



IMPLANTABLE ELECTRONICS FOR ORTHOPAEDIC SURGERY

Smart Interventions for Aseptic Loosening and Periprosthetic Joint
Infection

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*"If you want to find the secrets of the universe, think in terms of energy,
frequency and vibration."*

Nikola Tesla

Declaration of Originality

The material presented in this thesis is my own work with supervision from Dr Richard van Arkel and Dr Frederic Cegla. All published or unpublished material used in this thesis has been given full acknowledgement.

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Abstract

Implantable electronics are a key pillar of the ongoing revolution in healthcare towards precision medicine. In orthopaedics, commercial interest in the technology is high but translation has been impeded by inflated device architectures, which are incompatible with the clinical requirement for less invasive implants. In this research, minimalist principles were adopted by which processing and power were externalised to reduce footprint. As demonstrations, two smart implant concepts were developed to mitigate the most severe consequences of aseptic loosening and periprosthetic joint infection, the two most common causes of implant failure, by enabling early diagnosis and intervention. The first concept was a battery-free smart implant with an embedded ultrasound transducer: passive interrogation of the implant was used to extract fixation and temperature data. Fixation was robustly detected in two commercial implants amidst variation in reader and implant positioning, whilst temperature was measured to $\pm 1^\circ\text{C}$ as a proxy for infection with positioning controls. The second concept delivered controllable electromechanical stimuli to promote osseointegration. In an ex vivo organ model, expansive mineralised structures with high cell viability were observed on the implant surfaces of treated specimens, whilst passive controls exhibited near-zero proliferation or matrix deposition. Both concepts contained lead-based piezoelectric transducers as principal components, and a new lead-free piezoceramic (BNT-6BT) was evaluated for comparison. No cytotoxic effect was detected and its surface was conducive to cell proliferation, indicating that the piezoceramic could be exposed to – or even integrated with – biological tissue whilst part of a smart implant. The material was found to exhibit inferior piezoelectric properties compared to the original materials: estimated performance loss was severe for the first smart implant concept (~ 25 dB) but tolerable for the second (~ 10 dB). In summation, smart implants are a promising new technology for orthopaedic surgery, which could be delivered using streamlined battery-free architectures.

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Contents

List of Figures.....	xiii
List of Tables.....	xxiii
1. General Introduction	1
1.1. Research Motivation.....	2
1.2. Aims and Objectives	3
1.3. Structure.....	3
2. Aseptic Loosening, Periprosthetic Joint Infection and Smart Interventions: Current Concepts and State of the Art.....	5
2.1. Joint Replacement Surgery	6
2.1.1. Indications.....	6
2.1.2. Surgical Procedure	6
2.1.3. Implant Biomaterials.....	10
2.1.4. Fixation	10
2.1.5. Revision Surgery	12
2.2. Aseptic Loosening.....	12
2.2.1. Aetiopathogenesis.....	13
2.2.2. Diagnosis.....	14
2.2.3. Treatment.....	16
2.3. Periprosthetic Joint Infection	17
2.3.1. Aetiopathogenesis.....	17
2.3.2. Diagnosis.....	18
2.3.3. Treatment.....	20
2.3.4. Burden.....	20
2.4. Osseointegration: Mechanobiology and Enhancement	21
2.4.1. Cancellous Bone: Structure and Cellular Composition	21
2.4.2. Mechanotransduction in Bone Remodelling	23
2.4.3. Osseointegration.....	25

2.4.4.	Implant Design and Coatings	27
2.4.5.	Ultrasound Stimulation.....	27
2.4.6.	Electrical Stimulation.....	28
2.4.7.	Pharmacological Stimulation	29
2.5.	Smart Implants in Arthroplasty.....	30
2.5.1.	Power	31
2.5.2.	Communication	33
2.5.3.	Sensing	34
2.6.	Summary of Findings	35
3.	Smart Implants for Simultaneous Fixation and Infection Monitoring I: Development of a General Concept with Wireless, Battery-Free Operation	37
3.1.	Introduction.....	39
3.2.	Concept Overview	39
3.3.	Materials and Methods	41
3.3.1.	Experimental Setup	42
3.3.2.	Measurement Acquisition	43
3.3.3.	Piezoelectric Transducer Modelling	45
3.3.4.	Inductive Link Modelling.....	47
3.4.	Results.....	51
3.4.1.	Implant Fixation	51
3.4.2.	Temperature Calibration	52
3.4.3.	Signal-to-Crosstalk Ratio.....	53
3.4.4.	Signal-to-Noise Ratio	53
3.4.5.	Piezoelectric Transducer Analysis	55
3.4.6.	Inductive Link Analysis.....	55
3.5.	Discussion	60
3.6.	Summary of Findings	63
	Addendum: Tuning of the Wireless Response.....	64

4. Smart Implants for Simultaneous Fixation and Infection Monitoring II: Embodiment in Commercial Knee Replacement Systems	69
4.1. Introduction.....	71
4.2. Materials and Methods	72
4.2.1. Smart Implant Design	72
4.2.2. Signal Acquisition and Processing	74
4.2.3. Tibial Debonding.....	74
4.2.4. Temperature Calibration	75
4.2.5. Measurement Sensitivity.....	75
4.2.6. Statistical Analysis.....	76
4.3. Results.....	77
4.3.1. Measurement Acquisition	77
4.3.2. Debonding Detection	77
4.3.3. Temperature Calibration	79
4.3.4. Measurement Sensitivity.....	80
4.3.5. Persona Verification	84
4.4. Discussion	85
4.5. Summary of Findings	87
Addendum A: Sample Size Calculations	89
Addendum B: Post-hoc Testing of Temperature Measurements	90
5. Preclinical Evaluation of an Active Osseointegrative Implant in a Bioreactor: An Ex Vivo Organ-Level Model.....	91
5.1. Introduction.....	94
5.2. Concept Overview: Active Osseointegration.....	95
5.3. Materials and Methods	97
5.3.1. In Vitro Osteoconductivity Culture	97
5.3.2. Ex Vivo Active Osseointegration Culture	98
5.3.3. Live/Dead Staining	100
5.3.4. Mineralisation Staining	100

5.3.5.	Scanning Electron Microscopy.....	101
5.3.6.	Calcium Concentration	101
5.3.7.	Alkaline Phosphatase	101
5.3.8.	Media pH.....	101
5.3.9.	Histology.....	101
5.3.10.	Immunohistochemistry.....	102
5.4.	Results.....	103
5.4.1.	Cultivation.....	103
5.4.2.	Osteoconductivity	103
5.4.3.	Bone Ongrowth.....	103
5.4.4.	Media Biomarkers	107
5.4.5.	Histology.....	110
5.4.6.	Immunohistochemistry.....	110
5.5.	Discussion	115
5.6.	Summary of Findings	117
	Addendum A: Active Osseointegration Driving Voltages	119
	Addendum B: Supplemental Histology Images.....	123
	Active Osseointegrative Implant	124
	Low-Intensity Pulsed Ultrasound.....	126
	Passive Control (with Implant)	128
	Passive Control (without Implant).....	130
6.	Lead-Free Piezoceramics for Smart Biomedical Implants: Electromechanical, Biological, and Embodied Characterisations of BNT-6BT	133
6.1.	Introduction.....	135
6.2.	Fundamental Theory of Piezoceramics.....	136
6.3.	Materials and Methods	139
6.3.1.	Specimens	139
6.3.2.	Electromechanical Properties.....	140

6.3.3.	Material Suitability Assessment.....	140
6.3.4.	Acoustic Power Transfer	141
6.3.5.	Pulse-Echo Response.....	142
6.3.6.	In Vitro Cytotoxicity.....	142
6.3.7.	In Vitro Biocompatibility	143
6.3.8.	Ex Vivo Cytotoxicity.....	143
6.4.	Results.....	144
6.4.1.	Electromechanical Properties.....	144
6.4.2.	Material Suitability Assessment.....	151
6.4.3.	Acoustic Power Transfer	151
6.4.4.	Pulse-Echo Response.....	151
6.4.5.	Cytological Properties	156
6.5.	Discussion	159
6.6.	Summary of Findings	161
	Addendum: Compendium of Piezoceramic Material Properties	163
7.	Discussion and Concluding Remarks.....	171
7.1.	Clinical Challenge	172
7.2.	Research Contributions	172
7.2.1.	Contemporary Analysis of Arthroplasty Complications.....	172
7.2.2.	Simultaneous Fixation and Infection Monitoring	173
7.2.3.	Active Osseointegration	174
7.2.4.	Lead-Free Piezoceramic for Biomedical Implants.....	174
7.3.	Limitations.....	175
7.3.1.	Uncertain Aetiopathogeneses	175
7.3.2.	Ex Vivo Organ Models	176
7.4.	Future Perspectives.....	177
7.4.1.	High-Throughput Bioreactor and In Vivo Trials	177
7.4.2.	Closed-Loop Osseointegration and Multielement Designs.....	177

7.4.3. Direct Infection Detection	177
7.5. Conclusion.....	178
References.....	179
Copyright Authorisation.....	212

List of Figures

Figure 2.1. (a) Native knee anatomy, (b) total knee arthroplasty, (c) unicondylar knee arthroplasty with the medial compartment replaced, (d) patellofemoral arthroplasty, and (e) combined partial knee arthroplasty with the patellofemoral and medial compartments replaced.

Figure 2.2. (a) Native hip anatomy, (b) total hip arthroplasty with a metal-on-plastic articular contact, (c) hip resurfacing arthroplasty with metal-on-metal articular contact, and (d) hip hemiarthroplasty in which the native acetabulum is retained.

Figure 2.3. (a) Native shoulder anatomy, (b) anatomical total shoulder arthroplasty, (c) reverse total shoulder arthroplasty, and (d) shoulder hemiarthroplasty.

Figure 2.4. Osteolysis is a long-term result of cell imbalance in the periprosthetic tissue via debris-induced macrophage polarisation and stimulation of the osteoclast lineage – adapted from Goodman and Gallo (2019) and Mahon and Dunne (2018).

Figure 2.5. (a-b) Anteroposterior and lateral radiographs showing obvious periprosthetic lucency due to aseptic loosening (Arsoy et al., 2013), © 2013 Wolters Kluwer Health, Inc., (c) osteolytic bone resorption in the medial aspect of the tibia (Miller, 2005), © 2005 Elsevier, and (d-f) a case where the tibial component had completely debonded from the cement mantle without obvious radiographic indication (Murphy et al., 2021), © 2021 Cureus.

Figure 2.6. Fluid flow through the lacunocanicular network due to deformation stimulates mechanotransductive signalling in osteocyte cells.

Figure 2.7. The biochemical response of osteocytes to mechanical stimulus recruits osteoblasts and their progenitors to form new bone.

Figure 2.8. The secretion of osteopontin by macrophages during the clear out of iatrogenic debris produces a cement line on the exposed trabecular bone and implant surfaces, providing a foundation for de novo bone formation orchestrated by newly migrated osteoblasts.

Figure 2.9. Generic system architecture for acquiring data from an implantable medical device.

Figure 3.1. A coil and a shear-wave piezoelectric transducer are embedded within a joint prosthesis, shown as (a) an example embodiment within the tibial component of a cemented

total knee replacement, to differentiate between (b) a well-fixed implant and (c) a loose implant where the cement-implant interface has debonded and been infiltrated by joint fluid.

Figure 3.2. Equivalent electrical circuit of the implantable ultrasound system: impedance of the piezoelectric transducer is reduced to a single impedance, Z_{pz} ; coils in the three-port inductive link (Tx: Transmit; Ex: Embedded; Rx: Receive) are modelled using lumped parameters; tuning elements in the transmit and receive circuits are subscripted with a T; and loads on each coil are subscripted with an L.

Figure 3.3. Experimental setup representative of a transducer-embedded cemented orthopaedic implant from (a) side-on and (b) top-down views, along with (c) winding diagram for the three-coil inductive link.

Figure 3.4. A directly acquired pulse-echo response for the well-fixed state, which has been annotated for amplitude ratio, Γ , and arrival time, τ .

Figure 3.5. Well-fixed measurements were acquired with the setup submerged in fluid; loosening was simulated by (a) debonding the titanium plate from the cement with a lift-off moment; and loosened measurements were acquired with (b) the plate replaced and resting under its own weight.

Figure 3.6. Electrical network analogues of (a) a well-fixed implant and (b) a debonded implant.

Figure 3.7. Effect of varying coil separation, d , on the amplitude ratio, Γ , with the titanium plate well-fixed (—) and debonded (—); 95% prediction intervals for new measurements are plotted.

Figure 3.8. Linear calibration of arrival time, τ , to temperature, T , with 95% prediction intervals.

Figure 3.9. The effect of coil separation, d , on temperature measurement error, E_T , for 10,000-average measurements, shown with the trend in average measurements and 95% prediction intervals for new measurements.

Figure 3.10. The effect of coil separation, d , on signal-to-crosstalk ratio.

Figure 3.11. The effect on signal-to-noise ratio for measurements of amplitude ratio (Γ ; $\blacktriangle$) and arrival time (τ ; $\blacksquare$) due to (a) varying coil separation, d , with 5,000 signal averages and (b)

varying the number of averaged pulse-echo responses, N_p , with the coil separation fixed at 5 mm.

Figure 3.12. Measured (—) versus modelled impedance spectra of shear-mode piezoelectric transducer (Noliac CSAP03) in free-free (—), uncemented (—), and cemented (—) conditions.

Figure 3.13. Comparison of the modelled impedance spectra (a: magnitude; b: phase) between an unbonded piezoelectric transducer (—), a piezoelectric transducer bonded to an uncemented titanium plate (—), and a piezoelectric transducer bonded to a titanium plate that is cemented into bone (—).

Figure 3.14. Overlaid Monte Carlo simulations ($n = 1000$) illustrating sensitivity of the impedance spectra to (a, b) modelled variation in technique surgical technique, i.e. cement layer thickness, and (c, d) modelled variation in the acoustic properties of cancellous bone.

Figure 3.15. Measured (—) and fitted (—) impedance spectra for (a, b) the transmit coil with the receive coil loaded to $50\ \Omega$, (c, d) the embedded coil alone, and (e, f) the receive coil alone.

Figure 3.16. The pulse-echo response at 5 mm coil separation compared between wireless excitation through porcine tissue (—) and through air (—) without amplification or tuning.

Figure 3.A1. Hanning-windowed sinusoidal pulses with different numbers of cycles: (a) signal envelopes in the time domain and (b) power spectra in the frequency domain. The raw signal, power spectrum, and bandwidth for the pulse with five cycles is shown in black.

Figure 3.A2. The effect of tuning capacitance in the receive circuit from 1 pF (—) to 440 pF (— / —) on the transfer functions (a, b) from the generator to the transmit coil, (c, d) from the transmit coil to the embedded coil, (e, f) from the embedded coil to the receive coil, and (g, h) the transmit-to-embedded and transducer-to-embedded multiplied.

Figure 3.A3. The effect of tuning resistance in the receive circuit from $100\ \text{k}\Omega$ (—) to $820\ \Omega$ (— / —) on the transfer functions (a, b) from the generator to the transmit coil, (c, d) from the transmit coil to the embedded coil, (e, f) from the embedded coil to the receive coil, and (g, h) the transmit-to-embedded and transducer-to-embedded multiplied. Capacitance in the receive circuit was tuned to 440 pF.

Figure 4.1. The instrumented unicondylar knee prosthesis (a) shown cemented into a synthetic bone model and (b) showing the position of the shear-wave piezoelectric

transducer on the tibial component; (c) the reader used to acquire wireless pulse-echo measurements; and (d) the pulse-echo response.

Figure 4.2. The coordinate system centred on the intercondylar eminence of the tibia used to describe the position and orientation of the reader – embedded coil and external transmitter coil in black.

Figure 4.3. Signal-to-noise ratio for the relative amplitude (Γ) and time lag (τ) measurements shown as a function of the number of signal averages (N), with both variables increasing by ~20 dB/decade.

Figure 4.4. Violin plots showing a decrease in the relative amplitude of successive echoes (Γ) when implanted in synthetic bone and a subsequent increase when the implant-cement interface is compromised beneath the piezoelectric transducer.

Figure 4.5: (a) Cooling curve for the implant as measured by a thermocouple (T) and the correlated time profile for the time lag between the first and second echo (τ), with (b) the two variables calibrated by a linear fit.

Figure 4.6. Deviation in fixation measurement, Γ , from the mean value recorded in the neutral position, shown as violin plots, for varying coil translations and rotations, plus corresponding signal-to-noise ratio.

Figure 4.7. Fixation measurement sensitivity to the presence of (a) the femoral component and (b) anatomical tissue, shown as violin plots.

Figure 4.8. Deviation in temperature measurement, T , from the mean value recorded in the neutral position, shown as violin plots, for varying coil translations and rotations, plus corresponding signal-to-noise ratio in the underlying time lag measurement.

Figure 4.9. Temperature measurement sensitivity to the presence of (a) the femoral component and (b) anatomical tissue, shown as violin plots.

Figure 5.1. (a) The titanium surface of the active osseointegrative implant and (b) a surface roughness measurement ($R_a = 75 \mu\text{m}$),

Figure 5.2. Explantation of porcine cancellous bone from the distal femoral condyles: (a) resection to the knee capsule for ethanol immersion; (b) isolation of the distal femur; (c) exposure of the subchondral bone; (d-e) extraction of four cancellous bone cores ($\varnothing 10\text{mm}$)

from the lateral and femoral condyles at up to 25-mm length; and (f) division of cores into cylinders of 5-mm length.

Figure 5.3. Bioreactor chamber design for ex vivo evaluation of active osseointegration of cancellous bone into rough additive-manufactured titanium implant surface with two different treatment conditions: (A) active osseointegrative implant delivering direct stimulation (combined electromechanical) through the implant and (B) external LIPUS delivering indirect stimulation (mechanical only) through the bone.

Figure 5.4. Proliferation of MC3T3-E1 murine preosteoblasts on additive-manufactured rough titanium surface ($R_a = 75 \mu\text{m}$) observed by live-dead staining (a, c, e) and scanning electron microscopy (b, e, f; energy: 10 keV; beam current: 300 pA) at 7 days (a & b), 14 days (c & d), and 28 days (e & f). The black line directly beneath each image is scaled to 100 μm .

Figure 5.5. Live/dead (green/red) staining of cells from ongrowing tissue derived from porcine femoral condyle explant onto additive-manufactured rough titanium discs after 22 days in an ex vivo bioreactor; (a) higher proliferation of cells and higher viability was observed on the active osseointegrative implant after 21 days of treatment compared to (b) static culture.

Figure 5.6. Comparison of new bone formation on the titanium implant in three configurations: active osseointegrative implant (combined electrical-ultrasonic treatment; left); LIPUS stimulation only (ultrasonic treatment; centre); and passive control (no treatment; right). Widefield fluorescent microscopy (top) provides evidence of substantially enhanced mineralisation on the seventh (green) and fourteenth (red) days of culture for active implant specimens compared to LIPUS-only (weak enhancement) and control specimens. Widespread coverage of extracellular matrix was observed on the surface of active implant specimens under SEM (middle: secondary electron; bottom: back-scattered electron*; energy: 10 keV; beam current: 3 nA) at the three-week endpoint, with smaller depositions on the surface of B specimens and near-zero deposition in C specimens.

Figure 5.7. Scanning electron microscopy (back-scattered electron) revealed a mature bone fragment (length: ~1 mm) on an active osseointegrative implant surface that had begun to integrate with the semi-sintered particles on the rough titanium implant surface: (a) macroscopic view and (b) microscopic detail.

Figure 5.8. Comparison of day-seven (green) and day-fourteen (red) mineralisation at the interface to the implant (top) and through a transverse section of the bone (bottom; implant-

side up) for each configuration: (A; left) active osseointegrative implant, (B; centre) LIPUS stimulation only, and (C; right) passive control. Images are compensated for autofluorescence (Calcein: -7500; Alizarin Red S: -3500).

Figure 5.9. Mean fluorescence intensity in bone at the implant interface in channels of (a; day-seven) Calcein Green and (b; day-fourteen) Alizarin Red S between (A) active osseointegrative implant, (B) passive implant with LIPUS treatment, and (C) passive control. Asterisk (*) indicates significant difference ($p < 0.05$) relative to passive control.

Figure 5.10. ALP secretions across 21 days of culture between (A) active osseointegrative implant, (B) passive implant with LIPUS treatment, (C) passive control, and (D) passive control without implant. Asterisk (*) indicates significant difference ($p < 0.05$) relative to passive control.

Figure 5.11. Calcium levels across 21 days of culture between (A) active osseointegrative implant, (B) passive implant with LIPUS treatment, (C) passive control, and (D) passive control without implant, with comparison to baseline calcium concentration of media (— —). Asterisks indicates significant difference (*: $p < 0.05$; **: $p < 0.005$; ***: $p < 0.001$) relative to passive control.

Figure 5.12. Histological staining (a: H&E; b: Picrosirius Red; c: Masson-Goldner Trichrome; d: Movat Pentachrome) of an active osseointegrative implant specimen at the bone-implant interface, showing resection debris, non-collagenous fibrous tissue formation, and osteoid seams in apposition to the interface (red in Masson-Goldner and Movat stains).

Figure 5.13. Histological staining of an active osseointegrative implant specimen showing (a: H&E) a bone remodelling compartment close to the bone-implant interface with active osteoblast formation and osteoclast resorption and (b: Movat Pentachrome) new bone matrix deposited by osteoblasts in the bulk tissue.

Figure 5.14. Histological staining (Movat pentachrome) indicating new bone formation (red) at the bone-implant interface (top; a, b) and in the bulk tissue (middle; c, d) for the LIPUS-treated specimens (left, a, c) and the passive controls (right; b, d).

Figure 5.15. Osteopontin (OPN) expression at the bone-implant interface (left) and in the bulk trabecular structure (right) in (a, b) an active osseointegrative implant specimen, (c, d) the corresponding isotypic controls for the active osseointegrative implant specimen, (e, f) a LIPUS-treated specimen, and (g, h) a passive control. Annotations indicate OPN-positive

osteocytes (brown cytoplasm; ⊗), OPN-negative osteocytes (blue nuclei; *), osteoblasts (**), and osteoclasts (*).

Figure 5.A1. Configurations of the bioreactor for (A) delivery of active osseointegrative implant treatment, (B) delivery of LIPUS-only treatment, and (A*) calibration of the active osseointegrative implant dose.

Figure 5.B1. Bone specimens were sliced in the plane transverse to the bone-implant interface.

Figure 5.B2. Macroscopic histological staining (H&E) of cancellous bone after 21 days of active osseointegrative implant treatment. Three regions of interest are identified for more detailed analysis: (a) tissue in apposition to the actively stimulated titanium surface; (b) wound tissue adjacent to the open surface of the sample; (c) non-interfacial bulk tissue; and (d) tissue adjacent to the polymer base of the well.

Figure 5.B3. Masson-Goldner trichrome staining indicating osteoid seams and new bone matrix (both ruby red) after 21 days of active osseointegrative implant treatment (Treatment A) in representative regions of interest: (a) osteoid seams and new bone matrix are observed in direct apposition to the implant surface indicative of bone remodelling, with small bone fragments and fibrous tissue of haematopoietic origin in the bone marrow spaces; (b) less new bone matrix and osteoid seams are observed at the surface open to the media amidst debris from the original surgery; (c) new bone matrix is observed in the bulk tissue indicative of recent bone turnover; and (d) new bone matrix is observed on the opposite side of the implant without the fibrous tissue formation exhibited in apposition to the implant.

Figure 5.B4. Macroscopic histological staining (H&E) of cancellous bone after 21 days of LIPUS treatment (Treatment B); tissue was sectioned in the transverse plane. Three regions of interest are identified for more detailed analysis: (a) tissue adjacent to the titanium surface; (b) wound tissue adjacent to the open surface of the sample; (c) non-interfacial bulk tissue; and (d) tissue adjacent to the polymer base of the well where the ultrasonic treatment was applied.

Figure 5.B5. Masson-Goldner trichrome staining indicating osteoid seams and new bone matrix (both ruby red) after 21 days of LIPUS treatment (Treatment B) in representative regions of interest: (a) osteoid seams and new bone matrix were observed in direct apposition to the implant surface indicative of bone remodelling; (b) cutting debris from the original surgery with less new bone matrix and osteoid seams were seen at the surface open

to the media; (c) new bone matrix was observed in the bulk tissue indicative of recent bone turnover; and (d) cutting debris and some evidence of active bone remodelling were seen at the LIPUS-stimulated surface.

Figure 5.B6. Macroscopic histological staining (H&E) of cancellous bone after 22-day passive culture. Three regions of interest are identified for more detailed analysis: (a) tissue in apposition to the titanium surface; (b) wound tissue at the open surface of the sample; (c) non-interfacial bulk tissue; and (d) tissue adjacent to the polymer base of the well. A small amount of physal tissue (growth plate) was extracted during the original resection of this specimen (bottom left).

Figure 5.B7. Masson-Goldner trichrome staining indicating osteoid seams and new bone matrix (both ruby red) after passive culture in representative regions of interest: (a) osteoid seams and new bone matrix were observed within the periprosthetic tissue but not in direct apposition to the implant; (b) cutting debris and some evidence of remodelling were seen at the surface open to the media; (c) new bone matrix was observed in the bulk tissue indicative of recent bone turnover; and (d) less evidence of new bone matrix was observed at the surface opposite the implant.

Figure 5.B8. Macroscopic histological staining (H&E) of cancellous bone after 22-day passive culture without a titanium implant. Three regions of interest are identified for more detailed analysis: (a) tissue that was cut using an oscillating saw and was open to the media; (b) tissue that was cut using a holesaw and was open to the media; (c) non-interfacial bulk tissue; and (d) tissue adjacent to the polymer base of the well.

Figure 5.B9. Masson-Goldner trichrome staining indicating osteoid seams and new bone matrix (both ruby red) after passive culture in representative regions of interest: (a) osteoid seams and new bone matrix were observed at the open face of the bone where the implant had been in other configurations; (b) little evidence of remodelling was seen amidst the cutting debris on the side of the cylinder; (c) new bone matrix was observed in the bulk tissue indicative of recent bone turnover; and (d) less evidence of new bone matrix was observed at the surface opposite the implant.

Figure 6.1. Electric dipoles in polycrystalline piezoceramic material: (a) dipoles are randomly oriented before poling; (b) dipoles are coerced into alignment by a strong electric field during poling; and (c) remnant polarisation is retained post-poling.

Figure 6.2. Piezoelectric resonance modes as defined by EN 50324-2:2002: (a) Transverse Length, (b) Thickness Shear, (c) Longitudinal Length, (d) Thickness Extension, and (e) Planar Radial. Electrodes are shown in gold, polarisation is red, and mechanical deformation is blue.

Figure 6.3. Piezoceramic samples: (a) unelectroded transverse-length/thickness-shear mode samples of Material 1, (b) electroded radial/thickness-extension mode samples of Material 2, (c) electroded thickness-shear mode samples of Material 2, and (d) unelectroded thickness-shear mode samples of Material 2.

Figure 6.4. (a) BNT-6BT and PZT transducers mounted on a fracture fixation plate for acoustic energy harvesting and (b) schematic drawing of the acoustic power transfer setup.

Figure 6.5. Incisions for implantation of the BNT-6BT and PZT specimens were made from the cylindrical axis to the circumference of each bone core.

Figure 6.6. Impedance spectra (left; a, c, e, g) and resistance-conductance spectra (right; b, d, e, h) at the fundamental resonances of BNT-6BT transducers: (a, b) planar mode of conventionally manufactured BNT-6BT; (c, d) thickness-extension mode of conventionally manufactured BNT-6BT; and (e, f) thickness-shear mode of conventionally manufactured BNT-6BT; and (g, h) transverse length mode of additive-manufactured BNT-6BT.

Figure 6.7. Piezoelectric coefficients of PIC700 and AM-BNT-6BT in the thickness mode versus conventional PZT-based and other lead-free piezoceramic materials (● commercial; ○ research).

Figure 6.8. Energy harvesting performance of PIC700 in the thickness mode versus conventional PZT-based and other lead-free piezoceramic materials (● commercial; ○ research).

Figure 6.9. Pulse-echo transducer performance of PIC700 in the thickness mode versus conventional PZT-based and other lead-free piezoceramic materials (● commercial; ○ research).

Figure 6.10. Pulse-echo transducer performance of PIC700 in the shear mode versus conventional PZT-based and other lead-free piezoceramic materials (● commercial; ○ research).

Figure 6.11. Power output comparison for PZT and BNT-6BT transducers mounted on fracture fixation plate in response to continuous sinusoidal excitation with spatial averaging overlaid (source: Olympus I3-0208-S-SU; amplitude: 10 V; frequency: 2.25 MHz).

Figure 6.12. Pulse-echo comparison for (a, b) conventional PZT-based and (c, d) BNT-6BT transducers: (a, c) returning echoes signal and (b, d) Fourier spectra around centre frequency of the pulse, f_c .

Figure 6.13. ISO 10993-5 testing of additive-manufactured BNT-6BT (2B specimens) compared to PZT (Noliac NCE51) and cytotoxic control (10% DMSO): (a) indirect cytotoxicity and (b) direct cytotoxicity.

Figure 6.14. SEM images (backscatter electron; beam energy: 10 keV; beam current: 300 pA) of MC3T3-E1 ongrowth onto BNT-6BT showing (a, d) clusters of flattened cells with filopodia at seven days, (b, e) widespread cell proliferation and small deposits of extracellular matrix by 14 days, and (c, e) dense, near-total coverage of the BNT surface with further deposition of extracellular matrix by 21 days.

Figure 6.15. Confocal micrographs of tissue stained with Calcein-AM/Ethidium homodimer (live cells: green; dead cells: red) after 28 days in static ex vivo culture: (a) organic deposits were observed on the implanted BNT-6BT specimens without evidence of cell proliferation; (b) live cells (>75% viability) were observed on trabeculae adjacent to the BNT-6BT implant; and (c) live cells (>90% viability) were observed on trabeculae in the bulk tissue (>2 mm from the BNT-6BT implant or any incised surface).

Figure 6.16. Confocal micrographs of tissue stained with Calcein-AM/Ethidium homodimer (live cells: green; dead cells: red) after 28 days in static ex vivo culture: (a) acellular organic deposits were observed on the implanted BNT-6BT specimens; (b) viable cells were observed on trabeculae adjacent to the BNT-6BT implant; and (c) cell viability was also maintained on trabeculae in the bulk tissue (>2 mm from the BNT-6BT implant or any incised surface).

List of Tables

Table 2.1. EBJIS criteria for the diagnosis of clinically suspected periprosthetic joint infection.

Table 3.1. Coil specifications.

Table 3.2. Modelling parameters for PZT, epoxy, titanium, PMMA bone cement, synthetic cancellous bone, and organic cancellous bone.

Table 4.1. Statistical analyses for difference in fixation measurement due to reader positioning in several directions, presence of the femoral component (Fem.), and soft tissue (Ana.).

Table 4.2. Statistical analyses for differences in temperature measurement due to reader positioning in several directions.

Table 4.3. Statistical analyses for differences in temperature measurement due to the presence of the metallic femoral component (Fem.) and soft tissue (Ana.).

Table 4.A1. Games-Howell post-hoc comparisons for temperature measurement sensitivity in each direction with respect to the neutral position; mean significant differences are marked by an asterisk.

Table 5.A1. Thickness-mode properties of PRYY+0442 piezoelectric transducers.

Table 6.1. Electromechanical characterisation of additive-manufactured BNT-6BT in the transverse-length mode, planar, and thickness modes (properties measured as part of this work in bold) with comparison to the conventionally manufactured BNT-6BT material as measured by Pardo *et al.* (2021).

Table 6.2. Electromechanical characterisation of PIC700 in the planar (P), thickness-extension (TE), and thickness-shear (TS) modes with comparison to measurements by Pardo *et al.* (2021) and Fenu *et al.* (2021).

Table 6.3. Radial and thickness-extension properties of PIC181 (Hard PZT) were consistent with manufacturer-reported (PI Ceramic, 2020a)

Table 6.4. Thickness-shear mode properties of NCE51 (Soft PZT) were underestimated versus manufacturer-reported (PI Ceramic, 2020a)

Table 6.5. Figures of merits for PIC700 and AM-BNT-6BT referenced against commonly used PZT materials in implanted piezoceramic applications.

Table 6.A1. Some thickness-extension and thickness-shear mode properties for PZT-based and lead-free piezoceramics materials from commercial and academic sources

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Chapter 1

General Introduction

1.1. Research Motivation

Advances in wearable and implantable technology are enabling at-home medical diagnoses and real-time health monitoring across medicine (Song, Min and Gao, 2019), and a similar opportunity exists to develop ‘smart implants’ in orthopaedics.

In the United Kingdom, more than 100,000 hips and 100,000 knees are replaced annually as a routine surgical treatment for end-stage osteoarthritis (Scottish Arthroplasty Project, 2020; National Joint Registry, 2021), with similar rates in other OECD countries (OECD, 2022). Arthroplasty (joint replacement) first evolved in the late 1950s (Charnley, 1961); techniques have since matured and implant designs have been optimised; but the fundamental practice of implanting passive metal, polymer, or ceramic components has remained the same. Whilst functionalised implants have been used to collect orthopaedic research data almost since the advent of modern arthroplasty (Rydell, 1966; Waugh, 1966), the clinical translation of smart implants has proved a challenge. Indeed, the first-and-only smart implant cleared for commercial use received approval in 2021 for the collection of kinematic data (FDA, 2021), and no device to date has yet received clearance to support clinical decision making.

Contemporary arthroplasty procedures are characterised by good long-term survivorships (Learmonth, Young and Rorabeck, 2007; Patel *et al.*, 2019). Nevertheless, a low number of implant failures do occur: 4–5% of knee replacements and 3–7% of hip replacements are revised within ten years (National Joint Registry, 2021). Aseptic loosening and periprosthetic joint infection collectively account for more than 50% of procedures (National Joint Registry, 2021). Timely detection of both complications limits progressive tissue damage, improves the scope and quality of treatment options, and avoids the most severe consequences of implant failure (Moran, Byren and Atkins, 2010; Grammatopoulos *et al.*, 2017). However, current diagnostic protocols (radiographic, serological, histological, etc.) have limited accuracy, are reliant on patients self-reporting symptoms (e.g., pain), and require specialist clinical care and equipment. Both complications could therefore benefit from an implant-based technology for detection and treatment.

In consideration of the translational challenges that have beset previous smart implant concepts, a pragmatic approach to smart implant design is adopted in this thesis:

Arthroplasty is a mature, high-volume market; contemporary implant designs are both highly commoditised and highly optimised for biomechanical function; and any augmented functions must be low-cost and exert minimal footprint on current device architectures – simplicity is key.

This approach is used to guide the development of two smart implant concepts based on embedded piezoelectric transducers: (i) simultaneous implant fixation and infection monitoring for early detection of implant failure, and (ii) active stimulation of osseointegration to prevent aseptic loosening in cementless implants. Relevant clinical models – in vitro and ex vivo respectively – are used to analyse each concept as precursor to in vivo animal trials, and a new lead-free piezoceramic material (BNT-6BT) is evaluated to determine its suitability for use in these concepts and other smart biomedical implants.

1.2. Aims and Objectives

This thesis is targeted at implant designers; its intent is to develop cost-effective, implant-based technology for improving the clinical management of aseptic loosening and periprosthetic joint infection; and this overriding aim was discretised into the following specific objectives:

- (i) to understand the onset, progression, and treatment of aseptic loosening and periprosthetic joint infection and critically evaluate the requisite components for functionalising a mass-market orthopaedic implant;
- (ii) to develop an implant-based solution for detecting aseptic loosening and periprosthetic joint infection;
- (iii) to evaluate detection of aseptic loosening and periprosthetic joint infection with an implant-based solution in a clinically relevant model;
- (iv) to develop and evaluate an implant-based solution for treating aseptic loosening; and
- (v) to determine the electromechanical and biological characteristics of a lead-free piezoceramic and thereby evaluate its suitability for functionalised orthopaedic implants.

1.3. Structure

The state of the art in arthroplasty is outlined in Chapter 2, and detailed reviews of the causes (aetiologies), mechanisms (pathogeneses), diagnoses and treatments of aseptic loosening and periprosthetic joint infection are presented. Furthermore, the mechanobiological basis of osseointegration and methods of enhancing the bond between an implant and the host bone are reviewed. Finally, the general literature on instrumented orthopaedic implants is presented with consideration of functionalising an implant for detecting aseptic loosening and periprosthetic infection.

In Chapter 3, the fundamental concept for a wireless, battery-free smart implant to monitor implant fixation and temperature (a specific indicator of acute infection) is developed, with the concept envisaged as a platform technology that could be applied to multiple implants. A general model for the system is outlined and verified, and the concept is evaluated experimentally in its smallest practicable embodiment.

In Chapter 4, this general concept for implant fixation and temperature monitoring is applied to two commercial knee implants: a Persona Total Knee and an Oxford Fixed Lateral Partial Knee. The systems are characterised and evaluated.

The concept for an 'active osseointegrative implant' is developed in Chapter 5, wherein artificial electromechanical stimulation is delivered to the periprosthetic bone. The concept is preclinically evaluated in a purpose-built ex vivo bioreactor after 21 days of treatment: results are compared to bone stimulated by low-intensity pulsed ultrasound (LIPUS) and bone cultured under static conditions.

In Chapter 6, the electromechanical and biological properties of a new lead-free piezoceramic (BNT-6BT) are characterised to determine its suitability for implantable applications. The piezoceramic is embodied within an acoustic wireless power transfer system and the smart implant concept of Chapters 3 & 4; comparisons in performance are referenced against current lead-based piezoceramics.

Finally, a summary of the key findings is presented in Chapter 7, with discussions of the limitations of the work and perspectives for future research.

Chapter 2

Aseptic Loosening, Periprosthetic Joint Infection and Smart Interventions: Current Concepts and State of the Art

2.1. Joint Replacement Surgery

In 2019, the last year before COVID-19 disruption to elective surgery, primary joint replacement procedures were routinely practised in the United Kingdom for the knee ($n = 106,572$), hip ($n = 98,649$), and shoulder ($n = 7,660$) (National Joint Registry, 2021). Case volumes had been steadily rising – a trend reflected across other developed nations (OECD, 2022) – and have been projected to continue growing for at least the next 15 years (Culliford *et al.*, 2015; Pabinger, Lothaller and Geissler, 2015; Pabinger *et al.*, 2018). Procedures exist for other joints, such as the elbow, ankle, wrist and subtalar joint, and may be performed more frequently as the state of the art advances and evidence in their favour is generated (Reigstad and Røkkum, 2018; Muller *et al.*, 2020; Gajebasia *et al.*, 2021).

2.1.1. Indications

Joint replacement is primarily a pain-relieving, restorative treatment for osteoarthritis (Ferguson *et al.*, 2018; Price *et al.*, 2018): a whole-joint disease arising from an imbalance between rates of mechanical degradation and biological repair to the articular surfaces (Felson, 2013; Hunter and Bierma-Zeinstra, 2019). In the most advanced stages of the disease, which cannot be managed by pharmacological or psychological interventions (Sharma, 2021), osteoarthritis manifests with debilitating chronic pain and life-limiting disability (Litwic *et al.*, 2013). Indeed, it was reported in 2019 that 19% of hip patients and 12% of knee patients awaiting joint replacement in the UK were in a health state “worse than death” (Scott, MacDonald and Howie, 2019), rising to 35% and 22% during the COVID-19 pandemic (Clement *et al.*, 2021). Less commonly, the procedure is also used to treat inflammatory arthritis (Mertelsmann-Voss *et al.*, 2014), congenital joint deformity (Greber *et al.*, 2017), avascular necrosis (Lamb *et al.*, 2019), and femoral neck fractures (HEALTH Investigators, 2019).

2.1.2. Surgical Procedure

The surgical procedure involves excising damaged articular cartilage and subchondral bone and implanting an artificial prosthesis, alleviating pain and restoring anatomical function. In the knee (Fig. 2.1a), osteoarthritis varies across patients in its distribution between the three joint compartments: medial, lateral, and patellofemoral (Stoddart *et al.*, 2021). When operating on the knee, therefore, prostheses may be used to resurface the entire joint – total knee arthroplasty (TKA; Fig. 2.1b) – or individual compartments – partial knee arthroplasty (PKA). Partial knee arthroplasties are further subcategorised as unicondylar (UKA; Fig. 2.1c), patellofemoral (PFA; Fig. 2.1d), or combinations thereof (CPKA; Fig. 2.1e) (Garner, van Arkel and Cobb, 2019). Contemporary tibial components are baseplates supporting a meniscal

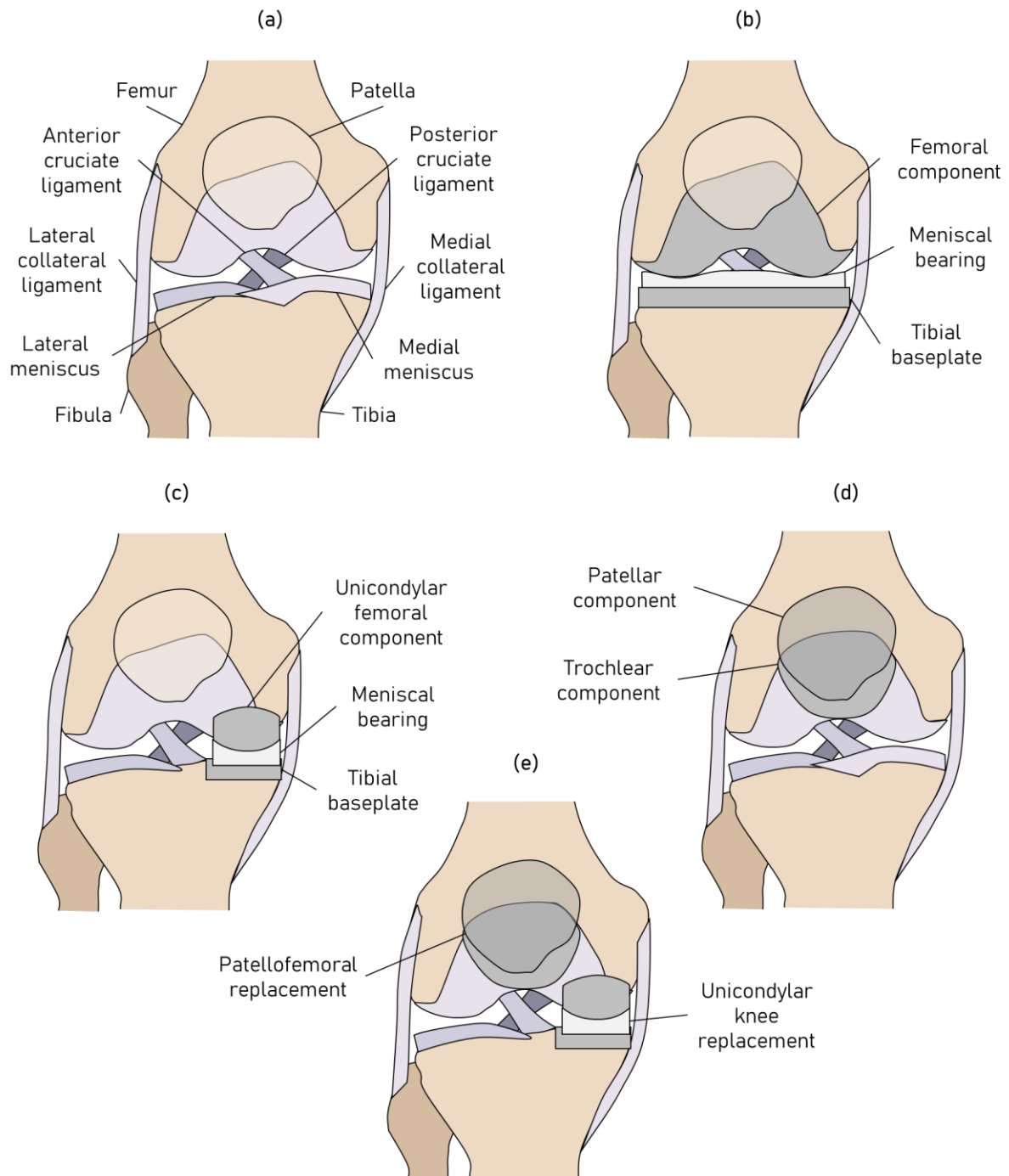


Figure 2.1. (a) Native knee anatomy, (b) total knee arthroplasty, (c) unicondylar knee arthroplasty with the medial compartment replaced, (d) patellofemoral arthroplasty, and (e) combined partial knee arthroplasty with the patellofemoral and medial compartments replaced.

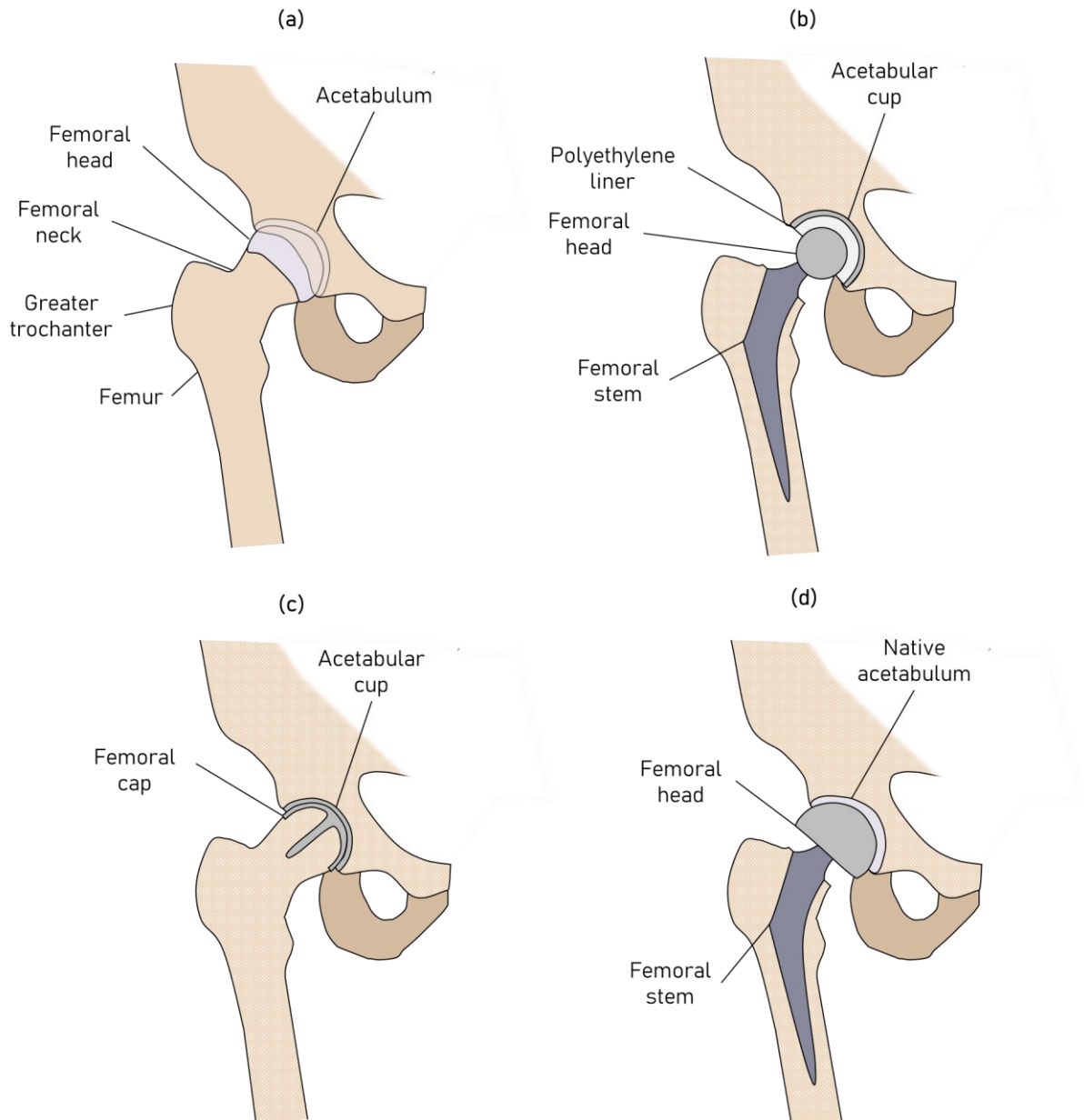


Figure 2.2. (a) Native hip anatomy, (b) total hip arthroplasty with a metal-on-plastic articular contact, (c) hip resurfacing arthroplasty with metal-on-metal articular contact, and (d) hip hemiarthroplasty in which the native acetabulum is retained.

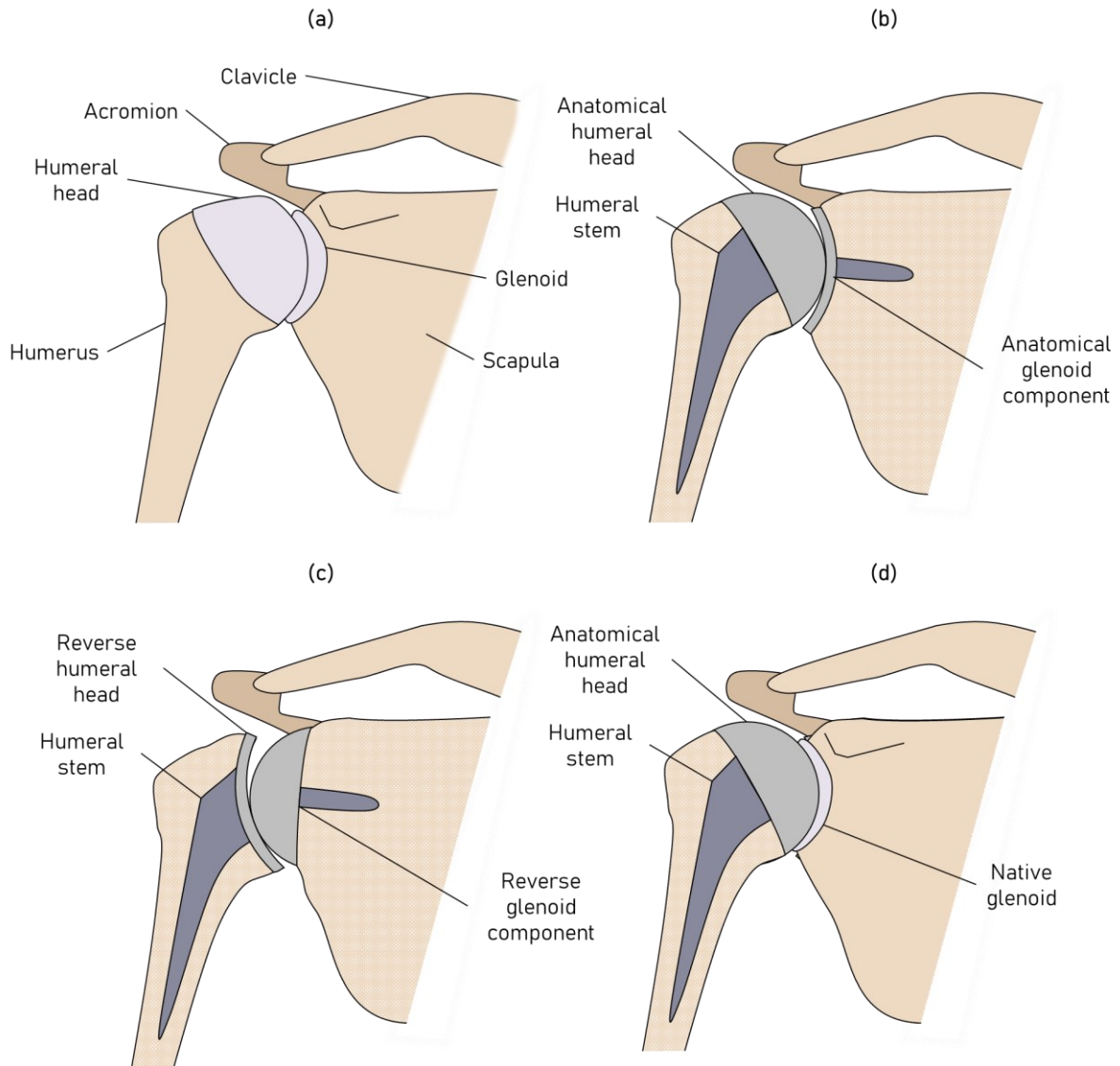


Figure 2.3. (a) Native shoulder anatomy, (b) anatomical total shoulder arthroplasty, (c) reverse total shoulder arthroplasty, and (d) shoulder hemiarthroplasty.

bearing, whilst femoral and patellar components resemble the anatomy of the distal femur and posterior aspects respectively. Plate thicknesses for the tibial and femoral components are typically in the range 2–5 mm, whilst the range for meniscal bearing thicknesses is 3–10 mm.

The hip joint (Fig. 2.2a) is formed between the femoral head and the pelvic acetabulum. In total hip arthroplasty (THA; Fig. 2.2b), the acetabulum is replaced with an artificial cup, whilst the femoral head and neck are replaced with a ball-and-stem prosthesis. Hip resurfacing arthroplasty (HRA; Fig. 2.2c), is a more conservative treatment, which retains the femoral neck and caps the femoral head (Logishetty, Muirhead-Allwood and Cobb, 2020). In hip hemiarthroplasty (HHA; Fig. 2.2d), only the femoral head and neck are replaced in a procedure that is mostly reserved for femoral neck fractures (van der Sijp *et al.*, 2018).

In anatomical total shoulder arthroplasty (ATSA; Fig. 2.3b), the ball-and-socket glenohumeral joint (Fig. 2.3a) is resurfaced with an anatomically similar prosthesis (Occhiboi and Clement, 2020). More common, however, in shoulder replacement is reverse total shoulder arthroplasty (RTSA; Fig. 2.3c) (Best *et al.*, 2021; National Joint Registry, 2021), in which the ball and socket components are reversed (Occhiboi and Clement, 2020). In cases of fracture or where the glenoid cannot accommodate a prosthetic component, a shoulder hemiarthroplasty (Fig. 2.3d) may be performed in which only the humeral head is replaced, but this procedure is decreasing in popularity (Best *et al.*, 2021).

2.1.3. Implant Biomaterials

Prostheses are typically anchored to the bone through metallic components with polymer or ceramic articulating surfaces. The metals most commonly used in joint prostheses include stainless steel, cobalt-chromium alloys, titanium, and titanium alloys (Navarro *et al.*, 2008). Polymer components are almost exclusively ultra-high-molecular-weight polyethylene (UHMWPE) (Navarro *et al.*, 2008), whilst zirconia-toughened alumina is the most widely used structural ceramic (Vogel *et al.*, 2021).

2.1.4. Fixation

Prostheses are stabilised with design features, such as keels, stems and collars (Strauss *et al.*, 2009; Demey *et al.*, 2011; Scott and Biant, 2012), but fixation into subchondral trabecular bone is ultimately achieved through two main strategies: cemented (Fig. 2.4a) or cementless (osseointegration; Fig. 2.4b). In 2019, most total knee arthroplasty prostheses were fixed using cement (97%); only 2% were cementless whilst <1% were a hybrid (National Joint Registry, 2021). The split is more even in unicondylar knee arthroplasty (62% cemented

versus 38% cementless/hybrid) (National Joint Registry, 2021). In total hip arthroplasty, most stems were cemented (62% versus 38%) whilst most cups were cementless (71% versus 29%) (National Joint Registry, 2021). Some socket-shaped implants, such as acetabular cups in THA (Brodt *et al.*, 2021) or glenoid components in ATSA (Strauss *et al.*, 2009), are also fixed with screws for further stability, but this is uncommon during primary surgery.

In cemented fixation, bone cement – polymethyl methacrylate (PMMA) – is applied between the prosthesis and the periprosthetic bone whilst viscous. The cement penetrates the interstices of porous trabecular bone and hardens to form a mechanical interlock (Miller *et al.*, 2014); the term ‘cement’ is therefore a misnomer as it implies fixation by adhesion. With an intermediate elasticity, the cement layer is also thought to distribute stress between stiff metallic implants and more compliant trabecular bone (Webb and Spencer, 2007). Bone cements may also contain bioactive additives to improve biocompatibility at the cement-bone interface or antimicrobial components to prevent infection (Soleymani Eil Bakhtiari *et al.*, 2021).

Cementless fixation, also referred to as osseointegration, harnesses the innate regenerative properties of bone to establish a direct structural and functional connection at the bone-implant interface (Shah, Thomsen and Palmquist, 2019). The process is dependent on the implant surface chemistry, topography (rough or porous), and loading environment to modulate the host inflammatory response and promote bone remodelling (Albrektsson and Wennerberg, 2019; Kohli, Stoddart and van Arkel, 2021). In well-integrated implants, cellular organisation and mineralisation patterns in the periprosthetic bone are comparable to what is observed in healthy, native tissue (Shah, Thomsen and Palmquist, 2019).

Delineating cemented and cementless by their respective benefits and detriments is challenging, with reported differences in outcome often disputed (Kandala *et al.*, 2014; S. L. Whitehouse *et al.*, 2014). Findings from small-cohort randomised controlled trials (RCTs) are unlikely to generalise across all implant designs and surgical techniques, whilst registry analyses often do not contain sufficient variables to fully explain differences in outcomes (S. L. Whitehouse *et al.*, 2014). Nevertheless, cemented prostheses have been linked with a slight increase in early mortality following hip arthroplasty (McMinn *et al.*, 2012; Garland *et al.*, 2017), whereas cementless prostheses have been associated with increased risk of implant failure (Hailer, Garellick and Kärrholm, 2010; McMinn *et al.*, 2012; Tanzer *et al.*, 2018). In total knee arthroplasty, cementless fixation has also been linked to increased post-operative pain (Beaupré *et al.*, 2007; Fricka, Sritulanondha and McAsey, 2015). A recent meta-analysis of six studies found there to be no significant difference in long-term functional outcome following

cementless versus cemented arthroplasty (Prasad *et al.*, 2020), but the effect on revision rates remains contentious (Bingham *et al.*, 2020; Nivbrant *et al.*, 2020; Prasad *et al.*, 2020).

2.1.5. Revision Surgery

Whilst joint replacement is widely considered successful, a low rate of implant failures inevitably occur for a variety of reasons (Liddle *et al.*, 2014; Evans *et al.*, 2019), which necessitate revision surgery. In the UK National Joint Registry, ten-year revision rates have been in the intervals of 4–5% for knee replacement and 3–7% for hip replacement (National Joint Registry, 2021). Whilst revision rates for both procedures have been trending downwards, annual case volumes have been increasing as arthroplasty has been practised more routinely (National Joint Registry, 2021).

The two most common indications for knee revision procedures in the UK in the last five years were aseptic loosening (29% including lysis) and periprosthetic joint infection (PJI; 25%) (National Joint Registry, 2021); aseptic loosening of the tibial component is one of the predominant concerns tempering the drive towards cementless fixation (Nivbrant *et al.*, 2020). The same overall trend is echoed in hip revision procedures where aseptic loosening (35%) and lysis (12%) are recorded separately; infection was indicated in 17% of procedures. Other common causes for revision surgery are progressive arthritis (knee: 16%; hip: n/a), instability (knee: 15%; hip: n/a), wear (knee: 11%; hip: 12%), periprosthetic fracture (knee: 5%; hip: 15%), and dislocation/subluxation (knee: 3%; hip: 17%) (National Joint Registry, 2021).

Aseptic loosening remains a common cause for revision following shoulder replacement but it has become less prevalent with the growing adoption of RTSA (Bacle *et al.*, 2017; Chalmers *et al.*, 2019); improved fixation of the glenoid component is a major differentiator between the techniques (Aibinder *et al.*, 2021). Infection is again a prevalent indication for revision following shoulder arthroplasty; instability and soft-tissue deficiency are also common (Chalmers *et al.*, 2019). This pattern of aseptic loosening and infection as the leading indications for revision is repeated following procedures for other joints (Reigstad and Røkkum, 2018; Syed and Ugwuoke, 2018; National Joint Registry, 2021).

2.2. Aseptic Loosening

Aseptic loosening is the loss of implant fixation in the absence of infection, typically accompanied by an inflow of joint fluid at the compromised interface. Most patients present with aseptic loosening following the onset of pain – a late-stage symptom. As a result, relatively little is known about the early development of aseptic loosening, which is often attributed to multiple factors. Nevertheless, the irreversible and progressive nature of the

condition inevitably requires revision for most patients. An overview of the various causes implicated in the development of aseptic loosening, methods of detection, and treatment options is presented in this section.

2.2.1. Aetiopathogenesis

Aseptic loosening may be induced by several biological or mechanical mechanisms, and its progression is frequently a result of their interplay (Sundfeldt *et al.*, 2006; Dattani, 2007). Historically, the predominant cause of loosening in cemented implants was osteolysis (Fig, 2.4) (Sharkey *et al.*, 2002), wherein wear debris caused resorption and subsequent weakening of periprosthetic bone (Abu-Amer, Darwech and Clohisy, 2007). Wear particles, which are mostly derived from the polyethylene liner and indigestible to phagocytic cells, polarise macrophages in the surrounding bone and trigger the expression of pro-inflammatory cytokines (Gallo *et al.*, 2013; Goodman and Gallo, 2019; Goodman *et al.*, 2022). Osteoclasts are recruited as part of this inflammatory response, whilst the function of osteoblasts is thought to be inhibited by the wear debris (Ollivere *et al.*, 2012). The long-term imbalance to the cells involved in bone remodelling eventually results in the loss of bone required for an implant-stabilising mechanical interlock (Mahon and Dunne, 2018).

Following improvements in implant materials and manufacturing, however, osteolysis rates have substantially reduced (Sharkey *et al.*, 2013; Lachiewicz, Kleeman and Seyler, 2018). The majority of loosening in contemporary cemented knee prostheses is now mechanical in origin: initiated at the cement mantle (Sharkey *et al.*, 2013; Thiele *et al.*, 2015; Delanois *et al.*, 2017). Indeed, loosening and debonding at the cement-bone interface has been observed in the absence of recognised osteolysis biomarkers (Yokhana *et al.*, 2019; Garceau *et al.*, 2020). Possible reasons for loss of fixation at the cement-bone interface specifically include inadequate interdigitation when using high-viscosity cement (Buller *et al.*, 2020), thermal necrosis caused by the exothermic polymerisation of the cement (Dunne and Orr, 2002; Huang, Yan and Lin, 2005; Webb and Spencer, 2007), and residual stresses caused by shrinkage of the cement after polymerisation (Orr and Dunne, 2004),

In recent years, there have been regular reports of a bias towards debonding at the implant-cement interface (Foran, Whited and Sporer, 2011; Arsoy *et al.*, 2013; Ries *et al.*, 2013; Hazelwood *et al.*, 2015; Kopinski *et al.*, 2016; Bonutti *et al.*, 2017; Kutzner *et al.*, 2018; Cerquiglini *et al.*, 2019; Sadauskas *et al.*, 2020; Keohane *et al.*, 2020; Murphy *et al.*, 2021), including a recent retrospective study of 149 revision knees in which failure was observed at the implant-cement interface in 140 prostheses (94%) (Martin *et al.*, 2021). High-viscosity cement has

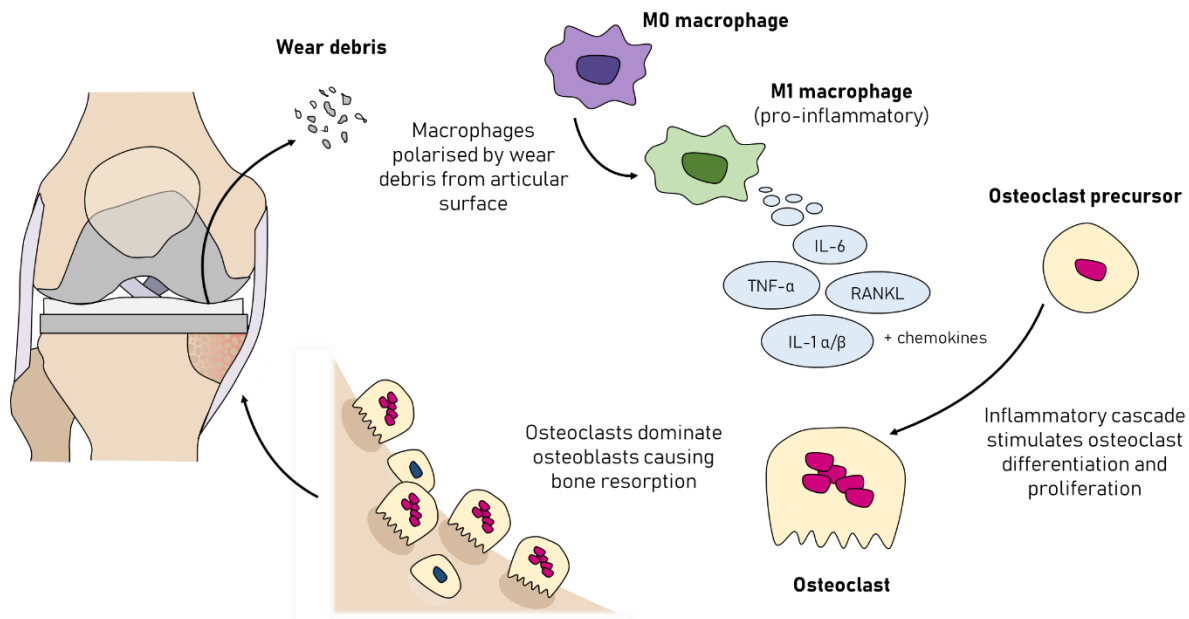


Figure 2.4. Osteolysis is a long-term result of cell imbalance in the periprosthetic tissue via debris-induced macrophage polarisation and stimulation of the osteoclast lineage – based on mechanisms presented in Goodman and Gallo (2019) and Mahon and Dunne (2018).

again been implicated as a reason for failure at the implant-cement interface (Buller *et al.*, 2020). Other possible causes include stress concentrations associated with short-stem prostheses (Ries *et al.*, 2013; Martin *et al.*, 2018), inadequate surface finish of the implant (van Tol *et al.*, 2013), and poor cementation technique (Randall *et al.*, 2019; Hampton *et al.*, 2020).

In cementless fixation, large micromotions at the bone-implant interface can cause the formation of a fibrous capsule, which ultimately leads to early loosening (Kohli, Stoddart and van Arkel, 2021). Late loosening following cementless fixation is often a result of periprosthetic bone resorption due to stress shielding (Rivière *et al.*, 2018; Brodt *et al.*, 2020). Osteolysis does not affect cementless fixation in the same way that it affects cemented fixation: many patients are asymptomatic and osseointegrated prostheses are often left in situ to avoid substantial damage to periprosthetic bone during removal (Aprato *et al.*, 2016; Kurcz *et al.*, 2018). Surgeons are instead advised to be cognisant of the risk and monitor for disease progression (Kurcz *et al.*, 2018).

2.2.2. Diagnosis

Patients with loose implants typically present with pain around the afflicted joint – often worsened by weight bearing – and impaired gait (Desy and Abdel, 2017). These factors are only weakly specific though as clinical indicators for loosening as they are also common presentations of periprosthetic joint infection and other implant failures (Shohat *et al.*, 2019).

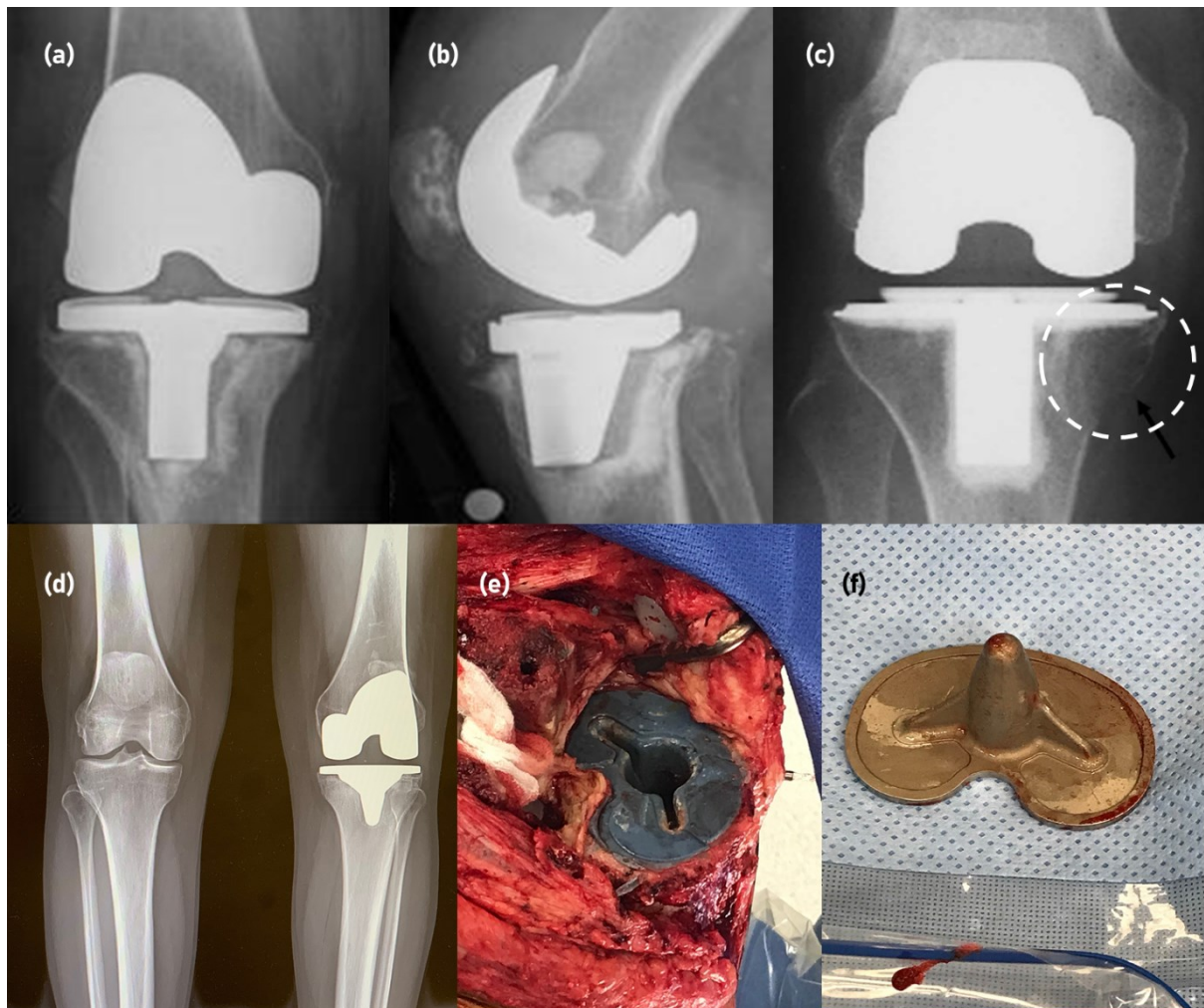


Figure 2.5. (a-b) Anteroposterior and lateral radiographs showing obvious periprosthetic lucency due to aseptic loosening (Arsoy *et al.*, 2013), © 2013 Wolters Kluwer Health, Inc, (c) osteolytic bone resorption in the medial aspect of the tibia (Miller, 2005), © 2005 Elsevier, and (d-f) a case where the tibial component had completely debonded from the cement mantle without obvious radiographic indication (Murphy *et al.*, 2021), © 2021 Cureus.

Suspected aseptic loosening is conventionally examined using radiographs (Fig. 2.5), which are effective in detecting gross loosening through implant malposition, periprosthetic lucency, or bone resorption (Miller, 2005). Radiographic examination, however, is either poorly sensitive to the early stages of aseptic loosening (Arsoy *et al.*, 2013; Barnsley and Barnsley, 2019) or poorly specific in determining implant stability (Chalmers *et al.*, 2017), and cannot be used alone to differentiate between septic and aseptic cases (Mandalia *et al.*, 2008). Indeed, aseptic loosening is often only confirmed intra- or postoperatively, with the preoperative assessment frequently being a misdiagnosis of a low-grade infection (Schiffner *et al.*, 2019).

Deep learning may improve detection of aseptic loosening from radiographs, but the only current study on this topic is small and limited by the current availability of data (Borjali *et al.*, 2019). Several radionuclide imaging techniques – scintigraphic (Kitchener *et al.*, 2006; Claassen *et al.*, 2014) and tomographic (Delank *et al.*, 2006; Bao *et al.*, 2021; Peng *et al.*, 2021) – have been implemented to provide more conclusive diagnoses of aseptic loosening (Barnsley and Barnsley, 2019), but these techniques are time-consuming, expensive, and often only available at specialist centres. Roentgen radiostereometric analysis (RSA), which has long been proposed as a method for predicting aseptic loosening (Ryd *et al.*, 1995), has likewise not permeated into regular clinical practice (Anil, Singh and Schwarzkopf, 2022). The technique involves the implantation of tantalum beads into the periprosthetic bone during surgery and tracking relative migration on follow-up radiographs

Vibrometry has also been explored as a technique to delineate between well-fixed and loose prostheses; loose implants distort the input waveform by generating multiple harmonics (Li, Jones and Gregg, 1996). In studies of femoral stem loosening, vibrations (<1000 Hz) have been applied to the lateral femoral condyle and measured at the greater trochanter using either an accelerometer (Rosenstein *et al.*, 1989; Li, Jones and Gregg, 1995, 1996; Georgiou and Cunningham, 2001) or Doppler-shift ultrasound (Rowlands, Duck and Cunningham, 2008). Accordingly, femoral stems (Puers *et al.*, 2000; Marschner *et al.*, 2009) and tibial knee prostheses (Arami *et al.*, 2018) have also been developed with embedded accelerometers for vibrometric analyses. The technique has been shown to outperform radiographic diagnosis in the clinic (Georgiou and Cunningham, 2001), but it is insensitive to early mechanical loosening, where the cement mantle remains intact and well-fixed, and implants with fibrous tissue at the interface (Li, Jones and Gregg, 1995, 1996).

Several other modified implants (Fig. 2.6) have been presented in the literature to detect aseptic loosening through changes in acoustic emission (Ruther *et al.*, 2011, 2014; Vogl *et al.*, 2020) and micromotion (Khokle *et al.*, 2019; Mohammadbagherpoor *et al.*, 2020; Khan *et al.*, 2021). The combined use of a piezoresistive bone cement containing carbon fibres and electrical impedance tomography has also been posited as a detection mechanism (Ghaednia, Owens, Keiderling, *et al.*, 2020; Ghaednia, Owens, Roberts, *et al.*, 2020).

2.2.3. Treatment

Aseptic loosening is an irreversible complication of arthroplasty. In the absence of comorbidities, the majority of aseptic loosening cases will be treated by replacing either the singular loose component or the entire prosthesis (Martin *et al.*, 2020). Patients at imminent risk of collapse – gross periprosthetic bone loss and concomitant implant malposition (>10°)

(Fehring *et al.*, 2017; Cox *et al.*, 2022) – are assigned high priority for revision surgery (<4 weeks) (Kalson *et al.*, 2021). Revision of a cemented component for aseptic loosening may be delayed for three months or more in cases without complications (Kalson *et al.*, 2021). Treatment for aseptic loosening of a cementless component, which is often more progressive, may be further delayed in favour of close monitoring to avoid unnecessary damage to the periprosthetic bone (Kurcz *et al.*, 2018). Revision prostheses are frequently augmented for greater stability in the restant bone stock (Sculco *et al.*, 2016). Debridement, cement filling, screws, and allografts may also be required in cases with osteolytic lesions or significant bone resorption (Maloney, 2005; Sculco *et al.*, 2016; Kurcz *et al.*, 2018).

2.3. Periprosthetic Joint Infection

Periprosthetic joint infection is a devastating complication of arthroplasty for patients, carrying a high mortality risk (Lum *et al.*, 2018; Drain *et al.*, 2022), and a major economic burden for healthcare providers (Kurtz *et al.*, 2012; Lenguerrand *et al.*, 2017; Akindolire *et al.*, 2020). As a complement to the previous section on aseptic loosening, this section details the varying disease pathways, diagnostic techniques, treatment options, and burden for patients that contract periprosthetic joint infection.

2.3.1. Aetiopathogenesis

As is the case with aseptic loosening, periprosthetic joint infection (PJI) is not a single condition but a catch-all for various aetiopathogeneses, with early (<3 months post-operation), delayed (3–24 months), or late (>24 months) presentations in acute or chronic forms. Most early and delayed presentations, which jointly account for two thirds of infections (Zimmerli, Trampuz and Ochsner, 2004), are thought to be initiated intraoperatively; incubation time varies according to virulence of the microbe. Highly virulent bacteria that commonly cause acute infection include *Staphylococcus aureus*, *Escherichia coli*, *Enterobacter*, *Klebsiella*, and *Pseudomonas aeruginosa*, whilst less virulent bacteria associated with delayed infection include *Staphylococcus epidermis* and *Cutibacterium* species (Izakovicova, Borens and Trampuz, 2019). Late infections are generally acquired via the bloodstream due to bacterial spread from a separate anatomical site (Lenguerrand *et al.*, 2018, 2019; Dufour *et al.*, 2019).

Acute infections are characterised by rapid-onset warmth, swelling, pain, and redness around the joint, often with features of systemic sepsis as planktonic bacteria enter the bloodstream (Barrett and Atkins, 2014). Chronic infections manifest with persistent discharge, discomfort, and sinus formation (Izakovicova, Borens and Trampuz, 2019); in most cases a mature biofilm is formed around the prosthesis that is recalcitrant to the host

immune response and antimicrobial treatment (Staats *et al.*, 2021). Low-grade chronic infections are often missed by current diagnostic criteria and may be accompanied by implant loosening (Dapunt *et al.*, 2016), which precipitates the clinical challenge of distinguishing septic from aseptic cases (Schiffner *et al.*, 2019; Hipfl *et al.*, 2021).

2.3.2. Diagnosis

Definition of periprosthetic joint infection is complex due to the varying presentations and pathogens implicated. Furthermore, several biomarkers of infection, such as erythrocyte sedimentation rate (ESR), percentage of polymorphonuclear neutrophils (PMN), and C-reactive protein levels, are all elevated during non-infective inflammation and may be within normal physiological limits in low-grade, chronic infections (McArthur *et al.*, 2015; Akgün *et al.*, 2018; Kheir *et al.*, 2018). Diagnosis therefore relies on consensus definitions (Parvizi *et al.*, 2011, 2018; Osmon *et al.*, 2013; McNally *et al.*, 2021). In the most recently published definition from the European Bone and Joint Infection Society (EBJIS) (McNally *et al.*, 2021), diagnosis relies on a combination of clinical, serological, cytological, synoviological, microbiological, histological, and radiological markers. Results from these tests are used to produce three levels of evidence: infection unlikely, infection unlikely and infection confirmed (Table 2.1).

D-dimer – a small protein fragment that plays a role in inflammation – has been proposed as another serological marker of infection (Leilei Qin *et al.*, 2020), and elevated levels were added as a minor criterion to the 2018 MusculoSkeletal Infection Society (MSIS) consensus definition (Parvizi *et al.*, 2018). However, recent meta-analyses have reported only limited diagnostic value in using D-dimer to confirm infection (Chen *et al.*, 2020; Lu *et al.*, 2020; Yan *et al.*, 2021; Balato *et al.*, 2022). Like the other bioanalytical tests in the EBJIS, D-dimer measurements still require specialist equipment and personnel for acquisition and interpretation, thus can only be accessed in the clinic.

Fever and erythema are reportedly the most specific clinical indicators of infection (96% and 95% respectively), often accompanying acute infection, but their overall sensitivity in detecting chronic infections is low (41% and 43%) (Shohat *et al.*, 2019). Indeed, thermographic imaging (Romanò *et al.*, 2012, 2013) and temperature-sensing implants (Karipott, Veetil, *et al.*, 2018) have been proposed as more accessible modalities for postoperative infection monitoring in orthopaedics. Direct infection detection using a smart implant has not yet been reported in literature, but techniques for measuring biofilm growth have been developed in other fields with the potential to be redeployed for periprosthetic joint infection (Ong *et al.*, 2001; Kim *et al.*, 2016; Ward *et al.*, 2018; Turolla *et al.*, 2019; Subramanian *et al.*, 2020).

Table 2.1. EBJIS criteria for the diagnosis of clinically suspected periprosthetic joint infection (McNally *et al.*, 2021), © 2021 British Editorial Society of Bone & Joint Surgery.

	Infection Unlikely (all findings negative)	Infection Likely (two positive findings)	Infection Confirmed (any positive finding)
Clinical and blood workup			
Clinical features	Clear alternative reason implant dysfunction (e.g. fracture, implant breakage, malposition, tumour)	1) Radiological signs of loosening within the first five years after implantation 2) Previous wound healing problems 3) History of recent fever or bacteraemia 4) Purulence around the prosthesis	Sinus tract with evidence of communication to the joint or visualisation of the prosthesis
C-reactive protein		>10 mg/L	
Synovial fluid cytological analysis			
Leukocyte count	<1500	>1500	>3000
Polymorphonuclear neutrophils	<65%	>65%	>80%
Synovial fluid biomarkers			
α -Defensin			Positive immunoassay or lateral flow assay
Microbiology			
Aspiration fluid		Positive culture	
Intraoperative fluid and tissue	All cultures negative	Single positive culture	Two or more positive samples with the same microorganism
Sonication	No growth	>1 CFU/ml of any organism	>50 CFU/ml of any organism
Histology			
High-power field (400x magnification)	Negative	Presence of five or more neutrophils in a single slide	Presence of five or more neutrophils in five or more slides
Others			
Nuclear imaging	Negative three-phase isotope bone scan	Positive white blood count (WBC) scintigraphy	

2.3.3. Treatment

For acute infections, where the prosthesis is well-fixed and the periprosthetic tissue is healthy, the first-choice surgical option is debridement, antibiotics and implant retention (DAIR) (Izakovicova, Borens and Trampuz, 2019), which has the lowest risk of ongoing complications (Middleton, Price and Alvand, 2022). In chronic cases and more challenging acute cases, which require retrieval and replacement of the afflicted prosthesis, two-stage procedures are the current gold-standard treatment, but one-stage exchanges are increasingly being performed with good prospective results (Izakovicova, Borens and Trampuz, 2019). Two- or three-stage procedures are necessary for patients with antimicrobial-resistant biofilms (Izakovicova, Borens and Trampuz, 2019). Complex cases that do not resolve satisfactorily after short- to medium-term antimicrobial treatment require prolonged suppressive antimicrobial treatment (Malahias *et al.*, 2020), joint fusion (arthrodesis) (Chalmers *et al.*, 2020), or amputation (Ryan *et al.*, 2019). Early diagnosis is critical for timely mitigation of the impact of periprosthetic joint infection, and is associated with better treatment outcomes (Moran, Byren and Atkins, 2010; Grammatopoulos *et al.*, 2017). Future treatment options could use ultrasound or pulsed electromagnetic fields to ablate infected tissue, chelating agents like EDTA to chemically disrupt biofilms, and bacteriophages, cell penetrating peptides, or immunotherapies to biologically target infective bacteria (Tsang, Morgan-Jones and Simpson, 2020).

2.3.4. Burden

The burden for patients that contract periprosthetic joint infection is stark: septic patients that undergo two-stage revision surgery can expect to be severely disabled for several months. Even when the infection is eradicated, these patients report inferior functional outcomes compared to aseptic revision cases (Sabah, Alvand and Price, 2021). The complication also carries ten-year post-revision risks of 4% and 7% for arthrodesis and amputation respectively (Son *et al.*, 2017), and in a recent meta-analysis, the one-year mortality rate following two-stage revision for total knee periprosthetic joint infection was 4.3%, growing to 21.6% at five years (Lum *et al.*, 2018). The trends following hip arthroplasty were near-identical: 4.1% at one year and 21.1% at five years (Natsuhara *et al.*, 2019). For perspective, the one-year risk following septic revision is reportedly five to six times higher versus aseptic revision (Zmistowski *et al.*, 2013; Choi and Bedair, 2014) and is higher or comparable to mortality rates for four of the five most commonly diagnosed cancers (Drain *et al.*, 2022). Furthermore, whilst post-revision mortality is associated with frailty and pathogenesis, there is no clear aetiology and no distinct effect of one- versus two-stage

treatment (Drain *et al.*, 2022). Mortality rates for patients that undergo arthrodesis or amputation are yet more severe (Son *et al.*, 2017; Orfanos *et al.*, 2020). Finally, the mean economic cost of a septic revision is reportedly three times higher than an aseptic case (Kallala *et al.*, 2015), with each deep surgical site infection estimated to cost the National Health Service £100,000 (Getting It Right First Time, 2020).

2.4. Osseointegration: Mechanobiology and Enhancement

Osseointegration aims to establish a structural and functional connection between the prosthesis and the host cancellous bone by way of natural remodelling (Brånemark *et al.*, 2001). As a phenomenon, osseointegration has been researched via in vitro (Ferraris *et al.*, 2011), in vivo (Colnot *et al.*, 2007), and ex vivo models (Dua, Jones and Noble, 2021). There are critical differences between osseointegration and normal fracture healing. Bone formation characteristic of fracture healing (endochondral ossification) involves the development of a cartilaginous callus populated by chondrocytes and progressive conversion into woven bone. In osseointegration, the process is similar to the direct process of bone formation that occurs in native bone, referred to as intramembranous ossification (Colnot *et al.*, 2007; Shah, Thomsen and Palmquist, 2019). Indeed, the formation of fibrous tissue at the implant-bone interface is known to be associated with fixation failure (Kohli, Stoddart and van Arkel, 2021).

2.4.1. Cancellous Bone: Structure and Cellular Composition

Encapsulated by compact shells of cortical bone, cancellous (spongy) bone occupies the internal volume of bone. In long bones, such as femora and tibiae, cancellous bone is only found in the epiphyses as the medullary cavity throughout the diaphysis (shaft) holds yellow bone marrow. Cancellous bone is characterised by its high porosity with a microstructure of trabecular rods and plates, which is optimised for load transfer (Prescott and Lidster, 2017).

There are three principal cell types involved in intramembranous remodelling of cancellous bone: osteocytes, osteoblasts, and osteoclasts. Osteocytes, which account for 90–95% of the cell population, are the most abundant cell type in cancellous bone (Jaalouk and Lammerding, 2009). Located within lacunae (cavities) of the extracellular matrix, osteocytes have long dendritic processes that connect to osteocytes in neighbouring lacunae through thin channels (diameter: ~100 nm), forming the lacunocanalicular network (Fig. 2.6) (Stewart *et al.*, 2020). The lacunocanalicular network is saturated by interstitial fluid: a water-based medium through which small ions are diffused and nutrients are transported (Cowin and Cardoso, 2015).

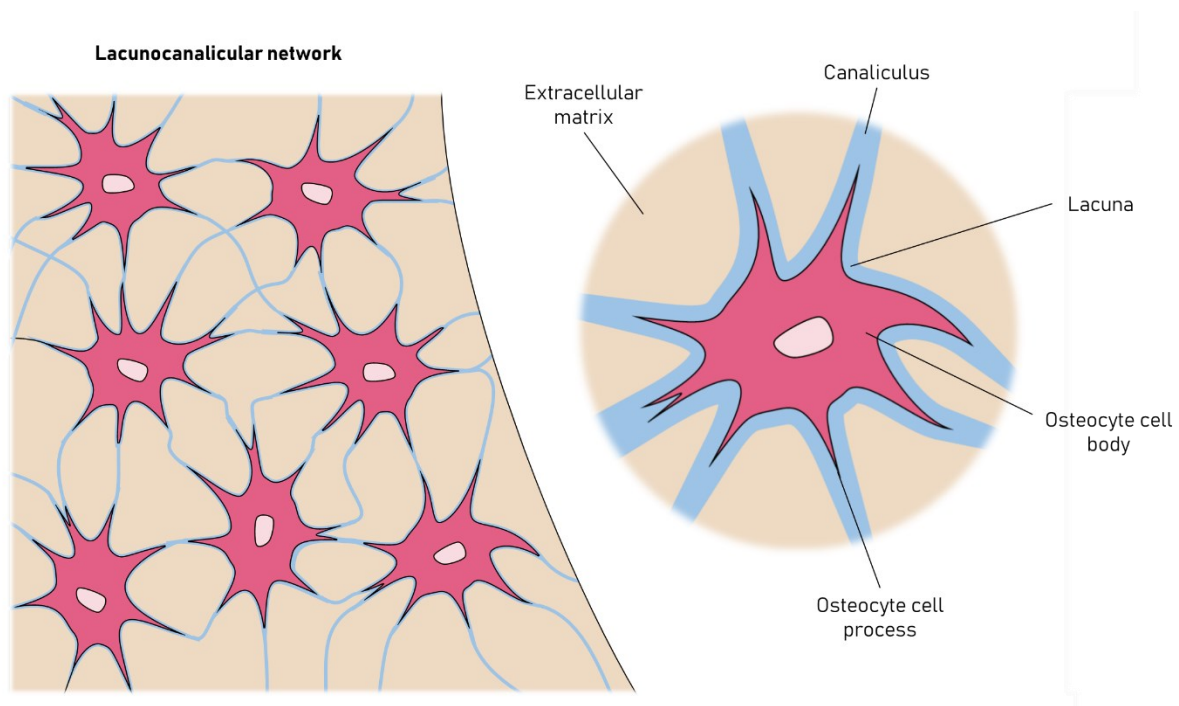


Figure 2.6. Fluid flow through the lacunocanalicular network due to deformation stimulates mechanotransductive signalling in osteocyte cells.

Osteoblasts are generally recruited from bone marrow stromal cells (BMSCs) via osteoblast progenitor and preosteoblast cell type. Osteoblasts are primarily responsible for synthesis of the bone extracellular matrix in two stages: osteoid formation and mineralisation. The osteoid is an organic tissue that consists of collagen (90% Type I with small amounts of Type III & V), proteoglycans, γ -carboxyglutamic acid-containing proteins, glycoproteins, and small integrin-binding ligand N-linked glycoproteins (SIBLINGS) (Lin *et al.*, 2020). The collagen in the osteoid is organised into fibrillar structures that determine the strength of the bone, whilst non-collagenous proteins have roles in mineral binding (osteocalcin and osteonectin), collagen folding (periostin), cell differentiation (thrombospondins and bone sialoproteins), and osteoclast regulation (osteopontin) (Lin *et al.*, 2020). The main mineral component of the extracellular component is hydroxyapatite (Ramesh, Moratti and Dias, 2018); the process of mineralisation stiffens the collagen fibrillar structure (Yerramshetty and Akkus, 2008). Alkaline phosphatase (ALP), which is expressed during osteoblast differentiation and promotes mineralisation, is a marker of early bone growth but its expression wanes as the osteoblasts mature (Vimalraj, 2020). Ultimately, through the processes of osteoid deposition and mineralisation, osteoblast cells (~20%) become embedded within the extracellular matrix and mature into osteocytes (Franz-Odendaal, Hall and Witten, 2006), with associated changes in gene expression (Plotkin and Bellido, 2016). Other osteoblast fates are to undergo programmed cell death (apoptosis) or to become bone-lining cells – inactive (quiescent)

osteoblasts that form a thin membrane over the trabecular surface called the endosteum (Mizoguchi and Ono, 2021).

Osteoclasts are large multinucleated cells derived from a macrophage lineage. Osteoclasts become polarised when in contact with bone, forming an apical membrane (ruffled border) forms through which hydrochloric acid is secreted into a resorptive pit (Ribet, Ng and Pavlos, 2021). The hydrochloric acid in the resorptive pit dissolves the hydroxyapatite-mineralised structure, exposing the collagen network for digestion (Soysa and Alles, 2016). A dense network of podosomes hermetically seals the apical membrane, whilst waste products are transported across the cell to the basolateral membrane for expulsion through the functional secretory domain (Ribet, Ng and Pavlos, 2021). This resorption process is essential for regulating bone mass and remodelling damaged trabeculae; suppression of osteoclast activity leads to increased microcrack accumulation and subsequently decreased mechanical strength (Jin *et al.*, 2017; Ma *et al.*, 2017).

Cancellous bone also hosts blood vessels and red bone marrow in the cavities between its trabecular structure – a microenvironment referred to as the bone marrow niche (Morrison and Scadden, 2014). Arterioles and capillaries supply the marrow and surrounding bone tissue with oxygen, nutrients, and growth factors; this blood supply collects in sinuses within the marrow before exiting via the central sinus (Nagasawa, 2006). The space between the sinuses is inhabited by adipose (fat) and cord-like haematopoietic (blood) tissues, which primarily consists of haematopoietic stem cells (HSCs) and mature cell types of this lineage (erythrocytes, granulocytes, megakaryocytes). Fenestrations in sinusoidal capillaries serve as conduits for mobile cells in the niche to pass in and out of circulation (Morrison and Scadden, 2014). Bone marrow stromal cells (BMSCs) also exist within this niche, which are recruited into osteoblasts and adipocytes during bone and fat formation respectively (Tencerova and Kassem, 2016)

2.4.2. Mechanotransduction in Bone Remodelling

Bone remodelling is known to be regulated by hormonal and mechanical stimuli, but the exact pathways are incompletely understood (Plotkin and Bellido, 2016). Whilst many cell types are mechanosensitive, including mesenchymal stem cells, osteoblast progenitors, osteoblasts, and osteoclasts (Thompson, Rubin and Rubin, 2012), mechanotransduction in mature bone tissue is accepted to be mediated by osteocytes (Bonewald, 2011; Lei Qin *et al.*, 2020; Robling and Bonewald, 2020). Mechanical deformation of bone drives interstitial fluid around the osteocytes within the lacunocanalicular network (van Tol *et al.*, 2020). This flow stimulates transmembranous mechanosensors and activates calcium channels leading to

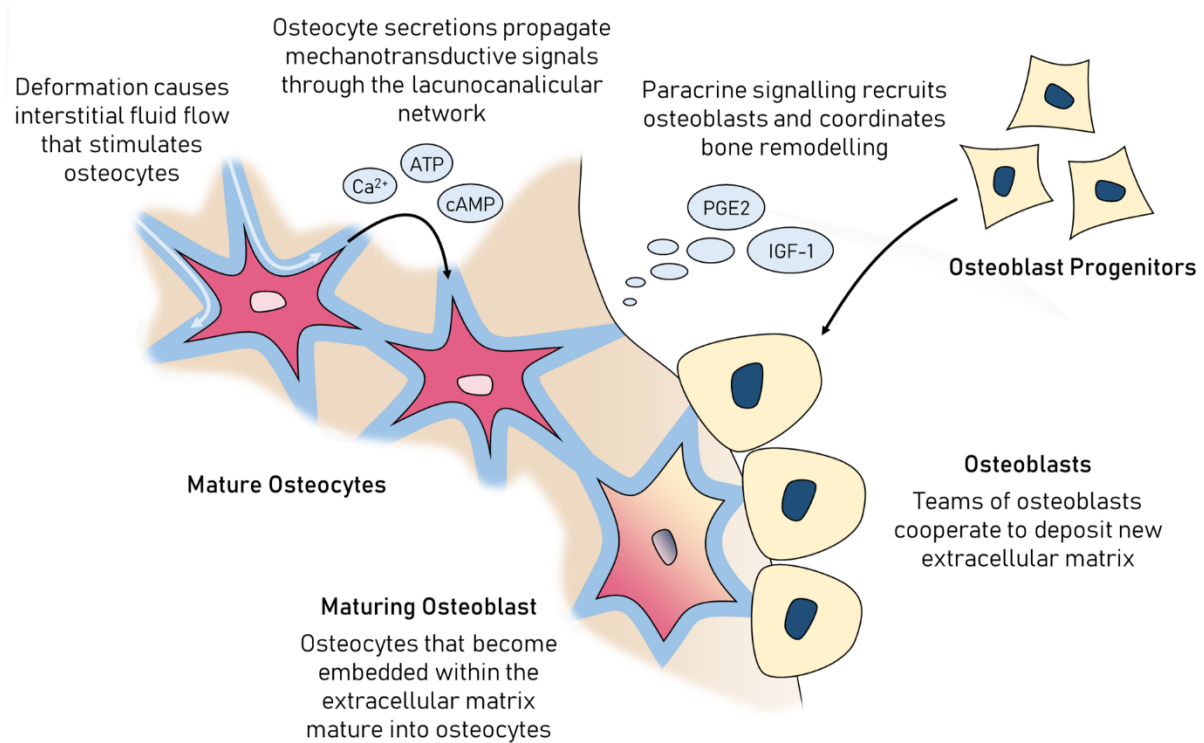


Figure 2.7. The biochemical response of osteocytes to mechanical stimulus recruits osteoblasts and their progenitors to form new bone.

biochemical signalling that regulates bone formation (Fig. 2.7) (Stewart *et al.*, 2020; Xu *et al.*, 2021). Primary cilia – hair-like organelles on the cell surface – have also been implicated in osteocyte mechanotransduction (Temiyasathit and Jacobs, 2010; Lei Qin *et al.*, 2020), having been shown to be mechanosensors in other cell types (Hoey *et al.*, 2012).

Mature osteocytes inherently secrete sclerostin (SOST), a protein which negatively regulates osteoblast formation, as well as macrophage colony stimulating factor (M-CSF) and receptor activator of nuclear factor κB ligand (RANKL), which promote osteoclast progenitor replication and osteoclast differentiation respectively (Xiong *et al.*, 2011; O'Brien, Nakashima and Takayanagi, 2013; Wang, Mazur and Wein, 2021). Mechanical stimulus suppresses sclerostin levels, which counteracts this tendency of bone towards resorption in its resting state (Morrell *et al.*, 2018), and prevents osteocyte apoptosis (programmed cell death) (Delgado-Calle and Bellido, 2022). Runx2 and Osx are the two transcription factors most crucial to the process of osteogenesis, regulating the expression of several osteoblast-specific proteins; both are activated by mechanical loading (Vimalraj *et al.*, 2015; Yavropoulou and Yovos, 2016). Osteocytes secrete several molecules as part of the mechanoreponse, including calcium (Ca^{2+}), adenosine triphosphate (ATP), and cyclic adenosine monophosphate (cAMP), which propagate mechanotransductive signals to neighbouring osteocytes in the lacunocanalicular network (Stewart *et al.*, 2020). Further, prostaglandin E2 (PGE2) released

by osteocytes acts on osteoblasts to control osteoid formation and mineralisation (Matsuzaka, Matsugaki and Nakano, 2021). Insulin-like growth factor 1 (IGF-1) is also produced in osteocytes and other cells in the osteoblast lineage in response to mechanical stimuli; its release is likely to contribute to coordinating bone remodelling (Tian, Wang and Bikle, 2018). Finally, direct coordination between osteoblasts and osteoclasts has been proposed as a composite function of the mechanoreponse (Wang *et al.*, 2020).

2.4.3. Osseointegration

Osseointegration is a multi-system process that involves immunological (Trindade *et al.*, 2018), inflammatory, angiogenic, and osteogenic responses, with crosstalk therein (Grosso *et al.*, 2017; Zhang *et al.*, 2021). In joint replacement surgery, bone is first resected using surgical drills and saws prior to implantation, which damages blood vessels and introduces autogenous bone fragments, bacteria, and other particulates (Davies, 2003; McKee, Pedraza and Kaartinen, 2011). Haemostasis is the first biological process to occur in the periprosthetic tissue post-surgery: fibrin-rich clots form to plug the injury site (Shiu *et al.*, 2014). Growth factors (PDGF: platelet-derived growth factor; TGF- β : transforming growth factor beta) released by thrombocytes during this initial phase trigger a wound-healing cascade that stimulates the recruitment, migration, and proliferation of osteoblasts and bone-marrow derived cells (Davies, 2003). Osteocytes, which are no more than 0.1 mm away from an intact capillary in normal bone (Ham, 1952), are necrotised in this ischaemic environment following the loss of circulation. (Davies, 2003).

The bone undergoes an inflammatory response after haemostasis that lasts several days: macrophages and neutrophils migrate to the wound site to clear the necrotic cell debris, bacteria, and other particulates (McKee, Pedraza and Kaartinen, 2011; Jennissen, 2016). Osteopontin is secreted by the incoming macrophages (McKee, Pedraza and Kaartinen, 2011); this osteopontin is a chemical attractant to additional osteopontin-secreting macrophages and accumulates with other proteins, e.g. bone sialoprotein, to form osteopontin-rich cement lines on exposed trabecular bone and implant surfaces (Fig. 2.8) (McKee and Nanci, 1996; Ayukawa *et al.*, 1998; Shah, Thomsen and Palmquist, 2019). These cement lines are mineralised whilst devoid of the collagen fibres that are characteristic of normal bone (Davies and Hosseini, 2000; Davies, 2007). Long-term predominance of M2-polarised macrophages (anti-inflammatory) in the periprosthetic tissue encourages osseointegration; a predominance of M1 phenotype (pro-inflammatory) contributes to loosening and resorption (Amengual-Peñafiel *et al.*, 2021).

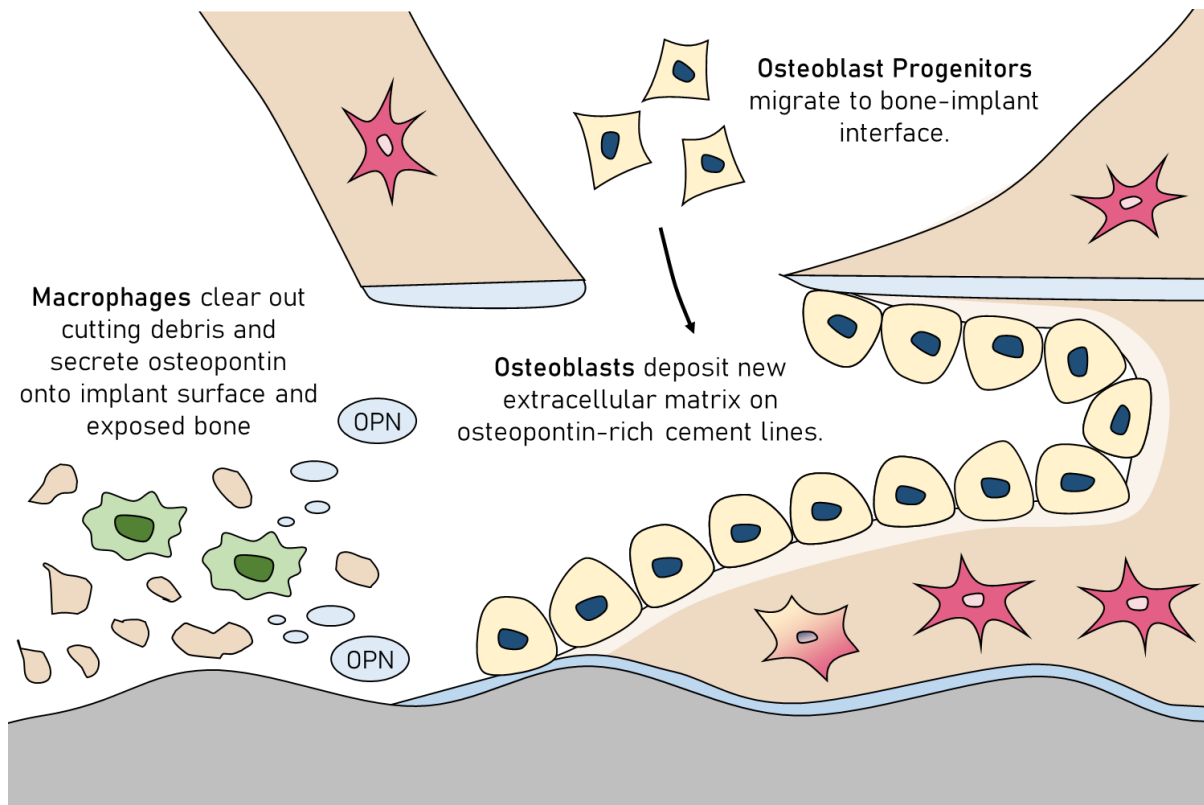


Figure 2.8. The secretion of osteopontin by macrophages during the clear out of iatrogenic debris produces a cement line on the exposed trabecular bone and implant surfaces, providing a foundation for de novo bone formation orchestrated by newly migrated osteoblasts.

De novo formation of periprosthetic bone from the cement lines is orchestrated by a fresh population of osteoblasts (McKee, Pedraza and Kaartinen, 2011), beginning approximately one week post-injury (Trindade *et al.*, 2018). There is evidence that this process of de novo bone formation also occurs within bone fragments that were cleaved from the bulk tissue during cutting (Shah and Palmquist, 2017). A second osteoid front also develops on the surface of titanium and some other metallic implants due to bone deposition directly on the implant surface (Puleo and Nanci, 1999). The oxide layer on surface of a titanium implant is electrochemically active, resulting in the layer thickening and the adsorption of calcium phosphate crystals that weakly resemble hydroxyapatite (Puleo and Nanci, 1999; Shah, Thomsen and Palmquist, 2019); ion flow in the other direction into the periprosthetic tissue and into the bloodstream is a source for toxicity and hypersensitivity reactions (Puleo and Nanci, 1999). De novo bone formation from the cement line on the implant (contact osteogenesis) and the resected bone (distance osteogenesis) is similar: collagenous osteoid is deposited by osteoblasts and then mineralised (Grandfield, 2015). Bone is initially deposited as irregular woven structures onto the implant surface, eventually bonding to the host bone

and remodelling into a hierarchical structure that is characteristic of normal bone over several months (Davies *et al.*, 2014; Grandfield, 2015).

Beyond the restoration of blood supply for nutrients and oxygen, osteogenesis is tightly coupled to angiogenesis during bone regeneration: vascular endothelial growth factor (VEGF), which regulates capillary formation, has been implicated in the recruitment of macrophages and immune cells during the initial inflammatory phase of healing (Barleon *et al.*, 1996; Street *et al.*, 2000), the promotion of osteogenic differentiation of mesenchymal stem cells for de novo bone formation (Grosso *et al.*, 2017), and the recruitment of osteoclasts for remodelling (Kristensen *et al.*, 2013).

2.4.4. Implant Design and Coatings

Hydroxyapatite, which is the main mineral constituent of human bone (Jeong *et al.*, 2019), is often used as a coating to accelerate osseointegration (Kamath *et al.*, 2021). Morphological and chemical modifications of the implant surface at the nanoscale may also promote osteogenic activity, such as osteoblast migration and differentiation onto the implant (Souza *et al.*, 2019). However, whilst surface coatings and modifications may provide satisfactory early results, the elastic mismatch between a stiff prosthesis and more compliant bone can cause long-term progressive bone loss in the periprosthetic tissue: a phenomenon referred to as stress shielding (Sanli, Arts and Geurts, 2016; Rivière *et al.*, 2018). Stiffness-matched structures have been developed to alleviate stress shielding and in vivo studies have demonstrated their potential to passively promote bone ingrowth (Ghouse *et al.*, 2019; Reznikov *et al.*, 2019). These cementless techniques nevertheless rely on bone metabolism, which is known to decline in elderly patients (Chan and Duque, 2002). Current clinical guidance therefore advises against its use in patients over 70 years of age (Getting It Right First Time, 2020), but the concept of age thresholds has been contested in preference to bedside decision making (Konan, Abdel and Haddad, 2019).

2.4.5. Ultrasound Stimulation

Ultrasound – MHz-frequency mechanical waves – is known to promote osteogenic activity in cell cultures and has been proposed as a biophysical means to stimulate osseointegration (McCarthy and Camci-Unal, 2021). Several relevant in vitro studies have shown ultrasonic stimulation drives differentiation of human stem cells (mesenchymal/adipose-derived) towards osteoblast lineages (Nagasaki *et al.*, 2015; Feng *et al.*, 2019; Ambattu, Gelmi and Yeo, 2022), upregulates biomarkers associated with bone maturation (Wang *et al.*, 2014; Cao *et al.*, 2017; Veronick *et al.*, 2018), and promotes ingrowth of seeded osteoblasts into porous scaffolds (Wu, Lin and Qin, 2015). Piezoelectric coatings, such as barium titanate, may further

enhance proliferation within a scaffold (Fan *et al.*, 2020). Whilst the exact mode of mechanotransduction with low-intensity pulsed ultrasound is not fully understood (McCarthy and Camci-Unal, 2021), observations of upregulated biomarkers (cyclooxygenase and prostaglandin E2) associated with fluid shear stress suggest a mechanism similar to that induced by physiological loading (Veronick *et al.*, 2018; Stewart *et al.*, 2020).

The effects on low-intensity pulsed ultrasound on osseointegration have also been studied in paired-limb trials in small animals (Tanzer, Kantor and Bobyn, 2006; Iwai *et al.*, 2007; Ustun *et al.*, 2008; Hsu *et al.*, 2011; Liu *et al.*, 2012; Zhou *et al.*, 2016; Ruppert *et al.*, 2019). Statistically significant increases in bone ingrowth into porous implants has been observed in canine ulnae (Tanzer, Kantor and Bobyn, 2006) and leporine femora (Iwai *et al.*, 2007); mild, statistically insignificant increases in compression strength were in the leporine specimens. Statistically significant increases in bone growth around screwed dental implants were observed in leporine (Ustun *et al.*, 2008; Hsu *et al.*, 2011; Liu *et al.*, 2012) and murine tibiae (Zhou *et al.*, 2016). Increases in pull-out strength force and screw-out torque were statistically significant in some studies (Hsu *et al.*, 2011; Liu *et al.*, 2012; Zhou *et al.*, 2016), but not all (Ustun *et al.*, 2008). Finally, ultrasound stimulation demonstrated statistically significant increases (38%; $P=0.002$) in the pull-out forces of intramedullary nails in murine femora (Ruppert *et al.*, 2019).

It is unclear what the effect of LIPUS on osseointegration would be in human subjects, particularly given the controversial efficacy of LIPUS treatments for fracture healing (Stewart *et al.*, 2020). A recent systematic review indicated no benefit of treatment (Schandelmaier *et al.*, 2017) and clinical practice guideline has since advised against routine use for fracture healing (Poolman *et al.*, 2017): both cited a lack of impartial evidence. These results may indicate that an ultrasound-induced increase in bone formation may not correlate with mechanical function (Rutten *et al.*, 2016). Alternatively, the structure of bone – a hard shell with a sponge-like interior – may mean that bone cells are not receiving the ultrasound stimulation due to reflections and attenuations respectively. An intermediate ex vivo study under tightly controlled conditions, e.g. (Dua, Jones and Noble, 2021), may explain the disparity in efficacy between in vitro testing, animal studies, and clinical trials.

2.4.6. Electrical Stimulation

There are three mechanisms of operation for electrically stimulating bone growth: direct-to-tissue, pulsed electromagnetic fields (inductive), and pulsed electric fields (capacitive) (Khalifeh *et al.*, 2018). Electrical stimulation has been shown to increase levels of

intracellular calcium ions, which are either released from internal stores or taken in from the interstitial fluid (Brighton *et al.*, 2001). This increase results in increased expression of the main osteogenic transcription factors: Runx2 and Osx (Stewart *et al.*, 2020). Furthermore, electrical stimulation has also been found to improve osteoblast-lineage cell adhesion and proliferation (Isaacson *et al.*, 2011; Bodhak *et al.*, 2012), differentiation (Gittens *et al.*, 2013), and survival (Pettersen, Shah and Ortiz-Catalan, 2021) on titanium surfaces during in vitro culture, which are all expected to benefit osseointegration of orthopaedic implants. In the diverse cellular environment of natural, the use of direct current has the potential to form resorption-inducing reactive oxygen species at the electrodes (Bax *et al.*, 1992), though this can be mitigated by using pulsed stimulation (Pettersen, Anderson and Ortiz-Catalan, 2021). Paired-limb animal studies suggest that electrical stimulation accelerates early healing (Song *et al.*, 2009; Bins-Ely *et al.*, 2017), but the advantage subsides beyond four weeks (Dergin *et al.*, 2013). Nevertheless, stimulation protocols vary across the small number of studies, with potential for further optimising parameters (Pettersen, Anderson and Ortiz-Catalan, 2021).

There are currently no commercially available systems for stimulating osseointegration around an implant, but several devices have been licensed for promoting fracture healing and spinal fusion. These include implantable electrodes with transcutaneous wires, namely OsteoGen Bone Growth and SpF Spinal Fusion stimulators (both Zimmer Biomet, Warsaw, IN, USA), plus several inductive and capacitive systems. In future, piezoelectric constructs could be used to generate the necessary electrical stimulation from physiological movements instead of relying on external power sources (Poon *et al.*, 2020; Yu *et al.*, 2021).

2.4.7. Pharmacological Stimulation

Several systemic drugs have been assessed for efficacy in enhancing osseointegration in animals trials but few have advanced through human clinical trials (Apostu *et al.*, 2017, 2018). Most of these systemic drugs have been repurposed from osteoporosis with the intent of boosting bone metabolism (Apostu *et al.*, 2018), but the quality of evidence is low. Risedronate, a bisphosphonate, has been shown to reduce bone resorption in small-scale clinical trials around a hip prosthesis following arthroplasty (Ren and Wang, 2018), but bisphosphonate-treated bone has also been shown to lose its microstructural integrity after long-term use (Ma *et al.*, 2017). Correlation to mechanical or clinical outcomes would be of greater benefit in these pharmacological studies. Future pharmacological interventions may use messenger ribonucleic acid (mRNA) to target osteogenic pathways and thereby enhance ingrowth, but this research is at an early stage (Balmayor, 2022).

2.5. Smart Implants in Arthroplasty

The field of orthopaedics has a history of using sensor-equipped implants as research tools (Rydell, 1966; Waugh, 1966; Bergmann *et al.*, 1988; Graichen and Bergmann, 1991; Graichen, Bergmann and Rohlmann, 1999; Morris *et al.*, 2001; D'Lima *et al.*, 2005). These implants have provided invaluable information for orthopaedic research but are not suitable for routine clinical practice. In the knee, for example, thickening of a tibial tray to accommodate electronic components will likely accelerate resorption in the periprosthetic bone (Martin *et al.*, 2017).

As orthopaedic surgeons are increasingly adopting temporary instrumented components for intraoperative assistance during total knee arthroplasty (Meere, Schneider and Walker, 2016), specifically the VERASENSE (OrthoSensor, Dania Beach, FL, USA) and eLIBRA (Zimmer Biomet, Warsaw, IN, USA) systems, there is a growing interest in the translation of permanently implanted smart prostheses as evidenced by several recent reviews (Karipott, Nelson, *et al.*, 2018; Ledet *et al.*, 2018; Nelson *et al.*, 2020; Iyengar *et al.*, 2021; Qiblawey *et al.*, 2021; Vickers *et al.*, 2021) and an FDA workshop (Baumann *et al.*, 2021). Furthermore, FDA market clearance for a smart joint prosthesis was awarded for the first time in 2021 (FDA, 2021). The Persona IQ (Zimmer Biomet, Warsaw, IN, USA) is equipped with an accelerometer-embedded stem extension to record post-operative range of motion and evaluate gait, but the device is not cleared to support clinical decision making and is only indicated for use in patients that would normally be indicated for a 58 mm stem extension. There is still an unmet need for a smart implant technology that generates objective data to inform clinical decision making without limiting the usage conditions of the original device.

Instrumented implants are required to capture data from the joint environment and transmit it to an external reader, such as a smartphone or other bespoke device. The generic architecture for an instrumented implant (Fig. 2.9) consists of four composite systems: power, communication, sensing/actuation, and processing. Architecture is nevertheless flexible and composite functions, such as powering or processing, can be fully or partially offloaded to the external reader to minimise the overall size of the implanted components. Modalities for power, communication, and sensing on a biomedical implant are detailed in this section as they relate to smart orthopaedic implants. Processing is beyond the scope of this section: whilst microprocessors have been embedded within smart orthopaedic implants (Graichen *et al.*, 2007), the field lags considerably behind the cutting-edge of low-power computing for biomedical implants (Reyserhove and Dehaene, 2019; Hong *et al.*, 2020; Nelson *et al.*, 2020).

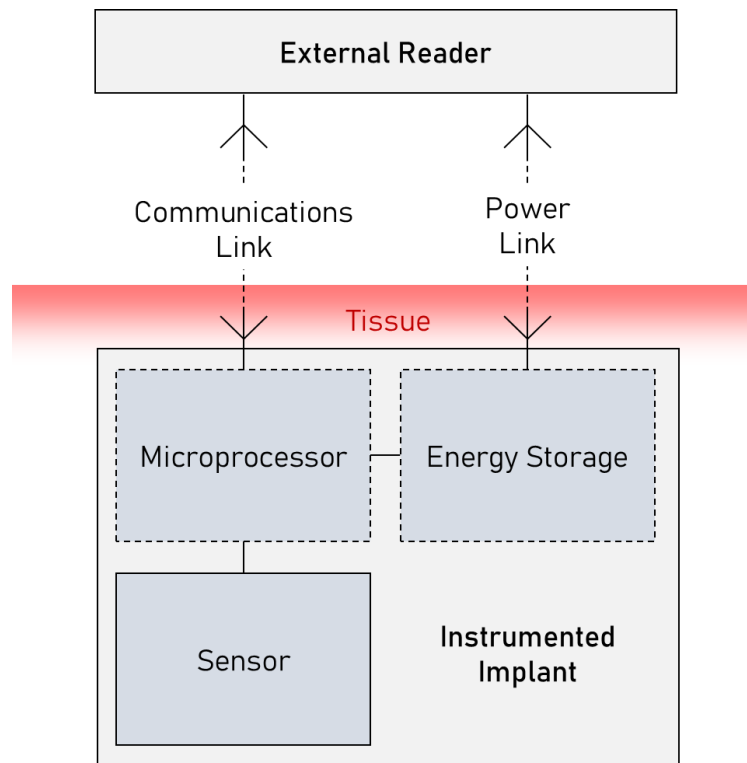


Figure 2.9. Generic system architecture for acquiring data from an implantable medical device.

2.5.1. Power

Wires through the skin present an infection risk to patients and can introduce system noise; most implantable electronic devices are therefore fitted with an energy storage device or other means of recharging. Historically, implantable electronic devices have been powered by on-board batteries, including the Persona IQ (Zimmer Biomet, Warsaw, IN, USA) – the only FDA-approved smart total joint prosthesis. However, there is an onus to minimise device size as implants should not excessively disrupt the natural anatomy and relying on battery power alone inflates device size and requires explantation for recharging. Many contemporary implantable electronic devices therefore use wireless power transfer strategies instead to recharge or source power on demand (Agarwal *et al.*, 2017). The first generation of smart implants for orthopaedic research featured wireless power transfer systems for recharging (Graichen and Bergmann, 1991; Rohlmann, Bergmann and Graichen, 1994; Graichen, Bergmann and Rohlmann, 1999), whilst later concepts have trended towards sourcing power on demand (D'Lima *et al.*, 2005; Damm *et al.*, 2010; Bergmann *et al.*, 2012). The most common wireless power transfer for biomedical implants include inductive (RamRakhyani, Mirabbasi and Chiao, 2011), ultrasonic (Taalla *et al.*, 2019), capacitive (Hossain *et al.*, 2021), radiative (Kim, Choi and Lee, 2022), and optical (Mujeeb-U-Rahman *et al.*, 2015),

Inductive Wireless Power Transfer

Inductive wireless power transfer is the most mature and widely used of these modalities for battery recharging or power on demand; the technique generally involves establishing a resonant magnetic field (commonly at a frequency of 13.56 MHz) between external transmitter and implanted receiver coils (Schormans, Valente and Demosthenous, 2018). The effect of tissue on time-varying magnetic fields is low at frequencies below 10 MHz, whilst the effect of blood is similarly low below 5 MHz (Sharma and Guha, 1975). The power that can be transmitted via an inductive link is limited for biosafety and proportional to coil size; ~100 mW may be achieved with large coils but ~1 mW is more typical for mm-sized coils (Ibrahim and Kiani, 2016). Inductive links are also characteristically sensitive to coil alignment, metallic components (a challenge for orthopaedic implants), and load variation, but stability is improving as the state of the art advances (Jia *et al.*, 2019; Pokharel *et al.*, 2021; Song *et al.*, 2021). Smart orthopaedic implants used for academic research have previously relied on inductive power supplies (Graichen and Bergmann, 1991; Rohlmann, Bergmann and Graichen, 1994; Graichen, Bergmann and Rohlmann, 1999; Morris *et al.*, 2001; D'Lima *et al.*, 2005; Damm *et al.*, 2010; Bergmann *et al.*, 2012).

Ultrasonic Wireless Power Transfer

Ultrasonic wireless power transfer has also been well researched and translated into commercial biomedical implants (Sieniewicz *et al.*, 2020). As comparative advantages over inductive links, ultrasonic links are more suitable for miniaturisation due to shorter wavelengths, less absorbed by tissue resulting in higher efficiency and safe power limits, and are not impaired by metallic components or hermetic sealing (Basaeri, Christensen and Roundy, 2016). Whilst insufficient for deeply implanted biomedical devices, the range of ultrasonic links is improved versus inductive links (Taalla *et al.*, 2019; Sedehi *et al.*, 2021); ultrasonic wireless power transfer is therefore a good candidate for smart orthopaedic implants.

Capacitive, Radiative and Optical Wireless Power Transfer

Capacitive links, which rely on the resonance between capacitive plates, can be used to transmit more power than an equivalent inductive link over short ranges (<10 mm) but they are not suitable for transmission to deep tissues (Hossain *et al.*, 2021), limiting their adoption. Radiative mid- and far-field electromagnetic techniques, which are still at an early stage of development, compromise efficiency but will likely be suitable for deeply implanted, miniature devices (Khan *et al.*, 2020). Optical power transfer, which involves near-infrared transmission and photovoltaic reception, is less researched than the other modalities within

the context of biomedical implants; its purported advantages also apply to miniaturised devices (Mujeeb-U-Rahman *et al.*, 2015). Conductive volumes.

Energy Harvesting

Orthopaedic implants are inherently designed for mechanical loading and are therefore also suitable platforms for energy harvesting. Mechanisms that have been applied to orthopaedic implants include piezoelectric (Safaei, Meneghini and Anton, 2018; Lange *et al.*, 2020) and triboelectric (Ibrahim *et al.*, 2019; Davis *et al.*, 2021). Expected power outputs are <1 mW for piezoelectric (Lange, Bader and Kluess, 2021) and <1 μ W for triboelectric energy harvesters (Ibrahim *et al.*, 2020).

2.5.2. Communication

The communications system for a smart implant is intrinsically linked to the power system, with selection often determined by transmission demands and resource constraints. Antenna-based systems draw power when uploading and downloading data using wireless protocols like Bluetooth Low Energy. Alternatively, a wireless power source can be modulated for simultaneous power and data transfer, though this harbours an inherent trade-off between power transfer efficiency and data transmission rate (Dehghanzadeh, Zamani and Mandal, 2021b).

Standalone Radiocommunication

Antennas can be used to establish a radiofrequency communication link to a smart implant or to integrate the implant within a wireless body area network (Teshome, Kibret and Lai, 2018). As the electronics of most smart implant systems are embedded within the metallic implant, which shields the transmission of RF signals, antennas must be housed within hermetically sealed augments (D'Lima *et al.*, 2005; Cushner *et al.*, 2021) or directly into the implant structure (Moura *et al.*, 2021). A series of harmonised standards have been developed specifically for active medical implants in the bands 9–315 kHz (European Telecommunications Standards Institute, 2016b), 402–405 MHz (European Telecommunications Standards Institute, 2016c), and 2.4835–2.5 GHz (European Telecommunications Standards Institute, 2015, 2016a). Smart orthopaedic implants have also been developed with general low-energy communication technologies, such as Bluetooth Low Energy (Silva *et al.*, 2013) and Zigbee (Valdastri *et al.*, 2008).

Simultaneous Power and Data Transfer

Simultaneous wireless power and data transfer to a biomedical implant has been demonstrated for inductive (Dehghanzadeh, Zamani and Mandal, 2021a), ultrasonic (Charthad

et al., 2015), and capacitive systems (Koruprolu *et al.*, 2018). Data is communicated by modulating the transmitted signal (Karimi, Schmid and Dehollain, 2021) with conventional modulation schemes including amplitude-shift keying, phase-shift keying, and frequency-shift keying (Trigui *et al.*, 2019), each of which has derivative subtypes. In active implants, a return link from the implant enables bidirectional communication, requiring onboard circuitry for modulation and demodulation. Active simultaneous wireless power and data transfer strategies have previously been deployed on smart orthopaedic implants to acquire in vivo data from human subjects, specifically pulse interval modulation schemes (Graichen *et al.*, 2007; Bergmann *et al.*, 2012). In passive implants, information is returned to the external reader through the same field by means of backscattering (Moore *et al.*, 2022) or load modulation (Jiang *et al.*, 2017). Whilst scarce in the literature, there are examples of passive load modulation being used to acquire data from an orthopaedic implant (Karipott, Veetil, *et al.*, 2018; Avaltroni, Nappi and Marrocco, 2021; Karipott *et al.*, 2022).

2.5.3. Sensing

Sensors that have been used to capture in vivo measurements from human subjects include strain gauges (Bergmann *et al.*, 1988), force transducers (Kirking *et al.*, 2006), thermistors (Bergmann *et al.*, 2012), inertial measurement units (Cushner *et al.*, 2021), and combinations thereof (Graichen *et al.*, 2007). Using these sensors, measurements of joint loads (Bergmann, Deuretzbacher, *et al.*, 2001), frictional heating (Bergmann, Graichen, *et al.*, 2001), and kinematics (Cushner *et al.*, 2021) after arthroplasty have been acquired from the hip (Bergmann, Deuretzbacher, *et al.*, 2001), knee (D'Lima *et al.*, 2006), and shoulder (Westerhoff *et al.*, 2009). Similar measurements have also been acquired from the spine following fixation (Rohlmann *et al.*, 1995) and vertebral body replacement (Rohlmann *et al.*, 2014). Proof-of-concept measurements have also been captured from sensor-embedded implants in benchtop and cadaveric tests: magnetoresistive sensors for joint kinematics measurement (Arami *et al.*, 2013; Arami, Vallet and Aminian, 2013) and loosening detection (Khokle *et al.*, 2019); accelerometers for loosening detection (Arami *et al.*, 2018); thermistors for temperature measurement as a proxy for infection (Karipott, Veetil, *et al.*, 2018); inductive proximity sensors for loosening detection (Mohammadbagherpoor *et al.*, 2020); and strain gauges for ligament tension (Karipott *et al.*, 2022).

Passive sensing mechanisms, which are amenable to battery-free, processor-free implants, have become increasingly common in the recent literature on the premise that these sensors are more suitable for mass clinical adoption (Wachs *et al.*, 2013; Karipott, Veetil, *et al.*, 2018; Karipott *et al.*, 2022). These designs commonly employ resonant circuits formed from

inductive, capacitive, and resistive elements, where the inductive element is an embedded coil and either the capacitive or resistive element is sensitive. Measurements are recorded through changes in the resonant behaviour of the sensor.

2.6. Summary of Findings

Based on this review of the literature, the following key trends were identified, which were then used to inform the work contained in subsequent chapters,

- Arthroplasty is a widely practised, highly successful treatment for end-stage osteoarthritis; aseptic loosening and periprosthetic joint infection together account for the majority of the small number of implant failures that do occur.
- The mechanisms underpinning aseptic loosening have evolved over time; osteolysis in the periprosthetic bone has become less prevalent as debonding failures at the implant-cement interface have become more common.
- Periprosthetic joint infection is a devastating complication of arthroplasty with varying presentations depending on the virulence of the pathogen and the mode of acquisition:
 - Early-onset, acute infections, which are characterised by fever (96%) and erythema (95%), can be specifically diagnosed by temperature measurements.
 - Late-onset, chronic infections are commonly misdiagnosed as aseptic loosening and involve biofilm formations that are often recalcitrant to treatment.
- Osseointegration is essential to the long-term survival of cementless prostheses; ultrasound and electrical stimulation have both shown osteogenic potential during in vitro cultures and paired-limb animal studies, but the optimal parameters and exact mechanobiology are not completely understood.
- Instrumented implants have been used for arthroplasty research for several decades but FDA market clearance for a smart prosthesis was achieved for the first time in 2021. Recent research into passive interrogation mechanisms, which have minimal footprint on device architecture, present a potential pathway to mass clinical translation of sensing technologies.

Chapter 3

Smart Implants for Simultaneous Fixation and Infection Monitoring I: Development of a General Concept with Wireless, Battery-Free Operation

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Hall, T. A. G., Cegla, F., and van Arkel, R. J. (2021) 'Simultaneous Detection of Loosening and Infection with a Simple Smart Implant', *Orthopaedic Research Society (ORS) 2021 Annual Meeting*, held online, 12–16 February.

3.1. Introduction

Recent developments in implantable electronics are enabling researchers, clinicians, and patients to acquire health monitoring data from their implants, though rates of translation vary between medical fields (Andreu-Perez *et al.*, 2015). Uptake of smart implants in orthopaedics has been slow: market clearance for the first-and-only smart joint prosthesis (Persona IQ, Zimmer Biomet, Warsaw, IN, USA) was awarded for the first time in 2021 (FDA, 2021) despite an extensive history of research-focused instrumented implants (Rydell, 1966; Waugh, 1966; Bergmann *et al.*, 1988; Graichen and Bergmann, 1991; Graichen, Bergmann and Rohlmann, 1999; Morris *et al.*, 2001; D'Lima *et al.*, 2005). For mass-market translation in this commoditised market, any proposed smart implant concept must be inexpensive and robust with minimal footprint on current implant architecture (Ledet *et al.*, 2012, 2018) – simplicity is key.

The two leading causes of implant failure in joint replacement are aseptic loosening and periprosthetic joint infection; together these complications account for 54% of knee and 64% of hip revision procedures in the UK over the last five years (National Joint Registry, 2021). Both complications benefit from early detection to prevent progressive tissue damage, but current diagnostic protocols for aseptic loosening (Barnsley and Barnsley, 2019) and infection (McNally *et al.*, 2021) are initiated by patient self-reporting and are yet to yield simple, definitive methods for early intervention. A detection mechanism for these complications based on low-cost, small-footprint embedded electronics has the potential to accelerate diagnoses and edify treatments without impacting current implant architectures, which are already highly optimised for biomechanical performance.

Recent research has independently investigated smart orthopaedic implants for the detection of aseptic loosening (Puers *et al.*, 2000; Ruther *et al.*, 2014; Arami *et al.*, 2018; Khokle *et al.*, 2019; Mohammadbagherpoor *et al.*, 2020) and infection using elevated temperature as a proxy (Karipott, Veetil, *et al.*, 2018). This chapter presents and evaluates a general concept for simultaneous monitoring of both complications with only two implanted components: a sensor and a coil.

3.2. Concept Overview

The proposed implantable electronic system (Fig. 3.1a) consists of a shear-wave piezoelectric transducer and three inductively coupled coils: one within the implant (embedded: Ex) and two external to the body (transmit: Tx; and receive: Rx). A toneburst in the transmit circuit excites a pulse-echo response in the embedded circuit via inductive

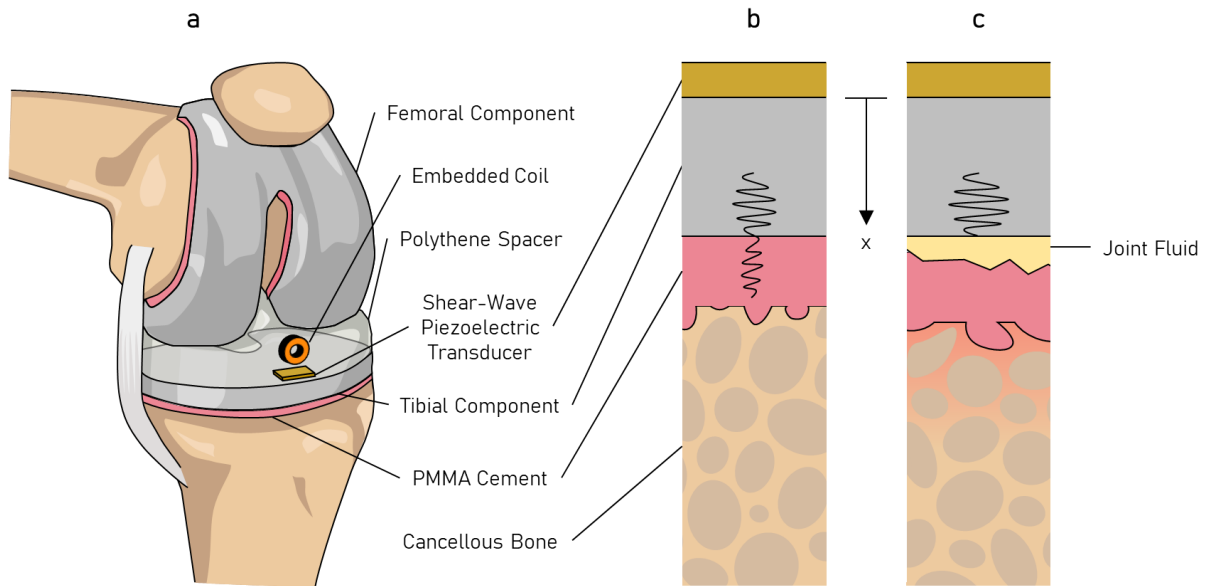


Figure 3.1. A coil and a shear-wave piezoelectric transducer are embedded within a joint prosthesis, shown as (a) an example embodiment within the tibial component of a cemented total knee replacement, to differentiate between (b) a well-fixed implant and (c) a loose implant where the cement-implant interface has debonded and been infiltrated by joint fluid.

coupling, which is picked up by the receive circuit. The majority of orthopaedic implants, such as total knees (97%), are fixed using bone cement (National Joint Registry, 2021): a polymethylmethacrylate (PMMA) filler up to 2 mm in thickness that provides a mechanical interlock between the implant and the periprosthetic bone. In a well-fixed implant, when an ultrasonic pulse hits the implant-cement interface, a fraction of its energy is reflected, and a fraction is transmitted through the interface (Fig. 3.1b). Successive echoes are recorded as the pulse continues to reverberate thereon.

Whilst aseptic loosening can occur at either the implant-cement or cement-bone interface, contemporary literature indicates a bias towards debonding at the implant-cement interface (Foran, Whited and Sporer, 2011; Arsoy *et al.*, 2013; Ries *et al.*, 2013; Hazelwood *et al.*, 2015; Kopinski *et al.*, 2016; Bonutti *et al.*, 2017; Kutzner *et al.*, 2018; Cerquiglini *et al.*, 2019; Sadauskas *et al.*, 2020; Keohane *et al.*, 2020; Murphy *et al.*, 2021), including a retrospective study of 149 revision knees in which failure was observed at the implant-cement interface in 140 prostheses (94%) (Martin *et al.*, 2021). In a debonded implant, the implant-cement interface is compromised and infiltrated by joint fluid (Sundfeldt *et al.*, 2006). Fluids do not sustain shear waves, meaning no pulse energy is transmitted through the implant-fluid interface, and all should be reflected (Fig. 3.1c). As attenuation and other losses still occur, loosening is detected as a rise in the reflected energy.

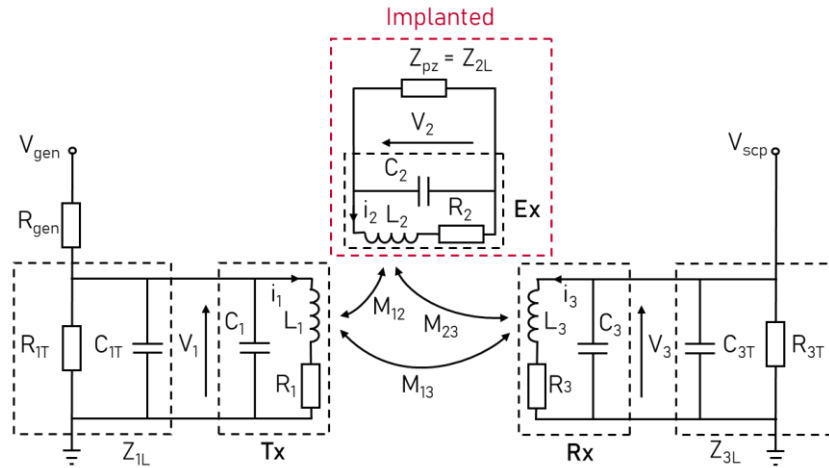


Figure 3.2. Equivalent electrical circuit of the implantable ultrasound system: impedance of the piezoelectric transducer is reduced to a single impedance, Z_{pz} ; coils in the three-port inductive link (Tx: Transmit; Ex: Embedded; Rx: Receive) are modelled using lumped parameters; tuning elements in the transmit and receive circuits are subscripted with a T; and loads on each coil are subscripted with an L.

The arrival time of successive echoes is determined by the ultrasonic shear-wave velocity, which follows a linear relationship with temperature (Wang, Zou and Cegla, 2018). Calibration of the arrival time to temperature allows the system to function as an internal thermometer. Fever is a highly specific (96%) symptom of acute infection (Shohat *et al.*, 2019): previous thermographic imaging studies have suggested an elevated skin surface temperature of +1 °C as indicative of infection (Romanò *et al.*, 2012, 2013).

In practical application, this wireless, battery-free concept could be applied as a platform technology to a broad range of cemented arthroplasties, including partial and total knees, shoulders, ankles, and elbows, subject to two constraints: the transducer must be mounted (i) normally incident to the interrogated implant interface and (ii) at sufficient distance for a complete pulse-echo response. The coil should be positioned independently for best coupling to external circuitry.

3.3. Materials and Methods

As embodiment of the concept is flexible dependent on implant architecture, fundamental proof-of-concept was demonstrated in a model representative of an orthopaedic implant using an embedded coil of the smallest practicable diameter (10 mm). In addition, the piezoelectric transducer and the inductive link were analysed as electrical networks (Fig. 3.2) with consideration of real-world effects (tissue and metal shielding) thereby characterising the system for future implant-specific embodiments.

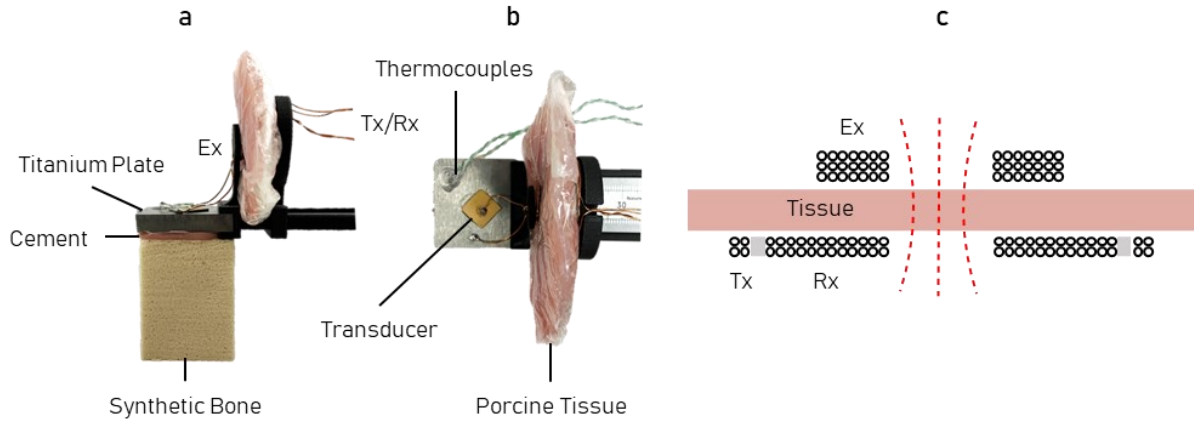


Figure 3.3. Experimental setup representative of a transducer-embedded cemented orthopaedic implant from (a) side-on and (b) top-down views, along with (c) winding diagram for the three-coil inductive link.

3.3.1. Experimental Setup

A representative model (Fig. 3.3) of a cemented orthopaedic implant was used to investigate the effects of tibial debonding and temperature variation on the pulse-echo response of a shear-wave piezoelectric transducer. The transducer (CSAP03, Noliac, Kvistgaard, Denmark; dimensions: $10 \times 10 \times 0.5 \text{ mm}^3$; resonant frequency: 1.75 MHz) was bonded to a titanium plate (dimensions: $30 \times 30 \times 5.7 \text{ mm}^3$) using epoxy adhesive (Loctite Double Bubble, Henkel, Düsseldorf, Germany). The coil was fixed to synthetic cancellous bone (1522-02, Sawbones Europe, Limhamn, Sweden; dimensions: $30 \times 30 \times 40 \text{ mm}^3$) via a layer of PMMA (Simplex, Kemdent, Swindon, UK; thickness: 2 mm) that was mixed according to the manufacturer's instructions. The ultrasonic properties of this synthetic bone have previously been shown to reflect those of organic cancellous bone (Hoffmeister *et al.*, 2018).

Wireless measurements were acquired using coils wound concentrically within nylon casings (Onyx, Markforged, Watertown, MA, USA). Coils (Fig. 3.3c; Table 3.1) were dimensioned by inner and outer diameter, D^I and D^O respectively, number of turns per layer, N^T , and number of layers, N^L . Enamelled copper wire (CUL 100/0,40, BLOCK, Verden, Germany; diameter: 0.4 mm) was used to wind each coil; the transmit and receive coils were separated by thin layers (0.5 mm) of PVC. The number of turns increased from the transmitter to the embedded coil to the receiver, stepping up voltage. Electrical contact from the embedded coil to the transducer was established via soldered connections to the free electrode and the underlying titanium plate (Fig. 3.2b). The outer diameter of the embedded coil was set to 10 mm to test system performance with a challengingly small coil (total volume of embedded components: 0.13 mm^3). In practice, larger diameters will be possible

on most orthopaedic implants. Porcine musculoskeletal tissue (sourced from the food chain) was used to simulate patient anatomy.

Table 3.1. Coil specifications.

i	Coil	D_i^I (mm)	D_i^O (mm)	N_i^T (-)	N_i^L (-)
1	Transmit (Tx)	26.0	27.7	2	2
2	Embedded (Ex)	3.8	10.0	3	7
3	Receive (Rx)	14.5	25.0	2	12

3.3.2. Measurement Acquisition

Pulse-echo responses (Fig. 3.4) were initiated with a five-cycle toneburst (centre frequency: 2 MHz) and recorded (sampling frequency: 50 MHz) using a portable, USB-powered oscilloscope (Handyscope HS5, TiePie Engineering, Sneek, Netherlands). Each measurement consisted of 10,000 averages recorded at 40 μ s intervals (25 kHz; total acquisition time: 0.4 s). Wireless signals were amplified pre-sampling by 40 dB (WaveMaker-Duet, Macro Design, London, UK) and filtered post-sampling by a fifth-order Butterworth filter (bandpass: 1.6–2.4 MHz). Reference temperature measurements were acquired using two Type K thermocouples (409–4908, RS Components, Corby, UK), mounted on the upper and lower sides of the titanium plate, and a digital data logger (TC-08, Pico Technology, St Neots, UK).

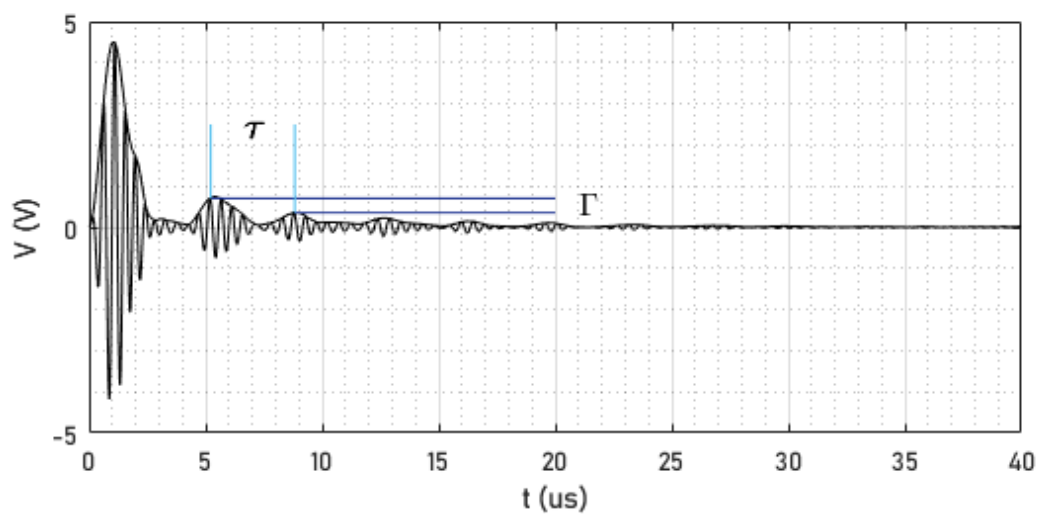


Figure 3.4. A directly acquired pulse-echo response for the well-fixed state, which has been annotated for amplitude ratio, Γ , and arrival time, τ .

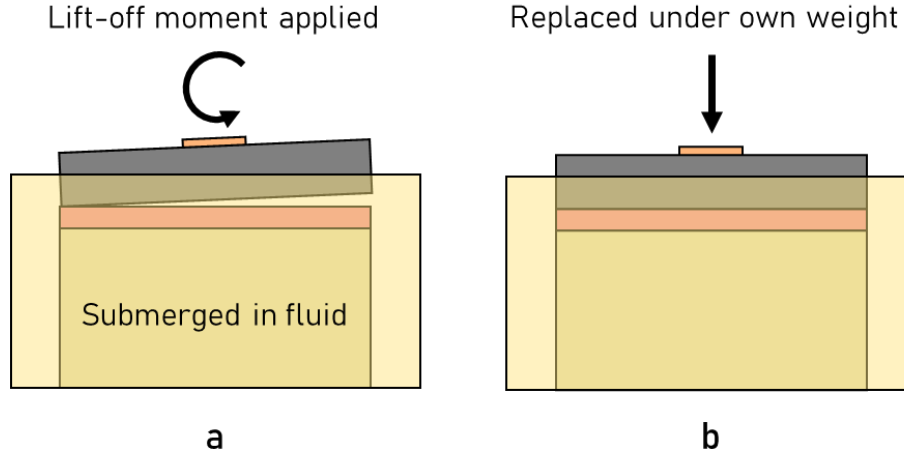


Figure 3.5. Well-fixed measurements were acquired with the setup submerged in fluid; loosening was simulated by (a) debonding the titanium plate from the cement with a lift-off moment; and loosened measurements were acquired with (b) the plate replaced and resting under its own weight.

Implant Fixation

Loosening was detected using the amplitude ratio, Γ , of the second echo relative to the first. This ratio was calculated using Hilbert envelopes, H , as

$$\Gamma = \frac{\max(H(E_2(t)))}{\max(H(E_1(t)))}, \quad (3.1)$$

where $E_1(t)$ and $E_2(t)$ are the isolated first and second echoes with the rest of the signal zeroed. Measurements for amplitude ratio ($n = 100$) were recorded when wired and wireless at several coil separations (2, 3, 4, 5, 6, 8, 10, 12 and 15 mm): first for the well-fixed implant state and again once loosened. Loosening was simulated with a lift-off moment that completely debonded the titanium from the PMMA (Fig. 3.5); the loose implant was maintained in contact with the cement under its own weight for subsequent measurements. In both states, the setup was submerged in phosphate-buffered saline to a level just above the implant-cement interface, allowing for joint fluid ingress.

Temperature Measurement

Temperature was calibrated to the arrival time, τ , between the first and second echoes. Arrival time was determined by cross-correlating the isolated first and second echoes, $E_1(t)$ and $E_2(t)$ respectively, with the rest of the signal zeroed. Gradient-based interpolation and upsampling up to 1 GHz was used to increase the resolution of the arrival time measurements. It was anticipated that arrival time would linearly correlate with temperature.

Calibration of the arrival time to temperature was performed at 5 mm coil separation with 10,000 averages per data point. To avoid thermal gradients, the setup was enveloped in insulating glass wool, then slowly heated and cooled through a 26–40°C temperature range over a period of six hours, recording data every 10 s. Reference temperature was measured by averaging the recordings from the two thermocouples. With the system at steady state, 100 wireless measurements of arrival time were recorded for each coil separation, using the calibration to recover temperature from the echo response. Error was computed between the ultrasonic measurement of temperature and the thermocouple reference measurement.

Signal-to-Crosstalk Ratio

The effect of the transmission distance between the external hardware and the embedded circuit was investigated through signal-to-crosstalk ratio (SXR). Transmission via the embedded circuit was considered the signal and direct transmission from transmit to receive was considered the crosstalk. First, the crosstalk, X , was recorded without the embedded circuit present. Then, the signal, S , at each coil separation was taken as the mean response of 100 measurements minus the crosstalk. The SXR was computed across the first and second echoes, bounded by t_1 and t_2 , using Hilbert transforms as

$$\text{SXR} = 20 \log_{10} \left(\frac{\int_{t_1}^{t_2} H(S(t)) dt}{\int_{t_1}^{t_2} H(X(t)) dt} \right). \quad (3.2)$$

Signal-to-Noise Ratio

The relationship between SNR and coil separation was quantified with 5,000 averages per measurement. The effect on SNR of increasing the number of averages per measurement, N_a , was investigated at 5 mm coil separation. SNR for each data point was computed from 100 consecutive amplitude ratio/arrival time measurements:

$$\text{SNR} = 20 \log_{10} \left(\frac{\mu}{\sigma} \right), \quad (3.3)$$

where μ and σ denote the mean and standard deviation respectively.

3.3.3. Piezoelectric Transducer Modelling

The shear-mode piezoelectric transducer was modelled in one dimension to determine its impedance, Z_{pz} , in the Fourier domain. The acoustic stacks for the well-fixed (Fig. 3.1b) and debonded (Fig. 3.1c) implants were converted into electrical network analogues (Fig. 3.6). Force, F , and velocity, v , on either side of the piezoelectric transducer were modelled in relation to the voltage, V , and current, i , via an impedance matrix (Auld, 1973),

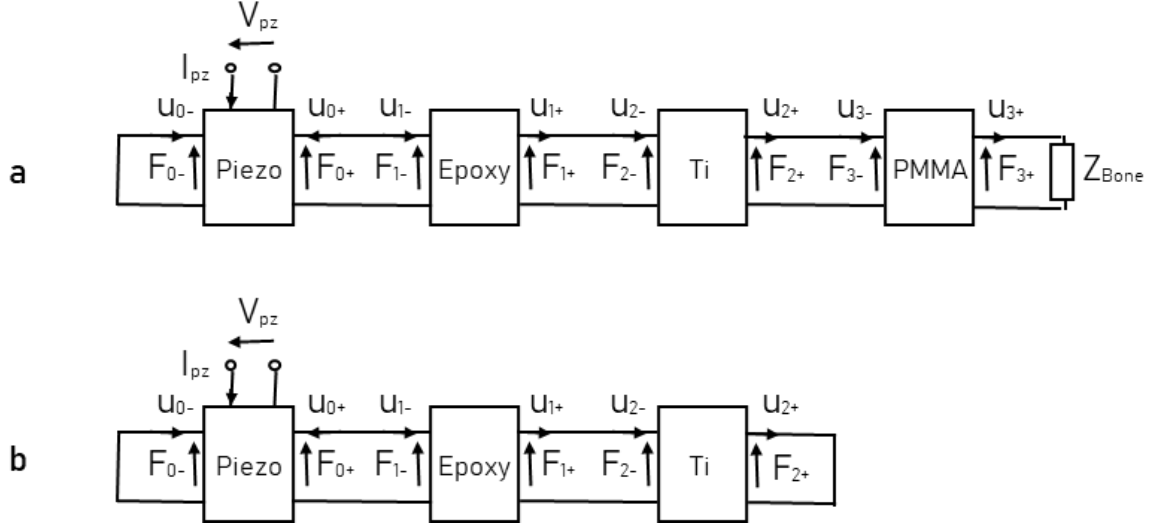


Figure 3.6. Electrical network analogues of (a) a well-fixed implant and (b) a debonded implant.

$$\begin{bmatrix} \hat{F}_{0+} \\ \hat{F}_{0-} \\ \hat{V}_{pz} \end{bmatrix}(\omega) = \begin{bmatrix} -jAZ_0 \cot kd_0 & -jAZ_0 \csc kd_0 & h_{x5}/j\omega \\ -jAZ_0 \csc kd_0 & -jAZ_0 \cot kd_0 & h_{x5}/j\omega \\ h_{x5}/j\omega & h_{x5}/j\omega & 1/j\omega C_0 \end{bmatrix} \begin{bmatrix} \hat{v}_{0+} \\ \hat{v}_{0-} \\ \hat{i}_{pz} \end{bmatrix}(\omega), \quad (3.4)$$

where A is the area of the transducer, Z_0 is the complex characteristic impedance of the layer incorporating attenuation losses (Wilcox *et al.*, 1998), k is the complex wavenumber incorporating attenuation losses (Wilcox *et al.*, 1998), d_0 is the thickness of the transducer, h_{x5} is a shear piezoelectric constant, and C_0 is the clamped capacitance of the transducer.

The force and velocity in elastic layers was modelled using a transfer matrix (Auld, 1973),

$$\begin{bmatrix} \hat{F}_{l+} \\ \hat{u}_{l+} \end{bmatrix}(\omega) = \begin{bmatrix} \cos(kd_l) & -jAZ_l \sin(kd_l) \\ (1/jAZ_l) \sin(kd_l) & \cos(kd_l) \end{bmatrix} \begin{bmatrix} \hat{F}_{l-} \\ \hat{u}_{l-} \end{bmatrix}(\omega). \quad (3.5)$$

Transfer matrices of consecutive layer were pre-multiplied to produce transfer matrices across multiple layers. In the well-fixed implant, the network was terminated after the cement layer with the characteristic acoustic impedance of bone – modelled as an infinite layer. In the loosened state, the network was instead terminated with zero acoustic impedance (shorted) after the titanium layer as the infiltrating joint fluid cannot sustain shear waves. The open side of the transducer was also shorted. These boundary conditions enabled the collapse of the impedance and transfer matrices to a single input impedance for each state, i.e. $Z_{pz} = \hat{V}_{pz}(\omega)/\hat{i}_{pz}(\omega)$. Electrical losses were incorporated into the transducer impedance using a parallel resistance of $1/(\omega C_0 \tan \delta_E)$ (Brown and Carlson, 1989).

Modelled impedances (acoustic properties in Table 3.2) were verified against those measured with a precision impedance analyser (4294A, Agilent Technologies, Santa Clara,

CA, USA) in the 0.01-10 MHz frequency range for (i) the transducer in a free-free condition, (ii) the transducer mounted on the titanium plate without cement, which is equivalent to the debonded state, and (iii) the transducer in the experimental setup representative of a well-fixed, cemented implant (Fig. 3.3). Monte Carlo simulations ($n = 1000$) were performed independently for an assumed variation in cement layer thickness ($d \sim N(\mu = 2 \text{ mm}, \sigma = 0.5 \text{ mm})$) and the measured variation in mechanical properties of cancellous bone (Töyräs *et al.*, 2002; Munford *et al.*, 2020), corresponding to effects of surgical technique and patient anatomy respectively.

Table 3.2. Modelling parameters for PZT, epoxy, titanium, PMMA bone cement, synthetic cancellous bone, and organic cancellous bone.

Material	ρ (kg/m ³)	c_{44}^D (GPa)	$\tan \delta_M$ (10 ⁻⁴)	ϵ_{11}^S (10 ⁻⁸ F/m)	h_{15} (10 ⁸ V/m)	$\tan \delta_E$ (10 ⁻⁴)
Modified PZT (NCE51)	7850	43.7	125	8.02	17.0	150
Epoxy	1140	4.0	1000	-	-	-
Titanium (cp-Ti)	4500	43.0	100	-	-	-
PMMA	1180	1.56	450	-	-	-
Synthetic Bone (Polyurethane Foam)	240	0.033	~1000	-	-	-
Organic Bone (Cancellous Tibia)	50-1000	0.008-0.04	400-1400	-	-	-

3.3.4. Inductive Link Modelling

The inductive link (Fig. 3.2) consisted of three coils: transmit (Tx), embedded (Ex), and receive (Rx), which were numbered 1, 2, and 3 respectively. The standard lumped parameter model (Massarini, Kazimierczuk and Grandi, 1996) was used to model each coil: an inductance, L_i , and mutual inductances to the other coils, M_{ij} , in series with a parasitic resistance, R_i , both of which are parallel to a parasitic capacitance, C_i , plus mutual inductances, M_{ij} . In this analysis, all coils were considered to be multi-layered solenoids wound from solid filament wire to match the proof-of-concept system – alternative geometries and wire types (e.g. Litz wire) are possible on actual implants.

Lumped Parameter Impedances

Self-inductance and mutual inductance were calculated from the constituent loops of each coil (RamRakhyani, Mirabbasi and Chiao, 2011):

$$L_i = \sum_{p=1}^{N_i} L_p + \sum_{p=1}^{N_i} \left(\sum_{q=1, p \neq q}^{N_i} M_{pq} \right) \quad (3.6) \quad \text{and} \quad M_{ij} = \sum_{p=1}^{N_i} \left(\sum_{q=1}^{N_j} M_{pq} \right), \quad (3.7)$$

where the self-inductance, L_p , for a circular coil with loop radius, r_p , and wire radius, $a_p \ll r_p$, is

$$L_p = \mu_0 r_p \left[\ln \left(\frac{8r_p}{a_p} \right) - 2 \right] \quad (3.8)$$

and the mutual inductance, M_{pq} , for concentric circular loops with separation, d_{pq} , is

$$M_{pq} = \mu_0 \sqrt{r_p r_q} \left[\left(\frac{2}{\alpha} - \alpha \right) K(\alpha) - \frac{2}{\alpha} E(\alpha) \right], \quad (3.9)$$

where

$$\alpha = \sqrt{\frac{4r_p r_q}{(r_p + r_q)^2 + d_{pq}^2}} \quad (3.10)$$

and $K(\alpha)$ and $E(\alpha)$ are complete elliptic integrals of the first and second kind.

The frequency-dependent AC resistance, R_i , was calculated from the DC resistance, R_i^{DC} , and the skin depth, δ_i , of each coil as (Lee, 2003)

$$R_i = R_i^{DC} \frac{a_i}{2\delta_i}, \quad (3.11)$$

where

$$R_i^{DC} = \frac{l_i}{\sigma \pi a_i^2}, \quad (3.12)$$

$$\delta_i = \frac{1}{\sqrt{\pi f \mu_0 \mu_r \sigma}}, \quad (3.13)$$

and l_i is the total length of the coil, σ is the conductivity of the wire, f is the excitation frequency, μ_0 is the permeability of free space, and μ_r is the relative permeability of the wire.

The parasitic capacitance of each coil was calculated using the model for tightly wound coils with a uniform square packing pattern (Massarini and Kazimierczuk, 1997; Yang, Liu and Basham, 2007)

$$C_i = \frac{1}{(N_i^T N_i^L)^2} \left[C_i^T (N_i^T - 1) N_i^L + C_i^L (N_i^L - 1) \sum_{k=1}^{N_i^L} (2k - 1)^2 \right], \quad (3.14)$$

where the turn-to-turn capacitance is

$$C_i^T = \epsilon_0 \epsilon_r \int_0^{\frac{\pi}{4}} \frac{2\pi \bar{r}_i a_i}{\varsigma + \epsilon_r a_i (1 - \cos \theta)} d\theta, \quad (3.15)$$

the layer-to-layer capacitance is

$$C_i^L = \epsilon_0 \epsilon_r \int_0^{\frac{\pi}{4}} \frac{4\pi \bar{r}_i a_i}{2\varsigma + 2\epsilon_r a_i (1 - \cos \theta) + \epsilon_r \eta} d\theta, \quad (3.16)$$

ϵ_0 is the permittivity of free space, ϵ_r is the relative permittivity of the insulating sheath, $\bar{r}_i$ is the average loop radius of the coil, ς is the thickness of the insulating sheath, and η is the separation between layers.

Frequency Response

The voltage across each inductive element in the three-port link (Fig. 3.2) is related to the through-flowing currents in the other elements in the time domain as

$$V_{L_i}(t) = L_i \frac{di_i}{dt} + \sum_j M_{ij} \frac{di_j}{dt} \quad (3.17)$$

and in the frequency domain as

$$\hat{V}_{L_i}(\omega) = j\omega L_i \cdot \hat{i}_i(\omega) + \sum_j j\omega M_{ij} \cdot \hat{i}_j(\omega). \quad (3.18)$$

Using Kirchhoff's Voltage Law to incorporate the parasitic resistances, the following matrix was generated:

$$\begin{bmatrix} \hat{V}_1 \\ \hat{V}_2 \\ \hat{V}_3 \end{bmatrix}(\omega) = \begin{bmatrix} R_1 + j\omega L_1 & j\omega M_{12} & j\omega M_{13} \\ j\omega M_{12} & R_2 + j\omega L_2 & j\omega M_{23} \\ j\omega M_{13} & j\omega M_{23} & R_3 + j\omega L_3 \end{bmatrix} \begin{bmatrix} \hat{i}_1 \\ \hat{i}_2 \\ \hat{i}_3 \end{bmatrix}(\omega). \quad (3.19)$$

Equivalent impedances for each port, e.g. $Z_1(\omega) = \hat{V}_1(\omega)/\hat{i}_1(\omega)$, were verified against precision impedance measurements (4294A, Agilent Technologies, Santa Clara, CA, USA; frequency range: 0.01-10 MHz) with 50 Ω loads on all other ports. Frequency response functions, e.g. $G_{v_2^3}(\omega) = \hat{V}_3(\omega)/\hat{V}_2(\omega)$, were calculated by considering the load on each coil, Z_{iL} .

Implant Effects

Orthopaedic implants are frequently manufactured from non-ferromagnetic metals, such as titanium and cobalt-chromium, with non-conductive polythene articular surfaces. Both the non-ferromagnetic metals and the polythene have permeabilities close to that of free space ($\mu_r \sim 1$), but alternating magnetic fields induce eddy currents within non-ferromagnetic metals. These eddy currents influence the original magnetic field, decreasing self- and mutual-inductance, and increasing effective series resistance (ESR) (J. Li *et al.*, 2017). At 1 MHz, the Q-factor of an IWPT coil is shown to decrease by a factor of ~ 10 when backed by a conductive aluminium plate (Stergiou and Zaspalis, 2016). To minimise the effect of the implant on transmission, the embedded coil was housed within a non-conductive polymer component, which was representative of a meniscal bearing in a total knee, where the free-space model remained most valid.

Tissue Effects

Orthopaedic implants are surrounded by muscle, tendon, ligament, fat, and bone. These tissues are typically free of magnetic materials, with their permeability assumed close to that of free space. As the self- and mutual inductances depend only on the geometry of the coil and the permeability of the surrounding material, effects on inductance are therefore negated (RamRakhyani, Mirabbasi and Chiao, 2011). Further, the effect of tissue on the attenuation of time-varying magnetic fields is low at frequencies below ~ 10 MHz, whilst the effect of blood is similarly low below ~ 5 MHz (Sharma and Guha, 1975). The permittivity of biological tissue is generally high: the relative permittivities of bone and muscle have been measured at orders of 10^2 to 10^4 between 1 and 10 MHz (Gabriel, Gabriel and Corthout, 1996). The self-capacitance of an implanted coil is therefore higher than that of an external coil (RamRakhyani, Mirabbasi and Chiao, 2011), but when encased within an implant structure, the effect of the tissue on the capacitance is weakened due to electrical insulation. AC resistance of a coil is generally not affected by the presence of biological tissue (RamRakhyani, Mirabbasi and Chiao, 2011). Considering the literature, the monitoring system was not expected to be insensitive to tissue and adhere to the free-space equations below 5 MHz – this assumption was verified in practice with porcine muscle tissue at a coil separation of 5 mm.

Tuning

All three coils (transmit, embedded, and receive; Fig. 3.2.) form parallel LC tank circuits, in which the self-resonant frequency, f_r , and selectivity, Q , are expressed as

$$f_{r,i} = \frac{1}{2\pi\sqrt{L_i C_i}} \quad (3.20) \quad \text{and} \quad Q = \frac{\omega L_i^{\text{eff.}}}{R_i^{\text{eff.}}}, \quad (3.21)$$

where $R_i^{\text{eff.}}$ and $L_i^{\text{eff.}}$ are the effective series resistance and inductance:

$$R_i^{\text{eff.}} = \frac{R_i}{(1 - \omega^2 L_i C_i)^2} \quad (3.22) \quad \text{and} \quad L_i^{\text{eff.}} = \frac{L_i}{1 - \omega^2 L_i C_i}. \quad (3.23)$$

These values were used to tune the system, though the inductive coupling between coils in the system splits and dampens the resonances predicted by the simple LC tank circuit model in practice. In the transmit circuit, which was voltage-driven, tuning for resonance and bandwidth did not greatly improve the frequency response of this circuit, and wireless measurements were acquired with the transmit circuit untuned.

In the embedded circuit, the behaviour of the piezoelectric transducer is mostly capacitive and acts in parallel to the parasitic capacitance. To minimise the number of implanted components, the number of turns in the embedded coil was determined by matching its inductance to the sum of its parasitic capacitance and the unloaded capacitance of the transducer, C_0 , for resonance at the centre frequency of the pulse (2 MHz).

In the receive circuit, the tuning capacitance, C_{3T} , was used to tune the self-resonant frequency to 2 MHz, whilst the parallel resistance, R_{3T} , was used to dampen resonant tails. Voltage pick-up improved with higher Q but longer resonant trails masked returning echoes, which led to an inherent trade-off. A capacitance of 440 pF and a resistance of 820 Ω of 5 were found to be a satisfactory compromise between the two competing effects; these values were used for all wireless measurements. More information on tuning is included in the addendum.

3.4. Results

3.4.1. Implant Fixation

Implant debonding led to increased amplitude ratio (Fig. 3.7); a two-way repeated-measures analysis of variance (dependent variable: amplitude ratio; independent variables: fixation and coil separation) indicated a main effect that amplitude ratio increased by 25% when loosened ($p < 0.001$). Prediction intervals for new measurements were distinct at each coil separation up to 12 mm at the 95% confidence level or better. Using a simple threshold to detect loosening, the two states were differentiated up to 8 mm at the 99.5% confidence level and up to 10 mm at 80%. Beyond 10 mm, the amplitude ratio dropped such that the two states were no longer discernible by a simple threshold

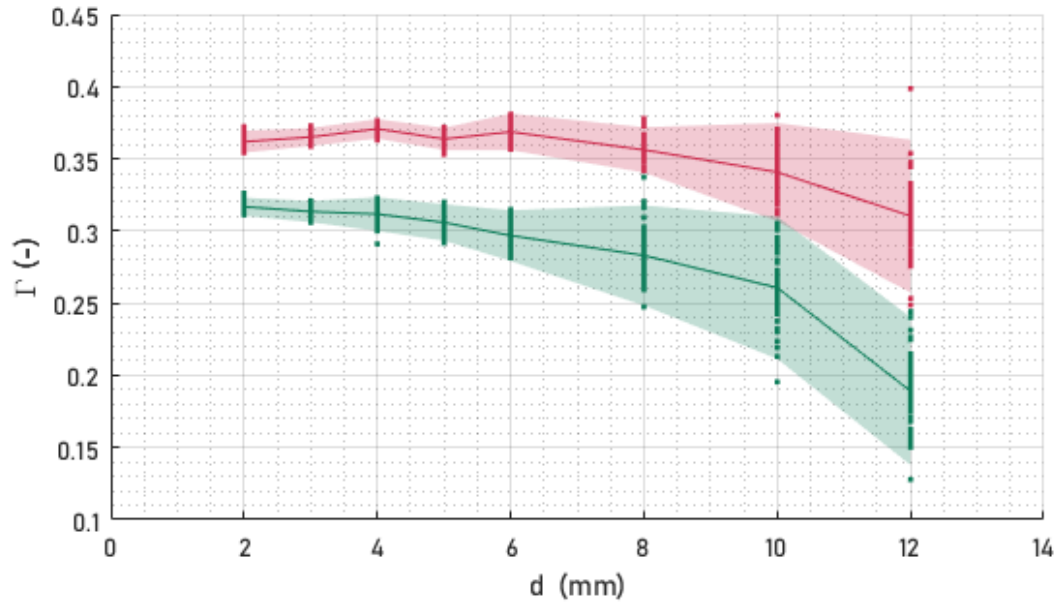


Figure 3.7. Effect of varying coil separation, d , on the amplitude ratio, Γ , with the titanium plate well-fixed (—) and debonded (—); 95% prediction intervals for new measurements are plotted.

3.4.2. Temperature Calibration

Arrival time and temperature were well calibrated by a linear relationship within the measurement range (Fig. 3.8): root-mean-square error was 0.19°C and the prediction interval for new measurements was $\pm 0.38^{\circ}\text{C}$ at the 95% confidence level. Ultrasonic measurements were accurate to within $\pm 1^{\circ}\text{C}$ of the reference temperature as measured by the thermocouple at up to 6 mm (95% confidence level; Fig. 3.9).

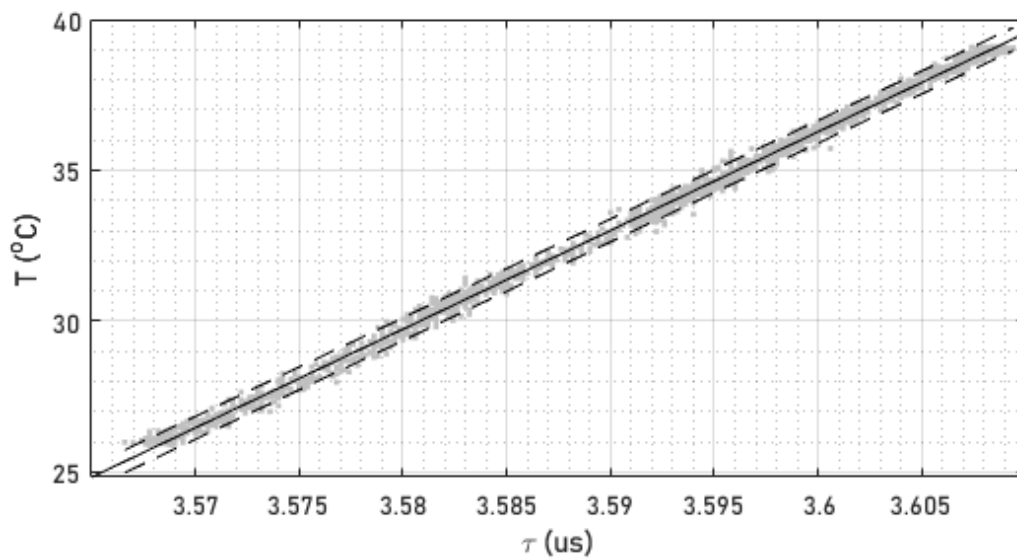


Figure 3.8. Linear calibration of arrival time, τ , to temperature, T , with 95% prediction intervals.

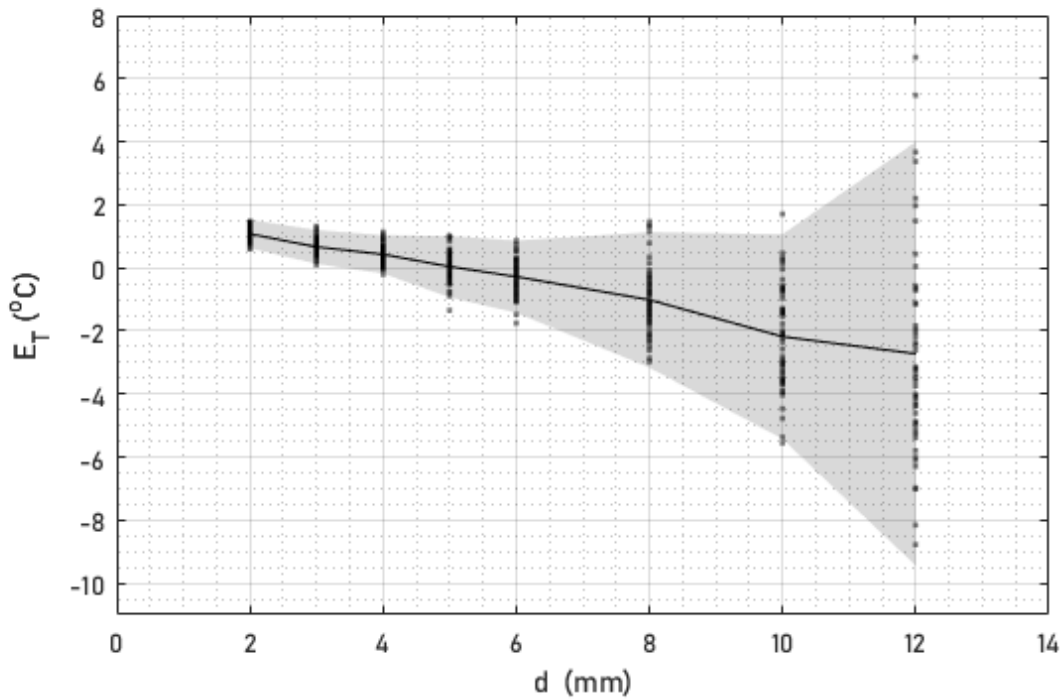


Figure 3.9. The effect of coil separation, d , on temperature measurement error, E_T , for 10,000-average measurements, shown with the trend in average measurements and 95% prediction intervals for new measurements.

3.4.3. Signal-to-Crosstalk Ratio

SXR decreased almost linearly with distance (Fig. 3.10). At low coil separations (≤ 5 mm), the signal was an order of magnitude stronger than the crosstalk ($\text{SXR} > 20$ dB). At greater separation (≥ 10 mm), the amplitude of the crosstalk was comparable to that of the echo response ($\text{SXR} < 10$ dB), restricting measurements in this range.

3.4.4. Signal-to-Noise Ratio

SNR was approximately 30 dB greater for arrival time measurements than amplitude ratio measurements. SNR for both arrival time and amplitude ratio decreased linearly with increasing coil separation up to 10 mm separation (Fig. 3.11a). Beyond 10 mm, SNR decreased more rapidly which is likely due to the crosstalk exceeding the signal (Figs. 3.10 & 3.11a). Both SNRs increased with the number of pulses by ~ 10 dB per decade (Fig. 3.11b). As pulses are consecutive, decade increases in the number of pulses are reflected in the measurement duration, leading to a trade-off between SNR and measurement practicality.

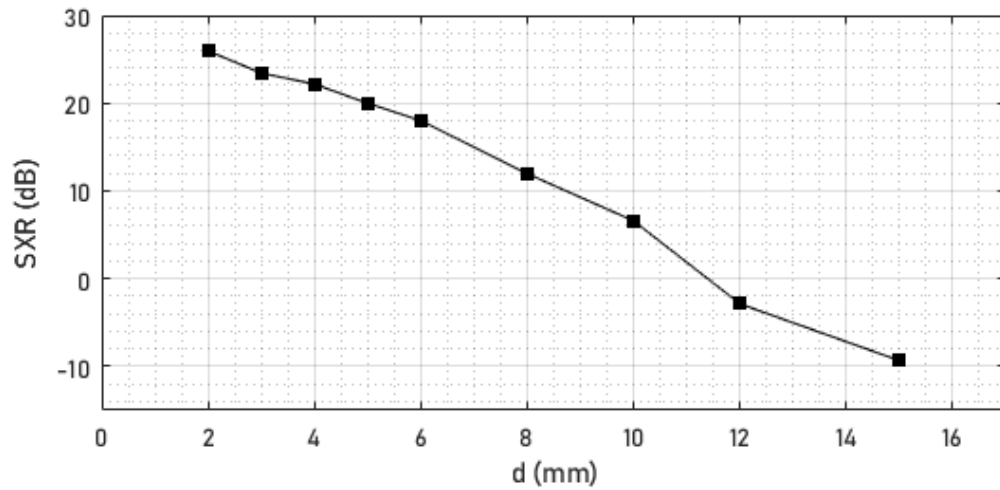


Figure 3.10. The effect of coil separation, d , on signal-to-crosstalk ratio.

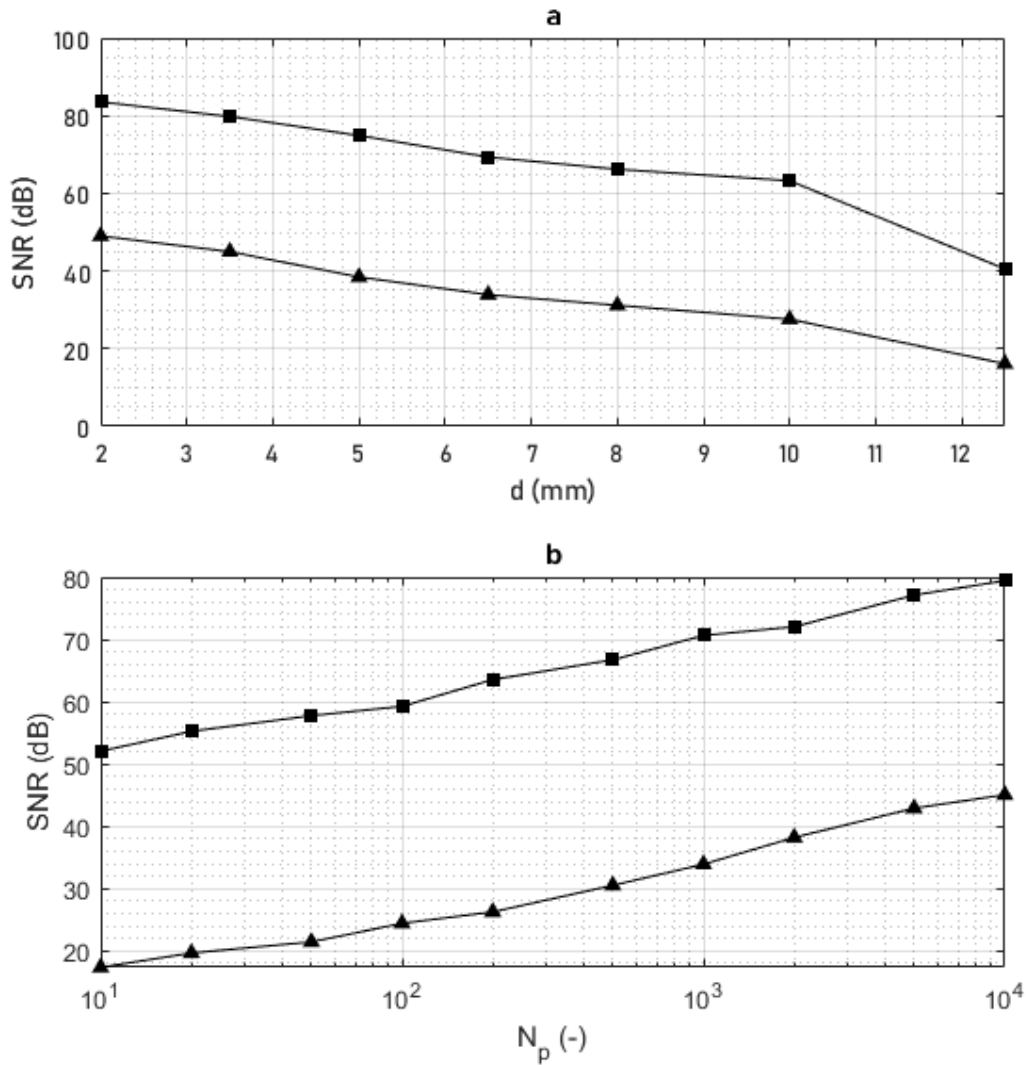


Figure 3.11. The effect on signal-to-noise ratio for measurements of amplitude ratio (Γ ; ▲) and arrival time (τ ; ■) due to (a) varying coil separation, d , with 5,000 signal averages and (b) varying the number of averaged pulse-echo responses, N_p , with the coil separation fixed at 5 mm.

3.4.5. Piezoelectric Transducer Analysis

The piezoelectric transducer model described in Section 3.3.3. was shown to accurately model the shear-mode resonance in the free-free condition as measured by a precision impedance analyser (Figs. 3.12a & -b; predicted resonance: 1.70 MHz; measured resonance: 1.69 MHz). Bonding the transducer to the titanium plate – representative of an implant – introduced secondary resonances around the primary shear-mode resonance, which were predicted by the transducer model (Figs. 3.12c & -d). The effect of cementing the titanium plate was to dampen and split these secondary resonances, which was again predicted by the model (Figs. 3.12e & -f; Fig. 3.13). Monte Carlo simulations indicated that behaviour around these secondary resonances was dependent on acoustic coupling between the titanium and cement layers, but not on the acoustic impedance of the bone (Fig. 3.14).

3.4.6. Inductive Link Analysis

Impedance spectra for each coil in the inductive link were well fitted to the lumped parameter model described in Section 3.3.4 (Fig. 3.15; fitted values: Table 3.3) in the frequency range of interest (<5 MHz). Fitted parasitic resistances for each coil exceeded those that were predicted, which were calculated without accounting for the lead wires to each coil. Fitted inductances were similar to predicted values for the transmit and embedded coils (+13% and -4.1%) and the transmit-receive coupling (-8.7%), but the self-inductance of the receive coil was considerably underestimated (-19%). Fitted parasitic capacitance values were significantly underpredicted for the embedded and receive coils, but the transmit coil was well matched. Transmission through porcine tissue did not affect wireless acquisition of the pulse-echo response.

Table 3.3. Fitted and predicted coil parameters (in bold) for each coil plus predicted mutual inductance at 5 mm coil separation between transmit/receive and embedded coil.

i	Coil	R_i (Ω)	L_i (μH)	C_i (pF)	M_{i1} (μH)	M_{i2} (μH)	M_{i3} (μH)
1	Transmit (Tx)	0.078	1.18	5.22	-	0.109	2.30
		0.046	1.04	4.23			2.52
2	Embedded (Ex)	0.112	3.05	1.63	0.109	-	0.703
		0.059	3.18	8.65			
3	Receive (Rx)	0.249	13.8	3.29	2.30	0.703	-
		0.201	17.2	25.8	2.52		

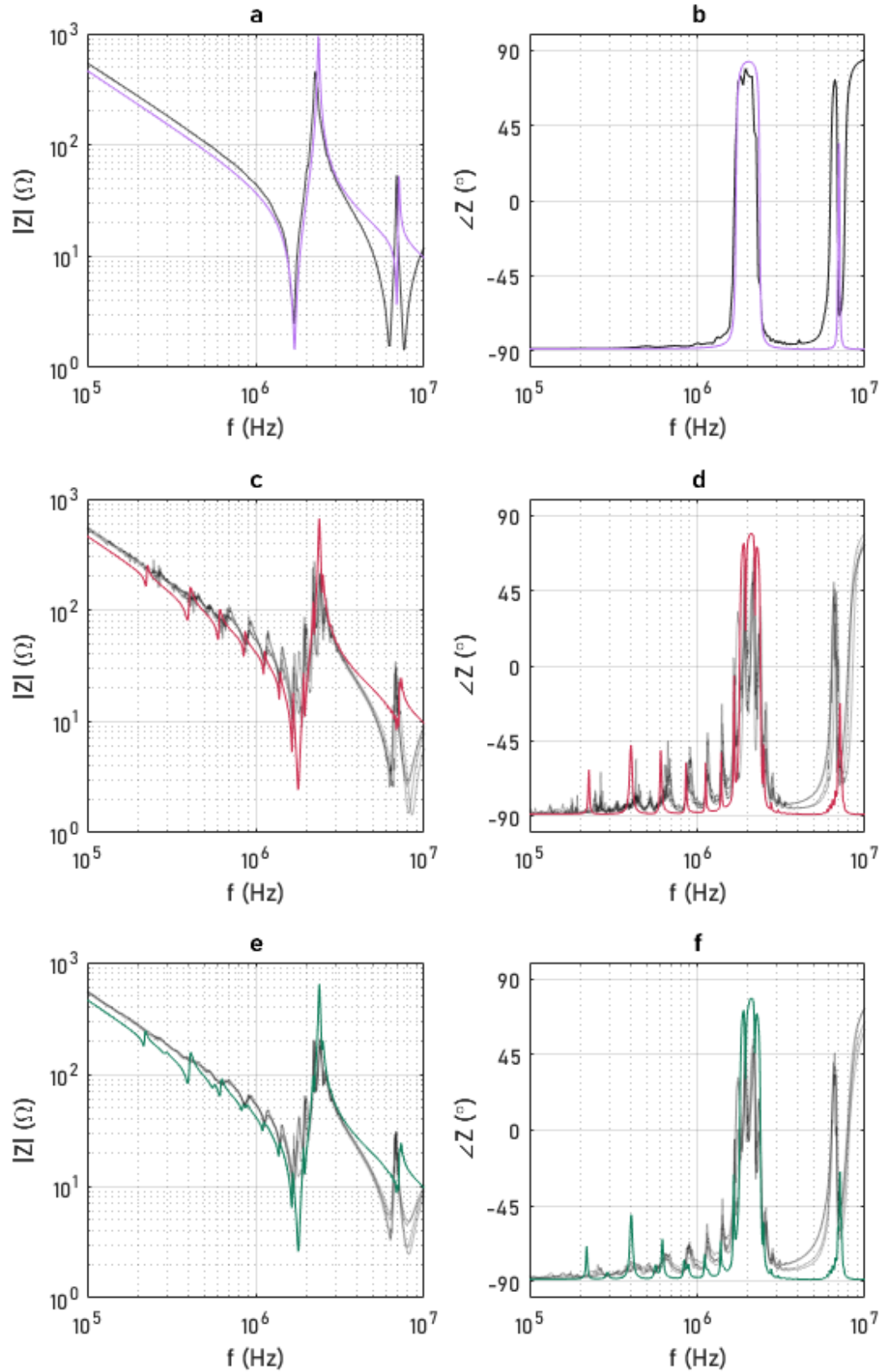


Figure 3.12. Measured (—) versus modelled impedance spectra of shear-mode piezoelectric transducer (Noliac CSAP03) in free-free (—), uncemented (—), and cemented (—) conditions.

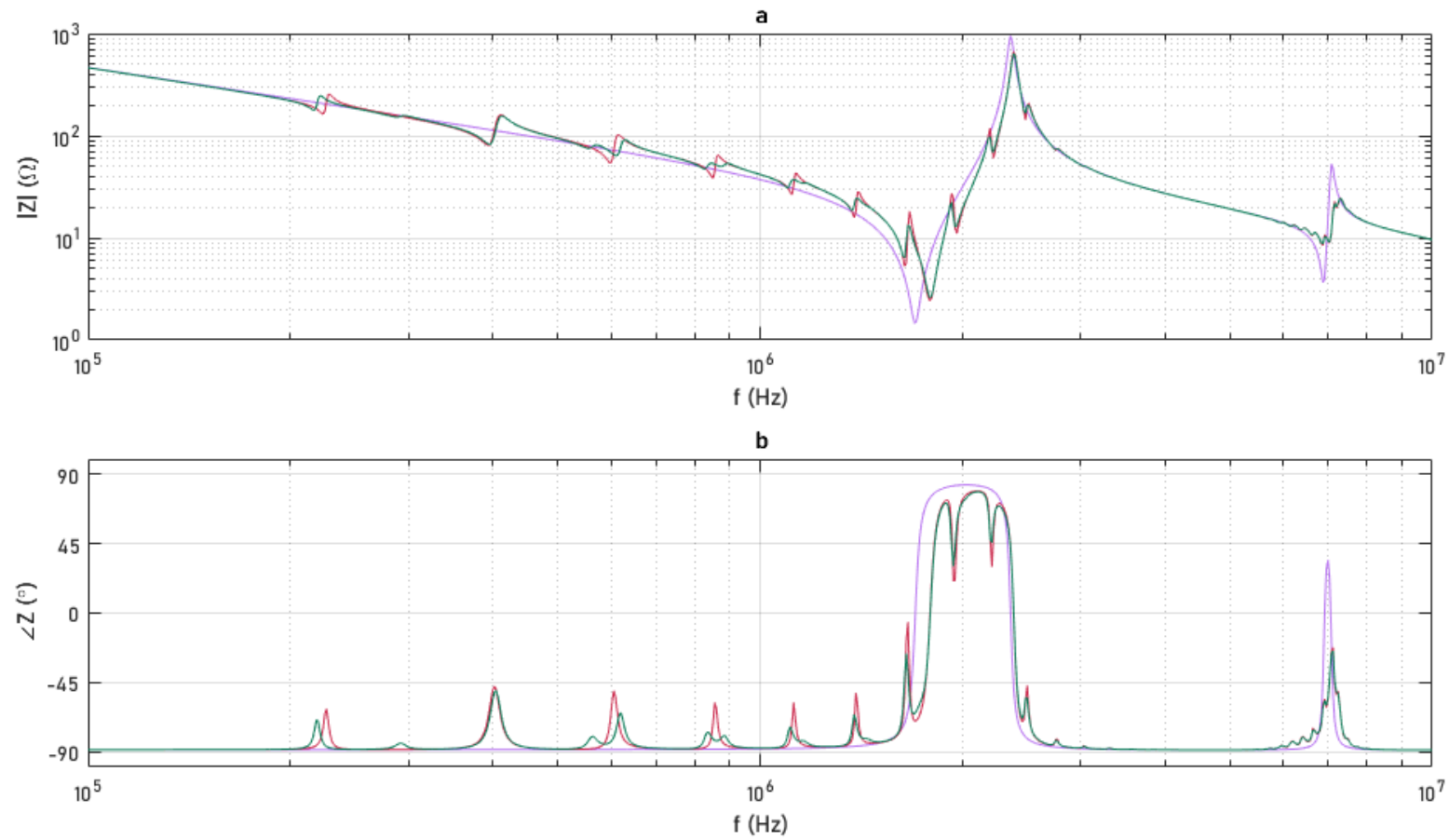


Figure 3.13. Comparison of the modelled impedance spectra (a: magnitude; b: phase) between an unbonded piezoelectric transducer (—), a piezoelectric transducer bonded to an uncemented titanium plate (—), and a piezoelectric transducer bonded to a titanium plate that is cemented into bone (—).

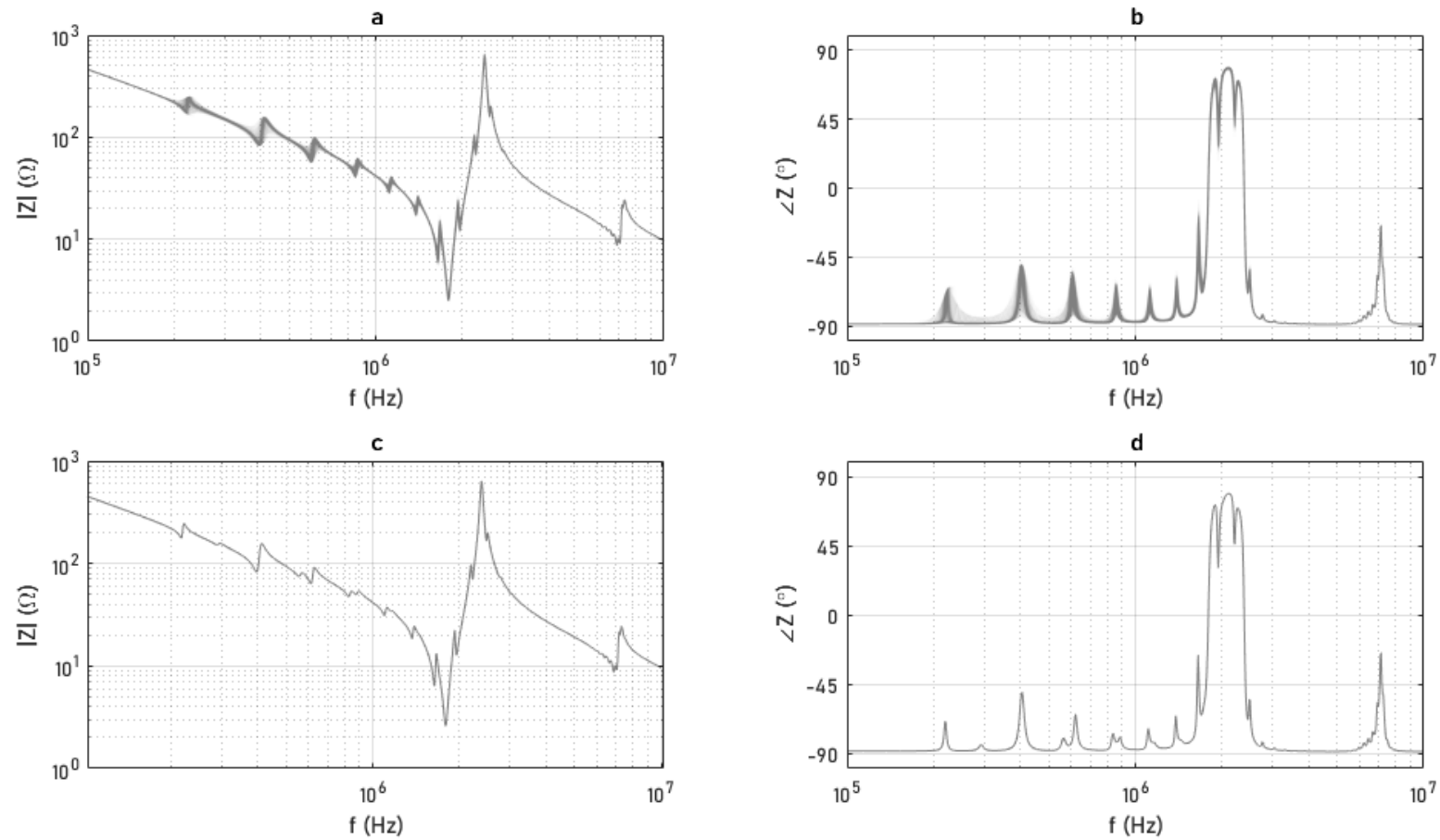


Figure 3.14. Overlaid Monte Carlo simulations ($n = 1000$) illustrating sensitivity of the impedance spectra to (a, b) modelled variation in technique surgical technique, i.e. cement layer thickness, and (c, d) modelled variation in the acoustic properties of cancellous bone.

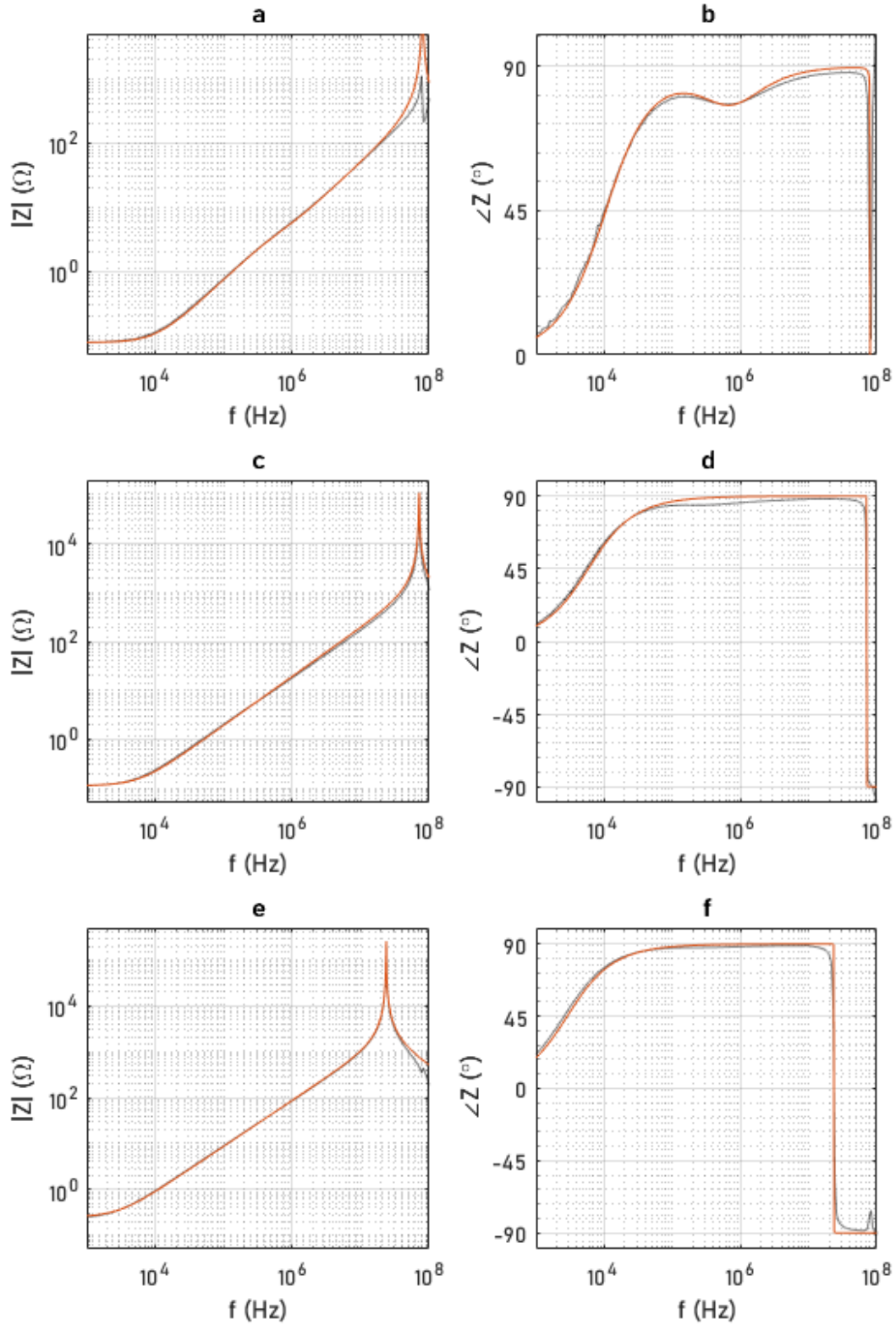


Figure 3.15. Measured (—) and fitted (—) impedance spectra for (a, b) the transmit coil with the receive coil loaded to 50 Ω , (c, d) the embedded coil alone, and (e, f) the receive coil alone.

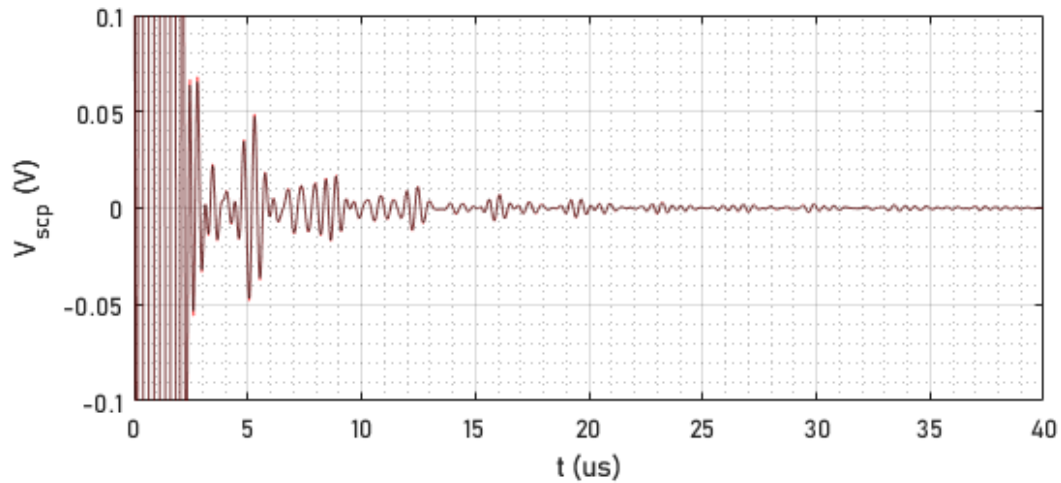


Figure 3.16. The pulse-echo response at 5 mm coil separation compared between wireless excitation through porcine tissue (—) and through air (—) without amplification or tuning.

3.5. Discussion

This study has demonstrated that simple smart implants with only two embedded electrical components could feasibly monitor loosening and temperature. To my knowledge, this is the first study to demonstrate simultaneous measurement of both phenomena within a single concept. The proof-of-concept data suggest that even with a small Ø10 mm embedded coil and a short acquisition time of 0.4 s, prediction intervals for loose and well-fixed knees were distinct up to 12 mm with 95% confidence. Temperature could be simultaneously measured at $\pm 1^\circ\text{C}$ with 95% confidence at depths up to 6 mm.

In practice, many orthopaedic implants, such as a total knee replacement, could accommodate much larger coils, which would improve pickup to the implant and extend range. Acquiring measurements over longer durations and driving stronger transmit signals would also improve accuracy and range. Furthermore, it was demonstrated that neither the behaviour of the piezoelectric transducer (through modelling) nor the inductive link (through measurement and literature) were affected by patient anatomy; anatomical effects can therefore be negated when applying the concept to a commercial implant. Metallic structures adversely affect the acquired measurements; the coil is therefore best embedded within a non-conductive polymer structure in any practical implementation. In implants where this cannot be avoided, the free-space model detailed in this study no longer applies, and it is necessary to use modelling tools, such as COMSOL Multiphysics, to simulate the behaviour of the inductive link. The transducer must be normally incident to the interrogated implant-

cement interface across a plate- or waveguide-like section and at sufficient distance for a complete pulse-echo response. Where practical, larger distances would improve measurement accuracy for temperature but not for loosening.

Measurements for the loose implant were acquired under the weight of the titanium plate rather than typical weight-bearing joint loads. Weight bearing would have negligible effect on ultrasonic properties but could have the effect of expelling fluid ingress and clamping the acoustic stack such that it behaves as if well-fixed. In practice, this adverse effect could be mitigated by acquiring measurements with the patient lying supine. The transducer provides a definitive measure of loosening, but only within its footprint. The concept is therefore not a means to detect partial loosening in its current embodiment. For implants where failure initiation is unpredictable, arrays of elements could enable earlier detection whilst the implant is still partially loosened and provide *in vivo* data to inform future implant designs. Temperature measured using the smart implant concept could be used for specific diagnoses of acute infection (Shohat *et al.*, 2019), but validation *in vivo* is required to determine its utility amidst other temperature-related phenomena, such as postoperative inflammation. Exercise elevates the temperature of an implant in the absence of infection due to frictional heating (Bergmann, Graichen, *et al.*, 2001), which could be mitigated by acquiring measurements after a period of rest. The temperature measurements could also be used intraoperatively as a control against thermal osteonecrosis: monitoring the temperature of the cement mantle whilst it sets to avoid cell damage and weakening of the periprosthetic bone (M. R. Whitehouse *et al.*, 2014).

Nuclear imaging has long been advocated as an alternative to plain radiographs to diagnose loosening, but small study sizes mean current available evidence is still at high risk of bias (Barnsley and Barnsley, 2019). A more recently explored imaging modality, electrical impedance tomography, used piezoresistive bone cement to detect loosening of a hip replacement in an experimental setup that simulated fluid ingress (Ghaednia, Owens, Keiderling, *et al.*, 2020; Ghaednia, Owens, Roberts, *et al.*, 2020). With this proposed concept measuring local implant fixation, direct performance comparisons cannot yet be drawn to these imaging modalities without *in vivo* testing of either concept. Several modified implants have previously been proposed to detect loosening (Puers *et al.*, 2000; Marschner *et al.*, 2009; Hao *et al.*, 2010; Ruther *et al.*, 2014; Arami *et al.*, 2018; Ponder, Meneghini and Anton, 2019), most of which were also evaluated under simulated conditions. Of those concepts that are passive, a magnetically excitable internal oscillator has been posited to detect loosening, with acoustic analysis determining osseointegration in rabbits *in vivo* (Ruther *et al.*, 2014). In

this study, excitation and acquisition were percutaneous, but at significantly less implantation depth (<2 mm) than the 12 mm range presented here. Inductive sensors have also recently been proposed to measure micromotion between the implant and the bone (Khokle *et al.*, 2019; Mohammadbagherpoor *et al.*, 2020), primarily for cementless arthroplasty. A biological threshold for micromotion has been widely reported for cementless arthroplasty, above which bone formation is adversely affected and loosening initiates (Jasty *et al.*, 1997; Kohli, Stoddart and van Arkel, 2021). For cemented applications, the focus of this paper, micromotion has been linked to aseptic loosening (Vanlommel *et al.*, 2011), but the relationship is less well characterised. Nevertheless, its measurement could become a useful prognostic tool in capturing the earliest stages of loosening. Practically, however, these concepts require electrical components to be implanted external to the implant, which increases procedural complexity, time, and risk. Further, these concepts have yet to be demonstrated in fully wireless operation and hence it is not possible to make a comparison of ranges. The simple smart implant approach taken in this paper has previously been explored for infection detection, using a thermistor embedded into a polymer tendon fixation screw and temperature similarly used as a proxy (Karipott, Veetil, *et al.*, 2018). The thermistor in this concept was calibrated to temperature with 0.1°C RMSE (Karipott, Veetil, *et al.*, 2018), compared to 0.19°C in this paper. As that concept is resonance-based, it demonstrated better range at a similar embedded coil diameter, with accuracy of $\pm 1^\circ\text{C}$ at up to 20 mm (Karipott, Veetil, *et al.*, 2018) versus up to 6 mm in this paper. This concept has effectively traded temperature measurement range for the capability to also measure loosening.

In only embedding two passive components, the material cost of the proposed concept would be ~1\$ per implant, removing barriers to in vivo study and eventual clinical translation. Further, with minimal modification to current implant architectures, there is potential for the concept to be classified as low-to-moderate risk, which could reduce the financial cost of regulatory approval by two-thirds (Karipott, Nelson, *et al.*, 2018). The limited set of design constraints permits flexible application to multiple cemented implants, offering the manufacturer a high degree of design freedom. Furthermore, with short measurement acquisition times, the external transmit/receive circuitry could be embodied for on-the-spot measurements or longer-term continuous monitoring. The next step for this concept is system characterisation whilst embodied within a commercial implant architecture, subsequently followed up with an in vivo trial.

3.6. Summary of Findings

This research was the first to present a smart implant concept for the simultaneous monitoring of loosening and infection:

- Pulse-echo responses could be elicited with only two embedded components (a piezoelectric transducer and a wire coil; total volume: 0.13 cm³; expected cost: ~\$1), which imposes minimal modification to contemporary implant architecture.
- Through a rise in amplitude of the reflected echoes, implant debonding was detectable at up to 12 mm coil separation.
- Through calibration of the arrival time of successive echoes, temperature (a specific indicator of acute infection) was measured with an accuracy of ± 1 °C up to 6 mm coil separation.
- Performance could be improved by increasing the number of signal averages, driving stronger signals in the transmit circuit or increasing amplification in the receive circuit, or incorporating larger coils.
- The response of the two subsystems – the piezoelectric transducer and the inductive link – are invariant with respect to patient anatomy at the frequencies of interest (<5 MHz), but the thickness of the cement layer does have an effect and the debonding response of each implant should therefore be calibrated.

Addendum: Tuning of the Wireless Response

The toneburst that was used to excite the system was a Hanning-windowed sinusoidal function, expressed as

$$x(t) = \text{Hann}(t) \cdot \sin(2\pi f_0 t),$$

where $\text{Hann}(t)$ is the Hann function is given by

$$\text{Hann}(t) = \begin{cases} \sin^2\left(\frac{\pi f_0 t}{N_c}\right), & 0 < t \leq \frac{N_c}{f_0}, \\ 0, & \text{otherwise,} \end{cases}$$

f_0 is the centre frequency of the pulse, and N_c is the number of cycles.

At 2 MHz centre frequency and 5 cycles (the acquisition parameters used for fixation and temperature measurement), the natural bandwidth of the pulse, b , was 0.8 MHz (1.6-2.4 MHz) and the corresponding selectivity was 2.5, where the selectivity is defined as

$$Q = \frac{f_0}{b}.$$

Higher numbers of cycles permit results in higher selectivity (Fig. 3.17), which benefits tuning, but the thickness of the sample limits the pulse length due to returning echoes. The measured impedances (Table 3.3) were input into a combined model of the piezoelectric transducer (Section 3.3.3) and the inductive link (Section 3.3.4); the effects of tuning capacitance and resistance in the receive circuit at 5 mm coil separation were investigated in the model and then applied in practice. The capacitance in the receive circuit (C_{3T} in Fig. 3.2) permitted tuning of the resonant frequency of the receive circuit to the centre frequency of the pulse (Fig. 3.18), whilst the resistance (R_{3T} in Fig. 3.2) was used to dampen the resonant peak introduced by tuning the capacitance (Fig. 3.19), thereby preventing resonant tails after each pulse that mask the returning echoes. Based on the simulations, it was anticipated that ~30 dB gain (one order of magnitude) in the returning signals would be achieved through tuning, which was reflected in practice (Fig. 3.20).

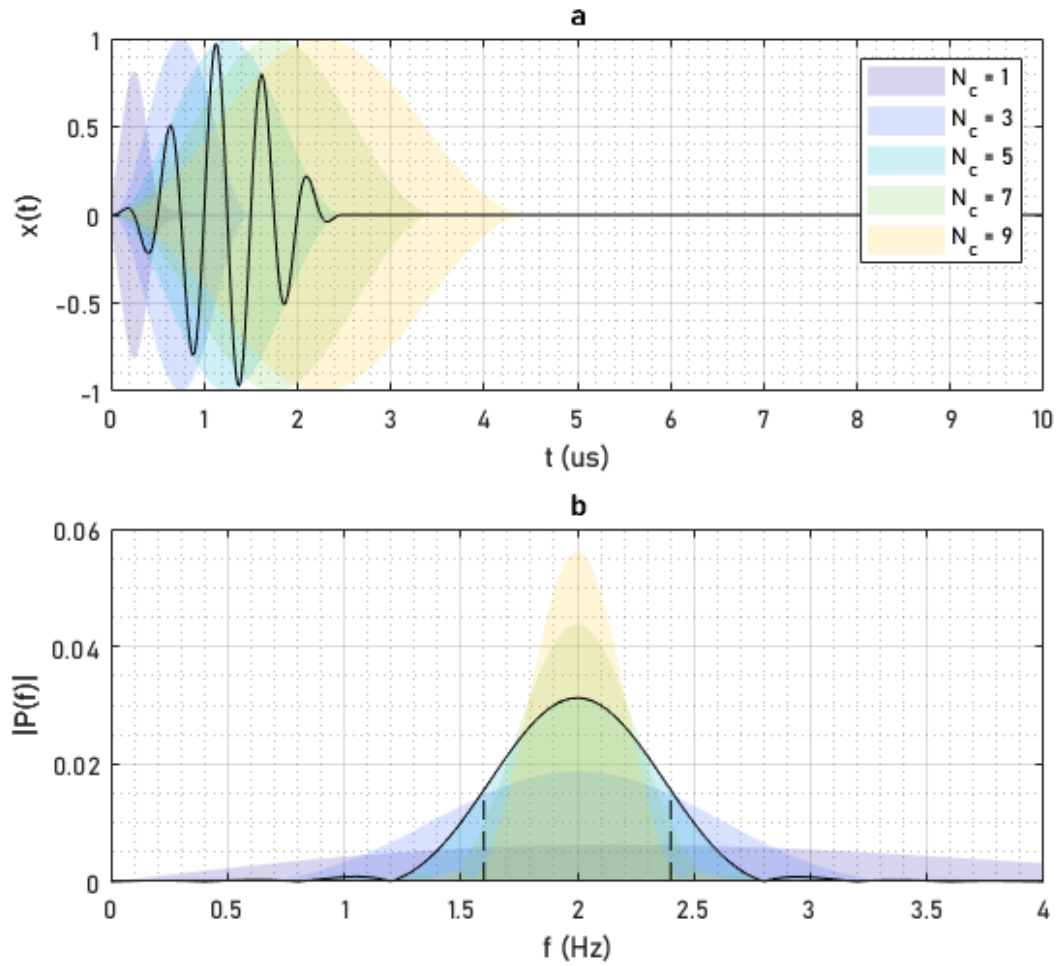


Figure 3.A1. Hanning-windowed sinusoidal pulses with different numbers of cycles: (a) signal envelopes in the time domain and (b) power spectra in the frequency domain. The raw signal, power spectrum, and bandwidth for the pulse with five cycles in shown in black.

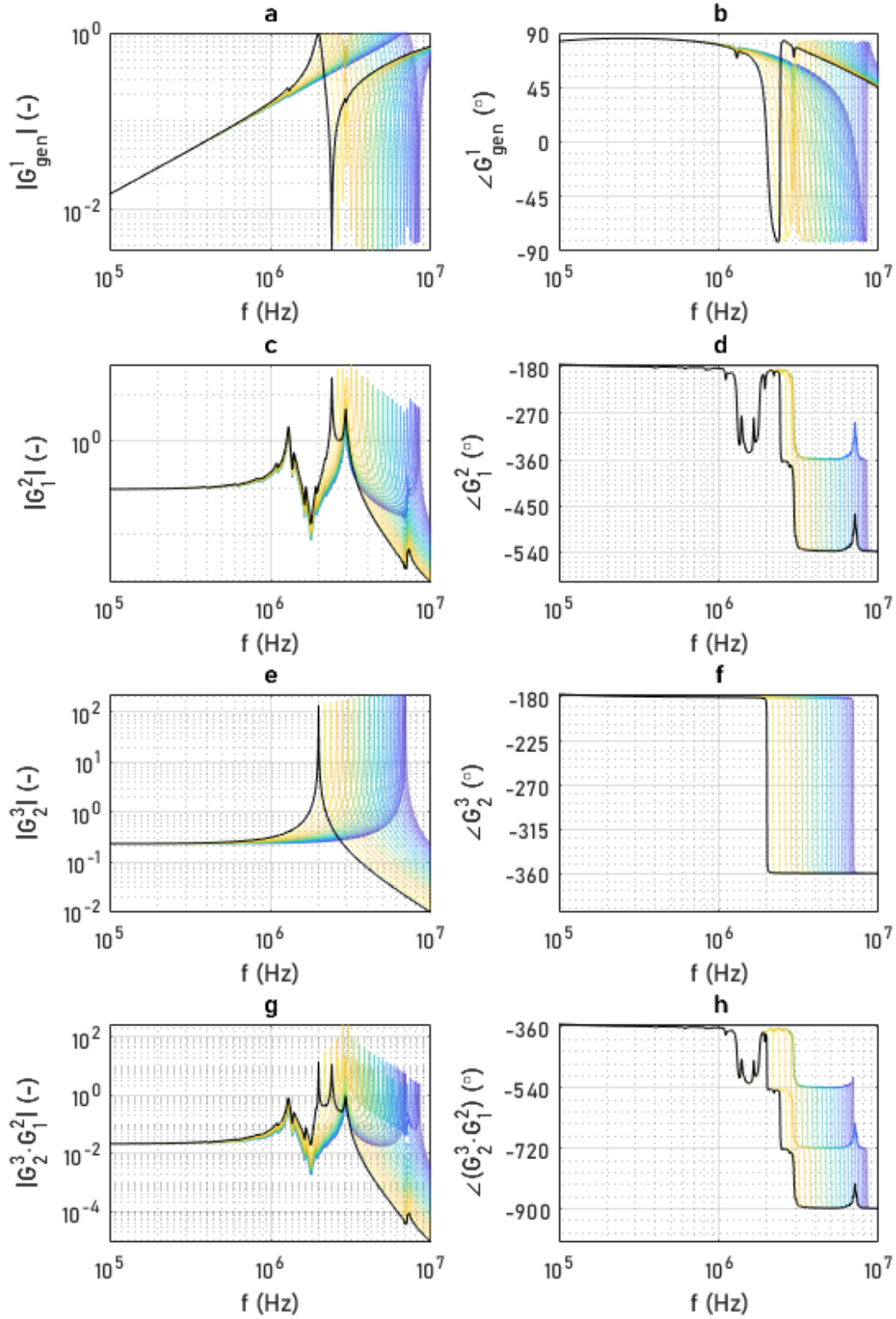


Figure 3.A2. The effect of tuning capacitance in the receive circuit from 1 pF (—) to 440 pF (—/—) on the transfer functions (a, b) from the generator to the transmit coil, (c, d) from the transmit coil to the embedded coil, (e, f) from the embedded coil to the receive coil, and (g, h) the transmit-to-embedded and transducer-to-embedded multiplied.

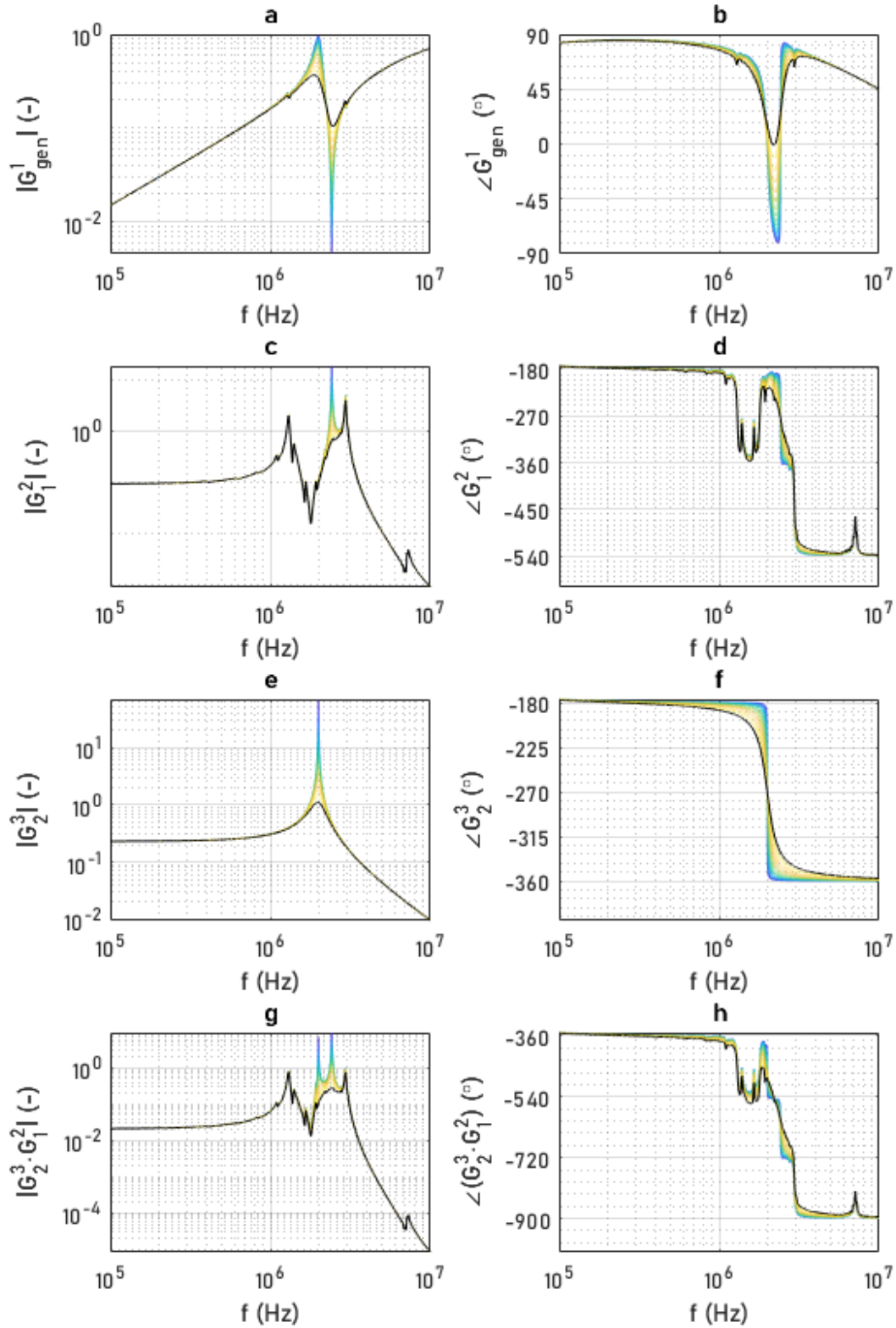


Figure 3.A3. The effect of tuning resistance in the receive circuit from $100 \text{ k}\Omega$ (—) to 820Ω (—/—) on the transfer functions (a, b) from the generator to the transmit coil, (c, d) from the transmit coil to the embedded coil, (e, f) from the embedded coil to the receive coil, and (g, h) the transmit-to-embedded and transducer-to-embedded multiplied. Capacitance in the receive circuit was tuned to 440 pF .

Chapter 4

Smart Implants for Simultaneous Fixation and Infection Monitoring II: Embodiment in Commercial Knee Replacement Systems

Acknowledgements

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Prior ethical approval was not required for the work in this chapter: animal tissue was sourced from the food chain and was declared by Dr Richard van Arkel in his annual return in compliance with Imperial College London Policy on the Use of Animals in Research.

Work from this chapter has been presented as

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4.1. Introduction

Aseptic loosening and periprosthetic joint infection are the two most common reasons for knee revision surgery in the UK, collectively accounting for more than half of procedures from 2015 to 2019 (National Joint Registry, 2021). Timely detection of these complications not only avoids their most severe, life-changing consequences, but by limiting progressive damage, the quality of treatment options is subsequently improved (Moran, Byren and Atkins, 2010; Grammatopoulos *et al.*, 2017).

As reported in Chapter 2, a bias towards aseptic failure at the implant-cement interface (tibial debonding) has been regularly reported in contemporary cemented knee arthroplasty (Foran, Whited and Sporer, 2011; Arsoy *et al.*, 2013; Ries *et al.*, 2013; Hazelwood *et al.*, 2015; Kopinski *et al.*, 2016; Bonutti *et al.*, 2017; Kutzner *et al.*, 2018; Cerquiglini *et al.*, 2019; Sadauskas *et al.*, 2020; Keohane *et al.*, 2020; Murphy *et al.*, 2021). Indeed, a 94% failure rate at the implant-cement interface was recorded in a recent retrospective study of 149 knees that were revised for aseptic loosening (Martin *et al.*, 2021). Whilst several causal factors have been implicated for this failure mode, including cementation technique (Randall *et al.*, 2019; Buller *et al.*, 2020; Hampton *et al.*, 2020), implant design (Ries *et al.*, 2013; Martin *et al.*, 2018), and surface finish (van Tol *et al.*, 2013), no common systematic mechanism or presentation has yet been identified.

Suspected aseptic loosening is conventionally examined using radiographs, which are effective in detecting gross loosening through implant malposition, radiolucency, or periprosthetic fracture. Radiographic examination, however, is either poorly sensitive to the early stages of aseptic loosening (Arsoy *et al.*, 2013; Barnsley and Barnsley, 2019) or poorly specific in determining implant stability (Chalmers *et al.*, 2017), and cannot be used alone to differentiate between septic and aseptic cases (Mandalia *et al.*, 2008). Indeed, aseptic loosening is often only confirmed intra- or postoperatively, with the preoperative assessment frequently being a misdiagnosis of a low-grade infection (Schiffner *et al.*, 2019). Several radionuclide imaging techniques – scintigraphic (Kitchener *et al.*, 2006; Claassen *et al.*, 2014) and tomographic (Delank *et al.*, 2006; Bao *et al.*, 2021; Peng *et al.*, 2021) – have been implemented to provide more conclusive diagnoses of aseptic loosening (Barnsley and Barnsley, 2019); radionuclide imaging has also been used to detect periprosthetic joint infection with reasonable success but these advanced imaging techniques are time-consuming and only available at specialist centres. Most commonly diagnosis for suspected periprosthetic joint infection consists of a workup of serological, cytological, microbiological, and histological tests (McNally *et al.*, 2021), with clinical features such as fever (elevated

temperature) and erythema considered as specific prompts for investigation of acute cases (Shohat *et al.*, 2019).

Instrumented implants have been proposed as a facile means for detecting aseptic loosening (Ruther *et al.*, 2014; Arami *et al.*, 2018; Khokle *et al.*, 2019; Mohammadbagherpoor *et al.*, 2020) and prompting investigation of periprosthetic joint infection (Karipott, Veetil, *et al.*, 2018), but no smart devices have yet translated beyond proof-of-concept into clinical practice. The concept developed in Chapters 3 has the potential to aid research and diagnosis for both conditions; passive monitoring provides a pathway to pre-empt patient self-reporting for clinical investigation and a means to elucidate the underlying aetiopathogeneses. In this chapter, the concept is embodied and evaluated within the tibial components of two commercial knee replacement systems: a total knee replacement and a partial knee replacement.

4.2. Materials and Methods

Two commercial cemented knee replacement systems were made ‘smart’ with embedded circuitry to detect tibial debonding and infection-related elevated temperature: Persona Total Knee and Oxford Fixed Lateral Partial Knee (both Zimmer Biomet, Warsaw, IN, USA). The measurement concepts were verified and an in-depth measurement sensitivity was conducted on the partial knee implant, which was expected to exhibit worse performance due to its smaller size. The debonding study was then replicated on the total knee implant to ensure that the transferability of the concept.

4.2.1. Smart Implant Design

The smart partial knee replacement (Fig. 4.1a) consisted of a standard femoral component (CoCr) and an instrumented fixed-bearing tibial component (UHMWPE/CoCr). The ultrasonic sensing element was a shear-wave piezoelectric transducer (material: NCE51; area: 5×5 mm²; resonant frequency: 3.5 MHz; Noliac, Kvistgaard, Denmark) affixed to the superior surface of the metallic subcomponent in a posterolateral position (Fig. 4.1b) using a two-part epoxy (Loctite Double Bubble, Henkel, Düsseldorf, Germany). Sized according to the method described in Chapter 3, the embedded coil was wound (15 turns) around the perimeter of the overmoulded polymer subcomponent (external groove: 1 × 1 mm) for inductive coupling to an external reader.

The smart total knee replacement similarly consisted of an unmodified femoral component (CoCr) and an instrumented fixed-bearing tibial component (UHMWPE/Ti); a piezoelectric transducer of the same specification was affixed in a medial position using the same epoxy

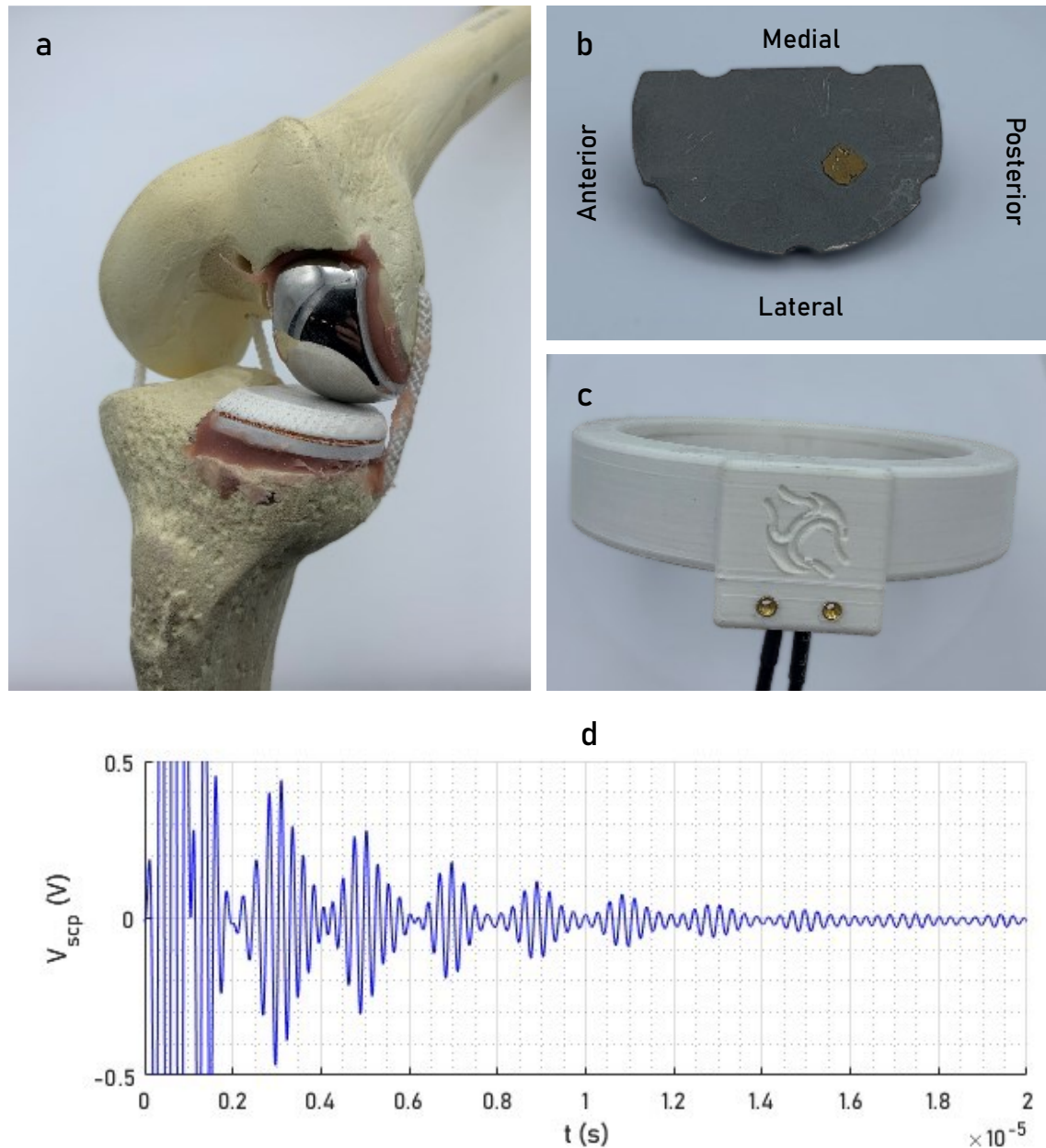


Figure 4.1. The instrumented unicondylar knee prosthesis (a) shown cemented into a synthetic bone model and (b) showing the position of the shear-wave piezoelectric transducer on the tibial component; (c) the reader used to acquire wireless pulse-echo measurements; and (d) the pulse-echo response.

technique; and the embedded coil (10 turns) was wound around the perimeter of the polymer bearing in a groove of the same dimensions. The same external reader (Fig. 4.1c) was used to acquire measurements from both implants. The reader consisted of a three-turn circular-coil transmitter (diameter: 105 mm) and a twelve-turn helical-coil receiver (diameter: 105 mm; height: 10 mm), which were used to initiate and record a pulse-echo measurement in

the embedded circuit (Fig. 4.1d). Signals of sufficient strength were acquired with this reader to negate the need for tuning.

4.2.2. Signal Acquisition and Processing

Raw signals were initiated by a five-cycle, Hanning-windowed toneburst (central frequency: 3.5 MHz) and the response was sampled at 100 MHz (Handyscope HS5, TiePie, Sneek, Netherlands). These signals were amplified (gain: 60 dB; WaveMaker Duet, Macro Design Ltd., London, UK), averaged across many measurements ($N > 5000$), bandpass-filtered (passband: 2–5 MHz), resampled at 10 GHz, and cross-correlated with the original signals. Hilbert envelopes were extracted from the processed signals and the time lag (τ) between the first and the second echoes was recorded, which was expected to exhibit a linear relationship with temperature in line with the results from Chapter 3. The fixation measurement (Γ) was computed as the arithmetic average of the relative amplitude between successive echoes for the first three echo pairs. Informed by the findings of Chapter 3, the relative amplitude was expected to increase when the implant was debonded.

In Chapter 3, it was also shown that signal-to-noise ratio (SNR) of the fixation and temperature measurements could be improved by increasing the number of signal averages. This property of the system was verified through a series of measurements acquired with an increasing number of averages: 500 to 500,000. The memory limit on the USB oscilloscope limited the number of signal averages acquired consecutively in a single recording to 5,000 (live acquisition time: 0.25 s). Higher numbers of averages were recorded as multi-batch measurements; total acquisition time inclusive of up- and download time through the serial interface was 1.25 s for 5,000-average measurements.

4.2.3. Tibial Debonding

The instrumented tibial and unmodified femoral components of both implants were cemented into synthetic knee models using polymethyl methacrylate (PMMA) bone cement (target layer thickness: ~2 mm). The knee models (Figs. 5.1a & -b), which consisted of synthetic tibia and femur (Sawbones 1146, Vashon Island, WA, USA) plus string lateral collateral, medial collateral, and posterior cruciate ligaments, were cut using standard instrumentation and surgical technique (Zimmer Biomet, 2016). Bone cement was mixed in a 1.5:1 mass-volume ratio of powder to liquid and applied whilst viscous to ensure good interdigitation at the cement-bone interface. Measurements ($n = 50$) were acquired post-cementation whilst the implants were “well-fixed”.

The implants were then loosened at the implant-cement interface with a manually applied anterior lift-off moment. Measurements ($n = 50$ per state) were acquired in each of three different states of loosening: partially debonded (loose directly beneath the transducer), fully debonded with no implant migration (in situ), and fully debonded with displacement from original position. In each measurement condition, the embedded and reader coils were coplanar with coil axes parallel to tibial proximal-distal axis, and the transmitter coil was concentric with the intercondylar eminence. The femoral component was moved through a range of flexion angles ($0-90^\circ$) for varying ligamentous tensions (uncontrolled) in each condition; each measurement for the total knee consisted of 5,000 signal averages and each measurement for the partial knee consisted of 25,000 to compensate for its smaller size (less inductive coupling).

4.2.4. Temperature Calibration

Time-lag measurements from the partial knee implant were calibrated to temperature wirelessly whilst the implant was uncemented. The setup was enveloped in insulating glass wool, heated to 45°C , and then allowed to cool over a period of four hours to 30°C . Reference temperature was recorded by a thermocouple affixed to the inferior surface of the implant. Each temperature measurement consisted of 500,000 averages: per signal (acquisition time: ~ 125 s). Time-lag and actual temperature were related using a linear fit; goodness of fit was evaluated using correlation coefficient, coefficient of determination, and root-mean-square-error.

4.2.5. Measurement Sensitivity

From the findings of Chapter 3, it was anticipated that signal strength would vary with respect to the positioning of the reader and the femoral component, both of which are variable with respect to the instrumented tibial components. Intrinsically, the near-field inductive coupling is strongly dependent on coil proximity, whilst eddy currents induced by the magnetic field in the metallic femoral component have the effect of attenuating transmission. The periprosthetic tissue also has the potential to degrade transmissions, but its effects were not expected to be as significant in the given frequency range (<10 MHz) based on the literature (Gurov and Selishchev, 2020) and the findings of Chapter 3. The extents to which these respective factors contributed to signal strength affected the temperature and fixation measurements (bias and signal-to-noise ratio) were quantified through a series of sensitivity studies on the smart partial knee implant, which was expected to be the most sensitive due to its smaller coil size and its consequent weaker coupling to the external reader. Each measurement in the sensitivity studies consisted of 5,000 signal averages.

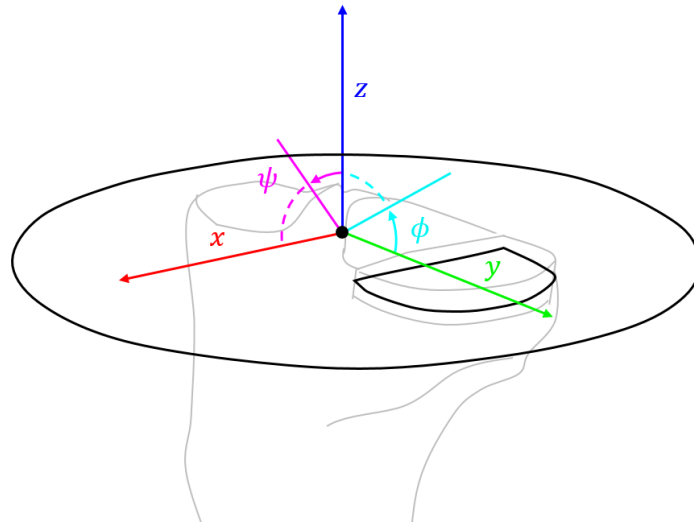


Figure 4.2. The coordinate system centred on the intercondylar eminence of the tibia used to describe the position and orientation of the reader – embedded coil and external transmitter coil in black.

The sensitivity of the system to reader positioning was investigated using a coordinate system that maps the position and orientation of the transmit coil relative to the intercondylar eminence (Fig. 5.2). Translations in x , y , and z were in the posteroanterior (PA), mediolateral (ML), and caudocranial (CC) directions respectively, whilst rotations in ϕ and ψ were angular deviations in the coil axis in the sagittal and coronal planes respectively. Rotation about the axis of the reader coils was not investigated. Position of the reader coil was varied from the neutral position ($x, y, z, \phi, \psi = 0$) in each direction independently (range: ± 10 mm / $\pm 10^\circ$; interval: 5 mm / 5°) with fifty measurements recorded in each pose. The femoral component was maintained at 30° flexion to negate implant effects and no tissue was present.

An extreme measure of sensitivity to implant positioning was determined from fifty measurements acquired with the femoral component maintained in 30° flexion and again with the femoral component removed; the external reader was maintained in the neutral position in both cases. Similarly, sensitivity to musculoskeletal tissue was established by comparing fifty measurements in the neutral position with and without a 10-millimetre-thick wall of porcine soft tissue lining the inside of the reader.

4.2.6. Statistical Analysis

Fixation measurements for each debonding state were analysed using a one-tail independent samples t-test with respect to the well-fixed state without any assumption of equal variance. Minimum sample sizes ($n = 2$) were computed a priori: statistical significance (α) and power ($1-\beta$) were set at standard values of 5% and 90% respectively; variance was recorded from 50 pre-cementation measurements and assumed homogeneous between groups; and mean

difference between well-fixed and debonded implants was estimated using the fixation results of Chapter 3.

Sensitivity to reader positioning was analysed in each measurement direction independently to determine the potential for a false-positive detection of infection or debonding. The effect on noise (variance) due to displacement was assessed using Levene's test for the equality of variance, whilst drift (mean difference) was assessed using one-way Welch ANOVAs (robust test for the equality of means; no assumption of homogeneity of variance). Sample sizes were determined a priori using a published R routine (Jan and Shieh, 2014) (α : 5%; $1-\beta$: 90%). The mean measurement and standard deviation vectors were again taken from 50 measurements recorded in the neutral position. Clinically important effect sizes were taken from the tibial debonding experiment for the loosening study and the mean differential temperature between an infected and an uninfected knee – 1.9 °C (Romanò *et al.*, 2013) – was used for temperature. The minimum sample size calculation (debonding $n = 4$; temperature: $n = 48$) modelled the scenario where the clinically important mean difference occurred at the extent of the displacement and standard deviation increased by 10%.

Two-tail independent samples t-tests were used to determine sensitivity to anatomy and the femoral component. Again, minimum sample sizes (debonding: $n = 3$; temperature: $n = 47$) were determined a priori (α : 5%; $1-\beta$: 90%), using variance from 50 measurements recorded in the neutral position, and computing effect size from the false-positive measurement error. Full details for all sample size calculations are included in the addendum to this chapter.

4.3. Results

4.3.1. Measurement Acquisition

In the series of measurements with increasing signal averages, signal-to-noise ratio for both relative amplitude (Γ) and time lag (τ) measurements were seen to increase by ~20 dB per decade increase in the number of averages (Fig. 4.3), which indicates that the central limit theorem holds for both measurements. Extracted from the linear fits, the SNR for 25,000-average measurements of relative amplitude was 42.2 dB, whilst an SNR of 75.7 dB was achieved for the 500,000-average measurements of time lag.

4.3.2. Debonding Detection

Compared to the well-fixed implant, the mean relative amplitude between successive echoes increased in all loosening states (Fig. 4.4): partially debonded beneath the transducer (+7.1%; 95% CI: +6.6 to +7.6%; $p < 0.001$), debonded in situ (+6.3%; 95% CI: +6.0% to +6.6%; $p < 0.001$), and

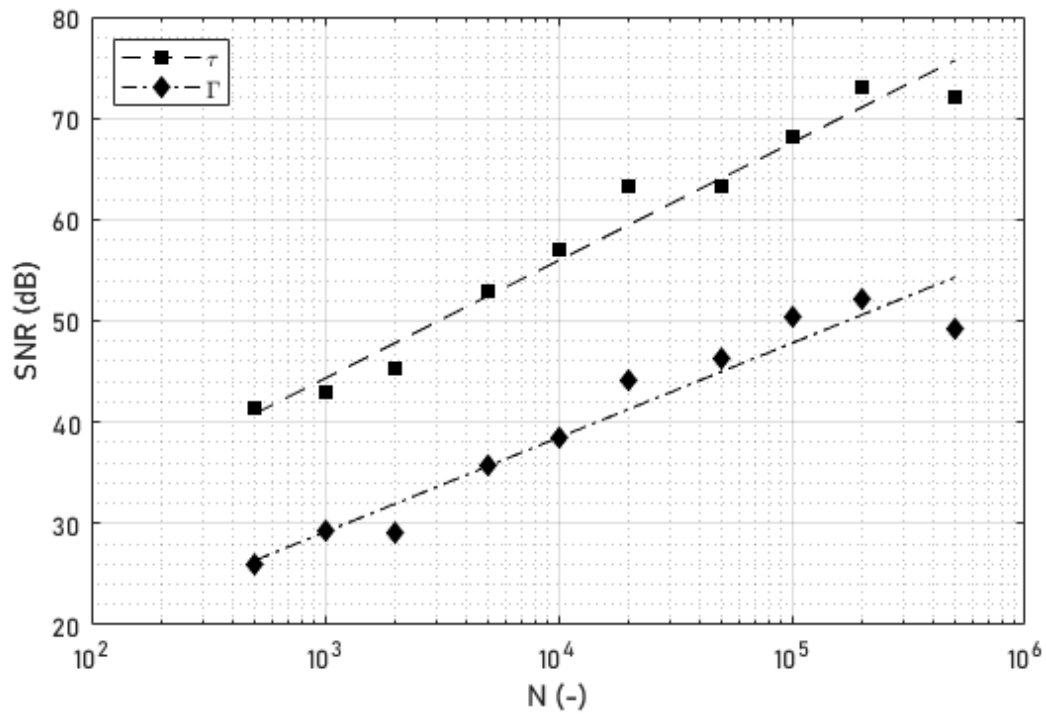


Figure 4.3. Signal-to-noise ratio for the relative amplitude (Γ) and time lag (τ) measurements shown as a function of the number of signal averages (N), with both variables increasing by ~ 20 dB/decade.

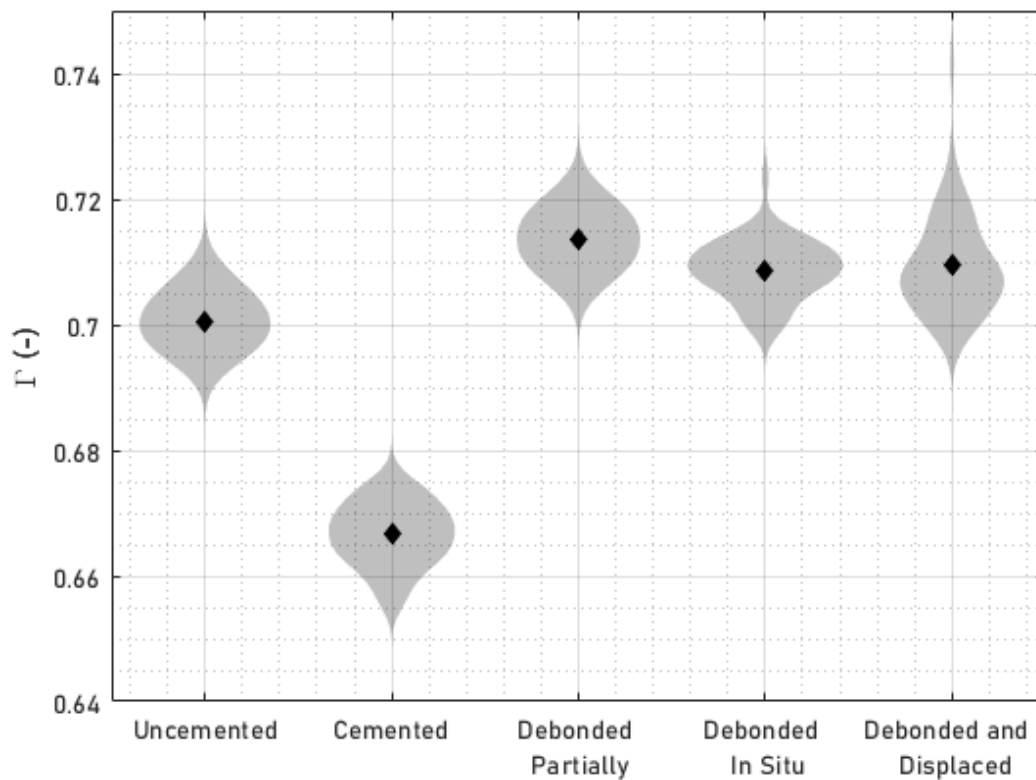


Figure 4.4. Violin plots showing a decrease in the relative amplitude of successive echoes (Γ) when implanted in synthetic bone and a subsequent increase when the implant-cement interface is compromised beneath the piezoelectric transducer.

debonded with displacement (+6.4%; 95% CI: +6.0% to +6.9%; $p < 0.001$). A similar trend is seen in the mean relative amplitude measurements before and after cementation (+5.1%; 95% CI: 4.6% to 5.6%; $p < 0.001$). Furthermore, measurement sets were distinct – no crossover in values – for each of the loosening states with respect to the well-fixed implant.

4.3.3. Temperature Calibration

The time lag between the first and second echo was correlated with temperature (Fig. 4.5; correlation coefficient: 0.997). The calibrated linear fit exhibited a sensitivity of 2.54 ± 0.21 ns/°C, a coefficient of determination (R^2) of 0.993, and a root-mean-square-error (RMSE) of 0.4 °C. At normal human body temperature of 37 °C, the 95% prediction interval for new measurements based on arrival time is ± 1.05 °C.

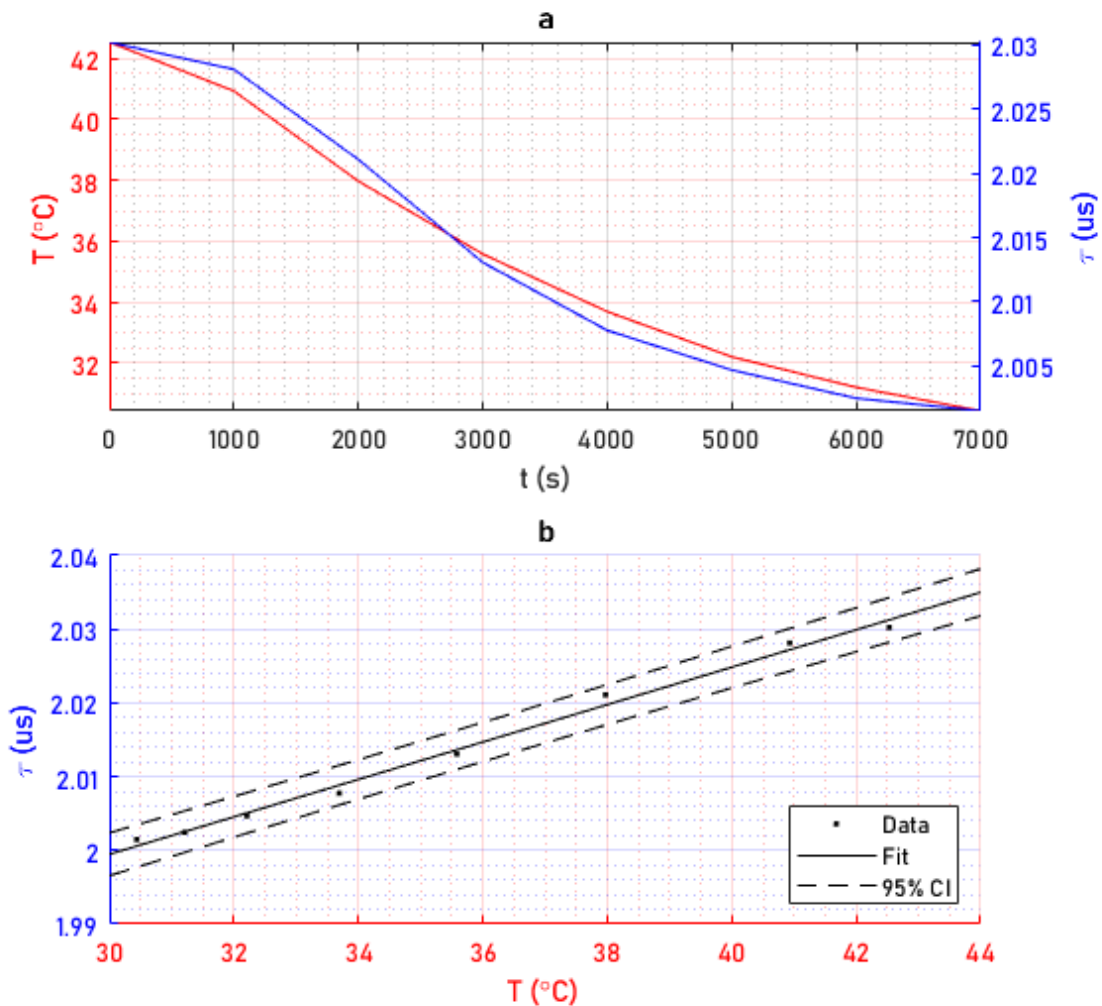


Figure 4.5: (a) Cooling curve for the implant as measured by a thermocouple (T) and the correlated time profile for the time lag between the first and second echo (τ), with (b) the two variables calibrated by a linear fit.

4.3.4. Measurement Sensitivity

Fixation measurements were robust to changes in reader positioning in all translational and rotational directions within the ranges investigated (Fig. 4.6; ± 10 mm and $\pm 10^\circ$). There was homogeneity of variances in the fixation measurements when the reader was displaced in the posteroanterior, sagittal, and coronal directions, but not in the mediolateral and caudocranial directions (Table 4.1). The SNR in the neutral position was 35.4 dB; the best SNR (lowest variance; 38.2 dB) was observed at +10 mm in mediolateral translation where the implant was in closest proximity to the reader; and the worst SNR (highest variance: 31.2 dB) was recorded at +10 mm caudocranial translation when the implant and the reader had the greatest planar displacement. No significant effect was detected on mean fixation measurement due to changes in reader positioning in any direction (Table 4.1).

Measurements of fixation were also shown to be highly robust to the metallic femoral component (Fig. 4.7a; Δ SNR: -1.29 dB) and soft tissue (Fig. 4.7b; Δ SNR: -0.72 dB). The mean differences in fixation measurement due to the femoral component (-0.002 ; 95% CI: -0.007 to $+0.003$) and due to soft tissue (-0.001 ; 95% CI: -0.006 to $+0.004$) were not statistically significant at the level powered (Table 4.1).

Table 4.1. Statistical analyses for difference in fixation measurement due to reader positioning in several directions, presence of the femoral component (Fem.), and soft tissue (Ana.).

	Homogeneity of Variances		Equality of Means	
	Stat.	Sig.	Stat.	Sig.
PA	$F(4,245) = 0.354$	$p = 0.841$	$F(4,122.413) = 1.187$	$p = 0.329$
ML	$F(4,245) = 3.264$	$p = 0.012$	$F(4,121.398) = 0.596$	$p = 0.666$
CC	$F(4,245) = 4.563$	$p = 0.001$	$F(4,121.816) = 0.898$	$p = 0.467$
Sag.	$F(4,245) = 0.501$	$p = 0.735$	$F(4,122.397) = 1.361$	$p = 0.252$
Cor.	$F(4,245) = 1.469$	$p = 0.212$	$F(4,122.189) = 0.591$	$p = 0.670$
Fem.	$F(1,98) = 2.219$	$p = 0.140$	$t(95.974) = 0.599$	$p = 0.551$
Ana.	$F(1,98) = 0.000$	$p = 0.999$	$t(97.310) = 0.435$	$p = 0.664$

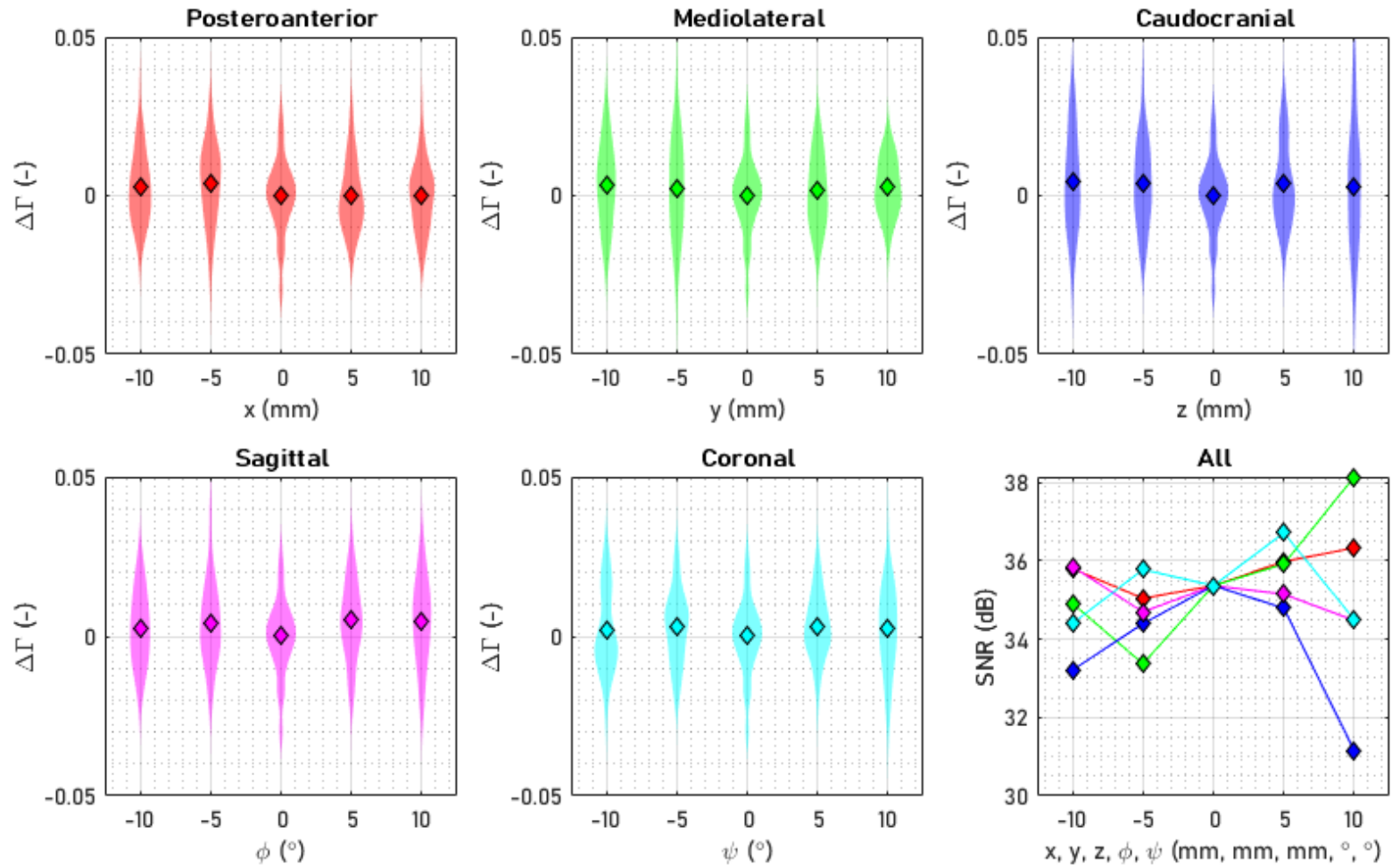


Figure 4.6. Deviation in fixation measurement, Γ , from the mean value recorded in the neutral position, shown as violin plots, for varying coil translations and rotations, plus corresponding signal-to-noise ratio.

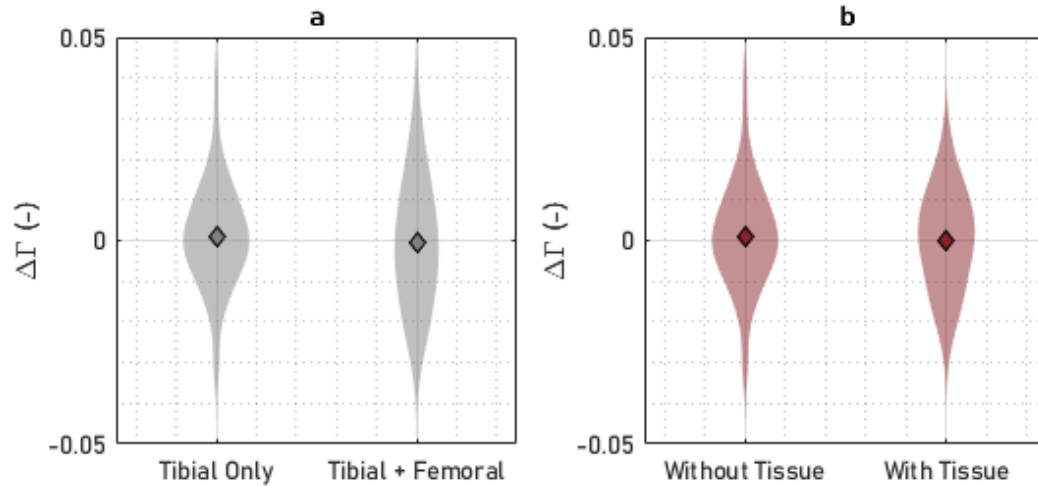


Figure 4.7. Fixation measurement sensitivity to the presence of (a) the femoral component and (b) anatomical tissue, shown as violin plots.

The time lag measurements, which are calibrated to temperature, had a higher SNR than the fixation measurements in the neutral position (Fig. 4.8; 48.9 dB). Like the fixation measurements, the best SNR (54.4 dB) was measured at +10 mm mediolateral translation and the worst SNR (45.5 dB) was recorded at +10 mm caudocranial translation. Similarly, there was homogeneity of variances in the posteroanterior, sagittal, and coronal directions, but not in the mediolateral or caudocranial directions (Table 4.2). Significant effects of reader positioning on the mean time lag measurement were observed in all directions (Table 4.2), with the largest mean difference of -4.77°C (95% CI: -6.65 to -2.73°C) was observed at +10 mm in caudocranial translation. Full Games-Howell post-hoc comparisons for each direction are included in the addendum to this chapter.

Table 4.2. Statistical analyses for differences in temperature measurement due to reader positioning in several directions.

	Homogeneity of Variances		Equality of Means	
	Stat.	Sig.	Stat.	Sig.
PA	$F(4,245) = 1.895$	$p = 0.112$	$F(4,122.313) = 8.032$	$p < 0.001$
ML	$F(4,245) = 6.735$	$p < 0.001$	$F(4,119.145) = 4.612$	$p = 0.002$
CC	$F(4,245) = 5.131$	$p < 0.001$	$F(4,121.654) = 40.138$	$P < 0.001$
Sag.	$F(4,245) = 0.947$	$p = 0.437$	$F(4,122.414) = 3.076$	$p = 0.019$
Cor.	$F(4,245) = 1.249$	$p = 0.291$	$F(4,122.324) = 7.263$	$p < 0.001$

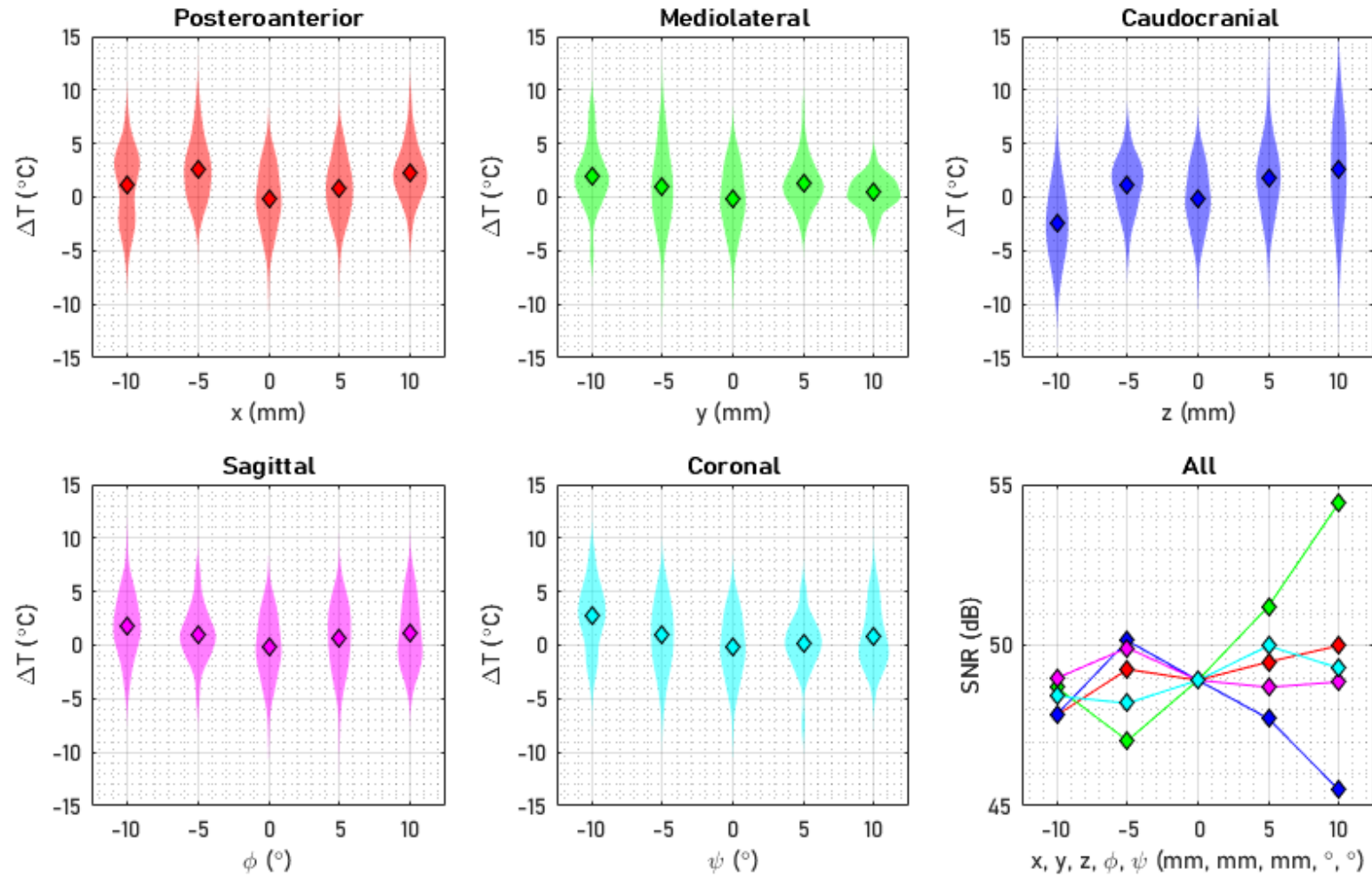


Figure 4.8. Deviation in temperature measurement, T , from the mean value recorded in the neutral position, shown as violin plots, for varying coil translations and rotations, plus corresponding signal-to-noise ratio in the underlying time lag measurement.

Temperature measurements were robust to the metallic femoral component (Fig. 4.9a; ΔSNR : -0.6 dB) and musculoskeletal tissue (Fig. 4.9b; -0.7 dB). Variance in temperature measurement with and without the femoral component was homogeneous, and the mean difference (-0.73 °C; 95% CI: -1.9 to 0.4 °C) was not statistically significant (Table 4.3). Likewise, the variance with and without soft tissue porcine tissue was homogeneous, and the mean difference (-1.1 °C; 95% CI: -2.3 to 0.1 °C) was not statistically significant.

Table 4.3. Statistical analyses for differences in temperature measurement due to the presence of the metallic femoral component (Fem.) and soft tissue (Ana.).

	Homogeneity of Variances		Equality of Means	
	Stat.	Sig.	Stat.	Sig.
Fem.	$F(1,98) = 0.084$	$p = 0.773$	$t(97.510) = 1.251$	$p = 0.214$
Ana.	$F(1,98) = 0.054$	$p = 0.817$	$t(97.368) = 1.919$	$p = 0.058$

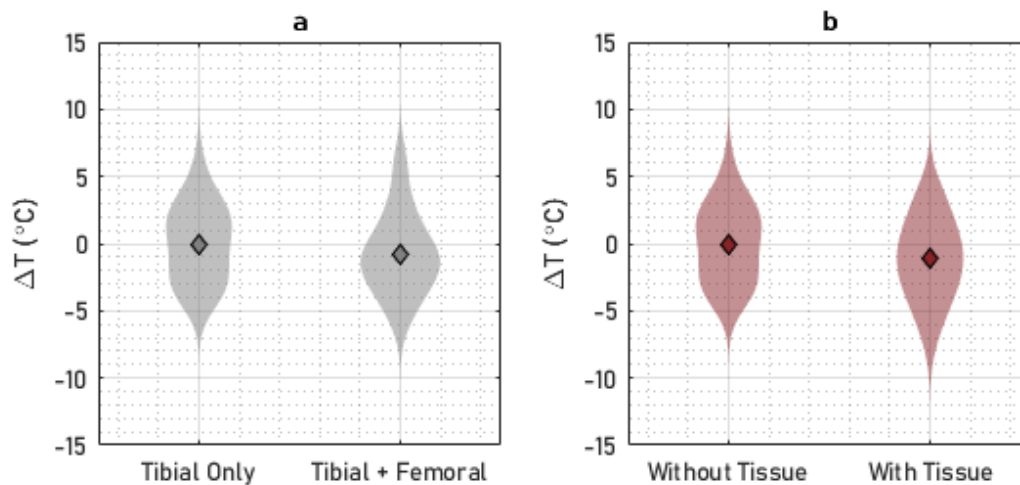


Figure 4.9. Temperature measurement sensitivity to the presence of (a) the femoral component and (b) anatomical tissue, shown as violin plots.

4.3.5. Persona Verification

Debonding detection results from the Oxford Fixed Lateral Partial Knee were replicated with the Persona Total Knee design. The mean relative amplitude between successive echoes (Γ) was 0.5938 ± 0.0021 when the implant was cemented, rising to 0.7876 ± 0.0019 (+32.6%; $p < 0.001$) and 0.7865 ± 0.0017 (32.5%; $p < 0.001$) when partially and fully debonded respectively. Again, there was zero crossover in values between the well-fixed and loosened states.

4.4. Discussion

In this chapter, the low-cost implant health monitoring concept developed in Chapters 3 was applied to two commercial knee replacement implants: an Oxford Fixed Lateral Partial Knee, and a Persona Total Knee (both Zimmer Biomet, Warsaw, IN, USA). Accuracy was evaluated for the two simultaneous detection mechanisms: implant-cement debonding and infection-related elevated temperature. Furthermore, the sensitivity of each measurement to the positioning of the external reader, femoral component, and musculoskeletal tissue was quantified. Even at the small scale of the partial knee implant, it was found that tibial debonding could be robustly detected. Temperature measurements were successfully calibrated, but fixed reader positioning was necessary to maintain calibration accuracy.

Loss of fixation beneath the transducer was detected when the implant was partially debonded, fully debonded in situ, and fully debonded with displacement (all $p < 0.001$) under varying degrees of ligamentous tension and femoral component position. Measurements were robust to the positioning of the external reader circuit, femoral component, and musculoskeletal tissue with the sensitivity studies powered to detect a false-positive reading. This is an advance on the generic system in Chapter 3, which attempted to evaluate the concept at the smallest practicable coil diameter ($\varnothing 10$ mm). The previous embodiment required tuning of the external reader towards resonance to boost signal amplitude, but the concomitant resonant tail from the initial pulse caused crosstalk that masked the return signal at higher coil separations. This embodiment with the coil wound around the perimeter of the tibial component had sufficient inductive coupling to the external reader to obviate the need for tuning.

The lift-off moment used to debond the implant simulated a mechanism for aseptic loosening described in literature (Chong, Hansen and Amis, 2010; Scott and Biant, 2012; Yokhana *et al.*, 2019) and produced a failure at the implant-cement interface that resembled contemporary clinical reports of tibial debonding (Foran, Whited and Sporer, 2011; Arsoy *et al.*, 2013; Ries *et al.*, 2013; Hazelwood *et al.*, 2015; Kopinski *et al.*, 2016; Bonutti *et al.*, 2017; Kutzner *et al.*, 2018; Cerquiglini *et al.*, 2019; Sadauskas *et al.*, 2020; Keohane *et al.*, 2020; Martin *et al.*, 2021; Murphy *et al.*, 2021). As identified in Chapter 2, however, exact failure mechanisms and timescales are yet to be fully described, and it is therefore challenging to prescribe a sensitivity and specificity for tibial debonding detection without clinical validation. It is expected that a single embedded transducer would suffice for a tibial-debonding mechanism characterised by fast-acting catastrophic failure, whereas a slow-acting propagation mechanism would necessitate an array of embedded piezoelectric transducers to enable any early intervention.

The use of synthetic bone in the experimental setup was an acceptable replacement for organic bone because the modelling in Chapter 3 demonstrated that the fixation measurement was primarily driven by the implant-cement interface, not the cement-bone interface. By that same logic, the use of synthetic bone of a single density was considered acceptable. In Chapter 3, cementation technique was observed to influence the magnitude of the acoustic effect of debonding at the implant-cement interface. The effect of technique was not investigated in this study, though it does vary between surgeons and manufacturers (Randall *et al.*, 2019). A defined range for cement mantle thickness could become instructional within surgical training to ensure measurement repeatability. It is expected that any manufacturing effects, such as epoxy thickness and piezoelectric transducer placement on the implant, would be quality-controlled to minimise variation. Measurement sensitivity to the reader position was investigated: ranges of ± 10 mm translation and 10° in rotation from alignment with the knee centre were set according to physical possibility in the mediolateral, posterior, sagittal, and coronal directions. In the caudocranial direction, the range of ± 10 mm in translation was an assumed limit and should be further evaluated as a human factor in further study. Measurement sensitivity to the femoral component was evaluated with and without the component as extreme cases, and no significant effect was observed, which was concordant with the acoustics-driven physical basis of the fixation measurement. Similarly, measurement sensitivity to tissue was evaluated with and without tissue, and no significant effect was detected, which was consistent with literature and previous tissue sensitivity evaluations in Chapter 3.

Associated with acute presentations, elevated temperature (fever) is a highly specific marker of infection (96%) that should prompt further clinical investigation (Shohat *et al.*, 2019). Simultaneous measurements of temperature from the implant recorded using the same external circuitry: a calibration with 0.4°C RMSE (95% PI: $\pm 1.05^\circ\text{C}$) was achieved with 500,000 signal averages per measurement (acquisition time: 125 s). It was also shown that temperature measurement accuracy could be further improved with longer acquisition times: if the external hardware was optimised then a 95% prediction interval for new measurements of 0.1°C could be achieved with an acquisition time of 20 s (extrapolated estimate). In patients with septic complications following knee arthroplasty, skin surface temperatures were found to increase by $1.6 \pm 0.6^\circ\text{C}$ (Romanò *et al.*, 2012). Elevated temperatures of $>1.0^\circ\text{C}$ in the absence of other explanatory factors, such as frictional heating (Bergmann, Graichen, *et al.*, 2001), could therefore be considered as a workup threshold, which is attainable in consideration of the calibration accuracy. In the generic setup from Chapter 3, shorter acquisitions (10,000 versus 500,000 signal averages) were required for a

95% prediction interval for new measurements of ± 1 °C at coil separations up to 6 mm, but measurements were range limited and declined rapidly thereafter.

Of all sensitivities considered, only displacement was found to affect measurements of temperature ($p < 0.05$ in all directions). The highest mean difference from the neutral position was recorded as -4.77 °C (95% CI: -6.65 to -2.73 °C), which significantly exceeded the temperature elevation associated with infection: 1.9 °C (Romanò *et al.*, 2013). Reader positioning must therefore be controlled in any clinical embodiment of the concept if the calibration accuracy is to be realised, such as by incorporating a feedback loop to guide the operator towards the neutral position. In the only other passive temperature monitoring concept for an orthopaedic implant, a resolution of 0.1 °C (no acquisition time stated) was achieved with stability up to 15 mm transverse or coaxial coil displacement (Karipott, Veetil, *et al.*, 2018); the underlying Q-factor measurements in this study were affected by porcine tissue (3%) but the relationship of this measurement to temperature is not clearly stated.

As the concept has not modified the external form of the implants, the smart implants could be used to generate *in vivo* data to address uncertainties around tibial debonding mechanisms and the relationship between infection and temperature, which would be the next step for translational research. The form factor of the modification is sufficiently small to apply the concept to other implants, particularly glenoid and humeral components in anatomical total shoulder arthroplasty for which loosening remains a clinical challenge (Grob *et al.*, 2021; Zmistowski *et al.*, 2021). Moreover, the low cost of the embedded piezoelectric transducer ($< \$1$) removes barriers to translation into regular clinical practice, which have beset previous smart implants.

4.5. Summary of Findings

Research in this chapter advanced the general smart implant concept for simultaneous loosening and infection monitoring developed in Chapter 3 by applying it to commercial knee replacement systems, generating the following findings:

- It was demonstrated that tibial debonding at the implant-cement interface of the smallest clinically relevant commercial knee implant (Oxford Fixed Lateral Partial Knee, Zimmer Biomet, Warsaw, IN, USA) could be reliably detected in a benchtop model with only two easily accommodated electrical components: a wire coil and a shear-wave piezoelectric transducer.
- Debonding results were replicated on a larger commercial knee implant (Persona Total Knee, Zimmer Biomet, Warsaw, IN, USA) in the same benchtop model.

- The smart partial knee implant was calibrated for simultaneous temperature measurements with a 95% prediction interval of ± 1.05 °C for new measurements, which could be reduced to ± 0.1 °C with longer acquisition times for an infection workup threshold of >1.0 °C elevated temperature.
- Unlike debonding detection, temperature measurement was sensitive (drift) to reader positioning and therefore requires a control measure to guide the operator in any clinical implementation.
- With the low cost and small footprint of the transducer (volume: 5 mm^3 ; estimated material cost: \$1), the concept is flexible and scalable as a platform technology that could be embedded within existing implant form factors. Relevant implants beyond the current embodiments in the knee include shoulder, hip, and ankle prostheses.
- The smart implant concept could be used for clinical research to elucidate uncertain aseptic loosening mechanisms and improve understanding of the relationship between temperature and infection, with the potential for future use in clinical practice.

Addendum A: Sample Size Calculations

For the debonding study, mean ($\mu = 0.706$) and standard deviation ($\sigma = 0.0059$) for the debonded implant were calculated from fifty measurements of the implant before cementation. The mean difference (-15%) due to cementation was estimated based on debonding detection results Chapter 3 (Fig. 3.7), whilst variance was assumed homogeneous for the purpose of calculation. Target significance (α) and power ($1-\beta$) were set to standard values of 5% and 90% respectively, and the allocation ratio (well-fixed vs. debonded) was set as even. The minimum sample size ($n > 2$ per group) was computed using G*Power 3.1 software (Faul *et al.*, 2007); higher sample sizes ($n = 50$ per group) were used in the eventual experimental protocol (actual power $> 99.9\%$).

For the reader positioning sensitivity study, the same mean was used as the basis for the loosening power calculation, but a higher standard deviation was used to account for the lower number of signal averages ($\sigma = 0.01309$). The clinically important mean difference that would trigger a false positive for loosening was drawn from the debonding detection results (Fig. 4.4; $\varepsilon = 0.049$). For temperature, standard deviation in the underlying time lag measurements were extracted from the same fifty measurements and converted to temperature using the fitted calibration (Fig. 4.5; $\sigma = 2.81$ °C). The clinically important mean difference was the average temperature differential between an infected and an uninfected knee ($\varepsilon = 1.9$ °C) (Romanò *et al.*, 2013). Target significance (α) and power ($1-\beta$) were again set to 5% and 90% respectively, and allocation ratios were set as even. For calculation purposes, the mean vector was set up to detect a clinically important mean difference at the extent of the displacement range, where standard deviation was assumed to increase by 10%, i.e.

$$\mu = [\mu \quad \mu \quad \mu \quad \mu \quad \mu + \varepsilon] \quad (4.1) \quad \text{and} \quad \sigma = [1.1\sigma \quad 1.05\sigma \quad \sigma \quad 1.05\sigma \quad 1.1\sigma]. \quad (4.2)$$

Minimum sample sizes were computed using an R program developed by Jan and Shieh (2014). The minimum sample size for loosening ($n > 4$ per group) was lower than the minimum sample size for temperature ($n > 48$ per group). As measurements were acquired simultaneously, the experimental design adhered to the higher sample size requirement, and 50 measurements were ultimately acquired per group.

The same mean (μ), standard deviation (σ), clinically important mean difference (ε), significance (α), and power ($1-\beta$) were used for the other sensitivity studies. Minimum samples were calculated using G*Power 3.1 software (Faul *et al.*, 2007) for debonding ($n > 3$ per group) and temperature ($n > 47$ per group); 50 were ultimately acquired per group.

Addendum B: Post-hoc Testing of Temperature Measurements

Table 4.A1. Games-Howell post-hoc comparisons for temperature measurement sensitivity in each direction with respect to the neutral position; mean significant differences are marked by an asterisk.

Direction	Interval (mm/°)	Mean Diff. (°C)	Std. Error (°C)	Sig. (-)	95% CI (°C)
PA	-10.0	-1.26	0.611	p = 0.250	(-2.97, +0.43)
	-5.0	-2.72*	0.564	p < 0.001	(-4.27, -1.13)
	+5.0	-0.95	0.556	p = 0.426	(-2.50, +0.59)
	+10.0	-2.44*	0.540	p < 0.001	(-3.96, -0.94)
ML	-10.0	-2.09*	0.579	p = 0.004	(-3.72, -0.47)
	-5.0	-1.17	0.655	p = 0.371	(-2.97, +0.63)
	+5.0	-1.39	0.509	p = 0.058	(-2.82, +0.04)
	+10.0	-0.54	0.456	p = 0.170	(-1.84, +0.74)
CC	-10.0	+2.31*	0.611	p = 0.002	(+0.62, +3.99)
	-5.0	-3.25*	0.536	p < 0.001	(-4.74, -1.76)
	+5.0	-3.92*	0.618	p < 0.001	(-5.64, -2.19)
	+10.0	-4.77*	0.728	p < 0.001	(-6.65, -2.73)
Sag.	-10.0	-1.96*	0.571	p = 0.008	(-3.56, -0.39)
	-5.0	-1.15	0.544	p = 0.218	(-2.66, +0.35)
	+5.0	-0.82	0.579	p = 0.618	(-2.43, +0.78)
	+10.0	-1.26	0.575	p = 0.188	(-2.85, -0.31)
Cor.	-10.0	-2.92*	0.591	p < 0.001	(-4.54, -1.29)
	-5.0	-1.03	0.599	p = 0.431	(-2.70, +0.63)
	+5.0	-0.35	0.540	p = 0.975	(-1.83, +1.17)
	+10.0	-0.61	0.559	p = 0.776	(-2.50, +0.62)

Chapter 5

Preclinical Evaluation of an Active Osseointegrative Implant in a Bioreactor: An Ex Vivo Organ-Level Model

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Work from this chapter has been presented as

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Abbreviations

ALP	Alkaline Phosphatase
BSE	Backscattered Electron (mode of scanning electron microscopy)
DMEM	Dulbecco's Modified Eagle Medium
DPBS	Dulbecco's Phosphate-buffered Saline
EDTA	Ethylenediaminetetracetic Acid
H&E	Haematoxylin & Eosin
HEPES	Hydroxyethyl Piperazineethanesulfonic Acid
LIPUS	Low-Intensity Pulsed Ultrasound
OPN	Osteopontin
PBS	Phosphate-buffered Saline
SEM	Scanning Electron Microscopy
UV	Ultraviolet
WFM	Widefield Microscopy
α -MEM	Minimum Essential Medium with α modification

5.1. Introduction

Cementless fixation, also referred to as osseointegration, harnesses the innate regenerative properties of the host bone to establish a direct structural and functional connection that anchors the implant (Shah, Thomsen and Palmquist, 2019). This biologically driven mode of fixation is clinically of interest as an alternative to cemented arthroplasty (the current criterion standard) because it has the potential to preserve bone stock, reduce intraoperative times, eliminate cement-related costs and complications, and improve outcomes for young, functionally active, and/or obese patients (Kamath *et al.*, 2021). Furthermore, whilst early cementless systems were beset by aseptic loosening failures, contemporary systems are now exhibiting comparable survivorships (Dalury, 2016; Kwong and Schneiderman, 2018).

In passive implants, osseointegration is dependent on the implant surface chemistry, topography, and loading environment, which modulate the host inflammatory response and promote bone remodelling (Albrektsson and Wennerberg, 2019; Kohli, Stoddart and van Arkel, 2021), meaning a low number of loosening failures do still occur: 1.51 uncemented total knees and 1.31 uncemented total hips per 1,000 prosthesis years are revised for loosening (National Joint Registry, 2021). Recently, there has been research interest in active osseointegrative implants that use controllable biophysical stimuli to artificially enhance and accelerate bone formation in periprosthetic tissue (Gittens *et al.*, 2013; Dos Santos *et al.*, 2016; Pettersen, Shah and Ortiz-Catalan, 2021). If clinical potential were fully realised, this new class of device would revolutionise arthroplasty in the clinic by facilitating faster post-operative return to activity, plus it could enable non-invasive interventions following a diagnosis of poor fixation (early or late).

Beneficial effects of electrical stimulation of the osteogenic processes that lead to osseointegration (e.g. osteoblast differentiation and proliferation) have been reported from simplified in vitro models, but parameters have not been optimised and the effects have not been conclusively replicated in humans (Pettersen, Anderson and Ortiz-Catalan, 2021). The osteogenic/osseointegrative effects of low-intensity pulsed ultrasound have also been explored in both in vitro models (Wang *et al.*, 2014; Nagasaki *et al.*, 2015; Wu, Lin and Qin, 2015; Cao *et al.*, 2017; Feng *et al.*, 2019; Jiang *et al.*, 2020; Ambattu, Gelmi and Yeo, 2022) and in vivo animal models (Tanzer, Kantor and Bobyn, 2006; Iwai *et al.*, 2007; Ustun *et al.*, 2008; Hsu *et al.*, 2011; Liu *et al.*, 2012; Zhou *et al.*, 2016; Ruppert *et al.*, 2019), but with stimulation from an external source and not an active osseointegrative implant. As is the case for electrical stimulation, the effects of low-intensity pulsed ultrasound are not well understood, have not been optimised, and have not been replicated in humans (McCarthy and Camci-Unal, 2021).

The requisite circuitry for delivering electrical power to an orthopaedic implant and exciting an embedded ultrasound transducer was presented in Chapters 3 and 4; this system could be functionally repurposed for stimulating bone growth as an active osseointegrative implant with dual electrical-ultrasonic stimulation. An *ex vivo* bioreactor model is developed in this chapter to evaluate the biological effects of an active osseointegrative implant, with comparisons to LIPUS stimulation from an external source and static controls. The model is an intermediate between *in vitro* studies of isolated biological processes and *in vivo* studies with many potentially confounding effects: it enables study under tightly controlled near-physiological conditions whilst preserving the inherent cellular diversity and extracellular structure of natural bone. *Ex vivo* bioreactor models have previously been developed to evaluate bone formation on orthopaedic implant surfaces in static and/or dynamic culture (Dua, Jones and Noble, 2021; Zankovic *et al.*, 2021).

5.2. Concept Overview: Active Osseointegration

Bone is cellularly diverse and hierarchically organised, and its response to the implantation of a prosthesis is highly dynamic and coordinated across multiple systems. The first phase of healing is haemostasis: fibrin-rich clots stem the blood flow from damaged vessels (Shiu *et al.*, 2014). Platelets release growth factors during haemostasis that recruit osteoblasts and bone-marrow derived cells into the healing response, whilst osteocytes in this environment may be necrotised by the loss of blood supply (Davies, 2003). The periprosthetic bone then undergoes an inflammatory phase to clear the necrotic cell debris, bacteria, and other particulates that may have been introduced to the wound site at the time of resection (McKee, Pedraza and Kaartinen, 2011; Jennissen, 2016). The incoming macrophages secrete osteopontin onto the damaged trabecular and implant surfaces (McKee, Pedraza and Kaartinen, 2011); this osteopontin accumulates and becomes mineralised as ‘cement lines’ whilst devoid of collagen fibres (McKee and Nanci, 1996; Ayukawa *et al.*, 1998; Shah, Thomsen and Palmquist, 2019).

De novo bone formation proceeds from these cement lines on both the damaged trabeculae (distance osteogenesis) and the implant itself (contact osteogenesis), and beginning approximately one week post-injury (Trindade *et al.*, 2018). The growth of both collagen-rich osteoid fronts is orchestrated by a newly migrated population of osteoblast (McKee, Pedraza and Kaartinen, 2011): levels of osteopontin in this new bone drop and osteocalcin becomes the dominant non-collagenous protein (Ayukawa *et al.*, 1998). Initial deposition of new bone onto the implant surface is irregular, and it takes several months after the two osteoid fronts have united to remodel into the characteristic hierarchical structure of normal bone (Davies

et al., 2014; Grandfield, 2015). This process of osteogenesis is energy intensive, and it depends on the restoration of bloody supply for nutrients and oxygen. The process of angiogenesis – the formation of new blood vessels – occurs in coordination with the formation and remodelling of new bone (Kristensen *et al.*, 2013; Grosso *et al.*, 2017).

In addition to cell signalling, it is widely accepted that bone remodelling is regulated by mechanical loading (Elliott *et al.*, 2016; Pagnotti *et al.*, 2019) and is principally mediated by osteocytes in mature physiological bone (Robling and Bonewald, 2020). Mechanical loading drives ion-rich interstitial fluid around osteocytes within the extracellular matrix (van Tol *et al.*, 2020), thereby stimulating mechanosensors, activating calcium channels, and inducing mechanotransductive signalling in these cells (Stewart *et al.*, 2020; Xu *et al.*, 2021). Mechanosensitivity has also been demonstrated in other cell types involved in osteogenesis (Pei *et al.*, 2021), including osteoblasts, mesenchymal stem cells, and osteoclasts, and angiogenesis (Chen *et al.*, 2021), with functional effects that include promoting osteogenic differentiation, upregulating bone formation, and regulating bone resorption.

As either a complementary or a supplementary therapy, ultrasound represents a potential method for mechanically stimulating osseointegration, albeit at MHz frequencies instead of the normal physiological range (~1 Hz). In vitro models have already demonstrated that ultrasonic stimulation promotes osteoblast differentiation (Nagasaki *et al.*, 2015; Ambattu, Gelmi and Yeo, 2022) and proliferation within porous scaffolds (Wu, Lin and Qin, 2015), but the exact mechanisms are incompletely understood and no optimal stimulation parameter set has been identified (Veronick *et al.*, 2018; Stewart *et al.*, 2020; McCarthy and Camci-Unal, 2021). Similarly, it has been theorised that electrical stimulation could drive mechanotransduction due to the ions present in the interstitial fluid and/or the inherent piezoelectricity of natural bone, but neither have exact mechanisms been clarified nor have parameters been optimised (Pettersen, Anderson and Ortiz-Catalan, 2021).

Previous research into LIPUS-enhanced osseointegration used external transducers to deliver ultrasound to the prosthetic bone (Tanzer, Kantor and Bobyn, 2006; Iwai *et al.*, 2007; Ustun *et al.*, 2008; Hsu *et al.*, 2011; Liu *et al.*, 2012; Zhou *et al.*, 2016; Ruppert *et al.*, 2019). However, it is challenging to deliver a controllable dose in practice due to the bioacoustics of bone: the hard cortical shell is a strong reflector of incoming ultrasound and the underlying cancellous bone – also referred to as ‘spongy bone’ – is known to be a strong attenuator (Wear, 2020). Such phenomena may partially explain the discrepancy between positive in vitro and mixed in vivo results surrounding the clinical application of LIPUS (Poolman *et al.*, 2017; Stewart *et al.*, 2020). Likewise, the control of indirect electrical stimulation – capacitive

or inductive – is inhibited by metallic implants, which interfere with the electromagnetic fields generated by external devices. Direct delivery from the implant would enable more precise stimulation in both cases, hence the concept for an active osseointegrative implant.

5.3. Materials and Methods

The effects of stimulation on early osseointegration were investigated by a series of cultures: (i) an in vitro culture of isolated osteoblast-like cells and (ii) an ex vivo culture of explanted porcine cancellous bone. The in vitro culture was used to confirm the osteoconductivity of the rough titanium implant surface. The effects of treatment with an active osseointegrative implant and an external LIPUS dose were investigated at organ level in the ex vivo culture: this method advances on in vitro methods by introducing physiological cellular diversity and extracellular structure, whilst conforming to the principles of the 3Rs (Prescott and Lidster, 2017).

5.3.1. In Vitro Osteoconductivity Culture

Murine preosteoblasts from the MC3T3-E1 cell line (ATCC CRL-2593) were proliferated for three passages in cell culture medium: α -MEM (ThermoFisher 11095080) supplemented with 10% foetal bovine serum (ATCC 30-2020) and 1% penicillin-streptomycin (ThermoFisher 15070063). At 75% confluency on the final passage, the cells were trypsinised and seeded directly onto the seeded on the rough surface of the additive-manufactured titanium discs (Fig. 5.1; cp-Ti; $R_a = 75 \mu\text{m}$; $\varnothing 10 \text{ mm} \times 3 \text{ mm}$; $n = 8$) at a density of 5,000 cells/cm². Specimens were cultured in twelve-well plates for 7, 14, 21, and 28 days ($n = 2$ per time point) in normoxic conditions at 37 °C and 5% CO₂ in cell culture medium: The cell culture medium was replaced every seven days.

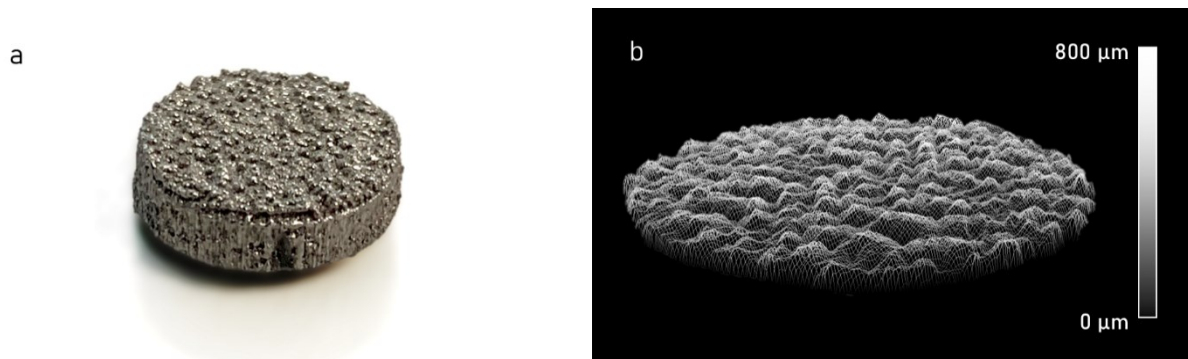


Figure 5.1. (a) The titanium surface of the active osseointegrative implant and (b) a surface roughness measurement ($R_a = 75 \mu\text{m}$).

5.3.2. Ex Vivo Active Osseointegration Culture

Fresh trabecular bone cylinders (Ø10 mm x 5 mm; n = 24) were explanted from distal porcine femora (age: 18 weeks; weight: ~75 kg); the donor animals had already been euthanised for unrelated research that did not affect bone metabolism or healing. Specimens were resected from the integument to the knee capsule, sectioned at the mid-femur and mid-tibia, and immersed in ethanol for seven minutes before being transferred to a laminar flow hood. The pursuant extraction of cancellous bone cylinders from the distal femoral condyles was conducted in a sterile manner (Fig. 5.2): power tools, attachments, and clamps were autoclaved; the bioreactor chamber was immersed in 70% ethanol after assembly and irradiated with ultraviolet (UV) light for 30 minutes on each side; and all other equipment was wiped with 70% ethanol and irradiated with UV.

Specimens were extracted using an oscillating saw blade and a diamond holesaw; ice-cold Dulbecco's phosphate-buffered saline (DPBS; ThermoFisher 14190250) with 1% penicillin/streptomycin (ThermoFisher 15070063) was used to minimise thermal necrosis whilst cutting. Specimens were washed in DPBS and vortexed for 30 seconds to reduce cutting debris. Within five hours of euthanization, all bone cores were prepared and immersed in cell culture medium, which was composed of DMEM/F-12 with HEPES (ThermoFisher 11330057) plus 10% foetal bovine serum (ThermoFisher 10500064) and 1% penicillin/streptomycin (ThermoFisher 15070063). During culture, bone cores were incubated in normoxic conditions at 37 °C and 5% CO₂.

Specimens were cultured in custom-built chambers (Fig. 5.3) and divided between four treatment conditions: A: active osseointegrative Implant with combined electrical-ultrasonic stimulation through the titanium surface (n = 6); B: low-intensity pulsed ultrasonic stimulation of the periprosthetic tissue (n = 6); C: passive control (n = 9); and D: passive control without the titanium implant (n = 3). Stimulation for the active osseointegrative implant was generated by a thickness-mode piezoelectric transducer (PI Ceramic PRYY+0442; Ø10 mm x 1 mm), which was embedded within a biocompatible polymer insert (Stratasys ABS-M30i). The titanium disc was inset and bonded to the piezoelectric transducer using a thin layer of epoxy (Loctite Double-Bubble). Electrical contact was established to the positive electrode by soldering and to the negative electrode with a biocompatible Steel 316L grub screw. PDMS was used to encapsulate the circuitry and provide a 3-mm thick backing for the transducer. The inserts were press-fit into the polycarbonate wells for culture and maintained contact with the samples under light static load. The transducer for the external

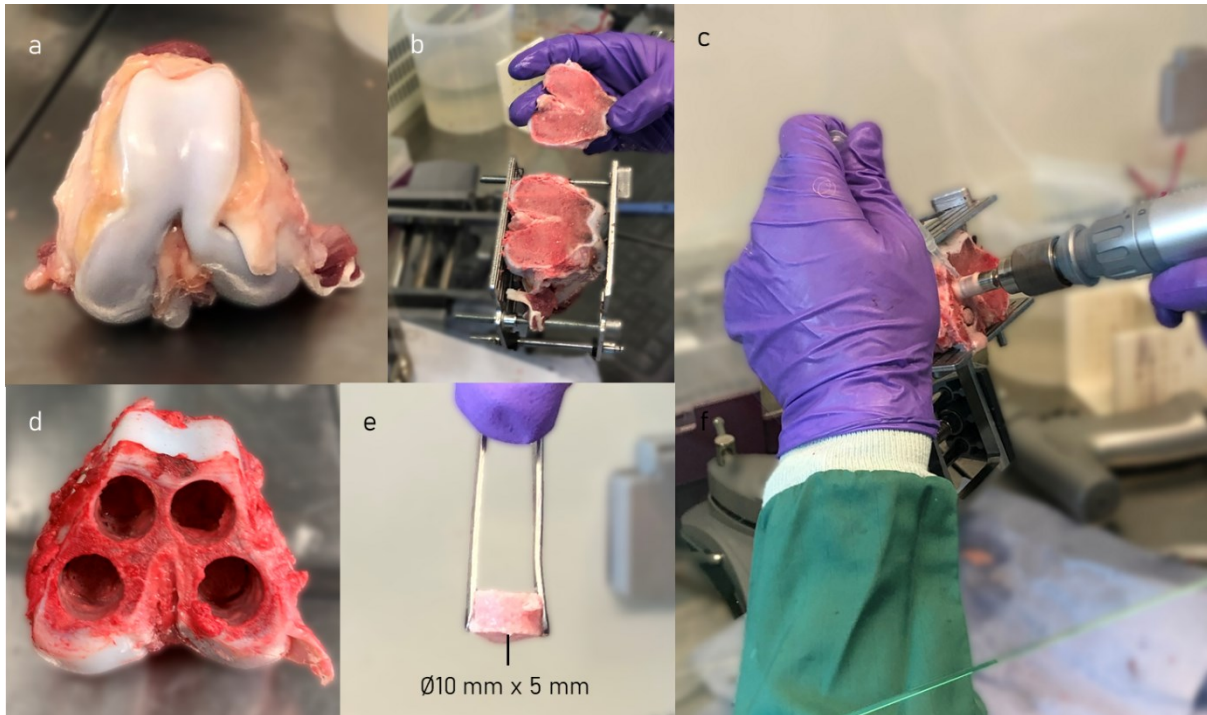


Figure 5.2. Explantation of porcine cancellous bone from the distal femoral condyles: (a) isolation of the distal femur; (b) exposure of the subchondral bone; (c-d) extraction of four cancellous bone cores (Ø10mm) from the lateral and femoral condyles at up to 25-mm length; and (e) division of cores into cylinders of 5-mm length.

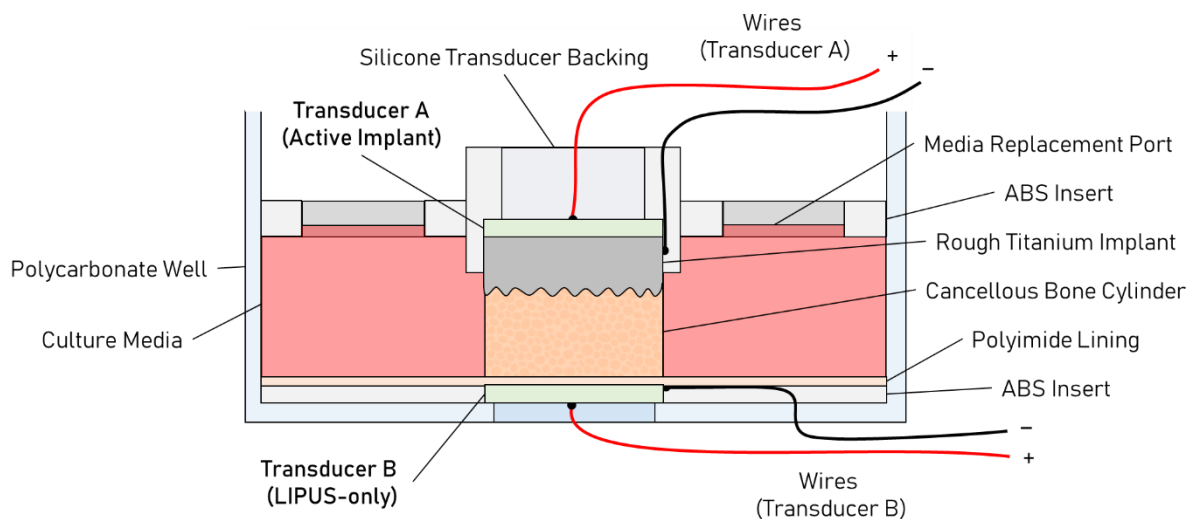


Figure 5.3. Bioreactor chamber design for ex vivo evaluation of active osseointegration of cancellous bone into rough additive-manufactured titanium implant surface with two different treatment conditions: (A) active osseointegrative implant delivering direct stimulation (combined electromechanical) through the implant and (B) external LIPUS delivering indirect stimulation (mechanical only) through the bone.

LIPUS culture was embedded into the base of the well using a thin layer of epoxy and a biocompatible polymer insert; the transducer was electrically isolated from the bone core by a 30- μm thick polyimide lining.

In both treatment conditions, treated bone cores were stimulated daily for 30 minutes with pulses of 2 MHz frequency, 200 μs length and 30 mW/cm^2 intensity repeating at 1 kHz. Stimulation was driven by an arbitrary waveform generator (TiePie Handyscope HS5) at voltages of 2.42 V and 1.57 V for the active osseointegrative implant and the LIPUS-only treatments respectively (Addendum A). Control specimens were acoustically isolated from treated specimens. Treatment began after 24 hours of acclimatisation to the ex vivo environment and lasted 21 days, at which point the culture was terminated. Fresh media (8 ml) was supplied to the specimens on the days 0, 8 and 15, and retrieved on days 7, 14 and 21. The media on days 7-8 and days 14-15 contained fluorescent dyes for mineral labelling and was replaced after 24 hours.

5.3.3. Live/Dead Staining

A two-colour assay (ThermoFisher L3224; Calcein-AM/Ethidium homodimer) was used to stain live/dead cells to determine viability and proliferation on the titanium implant surfaces: (i) after 7, 14, 21, and 28 days of in vitro culture ($n = 1$ per timepoint) and (ii) after 21 days of ex vivo culture ($n = 1$ per condition). Specimens were incubated with the stains for two hours and washed three times with phosphate-buffered saline to remove background fluorescence. Confocal images (Leica Microsystems TCS SP5) were acquired from all specimens; widefield microscopy images (Zeiss Axio Observer) were acquired from ex vivo discs to determine ongrowth at the macroscopic level.

5.3.4. Mineralisation Staining

Fluorophores (Calcein, Sigma-Aldrich C0875; Alizarin Red S, Sigma-Aldrich A5533) were administered on the seventh and fourteenth days of stimulation through the media (50 $\mu\text{g}/\text{ml}$) for 24 hours. Calcein (excitation: 470 nm; emission: 509 nm) and Alizarin Red S (excitation: 532 nm; emission: 620 nm) bind to the calcium ions in growing calcium phosphate/carbonate crystals, forming fluorescent complexes that label newly mineralised bone at each timepoint (van Gaalen *et al.*, 2010). Post-incubation, all titanium discs were imaged using widefield microscopy (Zeiss Axio Observer); images were also captured of the bone at the implant interface and through transverse sections. Bone autofluoresces at wavelengths in the visible spectrum; background levels of autofluorescence were therefore acquired from fluorophore-free (null) femoral bone specimens. Fluorescence values from these null values

were subtracted from the fluorophore-labelled bone images (95th percentile) and mean fluorescent intensity measurements (mean value).

5.3.5. Scanning Electron Microscopy

Titanium discs (n = 2 per in vitro timepoint; n = 3 per ex vivo condition) were fixed in 2.5% glutaraldehyde with 0.1 M phosphate buffer (pH 7.4) overnight, dehydrated through a series of ethanol solutions (20-100%; 7 minutes per solution), and air-dried for analysis. The discs were then sputter-coated with chromium (thickness: 15 nm) and imaged using a scanning electron microscope (TESCAN MIRA) for signs of cellular ongrowth.

5.3.6. Calcium Concentration

Media from each timepoint in the ex vivo culture was centrifuged upon retrieval and analysed for its calcium concentration using a colorimetric assay (Sigma-Aldrich MAK022; n = 3 for each condition). The chromogenic reagent (o-Cresolphthalein complexone) forms a violet-coloured complex (absorbance: 575 nm) with Calcium ions (Ca^{2+}) in alkaline solution. Absorbance readings were taken in triplicate for each sample, a series of standard calcium concentrations, fresh media, and blank media without any reagent. When reading media, 20 μL of retrieved media was diluted with distilled water to a volume of 50 μL .

5.3.7. Alkaline Phosphatase

The retrieved media (10 μL diluted to 20 μL) from the ex vivo culture was analysed for alkaline phosphatase activity (ALP) using a fluorometric assay (Sigma-Aldrich MAK411; excitation: 360 nm; emission: 440 nm). ALP is highly elevated in active osteoblast cells, which secrete the collagen I and non-collagenous proteins (osteocalcin, osteopontin, osteonectin, bone sialoprotein II, etc.) that constitute organic bone matrix; ALP is therefore a biomarker of bone formation (Rucci, 2008).

5.3.8. Media pH

Cell culture media (ThermoFisher 11330057) was supplemented with phenol red – a non-toxic pH indicator that is colour-sensitive in the range 6.8 to 8.2 (yellow to fuchsia). The colour of the media was monitored during the culture to ensure near-physiological pH (~7.4) was maintained. Secondary measures of pH were acquired directly from the media upon retrieval using indicator strips (VWR 315082P).

5.3.9. Histology

Bone specimens were fixed in 10% neutral buffered formalin overnight at room temperature, washed in 0.1 M phosphate-buffered saline (pH 7.4), and decalcified over 21 days in an acid solution (8% EDTA; 0.8% NaOH) with daily changes. After decalcification, specimens were

washed with tap water, dehydrated through a graded series of ascending alcohol solutions and toluene, and embedded in paraffin wax. Sections transverse to the bone-implant interface were cut from the centre of each specimen using a rotary microtome (Leica Biosystems RM2235) to a thickness of 7 µm and mounted on microscope slides. Slides were deparaffinised, rehydrated, and stained with Haematoxylin and Eosin (H&E; BioGnost HE-RTU-100T), Masson-Goldner's trichrome (BioGnost MGT-100T), Movat's Pentachrome (BioGnost MOV-100T), and Picrosirius Red (Abcam ab150681), according to manufacturer protocols.

5.3.10. Immunohistochemistry

Decalcified sections were deparaffinised in Citoclear (Genta Medical CIT050; 2 × 15 mins) and taken through secondary rinses in 99% industrial methylated spirit (Solmedia; IMS005; 2 × 30 mins). Endogenous peroxidases were blocked by incubating sections in 1% hydrogen peroxide in absolute methanol for 10 minutes, and sections were then rinsed in cold-running tap water for at least 10 minutes. Antigen retrieval was carried out by incubating sections in citrate buffer (pH 6) overnight: sections were put into the buffer whilst still cold and were allowed to warm gradually. The following day, sections were rinsed in PBS and a PAP pen ring was drawn around the sample. Sections were blocked by incubating in 5% Normal Goat Serum (Sigma N502L) in PBS for 1 hour at room temperature; excess serum was tapped off; and sections were rinsed in PBS (2 × 2 mins). Endogenous biotin, biotin receptors, and avidin binding sites were blocked with an Avidin/Biotin Blocking Kit (2BScientific SP-2001), which was used in accordance with the manufacturer's instructions, and sections were again rinsed in PBS (2 × 2 mins). Positive sections were incubated overnight with polyclonal rabbit anti-osteopontin primary antibody (Abcam ab231736; 1.25 µg/ml) in 5% goat serum; isotypic controls were incubated in Rabbit IgG at the same concentrations; and PBS controls were maintained in PBS overnight at 4 °C. All sections were rinsed the following day in wash buffer (pH 7.4; 3 × 5 mins), which was composed of 5 ml Triton X-100 (Millipore 648643) and 495 ml PBS. Sections were then incubated in biotinylated goat anti-rabbit secondary antibody (Jackson ImmunoResearch 111-066-046) at 1:250 PBS dilution for 1 hour at room temperature, followed by three five-minute rinses in the wash buffer. The VectaStain ABC kit (2BScientific PK-4000) was then applied to all sections according to the manufacturer's instructions, and sections were again rinsed in wash buffer (3 × 5 mins). Sections were incubated in DAB substrate (2BScientific SK-4100; 2-10 mins per sample) with microscopic control: the reaction was stopped with cold-running tap water when the target antigen was crisp brown and the background was clear. Nuclei were counterstained with Harris Haematoxylin for 20 seconds and blued in running tap water. Finally, sections were dehydrated, cleared, and

mounted. Slides were analysed qualitatively by two researchers without conversion into a scoring system, using adjectives such as “strong”, “weak”, or “absent” with modifiers like “more” or “less” (Fedchenko and Reifenrath, 2014).

5.4. Results

5.4.1. Cultivation

The *in vitro* specimens were cultured contamination-free for 28 days; high viability (>95%; Fig. 5.4) was maintained in all samples extracted on days 7, 14, 21 and 28. *Ex vivo* specimens ($n = 24$) were successfully explanted from the medial and lateral porcine femoral condyles; 22 specimens were cultured for 22 days, and two cultures (one C and one D specimen) were terminated on the tenth day due to contamination. Ongrown tissue of high viability was observed on the titanium discs of stimulated specimens (A & B; Fig. 5.5a), whilst ongrown tissue of less expanse and less viability was observed on the titanium discs of the passive controls (C; Fig. 5.5b). Anecdotally, all active osseointegrative implant specimens (A) and all-but-one LIPUS-stimulated specimens (B) had a weak degree of adhesion – enough for the bone to adhere to the implant under its own weight – at the implant-bone interface when the culture was terminated; no adhesion was observed in any of the passive controls (C). The media of active osseointegrative implant specimens was lighter upon retrieval (peach-coloured; pH ~7.1) than LIPUS-treated specimens and passive controls (red-coloured; pH ~7.4); pH values were confirmed using indicator strips.

5.4.2. Osteoconductivity

MC3T3-E1 murine preosteoblasts had proliferated over the entire rough titanium surface within seven days (Fig. 5.4a); the preosteoblasts had flattened on the surface with filopodia and there was early evidence of organic matrix deposition (Fig. 5.4b). By 14 days, cells had continued to proliferate (Fig. 5.4c) and organic structures spanning up to 200 μm between semi-sintered particles were observed (Fig. 5.4d). High density cell clusters were observed after 28 days of *in vitro* culture (Fig. 5.4e), which resulted in bone extracellular matrix that was more mature and more expansive than previous timepoints (Fig. 5.4f).

5.4.3. Bone Ongrowth

Specimens from the active osseointegrative implant (WFM; Fig. 5.6a) exhibited mineralisation across almost the entire surface on the seventh day of culture (Calcein Green) with continued mineralisation by the fourteenth day (Alizarin Red S). By the end of the three-week culture, there was near-total coverage of the titanium implant surface with extracellular matrix in

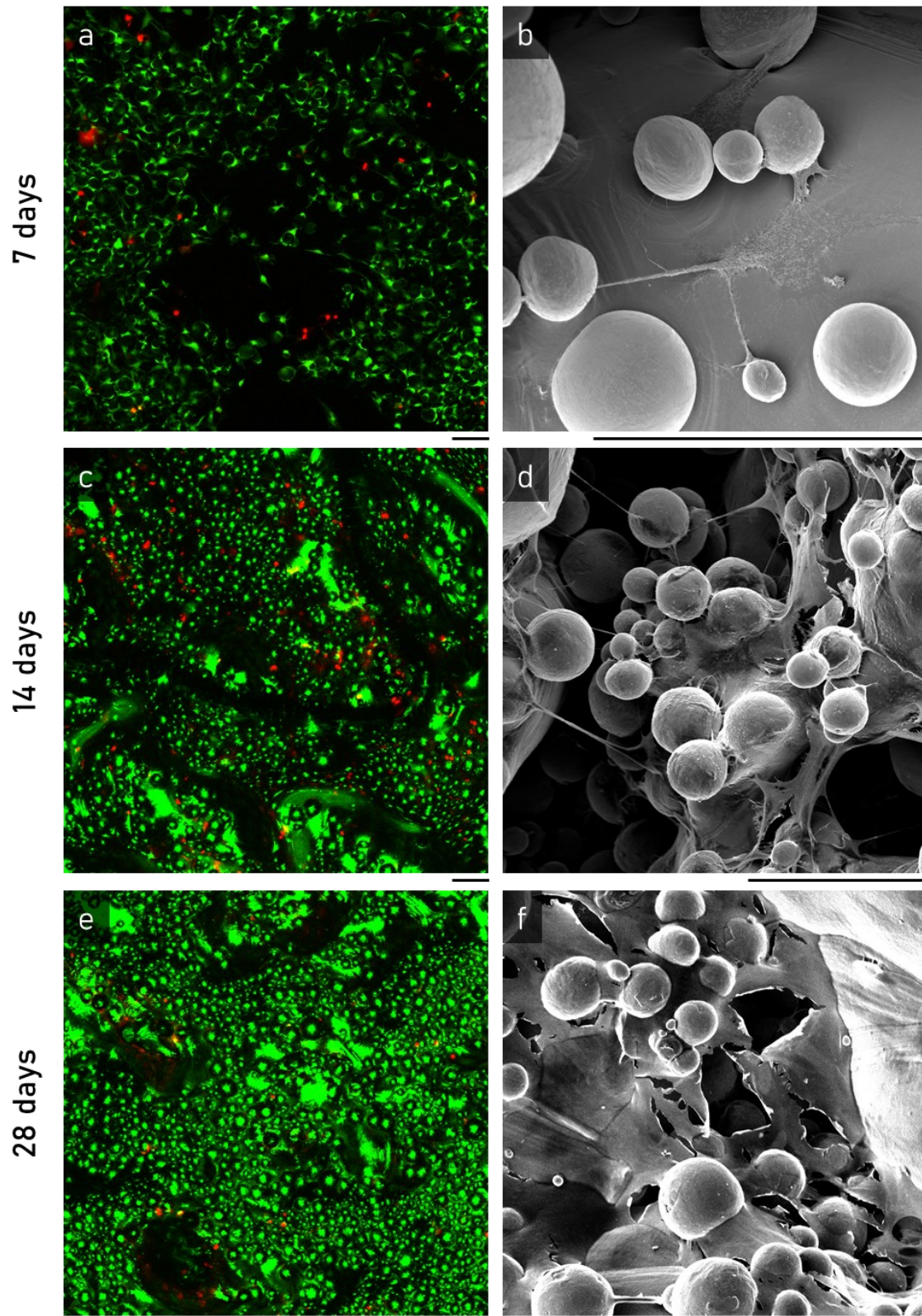


Figure 5.4. Proliferation of MC3T3-E1 murine preosteoblasts on additive-manufactured rough titanium surface ($R_a = 75 \mu\text{m}$) observed by live-dead staining (a, c, e) and scanning electron microscopy (b, e, f; energy: 10 keV; beam current: 300 pA) at 7 days (a & b), 14 days (c & d), and 28 days (e & f). The black line directly beneath each image is scaled to 100 μm .

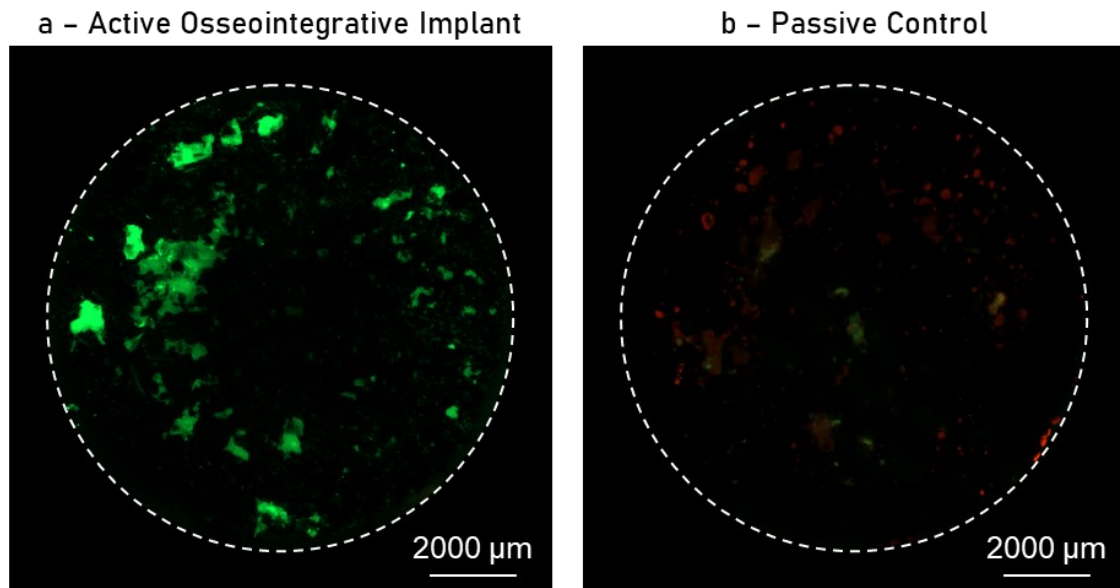


Figure 5.5. Live/dead (green/red) staining of cells from on-growing tissue derived from porcine femoral condyle explant onto additive-manufactured rough titanium discs after 22 days in an ex vivo bioreactor; (a) higher proliferation of cells and higher viability was observed on the active osseointegrative implant after 21 days of treatment compared to (b) static culture.

active osseointegrative implant specimens (SEM; Fig. 5.6d); continuous tissue formations had spanned distances up to 2 mm; and irregular woven bone structures had bridged between and enveloped semi-sintered particles on the implant surface (BSE; Fig. 5.6g). A large mature bone fragment – either debris from the initial extraction or separated due to resorption – was found on one disc from the electrical-ultrasonic treatment condition (BSE; Fig. 5.7a); continuous bone formation emanating from the fragment had begun to integrate with the semi-sintered particles on the titanium implant surface (BSE; Fig. 5.7b). A lesser amount of day-seven mineralisation was observed in specimens that had been subject to LIPUS stimulation via the tissue (WFM; Fig. 5.6b), dissipating to near-zero mineralisation by the fourteenth day. Extracellular matrix had also been deposited onto the titanium by the endpoint analysis in LIPUS-only specimens (SEM; Fig. 5.6e); tissue formations were less expansive and appeared less mature compared to active osseointegrative implant specimens; but similar woven structures were observed (BSE; Fig. 5.6h). In the static control (WFM; Fig. 5.6c), there was little to no mineralisation at any timepoint. Some cells and organic deposits were observed on the titanium implant surface of the static control specimens (SEM; Fig. 5.6f), but the surface was devoid of any mature, expansive organic structures (BSE; Fig. 5.6g).

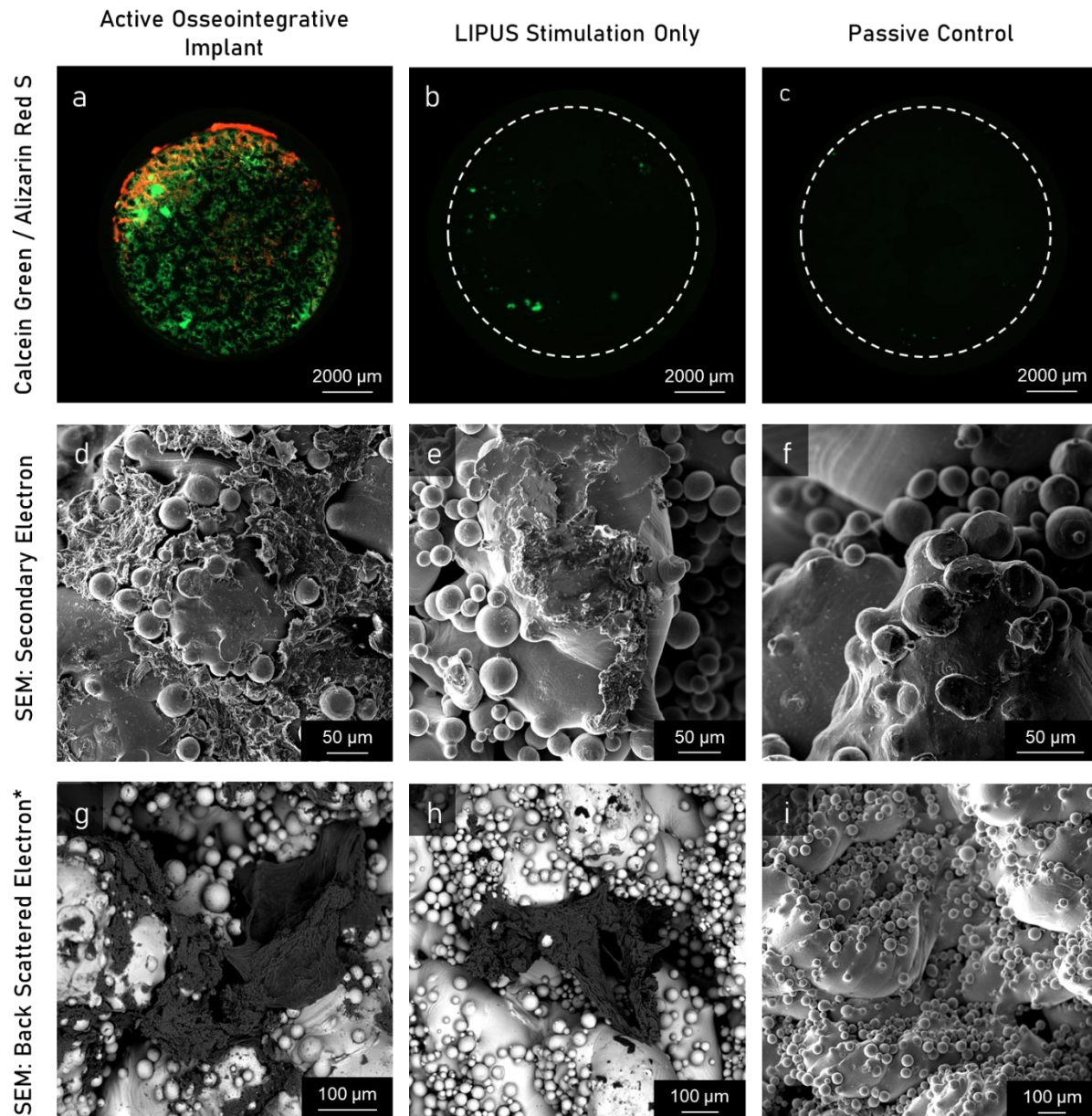


Figure 5.6. Comparison of new bone formation on the titanium implant in three configurations: active osseointegrative implant (combined electrical-ultrasonic treatment; left); LIPUS stimulation only (ultrasonic treatment; centre); and passive control (no treatment; right). Widefield fluorescent microscopy (top) provides evidence of substantially enhanced mineralisation on the seventh (green) and fourteenth (red) days of culture for active implant specimens compared to LIPUS-only (weak enhancement) and control specimens. Widespread coverage of extracellular matrix was observed on the surface of active implant specimens under SEM (middle: secondary electron; bottom: back-scattered electron*; energy: 10 keV; beam current: 3 nA) at the three-week endpoint, with smaller depositions on the surface of B specimens and near-zero deposition in C specimens.

*Figure (i) is Secondary Electron SEM

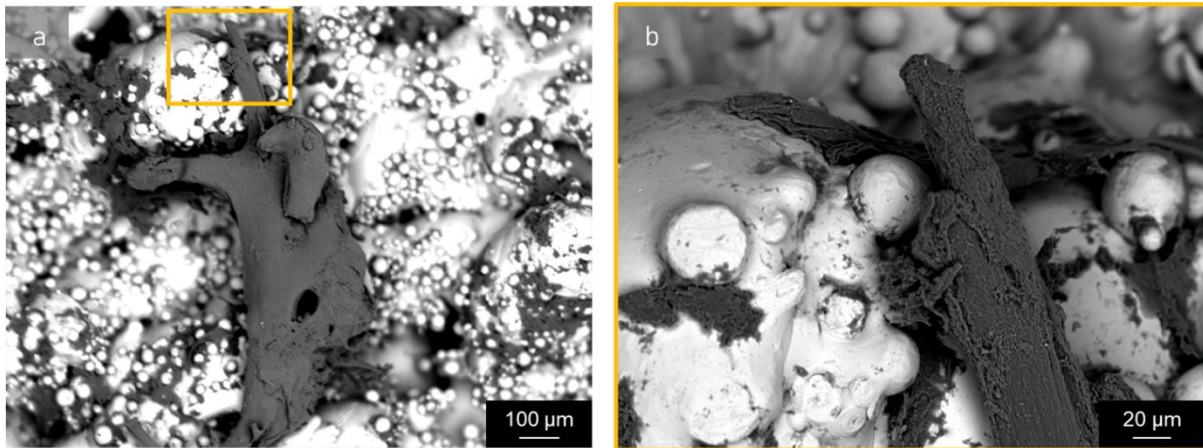


Figure 5.7. Scanning electron microscopy (back-scattered electron) revealed a mature bone fragment (length: ~1 mm) on an active osseointegrative implant surface that had begun to integrate with the semi-sintered particles on the rough titanium implant surface: (a) macroscopic view and (b) microscopic detail.

Active osseointegrative implant specimens exhibited substantially less mineralisation in the bone at the implant-bone interface on the seventh and fourteenth days (A; WFM; Fig. 5.8a) than either the purely LIPUS treated (B; WFM; Fig. 5.8b) or the static control (C; WFM; Fig. 5.8c); these trends were reflected in the transverse sections (WFM; Fig. 5.8d-f). Mean fluorescent intensity at the bone-implant interface from day-seven calcein staining was consistently higher in LIPUS-only specimens with respect to the static controls (Fig. 5.9; $p = 0.033$), indicating higher levels of mineralisation on day seven in these treated specimens. LIPUS-only specimens exhibited dense mineralisation in the lower 500-1000 μm of bone adjacent to the source of ultrasonic stimulation, which was not observed at any interface in any of the other samples. Fluorescence due to the day-fourteen staining at the implant-bone interface was comparable between LIPUS-only and control specimens (Fig. 5.8b-c): the staining was mostly concentrated in the periphery of the samples (Fig. 5.8e-f).

5.4.4. Media Biomarkers

ALP was secreted by all specimens throughout the 21-day culture period (Fig. 5.10), though levels of ALP secretions did decrease from an initial peak in the first seven days. In this initial period, ALP secretions by the active osseointegrative implant specimens were 52% lower than those of the passive control specimens ($p = 0.010$); LIPUS-only treatment had no effect on ALP secretions ($p = 0.808$); and ALP secretions without any titanium implant were increased by 55% ($p = 0.048$). There was no difference in ALP secretions beyond the initial seven-day period.

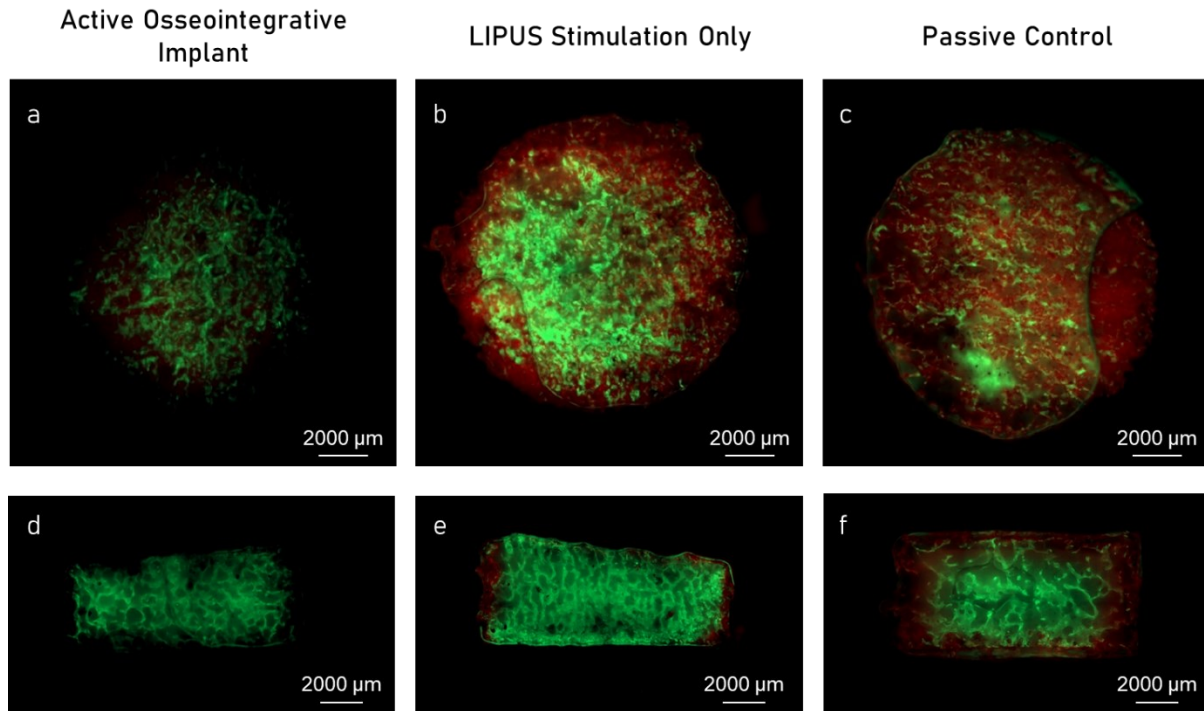


Figure 5.8. Day-seven (green) and day-fourteen (red) mineralisation at the interface to the implant (top) and through a transverse section of the bone (bottom; implant-side up) for each configuration: (A; left) active osseointegrative implant, (B; centre) passive implant with LIPUS treatment, and (C; right) passive control. Images are compensated for autofluorescence (Calcein: -7500; Alizarin Red S: -3500).

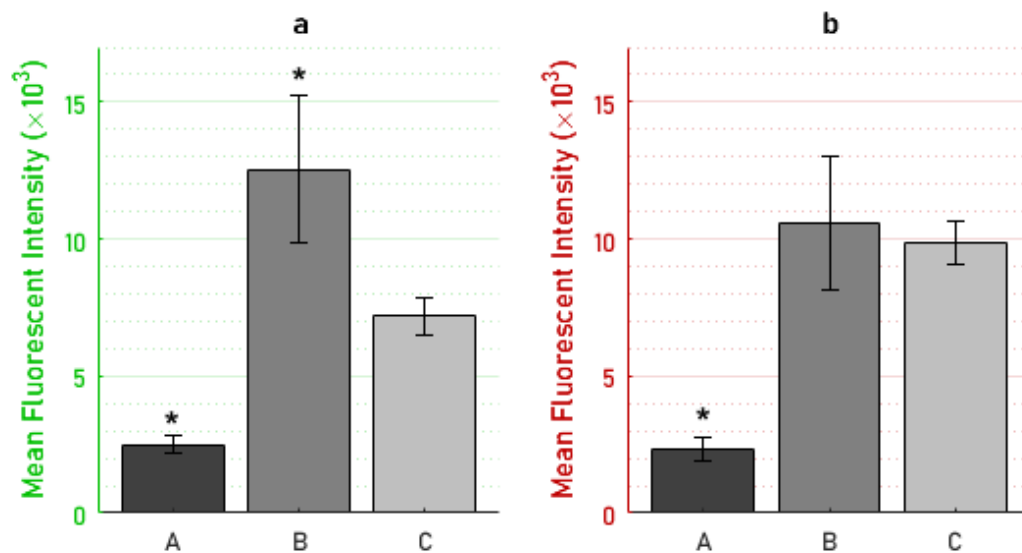


Figure 5.9. Mean fluorescence intensity in bone at the implant interface in channels of (a; day-seven) Calcein Green and (b; day-fourteen) Alizarin Red S between (A) active osseointegrative implant, (B) passive implant with LIPUS treatment, and (C) passive control. Asterisk (*) indicates significant difference ($p < 0.05$) relative to passive control.

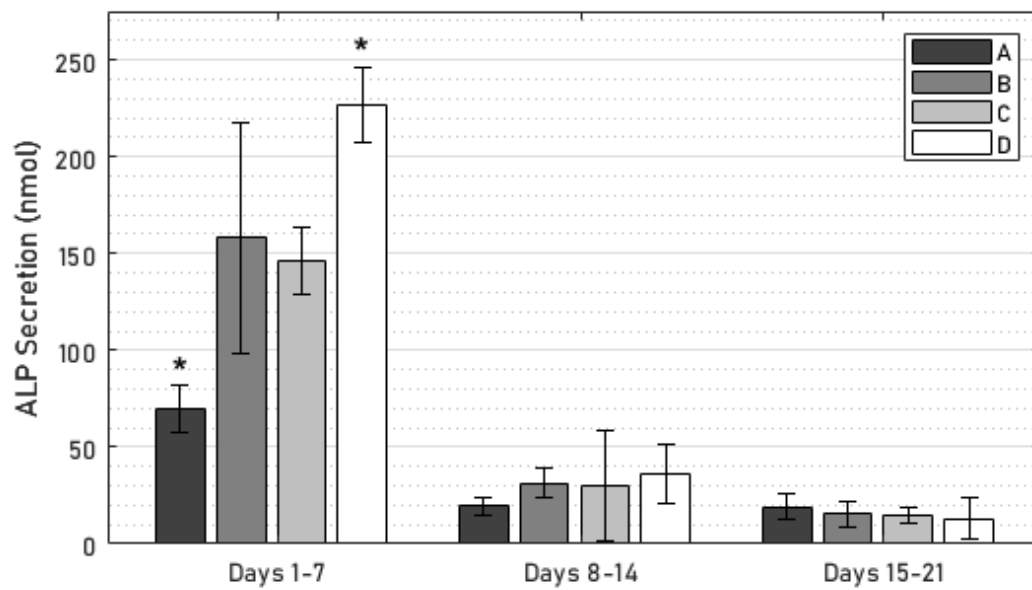


Figure 5.10. ALP levels across 21 days of culture between (A) active osseointegrative implant, (B) passive implant with LIPUS treatment, (C) passive control, and (D) passive control without implant. Asterisk (*) indicates significant difference ($p < 0.05$) relative to passive control.

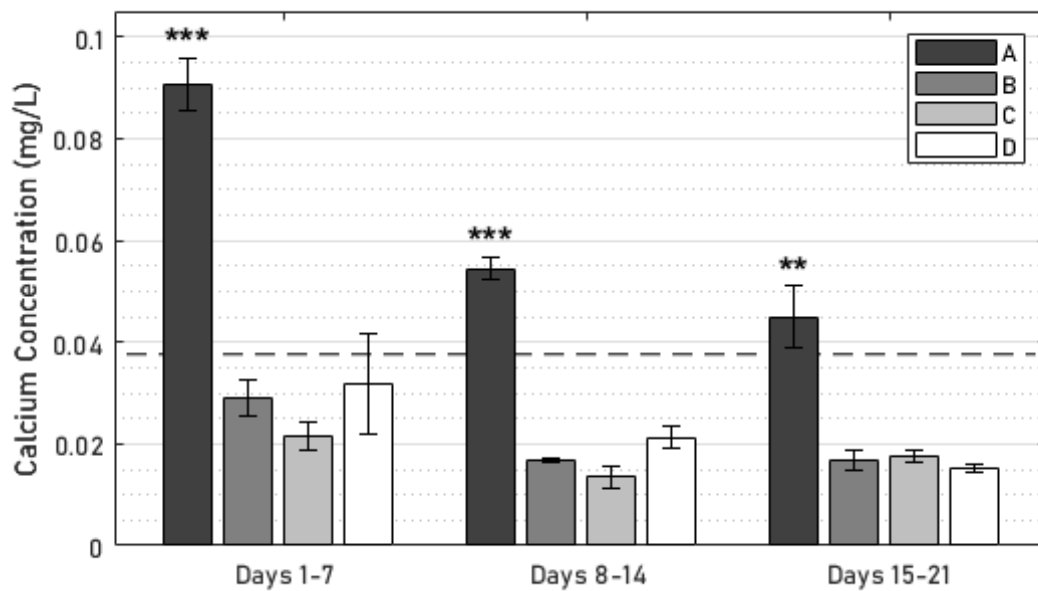


Figure 5.11. Calcium levels across 21 days of culture between (A) active osseointegrative implant, (B) passive implant with LIPUS treatment, (C) passive control, and (D) passive control without implant, with comparison to baseline calcium concentration of media (—). Asterisks indicates significant difference (*: $p < 0.05$; **: $p < 0.005$; ***: $p < 0.001$) relative to passive control.

Calcium levels were elevated above the media baseline in the active osseointegrative implant specimens at every timepoint (Fig. 5.11), indicating a flow of calcium from cellular or extracellular stores into the media. Whilst the elevation of calcium levels above the media baseline decreased at later timepoints, it remained high in the active osseointegrative implant specimens relative to the passive controls throughout (all $p < 0.01$). There was no difference in the calcium concentrations of the LIPUS-treated specimens or the passive controls, all of which were below the media baseline at every timepoint. In these specimens, calcium was absorbed from the media into cellular stores or mineralised into the extracellular matrix.

5.4.5. Histology

Histological analysis of the specimens treated with the active osseointegrative implant revealed bone fragments – cleaved from the bulk trabecular structure during the initial resection – amidst newly-formed non-collagenous fibrous tissue (Fig. 5.12). There was evidence of new bone matrix deposition (Figs. 5.12 & 5.13a) in direct apposition to the implant surface, growing from both the bulk trabecular structure and the resection debris fragments. Furthermore, bone remodelling (Fig. 5.13: formation and resorption) was seen in the bulk tissue of the active osseointegrative implant specimens. Less osteogenic activity was observed at the surfaces open to the media and in contact with the polymer well (Fig. 5.B2, -B3); similar resection debris and non-collagenous fibrous tissue formations were seen at these surfaces.

There were also similar bone fragments and non-collagenous tissue formations near the interface in the LIPUS-treated specimens and the passive controls, but less osteoid seams were observed in apposition to the titanium implant surface; (Figs. 5.14a & -b). Remodelling was evident in the bulk tissue, the surfaces open to the media, and the surfaces in contact with the polymer well in the LIPUS-only and passive control specimens (Figs. 5.14c & -d).

There was no indication of mass resorption of cancellous bone in any of the specimens.

5.4.6. Immunohistochemistry

Evidence of osteopontin expression was observed in all specimens: specific staining for osteopontin was brown, whilst nuclei were otherwise stained blue (Figs. 5.15a & -b vs. -c & d). At the bone-implant interface, there were more osteopontin-expressing osteocytes in specimens treated with the active osseointegrative implant (Fig. 5.15a) and LIPUS (Fig. 5.15e) than in the passive controls (Fig. 5.15g). Increased osteopontin expression was also observed in the bulk trabecular structure in specimens treated by the active

osseointegrative implant (Fig. 5.15b) and LIPUS stimulation (Fig. 5.15f) compared to the passive controls (Fig. 5.15h). Osteopontin was also expressed by osteoblasts and osteoclasts in remodelling zones of each specimen.

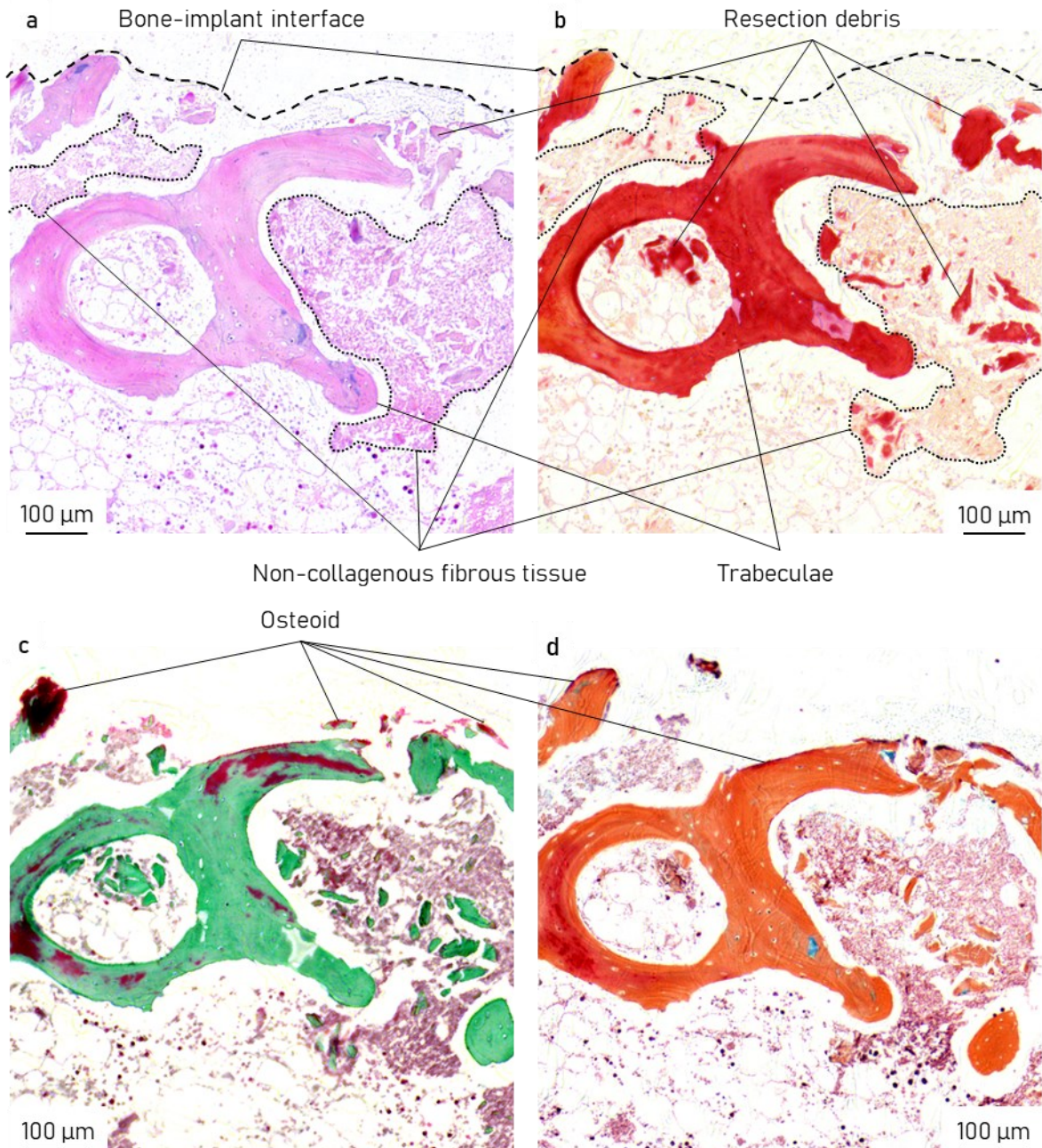


Figure 5.12. Histological staining (a: H&E; b: Picrosirius Red; c: Masson-Goldner Trichrome; d: Movat Pentachrome) of an active osseointegrative implant specimen at the bone-implant interface, showing resection debris, non-collagenous fibrous tissue formation, and osteoid seams in apposition to the interface (red in Masson-Goldner and Movat stains).

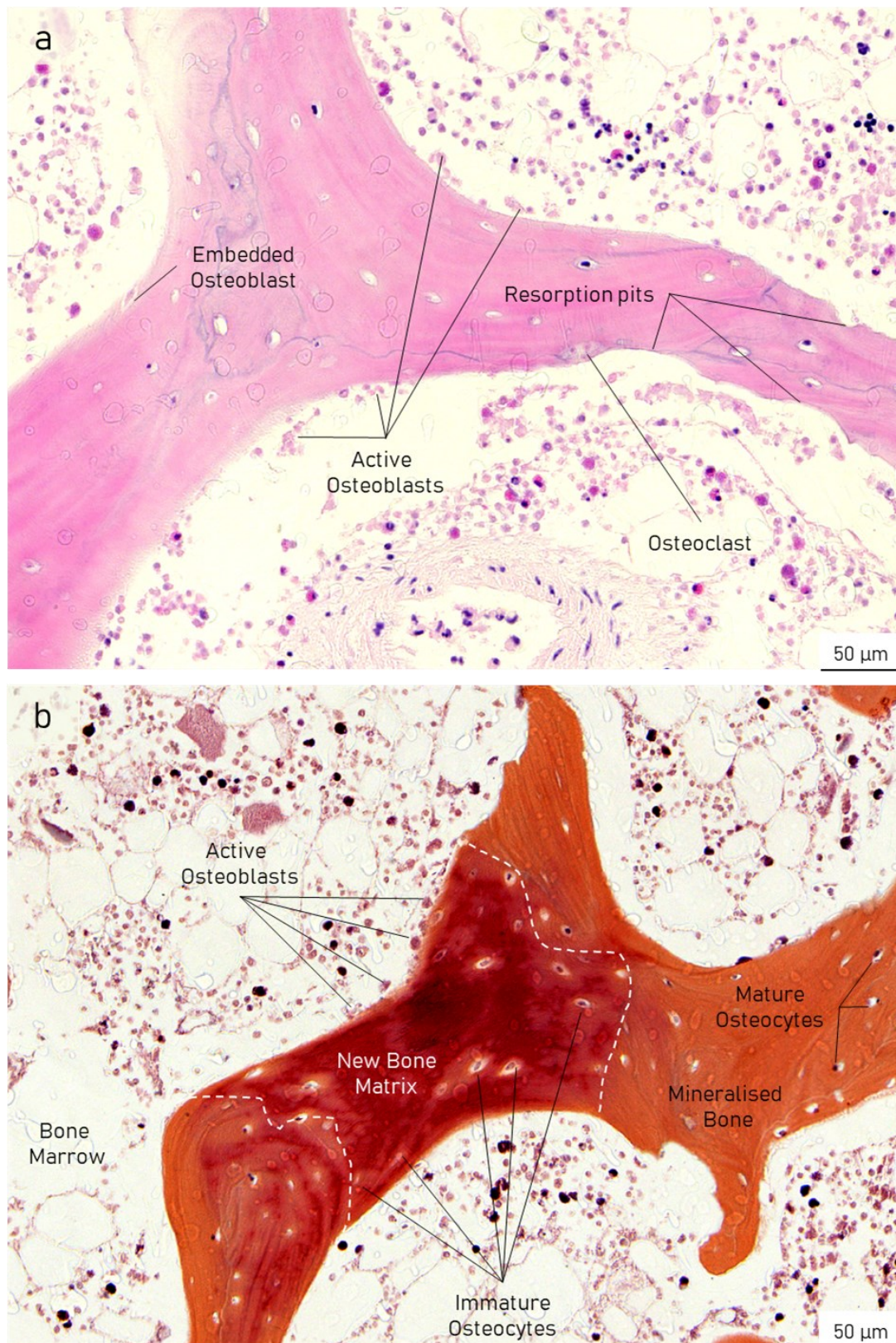


Figure 5.13. Histological staining of an active osseointegrative implant specimen showing (a: H&E) a bone remodelling compartment close to the bone-implant interface with active osteoblast formation and osteoclast resorption and (b: Movat Pentachrome) new bone matrix deposited by osteoblasts in the bulk tissue.

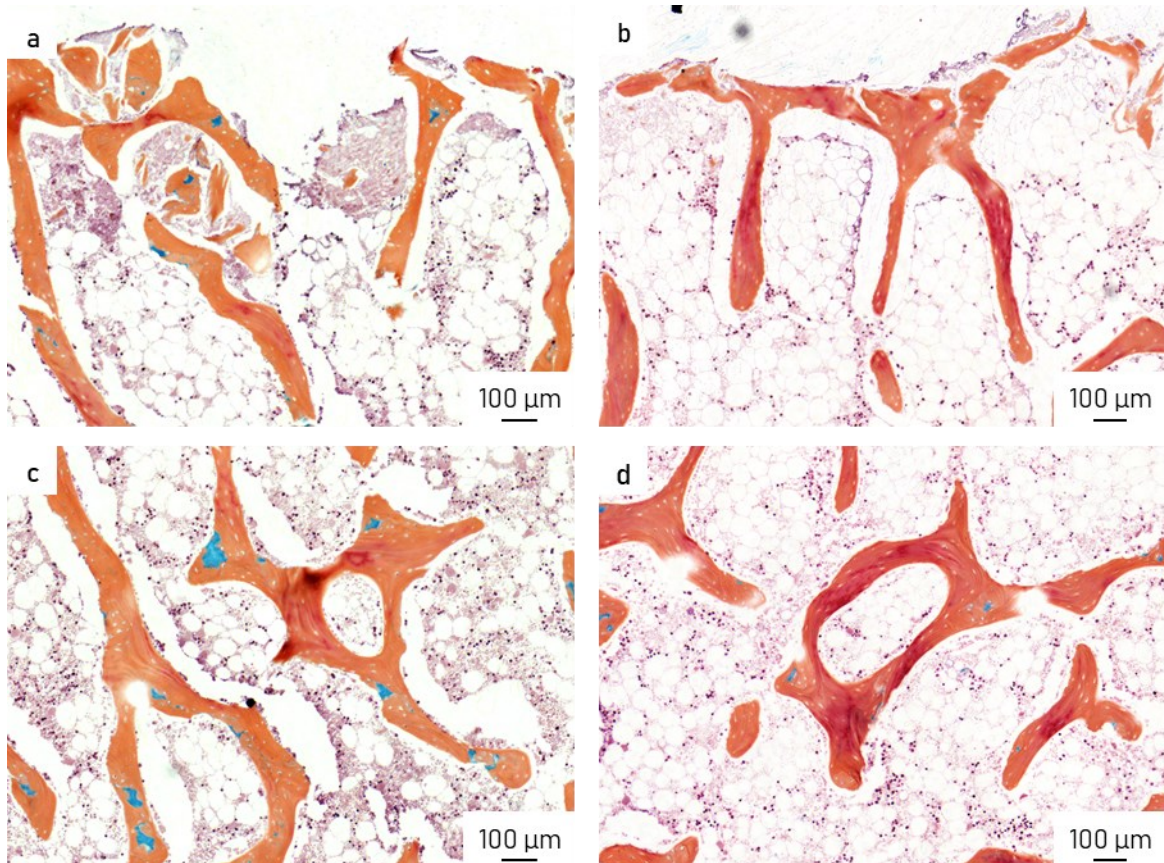


Figure 5.14. Histological staining (Movat pentachrome) indicating new bone formation (red) at the bone-implant interface (top; a, b) and in the bulk tissue (middle; c, d) for the LIPUS-treated specimens (left; a, c) and the passive controls (right; b, d).

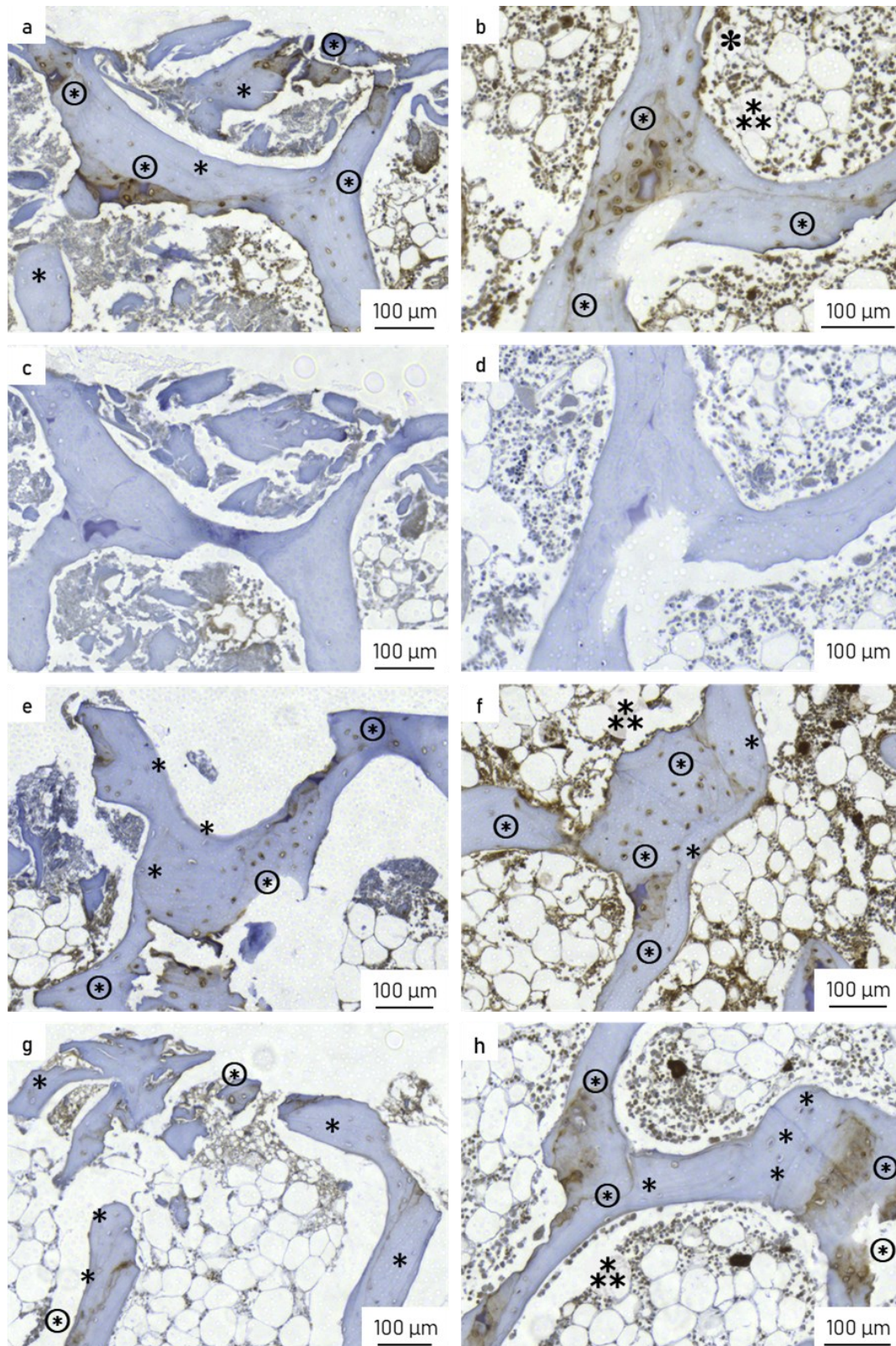


Figure 5.15. Osteopontin (OPN) expression at the bone-implant interface (left) and in the bulk trabecular structure (right) in (a, b) an active osseointegrative implant specimen, (c, d) the corresponding isotypic controls for the active osseointegrative implant specimen, (e, f) a LIPUS-treated specimen, and (g, h) a passive control. Annotations indicate OPN-positive osteocytes (brown cytoplasm; ⊙), OPN-negative osteocytes (blue nuclei; *), osteoblasts (**), and osteoclasts (*).

5.5. Discussion

This research was the first *ex vivo* study of an active osseointegrative implant: an intermediate between *in vitro* experiments on isolated cell types and *in vivo* trials in live animals. The model has advanced on earlier *in vitro* research by investigating the effects of active osseointegrative treatment under tightly controlled physiological conditions at organ level, wherein the cellular diversity and extracellular structure of natural bone was inherently captured. Effects of the active osseointegrative implant on new bone formation on the implant (contact osteogenesis) and in the periprosthetic tissue (distance osteogenesis) were referenced against LIPUS stimulation and static culture using mineralisation staining, biomarker analysis, and histological protocols.

An *in vitro* culture of murine preosteoblasts (MC3T3-E1) confirmed the osteoconductivity of the rough titanium implant surface as a prelude to the *ex vivo* study: cell viability (>95%) was maintained for 28 days and extensive networks of extracellular matrix were observed across the entire surface. In the *ex vivo* culture, calcium mineralisation on the active osseointegrative implant surfaces on the seventh and fourteenth days of treatment were highly elevated compared to the LIPUS-stimulated specimens (some mineralisation) and the passive controls (near-zero mineralisation). SEM revealed extensive formations of irregular woven bone on the surface of the active osseointegrative implant by the 21-day treatment endpoint, and new growth emanating from bone fragments had begun to integrate with the surface. Bone formations were less expansive in LIPUS-treated specimens and only small deposits were seen in the passive controls. Ongrown tissue on the active osseointegrative implant at the 21-day endpoint was also more viable than the passive controls. Histological and immunohistochemical analyses showed more active osteoid seams at the implant-bone interface in the active osseointegrative implant specimens compared to the specimens in the other conditions. Expression of osteopontin – a protein with a well-documented role in bone remodelling and cell adhesive interactions (Giachelli and Steitz, 2000; Icer and Gezmen-Karadag, 2018) – was also high at the bone-implant interface in the treated specimens (A & B).

There was evidence of bone remodelling in the bulk trabecular structure of all specimens: remodelling zones exhibiting both osteoblasts and osteoclasts indicative of normal bone formation and resorption were observed during the histological and immunohistochemical analyses. Expression of osteopontin was high in all samples but did appear higher in specimens from both treatment conditions: the active osseointegrative implant and the LIPUS stimulation. Histological differences in the bulk trabecular structure of each specimen

were less evident. In the fluorescent imaging, mineralisation was lower in the bone treated by the active osseointegrative implant on the seventh and fourteenth days of treatment. Levels of alkaline phosphatase – an enzyme involved in mineralisation (Golub and Boesze-Battaglia, 2007) – in the active osseointegrative implant specimens were also decreased in the first week of culture compared to the LIPUS-treated specimens and passive controls, between which no difference was detected. Calcium ion concentrations in the specimens treated by the active osseointegrative implant (combined electrical-ultrasonic stimulation) were elevated above the media baseline and the other specimens at every timepoint. This efflux of calcium and reduction in mineralisation is likely to be a result of the drop in pH levels (7.4 to 7.1): metabolic acidosis in mammals (systemic pH < 7.35) increases osteoclast-mediated resorption whilst inhibiting osteoblast-mediated collagen synthesis and mineralisation (Bushinsky *et al.*, 2001). This drop in pH levels could have been caused directly by the electrochemistry of the active osseointegrative implant or indirectly by increased metabolism within the bone. Suspected metabolic acidosis should be investigated by monitoring levels of Prostaglandin E2 (PGE2) (Bushinsky *et al.*, 2001); it could be addressed in culture with larger media volumes or higher change rates; and it may resolve naturally in vivo due to physiological pH regulation. Inorganic precipitation of calcium phosphate into cancellous bone due to supersaturation of the culture media was proposed as a cause for artefactual mineralisation in a previous study of ex vivo bone culture (Davies, 2005), but this is considered a weaker secondary effect given the correlated ALP levels.

Before this study, ex vivo models had been used to study osseointegration of an orthopaedic implant in response to passive physiological stimuli (no artificial stimulation): static (Zankovic *et al.*, 2021) and dynamic loading (Dua, Jones and Noble, 2021). In those studies, cell migration onto titanium implant surfaces had occurred within four weeks of culture (Dua, Jones and Noble, 2021; Zankovic *et al.*, 2021), and immature crystallite-like structures had formed by the seventh week (Dua, Jones and Noble, 2021). Those findings were consistent with this research: cells had migrated onto the titanium implant surface within three weeks of passive culture but had not deposited mineralised tissue. In vitro models have previously been applied to study the isolated subprocesses of osseointegration: ultrasound stimulation promotes osteoblast differentiation (Nagasaki *et al.*, 2015; Feng *et al.*, 2019; Ambattu, Gelmi and Yeo, 2022), maturation (Wang *et al.*, 2014; Cao *et al.*, 2017; Veronick *et al.*, 2018), and proliferation (Wu, Lin and Qin, 2015), whilst electrical stimulation has been shown to promote osteoblast differentiation (Gittens *et al.*, 2013), proliferation (Isaacson *et al.*, 2011; Bodhak *et al.*, 2012), and viability (Pettersen, Shah and Ortiz-Catalan, 2021). With expansive mineralised structures within three weeks of treatment, this ex vivo model elevates evidence of the

accelerated osteogenic effects of active osseointegrative treatment from cell level to organ level, thereby advancing the clinical readiness of the technology.

Collectively, these results suggest that early osseointegration at the bone-implant interface (contact and distance osteogenesis) is enhanced by the active osseointegrative implant, but the increased electroactivity may have adverse effects in periprosthetic bone if pH levels are not regulated. The LIPUS treatment demonstrated weaker enhancements in early osseointegration at the bone-implant interface but did not exhibit any adverse effects in the periprosthetic bone. Both treatment protocols used a single set of parameters, which was informed by literature but not optimised, and the underlying mechanisms for accelerated osseointegration are still to be understood. Furthermore, the osteogenic effects of active treatment beyond three weeks are unclear and may dissipate over time (Dergin *et al.*, 2013), which would need to be investigated in longer ex vivo cultures or in vivo animal trials. An in vivo animal trial would also encompass the responses of other systems, which are known to affect osseointegration but whose interactions are not captured by this ex vivo model. The effects of treatment amidst clot formation (haemostasis) and the restoration of blood supply (angiogenesis), which are both orchestrated by the vascular system, are unknown but not expected to predominate the fundamental osteogenic response. This preclinical evaluation was conducted on healthy, skeletally immature porcine tissue, whilst arthroplasty is characteristically performed on elderly patients, whose metabolisms, bone turnover, and mechanotransductive responses are all lower (Boskey and Coleman, 2010). Reduced osseointegration in elderly human tissue would therefore be expected in both passive and active conditions, though the relative effect on the response to treatment remains unclear. Further validation of treatment effects in this population could be obtained by repeating this evaluation with tissue sourced from arthroplasty procedures, such as femoral heads removed during total hip arthroplasty. Despite these limitations, this ex vivo model provides a platform for both optimising and understanding the early osteogenic effects of treatment as a cost-effective, 3Rs-compatible precursor to animal trials.

5.6. Summary of Findings

An innovative active osseointegrative implant was introduced in this chapter and was evaluated in an ex vivo organ model, which produced the following findings:

- By reconfiguring the embedded circuitry used in Chapters 3 & 4 (estimated material cost: \$1), it was possible to artificially accelerate the early phases of osseointegration with an active implant in an ex vivo organ model.

- Expansive mineralised structures with high cell viability were observed on the titanium implant surface within three weeks of treatment, and bone tissue had begun to integrate with the surface.
- Mineralisation in the bulk bone was lower during culture than the passive controls, which may be a result of metabolic acidosis caused by insufficient media replacement rates in the ex vivo model – this adverse effect should be investigated and addressed as a priority in follow-on research.
- Results from the passive controls (static load) were consistent with findings from previous ex vivo studies of osseointegration: cell proliferation onto titanium implant surfaces within 3–4 weeks without any mineralisation.
- The ex vivo model provides a platform for optimising and understanding the active osseointegrative implant under tightly controlled conditions at organ level as a cost-effective, low-ethical-impact alternative to in vivo animal trials.

Addendum A: Active Osseointegration Driving Voltages

The ultrasonic dose in the active osseointegrative implant and the LIPUS treatment were both delivered by a thickness-mode piezoelectric transducer (PI Ceramic PRYY+0442) according to the following parameters:

- 2 MHz sine wave frequency;
- 1 kHz pulse frequency;
- 20% duty cycle;
- 30 mW/cm² power; and
- 30 mins daily treatment duration,

which were within the ranges of previous studies of LIPUS on bone defect healing and osseointegration (Tanzer, Kantor and Bobyn, 2006; Iwai *et al.*, 2007; Ustun *et al.*, 2008; Hsu *et al.*, 2011; Liu *et al.*, 2012; Monden *et al.*, 2015; Zhou *et al.*, 2016; Ruppert *et al.*, 2019).

The driving voltage for the LIPUS treatment (B; Fig. 5.A1), wherein the ultrasound is delivered to the bone, was determined by way of a one-dimensional power calculation. The time-averaged transmitted power, $\langle P \rangle$, for the LIPUS piezoelectric transducer (Transducer B) excited in the sinusoidal regime, i.e. $U = |U|e^{i\omega t}$, was given as

$$\langle P \rangle = K^2 C_0 f_p |H(f)|^2 |U|^2 \quad (5.1)$$

where K^2 was the electromechanical coupling coefficient, C_0 was the static capacitance, f_p was the half-wavelength resonance frequency in the free condition, $|H(f)|$ was the frequency response function, and $|U|$ was the amplitude of the excitation voltage (Royer and Dieulesaint, 2000).

The frequency response for the thickness-mode transducer with one free face (air-backed) was modelled as

$$H(f) = \frac{1}{m \left(\frac{\pi f}{2f_p} \right)}, \quad (5.2)$$

where

$$m(\theta) = \sqrt{\frac{Z}{Z_p}} \left(\frac{K^2}{2\theta} - \cot 2\theta \right) \cot \theta + j \sqrt{\frac{Z_p}{Z}} \left(\frac{K^2}{\theta} - \cot \theta \right), \quad (5.3)$$

Z was the acoustic impedance of the propagating medium and Z_p was the acoustic impedance of the piezoelectric transducer.

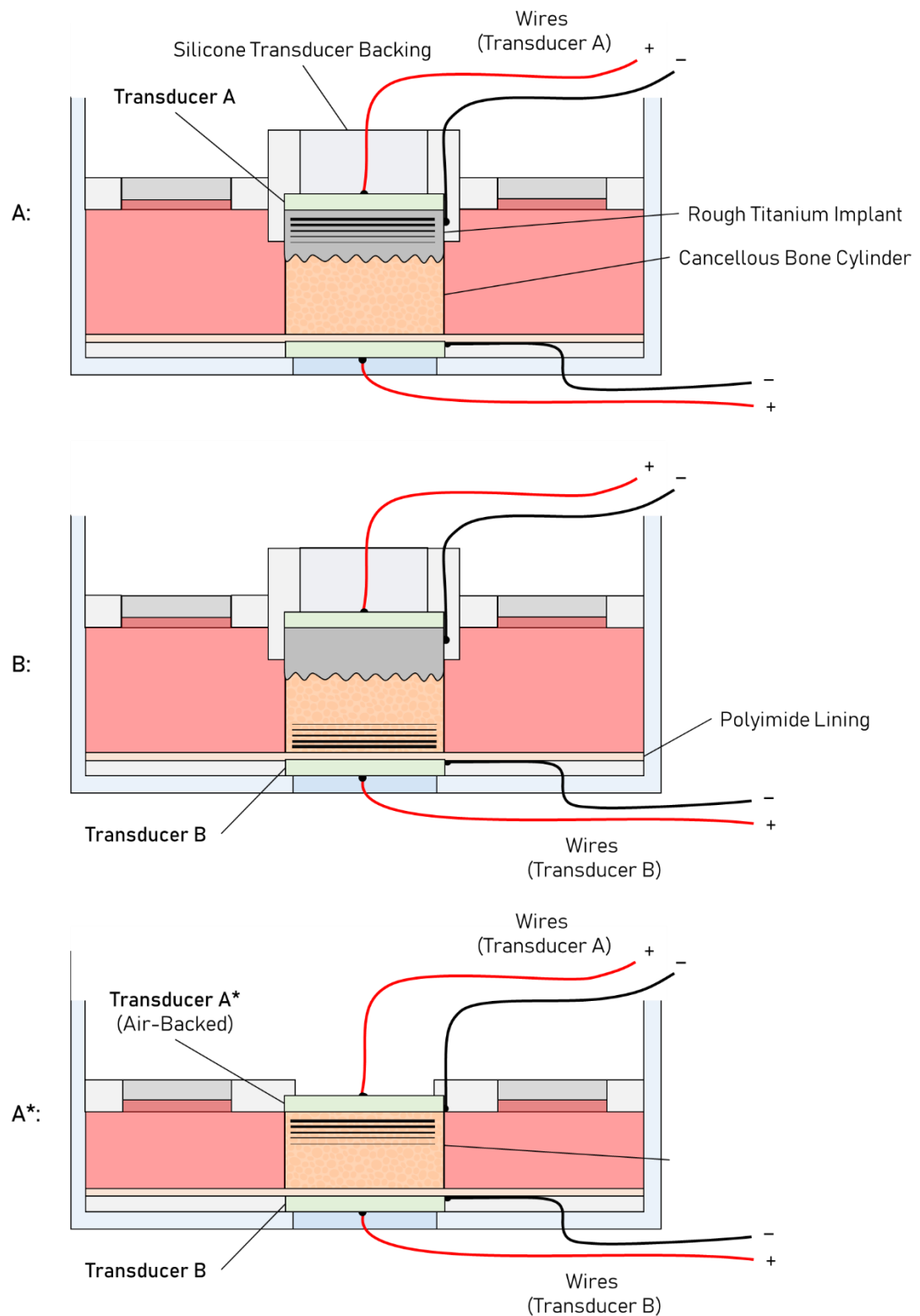


Figure 5.A1. Configurations of the bioreactor for (A) delivery of active osseointegrative implant treatment, (B) delivery of LIPUS-only treatment, and (A*) calibration of the active osseointegrative implant dose.

Transducer properties were all sourced directly or derived from the manufacturer's specifications (Table 5.A1). The thin polyimide layer was negated, and the piezoelectric transducer was assumed to transmit to the bone directly. A reference value was used for the acoustic impedance of cancellous bone: $7.75 \times 10^6 \text{ kg}/(\text{s} \cdot \text{m}^2)$ (Azhari, 2010), and the driving voltage required for $30 \text{ mW}/\text{cm}^2$ was calculated as 1.57 V.

Table 5.A1. Thickness-mode properties of PRYY+0442 piezoelectric transducers.

Parameter	Symbol	Value	Source
Outer diameter	D	10 mm	(PI Ceramic, 2020b)
Thickness	d	1 mm	(PI Ceramic, 2020b)
Resonant frequency	f_p	2.11 MHz	(PI Ceramic, 2020b)
Coupling coefficient	K	0.46	(PI Ceramic, 2020b)
Static capacitance	C_0	0.837 nF	(PI Ceramic, 2020b)
Density	ρ	$7.85 \text{ g}/\text{cm}^3$	(PI Ceramic, 2020a)
Speed of sound	V_p	4,220 m/s	$V_p = 2d \cdot f_p$
Acoustic impedance	Z_p	$33.1 \times 10^6 \text{ kg}/(\text{s} \cdot \text{m}^2)$	$Z_p = \rho_p \cdot V_p$

In the active osseointegrative implant treatment (A; Fig. 5.A1), the ultrasound was delivered to the bone via the rough titanium implant. The titanium implant surface, which had previously been characterised (van Arkel *et al.*, 2018), had random roughness at multiple scales by design (randomised sinusoidal contours) and by manufacture (semi-sintered titanium particles), which introduced complex acoustic scattering that could not be easily modelled. Instead, the driving voltage for the active osseointegrative implant treatment was calibrated experimentally.

In the calibration setup (A*; Fig. 5.A1), an air-backed transducer was used to transmit acoustic waves to the bone directly, and the voltage received by Transducer B (after attenuation through the bone) was recorded. The driving voltage in the active osseointegrative implant (Transducer A) was then raised until an equivalent voltage was received through the same cancellous bone cylinder. This tuning was repeated on three cancellous bone specimens ($\emptyset 10 \text{ mm} \times 5 \text{ mm}$), which had been extracted from porcine

specimens (Medmeat Ltd; fresh frozen; one freeze-thaw cycle) using the surgical technique detailed in Section 5.3.2. The experimentally calibrated driving voltage required for the active osseointegrative implant was 2.42 V.

Addendum B: Supplemental Histology Images

Histological analysis was conducted on all treatment and control conditions with bone sectioning in the plane transverse to the bone-implant interface (Fig. 5.B1). A series of images characterising the biological response of the bone tissue in response to each condition are provided as supplementary material in this addendum (Figs. 5.B2-B9).

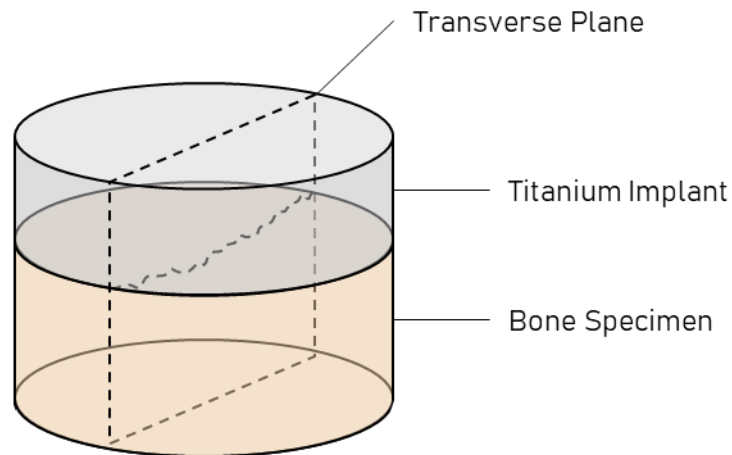


Figure 5.B1. Bone specimens were sliced in the plane transverse to the bone-implant interface.

Active Osseointegrative Implant

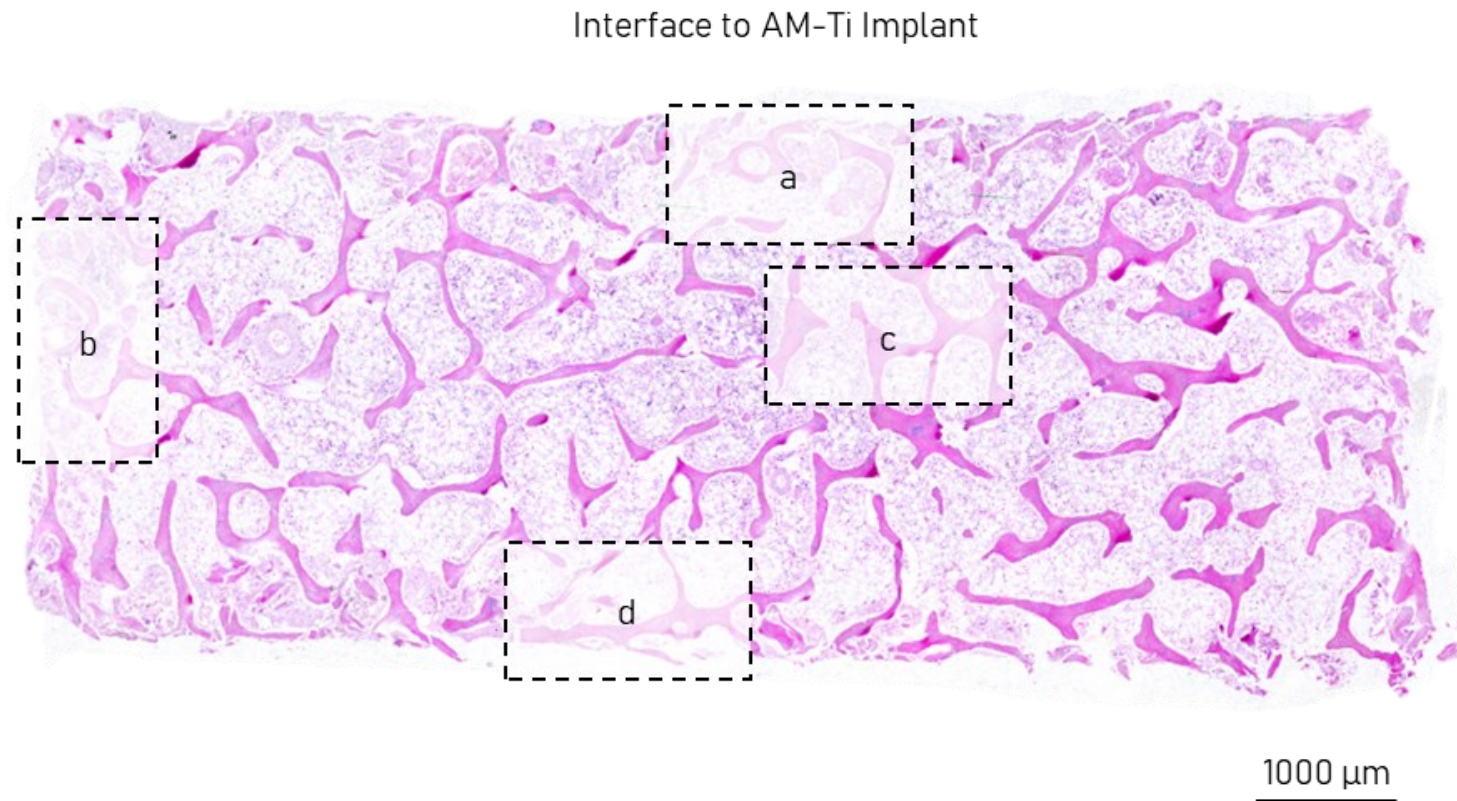


Figure 5.B2. Macroscopic histological staining (H&E) of cancellous bone after 21 days of active osseointegrative implant treatment. Three regions of interest are identified for more detailed analysis: (a) tissue in apposition to the actively stimulated titanium surface; (b) wound tissue adjacent to the open surface of the sample; (c) non-interfacial bulk tissue; and (d) tissue adjacent to the polymer base of the well.

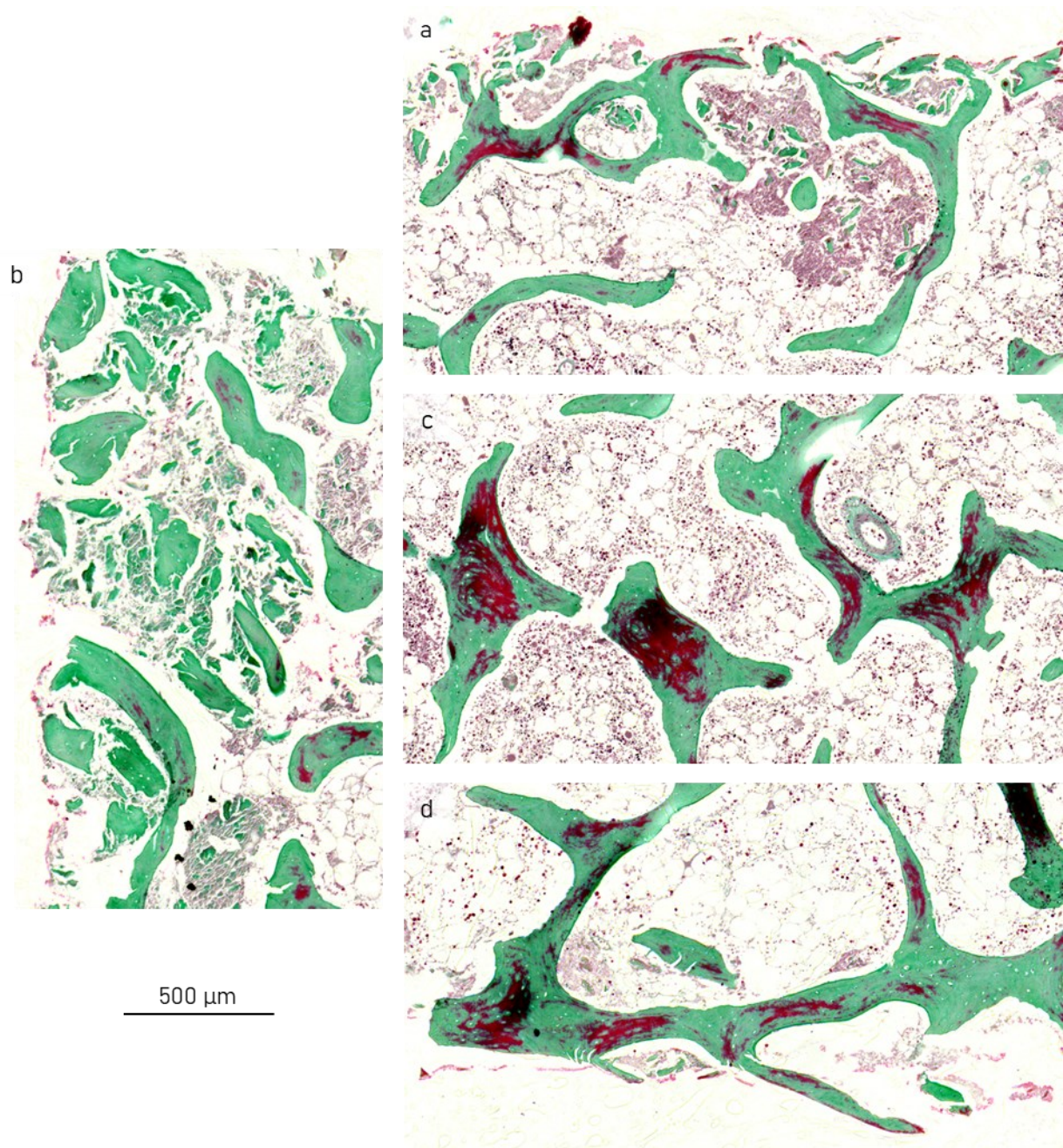


Figure 5.B3. Masson-Goldner trichrome staining indicating osteoid seams and new bone matrix (both ruby red) after 21 days of active osseointegrative implant treatment (Treatment A) in representative regions of interest: (a) osteoid seams and new bone matrix are observed in direct apposition to the implant surface indicative of bone remodelling, with small bone fragments and fibrous tissue of haematopoietic origin in the bone marrow spaces; (b) less new bone matrix and osteoid seams are observed at the surface open to the media amidst debris from the original surgery; (c) new bone matrix is observed in the bulk tissue indicative of recent bone turnover; and (d) new bone matrix is observed on the opposite side of the implant without the fibrous tissue formation exhibited in apposition to the implant.

Low-Intensity Pulsed Ultrasound

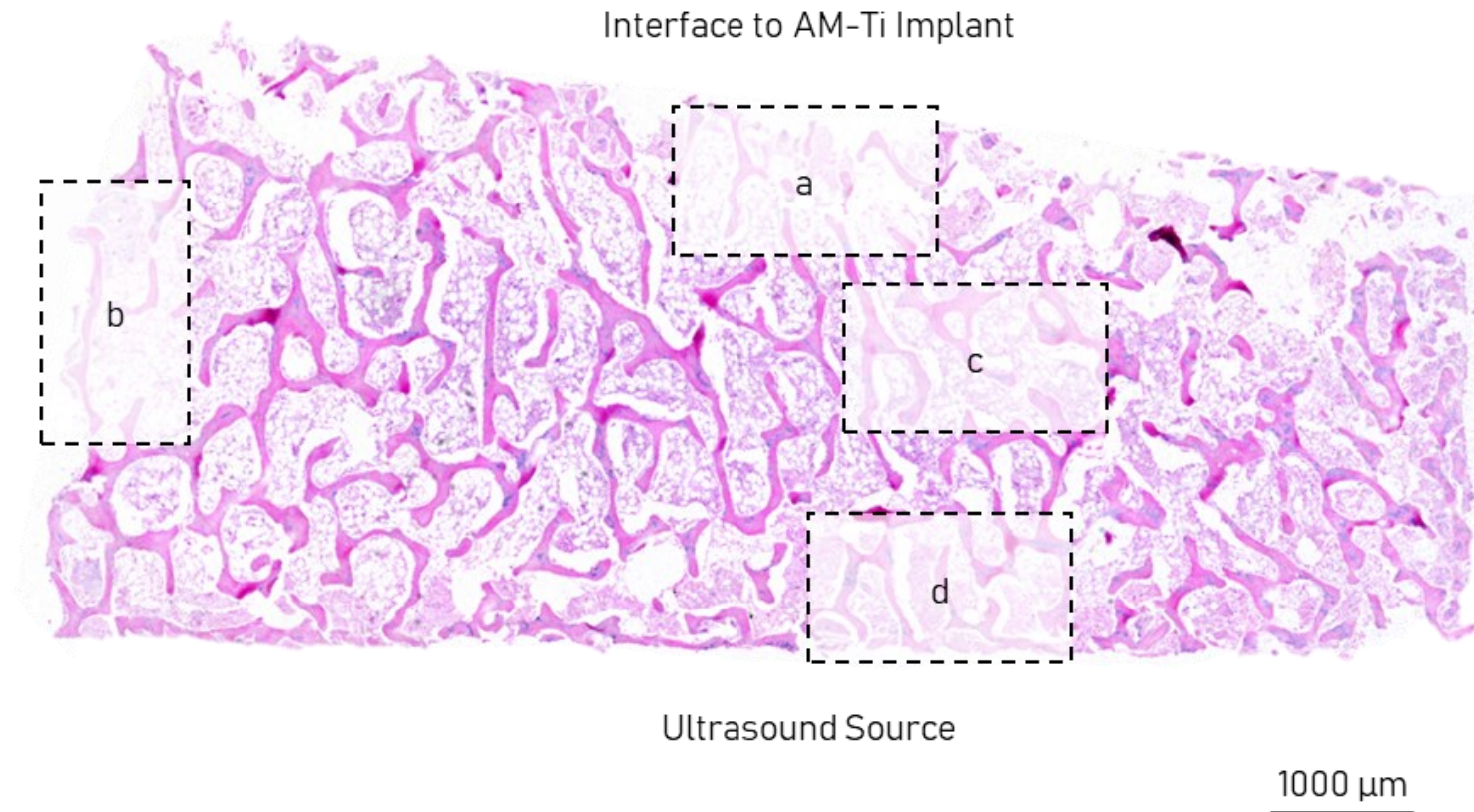


Figure 5.B4. Macroscopic histological staining (H&E) of cancellous bone after 21 days of LIPUS treatment (Treatment B); tissue was sectioned in the transverse plane. Three regions of interest are identified for more detailed analysis: (a) tissue adjacent to the titanium surface; (b) wound tissue adjacent to the open surface of the sample; (c) non-interfacial bulk tissue; and (d) tissue adjacent to the polymer base of the well where the ultrasonic treatment was applied.

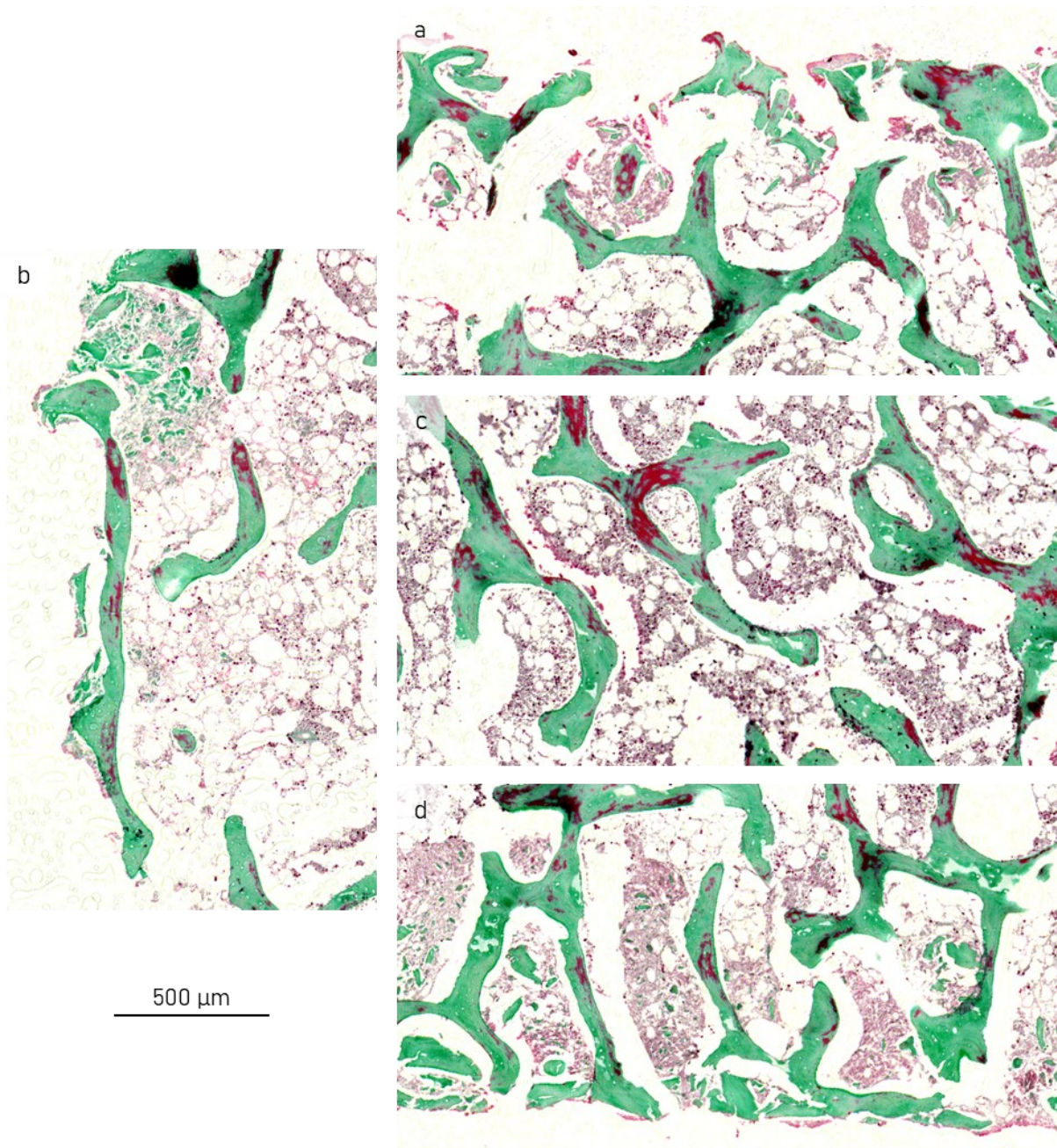


Figure 5.B5. Masson-Goldner trichrome staining indicating osteoid seams and new bone matrix (both ruby red) after 21 days of LIPUS treatment (Treatment B) in representative regions of interest: (a) osteoid seams and new bone matrix were observed in direct apposition to the implant surface indicative of bone remodelling; (b) cutting debris from the original surgery with less new bone matrix and osteoid seams were seen at the surface open to the media; (c) new bone matrix was observed in the bulk tissue indicative of recent bone turnover; and (d) cutting debris and some evidence of active bone remodelling were seen at the LIPUS-stimulated surface.

Passive Control (with Implant)

Interface to AM-Ti Implant

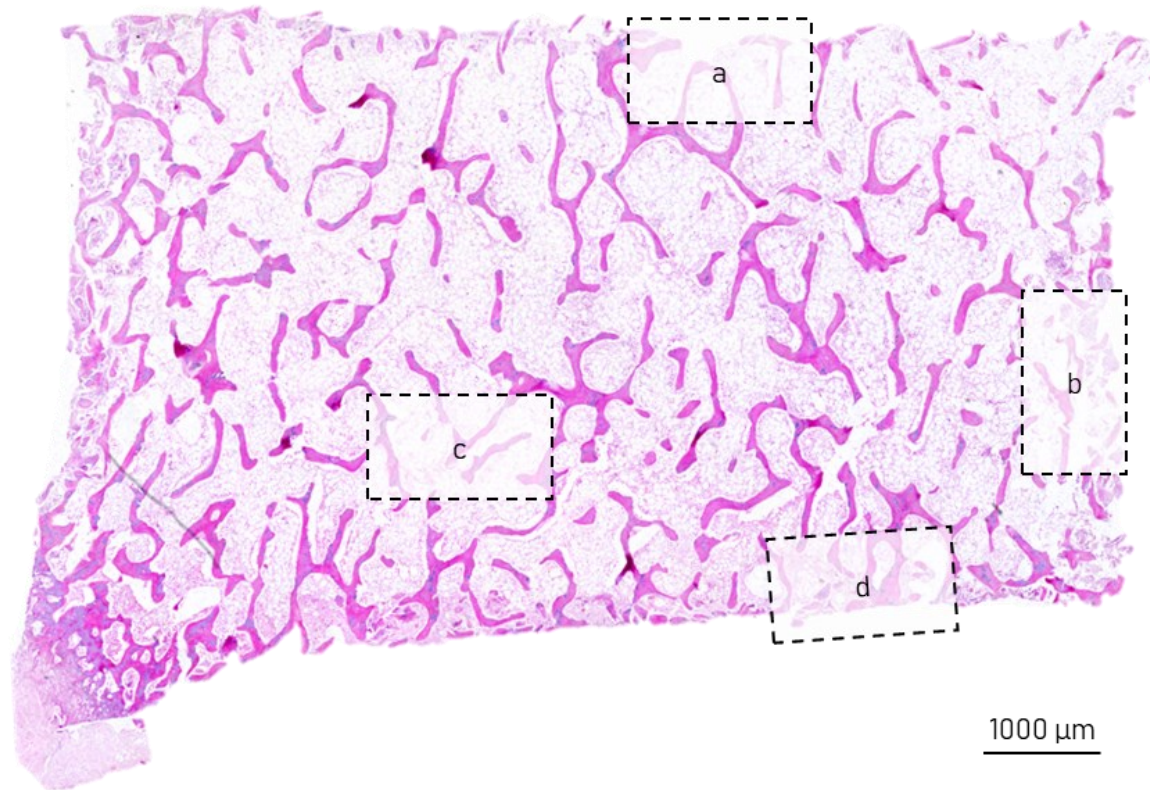


Figure 5.B6. Macroscopic histological staining (H&E) of cancellous bone after 22-day passive culture. Three regions of interest are identified for more detailed analysis: (a) tissue in apposition to the titanium surface; (b) wound tissue at the open surface of the sample; (c) non-interfacial bulk tissue; and (d) tissue adjacent to the polymer base of the well. A small amount of physal tissue (growth plate) was extracted during the original resection of this specimen (bottom left).

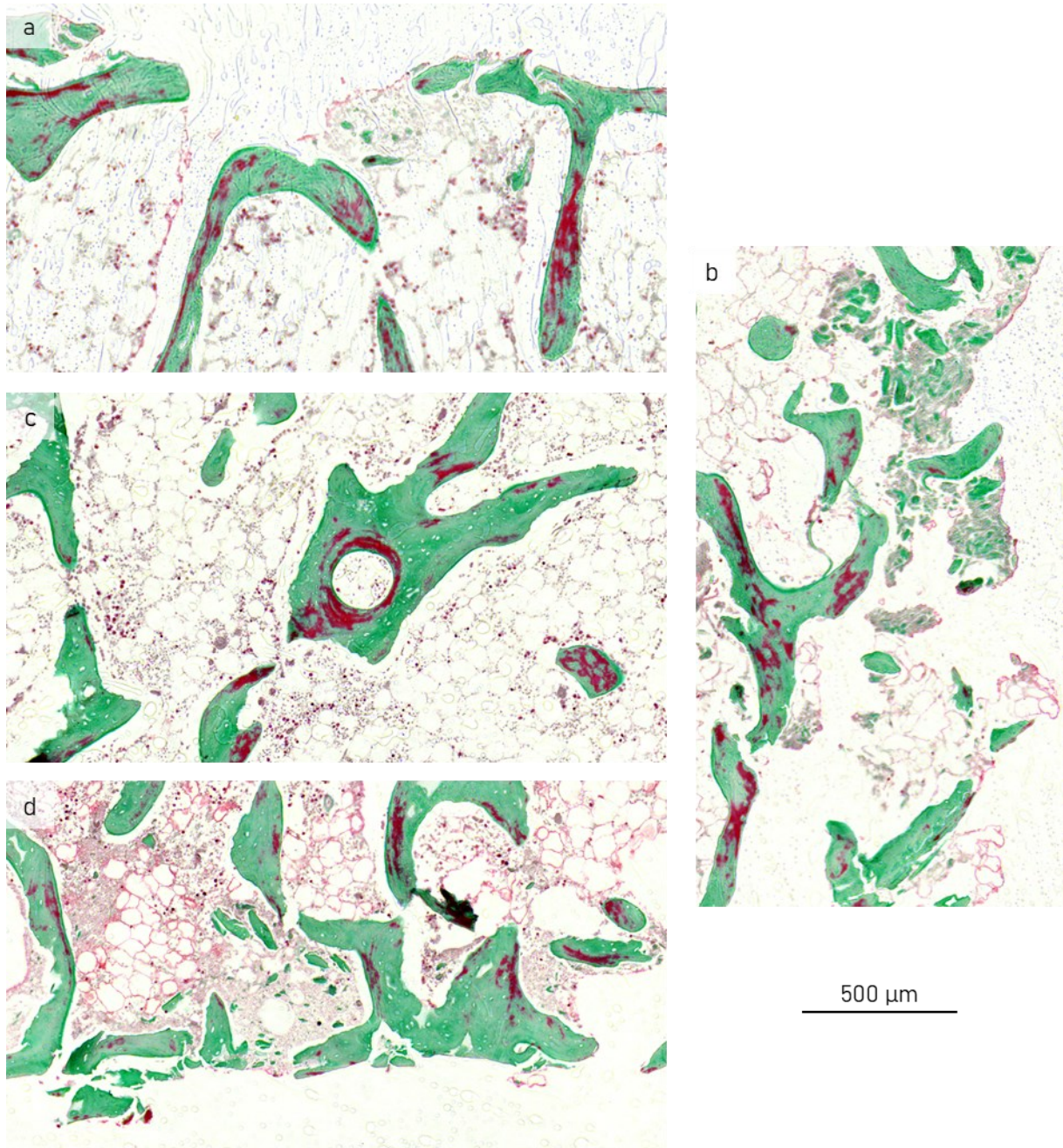


Figure 5.B7. Masson-Goldner trichrome staining indicating osteoid seams and new bone matrix (both ruby red) after passive culture in representative regions of interest: (a) osteoid seams and new bone matrix were observed within the periprosthetic tissue but not in direct apposition to the implant; (b) cutting debris and some evidence of remodelling were seen at the surface open to the media; (c) new bone matrix was observed in the bulk tissue indicative of recent bone turnover; and (d) less evidence of new bone matrix was observed at the surface opposite the implant.

Passive Control (without Implant)

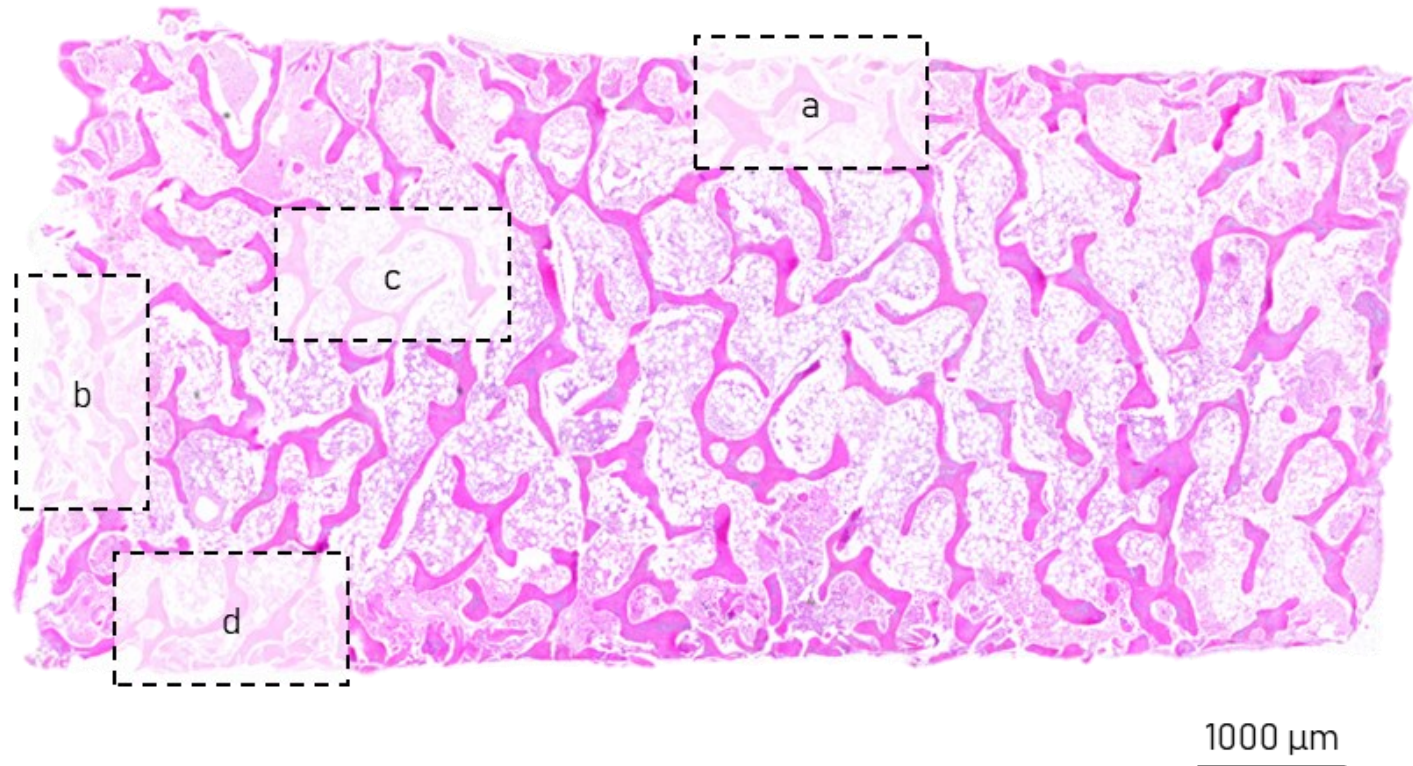


Figure 5.B8. Macroscopic histological staining (H&E) of cancellous bone after 22-day passive culture without a titanium implant. Three regions of interest are identified for more detailed analysis: (a) tissue that was cut using an oscillating saw and was open to the media; (b) tissue that was cut using a holesaw and was open to the media; (c) non-interfacial bulk tissue; and (d) tissue adjacent to the polymer base of the well.

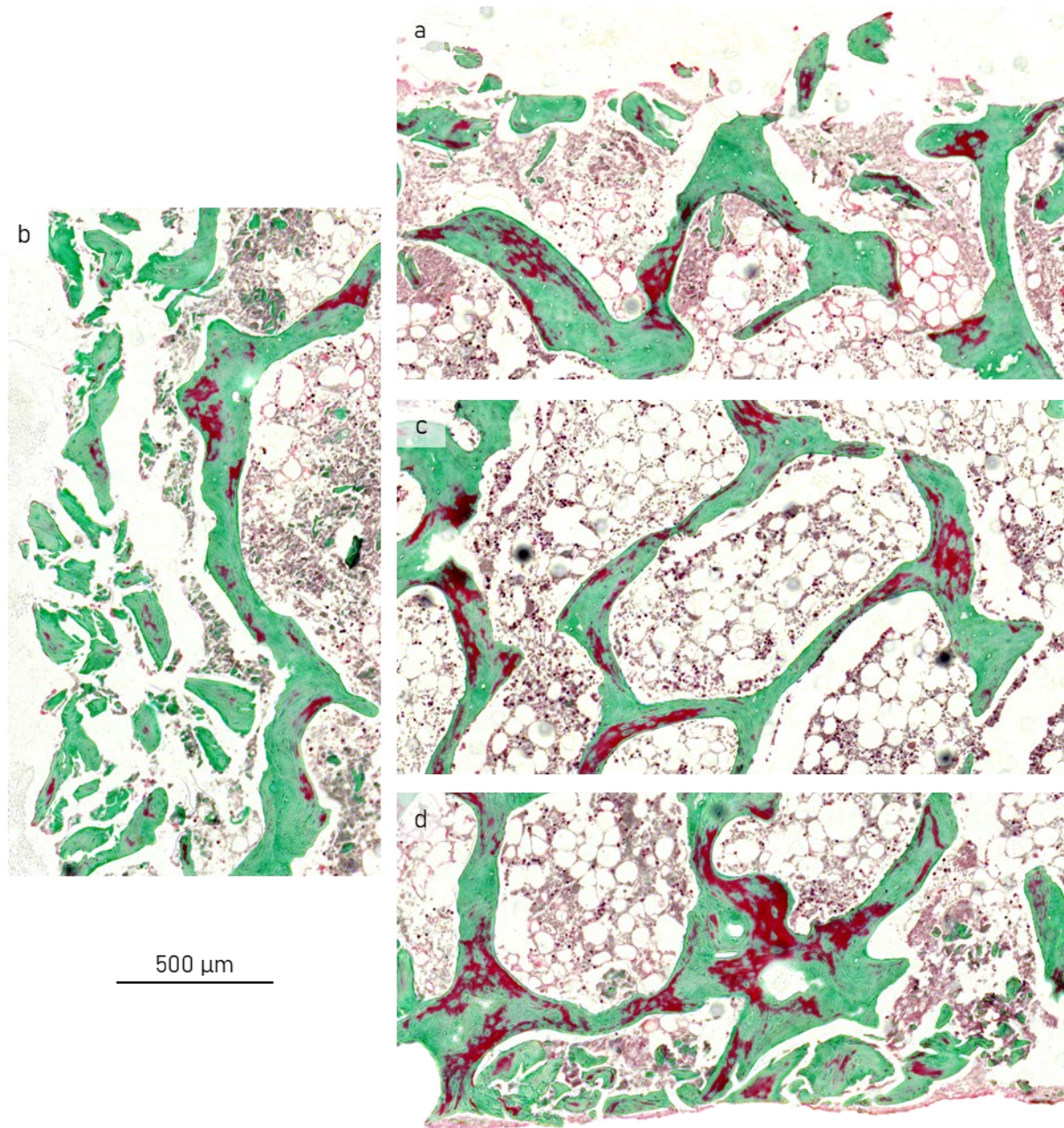


Figure 5.B9. Masson-Goldner trichrome staining indicating osteoid seams and new bone matrix (both ruby red) after passive culture in representative regions of interest: (a) osteoid seams and new bone matrix were observed at the open face of the bone where the implant had been in other configurations; (b) little evidence of remodelling was seen amidst the cutting debris on the side of the cylinder; (c) new bone matrix was observed in the bulk tissue indicative of recent bone turnover; and (d) less evidence of new bone matrix was observed at the surface opposite the implant.

Chapter 6

Lead-Free Piezoceramics for Smart Biomedical Implants: Electromechanical and Biological Characterisations of BNT-6BT

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Notation

This chapter makes use of standard notation for electromechanical fields and constants of poled piezoceramics. Superscripts S , T , E and D respectively denote boundary conditions: constant strain (mechanically clamped), constant stress (mechanically free), constant electric field (short circuit), and electrical displacement (open circuit). Subscripts indicate direction in Kelvin-Voigt notation.

6.1. Introduction

Both smart implant concepts developed in this thesis have depended on piezoelectric ceramics: the first was an instrumented implant to detect tibial debonding and infection (Chapters 3 & 4) and the second was an active implant for accelerating osseointegration (Chapter 5). Several other applications for implanted piezoceramics are emerging or are already in practice: wireless power transfer to therapeutic devices such as cardiac pacemakers (Jin *et al.*, 2021) and tumour photosensitisers (Zhou *et al.*, 2015); wireless data transfer to and from neural interfaces (Charthad *et al.*, 2018; Ghanbari *et al.*, 2019); energy harvesting from physiological motion in the heart, lungs, and diaphragm (Dagdeviren, Yang, *et al.*, 2014); and in vivo mechanical sensing of joint loads (D'Lima *et al.*, 2005), arterial pressures (Dagdeviren, Su, *et al.*, 2014), and tympanic membrane vibrations (İlik *et al.*, 2018). The naturally occurring piezoelectricity of bone has also been implicated in its healing response: electric displacement of the fibrillar collagen architecture caused by loading opens calcium channels in osteocytes and thereby evokes a pro-osteogenic signalling response (Kao *et al.*, 2019). Piezoceramics have therefore also been suggested as electroactive, power-source-independent scaffold materials for supraphysiological tissue regeneration (Rajabi, Jaffe and Arinzeh, 2015).

Historically, the best performing piezoceramics have been lead-based, principally lead zirconate titanate (PZT), but lead is highly toxic even in small doses (Agency for Toxic Substances and Disease Registry, 2020). EU legislation (Directive 2011/65/EU, 2011) has led to lead-based piezoceramics being phased out across many industry sectors and has fostered research into lead-free alternatives (Rödel and Li, 2018). Whilst active implantable medical devices are currently exempt from restrictions, the scope of restrictions has already narrowed from an exemption for all medical devices when the legislation was first introduced – the exemption for PZT-containing in vitro diagnostic equipment will lapse in 2023 (Directive 2011/65/EU, 2011) – and is expected to narrow further.

There are currently three families of lead-free piezoceramic materials that are considered candidates to replace PZT, which are based on potassium sodium niobate (KNN) (Wu, Xiao and Zhu, 2015; Tokay and Yazıcı, 2022), barium titanate (BT) (Acosta *et al.*, 2017), and bismuth sodium titanate (BNT) (Tokay and Yazıcı, 2022). Of these families, the excellent piezoelectric properties of KNN-based piezoceramics incited current lead-free research interest (Saito *et al.*, 2004), and this family has in turn been the subject of intense development efforts (Wu, Xiao and Zhu, 2015). Large-scale preparation and processing of KNN-based piezoceramics is more challenging than current lead-based techniques (Villafuerte-Castrejón *et al.*, 2016;

Zhang, Zheng and Wu, 2020; Tokay and Yazıcı, 2022), and commercial translation of KNN-based piezoceramics has so far lagged behind research progress (Thong *et al.*, 2019). BT-based ceramics – calcium- and zirconium-doped barium titanate (BCZT) is of particular interest – exhibit high piezoelectric coefficients but poor thermal stability (Acosta *et al.*, 2017). this characteristic, which is not detrimental to medical applications, and challenges in piezoceramic synthesis has limited commercial uptake of BT-based piezoceramics (Villafuerte-Castrejón *et al.*, 2016). BNT-based piezoceramics demonstrate more modest piezoelectric properties than the KNN- and BT-based families (Villafuerte-Castrejón *et al.*, 2016), but thermal behaviour is more stable and manufacturing techniques are more conventional (Tokay and Yazıcı, 2022). In the BNT-based family, BT-doped BNT in the stoichiometric ratio $0.94\text{Bi}_{0.5}\text{Na}_{0.5}\text{TiO}_3\text{--}0.06\text{BaTiO}_3$ (BNT-6BT) has received considerable research interest and was recently commercialised by PI Ceramics (PIC700).

In this chapter, BNT-6BT is characterised to determine its suitability for deployment in implantable electronics and electroactive scaffolds. Ceramics from two fabrication techniques are considered: the conventional solid-state sintering method and additive manufacturing. The conventional ceramic method is well suited to the bulk manufacture of disc and plate transducers, such as those used in Chapters 3, 4 & 5, whilst the additive manufacturing technique the offers more design freedom and could be used to produce scaffolds. In this chapter, the electromechanical properties of both materials are characterised and referenced against figures of merit for various applications: pulse-echo measurement (Chapters 3 & 4), resonance-mode excitation (Chapter 5), energy harvesting, and pressure sensing. Furthermore, the cytotoxicity and biocompatibility of BNT-6BT were assessed to determine its suitability for in vivo applications.

6.2. Fundamental Theory of Piezoceramics

Piezoceramics generate a voltage in response to applied stress and vice versa: the mechanical deformation of non-centrosymmetric crystals causes the asymmetric displacement of positive and negative ions within the ceramic structure, and thus a net charge develops. Piezoelectricity arises from atomic polarisation within the crystal structure of certain ceramics. When manufactured, most piezoceramics are polycrystalline with randomly oriented dipoles, which counteract at the macroscopic level when mechanical deformation or an electric field is applied (Fig. 6.1a). The materials are therefore ‘poled’ with a high-voltage electric field to generate a net polarisation (Fig. 6.1b), which remains in the material after the electric field has been removed – remnant polarisation (Fig. 6.1c).

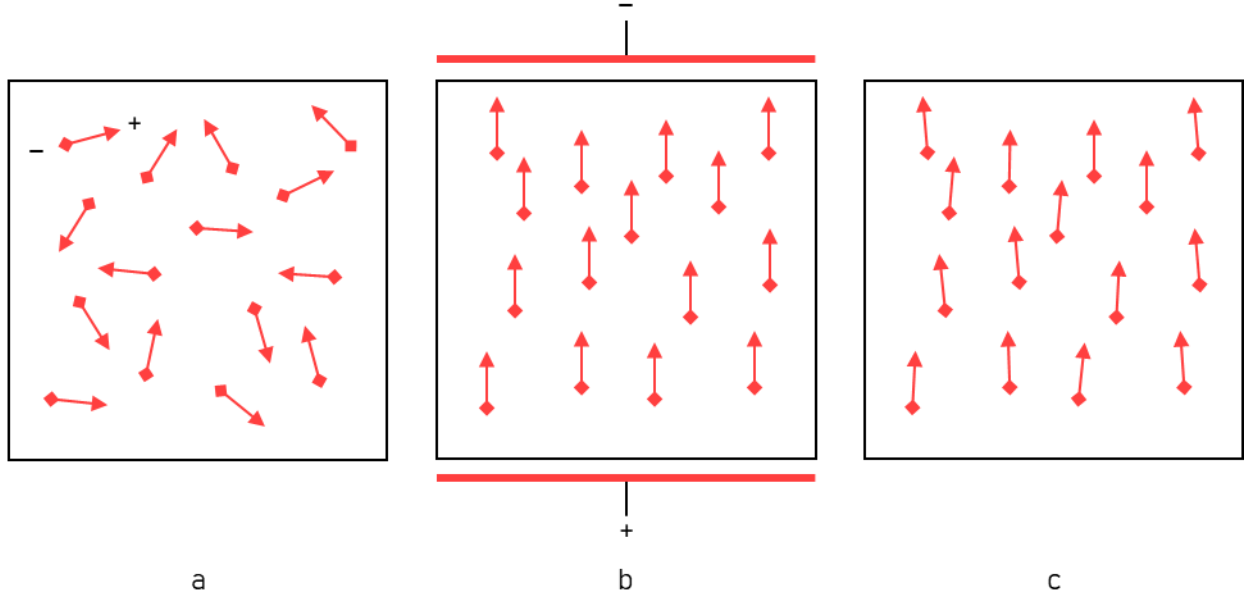


Figure 6.1. Electric dipoles in polycrystalline piezoceramic material: (a) dipoles are randomly oriented before poling; (b) dipoles are coerced into alignment by a strong electric field during poling; and (c) remnant polarisation is retained post-poling.

There are four sets of piezoelectric coefficients: piezoelectric charge or strain coefficients ($d_{i\alpha}$), piezoelectric stress coefficients ($e_{i\alpha}$), piezoelectric voltage coefficients ($g_{i\alpha}$), and piezoelectric stiffness coefficients ($h_{i\alpha}$), which correspond to the four forms of the piezoelectric constitutive equations:

Strain-Charge form:

$$S_{\alpha} = s_{\alpha\beta}^E T_{\beta} - d_{i\alpha} E_i, \quad i, j = 1, 2, 3 \text{ and } \alpha, \beta = 1, \dots, 6 \quad (6.1)$$

$$D_i = d_{i\alpha} T_{\alpha} + \varepsilon_{ij}^T E_j. \quad (6.2)$$

Strain-Voltage form:

$$S_{\alpha} = s_{\alpha\beta}^D T_{\beta} - g_{i\alpha} D_i, \quad (6.3)$$

$$E_i = -g_{i\alpha} T_{\alpha} + \beta_{ij}^T D_j. \quad (6.4)$$

Stress-Charge form:

$$T_{\alpha} = c_{\alpha\beta}^E S_{\beta} - e_{i\alpha} E_i, \quad (6.5)$$

$$D_i = e_{i\alpha} S_{\alpha} + \varepsilon_{ij}^S E_j. \quad (6.6)$$

Stress-Voltage form:

$$T_{\alpha} = c_{\alpha\beta}^D S_{\beta} - h_{i\alpha} D_i, \quad (6.7)$$

$$E_i = -h_{i\alpha} S_{\alpha} + \beta_{ij}^S D_j, \quad (6.8)$$

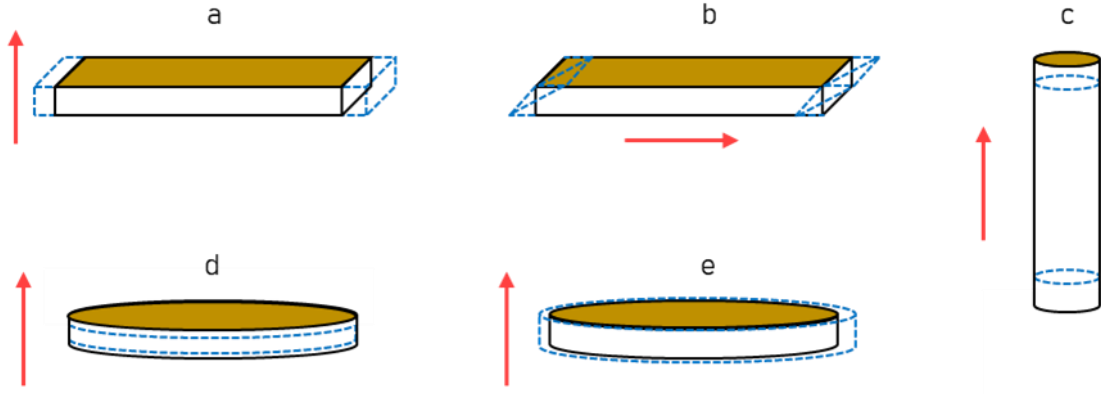


Figure 6.2. Piezoelectric resonance modes as defined by EN 50324-2:2002: (a) Transverse Length, (b) Thickness Shear, (c) Longitudinal Length, (d) Thickness Extension, and (e) Planar Radial. Electrodes are shown in gold, polarisation is red, and mechanical deformation is blue.

where S_α , T_α , D_i and E_i respectively denote the strain, stress, charge displacement and electric fields; $s_{\alpha\beta}$ and $c_{\alpha\beta}$ are the mechanical coefficients for compliance and stiffness respectively; and ε_{ij} is the dielectric permittivity matrix with β_{ij} as its inverse.

The materials of interest in this chapter – BNT-6BT and PZT – both exhibit perovskite structures with coexistent rhombohedral and tetragonal phases (Damjanovic, 2005; Kang and Koh, 2015; Nesterović *et al.*, 2021). After poling, both piezoceramics can be treated as transversely isotropic materials and therefore characterised by ten base material coefficients (ignoring losses):

$$c_{\alpha\beta}^E = \begin{bmatrix} c_{11} & c_{12} & c_{13} & 0 & 0 & 0 \\ & c_{11} & c_{13} & 0 & 0 & 0 \\ & & c_{33} & 0 & 0 & 0 \\ & & & c_{55} & 0 & 0 \\ \text{sym.} & & & & c_{55} & 0 \\ & & & & & \frac{c_{11} - c_{12}}{2} \end{bmatrix}, \quad (6.9)$$

$$e_{i\alpha} = \begin{bmatrix} 0 & 0 & 0 & 0 & e_{15} & 0 \\ 0 & 0 & 0 & e_{15} & 0 & 0 \\ e_{31} & e_{31} & e_{33} & 0 & 0 & 0 \end{bmatrix}, \quad (6.10)$$

$$\varepsilon_{ij}^S = \begin{bmatrix} \varepsilon_{11} & 0 & 0 \\ 0 & \varepsilon_{11} & 0 \\ 0 & 0 & \varepsilon_{33} \end{bmatrix}. \quad (6.11)$$

Electromechanical coupling factors (k) measure the conversion efficiency between electrical and acoustic energy in piezoelectric materials and correspond to resonance modes (Fig. 6.2): the Transverse Length (TL: k_{13}), Thickness Shear (TS: k_{15}), Longitudinal Length (LL: k_{33}), Thickness Extension (TE: k_t), and Planar Radial (P: k_p) modes. Dynamic impedance

measurements at and around these resonance modes are used to calculate the material coefficients in Equations 6.1–6.11. Full details of the relationships are captured by European standard EN 50324-2:2002 (British Standards Institution, 2002).

Piezoelectric losses are modelled using complex components and often quoted as loss tangents, i.e. $\tan \delta = \chi''/\chi'$, where χ' and χ'' are the real and imaginary components of a coefficient respectively. The mechanical quality factor (Q_M) is the reciprocal of the mechanical loss tangent.

6.3. Materials and Methods

6.3.1. Specimens

BNT-6BT from two synthesis routes (Fig. 6.3) were investigated as part of this research: Synthesis Route 1 was a commercial material manufactured by the conventional ceramic method (PI Ceramic PIC700) and Synthesis Route 2 was an additive-manufactured piezoceramic (AM-BNT-6BT). Synthesis Route 1 was sintered and poled as a bulk material in an oil bath by PI Ceramic (Lederhose, Germany) according to its standard protocols. Samples were cut from the bulk material and lapped to specified geometries, and silver electrodes were applied. Discs (1A; $\varnothing 10 \times 1.25 \text{ mm}^3$; Fig. 6.3b) were used for the planar and thickness-extension modes, and plates (1B; $5 \times 5 \times 0.325 \text{ mm}^3$; Figs. 6.3c & -d) were used for the thickness-shear modes.

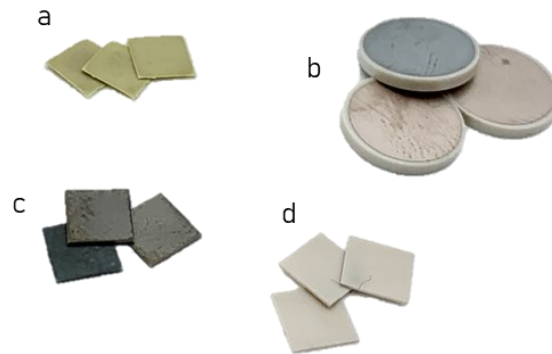


Figure 6.3. Piezoceramic samples: (a) unelectroded transverse-length/thickness-shear mode samples of AM-BNT-6BT (Specimens 2B), (b) electroded radial/thickness-extension mode samples of PIC700 (Specimens 1A), (c) electroded thickness-shear mode samples of PIC700 (Specimens 1B), and (d) unelectroded thickness-shear mode samples of PIC700 (Specimens 1B)..

Synthesis Route 2 involved tape casting from an alcohol-based slurry at room temperature followed by lamination and pressing. Dried tapes and laminated films were sintered and cut at 1150 °C in air for 2 hours. The piezoelectric properties of BNT-6BT had already been measured in the planar and thickness-extension modes by the material developer (SINTEF AS, Trondheim, Norway); samples were therefore manufactured for characterisation in the transverse-length and thickness-shear modes with two geometries: $5 \times 5 \times 0.9 \text{ mm}^3$ (2A) and $5 \times 5 \times 0.2 \text{ mm}^3$ (2B; Fig. 6.1a). Electrodes for poling the transverse-length mode (perpendicular to the plate) and the thickness-shear mode (parallel to the plate) were applied using silver lacquer (RS Components 186-3600) and annealed at 700 °C for four hours. Samples were poled in silicone oil at 3 kV/mm at 150 °C for 30 minutes and field-cooled to below 40 °C (high-voltage power supply: Genvolt 73030; hotplate: Stuart US152). Electrodes on the thickness-shear mode specimens were removed and reapplied without annealing, which would otherwise depolarise the samples.

6.3.2. Electromechanical Properties

Electromechanical properties of both materials were measured according to European standard EN 50324-2:2002 (British Standards Institution, 2002); five of each PIC700 geometry and three of each AM-BNT-6BT geometry were evaluated. Impedance measurements around each resonance were acquired using a precision impedance analyser (Agilent 4294A) at high-bandwidth with sixteen averages per measurement. Relationships between resonant frequency pairs were used to calculate coupling factors and the dielectric, elastic, and piezoelectric constants. Well-characterised PZT materials with similar dimensions (P/TE: PI Ceramic PIC181, $\emptyset 10 \times 1 \text{ mm}^3$; TS: Noliac NCE51, $5 \times 5 \times 0.5 \text{ mm}^3$) were used to verify the accuracy of the measurement setup.

6.3.3. Material Suitability Assessment

The suitability of the characterised BNT-6BT materials was determined for several current and prospective in vivo applications: sensing, actuation, stimulation, energy harvesting, and pulse-echo measurement. Figures of merit were used as predictors of performance in each application, which were then referenced against current PZT-based piezoceramics and potential lead-free alternatives from commercial and academic sources (Addendum).

High piezoelectric charge/strain coefficients ($d_{i\alpha}$), which cause materials to exhibit high displacement in response to applied voltage, were regarded as appropriate for actuator materials (Zheng *et al.*, 2018). Materials with high piezoelectric voltage coefficients ($g_{i\alpha}$) were

considered desirable for electrically stimulated tissue regeneration (Rajabi, Jaffe and Arinzeh, 2015) due to high output voltages generation in response to applied stress. Materials with high $d_{i\alpha} \cdot g_{i\alpha}$ were regarded as ideal sensors (Rödel *et al.*, 2015)

Two different figures of merit were used for off-resonance and on-resonance piezoelectric energy harvesting (Priya, 2010), which corresponded to energy harvesting at low frequencies (<1 kHz; e.g. physiological motion) and high frequencies (>100 kHz; e.g. acoustic power transfer). In the thickness-extension mode, these figures of merit were

$$\text{FOM}_{\text{off-res.}} = \frac{d_{33} \cdot g_{33}}{\tan \delta_E}, \quad (6.12)$$

$$\text{FOM}_{\text{on-res.}} = k_t^2 \cdot Q_M, \quad (6.13)$$

where $\tan \delta_E$ was the dielectric loss tangent. Equation 6.13 is frequently normalised by the compliance coefficient (c_{33}^E), but this parameter was underreported for the comparator materials in the literature.

For pulse-echo transducers, the transmission efficiency and receiver sensitivity parameters are frequently used as figures of merit (Zhang *et al.*, 2015). In the thickness-extension mode, these parameters are

$$\text{TP}_t = \frac{k_t}{1 - k_t^2} \sqrt{\frac{\varepsilon_{33}^S}{c_{33}^D}}, \quad (6.14)$$

$$\text{RP}_t = \frac{k_t}{\sqrt{c_{33}^D \varepsilon_{33}^S}}, \quad (6.15)$$

and in the thickness-shear mode, they are

$$\text{TP}_{15} = \frac{k_{15}}{1 - k_{15}^2} \sqrt{\frac{\varepsilon_{11}^S}{c_{15}^D}}, \quad (6.16)$$

$$\text{RP}_{15} = \frac{k_{15}}{\sqrt{c_{15}^D \varepsilon_{11}^S}}. \quad (6.17)$$

6.3.4. Acoustic Power Transfer

The performance of BNT-6BT in acoustic power transfer applications (Fig. 6.4) was demonstrated using commercial thickness-extension-mode specimens (1A; $n = 3$) mounted on an orthopaedic fracture fixation plate (3 mm stainless steel) and backed by synthetic bone

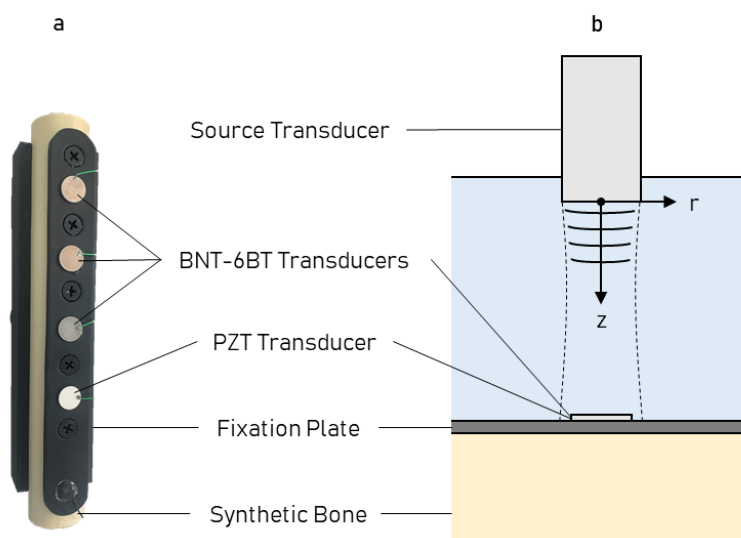


Figure 6.4. (a) BNT-6BT and PZT transducers mounted on a fracture fixation plate for acoustic energy harvesting and (b) schematic drawing of the acoustic power transfer setup.

(London Bone Company GB/0712). The transducers were connected to a parallel load of $50\ \Omega$ and an oscilloscope (TiePie Handyscope HS5), and piezoelectric responses to continuous sinusoidal transmission from a second ultrasonic transducer (Olympus I3-0208-S-SU; amplitude: 10 V; frequency: 2.25 MHz) were recorded whilst the setup was immersed in degassed water (temperature: $\sim 20\ ^\circ\text{C}$). Output power was calculated at varying axial displacements (range: 5–70 mm; interval 0.1 mm) using the power spectral density of the received signals, and measurements were referenced against an equivalent PZT transducer (PI Ceramic PRYY+0442).

6.3.5. Pulse-Echo Response

Three BNT-6BT shear plates (1B) were affixed to the superior surface of the tibial component in the smart implant design of Section 4.2.1 as substitutes for the original PZT-based transducer. Pulse-echo measurements (cycles: 5; frequency: 4.6 MHz; voltage: 10 V) were acquired in a wired configuration to determine and bandwidths were extracted from Fourier spectra of the recorded signals for comparison of the two materials.

6.3.6. In Vitro Cytotoxicity

The in vitro cytotoxicity of BNT-6BT was evaluated according to ISO 10993-5:2009 (International Organization for Standardization, 2009): an indirect test for leaching and a direct test for ongrowth were conducted. Unpoled, non-electroded BNT-6BT samples (1B; $n = 3$) were sterilised by immersion in 70% ethanol solution and irradiation by UV light for 30 mins on either side. In the direct test, murine preosteoblasts from the MC3T3-E1 cell line (ATCC CRL-2593) were seeded directly on the samples at a density of 50,000 cells/cm² and

cultured for 24 hours (37 °C; 5% CO₂) in DMEM (ThermoFisher 11330057). In the indirect test, samples were incubated in media for 24 hours at 37 °C prior to testing, and 12,500 cells/well were cultured in serial dilutions of the extracted media (0%, 25%, 50% and 100%). PZT samples (Noliac NCE51; 5×5 mm²; n = 3) were used as a comparator, and 10% DMSO (ATCC 4-X) was used as a cytotoxic control. Fluorescence readings for metabolic activity were acquired in triplicate after 30 minutes incubation with alamarBlue Cell Viability Reagent (ThermoFisher DAL1025; 10% media volume; excitation: 560 nm; emission: 590 nm).

6.3.7. In Vitro Biocompatibility

Murine preosteoblasts from the MC3T3-E1 cell line (ATCC CRL-2593) were proliferated for three passages in cell culture medium: α -MEM (ThermoFisher 11095080) supplemented with 10% foetal bovine serum (ATCC 30-2020) and 1% penicillin-streptomycin (ThermoFisher 15070063). At 75% confluency on the final passage, the cells were trypsinised and seeded directly onto the BNT-6BT samples (2B; n = 4) at a density of 5,000 cells/cm². Specimens were cultured in twelve-well plates for 7, 14, 21, and 28 days in normoxic conditions at 37 °C and 5% CO₂; cell culture medium was replaced every seven days. Viability was determined at each timepoint by staining samples with Calcein-AM/Ethidium homodimer (ThermoFisher L3224) and acquiring confocal images (Leica Microsystems TCS SP5). After imaging, samples were fixed in 2.5% glutaraldehyde with 0.1 M phosphate buffer (pH 7.4) overnight, dehydrated through a series of ethanol solutions (20-100%; 7 minutes per solution), and air-dried for analysis. Samples were then sputter-coated with chromium (thickness: 15 nm) and imaged using a scanning electron microscope (TESCAN MIRA) for signs of cellular ongrowth.

6.3.8. Ex Vivo Cytotoxicity

Fresh trabecular bone cores (Ø10 mm x 5 mm; n = 10) were explanted from a single distal porcine femur in accordance with the method described in Section 5.3.2; the donor animals had already been euthanised for unrelated research that did not affect bone metabolism or healing. BNT-6BT specimens (1B; n = 4) were implanted into separate bone cores: the ceramic specimens were sterilised by immersion in 70% ethanol for 30 minutes and irradiation with UV light for 30 minutes on each side; bone cores were washed in Dulbecco's phosphate-buffered saline (DPBS; ThermoFisher 14190250) with 1% penicillin/streptomycin (ThermoFisher 15070063) to remove cutting debris and vortexed for 30 seconds to reduce cutting debris; incisions were made into the bone cores with a scalpel through the midplane of the cylinder from its axis to its circumference (Fig. 6.5); and ceramic specimens were press-fit into the incisions. Two bone cores were incised without implantation of any piezoceramic and included as controls. All bone cores were prepared and incubated (37 °C;

5% CO₂; normoxic) within five hours of euthanasia of the animal. Cell culture medium, which consisted of DMEM/F-12 with HEPES (ThermoFisher 11330057) plus 10% foetal bovine serum (ThermoFisher 10500064) and 1% penicillin/streptomycin (ThermoFisher 15070063), was replaced every seven days. The culture was terminated after 28 days; each bone core was stained with Calcein-AM/Ethidium homodimer (ThermoFisher L3224); and each core was imaged for cell viability (Leica Microsystems TCS SP5 MP). Images were acquired from the surface of the piezoceramic, from bone tissue adjacent to the piezoceramic, and from tissue that had been freshly incised post-staining.

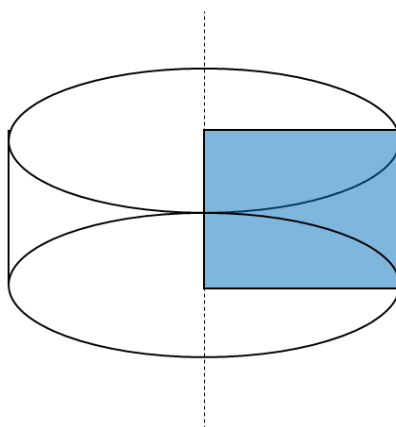


Figure 6.5. Incisions for implantation of the BNT-6BT and PZT specimens were made from the cylindrical axis to the circumference of each bone core.

6.4. Results

6.4.1. Electromechanical Properties

The commercial BNT-6BT material (PIC700; 2A & 2B) was characterised in the radial, thickness-extension, and thickness-shear modes (Table 6.1; Figs. 6.6a-f). Results from two other PIC700 studies (Fenu *et al.*, 2021; Pardo *et al.*, 2021), which were published after this characterisation, have been included for comparison. The 0.9-mm-thick additive-manufactured BNT-6BT specimens (2A) were characterised in the transverse length mode (Table 6.2; Figs. 6.6g & -h), but not in the shear mode as the lacquered electrodes were poorly adherent to the piezoceramic surface without annealing. The 0.2-mm-thick specimens (2B) did not tolerate poling in either mode: voltages were unstable above 1.5 kV/mm and blackened cracks were found in the samples upon retrieval. Reference measurements were acquired of PIC181 in the planar and thickness-extension modes (Table 6.3) and NCE51 in the thickness-shear mode (Table 6.4): dielectric and mechanical properties were in good agreement (<10%); radial and thickness-extension piezoelectric coefficients were in reasonable agreement (<20%); and shear coefficients were greatly underestimated (~50%),

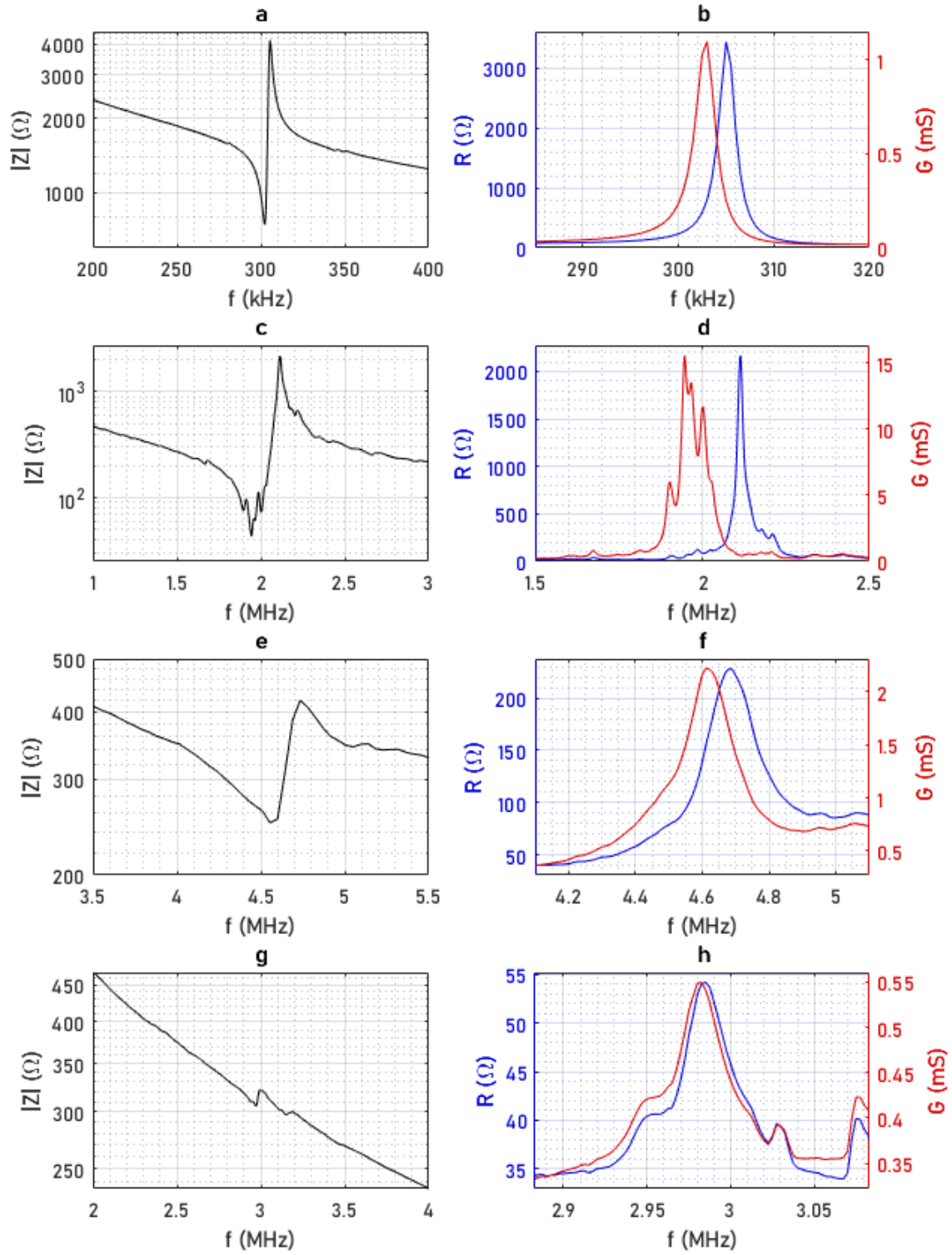


Figure 6.6. Impedance spectra (left; a, c, e, g) and resistance-conductance spectra (right; b, d, e, h) at the fundamental resonances of BNT-6BT transducers: (a, b) planar mode of conventionally manufactured BNT-6BT; (c, d) thickness-extension mode of conventionally manufactured BNT-6BT; and (e, f) thickness-shear mode of conventionally manufactured BNT-6BT; and (g, h) transverse length mode of additive-manufactured BNT-6BT.

Table 6.1. Electromechanical characterisation of PIC700 in the planar (P), thickness-extension (TE), and thickness-shear (TS) modes with comparison to measurements by Pardo *et al.* (2021) and Fenu *et al.* (2021).

	Symbol	Hall	Pardo	Fenu-IEEE	Fenu-LM	Fenu-NM	Units
Dielectric Properties							
Relative permittivities	$\varepsilon_{33}^T/\varepsilon_0$	648 ± 4	648	628	611	557	-
	$\varepsilon_{33}^S/\varepsilon_0$	539 ± 11	472	527	485	439	-
	$\varepsilon_{11}^T/\varepsilon_0$	593 ± 78	496	589	533	613	-
	$\varepsilon_{11}^S/\varepsilon_0$	553 ± 86	554	533	490	510	-
Dielectric loss tangent	$\tan \delta_E$	205 ± 1	700*	500*	-	-	$\times 10^{-4}$
Piezoelectric Properties							
Electromechanical coupling factors	k_p	0.088 ± 0.021	0.147	-	-	-	-
	k_t	0.401 ± 0.019	0.435	0.39	0.414	0.418	-
	k_{33}	0.438 ± 0.025	0.411	0.38	0.455	0.460	-
	k_{15}	0.258 ± 0.049	0.322	-	-	-	-
Piezoelectric constants	d_{33}	116 ± 8	89.7	88.1	101	97.1	pC/N
	d_{15}	78.8 ± 8.3	102.9	99.9	93.8	142	pC/N
	g_{33}	20.3 ± 0.1	15.6	-	-	-	mV·m/N

	g_{15}	15.3 ± 3.2	20.93	-	-	-	mV·m/N
	e_{33}	8.79 ± 0.36	11.1	10.2	11.1	10.8	C/m ²
	e_{15}	4.36 ± 0.79	4.96	4.96	4.10	6.40	C/m ²
Mechanical Properties							
Elastic stiffnesses	c_{33}^E	8.44 ± 0.09	12.3	13.1	12.8	12.9	$\times 10^{10}$ N/m ²
	c_{33}^D	10.1 ± 0.1	16.1	15.27	15.7	15.9	$\times 10^9$ N/m ²
	c_{55}^E	5.51 ± 0.46	4.81	4.96	4.37	4.51	$\times 10^9$ N/m ²
	c_{55}^D	5.91 ± 0.63	5.37	-	-	-	$\times 10^9$ N/m ²
Elastic compliances	s_{33}^E	12.3 ± 0.2	8.98	-	-	-	$\times 10^{-12}$ m ² /N
	s_{33}^D	9.94 ± 0.07	7.46	-	-	-	$\times 10^{-12}$ m ² /N
	s_{55}^E	18.2 ± 1.6	20.8	-	-	-	$\times 10^{-12}$ m ² /N
	s_{55}^D	17.0 ± 1.9	18.6	-	-	-	$\times 10^{-12}$ m ² /N
Mechanical loss tangent	$\tan \delta_M$	76 ± 16	60*	200*	20	25	$\times 10^{-4}$

Table 6.2. Electromechanical characterisation of additive-manufactured BNT-6BT in the transverse-length mode, planar, and thickness modes (properties measured as part of this work in bold) with comparison to the conventionally manufactured BNT-6BT material as measured by Pardo *et al.* (2021).

	Symbol	AM BNT-6BT (Hall / SINTEF)	Conv. BNT-6BT (Pardo)	Units
Dielectric Properties				
Relative permittivity	$\epsilon_{33}^T/\epsilon_0$	946 ± 76 / 638 ± 11	648	-
Dielectric loss tangent	$\tan \delta_E$	613 ± 99 / 300	340	$\times 10^{-4}$
Piezoelectric Properties				
Electromechanical coupling factors	k_p	0.15	0.147	-
	k_t	0.22	0.435	-
	k_{31}	0.088 ± 0.037	0.076	-
Piezoelectric constants	d_{33}	121	89.7	pC/N
	d_{31}	-19.3 ± 8.2	-21.1	pC/N
	g_{33}	21	15.6	mV·m/N
	g_{31}	-2.36 ± 1.01	-3.69	mV·m/N
Mechanical Properties				
Elastic compliances	s_{11}^E	6.08 ± 0.34	8.60	$\times 10^{-12}$ m ² /N
	s_{11}^E	6.02 ± 0.36	8.52	$\times 10^{-12}$ m ² /N
Mechanical loss tangent	$\tan \delta_M$	104 ± 83	67	$\times 10^{-4}$

Table 6.3. Radial and thickness-extension properties of PIC181 (Hard PZT) were consistent with manufacturer-reported data (PI Ceramic, 2020a).

	Symbol	Hall	Datasheet	Units
Dielectric Properties				
Relative permittivity	$\varepsilon_{33}^T/\varepsilon_0$	1190	1200	-
Dielectric loss tangent	$\tan \delta_E$	<30	3	$\times 10^{-4}$
Piezoelectric Properties				
Electromechanical coupling factors	k_p	0.594	0.56	-
	k_t	0.457	0.46	-
Piezoelectric constants	d_{33}	218	265	pC/N
	g_{33}	20.9	23	mV·m/N
Mechanical Properties				
Elastic stiffness	c_{33}^D	16.9	17	$\times 10^{10}$ N/m ²
Elastic compliance	s_{33}^E	10.5	13.3	$\times 10^{-12}$ m ² /N
Mechanical loss tangent	$\tan \delta_M$	<30	5	$\times 10^{-4}$

Table 6.4. Thickness-shear mode properties of NCE51 (Soft PZT) were underestimated versus manufacturer-reported (PI Ceramic, 2020a)

	Symbol	Hall	Datasheet	Units
Dielectric Properties				
Relative permittivities	$\varepsilon_{11}^T/\varepsilon_0$	1770	1940	-
	$\varepsilon_{11}^S/\varepsilon_0$	958	906	-
Dielectric loss tangent	$\tan \delta_E$	147	150	$\times 10^{-4}$
Piezoelectric Properties				
Electromechanical coupling factor	k_{15}	0.678	0.730	-
Piezoelectric constants	d_{15}	266	669	pC/N
	g_{15}	18.6	38.9	mV·m/N
	e_{15}	12.6	13.7	C/m ²
Mechanical Properties				
Elastic stiffnesses	c_{55}^D	4.08	4.37	$\times 10^{10}$ N/m ²
	c_{55}^E	2.20	2.05	$\times 10^{10}$ N/m ²
Elastic compliances	s_{55}^D	24.5	22.9	$\times 10^{-12}$ m ² /N
	s_{55}^E	45.4	48.9	$\times 10^{-12}$ m ² /N
Mechanical loss tangent	$\tan \delta_M$	230	125	$\times 10^{-4}$

6.4.2. Material Suitability Assessment

Piezoelectric coefficients for the conventional solid-state and additive-manufactured BNT-6BT materials (PIC700 and AM-BNT-6BT respectively) were near-equivalent. Referencing the materials for sensing (Fig. 6.7), charge coefficients (d_{33}) were ~10 dB lower than a standard PZT material (PZT-5A) for the same application, whilst voltage coefficients were similar (Table 6.5). Performance in sensing applications was comparable to the other lead-free alternatives: KNN-based and BT-based piezoceramics. Figures of merit for PIC700 were substantially lower in off-resonance (−24.9 dB) and on-resonance (−31 dB) energy harvesting applications compared to a standard PZT material (PIC181). Predicted performance was comparable to KNN-based piezoceramics but considerably lower than BT-based piezoceramics (Fig. 6.8; 10–15 dB in both modes). Transmit efficiency and receiver sensitivity parameters for pulse-echo transducers in the thickness-extension mode were similar for all piezoceramic families (Fig. 6.9). In the shear mode, transmit efficiency was considerably reduced (−27 dB) in comparison to a standard PZT material (NCE51), whilst receiver sensitivity was slightly diminished (−5.6 dB). Shear-mode performance was similarly reduced in the KNN-based and BT-based families (Fig. 6.10). These figures of merit do not account for transducer bandwidths, which are typically tuned with impedance matching and transducer backing.

6.4.3. Acoustic Power Transfer

An acoustic power transfer link was established between an external transducer and a BNT-6BT (PIC700) thickness-extension mode transducer mounted on a fracture fixation plate: 100 mW of power was delivered through 5 mm of water. Standing wave phenomena were observed and the spatially averaged received power exponentially decreased as the transmission distance was increased (Fig. 6.11). An acoustic power link was also established to an equivalent PZT-based transducer (PIC181): the average drop in received power associated with using the BNT-6BT transducer was 64% (−8.8 dB) across the 5–70 mm range.

6.4.4. Pulse-Echo Response

Pulse-echo responses from the tibial baseplate were acquired without amplification and without transducer backing for the original PZT-based transducer and a BNT-6BT alternative (Fig. 6.12). The amplitude of returning echoes to the BNT-based transducer signal was greatly diminished in comparison to the PZT-based transducer (−25 dB at the centre frequency). Bandwidth was also narrower with the BNT-based transducer, thereby resulting in longer ringdown times after each pulse. In practice, the BNT-based transducer would be 'broadbanded' to negate ringdown, though this process would further reduce the amplitude.

Table 6.5. Figures of merits for PIC700 and AM-BNT-6BT referenced against commonly used PZT materials in implanted piezoceramic applications.

Application(s)	Ref. Material	Parameter	Ref. Value	PIC700	AM-BNT-6BT
Sensing	PZT-5A	d_{33} ($\times 10^{-12}$ C/N)	400	116 (-11 dB)	121 (-10 dB)
		g_{33} ($\times 10^{-3}$ V·m/N)	25.1	20.3 (-1.8 dB)	21 (-1.5 dB)
Energy Harvesting	PIC181	FOM _{off-res.} ($\times 10^{-10}$ N/m ²)	20.3	1.15 (-24.9 dB)	-
		FOM _{on-res.} (-)	423	12.2 (-31 dB)	-
Pulse-Echo (Thickness Mode)	PZT-5A	TP _t ($\times 10^{-12}$ /V)	68.3	41.6 (-4.3 dB)	-
		RP _t ($\times 10^{-3}$ C/m ²)	13.6	18.3 (+2.6 dB)	-
Pulse-Echo (Shear Mode)	NCE51	TP ₁₅ ($\times 10^{-12}$ /V)	489	20.5 (-27 dB)	-
		RP ₁₅ ($\times 10^{-3}$ C/m ²)	39.0	15.1 (-5.6 dB)	-

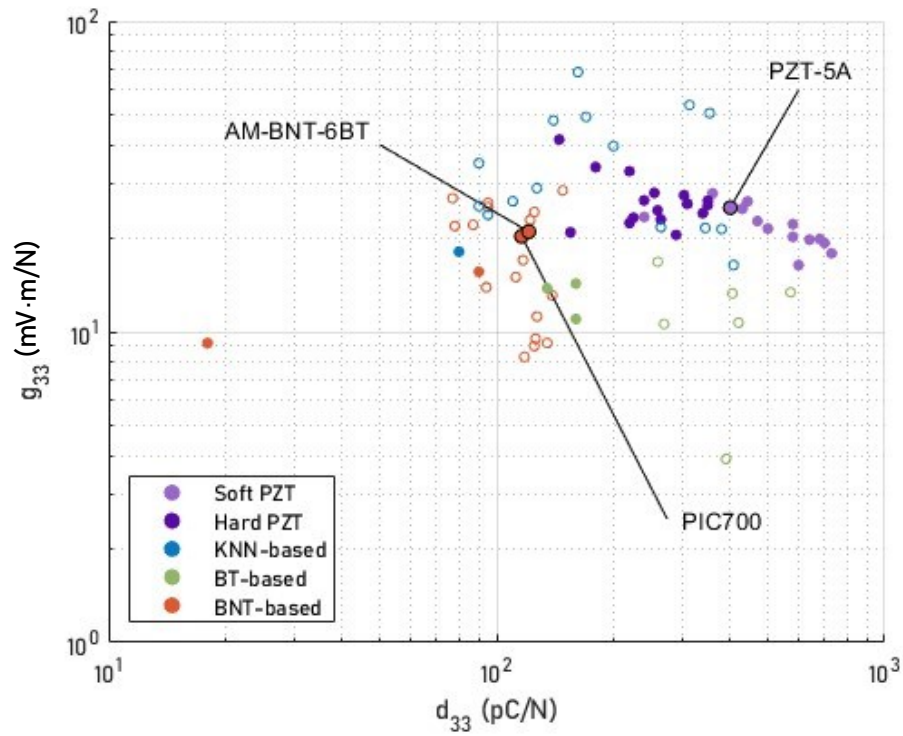


Figure 6.7. Piezoelectric coefficients of PIC700 and AM-BNT-6BT in the thickness mode versus conventional PZT-based and other lead-free piezoceramic materials (● commercial; ○ research).

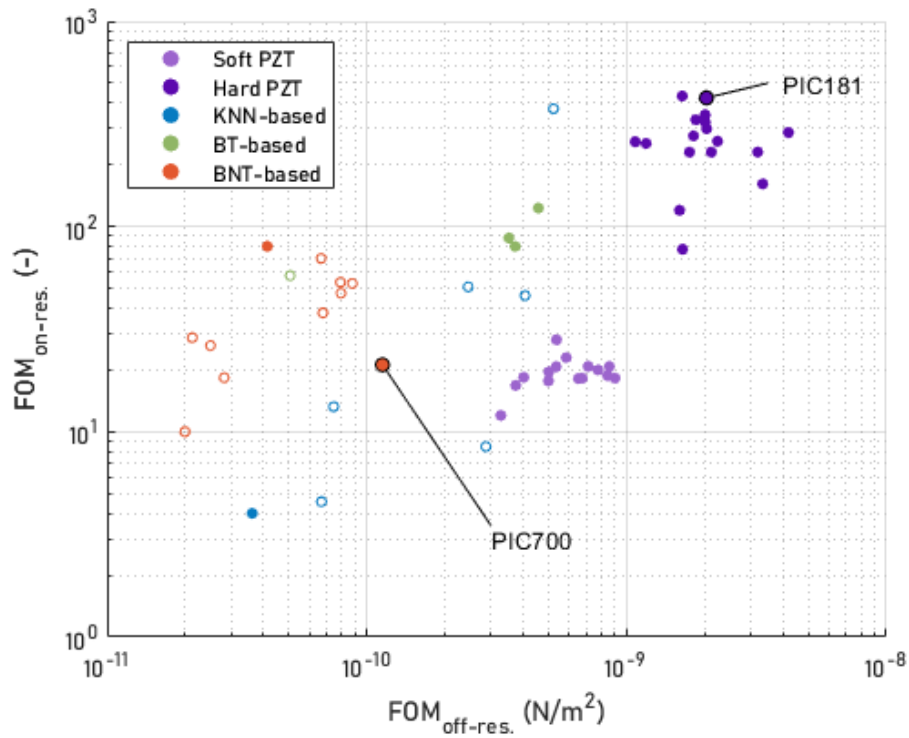


Figure 6.8. Energy harvesting performance of PIC700 in the thickness mode versus conventional PZT-based and other lead-free piezoceramic materials (● commercial; ○ research).

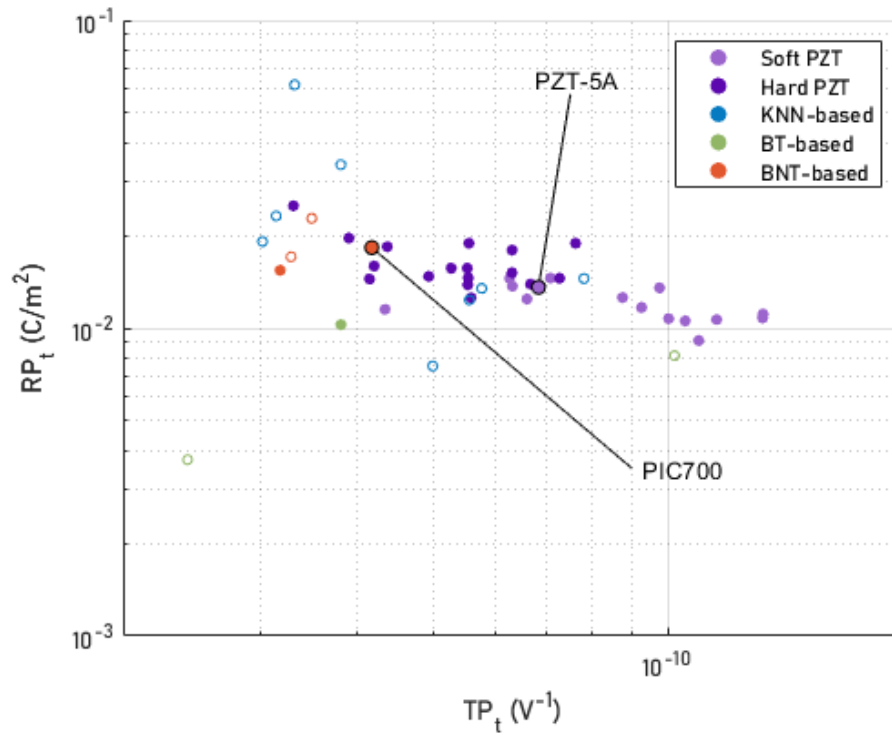


Figure 6.9 Pulse-echo transducer performance of PIC700 in the thickness mode versus conventional PZT-based and other lead-free piezoceramic materials (● commercial; ○ research).

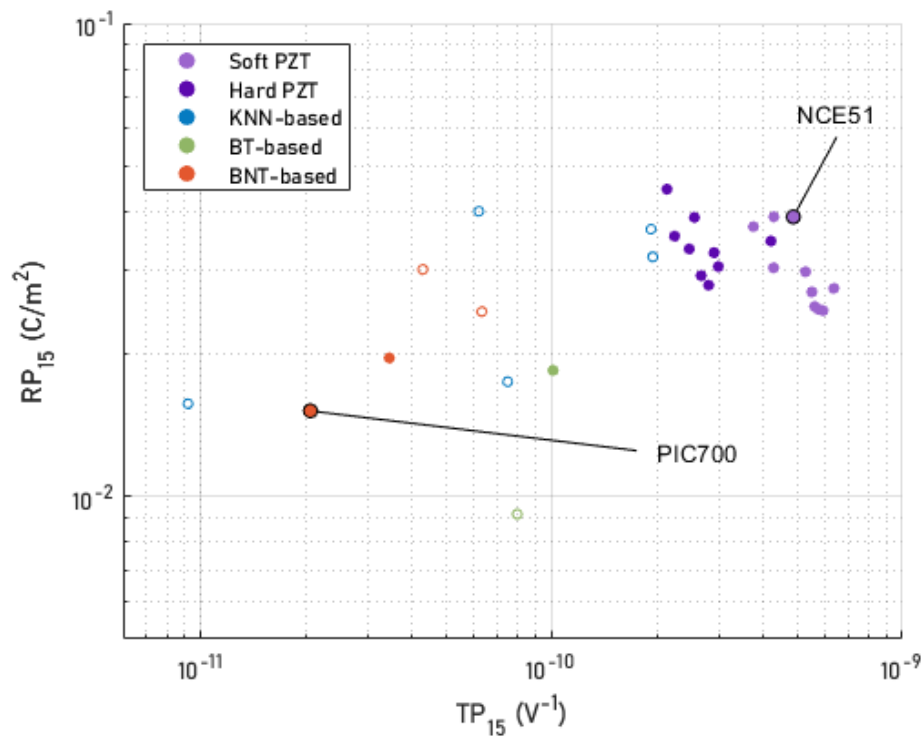


Figure 6.10. Pulse-echo transducer performance of PIC700 in the shear mode versus conventional PZT-based and other lead-free piezoceramic materials (● commercial; ○ research).

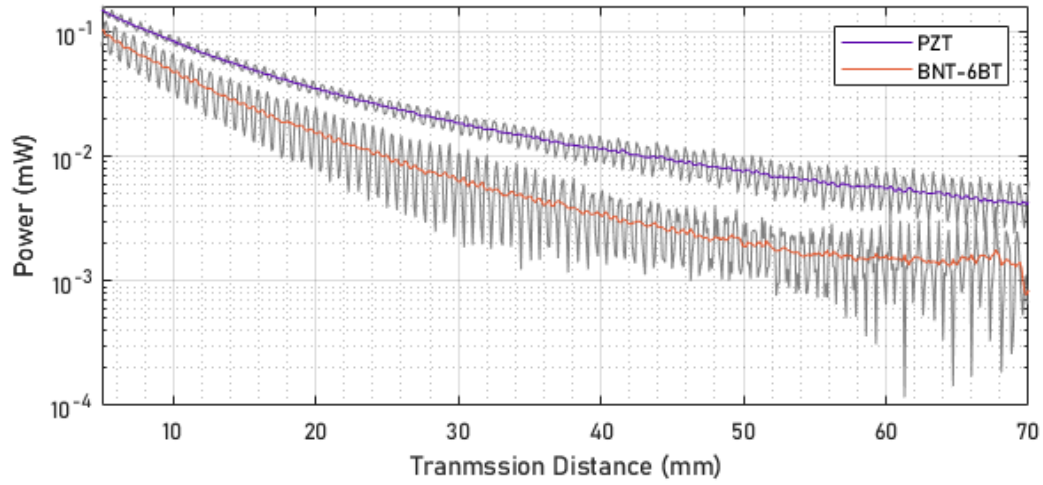


Figure 6.11. Power output comparison for PZT and BNT-6BT transducers mounted on fracture fixation plate in response to continuous sinusoidal excitation with spatial averaging overlaid (source: Olympus I3-0208-S-SU; amplitude: 10 V; frequency: 2.25 MHz).

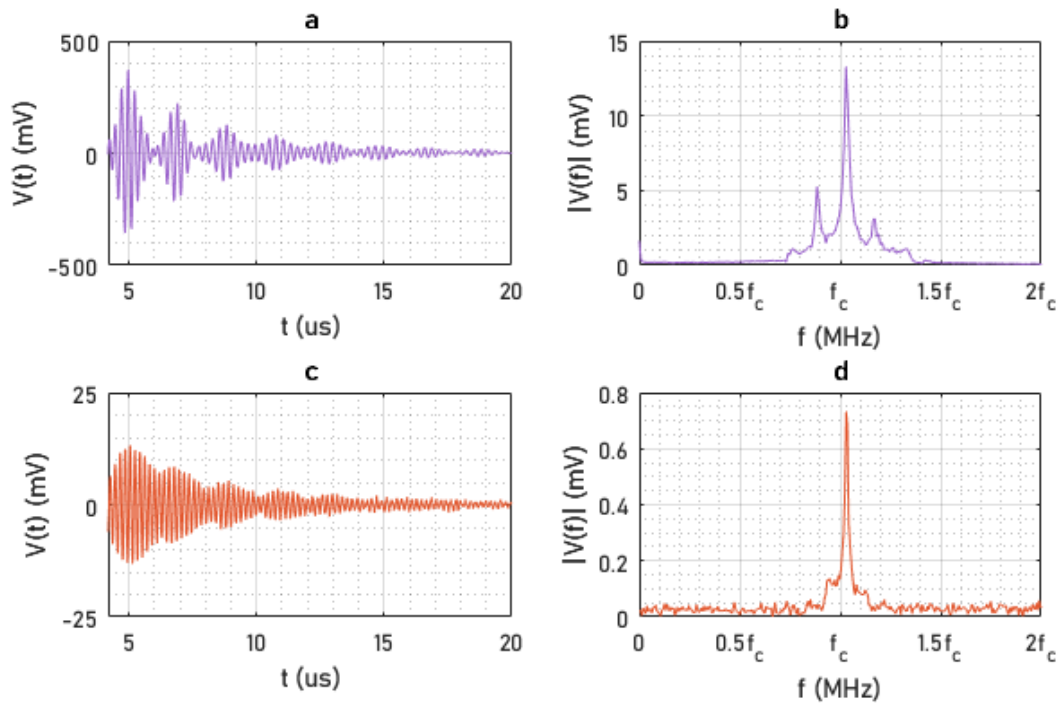


Figure 6.12. Pulse-echo comparison for (a, b) conventional PZT-based and (c, d) BNT-6BT transducers: (a, c) returning echoes signal and (b, d) Fourier spectra around centre frequency of the pulse, f_c .

6.4.5. Cytological Properties

The viability of MC3T3-E1 murine preosteoblasts was above 70% of the 24-hour baseline value (ISO 10993-5 cytotoxicity threshold) and no significant effect due to BNT-6BT (2B specimens) was observed in both in vitro cytotoxicity assays: indirect elution (Fig. 6.13a; 86%; $p = 0.359$) or direct contact (Fig. 6.13b; 99%; $p = 0.926$). No cytotoxic effect was observed due to the PZT reference material (Noliac NCE51), but an effect was detected in the cytotoxic control (10% DMSO; 37%).

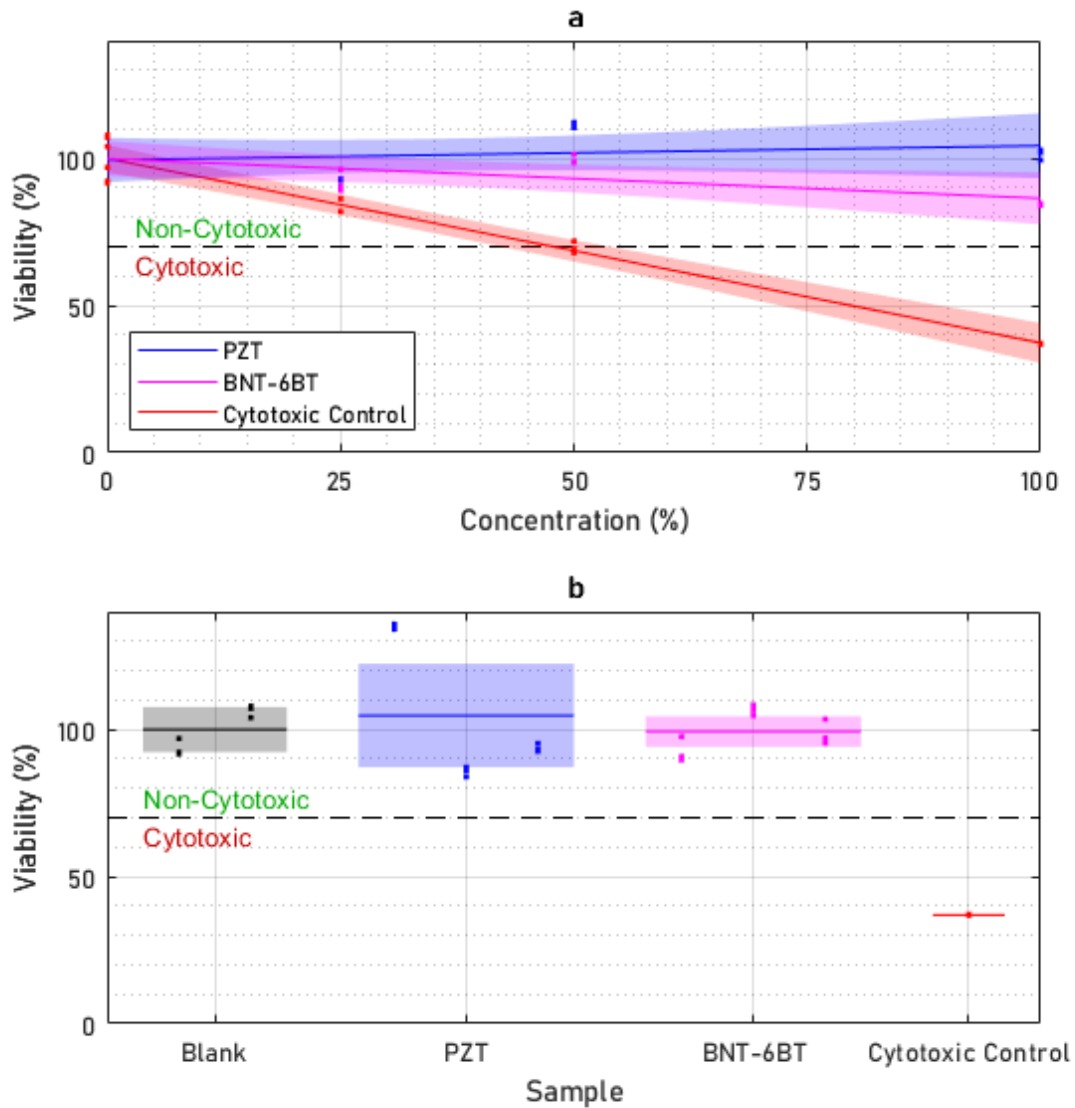


Figure 6.13. ISO 10993-5 testing of additive-manufactured BNT-6BT (2B specimens) compared to PZT (Noliac NCE51) and cytotoxic control (10% DMSO): (a) indirect cytotoxicity and (b) direct cytotoxicity.

In the *in vitro* biocompatibility test, high viability of MC3T3-E1 cells on BNT-6BT (1B specimens) was observed through the first 21 days of culture (Fig. 6.14a, -b, -d & -e), reaching 100% confluence on the piezoceramic surface by this time point. Flattened cells with lamellipodia were seen growing in small clusters on BNT-6BT after seven days of culture (Fig. 6.15a & -d); cell density had increased and small deposits (~50 μm) of extracellular matrix were observed on day 14 (Fig. 6.15b & -e); and continued proliferation through to day 21 had resulted in dense cell coverage and further deposition of immature extracellular matrix on the piezoceramic surface (Fig. 6.15c & -f). Viability staining on day 28 of culture indicated that the BNT-6BT surface was overconfluent with cells (Fig. 6.14c), and cell death had begun to occur (Fig. 6.14f).

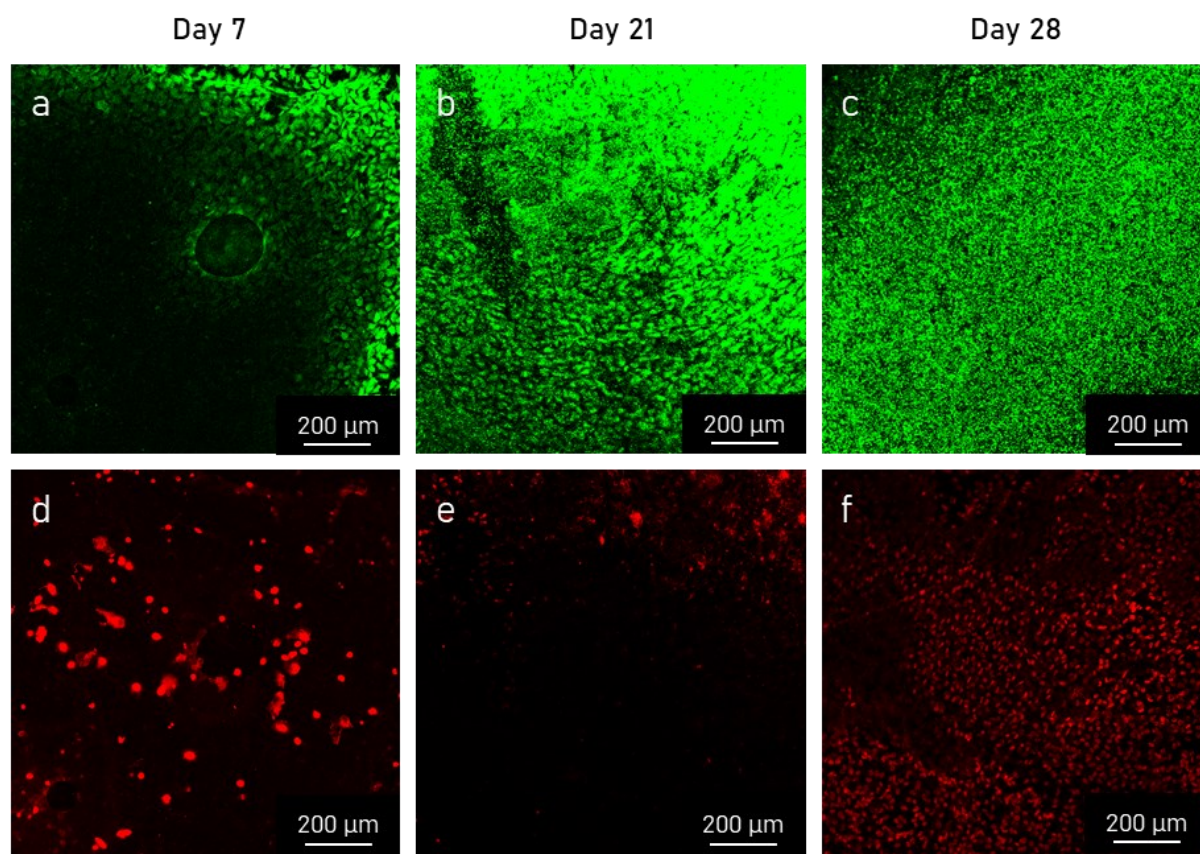


Figure 6.14. Separate confocal micrographs for (a, b, c) live cells and (d, e, f) dead cells on the surface of BNT-6BT specimens after staining with Calcein-AM/Ethidium homodimer: (a, d) clusters of live cells with some cell death was observed after seven days; (b, e) cells had proliferated and increased in density on the piezoceramic surface by day 21; and (c, f) near-total saturation of the piezoceramic surface accompanied by cell death was seen on day 28 of culture.

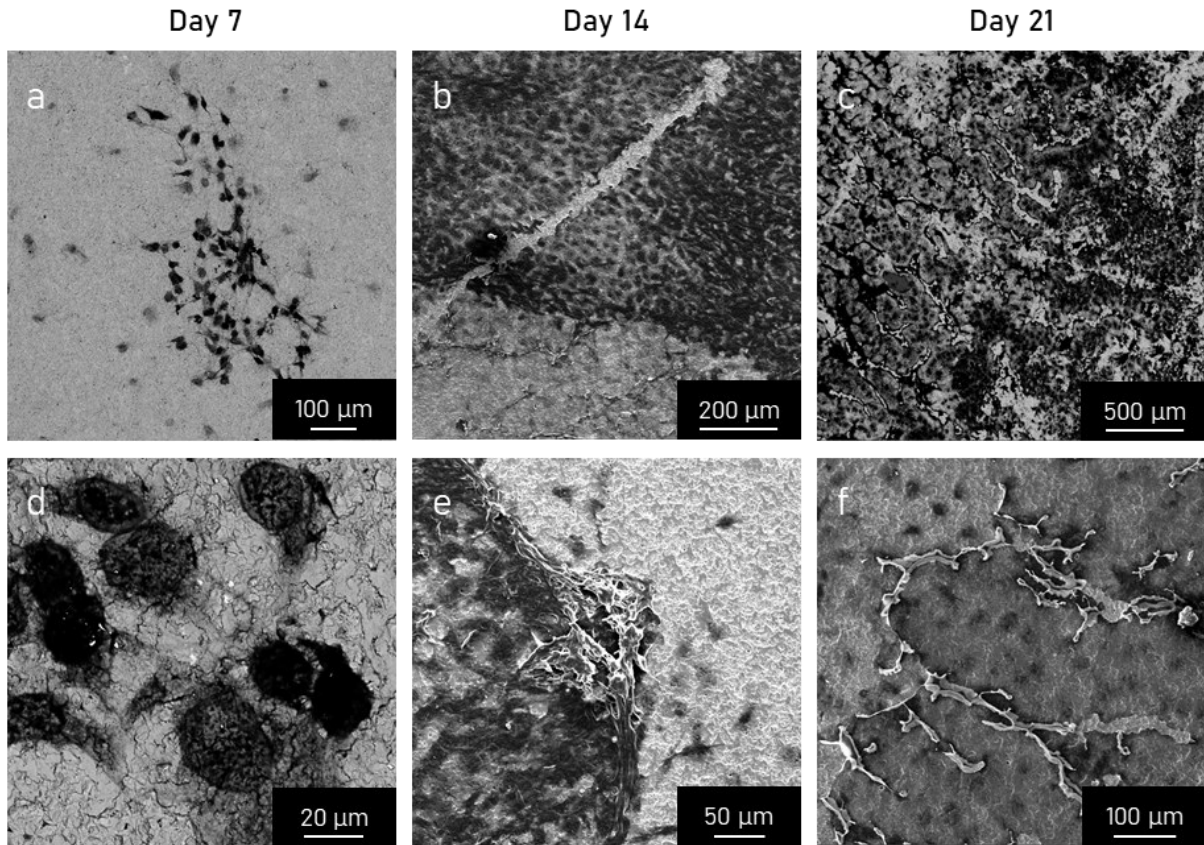


Figure 6.15. SEM images (backscatter electron; beam energy: 10 keV; beam current: 300 pA) of MC3T3-E1 ongrowth onto BNT-6BT showing (a, d) clusters of flattened cells with lamellipodia at seven days, (b, e) widespread cell proliferation and small deposits of extracellular matrix by 14 days, and (c, f) dense, near-total coverage of the BNT-6BT surface with further deposition of extracellular matrix by 21 days.

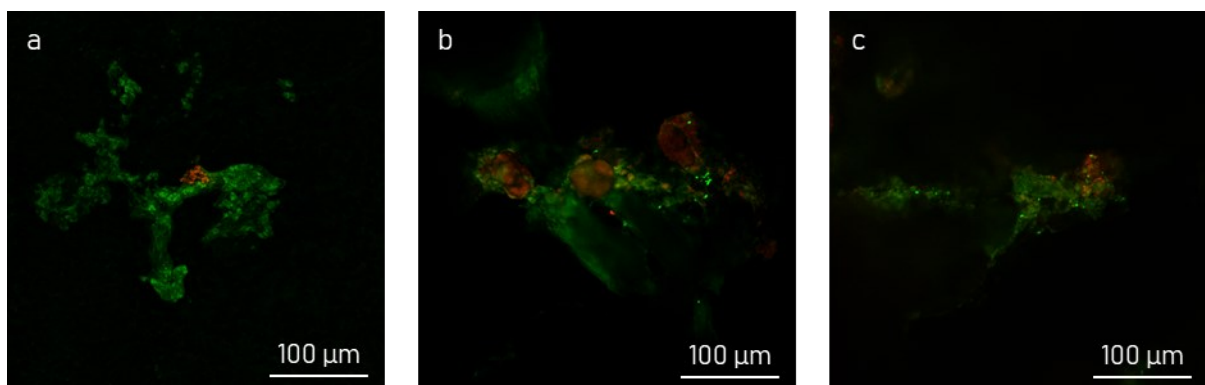


Figure 6.16. Confocal micrographs of tissue stained with Calcein-AM/Ethidium homodimer (live cells: green; dead cells: red) after 28 days in static ex vivo culture: (a) acellular organic deposits were observed on the implanted BNT-6BT specimens; (b) viable cells were observed on trabeculae adjacent to the BNT-6BT implant; and (c) cell viability was also maintained on trabeculae in the bulk tissue (>2 mm from the BNT-6BT implant or any incised surface).

After 28 days of ex vivo culture, organic tissue (~100 μm) was observed on the implanted BNT-6BT specimens but there was no evidence of cell proliferation onto the piezoceramic (Fig. 6.16a). High viability was maintained in the cancellous bone tissue adjacent to the implant (Fig. 6.16b) and in the bulk tissue (Fig. 6.16c), indicating no considerable harmful effect of BNT-6BT on bone viability in the first 28 days of implantation.

6.5. Discussion

This chapter presents the most comprehensive assessment of BNT-6BT as a lead-free piezoceramic for in vivo biomedical applications, investigating BNT-6BT from two synthesis routes, solid state (PIC700) and additive manufacturing (AM-BNT-6BT), and considering several applications, including sensing, power transfer, and tissue regeneration. The electromechanical and biological properties of both materials were evaluated with reference to conventional PZT materials and leading lead-free alternatives: KNN- and BT-based piezoceramics. The solid-state BNT-6BT was also demonstrated in two smart implant systems: acoustic power transfer to a functionalised fracture fixation plate and pulse-echo response for fixation monitoring in a partial knee replacement.

PIC700 specimens were manufactured and poled as a bulk material before being cut to size: these specimens were electromechanically characterised according to European Standard EN 50324-2:2002 in the radial, thickness-extension, and thickness-shear modes. Reference measurements on PZT materials were consistent with manufacturer-reported values in the radial and thickness-extension modes, but thickness-shear properties were considerably underestimated by ~50%. – an artefact of coupling with lateral modes (Pardo, A. García, *et al.*, 2011). Since this research was undertaken, PIC700 has been characterised in two other publications (Fenu *et al.*, 2021; Pardo *et al.*, 2021), and there was good agreement between all studies. Piezoelectric coefficients of PIC700 (d_{33} : 116 pC/N; g_{33} : 20.3 mV·m/N) were weaker than standard PZT materials (d_{33} : ~400 pC/N; g_{33} : ~25 mV·m/N) but comparable to undoped lead-free piezoceramics: KNN (d_{33} : ~100 pC/N; g_{33} : ~25 mV·m/N) and BT (d_{33} : ~150 pC/N; g_{33} : ~15 mV·m/N). Doped KNN- and BT-based piezoceramics with higher coefficients have been produced, notably BCZT (d_{33} : ~500 pC/N; g_{33} : ~10 mV·m/N), but these materials are yet to reach commercialisation. For sensing, energy harvesting, and pulse-echo measurement, which are all underlying functions of current and prospective implantable electronic systems, performance losses of up to 30 dB were associated with the use of PIC700 as an alternative to standard PZT materials. These predictions were reflected in the acoustic power transfer (loss: -8.8 dB) and shear-wave pulse-echo response (-25 dB) demonstrations.

In contrast to the PIC700 specimens, the AM-BNT-6BT specimens were manufactured to size and then poled. Properties for the thickness-extensional mode had previously been measured by SINTEF and the transverse length mode was added by this research. Characterisation in the thickness-shear mode was unsuccessful due to challenges in reapplying electrodes after poling without annealing. There were also issues when poling thin AM-BNT-6BT specimens (thickness: 0.2 mm) as the material cracked at high voltages. Poling challenges have previously been cited for BNT-based materials due to their large coercive field and relatively high conductivity (Villafuerte-Castrejón *et al.*, 2016). Piezoelectric coefficients (d_{33} : 121 pC/N; d_{31} : -19.3 pC/N; g_{33} : 21 mV·m/N; g_{31} : -2.4 mV·m/N) were concordant with solid-state BNT-6BT (PIC700): similar functional performance should therefore be expected.

The short-term cytological properties of BNT-6BT appear promising: cell viability was above the cytotoxicity threshold in both the ISO 10993-5 indirect elution and direct contact assays of unpoled AM-BNT-6BT. Additionally, no effect on cell viability was detected when poled PIC700 was implanted in bone and cultured *ex vivo*. These experiments on murine preosteoblast cells (MC3T3-E1) and porcine bone support the conclusions of the only previous biocompatibility study of BNT-6BT (Esquivel-Gaon *et al.*, 2015), which found no short-term harmful effect of BNT-6BT nanoparticles on lung carcinoma epithelial cells (A549). Long-term ion release is an important concern for all piezoceramics, but the effects were neither investigated in this research nor identified in wider literature. Ion release has been reported in PZT (Chen *et al.*, 2002), KNN (Yu *et al.*, 2011) and BT (Nesbitt *et al.*, 1981), and similar behaviour should therefore be anticipated in BNT-6BT. Nonetheless, the ionic components of BNT-6BT are generally regarded as non-toxic: bismuth(III) compounds have several medical uses (Larsen *et al.*, 2003; Delchier, Malfertheiner and Thieroff-Ekerdt, 2014; Bartoli, Jagdale and Tagliaferro, 2020), though prolonged intake above the rate of excretion can cause encephalopathy through accumulation (Borbinha *et al.*, 2019); sodium is naturally occurring in the body; and barium titanate is otherwise considered highly biocompatible (Park *et al.*, 1981). Additionally, ion release from piezoceramics may terminate after an initial period as indicated by dissolution studies of BCZT, a BT-based piezoceramic, and could potentially be addressed by pre-conditioning the material prior to implantation (Poon, 2020),

Murine preosteoblasts (MC3T3-E1) proliferated on poled PIC700 when cultured *in vitro* with some evidence of extracellular matrix formation, which suggests BNT-6BT is conducive to osseointegration. Prior investigations of pure BNT found that MC3T3-E1 cell proliferation and bone-like apatite formation depended on polarity, which could be harnessed for the

regeneration of bone tissues (Hermann-Muñoz *et al.*, 2020). The piezoelectric coefficients found in our study BNT-6BT are an order of magnitude stronger than pure BNT, two or three orders of magnitude stronger than hydroxyapatite (Silva *et al.*, 2001) and natural bone (Bur, 1976), and in near-parity with barium titanate. BT-based materials have been more extensively studied in supraphysiological piezoelectric implants than other piezoceramics: BT implants (Park *et al.*, 1981), BT-based composites (Jianqing, Huipin and Xingdong, 1997) and BT foams with hydroxyapatite coating (Zarkoob *et al.*, 2012) have been shown to promote in vitro or in vivo bone growth and remodelling. Subsequently, BT-based piezoceramics have been integrated into biomedical implants using techniques including 3D printing (Polley *et al.*, 2020; Yang *et al.*, 2020; Mancuso *et al.*, 2021), spray deposition (Poon, 2020), and electrospinning (Y. Li *et al.*, 2017), though fabrication of complex electroactive scaffolds with high BT content remains a challenge. Given the manufacturability and biocompatibility demonstrated in this paper, BNT-6BT constitutes a strong candidate for the future production of electroactive implants with high piezoceramic content. Similar additive techniques could be adopted to manufacture porous BNT-6BT scaffolds for piezoelectric bone stimulation.

Future study on the bioactivity of this material should apply mechanical loading during culture and conduct detailed morphochemical analyses of extracellular matrix depositions to fully capture the effects of supraphysiological electromechanical coupling on tissue formation. Such a study could be conducted in a dynamic compression bioreactor with time-lapsed imaging (Schädli *et al.*, 2022).

6.6. Summary of Findings

Research in this chapter comprehensively evaluated the electromechanical and biological properties of two BNT-6BT materials from different synthesis routes (solid state and additive manufacture) to determine suitability for use within smart biomedical implants. The following findings were produced:

- Piezoelectric properties of BNT-6BT were 5-31 dB inferior to standard PZT-based materials: the material is most viable a lead-free substitute in soft PZT applications, such as pressure sensing and thickness-mode pulse-echo measurements, with moderate performance losses (<10 dB).
- Piezoelectric properties were comparable to commercially available KNN and BT; more fundamental research is therefore necessary to synthesise lead-free piezoceramics for all applications; and some superior results have already been reported with doped KNN- and BT-based materials.

- No cytotoxic effects of BNT-6BT were detected: the material therefore has the potential to be incorporated within implantable electronic devices without hermetic sealing, which should be confirmed by in vivo studies of its long-term biological effects.
- BNT-6BT was conducive to the proliferation of MC3T3-E1 murine preosteoblasts: future research may consider bioactive scaffolds integrated with BNT-6BT as a potential biomaterial for bone repair.

Addendum: Compendium of Piezoceramic Material Properties

Table 6.A1. Some thickness-extension and thickness-shear mode properties for PZT-based and lead-free piezoceramics materials from commercial and academic sources

Family	Name	d_{33} (pC/N)	d_{15} (pC/N)	g_{33} (mV/m)	g_{15} (mV/m)	c_{33}^D (10^{10} N/m ²)	c_{55}^D (10^{10} N/m ²)	s_{33}^E (10^{-12} m ² /N)	s_{55}^E (10^{-12} m ² /N)	$\epsilon_{33}^S/\epsilon_0$ (-)	$\epsilon_{11}^S/\epsilon_0$ (-)	k_t (-)	k_{15} (-)	$\tan \delta_E$ (10^{-4})	Q_M (-)	Reference
Soft PZT	5A	400	550	25.1	26.7	15.5	3.9	20.4	45.8	910	940	0.48	0.67	200	85	(TJ Piezo, 2021)
	5B	430	610	24.9	39.0	17.5	4.3	21.1	47.2	960	870	0.48	0.71	200	90	
	5C	470	610	22.7	30.3	16.3	4.8	20.9	39.7	1140	1210	0.51	0.69	150	80	
	5D	580	740	22.2	30.0	16.6	4.9	23.0	42.9	1300	1340	0.51	0.72	150	80	
	5E	580	740	20.2	25.2	17.9	6.8	21.6	33.7	1480	1470	0.52	0.75	200	85	
	5H	640	780	19.8	27.1	15.0	4.5	23.5	43.9	1690	1680	0.5	0.70	150	75	
	5HD	680	840	19.9	27.3	16.8	5.1	23.8	42.5	1660	1600	0.53	0.74	150	65	
	5X	700	830	19.3	24.9	14.5	4.7	25.0	41.8	1880	1900	0.53	0.70	200	65	
	5XD	730	805	17.9	24.7	16.2	6.1	23.9	36.3	1710	1660	0.55	0.74	200	60	
	PIC151	500	610	21.5	33.9	15.7	-	19.4	-	1107	1143	0.53	0.65	200	100	(PI Ceramic, 2020a)
	PIC152	240	235	23.4	23.7	16.6	-	14.8	-	864	867	0.41	0.46	150	100	
	PIC153	600	780	16.4	23.3	15.5	-	20.0	-	2105	1975	0.49	0.66	300	50	

Chapter 6 – Lead-Free Piezoceramics for Smart Biomedical Implants

Family	Name	d_{33} (pC/N)	d_{15} (pC/N)	g_{33} (mV/m)	g_{15} (mV/m)	c_{33}^D (10^{10} N/m ²)	c_{55}^D (10^{10} N/m ²)	s_{33}^E (10^{-12} m ² /N)	s_{55}^E (10^{-12} m ² /N)	$\epsilon_{33}^S/\epsilon_0$ (-)	$\epsilon_{11}^S/\epsilon_0$ (-)	k_t (-)	k_{15} (-)	$\tan \delta_E$ (10^{-4})	Q_M (-)	Reference
Soft PZT	PIC155	360	540	27.9	46.0	15.8	-	19.3	-	782	809	0.48	0.65	250	80	(PI Ceramic, 2020a)
	PIC255	400	550	25.0	28.4	15.4	-	19.0	-	864	988	0.47	0.66	200	80	
	NCE51	443	669	26.3	38.9	16.2	4.37	21.3	48.9	823	906	0.50	0.73	150	80	(Noliac, 2022)
Hard PZT	4A	145	320	41.6	44.1	17.4	5.0	12.8	34.5	240	480	0.48	0.65	30	1400	(TJ Piezo, 2021)
	4B	180	380	33.9	39.0	18.8	5.5	16.0	33.2	360	610	0.48	0.67	30	1300	
	4C	220	330	32.9	35.2	17.9	6.4	16.9	27.5	430	610	0.48	0.66	40	1200	
	4D	310	380	25.8	29.4	16.2	8.6	17.5	22.9	730	750	0.49	0.70	50	500	
	4E	350	410	25.6	28.1	17.0	8.0	19.3	24.2	820	860	0.51	0.69	40	1000	
	4F	350	580	26.4	34.7	17.4	5.3	18.8	39.4	750	920	0.47	0.72	50	1500	
	4G	340	450	24.1	30.5	16.7	5.2	17.5	33.3	840	980	0.49	0.65	50	1800	
	8A	240	400	26.5	33.4	17.4	4.7	15.9	34.7	610	830	0.48	0.62	30	1000	
	8B	260	440	24.6	32.5	17.8	5.0	15.2	34.5	690	890	0.48	0.65	20	1000	
	PIC181	265	475	23.0	37.2	17.0	-	13.3	-	649	754	0.46	0.63	30	2000	(PI Ceramic, 2020a)
	PIC184	220	421	22.4	35.8	15.8	-	13.7	-	546	722	0.44	0.65	30	400	
	PIC144	225	419	23.3	33.9	16.6	-	14.3	-	640	866	0.48	0.65	30	1000	

Chapter 6 – Lead-Free Piezoceramics for Smart Biomedical Implants

Family	Name	d_{33} (pC/N)	d_{15} (pC/N)	g_{33} (mV/m)	g_{15} (mV/m)	c_{33}^D (10^{10} N/m ²)	c_{55}^D (10^{10} N/m ²)	s_{33}^E (10^{-12} m ² /N)	s_{55}^E (10^{-12} m ² /N)	$\epsilon_{33}^S/\epsilon_0$ (-)	$\epsilon_{11}^S/\epsilon_0$ (-)	k_t (-)	k_{15} (-)	$\tan \delta_E$ (10^{-4})	Q_M (-)	Reference
Hard PZT	PIC241	290	265	20.5	33.2	17.6	-	14.3	-	863	935	0.46	0.63	50	1200	(PI Ceramic, 2020a)
	PIC300	155	155	20.9	29.3	16.3	-	12.0	-	614	853	0.43	0.62	30	1400	
	NCE40	304	-	27.5	-	12.7	4.3	14.6	34.5	638	-	0.48	-	25	700	
	NCE41	310	-	25.9	-	11.6	4.8	16.0	39.5	684	-	0.50	-	40	1400	
	NCE81	255	-	28.0	-	12.7	4.3	15.0	34.5	551	-	0.47	-	17	1300	
BNT	Pz46	18	-	9.2	-	-	-	-	-	211	-	0.20	-	40	2000	(Meggit, 2017a)
	BNT	95	-	25.2	-	-	-	-	-	-	-	-	-	320	-	(Naderer <i>et al.</i> , 2014)
	BNT	77	-	26.9	-	-	-	-	-	-	-	-	-	214	-	(Kanie <i>et al.</i> , 2011)
	BNT-6BT	125	194	24.3	29.9	-	-	10.0	23.3	538	551	0.53	0.50	130	-	(Takenaka, Maruyama and Sakata, 1991)
	BNT-4BT	95	110	26.0	30.3	13.3	5.4	9.0	21.8	318	349	0.44	0.39	370	361	(Pardo, Á. García, <i>et al.</i> , 2011)
	BNT-6BT	148	159	28.5	24.6	13.6	4.9	9.2	24.2	457	610	0.40	0.40	480	330	(Pardo, Álvaro, <i>et al.</i> , 2011)
	BNT-6BT	117	-	17.0	-	-	-	-	-	583	-	0.43	-	250	256	(Li, Feng and Yao, 2004)

Chapter 6 – Lead-Free Piezoceramics for Smart Biomedical Implants

Family	Name	d_{33} (pC/N)	d_{15} (pC/N)	g_{33} (mV/m)	g_{15} (mV/m)	c_{33}^D (10^{10} N/m ²)	c_{55}^D (10^{10} N/m ²)	s_{33}^E (10^{-12} m ² /N)	s_{55}^E (10^{-12} m ² /N)	$\epsilon_{33}^S/\epsilon_0$ (-)	$\epsilon_{11}^S/\epsilon_0$ (-)	k_t (-)	k_{15} (-)	$\tan \delta_E$ (10^{-4})	Q_M (-)	Reference
BNT	BNT-6BT-La	125	-	9.0	-	-	-	-	-	626	-	0.38	-	450	182	(Li, Feng and Yao, 2004)
	BNT-6BT-Nb	118	-	8.3	-	-	-	-	-	637	-	0.38	-	460	199	
	BNT-6BT-Co	139	-	13.1	-	-	-	-	-	567	-	0.46	-	230	253	
	BNT-6BT-La-Nb	135	-	9.2	-	-	-	-	-	640	-	0.38	-	440	127	
	BNT-6BT-La-Co	127	-	11.2	-	-	-	-	-	622	-	0.38	-	210	263	
	BNT-2BT	78	-	21.9	-	-	-	-	-	587	-	0.46	-	173	-	(Chu <i>et al.</i> , 2002)
	BNT-4BT	87	-	22.1	-	-	-	-	-	592	-	0.45	-	207	-	
	BNT-6BT	122	-	22.9	-	-	-	-	-	597	-	0.40	-	179	-	
	BNT-8BT	112	-	15.0	-	-	-	-	-	628	-	0.42	-	204	-	
	BNT-10BT	94	-	13.9	-	-	-	-	-	633	-	0.41	-	239	-	
	BNT-BKT-BT	126	-	9.5	-	-	-	-	-	1063	-	0.50	-	600	40	(Fernandez-Benavides <i>et al.</i> , 2018)

Chapter 6 – Lead-Free Piezoceramics for Smart Biomedical Implants

Family	Name	d_{33} (pC/N)	d_{15} (pC/N)	g_{33} (mV/m)	g_{15} (mV/m)	c_{33}^D (10^{10} N/m ²)	c_{55}^D (10^{10} N/m ²)	s_{33}^E (10^{-12} m ² /N)	s_{55}^E (10^{-12} m ² /N)	$\epsilon_{33}^S/\epsilon_0$ (-)	$\epsilon_{11}^S/\epsilon_0$ (-)	k_t (-)	k_{15} (-)	$\tan \delta_E$ (10^{-4})	Q_M (-)	Reference
KNN	Pz61	80	-	18.1	-	-	-	-	-	382	-	0.40	-	400	25	(Meggit, 2017b)
	KNN	110	-	26.3	-	-	-	-	-	319	-	0.45	-	300	-	(Biol, Damjanovic and Setter, 2006)
	KNN	90	-	25.4	-	-	-	-	-	285	-	0.40	-	250	-	(Ringgaard and Wurlitzer, 2005)
	Doped KNN	140	-	47.9	-	-	-	-	-	257	-	0.40	-	400	-	
	KNN	127	306	29.0	36.9	21.4	6.3	10.1	27.0	306	545	0.46	0.64	150	240	(Zhang <i>et al.</i> , 2007)
	KNN-LS	265	340	21.7	32.2	15.9	4.4	15.0	33.3	830	810	0.46	0.57	200	40	
	KNN-KCN	90	125	34.9	35.7	12.9	4.6	9.3	22.0	190	310	0.50	0.45	60	1500	(Zhang <i>et al.</i> , 2009)
	KNN-Ta	162	45	68.5	17.4	23.2	8.90	15.5	12.0	54	272	0.65	0.23	-	-	
	KNN-LT	354	171	50.6	17.5	15.7	8.06	27.0	15.4	272	887	0.45	0.44	-	-	
	KNN	95	-	23.8	-	-	-	-	-	-	-	-	-	-	-	(Guo, Kakimoto and Ohsato, 2005)
	KNN-LT	200	-	39.6	-	-	-	-	-	-	-	-	-	-	-	
	KNN-LN	235	-	-	-	-	-	-	-	-	-	0.48	-	-	-	(Guo, Kakimoto and Ohsato, 2004)
	KNN-LN	170	-	49.2	-	-	-	-	-	-	-	-	-	275	-	(Hou <i>et al.</i> , 2012)

Chapter 6 – Lead-Free Piezoceramics for Smart Biomedical Implants

Family	Name	d_{33} (pC/N)	d_{15} (pC/N)	g_{33} (mV/m)	g_{15} (mV/m)	c_{33}^D (10^{10} N/m ²)	c_{55}^D (10^{10} N/m ²)	s_{33}^E (10^{-12} m ² /N)	s_{55}^E (10^{-12} m ² /N)	$\epsilon_{33}^S/\epsilon_0$ (-)	$\epsilon_{11}^S/\epsilon_0$ (-)	k_t (-)	k_{15} (-)	$\tan \delta_E$ (10^{-4})	Q_M (-)	Reference
KNN	KNN-LN	314	-	53.7	-	-	-	-	-	-	-	-	-	-	-	(Zhao, Zhang and Li, 2007)
	KNS-BNKZ	490	-	-	-	-	-	-	-	1200	-	0.55	-	200	-	(Ou-Yang <i>et al.</i> , 2015)
	KNS-BNZH	380	690	21.4	35.5	12.7	5.1	16.8	43.9	975	1100	0.48	0.74	200	200	(Qiao <i>et al.</i> , 2020)
	KNN-LS-BCZ	345	225	21.6	22.5	19.4	4.6	14.0	26.7	844	908	0.47	0.46	1000	~60	(Carreño-Jiménez, Reyes-Montero and López-Juárez, 2022)
	KNN-LS-BZ	408	305	16.4	18.3	18.6	4.2	17.0	29.2	1628	1514	0.39	0.44	1000	~30	
BT	SM511	160	-	14.3	-	-	-	-	-	1000	-	0.32	-	50	1000	(Steiner & Martins, 2022)
	BT	135	207	13.8	18.3	19.5	7.7	9.3	16.9	880	990	0.40	0.48	50	500	(TJ Piezo, 2021)
	BT	160	-	11	-	-	-	-	-	1279	-	0.26	-	50	1300	(APC International, 2022)
	BT-Li	260	-	16.8	-	-	-	-	-	-	-	-	-	-	357	(Kimura <i>et al.</i> , 2013)
	BT-LiF	270	-	10.6	-	-	-	-	-	-	-	-	-	120	-	(Yang <i>et al.</i> , 2012)
	BCZT	620	-	-	-	-	-	-	-	-	-	-	-	-	-	(Liu and Ren, 2009)
	BCZT	572	-	13.4	-	-	-	-	-	-	-	-	-	150	125	(Tian <i>et al.</i> , 2013)

Chapter 6 – Lead-Free Piezoceramics for Smart Biomedical Implants

Family	Name	d_{33} (pC/N)	d_{15} (pC/N)	g_{33} (mV/m)	g_{15} (mV/m)	c_{33}^D (10^{10} N/m ²)	c_{55}^D (10^{10} N/m ²)	s_{33}^E (10^{-12} m ² /N)	s_{55}^E (10^{-12} m ² /N)	$\epsilon_{33}^S/\epsilon_0$ (-)	$\epsilon_{11}^S/\epsilon_0$ (-)	k_t (-)	k_{15} (-)	$\tan \delta_E$ (10^{-4})	Q_M (-)	Reference
	BCZT	390	278	3.9	12.6	16.2	4.5	6.5	20.8	2876	2864	0.24	0.31	300	~1000	(Reyes-Montero <i>et al.</i> , 2018)
	BCZT-Zn	420	-	10.7	-	10.8	-	13.8	-	2788	-	0.42	-	-	135	(Tuan <i>et al.</i> , 2019)
	BCST	405	-	13.3	-	-	-	-	-	-	-	-	-	-	117	(Chen <i>et al.</i> , 2013)

Chapter 7

Discussion and Concluding Remarks

7.1. Clinical Challenge

Implantable electronics are key enablers for personalised health monitoring and precision medicine (Song, Min and Gao, 2019). Advances in miniaturisation and biomaterials have already produced implantable electronic medical devices that have been authorised for use in the fields of ophthalmic, neurological, cardiothoracic, otologic, and endocrine surgery (Fitzpatrick, 2015). In orthopaedics, aseptic loosening and periprosthetic joint infection are the two most pervasive causes of revision surgery following arthroplasty, and both complications were identified in Chapter 2 as lacking sufficiently timely and accurate diagnostic protocols (Mandalia *et al.*, 2008; Barnsley and Barnsley, 2019; Schiffner *et al.*, 2019). An implantable electronic monitoring system embedded within the prosthesis could therefore enable early diagnoses and moreover be used as a basis for delivering patient-specific interventions.

Whilst orthopaedic implants with embedded circuitry have been used for several decades prior to collect research data (Rydell, 1966; Waugh, 1966; Bergmann *et al.*, 1988, 2012; Rohlmann, Bergmann and Graichen, 1994; D'Lima *et al.*, 2005), none had received regulatory approval for clinical use in arthroplasty prior to this research. Since embarking on this research, the first – and so far only – smart joint prosthesis has been cleared for the collection of kinematic data (FDA, 2021), but practical use is subject to a restricted set of indications and the device has not been authorised to support clinical decision making – a translation barrier still exists. The challenge of this research was to develop cost-effective technology for functionalising mass-market implants, which would thereby improve the management of aseptic loosening and periprosthetic joint infection

7.2. Research Contributions

A pragmatic approach towards smart implant design was adopted in this research, which was guided by the analysis of the literature in Chapter 2. Two new concepts for the mitigation of post-arthroplasty complications were introduced and evaluated in clinically relevant models. Additionally, the suitability of a lead-free piezoceramic material for smart implant applications has also been investigated.

7.2.1. Contemporary Analysis of Arthroplasty Complications

Arthroplasty technology has continually advanced since the first procedures were introduced in the late 1950s: the nature and prevalence of complications have similarly evolved as failure mechanisms have emerged and been addressed. The current state of the art was profiled in Chapter 2 through a detailed review of the contemporary literature on

complications of arthroplasty, which covered aetiologies, diagnoses, and treatments. In contemporary arthroplasty, the two dominant indications for revision surgery were identified as aseptic loosening and periprosthetic joint infection. Used as an overarching term to describe the loss of fixation in the absence of infection, the underlying mechanisms and clinical presentations for aseptic loosening have changed following improvements in the wear performance of implants. Once associated with macrophage-induced resorption of the host bone (osteolysis), aseptic loosening in cemented implants has been more commonly characterised by debonding since 2010, with a bias towards the implant-cement interface. In cementless arthroplasty, early loosening was attributed to excessive micromotion leading to fibrosis, whilst late loosening was attributed to stress-shielding, with both mechanisms induced by aphysiological mechanical stimuli in the host bone. Similarly, periprosthetic joint infection had mixed aetiologies with varying presentations: acute infections were characterised by fever and erythema, whilst chronic infections were found to frequently involve treatment-resistant bacterial biofilms. Both conditions were found to lack detailed understanding of the failure mechanisms as *in vivo* data is only available at single timepoints from current diagnostic modalities (radiographic, histological, bacteriological, and biochemical), typically after the development of symptoms. An extant need was therefore identified for implant-based monitoring systems to provide time-series data to understand progression of both conditions and enable early interventions.

7.2.2. Simultaneous Fixation and Infection Monitoring

Requiring only two embedded components (a shear-wave piezoelectric transducer and a wire coil), the first smart implant concept used wireless pulse-echo ultrasound to simultaneously monitor fixation at the implant-cement interface and implant temperature. This smart implant concept is the first to capture diagnostic information on both of the two most common post-arthroplasty complications: implant-cement debonding is the dominant mechanism of aseptic loosening in contemporary arthroplasty implant (Chapter 2) and elevated temperature is a specific marker of acute periprosthetic joint infection (Chapter 2). Modelling and experimental investigations of the fundamental concept (Chapter 3) indicated that patient anatomy affected neither the inductive link nor the acoustic pulse-echo response in the frequency range of interest, but the pulse-echo response was affected by cementation technique. Fixation measurements should therefore be calibrated in a well-fixed state post-surgery: rises from the baseline measurement would then indicate implant-cement debonding. Debonding at the implant-cement interface was reliably detected when the concept was embodied within the tibial component of commercial knee prostheses (Chapter 4): the underlying fixation measurements were unaffected by reader positioning, positioning

of the femoral component, and transmission through musculoskeletal tissue. However, temperature measurements in the commercially embodied concept did drift dependent on reader positioning, and control measures are therefore required to ensure stable temperature measurement within a workup threshold of 1 °C. In summary, the concept is flexible, scalable, and low-cost (estimated material cost: \$1 per implant), and it could therefore be deployed as a platform to multiple cemented implant designs, including knee, hip, shoulder, and ankle prosthesis.

7.2.3. Active Osseointegration

A second smart implant concept to enhance osseointegration into cementless implants was introduced in Chapter 5: dual electrical-ultrasonic stimulation was delivered to the periprosthetic tissue to promote osteogenesis. Previous research had investigated the independent osteogenic effects of electrical and ultrasonic stimulation at cell level, demonstrating promising results from in vitro cultures of osteoblast-lineage cells, but in vivo results with external stimulation had proven less repeatable and clinical efficacy had been contested (Chapter 2). This discrepancy may partly be due to the difficulties in bridging in vitro cell models, where intercellular diversity and macrostructural interactions with the stimulation factor are limited, and live animal studies, where these factors become pertinent but inevitably challenging to control. In Chapter 5, the concept was evaluated at organ level in a novel ex vivo bioreactor model: wherein the inherent cellular diversity and extracellular matrix of natural bone were preserved and physiologically relevant conditions were tightly controlled. Findings from the passive condition were consistent with previous ex vivo bioreactor models of osseointegration, and results from the active condition suggested considerably accelerated cell proliferation and deposition of extracellular matrix onto the implant surface with active osseointegrative treatment. No detrimental effect of stimulation was observed in histological and immunochemical analyses, but ALP levels and calcein mineralisation in the bulk cancellous bone tissue were decreased, which could plausibly be an artefact of the ex vivo method (metabolic acidosis). Nevertheless, the ex vivo model provides a platform for further investigation of the underlying electromechanobiology and optimisation of the stimulation parameters.

7.2.4. Lead-Free Piezoceramic for Biomedical Implants

The electromechanical and biological properties of a new lead-free piezoceramic biomaterial, BNT-6BT, were characterised in Chapter 6, and the suitability of the material for current and prospective applications within implantable electronics was referenced against standard lead zirconate titanate (PZT) materials. Sensing, energy scavenging (off-resonant

energy harvesting), acoustic power transfer (on-resonant energy harvesting), pulse-echo response (thickness-extension and thickness-shear modes), and tissue stimulation were all considered, producing the most comprehensive functional analysis of BNT-6BT. The piezoelectric properties of BNT-6BT were generally inferior to PZT but comparable to other commercially available lead-free materials, potassium sodium niobate (KNN) and barium titanate (BT). Moderate performance losses (<10 dB) may be tolerable for certain applications, such as acoustic power transfer and transmission (as in Chapter 5) in the thickness-extension mode. However, more severe losses in other applications are too detrimental for BNT-6BT to be considered an alternative to standard PZT material: the drop in amplitude of the shear-mode pulse-echo response (–25 dB) is unworkable for the smart implant concept of Chapters 3 & 4. For these applications, there is an ongoing need to conduct fundamental research into the synthesis of lead-free piezoceramics with enhanced properties. No short-term cytotoxic effects due to BNT-6BT were detected and the material was conducive to cell growth (MC3T3-E1 murine preosteoblasts), which could facilitate applications where the piezoceramic is required to be exposed to – or even integrated with – biological tissue.

7.3. Limitations

Both smart implant concepts and the piezoceramic material were evaluated in benchtop experimental models, which inherently simplify the complex reality of any clinical deployment. Specific limitations of the various models were discussed in the preceding chapters. An overview of the key limitations is presented in this section.

7.3.1. Uncertain Aetiopathogeneses

The first smart implant concept (Chapter 3 & 4) was developed for the detection of the two most prevalent revision-causing complications of arthroplasty: aseptic loosening and periprosthetic joint infection. Multiple aseptic loosening failure modes have been described in literature (Chapter 2), varying in prevalence over time and between patients. The fixation sensing mechanism in this smart implant concept was designed to detect the most common failure mode: tibial debonding. Computational modelling (Chapter 3) indicated that implant-cement fixation sensing would be consistent amidst variation in the mechanical properties of the periprosthetic tissue. Whilst this promotes the reliable detection of tibial debonding, the sensing mechanism is consequently expected to be insensitive to the non-negligible number of aseptic loosening failures that induced in the bone, such as osteolysis, or at the bone-cement interface. Similarly, the infection detection mechanism is based on proxy measurements of elevated temperature (Chapters 3 & 4). Elevated temperature is a specific marker of acute infection (96%; Shohat *et al.*, 2019), but its overall sensitivity for the detection

of chronic infection is low (41%; Shohat *et al.*, 2019). Therefore, whilst the detection mechanism has the potential to provide early warning of rapid-onset presentations of periprosthetic joint infection, which are strongly associated with systemic sepsis, the concept is unlikely to edify the clinical response to chronic infections. Ultimately, the clinical efficacy of this smart implant concept will be determined by prevalence rates for the various failure modes. Both detection mechanisms ultimately require in vivo deployment for a more accurate determination of clinical efficacy: the data generated would also serve to elevate understanding of the underlying aetiopathogeneses.

7.3.2. Ex Vivo Organ Models

The active osseointegrative implant (Chapter 5) and the lead-free piezoceramic material (Chapter 6) were evaluated in ex vivo organ models: an emergent technique designed to bridge the gap between in vitro cell culture and in vivo animal trials. In prior research, ex vivo bone organ models had mostly been used for biological and pharmaceutical studies: the development of ex vivo models of osseointegration is highly novel, experimental, and yet to be fully referenced against in vivo results. Use of an ex vivo model to evaluate the active osseointegrative implant preserved the cellular diversity and spatial complexity of natural bone, but the model was not a perfect replication of the in vivo environment. Particularly, the explants were deficient of blood supply and interactions with other organ systems, thereby impeding processes like haemostasis and angiogenesis, which are known to be involved in osseointegration. Tissue was sourced from skeletally immature porcine donors with no musculoskeletal defects, whereas arthroplasty prostheses will be implanted into elderly human patients in clinical practice. Therefore, whilst relative trends from these experiments are likely to correlate with in vivo data, absolute discrepancies between ex vivo porcine and in vivo human results are to be expected, and secondary effects from systemic interactions will be absent. Furthermore, results in the ex vivo study were obtained from porcine tissue over periods of 21 days (active osseointegration) and 28 days (lead-free piezoceramic), with incubation time limited by the ex vivo model. The long-term biological effects of both protocols in humans therefore require further research. Despite these limitations, the ex vivo models provide a cost-effective, iterable, ethically compliant platform for understanding the fundamental biological processes and optimising treatment protocols in a near-physiological environment before validation in an in vivo animal trial.

7.4. Future Perspectives

The smart implant concepts developed in this research (Chapters 3, 4 & 5) were novel and exploratory, which consequently led to the identification of several opportunities for follow-up research and refinement.

7.4.1. High-Throughput Bioreactor and In Vivo Trials

Active osseointegrative implants are a novel concept for which the set of possible stimulation parameters (waveform, frequency, amplitude, duration, etc.) is vast and unexplored – only a single set of parameters was trialled in Chapter 5. Rapid exploration of these possibilities could be achieved using a ‘high-throughput bioreactor’ in which numerous specimens (>50) are cultured concurrently with varying stimulation protocols. Supported by quantitative measures, this approach would develop understanding of the biological effects of stimulation at pace and enable optimisation prior to an in vivo trial – an inevitable step in the pathway to clinical translation. Example metrics that could be implemented as a basis for optimisation include percentage bone on-/ingrowth (widefield microscopy/ μ CT), time-offset fluorochrome double-staining (histomorphometry), and quantitative monitoring of osteoblast-related gene expression (RT-qPCR),

7.4.2. Closed-Loop Osseointegration and Multielement Designs

The two smart implant concepts presented in this research were explored individually, though they share the same principles of operation: wireless excitation of an embedded piezoelectric transducer. With different resonant frequencies, both concepts could be embedded within the same implant and operated independently without loss of performance. Capable of monitoring and actively stimulating fixation, such an implant could be used for closed-loop osseointegration. By the same frequency spacing principle, multiple functional elements could be embedded within the same implant to monitor or stimulate fixation at multiple points, respectively enabling the detection of partial loosening or the targeted delivery of active osseointegrative treatment.

7.4.3. Direct Infection Detection

The first smart implant concept in this thesis used elevated temperature as a proxy for infection, which has the potential to enable early diagnosis of acute infection. The treatment of low-grade chronic infections could be edified with more direct methods of detection, with two embodiments of an implantable infection sensor envisaged:

- (1) specific identification of bacteria (via surface proteins or biomarkers) would instruct the selection of antibiotics to target the causative pathogen; and

- (2) quantitative measurement of bacterial biofilms, which are often resistant once established, would facilitate in vivo monitoring of treatment efficacy and could further be combined to measurements of antibiotic concentration for closed-loop antibiotic treatment.

Neither of these embodiments currently exist in a form amenable to low-cost implant functionalisation, but the approach towards smart implant design adopted in this research could serve as the basis for the design of a future system. If a direct detection method were to be realised, it would also have benefits beyond arthroplasty: surgical site infections impart major clinical and financial burdens to patients and healthcare providers in other orthopaedic procedures, particularly fracture fixation (Metsemakers *et al.*, 2018), and other specialties, including neurological and cardiothoracic surgery (Badia *et al.*, 2017).

7.5. Conclusion

Smart implants are an exciting new technology for the field of orthopaedic surgery. Focusing on the management of aseptic loosening and periprosthetic joint infection, this research has demonstrated that traditional monobloc implants can be augmented with minimal onboard circuitry to generate diagnostic information and deliver therapeutic interventions. Implantable electronic systems with small footprints and low cost do not conflict with the primary drivers of implant design (biomechanical function and economic cost) and could therefore be integrated as a platform technology to entire portfolios of implant.

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