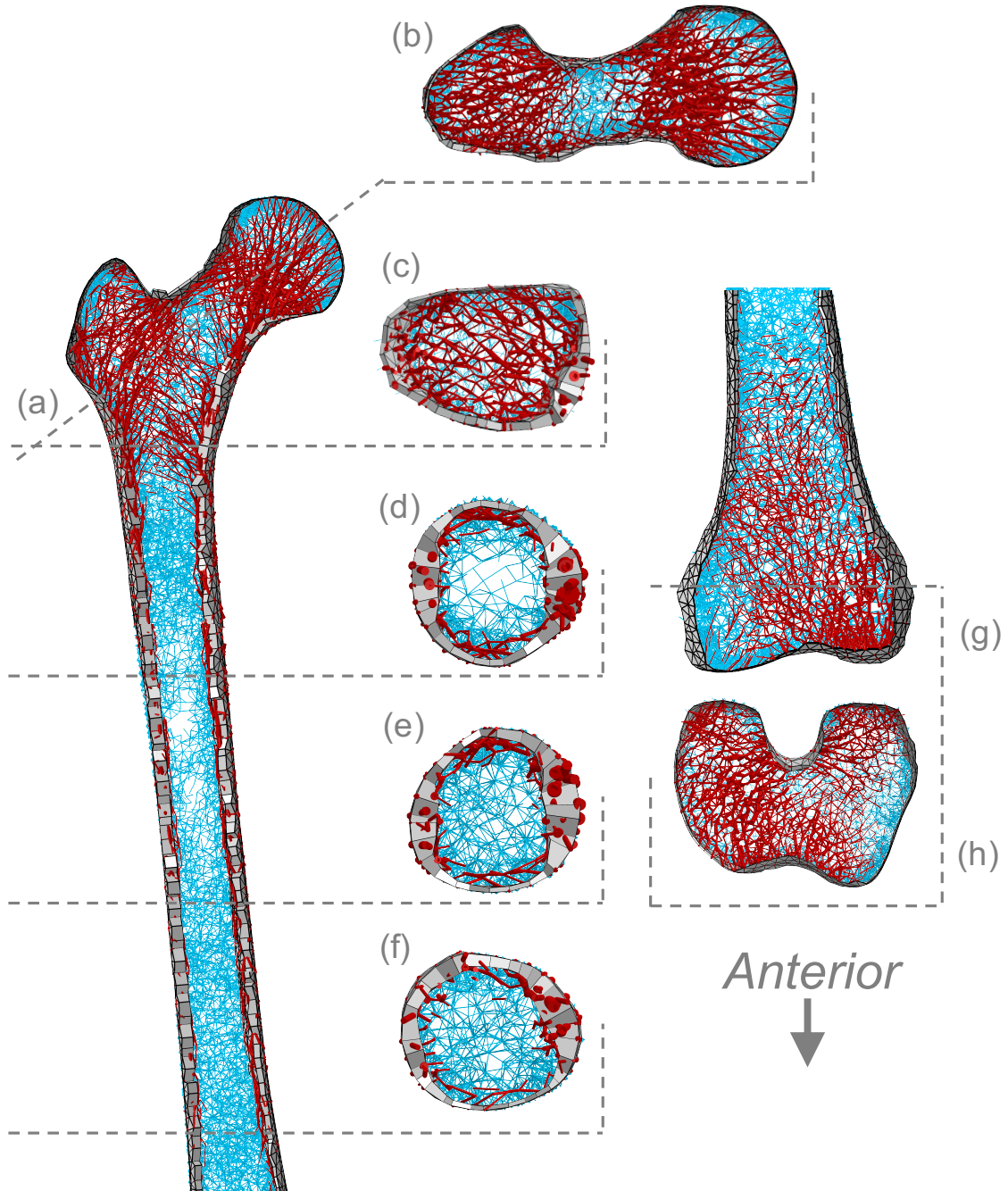


Figure 5.15: Converged femoral bone structure in the control femur. Optimised to an full able-bodied loading scenario. Recreated here from Chapter 3 for comparison to the AK amputee femur.

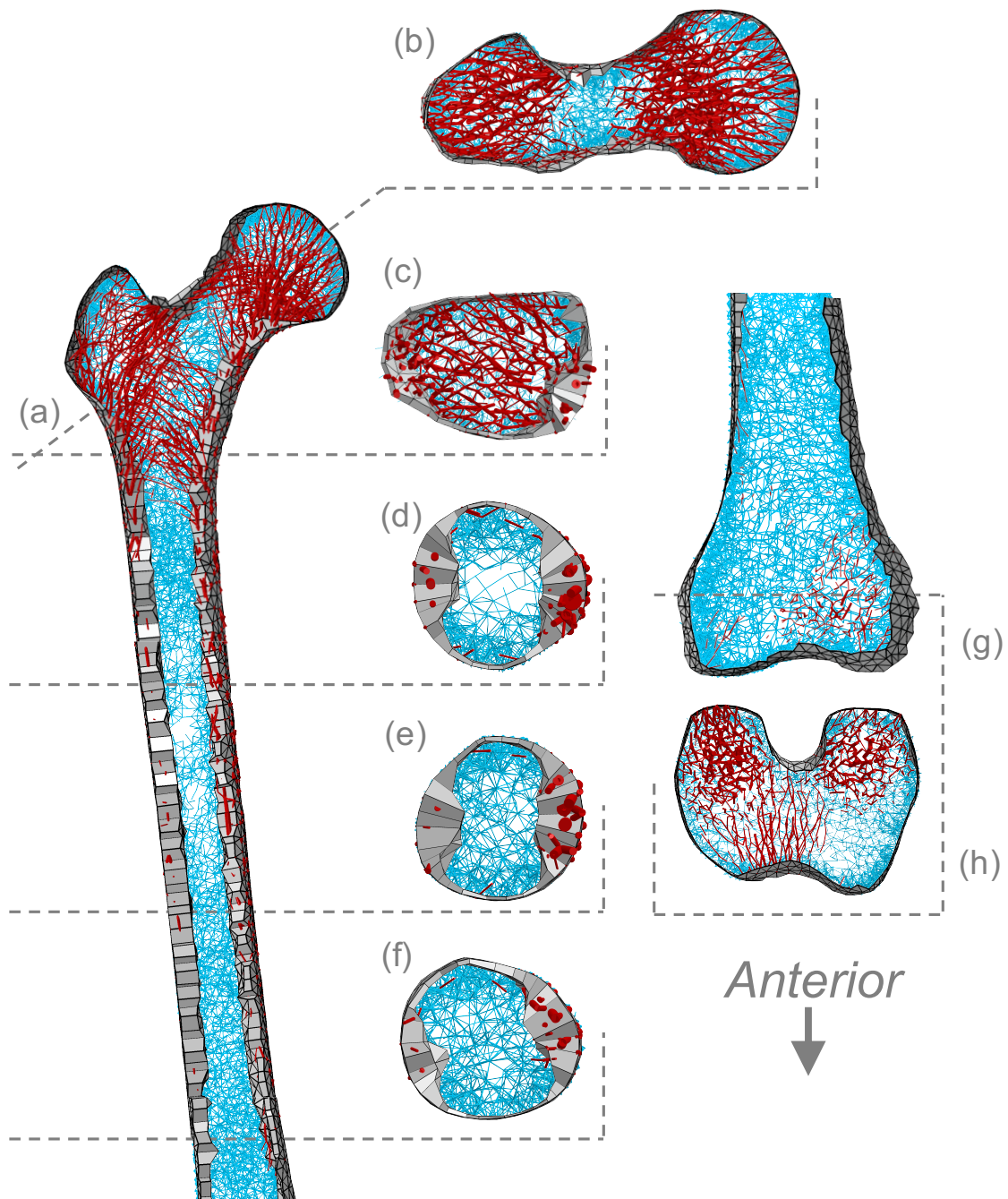


Figure 5.16: Converged femoral bone structure in the control femur. Optimised to an able-bodied loading scenario of gait only. Recreated here from Chapter 3 for comparison to the AK amputee femur.

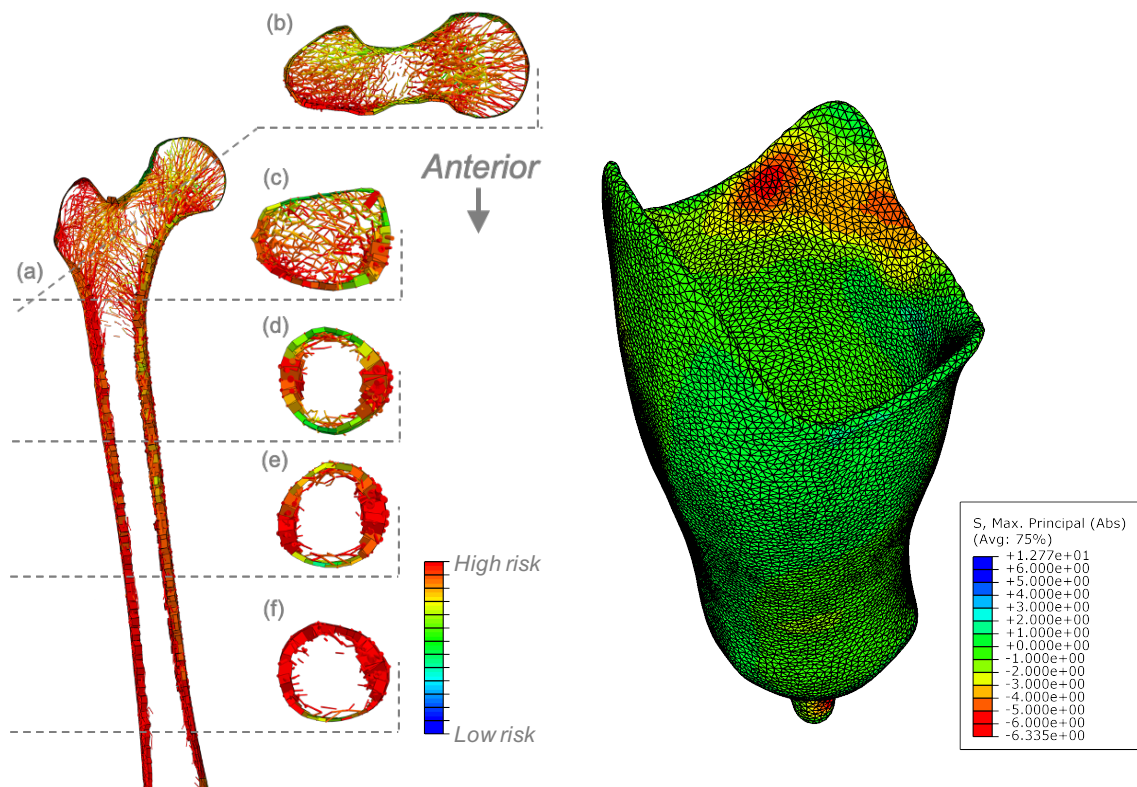


Figure 5.17: Left: Bone resorption risk associated with loading through an ischial containment socket when 50% of load is taken through the medial brim of the socket. Right: Stress distribution in the prosthetic socket.

5.5 Discussion

5.5.1 Musculoskeletal modelling and amputee movement

MSK modelling results demonstrate the potential for increased loading at the hip during AK amputee gait when compared to the AB counterpart. Less controlled movement (higher accelerations and decelerations) results in increased ground-reaction forces which are in turn reflected at the joint level in terms of hip and knee reaction force. Range of motion at the hip is increased in both frontal and sagittal planes, particularly favouring increased flexion and abduction. Consequently, we see an increased kinetic burden placed on the joint when compared to the AB control subject. As a result of both changes in body position and increased ground-reaction force, the model predicts greatly increased hip muscle force generation during gait and an increased total hip closing force. At the knee, however, the loss of active muscles means total closing force amounts to the magnitude of ground-reaction force only. This represents a significant reduction compared to the control subject.

With this being a single-subject case study, the usefulness of comparing results directly to the literature can be limited, however, in qualitative terms the general trends identified in these MSK results do match many of those found in previous larger population based studies of amputee gait. At heel-strike through to the loading response, the AK subject demonstrates an increased angle of hip flexion compared to control that results in an increased peak hip extension moment when compared to control. This is in agreement with results from studies by Jarvis (2020), McNealy (2008) and Henson (2020) among others. Knee kinematics demonstrate a less pronounced loading response at the knee (less flexion) which has also been a commonly identified trend throughout literature (Henson *et al.*, 2020; Taheri & Karimi, 2012). Demonstrable hip drop occurs during stance in each leg. This could be a sign of abductor weakness or a short prostheses. Most commonly, amputees compensate for Trendelenburg gait by leaning over the stance leg to shift the centre of mass and reduce burden on the abductor muscles of the hip (Devan *et al.*, 2015). The AK amputee subject tested does not seem to employ such compensatory measures. During stance, the subject demonstrates slightly reduced frontal hip moments when compared to the control subject, also seen in the larger population study by Henson (2020). Late stance into pushoff sees a higher hip extension angle than is typically found

in AK subjects (Rabuffetti *et al.*, 2005; Hagberg *et al.*, 2005; Klotz *et al.*, 2011; Henson *et al.*, 2020). Peak hip flexion moment also occurs here, higher than in the control subject as in studies by Henson (2020) and McNealy (2008). Both primary and secondary peaks in amputee ground-reaction force are increased compared to control unlike in the population study by Henson (2020) where no statistical difference is found between peak amputee and peak control ground-reaction force. Although no other studies were found comparing between bilateral amputee ground-reaction force and control.

Swing phase sees a greatly increased hip abduction compared to controls. This circumduction of the leg during swing is commonly seen across the literature as a means of ensuring proper clearance of the swinging leg above the ground (Berger, 1992). Throughout the whole gait cycle the AK subject maintains a high degree of anterior pelvic tilt, consistent with findings by many others (Jarvis *et al.*, 2020; Henson *et al.*, 2020; Berger, 1992; Goujon-Pilet *et al.*, 2008; Rabuffetti *et al.*, 2005; Sjödahl *et al.*, 2002). The subject also demonstrates increased step width and hip abduction during gait - another finding that is highly consistent with existing literature (Berger, 1992; Jarvis *et al.*, 2020; Henson *et al.*, 2020). In the coronal plane, results show a significant asymmetry in terms of pelvic and hip rotation which likely influences kinematics elsewhere. This is unreported in other studies.

In terms of muscle forces, many studies highlight the increased burden placed on the muscles of the hip in AK amputees. Wentink (2013) and Jaegers (1995) confirm this by EMG. This is in direct agreement with predicted muscle forces by our MSK model. There are some specific differences in terms of individual muscle activation between results of this study and the study by Henson (2020). For example, Henson’s models show greatly reduced contribution of the rectus femoris compared to control subjects while this study presents the opposite. However, in general, the two studies show good agreement. Both demonstrate an overall increase in function at the hip flexors, extensors, abductors and adductors. In fact, many studies present this increased demand on the hip joint as a potential contributor to increased prevalence of osteoarthritis in amputees (Sagawa *et al.*, 2011; Lloyd, 2010; Gailey *et al.*, 2008).

In general, we see good agreement between results from MSK modeling of the AK subject and those found in pre-existing studies. This gives us confidence in the functionality of the model and the data acquisition pipeline. Despite these agreements the results from this single case study can not be considered fully representative of the

wider bilateral AK amputee population. McNealy (2008) specifically stressed the greatly increased variation in kinematic and kinetic data between bilateral amputees compared to a population of controls. It is important to acknowledge the inherent individualisation of motion results in any single subject, although the concepts presented can certainly be considered transferable.

As a bilateral AK amputee the subject struggles with greatly reduced proprioception. Loss of active ankle and knee joints in both legs can greatly hinder lower body control, in particular, deceleration of the body centre of mass upon contact with the ground. Additionally, contact comes only via both prostheses and prosthetic sockets. Nerve damage on the skin of the residual limb of traumatic amputees has also been well-documented (Clasper & Ramasamy, 2013). All of this is likely to have a considerable adverse affect on the amputee's ability to 'feel' and react to contact with the floor during ambulation resulting in less controlled movements and consequently explaining the increased accelerations and decelerations measured compared to in the control subject. This will naturally lead to greater reaction forces transmitted through the subject from the ground up. The ankle and knee provide significant forward propulsion during gait (particularly the ankle joint). Figure 3.10 in Chapter 3 demonstrates this explicitly. The gastrocnemius provides over twice as much force per unit weight during late stance and push-off than any other muscle. Therefore, its absence in the AK amputee leaves a significant gap to be filled by the remaining muscles and joints. Compensation for reduced power at the ankle and knee could contribute to the increased muscle recruitment at the hip of the AK amputee model - with hip extensors working harder during stance to drive the body centre of mass forward and hip flexors working harder during swing to carry the front leg through to heel-strike. The effect of both these factors is presented in Figure 5.11. Total joint closing force represents the passive effect of loading from ground-reaction force as well as the active effect of loading by muscles and ligaments acting on/across each joint. Both the first and second peak in amputee hip joint closing force are over 50% higher than respective peaks in the control subject which provides significant potential from a bone loading and stimulation perspective. This potential is, however, curbed by the reduced total knee joint closing force. The implications of altered, but increased, loading in the AK amputee are positive from a perspective of bone stimulation by osteocyte signalling.

5.5.2 Finite element modelling

Despite increased loading at the hip, FE results demonstrate a significant reduction in stimulation of the femur in the AK subject. Strain stimulation and bone resorption risk plots show significant portions of the proximal and distal femur at high risk of bone deterioration due to reduced loading. Predictive modelling confirms the subsequent deleterious effect of this reduced loading on bone structure and density. Key trabecular trajectories in the proximal femur and the antero-posterior walls of the distal cortex in the femoral shaft present with the most significant bone loss. Such pronounced deterioration can undoubtedly lead to very large increases in lifetime risk of hip fracture.

Overall reduced loading in the structure of the amputated femur can be attributed to a variety of factors. The prosthetic socket has a significant shielding effect on direct joint loading (loading from ground reaction forces through the skeleton). This comes from both dissipation of forces into the musculature of the residuum and from intentional offloading of the distal femur through designed suspension of the residuum. The femoral shaft (and distal femur) also experiences reduced direct muscle loading from the loss of active muscle attachments. Equally, loss of active muscles crossing the knee joint contribute to an overall reduced knee closing force as seen in MSK modeling which has a direct effect on loading of the femoral structure.

The prosthetic socket plays a major role in reduced loading of the femur. In an unamputated leg, direct force transfer can take place predictably through the skeleton. Force from the ground through the shank of the leg transfers into the knee joint and directly into the condyles of the femur. In an AK amputee, the prosthetic socket provides a significant break to this chain. Joint forces are spread over the musculature of the residuum before being more evenly spread over the entire surface of the bone. Significantly less load is resisted longitudinally by the femur as it would be in an AB individual. Additionally, the majority of prosthetic sockets are intentionally designed to offload the end of the residuum (and cut femur) by distal suspension. Socket suspension causes a subtle bridging of load (Figure 5.18), effectively bypassing the distal-most femur and further discouraging end-loading. Although both design features contribute to improved socket comfort, they alter the physiological load-path of weight through the femur and hip. Subsequently contributing to reduced bone stimulation. The concepts that govern

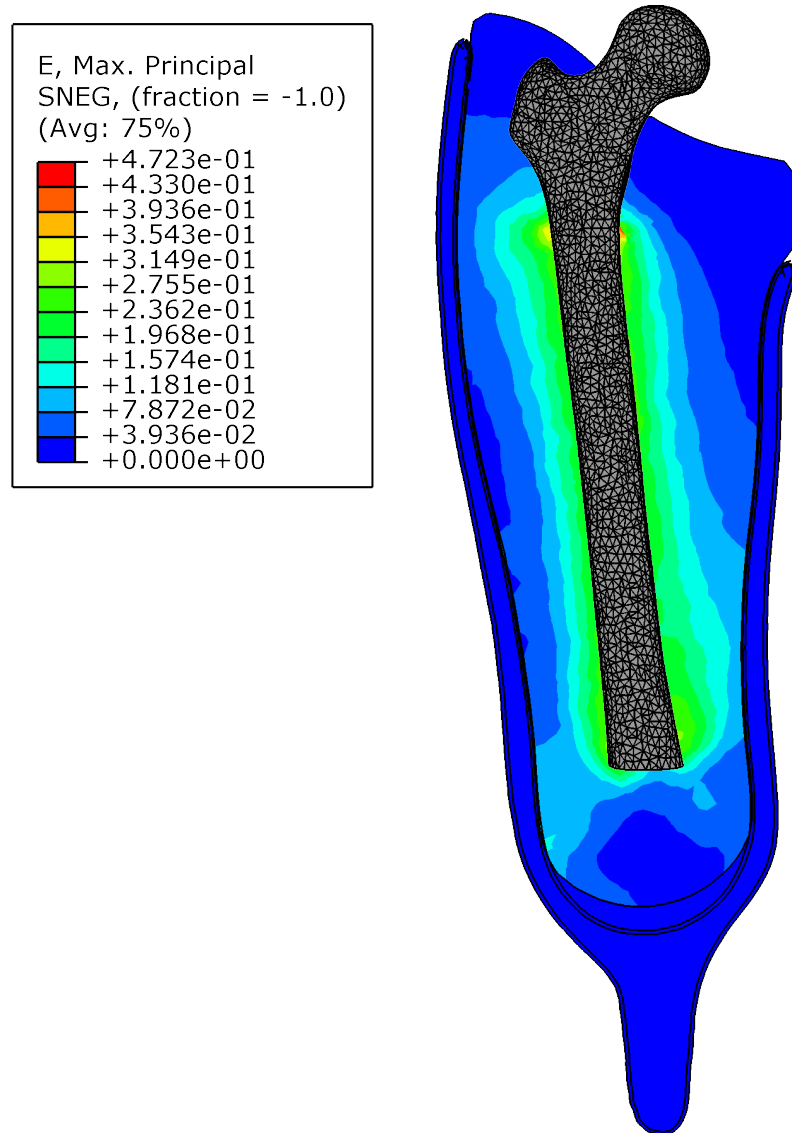


Figure 5.18: Demonstration of the bridging effect of load secondary to socket suspension. The figure shows maximum principle strain values in the residuum of an AK amputee, taken from a single frame of gait.

prosthetic socket fit and comfort are seemingly at odds with those that encourage normal physiological loading of the amputated skeleton.

This is further illustrated when modelling ischial weight bearing as in quadrilateral and ischial containment sockets. Ischial containment sockets employ similar concepts of distal suspension and distribution of force while also re-routing a percentage of load directly into the ischial tuberosity through the medial brim of the prosthetic socket. Figure 5.17 displays the bone stimulation and subsequent bone deterioration risk plot when ischial containment is employed for a simplified loading scenario. Although the missing muscle forces indeed account for some reduced stimulation, ischial loading can be seen to have a hugely detrimental effect on direct joint load transfer into the femur; significantly increasing bone resorption risk. At the very least, such dramatic results in terms of bone stimulation and risk of resorption highlight the need to fully understand the relative breakdown of weight-bearing that occurs during ischial containment so that the issue can be modelled and interpreted more accurately.

As a result of amputation above the knee, the subject also misses out on significant indirect joint loading by muscle contribution to the closing force of the knee joint and direct bone loading by muscles pulling against the surface of the bone. Fewer active muscles attach to the distal aspects of the AK femur compared to in the femur of the control subject. The contribution of the gastrocnemius, biceps femoris, rectus femoris and other smaller muscles to the total knee closing force in the control subject is significant. None of these remain active or present in the AK subject. As such total knee closing force exactly mirrors knee reaction force which closely replicates the magnitude of the ground reaction force. This is significantly reduced compared to the AB subject and thus contributes to reduced loading at the amputated socket even before shielding of forces by the socket can occur.

Separating the loading effect of muscle forces and joint reaction forces in § 5.4.9 highlights a large discrepancy between bone loading as a result of each. The increased activity of muscles working to move the hip provide the vast majority of stimulation to the amputated femur as seen in slice (a) of Figure 5.13. Slice (b) confirms the hypothesis discussed previously as ground reaction forces end up dissipating into the socket and residuum soft tissue rather than reaching the femur. Completing the same analysis on the control model finds a significantly smaller discrepancy between the effect of joint and muscle loading - both contributing meaningfully to physiological loading. Slice (a) in

Figure 5.13 also highlights the global bending effect of muscle forces, meaning the overall bending effect created by muscle loading on mainly the posterior aspects of the femur. As well as placing bone at individual insertion points into tension, the larger effect of muscles working in unison forces the femoral shaft to bend in the posterior direction. The anterior of the femoral shaft experiences an overall compressive stress while the posterior side experiences a tensile stress. Typically, this effect might be compounded by joint loading from the knee and hip reaction forces due to the natural curvature of the healthy femur, however, we can tell that this is not the case in the AK subject.

Looking at the positive stimulation effect of increased hip muscle activity in the proximal femur in more detail, many areas surrounding the origin and insertion points of highly active muscles (higher force generation than in the control subject) transfer substantial loads. These seem to translate into areas of low/no resorption risk in bone resorption plots. For example, in the AK subject the highly active adductor muscles attach primarily along the posterior aspects of the femur from medial of the gluteal tuberosity down the linea aspera. This corresponds to a line of low resorption risk in Figure 5.12. This is similarly the case at the insertion points of the psoas and gluteus minimus muscles on the lesser and greater trochanter respectively. The direct effect of muscle insertions can be seen in both the cortical bone and neighbouring trabeculae. On the other hand, previously active muscle insertions affected or missing due to amputation leave significant gaps in muscle loading. This is primarily the case in the distal femur where muscles crossing the knee joint in an AB individual (such as the vastus muscles and the gastrocnemius) are either absent or inactive. This is potentially a reason that resorption risk gets worse as you descend distally along the shaft of the AK femur.

In the proximal femur, the secondary tensile and principle compressive trabecular trajectories seem to be at high risk of bone resorption due to reduced loading. The other trajectories are certainly at some risk according to Figure 5.12, although, the risk is less pronounced. Certain trajectories within the the greater trochanter and principle tensile groups, for example, show sufficiently high levels of loading ($>1000m\mu e$) while other elements in the same group do not. Predictive modelling demonstrates the potential long-term effect of results from the bone resorption risk plots. Comparing the internal structure of the control femur to that adapted over 5 years of remodelling cycles post-amputation shows interesting patterns of bone loss and gain. Overall, the femur loses almost 20% of its bone volume which would correspond to the loss significant bone density and in terms

of DXA score and represent a huge increase in lifetime risk of femoral fracture. Most significant trabecular bone loss in the proximal femur takes place through the secondary tensile and secondary compressive groups. There is also a noticeable widening of Ward's triangle as trabecular bone loss in the principle trajectories begins to proceed outward from the centre of the neck. Both of these patterns have been previously identified as the first stages of osteoporotic bone loss in a study by Manmohan Singh(2014). The study highlights the relationship between internal stress in the femur and the development and loss of particular trajectories, hypothesising that the principle compressive trajectory is the last to fade. It is also important to note that some trabecular thickening is predicted at the posterior side of the lesser and greater trochanter. This could be due to increased muscle force at these insertion points highlighting, once again, the positive potential of increased muscle activity on bone preservation.

Distally, there is huge loss of, particularly, smaller elements (those shown as light blue in Figure 5.14) in the trabecular bone creating a much more prominent intramedullary canal. There is also noticeable thinning of the medial and lateral walls in the femoral cortex of the AK subject while the anterior and posterior walls experience some thickening. This reflects results from previously discussed resorption risk plots. This speaks to the bias of anteroposterior loading in the AK subject compared to in the mediolateral plane. Bone distal to the transverse slice taken in Figure 5.14, slice (f), shows bone loss in all directions. This can be attributed to reduced longitudinal loading from socket suspension which sees forces bridge over the distal-most aspect of the amputated femur. Looking at cortical bone, significant thinning takes place in the medial and lateral cortex (Figure 5.14a) while some thickening actually occurs in the midshaft of the anterior and posterior cortex (5.14 slices d and e). This speaks, once again, to the relative bias of load transfer in the anteroposterior plane compared to the mediolateral plane of the amputated femur - possibly in large part due to the over-reliance on muscle forces acting along the posterior surface of the femur for stimulation and the lack of direct longitudinal loading from the knee joint.

Finally, comparing between the internal femur architecture of Figures 5.14 and 5.16 suggests the loss of bone structure can be more heavily attributed to amputation and socket design than a reduced loading envelope. The AB control femur adapted to walking only still demonstrates a much more densely, and evenly, populated proximal structure than the femur adapted post AK amputation.

Overall, these results certainly corroborate clinical findings from Chapter 2. Predictive modelling highlights the potential for bone loss to manifest itself just as a result of altered loading in an AK amputee subject. The extent of reduced loading post-amputation will play a major role in BMD loss at the hip and subsequent diagnosis of either osteopenia or osteoporosis in a young amputee. This nature of this bone loss (being so heavily mechanically load-driven) once again suggests that a clear distinction from postmenopausal or age-related osteoporosis would be beneficial. Results demonstrate the potential for *unloading osteopenia* in AK amputees. Equally, they should place additional scrutiny on current approaches to prosthetic socket design; highlighting the danger of prioritising socket comfort over socket function and long-term integration with the human body.

5.5.3 Limitations

Each model does have limitations, the majority pertaining to simplifications and assumptions made throughout the modelling process. In MSK, for example, modelling ischial containment would be expected to reduce loading at the hip and knee joint. This would require the addition of a new joint between the medial brim of the socket and the ischial tuberosity of the pelvis. However, the direct loading effect of each of these design features has yet to be quantified. Therefore the added complexity in modelling each would not necessarily bring more accurate results. Regardless of simplifications made in MSK modelling, results are in agreement with many trends identified in literature. Moreover, maximum marker errors and recorded root mean square errors were below 2cm throughout suggesting the model was able to track experimental data sufficiently well.

Perhaps the major limitation of this study is the lack of other key loading activities included in the full physiological loading scenario. Prior research done within the Structural Biomechanics group has highlighted the importance of a complete loading profile in prediction of bone structure. Figure 3.19 in Chapter 3 demonstrates the relative stimulation of different activities on different areas of the AB femur. By only including loading from gait and stance, we expect femoral loading to be somewhat reduced compared to if sit-to-stand, stand-to-sit, stair ascent and stair descent activities were also included. Having said that, the author has not found an equivalent to Morlock's (2001) in the amputee population. Therefore imposing a full AB routine in amputee remodelling might

be inappropriate. Bilateral amputee difficulty with ambulation on stairs, for example, has been documented (Narang *et al.*, 1984; Datta *et al.*, 1992). Looking forward, introduction of sit-to-stand and stand-to-sit activities to the loading scenario would be beneficial when a properly instrumented chair with instrumented handles is made available.

In general, despite various simplifications and assumptions, I believe the study achieved its aims. Results demonstrate the huge potential of using this modelling Framework in predicting and understanding bone loss and remodelling - not just in the amputee population. More specifically, the study demonstrates the significant effect that mechanical loading and bone remodelling plays in bone loss - in absence of any hormonal changes/effects. This suggests that bone changes in the young AK amputee population could be a healthy remodelling response to altered loading rather than a systemic problem such as in age-related and postmenopausal osteoporosis.

Chapter 6

Conclusions and future work

The final chapter outlines the most important findings from the thesis as well as the author's perspective on future work. Comparisons are drawn between both amputee subjects and the able-bodied control. The most important overall findings are discussed, particularly, the main drivers for bone loss in each type of amputee and how they differ. Clinical results from Chapter 2 provide additional context when evaluating the effectiveness of the modelling pipeline in predicting mechanical bone loading and subsequent bone loss post amputation. The results of this research have key implications for the amputee population in terms of existing socket design, treatment pathways and quality of life. The future work section highlights the vast potential for progress using the presented models and the modelling framework within and without the domain of lower limb amputee research. Finally, the summary of achievements section explains the main findings and achievements of each chapter and evaluates to what extent the aims and objectives of the research have been met.

6.1 Below-knee and above-knee

In each modelling chapter, comparisons were made between amputee and control conditions. At this point, we have an opportunity to compare between all three conditions, and to place modelling results from the below-knee subject in context with modelling results from the above-knee subject. The purpose of both models was to relate altered loading and subsequently altered stimulation within the hip and the femur to potential bone deterioration. Although bone loss occurs in both subjects, the degree of bone loss is considerably worse in the above knee bilateral amputee and the main drivers behind bone loss in each subject are distinct. Musculoskeletal and finite element modelling have drawn attention to many prominent differences in loading at the level of the prosthesis, joints and muscles which could affect bone structure.

In the below-knee subject, loading asymmetry (favouring increased forces acting on the intact limb) lead to a less extensive loading envelope through all daily activities. The distinct reduction of anteroposterior and mediolateral joint forces acting at the knee compared to control ultimately saw a predicted trabecular bone loss in the femur of up to 12% within 5 years of amputation.

In the bilateral above-knee subject, joint forces acting at the knee are also greatly reduced. This is a consequence of missing muscle contribution to joint closing rather than any functional compensation by the opposing limb. Additionally, variation in loading is reduced by the absence of stair ascent, stair descent, sit to stand and stand to sit activities from the above-knee loading envelope. The secondary effect of loading through an above-knee prosthetic socket also limits direct longitudinal loading into the femur and hip. Instead, significant force is distributed and dissipated over the bulk of the residuum musculature. The compounding effect of all three of these leads to much higher predicted bone loss in the femur of the above knee amputee (a deterioration of almost 20% trabecular bone volume in 5 years).

Modelling one unilateral below-knee amputee and one bilateral through-knee/above-knee amputee provided a unique opportunity to investigate the two populations that experience the least and most prominent bone loss, respectively, according to findings from the clinical localisation study carried out in Chapter 2. Predicted bone loss in each subject reflected this trend and provided additional insight into the aetiology of bone loss

in each population. This goes some way towards proving the effectiveness of the presented modelling framework and the patient-specific models used within it.

Most importantly, the research detailed within this thesis has very important implications on the young lower-limb amputee population. The author believes that there needs to be a clear distinction between a diagnosis of osteoporosis and mechanically induced, region specific BMD loss in this group. Altered mechanical loading (whether due to socket design, absent activities or reduced muscle loading) can be considered the main driver behind localised bone loss. This separates it from the systemic bone loss that occurs in populations commonly associated with osteopenia and osteoporosis. Osteoporosis is typically associated with endocrine changes in the aging or post-menopausal population. As a result, it is treated by hormone replacement therapy or bone-preserving medication such as bisphosphonates and denosumab. The long-term use of both would be inappropriate for a young population given the, well-documented, adverse side-effects. Moreover, the use of systemic treatments for a localised issue risks introducing additional problematic side-effects.

More specifically, systemically slowing the rate of bone remodelling in a population experiencing localised reductions in osteocyte signalling is likely to cause a long-term decrease in bone quality affecting the whole skeleton. Anabolic treatments in a military population with already heightened testosterone (Reijnen *et al.*, 2015) could be otherwise dangerous, for example by increasing risk of heart attack (Morgentaler *et al.*, 2015). The author therefore advocates the use of a new diagnostic term in amputees where BMD loss is localised to the amputated limb. As mentioned throughout the thesis, a diagnosis of *unloading osteopenia* should be used, thereby creating a clear diagnostic distinction between systemic osteoporosis and BMD loss following amputation.

Unloading osteopenia characterises bone loss resulting from a healthy adaptation to a long-term change in loading environment. Rather than bone loss resulting from chemical, hormonal or any systemic physiological differences affecting bone remodelling, formation and resorption. This distinction could have the secondary positive impact of enhancing patient outlook. The author believes that a diagnosis of typical osteoporosis carries the ingrained implication that the problem is systemic and irreversible. This could have a negative psychological impact and, subsequently, risks adversely affecting the patient's personal outlook on rehabilitation potential. It could also stifle further research into the, potentially beneficial, effect of end-loading, direct fixation and targeted physiotherapy in

preventing and reversing bone loss and fracture risk in lower-limb amputees. In reality, the author believes that, in the same way bone density can be lost due to reduced bone loading in young amputees, it has the potential to be preserved (or even gained) by increased bone stimulation through increased muscle and joint loading.

6.2 Future work

The research in this thesis has highlighted the nature of bone loss in young lower-limb amputees, proving that it is driven chiefly by reduced loading through the femur of the amputated limb. This is an important discovery in that it should alter treatment pathways and improve rehabilitation outlook for any amputee diagnosed with site specific low BMD. The modelling framework presented in this thesis could be used to test future rehabilitation and preventative measures. The greatest strength of in-silico modelling can be its relative speed compared to clinical studies, particularly those seeking to investigate the long-term effects of bone remodelling/degradation. The effectiveness of proposed solutions in preserving, preventing or even reversing bone deterioration can be determined significantly more quickly than through a clinical longitudinal study. Then in turn, results of in-silico modelling can be used to supplement, inform or influence future clinical research and surgical intervention, saving time and resources in the process. With ongoing advances in computational power and clinical research tools, patient-specific computational models could be used to guide patient-specific treatment strategies in the near future. This would carry an advantage over generic modelling in terms of accuracy provided patient-specific models are driven by patient-specific data. However, in terms of bone loss I would expect the fundamental trends identified in this thesis to remain the same. Ultimately, the main driving factor for bone loss and altered loading in most amputees will be the stark difference between loading pre-amputation and post-amputation.

The loading effect of key socket design features can be investigated in more detail (as was done crudely in §5.3.3) such as ischial containment and socket suspension. Or perhaps more importantly, the effect of removal of these key design features to allow for more physiological loading. Entirely new socket concepts could also be proposed and tested with the only limiting factor being the users ability to replicate a given design in finite element analysis. Additional modelling scenarios could be introduced to test the effect of using different prostheses (such as powered ankle and knee joints) or the effect of residuum limb length. The benefit of powered prostheses has been demonstrated in creating more efficient gait post-amputation. Naturally, this could also lend itself to more symmetric and consistent loading at the hip joint. Equally, understanding the effect of residual limb length on gait and joint loading has the potential to inform and guide future surgical interventions.

The framework can also be applied to direct fixation and osseointegration which, the author hypothesises, would present a significantly improved bone loading profile compared to use of an external prosthetic. One would expect loading to more closely replicate physiological loading pre-amputation. Furthermore, the improved mobility and movement capacities of direct fixation subjects (Hebert *et al.*, 2017) would also lend itself to a more varied daily loading profile. In general, the framework provides a unique opportunity to further investigate the long-term effect of exercise regimes, targeted physiotherapy and changes to socket design on bone loading, bone structure and bone health.

In a broader sense, the adverse effects of current prosthetic sockets on physiological joint loading raise the need for further research into socket design and concepts. The concepts of ischial weight-bearing and limb suspension have been in use since the 1980s (Schuch & Pritham, 1999). John W. Michael's (Michael, 1990; Edwards, 2000) remarks made in 1990 can still be considered relevant today: in the last 40 years changes to socket design have been "evolutionary rather than revolutionary" despite huge advances in amputation-related research and prosthesis design during that time. Having said that, at this point it is important to note, once again, that lower-limb amputees suffer with a variety of other primary and secondary issues associated with amputation and use of prosthetics - not just *unloading osteopenia*. The reality is that a solution to long-term bone deterioration (particularly in terms of socket design) might not also be a solution to socket comfort, pressure sores and skin degradation (or many other problems). This does, however, raise an important debate over socket comfort versus function which, in terms of bone preservation, seem to be competing entities.

From a clinical perspective, bone biomarkers are now commonly used in clinical diagnosis of systemic osteoporosis (Ji & Yu, 2015) and could be valuable in confirming the cause of bone loss in the young amputee population clinically. Investigating the levels of bone formation and bone resorption biomarkers in young amputees suffering with *unloading osteopenia* would be a useful step towards determining the aetiology of bone loss at a cellular level. It would also contribute greatly to evaluating the efficacy of currently used endocrine/chemical treatments which the author already believes to be inappropriate for the young amputee population. Having said that, given the localisation of deterioration in amputees, it is also possible that global bone biomarkers fail to capture local differences properly.

Finally, in future studies it would be beneficial to measure both the short and long-term progression of bone loss. Capturing DXA data within the first months of amputation and periodically after would help to determine how much bone loss could be attributed to the period of initial bedrest associated with intense trauma and recovery from surgery. One study by Bemben (Bemben *et al.*, 2017) tracked the progression of BMD loss in amputees over the first-year post-amputation. A similar study with longer-term call-back, 5 or even 10 years post-amputation, would be interesting to isolate the, post-recovery, day-to-day changes in BMD.

6.3 Summary of achievements

The first part of this thesis detailed a clinical study into the localisation of bone loss in the young, lower limb amputee population. Using a subset of ADVANCE data, the independent state of bone mineral density was compared at the hip and spine of military amputees and controls using DXA. Eighty-two traumatic military amputees of varying amputation type and level were matched, by age, to eighty-six healthy military controls. Comprehensive demographic information and participant characteristics were collected for each subject consisting of ethnicity, body composition, history of substance use and current activity levels. DXA data at the spine and hip was compared between individual subjects, amputation levels and between amputees and controls.

Results showed a clear difference in the relationship between BMD at the hip and spine of the control population and the amputee population. While in controls, Z-score at both sites were statistically similar, in amputees, Z-score in the hip was statistically lower than in the spine. Mean Z-score at the spine of amputee and control groups was also statistically similar whereas, at the hip, Z-score was significantly lower (almost 1.5 standard deviations lower) in the amputee population. This evidence supports the previously identified trend of low BMD in the lower-limb amputee population but more importantly, it marks the first time that bone loss has been proven to be localised to the amputated hip and femur. Demographically, both groups analysed were statistically similar, thus differences in BMD can be solely attributed to the effect of amputation. Additionally, analysing a younger population negated the potential effect of age-related or post-menopausal osteoporosis. Another degree of localisation was seen in unilateral amputees, where mean Z-score was significantly lower in the amputated limb than the contralateral. This study suggested that bone loss occurring in the young amputee population could be region specific and mechanically induced. As such, it promoted additional research into determining why.

The second part of the thesis introduced a computational modelling framework that interfaces experimental motion data, musculoskeletal modelling and finite element modelling to analyse the effect of daily living activities on loading at the femur and hip. Firstly, the framework was used to create an able-bodied structural femur model that would become the starting point for further analyses into the effect of loading in both amputees. The introduction of the framework in this context provided a point of comparison for each amputee modelling scenario as control data was collected from a size

and weight-matched healthy subject. The modelling framework presented spatiotemporal, muscle and joint force results for each subject during standing, walking, sit-to-stand, stand-to-sit, stair-ascent and stair-descent activities. Finite element modelling of the femur environment determined the direct effect of these forces on the structure of the bone by standard and predictive analyses, whereby cortical and trabecular bone volume adjusts and optimises using a phenomenological strain-driven adaptation algorithm.

Control modelling highlighted the importance of a varied loading scenario in creation of the femur cortical and trabecular structure. While walking contributed the most volume to overall bone structure, sit-to-stand, stand-to-sit, stair-ascent and stair-descent activities provided certain loading profiles (namely more pronounced anterior loading at the knee) that proved important in stimulation of particular regions of the femur.

In the final two parts of the thesis, the framework was adapted and used to determine the aetiology of bone loss in two amputee subjects: one unilateral below-knee and one bilateral above-knee/through-knee subject. More specifically, in-silico modelling evaluated the potential role of altered mechanical loading post-amputation on femur loading and, subsequent, loss of bone structure. The chapters follow the development of patient-specific musculoskeletal models in OpenSim and the corresponding finite element models in ABAQUS. Results suggest that reduced loading is the main factor in localised bone loss in the amputated limb. Bone resorption risk is considerably more prominent in the above-knee amputee than in the below-knee, but a considerable resorption risk is present in each. Stark differences in loading scenario and femur stimulation have been identified in both amputee conditions compared to control. The main driver for bone loss in the below-knee amputee was reduced variety of loading at the knee joint, stemming mainly from functional compensation of the intact limb. The amputated limb contributed substantially less to balance and movement than the intact limb; knee joint forces acting in the antero-posterior direction of the control subject were severely reduced in the below-knee amputee. In the above-knee amputee, a reduced loading envelope, the absence of muscles acting across the knee joint and the shielding effect of loading through a prosthetic socket all contributed to an even worse prognosis in terms of bone loss by significantly offloading the amputated femur. Predictive modelling of each scenario demonstrated the potential for 12% and 20% reduction in trabecular bone volume (in the first 5 years) in the femur of the below-knee and above-knee subjects, respectively.

Importantly, this clearly distinguishes *unloading osteopenia* in the amputee subjects from systemic age-related and post-menopausal osteoporosis. This needs be reflected in future treatment strategies, clinical diagnoses and the future research directions previously outlined.

References

- Adachi, T., Kameo, Y., & Hojo, M. 2010. Trabecular bone remodelling simulation considering osteocytic response to fluid-induced shear stress. *Philosophical Transactions: Mathematical, Physical and Engineering Sciences*, **368**(1920), 2669–2682.
- Adamczyk, P., & Kuo, A. 2015. Mechanisms of gait asymmetry due to push-off deficiency in unilateral amputees. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, **23**(5), 776–785.
- Akarsu, S., Tekin, L., Safaz, I., Göktepe, AS., & Yazicioğlu, K. 2012. Quality of life and functionality after lower limb amputations: comparison between uni- vs. bilateral amputee patients. *Orthotics International*, **37**(1), 9–13.
- American Academy of Orthopedic Surgeons. 1992. Chapter 26: Skin problems of the amputee. *In: Atlas of limb prosthetics: Surgical and prosthetic principles*. USA: Mosby.
- Ames, G., & Cunradi, C. 2004. Alcohol use and preventing alcohol-related problems among young adults in the military. *Alcohol Research and Health*, **28**(4), 252–257.
- Babor, T., Higgins-Biddle, J., Saunders, J., & Monteiro, M. 2001. Audit: The alcohol use disorders identification test guidelines for use in primary care, second edition. *World Health Organisation*.
- Bae, T., Choi, K., Hong, D., & Mun, M. 2007. Dynamic analysis of above-knee amputee gait. *Clinical Biomechanics*, **22**(5), 557–566.
- Barre, A., & Armand, S. 2014. Biomechanical toolkit: Open-source framework to visualize and process biomechanical data. *Computer Methods and Programs in Biomedicine*, **1**(114), 80–87.

- Bateni, H., & Olney, S. 2002. Kinematic and kinetic variations of below-knee amputee gait. *Journal of Prosthetics and Orthotics*, **14**(1), 2–10.
- Bemben, D., Sherk, V., Ertl, W., & Bemben, M. 2017. Acute bone changes after lower limb amputation resulting from traumatic injury. *Osteoporosis International*, **28**(7), 2177–2186.
- Bennett, A., Dyball, D., Boos, C., Fear, N., Schofield, S., Bull, A., & Cullinan, P. 2020. Study protocol for a prospective, longitudinal cohort study investigating the medical and psychosocial outcomes of UK combat casualties from the Afghanistan war: The ADVANCE Study. *BMJ Open*, **10**(10), 1–11.
- Berg, H., Eiken, O., Miklavcic, L., & Mekjavcic, I. 2007. Hip, thigh and calf muscle atrophy and bone loss after 5-week bedrest inactivity. *European Journal of Applied Physiology*, **99**(1), 283–289.
- Berger, N. 1992. Chapter 14: Analysis of amputee gait. *In: Atlas of limb prosthetics: Surgical, prosthetic, and rehabilitation principles*. USA: Mosby.
- Bergmann, G., Bender, A., Graichen, F., Dymke, J., Rohlmann, A., Trepczynski, A., Heller, M., & Kutzner, I. 2014. Standardized loads acting in knee implants. *PLOS ONE*, **9**(1).
- Bergmann, G., Bender, A., Dymke, J., Duda, G., & Damm, P. 2016. Standardized loads acting in hip implants. *PLOS ONE*, **11**(5).
- Berridge, D., Slack, R., Hopkinson, B., & Makin, G. 1989. Survey of Amputation Sepsis Wound. *Journal of Hospital Infection*, **13**, 167–172.
- Bertani, A., Mathieu, L., Dahan, J. L., Launay, F., Rongi  ras, F., & Rigal, S. 2015. War-related extremity injuries in children: 89 cases managed in a combat support hospital in Afghanistan. *Orthopaedics and Traumatology: Surgery and Research*, **101**(3), 365–368.
- Beyaert, C., Grumillier, C., Martinet, N., Paysant, J., & Andr  , J. 2008. Compensatory mechanism involving the knee joint of the intact limb during gait in unilateral below-knee amputees. *Gait and Posture*, **28**(2), 278–284.
- Bovi, G., Rabufetti, M., Mazzoleni, P., & Ferrarin, M. 2011. A multiple-task gait analysis approach: Kinematic, kinetic and emg reference data for healthy young and adult subjects. *Gait Posture*, **33**(1), 6–13.

- Brandt, A., Wen, Y., & Liu, M. 2017. Interactions between transfemoral amputees and a powered knee prosthesis during load carriage. *Scientific Reports*, **7**.
- Breakey, J. 1976. Gait of unilateral below-knee amputees. *Orthotics and Prosthetics*, **30**(3), 17–24.
- Brennan, J., & Childress, D. 1991. Fe and experimental investigation of above-knee amputee limb prosthesis systems: a comparative study. *ASME Advances in Bioengineering*, **20**(5), 547–550.
- Broomhead, P., Clark, K., Dawes, D., Hale, C., Lambert, A., Quinlivan, Di, Randell, T., Shepherd, R., & Withpetersen, J. 2012. Evidence based clinical guidelines for the physiotherapy management of adults with lower limb prosthesis. *British Association of Chartered Physiotherapists in Amputee Rehabilitation*.
- Burke, M., Roman, V., & Wright, V. 1978. Bone and joint changes in lower limb amputees. *Annals of the Rheumatic Diseases*, **37**(3), 252–254.
- Butowicz, Courtney M., Dearth, Christopher L., & Hendershot, Brad D. 2017. Impact of Traumatic Lower Extremity Injuries beyond Acute Care: Movement-Based Considerations for Resultant Longer Term Secondary Health Conditions. *Advances in Wound Care*, **6**(8), 269–278.
- Caetano-Lopes, J., Canhão, H., & Fonseca, J. 2007. Osteoblasts and bone formation. *Acta Reumatológica Portuguesa*, **32**(2), 103–110.
- Carbone, V., Fluit, R., Pellikaan, R., van der Krogt, R., Janssen, D., Damsgaard, M., Vigneron, L., Feilkas, T., Koopman, H., & Verdonshot, N. 2015. Tlem 2.0 a comprehensive musculoskeletal geometry dataset for subject-specific modeling of lower extremity. *Journal of Biomechanics*, **48**(5), 734 – 741.
- Ceroni, D., Martin, X., & Farpour-lambert, N. 2012. Effects of Cast-Mediated Immobilization on Bone mineral content mineral density. *The Journal of Bone and Joint Surgery*, **3**(94), 208–216.
- Charmetant, C., Phaner, V., Condemine, A., & Calmels, P. 2010. Diagnosis and treatment of osteoporosis in spinal cord injury patients: A literature review. *Annals of Physical and Rehabilitation Medicine*, **53**(10), 655–668.

- Clasper, Jon, & Ramasamy, Arul. 2013. Traumatic amputations. *British journal of pain*, **7**(2), 67–73.
- Cleather, D., Goodwin, J., & Bull, A. 2013. Hip and knee joint loading during vertical jumping and push jerking. *Clinical Biomechanics*, **28**(1), 98–103.
- Cole, J., & van der Meulen, M. 2010. Whole bone mechanics and bone quality. *Clinical Orthopaedics and Related Research*, **469**(8), 2139–2149.
- Compston, J. 2011. Clinical Question: What is the best approach to managing glucocorticoid-induced osteoporosis? *Clinical Endocrinology*, **74**(5), 547–550.
- Cosman, F., de Beur, S., LeBoff, M., Lewiecki, E., Tanner, B., Randall, S., & Lindsay, R. 2014. Clinician’s Guide to Prevention and Treatment of Osteoporosis. *Osteoporosis International*, **25**(10), 2359–2381.
- Crapo, R., Casaburi, R., Coates, A., Enright, P., N., MacIntyre, & McKay, R. 2002. Ats statement: Guidelines for the six-minute walk test. *American Journal of Respiratory and Critical Care Medicine*, **1**(166), 111–117.
- Cutti, A., Verni, G., Migliore, G., Amoresano, A., & Raggi, M. 2018. Reference values for gait temporal and loading symmetry of lower-limb amputees can help in refocusing rehabilitation targets. *Journal of NeuroEngineering and Rehabilitation*, **15**(1), 61.
- Datta, D., Nair, P., & Payne, J. 1992. Outcome of prosthetic management of bilateral lower-limb amputees. *Disability and Rehabilitation*, **14**(2), 98–102.
- DeLisa, J.A. 1998. *Gait analysis in the science of rehabilitation*. USA: DIANE Publishing.
- Delp, S., Loan, P., Hoy, M., Zajac, F., Topp, E., & Rosen, J. 1990. An interactive graphics-based model of the lower extremity to study orthopaedics surgical procedures. *IEEE transactions on bio-medical engineering*, **37**, 757–767.
- Delp, S., Arnold, A., Anderson, F., Loan, P., & Thelen, D. 2007. Opensim: Open-source software to create and analyze dynamic simulations of movement. *Journal of Biomechanics*, **54**(11), 1940–1950.
- Delp, S., Hicks, J., Ajay, S., Ayman, H., Dembia, C., Ochida, T., Ong, C., & Dunne, J. 2008. User guide. *SimTK, OpenSim*.

- Demontiero, O., Vidal, C., & Duque, G. 2011. Aging and bone loss: new insights for the clinician. *Therapeutic advances in musculoskeletal disease*, **4**(2), 61–76.
- Devan, H., Carman, A., Hendrick, P., Hale, L., & Ribeiro, D. 2015. Spinal, pelvic, and hip movement asymmetries in people with lower-limb amputation: Systematic review. *Journal of Rehabilitation Research and Development*, **52**(1), 1–19.
- Dickinson, A., Steer, J., & Worsley, P. 2017. Finite element analysis of the amputated lower limb: A systematic review and recommendations. *Medical Engineering and Physics*, **43**, 1–18.
- D’Lima, D., Fregly, B., Patil, S., Steklov, N., & Colwell, C. 2012. Knee joint forces: prediction, measurement, and significance. *Proceedings of the Institution of Mechanical Engineers*, **2**(226), 95–102.
- Drake, M., Clarke, B., & Khosla, S. 2008. Bisphosphonates: Mechanism of action and role in clinical practice. *Mayo Clinic Proceedings*, **83**(9), 1032–1045.
- Dumas, R., Cheze, L., & Verriest, J. 2007. Adjustments to mcconville et al. and young et al. body segment inertial parameters. *Journal of Biomechanics*, **40**(3), 543–553.
- Durmus, D., Safaz, I., Adigüzel, E., Uran, A., Sarisoy, G., Goktepe, A., & Tan, A. 2015. The relationship between prosthesis use, phantom pain and psychiatric symptoms in male traumatic limb amputees. *Comprehensive Psychiatry*, **59**, 45–53.
- Edwards, D., Phillip, R., Bosanquet, N., Bull, A., & Clasper, J. 2015. What Is the Magnitude and Long-term Economic Cost of Care of the British Military Afghanistan Amputee Cohort? *Clinical Orthopaedics and Related Research*, **473**(9), 2848–2855.
- Edwards, M. 2000. Below knee prosthetic socket designs and suspension systems. *Physical Medicine and Rehabilitation Clinics of North America*, **11**(3), 585–593.
- Ehde, D., Czerneicki, J., Smith, D., Campbell, K., Edwards, W., Jensen, M., & Robinson, L. 2000. Chronic phantom sensations, phantom pain, residual limb pain, and other regional pain after lower limb amputation. *Archives of Physical Medicine and Rehabilitation*, **8**(81), 1039–1044.
- Eng, J., & Winter, D. 1995. Kinetic analysis of the lower limbs during walk- ing: What information can be gained from a three-dimensional model? *Journal of Biomechanics*, **28**(6), 753–758.

- Ephraim, P., Wegener, S., MacKenzie, E., Dillingham, T., & Pezzin, L. 2005. Phantom pain, residual limb pain, and back pain in amputees: results of a national survey. *Archives of Physical Medicine and Rehabilitation*, **10**(86), 1910–1919.
- Esfandiari, E., Yavari, A., Karimi, A., Masoumi, M., Soroush, M., & Saeedi, H. 2018. Long-term symptoms and function after war-related lower limb amputation: A national cross-sectional study. *Acta Orthopaedica et Traumatologica Turcica*, **52**(5), 348–351.
- Eshragi, A., Osman, N., Karimi, M., Gholizadeh, H., Soodmand, E., & Abas, W. 2014. Gait biomechanics of individuals with transtibial amputation: Effect of suspension system. *PLOS One*, **5**(9), e96988.
- Eviö, S., Tiitinen, A., Laitinen, K., Ylikorkala, O., & Välimäki, M. 2004. Effects of Alendronate and Hormone Replacement Therapy, Alone and in Combination, on Bone Mass and Markers of Bone Turnover in Elderly Women with Osteoporosis. *Journal of Clinical Endocrinology and Metabolism*, **89**(2), 626–631.
- Fang, L., Jia, X., & Wang, R. 2007. Modeling and simulation of muscle forces of trans-tibial amputee to study effect of prosthetic alignment. *Clinical Biomechanics*, **22**(10), 1125–1131.
- Fantozzi, S., Garofalo, P., Cutti, A., & Stagni, R. 2011. 3D Joint Moments in Transfemoral and Transtibial Amputees: When Is the "Ground Reaction Vector Technique" an Alternative To Inverse Dynamics? *Journal of Mechanics in Medicine and Biology*, **12**(04), 1250061.
- Fattal, C., Mariano-Goulart, D., Thomas, E., Rouays-Mabit, H., Verollet, C., & Maimoun, L. 2011. Osteoporosis in persons with spinal cord injury: The need for a targeted therapeutic education. *Archives of Physical Medicine and Rehabilitation*, **92**(1), 59–67.
- Favier, C. 2019. Combined musculoskeletal and finite element modelling of the lumbar spine and lower limbs. *Imperial College London, Department of Civil and Environmental Engineering*.
- Ferreira, A., Neves, E., Melanda, A., Pauleto, A., Iucksch, D., Knaut, L., Silva, R., & Faucz Munhoz da Cunha, R. 2014. Transtibial amputee gait: Kinematics and temporal-spatial analysis. *IFMBE Proceedings*, **41**(01).

- Fey, N., Silverman, A., & Neptune, R. 2010. The influence of increasing steady-state walking speed on muscle activity in below-knee amputees. *Journal of Electromyography and Kinesiology*, **20**(1), 155–161.
- Firestein, G., Gabriel, S., McInnes, I., & O'Dell, J. 2017. *Kelley and firestein's textbook of rheumatology*. Philadelphia, PA, USA: Elsevier.
- Flint, J., Wade, A., Stocker, D., Pasquina, P., Howard, R., & Potter, B. 2014. Bone mineral density loss after combat-related lower extremity amputation. *Journal of Orthopaedic Trauma*, **28**(4), 238–244.
- Frost, A., Norman, G., Ruta, A., Snow, T., & Millard-Stafford, M. 2017. Limitations of body mass index for counseling individuals with unilateral lower extremity amputation. *Prosthetics and Orthotics International*, **2**(41), 186–193.
- Frost, H. 2003. Bone's mechanostat: A 2003 update. *The Anatomical Record*, **275**(A), 1081–1101.
- Gailey, R., Roach, K., Applegate, B., Licht, S., Maguire, M., & Nash, M. 2002. The amputee mobility predictor: An instrument to assess determinants of the lower-limb amputee's ability to ambulate. *Archives of Physical Medicine and Rehabilitation*, **83**(5), 613–627.
- Gailey, R., Allen, K., Castles, J., Kucharik, J., & Roeder, M. 2008. Review of secondary physical conditions associated with lower-limb amputation and long-term prosthetic use. *Journal of Rehabilitation Research and Development*, **45**(1), 15–29.
- Garden, R. 1961. The structure and function of the proximal end of the femur. *Journal of Bone and Joint Surgery, British Volume*, **43**(3), 576–589.
- Geraldes, D., Modenese, L., & Phillips, A.T.M. 2016. Consideration of multiple load cases is critical in modelling orthotropic bone adaptation in the femur. *Biomechanics and Modeling in Mechanobiology*, **15**(5), 1029–1042.
- Golds, G., Houdek, D., & Arnason, T. 2017. Male Hypogonadism and Osteoporosis: The Effects, Clinical Consequences, and Treatment of Testosterone Deficiency in Bone Health. *International Journal of Endocrinology*, **2017**.
- Goujon-Pilet, H., Sapin, E., Fode, P., & Lavaste, F. 2008. Three-dimensional motions of trunk and pelvis during transfemoral amputee gait. *Archives of Physical Medicine and Rehabilitation*, **89**(1), 87–94.

- Haas, A. 1925. *Introduction to theoretical physics. vol. 2.* American Chemical Society, Constable Limited.
- Hadjidakis, D., & Androulakis, I. 2006. Bone remodeling. *Annals of the New York Academy of Sciences*, **1092**, 385–396.
- Hagberg, K., Häggström, E., Uden, M., & Brånemark, R. 2005. Socket versus bone-anchored trans-femoral prostheses: hip range of motion and sitting comfort. *Prosthetics and Orthotics International*, **29**(2), 153–163.
- Hammond, E., Metcalf, H., McDonald, J., & Sadowsky, C. 2014. Bone mass in individuals with chronic spinal cord injury: Associations with activity-based therapy, neurologic and functional status, a retrospective study. *Archives of Physical Medicine and Rehabilitation*, **95**(12), 2342–2349.
- Hanley, D., Adachi, J., Bell, A., & Brown, V. 2012. Denosumab: Mechanism of action and clinical outcomes. *International Journal of Clinical Practice*, **66**(12), 1139–1146.
- Hart, N., Nimphius, S., Rantalainen, T., Ireland, A., Siafarikas, A., & Newton, R. 2017. Mechanical basis of bone strength: influence of bone material, bone structure and muscle action. *Journal of Musculoskeletal and Neuronal Interactions*, **17**(3), 114–139.
- Hebert, J., Rehani, M., & Stiegelmar, R. 2017. Osseointegration for lower-limb amputation: A systematic review of clinical outcomes. *JB JS Reviews*, **5**(10), e10.
- Heller, M., Bergmann, G., Deuretzbacher, G., Durselen, L., Pohl, M., Claes, L., Haas, N., & Duda, G. 2001. Musculo-skeletal loading conditions at the hip during walking and stair climbing. *Journal of Biomechanics*, **34**(7), 883–893.
- Henao, S., Orozco, C., & Ramírez, J. 2020. Influence of gait cycle loads on stress distribution at the residual limb/socket interface of transfemoral amputees: a finite element analysis. *Science Reports*, **10**, 4985.
- Henson, D., Bull, A., & McGregor, A. 2020. Understanding the musculoskeletal function of bilateral through and above-knee amputees. *Ph.D thesis, Imperial College London*.
- Highsmith, J., Schulz, B., Hart-Hughes, S., & Latlief, G. 2010. Differences in the spatiotemporal parameters of transtibial and transfemoral amputee gait. *Journal of Prosthetics and Orthotics*, **22**(1), 26–30.
- Hill, P. 1998. Bone remodelling. *British Journal of Orthodontics*, **25**(2), 101–107.

- Hoffman, M., Sheldahl, L., Buley, K., & Sandford, P. 1997. Physiological comparison of walking among bilateral above-knee amputee and able-bodied subjects, and a model to account for the differences in metabolic cost. *Archives of Physical Medicine and Rehabilitation*, **78**(4), 385–392.
- Holzer, L., Sevelde, F., Fraberger, G., Bluder, O., Kicking, W., & Holzer, G. 2014. Body image and self-esteem in lower-limb amputees. *PLoS ONE*, **9**(3), 1–8.
- Horsman, K., Koopman, H., van der Helm, F., Prosé, L., & Veeger, H. 2007. Morphological muscle and joint parameters for musculoskeletal modelling of the lower extremity. *Clinical Biomechanics*, **10**(23), 1303.
- Hoy. 1990. A musculoskeletal model of the human lower extremity: the effect of muscle, tendon, and moment arm on the moment-angle relationship of musculotendon actuators at the hip, knee and ankle. *Journal of Biomechanics*, **22**, 157–169.
- Huang, S., & Ferris, D. 2012. Muscle activation patterns during walking from transtibial amputees recorded within the residual limb-prosthetic interface. *Journal of NeuroEngineering and Rehabilitation*, **9**(1), 1.
- Hungerford, D., & Cockin, J. 1974. Abstract: The fate of the retained lower limb joints in world war ii amputees. *British Orthopaedic Association Autumn Meeting*.
- Hurley, G., Mckenney, R., Robinson, M., Zadavec, M., & Pierrynowski, M. 1990. The role of the contralateral limb in below-knee amputee gait. *Prosthetics and Orthotics International*, **14**(1), 33–42.
- Isakov, E., Keren, O., & Benjuya, N. 2000. Trans-tibial amputee gait: Time-distance parameters and EMG activity. *Prosthetics and Orthotics International*, **24**(3), 216–220.
- Iwamoto, J., Takeda, T., & Sato, Y. 2005. Interventions to prevent bone loss in astronauts during space flight. *Keio Journal of Medicine*, **54**(2), 55–59.
- Jaegers, S., Arendzen, J., & de Jongh, H. 1995. Prosthetic gait of unilateral transfemoral amputees: a kinematic study. *Archives of Physical Medicine and Rehabilitation*, **76**(8), 736–743.
- Jang, I., Kim, I., & Kwak, B. 2009. Analogy of strain energy density based bone-remodeling algorithm and structural topology optimization. *Journal of Biomechanical Engineering*, **131**(1), 011012.

- Jarvis, H., Reeves, N., Twiste, R., Phillips, R., Etherington, J., & Bennett, A. 2020. Can high-functioning amputees with state-of-the-art prosthetics walk normally? a kinematic and dynamic study of 40 individuals. *Annals of Physical Rehabilitation and Medicine*, [Online before print].
- Jensen, T., Krebs, B., Nielsen, J., & Rasmussen, P. 1985. Immediate and long-term phantom limb pain in amputees: Incidence, clinical characteristics and relationship to pre-amputation limb pain. *Pain*, **21**(3), 267–278.
- Ji, M., & Yu, Q. 2015. Primary osteoporosis in postmenopausal women. *Chronic diseases and translational medicine*, **1**(1), 9–13.
- Kanis, J., Oden, A., Johnell, O., Johansson, H., De Laet, C., Brown, J., Burckhardt, P., Cooper, C., Christiansen, C., Cummings, S., Eisman, J., Fujiwara, S., Glüer, C., Goltzman, D., Hans, D., Krieg, D., La Croix, A., McCloskey, E., Mellstrom, D., Melton, L., Pols, H., Reeve, J., Sanders, K., Schott, A., Silman, A., Torgerson, D., van Staa, T., Watts, N., & Yoshimura, N. 2007. The use of clinical risk factors enhances the performance of bmd in the prediction of hip and osteoporotic fractures in men and women. *Osteoporosis International*, **18**(8), 1033–1046.
- Kannus, P., Haapasalo, H., Sievänen, H., Oja, P., & Vuori, I. 1994. The site-specific effects of long-term unilateral activity on bone mineral density and content. *Bone*, **1**(15), 279–284.
- Kennel, K., & Drake, M. 2009. Adverse effects of bisphosphonates: Implications for osteoporosis management. *Mayo Clinic Proceedings*, **84**(7), 632–638.
- Kerr, C., Bottomley, C., Shingler, S., Giangregorio, L., de Freitas, H., Patel, C., Randall, S., & Gold, D. 2017. The importance of physical function to people with osteoporosis. *Osteoporosis International*, **28**(5), 1597–1607.
- Kersting, U., Gurney, J., Søren, L., & Rasmussen, J. 2010. An individualized musculoskeletal model for the analysis of amputee running. *Pages 142–144 of: Proceedings of the 28th conference of the international society of biomechanics in sports*. Marquette, MI, USA: International Society of Biomechanics, ISB.
- Kim, H., Howard, G., & Cunningham, J. 2009. Do trabeculae of femoral head represent a structural optimum? *13th International Conference on Biomedical Engineering, IFMBE Proceedings*, **23**, 1636–1639.

- Klotz, R., Colobert, B., Botino, M., & Permentiers, I. 2011. Influence of different types of sockets on the range of motion of the hip joint by the transfemoral amputee. *Annals of Physical and Rehabilitation Medicine*, **54**(7), 399–410.
- Kramer, A., Gollhofer, A., Armbrecht, G., Felsenberg, D., & Gruber, M. 2017. How to prevent the detrimental effects of two months of bed-rest on muscle, bone and cardiovascular system: An RCT. *Scientific Reports*, **7**(1), 1–10.
- Krouskop, T., Muilenberg, A., Dougherty, D., & Winningham, D. 1987. Computer-aided design of a prosthetic socket for an above-knee amputee. *Journal of Rehabilitation Research and Development*, 31–38.
- Kulkarni, J., Adams, J., Thomas, E., & Silman, A. 1998. Association between amputation, arthritis and osteopenia in British male war veterans with major lower limb amputations. *Clinical Rehabilitation*, **12**(4), 348–353.
- Lacroix, D., & Ramírez Patiño, J. 2011. Finite element analysis of donning procedure of a prosthetic transfemoral socket. *Annals of Biomedical Engineering*, **39**(12), 2972–2983.
- Lancer, H., Smitham, P., & Ray, P. 2016. Bilateral Neck of Femur Fractures in a Bilateral Below-Knee Amputee: A Unique Case. *Case Reports in Orthopedics*, **2016**, 1–4.
- LaPrè, A., Price, M., Wedge, R., & Umberger, B. 2017. Approach for gait analysis in persons with limb loss including residuum and prosthesis socket dynamics. *International Journal for Numerical Methods in Biomedical Engineering*, **34**(4), 2936.
- Lau, R., & Guo, X. 2011. A Review on Current Osteoporosis Research: With Special Focus on Disuse Bone Loss. *Journal of Osteoporosis*, **2011**, 1–6.
- Leblanc, A., Schneider, V., Evans, H., Engelbretson, D., & Krebs, J. 1990. Bone mineral loss and recovery after 17 weeks of bed rest. *Journal of Bone and Mineral Research*, **5**(8), 843–850.
- LeBlanc, A., Spector, E., Evans, H., & Sibonga, J. 2007. Skeletal responses to space flight and bed rest: a review. *Journal of Musculoskeletal and Neuronal Interactions*, **7**(1), 33–47.
- Leclercq, M., Bonidan, O., Haaby, E., Pierrejean, C., & Sengler, J. 2003. Étude de la masse osseuse par ostéodensitométrie dans une population de 99 amputés de membre

- inférieur Study of bone mass with dual energy x-ray absorptiometry in a population of 99 lower limb amputees. *Annales de Réadaptation et de Médecine Physique*, **46**(1), 24–30.
- Lee, H., Lee, J., & Kim, H. 2019. Activities of ankle muscles during gait analyzed by simulation using the human musculoskeletal model. *Journal of Exercise Rehabilitation*, **2**(15), 229–234.
- Lee, V., Solomonidis, S., & Spence, WD. 1994. Biomechanical modelling of the interface between residual limb/prosthesis interface for transfemoral amputees using finite element analysis. *Proceedings of the Eighth International Conference on Biomedical Engineering*, 333–335.
- Lin, S., & Bose, N. 2008. Six-minute walk test in persons with transtibial amputation. *Archives of Physical Medicine and Rehabilitation*, **12**(89), 2354–2359.
- Linberg, A., Roach, K., Campbell, S., Stoneman, P., Gaunard, I., Raya, M., Gomez-Orozco, C., & Gailey, R. 2013. Comparison of 6-minute walk test performance between male active duty soldiers and servicemembers with and without traumatic lower-limb loss. *Journal of rehabilitation research and development*, **50**(11), 931–940.
- Liu, M., Anderson, F., Schwartz, M., & Delp, S. 2008. Muscle contributions to support and progression over a range of walking speeds. *Journal of Biomechanics*, **41**(15), 3243–3252.
- Lloyd, C.H. 2010. Strength asymmetry and osteoarthritis risk factors in unilateral trans-tibial, amputee gait. *Gait posture*, **32**(3), 296–300.
- Loeb, G., & Davoodi, R. 2016. Musculoskeletal Mechanics and Modeling. *Scholarpedia*, **11**(11), 12389. revision #169693.
- Lohman, T., Roche, A., & Martorell, R. 1988. *Anthropometric standardization reference manual*. United Kingdom: Human Kinetics.
- Mak, A., Yu, Y., Hong, L., & Chan, C. 1992. Finite element models for analyses of stresses within above-knee stumps. *Proceedings of 7th World Congress of ISPO*, 147.
- Marino, M., Pattni, S., Greenberg, M., Miller, A., Hocker, E., Ritter, S., & Mehta, K. 2015. Access to prosthetic devices in developing countries: Pathways and challenges.

- Proceedings of the 5th IEEE Global Humanitarian Technology Conference, GHTC 2015*, 45–51.
- Masmoudi, K., Rbai, H., Fradj, A., Saâdena, J., & Boughattas, A. 2016. Primary Total Hip Replacement for a Femoral Neck Fracture in a Below-Knee Amputee. *Journal of Orthopaedic Case Reports*, **6**(3), 63–66.
- McNealy, L., & Gard, S. 2008. Effect of prosthetic ankle units on the gait of persons with bilateral trans-femoral amputations. *Prosthetics and Orthotics International*, **32**(1), 111–126.
- Metzger, C., Burr, D., & Allen, M. 2020. *Encyclopedia of bone biology*. USA: Academic Press.
- Michael, J. 1990. Current concepts in above-knee socket design. *Instr Course Lect*, **39**, 373–378.
- Michaud, S., Gard, S., & Childress, D. 2000. A preliminary investigation of pelvic obliquity patterns during gait in persons with transtibial and transfemoral amputation. *Journal of Rehabilitation Research and Development*, **37**(1), 1–10.
- Miller, C., Williams, J., Durham, K., Hom, S., & Smith, J. 2017. The effect of a supervised communityâbased exercise program on balance, balance confidence, and gait in individuals with lower limb amputation. *Prosthetics and Orthotics International*, **41**(5), 446–454.
- Miller, W., Deathe, A., Speechley, M., & Koval, J. 2001. The influence of falling, fear of falling, and balance confidence on prosthetic mobility and social activity among individuals with a lower extremity amputation. *Archives of Physical Medicine and Rehabilitation*, **82**(9), 1238–1244.
- Minus, M., & Kumar, S. 2005. The processing, properties, and structure of carbon fibers. *JOM*, **57**, 52–58.
- Moayyeri, El Maghraoui, A., Mouinga Abayi, D., Rkain, H., & Mounach, A. 2007. Discordance in Diagnosis of Osteoporosis Using Spine and Hip Bone Densitometry. *Journal of Clinical Densitometry*, **10**(2), 153–156.
- Modenese, L, & Phillips, A.T.M. 2012. Prediction of hip contact forces and muscle activations during walking at different speeds. *Multibody System Dynamics*, **28**(1-2), 157–168.

- Modenese, L., Phillips, A., & Bull, A. 2011. An open source lower limb model: Hip joint validation. *Journal of Biomechanics*, **44**(12), 2185–2193.
- Modenese, L., Gopalakrishnan, A., & Phillips, A. 2013. Application of a falsification strategy to a musculoskeletal model of the lower limb and accuracy of the predicted hip contact force vector. *Journal of Biomechanics*, **46**(6), 1193–1200.
- Morgentaler, A., Miner, M., Caliber, M., Guay, A., Khera, M., & Traish, A.. 2015. Testosterone Therapy and Cardiovascular Risk: Advances and Controversies. *Mayo Clinic Proceedings*, **90**(2), 224–251.
- Morlock, M., Schneider, E., Bluhm, A., Vollmer, M., Bergmann, G., Muller, V., & Honl, M. 2001. Duration and frequency of every day activities in total hip patients. *Journal of Biomechanics*, **7**(34), 873–881.
- Mounach, A., Rezqi, A., Ghozlani, I., Achemlal, L., Bezza, A., & El Maghraoui, A. 2012. Prevalence and Risk Factors of Discordance between Left- and Right-Hip Bone Mineral Density Using DXA. *ISRN Rheumatology*, **2012**, 1–6.
- Narang, I., Mathur, B., Singh, P., & Jape, V. 1984. Functional capabilities of lower limb amputees. *Prosthetics and Orthotics International*, **8**(1), 43–51.
- No authors listed. 1993. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *American Journal of Medicine*, **94**(6), 646–650.
- Nolan, L., Wit, A., Dudziński, K., Lees, A., Lake, M., & Wychowski, M. 2003. Adjustments in gait symmetry with walking speed in trans-femoral and trans-tibial amputees. *Gait and Posture*, **17**(2), 142–151.
- Nordin, B. 1979, republished in 2012. Treatment of Postmenopausal Osteoporosis. *Drugs, republished in practical therapeutic*, **18**, 484–492.
- Nägele, E., Kuhn, V., Vogt, H., Link, T., Müller, R., E., Lochmüller, & Eckstein, F. 2004. Technical considerations for microstructural analysis of human trabecular bone from specimens excised from various skeletal sites. *Calcified Tissue International*, **75**, 15–22.
- O’Brien, T., Reeves, N., Baltzopoulos, V., Jones, D., & Maganaris, C. 2009. In vivo measurements of muscle specific tension in adults and children. *Experimental Physiology*, **95**, 202–210.

- Orwoll, E., Adler, R., Amin, S., Binkley, N., Lewiecki, E., Petak, S., Shapses, S., S., Watts, N., & Sibonga, J. 2013. Skeletal health in long-duration astronauts: Nature, assessment, and management recommendations from the nasa bone summit. *Journal of Bone and Mineral Research*, **28**(6), 1243–1255.
- Paternò, L., Ibrahimi, M., Gruppioni, E., Mencias, A., & Ricotti, L. 2018. Sockets for limb prostheses: A review of existing technologies and open challenges. *IEEE Transactions on Biomedical Engineering*, **65**(9), 1996–2010.
- Pereira, A., & Sheffellbine, S. 2014. The influence of load repetition in bone mechanotransduction using poroelastic finite-element models: the impact of permeability. *Biomechanics and modeling in mechanobiology*, **13**(1), 215–225.
- Pereira Silva, J., Costa Dias, F., Fonseca, J., Canhao, H., Resende, C., & Viana Queiroz, M. 2004. Low bone mineral density in professional scuba divers. *Clinical Rheumatology*, **23**(1), 19–20.
- Perry, J., Burnfield, J., Newsam, C., & Conley, P. 2004. Energy expenditure and gait characteristics of a bilateral amputee walking with c-leg prostheses compared with stubby and conventional articulating prostheses. *Archives of Physical Medicine and Rehabilitation*, **85**(1), 1711–1717.
- Phillips, A., Villette, C., & Modenese, L. 2015. Femoral bone mesoscale structural architecture prediction using musculoskeletal and finite element modelling. *International Biomechanics*, **2**(1), 43–61.
- Phillips, A.T.M. 2011. Structural optimisation: Biomechanics of the femur. *Engineering and Computational Mechanics*, **165**.
- Plotkin, L. 2014. Apoptotic osteocytes and the control of targeted bone resorption. *Current Osteoporosis Reports*, **12**(1), 121–126.
- Pothuaud, L., van Rietbergen, B., Charlot, C., Ozhinsky, E., & Majumdar, S. 2004. A new computational efficient approach for trabecular bone analysis using beam models generated with skeletonized graph technique. *Computer Methods in Biomechanics and Biomedical Engineering*, **7**(4), 205–213.
- Pritham, C.H. 1990. Biomechanics and shape of the above-knee socket considered in light of the ischial containment concept. *Prosthetics and Orthotics International*, **14**(1), 9–21.

- Rabuffetti, M., Recalcati, M., & Ferrarin, M. 2005. Trans-femoral amputee gait: Socket–pelvis constraints and compensation strategies. *Prosthetics and Orthotics International*, **29**(2), 183–192.
- Rabuffetti, M., Recalcati, M., & Ferrarin, M. 2005. Trans-femoral amputee gait: Socket–pelvis constraints and compensation strategies. *Prosthetics and Orthotics International*, **29**(2), 183–192.
- Ramasamy, E., Avci, O., Dorow, B., Chong, S., Gizzi, L., Steidle, G., Schick, F., & Rohrlé, O. 2018. An efficient modelling-simulation-analysis workflow to investigate stump-socket interaction using patient-specific, three-dimensional, continuum-mechanical, finite element residual limb models. *Frontiers in Bioengineering and Biotechnology*, **6**, 126.
- Ramírez, J., Isaza, J., Mariaka, I., & Vélez, J. 2011. Analysis of bone demineralization due to the use of exoprosthesis by comparing Young’s Modulus of the femur in unilateral transfemoral amputees. *Prosthetics and Orthotics International*, **35**(4), 459–466.
- Recker, R., Lappe, J., Davies, K., & Heaney, R. 2004. Bone remodeling increases substantially in the years after menopause and remains increased in older osteoporosis patients. *Journal of Bone and Mineral Research*, **19**(10), 1628–1633.
- Reijnen, A., Geuze, E., & Vermetten, E. 2015. The effect of deployment to a combat zone on testosterone levels and the association with the development of posttraumatic stress symptoms: A longitudinal prospective Dutch military cohort study. *Psychoneuroendocrinology*, **51**, 525–533.
- Rethnam, U., Yesupalan, R., Shoaib, A., & Ratnam, T. 2008. Hip fracture fixation in a patient with below-knee amputation presents a surgical dilemma: A case report. *Journal of Medical Case Reports*, **2**, 3–5.
- Richards, T., Pittahankel, A., Pursell, R., & Galland, R. 2005. Mrsa in lower limb amputation and the role of antibiotic prophylaxis. *Journal of Cardiovascular Surgery*, **46**, 37–41.
- Riddle, R., & Donahue, H. 2009. From streaming-potentials to shear stress: 25 years of bone cell mechanotransduction. *Journal of Orthopedic Research*, **27**(2), 143–149.

- Riley, P., Paolini, G., Croce, U., Paylo, K., & Kerrigan, C. 2007. A kinematic and kinetic comparison of overground and treadmill walking in healthy subjects. *Gait Posture*, **26**(1), 17–24.
- Rittweger, J., & Felsenberg, D. 2009. Recovery of muscle atrophy and bone loss from 90 days bed rest: Results from a one-year follow-up. *Bone*, **44**(2), 214–224.
- Rittweger, J., Frost, H., Schiessl, H., Oshima, H., Alkner, B., Tesch, P., & Felsenberg, D. 2005. Muscle atrophy and bone loss after 90 days' bed rest and the effects of flywheel resistive exercise and pamidronate: Results from the ltbr study. *Bone*, **36**(6), 1019–1029.
- Robbins, C., Vreeman, D., Sothmann, M., Wilson, S., & Oidridge, N. 2009. A review of the long-term health outcomes associated with war-related amputation. *Military Medicine*, **174**(6), 588–592.
- Rucci, N. 2008. Molecular biology of bone remodelling. *Clinical Cases In Mineral and Bone Metabolism : The Official Journal Of The Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases*, **5**(1), 49–56.
- Rupler, M., Würger, T, Roschger, P., Zwettler, E., Peterlik, H., Fratzl, P., & Klaushofer, K. 2012. Microcracks and osteoclast resorption activity in vitro. *Calcified Tissue International*, **90**(3), 230–238.
- Rush, P., Wong, J., Kirsh, J., & Devlin, M. 1994. Osteopenia in patients with above knee amputation. *Archives of Physical Medicine and Rehabilitation*, **75**(1), 112–115.
- Russow, G., Jahn, D., Appelt, J., Märdian, S., Tsitsilonis, S., & Keller, J. 2019. Anabolic therapies in osteoporosis and bone regeneration. *International Journal of Molecular Sciences*, **20**(1).
- Rábago, C., & Wilken, J. 2016. The prevalence of gait deviations in individuals with transtibial amputation. *Military Medicine*, **181**(S4), 30–37.
- Sagawa, Y., Turcot, K., Armand, S., Thevenon, A., Vuillerme, N., & Watelain, E. 2011. Biomechanics and physiological parameters during gait in lower-limb amputees: a systematic review. *Gait Posture*, **33**(4), 511–526.
- Sahu, A., Sagar, R., Sarkar, S., & Sagar, S. 2016. Psychological effects of amputation: A review of studies from india. *Industrial psychiatry journal*, **25**(1), 1–10.

- Salawu, A., Middleton, C., Gilbertson, A., Kodavali, K., & Neumann, V. 2006. Stump ulcers and continued prosthetic limb use. *Prosthetics and Orthotics International*, **30**(3), 279–285.
- Sambrook, P., & Hunter, D. 2000. Bone loss: Epidemiology of bone loss. *Arthritis Research Therapy*, **2**(441).
- Sanchis-Moysi, J., Dorado, C., Vincente, G., Serrano, J., Rodriguez, L., & Calbet, J. 2002. Bone mass, bone mineral density and muscle mass in professional golfers. *Journal of Sports Sciences*, **20**(8), 591–597.
- Sanchis-Moysi, J., Dorado, C., , Serrano-Sanchez, J., Olmedillas, H., & Calbet, J. 2010. Bone and lean mass inter-arm asymmetries in young male tennis players depend on training frequency. *European journal of applied physiology*, **1**(110), 83–90.
- Sanderson, D., & Martin, P. 1996. Joint kinetics in unilateral below-knee amputee patients during running. *Archives of Physical Medicine and Rehabilitation*, **77**(12), 1279–1285.
- Schaarschmidt, M., Lipfert, S., Meier-Gratz, C., Scholle, H., & Seyfarth, A. 2012. Functional gait asymmetry of unilateral transfemoral amputees. *Human Movement Science*, **31**(4), 907–917.
- Schuch, C., & Pritham, C. 1999. Current transfemoral sockets. *Clinical Orthopaedics and Related Research*, 48–54.
- Segal, A., Orendurff, M., Klute, G., M., McDowell, Pecoraro, J., Shofer, J., & Czerniecki, J. 2006. Kinematic and kinetic comparisons of transfemoral amputee gait using c-leg® and mauch sns® prosthetic knees. *Journal of Rehabilitation Research and Development*, **43**(7), 857–870.
- Shaffler, M., & Kennedy, O. 2012. Osteocyte signaling in bone. *Current Osteoporosis Reports*, **2**(10), 118–125.
- Sherk, V., Bembien, M., & Bembien, D. 2008. BMD and bone geometry in transtibial and transfemoral amputees. *Journal of Bone and Mineral Research*, **23**(9), 1449–1457.
- Sherman, K., Roberts, A., Murray, A., Deans, S., & Jarvis, H. 2019. Daily step count of british military males with bilateral lower limb amputations: A comparison of in-patient rehabilitation with the consecutive leave period between admissions. *Prosthetics and Orthotics International*, **43**(2), 188–195.

- Shinchuk, L., Morse, L., Huancahuari, N., Arum, S., Chen, T., & Holick, M. 2006. Vitamin D Deficiency and Osteoporosis in Rehabilitation Inpatients. *Archives of Physical Medicine and Rehabilitation*, **87**(7), 904–908.
- Silverman, A., & Neptune, R. 2014. Three-dimensional knee joint contact forces during walking in unilateral transtibial amputees. *Journal of Biomechanics*, **47**(11), 2556–2562.
- Silverman, A., Fey, N., Portillo, A., Walden, J., Bosker, G., & Neptune, R. 2008. Compensatory mechanisms in below-knee amputee gait in response to increasing steady-state walking speeds. *Gait and Posture*, **28**(4), 602–609.
- Singh, M., Nagrath, A., & Maini, P. 2014. Changes in trabecular pattern of the upper end of the femur as an index of osteoporosis. *Classic Papers in Orthopaedics*, 129–132.
- Singleton, J., Gibb, I., Bull, A., & Clasper, J. 2014. Blast-mediated traumatic amputation: Evidence for a revised, multiple injury mechanism theory. *Journal of the Royal Army Medical Corps*, **160**(2), 175–179.
- Sjödahl, C., Jarnlo, G., Söderberg, B., & Persson, B. 2002. Kinematic and kinetic gait analysis in the sagittal plane of trans-femoral amputees before and after special gait re-education. *Prosthetics and Orthotics International*, **26**(2), 101–112.
- Sloot, L., & van der Krogt, M. 2018. Interpreting joint moments and powers in gait. *In: Handbook of human motion*. New York, NY, USA: Springer International Publishing.
- Smith, D., Ehde, D., Legro, M., Reiber, G., del Aquila, M., & Boone, D. 1999. Phantom limb, residual limb, and back pain after lower extremity amputations. *Clinical Orthopaedics and Related Research*, 29–38.
- Smith, É., Comiskey, C., Carroll, Á., & Ryall, N. 2011. A study of bone mineral density in lower limb amputees at a national prosthetics center. *Journal of Prosthetics and Orthotics*, **23**(1), 14–20.
- Smith, M. 2009. *Abaqus/standard user's manual, version 6.9*. United States: Dassault Systèmes Simulia Corp.
- Sozen, T., Ozisik, L., & Calik Basaran, N. 2016. An overview and management of osteoporosis. *European Journal of Rheumatology*, **4**(1), 46–56.

- Specker, B., Wey, H., & Smith, E. 2010. Rates of bone loss in young adult males. *International Journal of Clinical Rheumatology*, **5**(2), 215–218.
- Steinberg, N., Gottlieb, A., Siev-Ner, I., & Plotnik, M. 2019. Fall incidence and associated risk factors among people with a lower limb amputation during various stages of recovery—a systematic review. *Disability and Rehabilitation*, **41**(15), 1778–1787.
- Stephenson, P., & Seedhorn, B. 1999. Cross-sectional geometry of the human femur in the mid-third region. *Proceedings of the institution of mechanical engineers*, **213**(H), 159–166.
- Sugiyama, T., Meakin, L., Browne, W., Galea, G., Price, J., & Lanyon, L. 2012. Bones' adaptive response to mechanical loading is essentially linear between the low strains associated with disuse and the high strains associated with the lamellar/woven bone transition. *Journal of Bone and Mineral Research*, **27**(8), 1784–1793.
- Taheri, A., & Karimi, M. 2012. Evaluation of the gait performance of above-knee amputees while walking with 3r20 and 3r15 knee joints. *Journal of Research in Medical Sciences*, **17**(3), 258–263.
- Takechi, H. 1977. Trabecular architecture of the knee joint. *Acta Orthopaedica Scandinavica*, **48**, 673–681.
- Talbot, L., Brede, E., & Jeffrey Metter, E. 2017. Psychological and physical health in military amputees during rehabilitation: Secondary analysis of a randomized controlled trial. *Military Medicine*, **182**(5), e1619–e1624.
- Tan, C., Battaglino, R., & Morese, L. 2013. Spinal cord injury and osteoporosis: Causes, mechanisms, and rehabilitation strategies. *International Journal of Physical Medicine Rehabilitation*, **1**(4), 1–5.
- Tanaka, Y., Nakayamada, S., & Okada, Y. 2005. Osteoblasts and osteoclasts in bone remodeling and inflammation. *Current Drug Targets - Inflammation Allergy*, **4**(3), 325–328.
- Tavani, A., & La Vecchia, C. 1999. The adverse effects of hormone replacement therapy. *Drugs and Aging*, **14**(5), 347–357.
- Torres-Moreno, R. 1991. Biomechanical analysis of the interaction between the above-knee residual limb and the prosthetic socket. *Ph.D Dissertation. University of Strathclyde*.

- Treece, G., Gee, A., Mayhew, P., & Poole, K. 2010. High resolution cortical bone thickness measurement from clinical ct data. *Medical Image Analysis*, **14**(3), 276–290.
- Tugcu, I., Safaz, I., Yilmaz, B., Göktepe, A., Taskaynatan, M., & Yazicioglu, K. 2009. Muscle strength and bone mineral density in mine victims with transtibial amputation. *Prosthetics and Orthotics International*, **33**(4), 299–306.
- Turner, C., Rho, J., Takano, Y., Tsui, T., & Pharr, G. 1999. The elastic properties of trabecular and cortical bone tissues are similar: results from two microscopic measurement techniques. *Journal of Biomechanics*, **32**(4), 437–441.
- van Arkel, R., Modenese, L., Phillips, A., & Jeffers, J. 2013a. Hip abduction can prevent posterior edge loading of hip replacements. *Journal of Orthopaedic Research*, **31**(8), 1172–1179.
- van Arkel, R., Modenese, L., Phillips, A.T.M., & Jeffers, J. 2013b. Hip abduction can prevent posterior edge loading of hip replacements. *Journal of Orthopaedic Research*, **31**(8), 1172–1179.
- van Lenthe, G., Stauber, M., & Müller, R. 2006. Specimen-specific beam models for fast and accurate prediction of human trabecular bone mechanical properties. *Bone*, **39**(6), 1182–1189.
- Vernon, M., Kay, P., & NICE. 2018. Nice impact falls and fragility fractures. *National Institute for Health and Care Excellence*.
- Villette, C. 2016. Structural meso and microscale finite element based approaches for the prediction of bone architecture and fracture. *Imperial College London, Department of Civil and Environmental Engineering*.
- Villette, C., & Phillips, A.T.M. 2018. Rate and age-dependent damage elasticity formulation for efficient hip fracture simulations. *Medical Engineering and Physics*, **61**, 1–12.
- Villette, C., Zhang, J., & Phillips, A. 2019. Influence of femoral external shape on internal architecture and fracture risk. *Biomechanics and Modeling in Mechanobiology*, 1251–1261.
- Visser, J., McCarthy, I., Marks, L., & Davis, R. 2011. Is hip muscle strength the key to walking as a bilateral amputee, whatever the level of amputations? *Prosthetics and Orthotics International*, **34**(4), 451–458.

- Waller, M., McGuire, A., & Dobson, A. 2015. Alcohol use in the military: associations with health and wellbeing. *Substance Abuse Treatment, Prevention and Policy*, **10**(27).
- Wentink, E., Prinsen, E., Rietman, J., & Veltink, P. 2013. Comparison of muscle activity patterns of transfemoral amputees and control subjects during walking. *Journal of NeuroEngineering and Rehabilitation*, **10**(1), 87.
- White, D., Griffith, R., & Wilson, I. 1992. Report 46. *Journal of the International Commission on Radiation Units and Measurements*, **24**(1).
- Wilmet, E., Ismail, A., Heilporn, A., Welraeds, D., & Bergmann, P. 1995. Longitudinal study of the bone mineral content and of soft tissue composition after spinal cord section. *Paraplegia*, **33**(11), 674–677.
- Winiarski, S., Pietraszewska, J., & Pietraszewski, B. 2019. Three-dimensional human gait pattern: Reference data for young, active women walking with low, preferred, and high speeds. *Biomedical Research International*, **2019**.
- Winter, D., & Sienko, S. 1988. Biomechanics of below-knee amputee gait. *Journal of Biomechanics*, **21**(5), 361 – 367.
- Winter, D., Sidwall, H., & Hobson, D. 1974. Measurement and reduction of noise in kinematics of locomotion. *Journal of Biomechanics*, **7**(2), 157–159.
- Woodson, G. 2010. Dual x-ray absorptiometry t-score concordance and discordance between hip and spine measurement sites. *Journal of Clinical Densitometry*, **3**(4), 319–324.
- Wu, G. 2002. Isb recommendation on definitions of joint coordinate system of various joints for the reporting of human joint motion–part i: ankle, hip, and spine. *Journal of Biomechanics*, **4**(35), 543–548.
- Zachariah, S., & Sanders, J. 2000. Finite element estimates of interface stress in the transtibial prosthesis using gap elements are different from those using automated contact. *Journal of Biomechanics*, **33**, 895–899.
- Zaharie, D. 2018. Computational models to predict pelvic bone architecture and fracture. *Imperial College London, Department of Civil and Environmental Engineering*.

- Zaharie, D., & Phillips, A. 2018. Pelvic construct prediction of trabecular and cortical bone structural architecture. *Journal of Biomechanical Engineering*, **140**(9).
- Zerwekh, J., Ruml, L., Gottschalk, F., & Pak, C. 1998. The effects of twelve weeks of bed rest on bone histology, biochemical markers of bone turnover, and calcium homeostasis in eleven normal subjects. *Journal of Bone and Mineral Research*, **13**(10), 1594–1601.
- Zhang, L., Zhu, M., Shen, L., & Zheng, F. 2013. Finite element analysis of the contact interface between trans-femoral stump and prosthetic socket. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 1270–1273.
- Zhang, M., Mak, A., & Roberts, V. 1998. Finite element modelling of a residual lower-limb in a prosthetic socket: a survey of the development in the first decade. *Medical Engineering and Physics*, **20**(5), 360 – 373.

Publications

Conference oral presentations

Kaufmann, J.J., Phillips A.T.M. and McGregor A.H. (2020). A combined musculoskeletal and finite element approach to investigating bone health in above-knee amputees. *2020 British Orthopaedic Research Society Annual Meeting*

Kaufmann, J.J., Phillips A.T.M. and McGregor A.H. (2019). A combined clinical and computational approach to investigating bone health in lower-limb amputees. *The Blast Injury Conference 2019*

Kaufmann J.J., Phillips A.T.M. and McGregor A.H. (2019). Taking a computational approach to investigating bone health in lower-limb amputees. *TGCS - 17th International Symposium on Computer Simulation in Biomechanics*

Kaufmann J.J., Phillips A.T.M. and McGregor A.H. (2019). Taking a combined approach to investigating bone health in lower-limb amputees. *XXVII Congress of the International Society of Biomechanics*

Kaufmann, J.J., Phillips A.T.M. and McGregor A.H. (2018). Investigating bone health in lower-limb amputees. *The Blast Injury Conference 2018*

Kaufmann, J.J., Phillips A.T.M and McGregor A.H. (2018). Investigating bone health in lower-limb amputees. *14th Annual Bath Biomechanics Symposium*

Kaufmann J.J., Phillips A.T.M., McGregor A.H. (2018). Investigating bone health in above-knee amputees. *Virtual Physiological Human Annual Congress*

Conference poster presentations

Kaufmann, J.J., Phillips A.T.M and McGregor A.H. (2018). Investigating bone health in lower-limb amputees. *8th World Congress of Biomechanics*

