Project Details	
Project Code	MRCPHS26Br Rayfield
Title	Determining jaw joint mechanics by characterising shape, genetics and material properties in wild type and mutant zebrafish
Research Theme	PHS
Project Type	Wet lab
Summary	This project explores how joints respond to mechanical forces throughout life, using zebrafish as a model to understand joint ageing and degeneration. By combining advanced imaging and mechanical testing, the student will study how joint shape, genetics, and tissue properties influence joint health in wild type and mutant fish. Computer models will predict how these factors affect strain and wear in the jaw. The aim is to uncover how joint tissue degradation with age and mutation of osteoarthritis susceptibility genes affects jaw mechanics, informing new strategies for improving joint health in ageing humans and animals.
Description	**Project Summary:** The skeleton must remain functional throughout life, adapting to mechanical loads during growth and everyday activity. Nowhere is this more critical than in joints, where forces are concentrated and coordinated movement depends on tissue shape, material properties, and the interaction between muscles and skeletal elements. Joint tissues, especially cartilage, are highly mechanosensitive and respond dynamically to changes in loading and use. However, the relative contributions of joint morphology, genetic patterning, and tissue stiffness to joint biomechanics are not well understood, despite their important in disease. The degenerative joint condition osteoarthritis affects more than 10 million people in the UK, it has a complex etiology and we know that both genetic susceptibility and load are major risk factors. In this project, we will investigate the interplay between genetic patterning and mechanical performance in the zebrafish jaw joint, using a combination of mutantlines carrying mutations in osteoarthritis susceptibility genes, advanced imaging, materials testing, and finite element (FE) modelling. By characterising how jaw shape and mechanical properties influence strain distributions during loading, we aim to identify the key determinants of joint function across development and into maturity. Research Aims and Objectives: • Quantify the mechanical performance of the zebrafish jaw joint from early development through to adult stages. • Determine how genetically induced changes in joint shape affect biomechanical function using zebrafish mutants carrying mutations in osteoarthritis risk genes. • Evaluate the relative contributions of joint shape, material properties, and muscle activity to strain distribution and deformation in the jaw. • Validate biomechanical predictions against empirical data from live and ex vivo loading experiments. • Link mechanical strain to cellular responses such as senescence and autophagy using molecular reporter lines.

Research Plan and Methods

This project will use zebrafish, both wild-type and craniofacial mutants, to study how genetic patterning and mechanical loading interact to shape joint function. Focusing on the lower jaw joint, we will track developmental changes from larvae to adults, integrating imaging, materials testing, and biomechanical modelling.

To characterise joint shape, we will use light-sheet microscopy in juveniles and microCT scanning in older fish. These 3D datasets will be analysed using geometric morphometrics to quantify variation in joint morphology across development and between genotypes.

Material properties of cartilage and bone will be measured using atomic force microscopy (AFM) and nano-indentation, providing stiffness data to inform finite element (FE) models. These models will simulate jaw loading and allow us to test how joint shape and tissue stiffness influence strain distribution.

We will validate FE model predictions using ex vivo mechanical loading during microCT scanning, comparing predicted strain patterns to real deformation using morphometric analyses.

To link mechanical strain to cellular responses, we will use transgenic zebrafish reporter lines marking autophagy and senescence. This will reveal how mechanical environments influence joint cell behaviour. Where key findings suggest conserved mechanisms, we will test them in loaded mouse joint tissues.

This multidisciplinary approach will clarify how joint form and function are influenced by genetic and biomechanical factors, using zebrafish mutants as a powerful model system.

Expected Outcomes

This project is expected to yield new insights into how joint shape, material properties, and muscle activity interact to influence mechanical performance in the vertebrate skeleton. By integrating data from zebrafish mutants with altered craniofacial patterning, we will disentangle the relative contributions of genetic factors and biomechanical forces to joint function. The development and validation of finite element models will provide a predictive framework for understanding how changes in shape or stiffness affect strain distribution within joints. These models will also offer a tool for exploring broader questions in skeletal biomechanics.

In parallel, we anticipate identifying specific cellular responses—such as autophagy and senescence—that are spatially linked to regions of mechanical strain, providing a mechanistic link between biomechanical loading and tissue maintenance or degeneration. Validation of these findings in mouse joints will help assess their relevance across species.

Ultimately, the project will advance our understanding of how genetically patterned structures are refined and maintained through mechanical use, with implications for joint health and skeletal disease.

Significance and Impact:

This project will bridge genetics, biomechanics, and developmental biology to address fundamental questions about joint function. By focusing on zebrafish mutants with altered joint morphology, we can decouple genetic and mechanical influences on tissue health and degeneration. The tools and data generated will be applicable across

	vertebrate systems and have relevance for understanding mechanically driven joint disorders such as osteoarthritis. In the longer term, these findings may inform intervention strategies aimed at preserving joint function in the face of genetic or biomechanical challenges.
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