Institution: University of Portsmouth		
Unit of Assessment: UoA 12: Engineering		
Title of case study: Impact arising from advances in X-ray computed tomography for the bioengineering sector		
Period when the underpinning research was undertaken: 2014-2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Gianluca Tozzi	Reader in Bioengineering	01/02/2012 - present
Period when the claimed impact occurred: 2016-2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Significant commercial impacts have been achieved, including substantial economic gains, new product creation, technology improvements, commercial visibility, job creation and new medical insights based on groundbreaking research undertaken by the University of Portsmouth (UoP) Zeiss Global Centre (ZGC) in X-ray computed tomography (XCT) for bioengineering.

This multidisciplinary research has pushed the boundaries of lab-based 3D X-ray microscopy and was conducted in close collaboration with international industry partners operating in bioengineering (Biotrics, GSK), imaging (Zeiss, Thermofisher Scientific, LaVision) as well as UK National Facilities (Diamond Light Source) and healthcare professionals (consultant orthopaedic surgeons at the Royal National Orthopaedic Hospital, London).

2. Underpinning research

This Case Study is focusing on the use of X-ray imaging (computed tomography – CT) for the analysis and evaluation of biomaterials and biological tissues for bioengineering research.

Research environment

Since 2011 research has developed at the UoP combining X-ray computed tomography (XCT) and *in situ* mechanical evaluation of biological tissues and biomaterials. This has been achieved through the use of emerging techniques such as digital volume correlation (DVC), which is today recognised worldwide as a UoP specialism in the Bioengineering community (as exemplified by a recent invited Frontiers Webinar on the topic form the Journal of the Mechanical Behavior of Biomedical Materials: https://youtu.be/2v_aH32g778). This expertise is reflected in the establishment in 2016 of the Zeiss Global Centre (ZGC) http://bit.ly/ZGCUoP through a strategic partnership with Carl Zeiss Ltd. The ZGC supports research across different faculties/departments at UoP and involves many collaborators in Europe and worldwide.

Importance of the research

In-depth understanding of tissue/biomaterial morphological, mechanical and functional properties in healthy and pathological conditions is of vital importance and fully aligned with the remit of UKRI themes such as EPSRC Healthcare Technologies (e.g Developing Future Therapies, Optimising Treatment). Technological advances in XCT-based research of biological tissues and biomaterials, incorporating additional evaluations such as mechanics and DVC, has enabled this understanding and brought about new knowledge that has provided a novel platform for the treatment of musculoskeletal conditions and oral care, and has translated into economic and technological growth for organisations.

Research at UoP

Prior to 2014, XCT-based technology in the field of bioengineering, particularly in musculoskeletal research, was predominantly dedicated to obtaining detailed subject-specific geometries to assess morphology (e.g. bone morphometric parameters) or aid more detailed numerical simulation (e.g. subject-specific finite element models). Techniques such as XCT-based digital volume correlation (DVC) were still relatively unknown in biomaterials research and completely unexplored in the field of dentistry and oral care, in part due to the limited presence and availability of commercial DVC software solutions. In fact, paper (R1, 2013) is considered to be the first UK research to use a commercial DVC in the bio-area. From that paper, it was evident how the unique ability of DVC in

capturing 3D full-field strains only from XCT images would lead a step-change in the understanding of the mechanical performance of biomaterials in both simulated and real biological environments, particularly for the healthcare industry. Another vital question that was not fully addressed in the previous REF period, given the relative infancy of the technique, was in relation to the reliability of displacement/strain measurement in tissues and biomaterials from different DVC strategies and software solutions, as this could obviously jeopardise any mechanical evaluation from the technique. This problem was even more important when thinking to scale DVC measurement based on lower-resolution XCT images, such as the ones from clinical CT and in particular new emerging weight-bearing CT systems (e.g. pedCAT, Curvebeam, launched in 2013). Thus, hampering any reliable translation of the technology into clinical practice for the assessment of pathologies and trauma.

Research conducted at UoP by Gianluca Tozzi since 2014 focused on enhancing knowledge and translation to impact in:

1. Function/structure relationship of biological tissues and biomaterials through advanced XCT imaging and DVC analysis. Work carried out in this area includes comprehensive evaluation of bone (R2), teeth (R3), and biomaterials (R4, R5) via XCT-based evaluations both *in vitro* and *ex vivo*. The work pushed the boundaries of XCT in such materials and established new criteria to use digital volume correlation (DVC) technique for understanding tissue micromechanics.
2. Scaling up XCT/DVC to clinical CT. Important research has been recently conducted to propose DVC as a diagnostic tool to understand musculoskeletal mechanics (i.e. subtalar joint motion), with the aim to develop ad-hoc joint replacements (currently not available on the market) to be used in pathological conditions such as osteoarthritis (R6).

3. References to the research

(R1) Madi, K., **Tozzi, G**., Zhang, Q.-H., Tong, J., Cossey, A., Au, A., Hollis, D. & Hild, F. (2013). Computation of full-field displacement in a scaffold implant using Digital Volume Correlation and Finite Element Analysis. *Medical Engineering & Physics 35*(9), 1298-1312. https://doi.org/10.1016/j.medengphy.2013.02.001

(R2) Palanca, M., **Tozzi, G**., Cristofolini, L., Viceconti, M., & Dall'Ara, E. (2015). 3D Local Measurements of bone strain and displacement: Comparison of three Digital Volume Correlation approaches. *Journal of Biomechanical Engineering*, *137*(7), 071006. https://doi.org/10.1115/1.4030174

(R3) Lu, X., Pena Fernandez, M., Bradley, R., Rawson, S., O'Brian, M., Hornberger, B., Leibowitz, M., **Tozzi, G.**, & Withers, P. (2019). Anisotropic crack propagation and deformation in dentin observed by four-dimensional x-ray nano-computed tomography. *Acta Biomaterialia, 96*, 400-411. https://doi.org/10.1016/j.actbio.2019.06.042

(R4) **Tozzi, G**., Zhang, Q.-H., & Tong, J. (2014). Microdamage assessment of bone-cement interfaces under monotonic and cyclic compression. *Journal of Biomechanics, 47*(14), 3466-3474. https://doi.org/10.1016/j.jbiomech.2014.09.012

(R5) Peña Fernández, M., Dall'Ara, E., Bodey, A., Parwani, R., Barber, A., Blunn, G. & **Tozzi, G**. (2019). Full-field strain analysis of bone-biomaterial systems produced by the implantation of osteoregenerative biomaterials in an ovine model. *ACS Biomaterials Science and Engineering 5*, 2543-2554. https://doi.org/10.1021/acsbiomaterials.8b01044

(R6) Peña Fernández, M., Hoxha, D., Chan, O., Mordecai, S., Blunn, G., **Tozzi, G.** & Goldberg, A., (2020). Centre of rotation of the human subtalar joint using weight-bearing clinical computed tomography. *Scientific Reports, 10*(14), 1035. https://doi.org/10.1038/s41598-020-57912-z

Evidence for the quality of research

These outputs are a representative selection of related work. All employ robust design, appropriate research techniques and are published in respected peer-reviewed academic journals that are relevant to the discipline. For example, R1 is a pivotal paper for DVC application in the area of

Biomaterials and cited 79 times; R2 was Editors' Choice paper for 2015 and cited 60 times; R4 is the first paper on use of DVC in bone-biomaterial systems and cited 38 times; R6 has attracted world-wide media attention (e.g. http://bit.ly/XrayUoP) and already cited 4 times.

Research grant funding

(G1) **Tozzi, G**. *In situ XCT & DVC of MG-based bone-screw and plate-screw systems - continuation*. Funded by Biotrics Bioimplants GmbH, January 2020-July 2021 (GBP93,578)

(G2) **Tozzi, G**. *In situ XCT & DVC of MG-based bone-screw and plate-screw systems*. Funded by Biotrics Bioimplants GmbH, January 2019-January 2020 (GBP92,475)

(G3) **Tozzi, G**. & Barber, A. *4D MicroCT Evaluation and Digital Volume Correlations (DVC) of Mg-Based Alloys*. Funded by Botiss Medical AG, February 2018-July 2021 (GBP52,500).

(G4) **Tozzi, G** & Roldo, M. *Development of imaging capability to evaluate biofilm removal from dentures*. Funded by GlaxoSmithKline, January 2020-May 2020 (GBP24,527).

(G5) **Tozzi, G**. *Multiscale Imaging and Mechanical Evaluation of Biomaterials in the Oral Cavity*. Funded by GlaxoSmithKline, November 2017-January 2018 (GBP32,020)

(G6) **Tozzi, G.** (PI). *DVC Application to Clinical CT Images*. Funded by University College London, March 2018-September 2018 (GBP5,000).

(G7) **Tozzi, G.**, Barber, A., Lupton, C., & Karabela, A. *SR-microCT assessment of bone-biomaterial integration for osteoregenerative biomaterials*. Funded by Diamond Light Source, May 2016 (GBP76,800)

4. Details of the impact

This research has had significant commercial impact for companies in the global optoelectronics, digital visualisation and bioimplants industries, as well as impact for the health profession and data analysis services provided by the Diamond Light Source. Specifically, this has led to impact for:

- Carl Zeiss Ltd. (Microscopy), whose strategic priorities for their microscopy solutions were influenced by our work in the characterisation of biomaterials, enabling them to increase their market presence in that area (S1, S8, S9).
- LaVision UK Ltd, a software company who improved their product on the basis of our research returning increased income (S2).
- Thermo Fisher Scientific, a major scientific equipment manufacturer who used our data to launch new software solutions (S3, S10).
- Biotrics bioimplants GmbH, a provider of bioimplants who have optimised product design and manufacturing processes and produced two new product lines, as well as taken on new staff and allocated additional R&D budget (S4).
- GlaxoSmithKline plc (Consumer Healthcare), a world-leading provider of oral care products who improved their products, substantiated their marketing claims and captured significant income (S5).
- The orthopaedic foot and ankle clinical profession, whose fundamental understanding of how the ankle works was changed (S6).
- The Diamond Light Source, by enhancing its tomography services to industry and academia through the first benchmark validation of the Savu tomographic reconstruction, a high-throughput system for high-quality tomographic reconstruction of large datasets across Diamond (S7).

Increasing market presence and supporting strategic prioritisation

In the Zeiss Global Centre at UoP, Tozzi's team undertook collaborative research with Carl Zeiss Ltd. into the competence of biological structures and biomaterials through advanced XCT, showcasing Zeiss capability and technology in XCT (R5). Since 2019, the research at ZGC **has supported Zeiss promotional activities** (S8) including the first use of phase-contrast capability

in Zeiss Versa systems to resolve and mechanically evaluate (via DVC) cartilage-bone interface (S9). All this **helped Zeiss to increase their presence in the biomaterials application field** and **due to Tozzi's research, the biomaterials topic has now become a strategic priority at Zeiss** by steering the direction of their Materials Science Sector team in the future development of applications in this area (S1).

Improved products and equipment for measuring strain for bioengineering applications

In order to allow reliable measurement of displacement/strain in any engineering materials, including biomaterials, a deeper understanding of different DVC software strategies was conducted (R2). The work was of major interest to DVC software developers such as **LaVision**, who relied on that knowledge to improve the correlation workflow in their latest commercial package (DaVis10). LaVision are the leading supplier of laser imaging systems in top selling application fields like fluid mechanics (e.g. aerodynamics, microfluidics), combustion (e.g. automotive, power generation) as well as spray and particle diagnostics (e.g. engines, pharma). As a result of Tozzi's research, the improved software solution, since its launch in November 2017, has been utilised by other academics working in the field of bioengineering **generating considerable income for LaVision (~GBP150,000)** and delivering specific benefits to LaVision clients (S2).

Furthermore, the constant advancement and dissemination of the technique from the research attracted the attention of **Thermo Fisher Scientific**, a leading global provider of software applications, ranging from acquisition and imaging automation frameworks to advanced 3D data quantification and simulation digital solutions. Thermo Fisher Scientific developed an appetite for development and commercialisation of a new DVC module (2017) to be used within their existing Avizo platform (S10). In this case, this new package performance was finely tuned by using a dataset of XCT images of bone-biomaterial systems from (R4), which provided the required level of complexity to test the correlation strategy in this new DVC software. Since the launch of the product in 2017, **the Avizo DVC module has had a significant impact on their sales in the material and living sciences,** with several dozen customers using it daily to compute 3D full-field displacement and strains in materials (S3).

Commercial benefits for industry in the area of biomaterials for orthopaedics and oral care

The ZGC at UoP has established two major research collaborations with **Biotrics bioimplants** and **GlaxoSmithKline** (GSK).

Biotrics is operating in the area of biodegradable biomaterials such as Magnesium(Mg)-based alloys. Due to our research in bone-biomaterial systems [R4, R6], they have implemented advanced XCT and DVC at ZGC to fully characterise the mechanics-corrosion interplay in a range of their Mg products (both *in vitro* and *ex vivo*). Three funded projects (total of ~GBP250,000 (G1-3)) were aimed at optimising product design and manufacturing processes, and ultimately commercialising the latest generation of scaffolds for improved clinical performance. As a result, since 2019 the **Mg-based implant area has become a strategic priority in Biotrics, which has contributed to the hiring of 10 scientific/technical staff and allocated a budget for magnesium research and development in the region of EUR5million** (S7).

GSK is one of the world-leading over-the-counter (OTC) healthcare companies with business-generated sales of GBP9 billion in 2019. The ZGC has been collaborating with **GSK** since 2016 on a number of projects (most recently (G4, G5) for a total funding of ~GBP56,000) using XCT-based technology. As a result, **GSK** has been able to refine and further develop their oral care products and technology in the field of denture care, where **the work substantiated the launch claims and expert marketing for a new ultrasonic denture bath for the Japan market, totalling GBP1.7million in innovation sales** (S5). Also, due to our recent use of DVC in tooth biomechanics (R3), there is now **an interest within Microbiological Sciences and Oral Care Innovation at GSK to use the brushing model combined with XCT and DVC** for future product development.

Impact for the health profession: Changing the fundamental understanding of how the ankle works

Our published research in Nature Scientific Reports (R6), from research funded in 2017 (G6), has enabled the use of DVC for an unprecedented understanding of human subtalar joint mechanics from clinical images. The Director of the London Ankle & Arthritis Centre and national lead for ankle replacements on behalf of the British Orthopaedic Foot & Ankle Society stating that: '**This was a highly novel finding and information has had a fundamental impact on our understanding of how this complex joint works,** its role in ankle sprains, instability in the case of flat feet (which affects more than 20% of the population), and in the development of ankle and foot arthritis. To date, the subtalar joint is still treated by fusion which is a procedure to stiffen the joint and remove any motion. The longer-term consequence of this is gradual wear and tear of adjacent joints and progressive pain and disability. **This research is paving the way for a new joint replacement for the subtalar joint, which will be the biggest advance in foot and ankle surgery of the century'** (S6).

Enhancing Diamond Light Source tomography services to academia and industry

Research undertaken with the **STFC-funded Diamond Light Source** (G7, R5) served as **the first benchmark validation of the Savu tomographic reconstruction toolkit** (S7), which since 2016 is the standard procedure implemented and used by all the users (academia and industry) at Diamond.

5. Sources to corroborate the impact

(S1) Testimonial letter from Jatin Ladha (Account Manager at ZEISS Research Microscopy Solutions) as representative of Carl Zeiss Ltd 23/12/2020.

(S2) Testimonial letter from Dave Hollis (Technical Director for LaVision UK) as representative of LaVision 11/11/2020.

(S3) Testimonial letter from Laurent Galmiche (Senior Sales Manager for MSD Division) as representative of Thermo Fisher Scientific 05/03/2021.

(S4) Testimonial letter from Frank Witte (Chief Scientist Officer and Chief Technology Officer for Magnesium Technology) as representative of Biotrics 04/01/2021.

(S5) Testimonial letter from Rob Howlin (Senior Microbiologist at GSK Consumer Healthcare) as representative of GSK 23/12/2020.

(S6) Testimonial letter from Andy Goldberg (Consultant Orthopaedic Surgeon and Director of the London Ankle & Arthritis Centre) 30/12/2020.

(S7) Online source for SAVU software at Diamond Light Source

(S8) Online source for Zeiss promotional activity in relation to the Musculoskeletal research

(S9) Online source for Zeiss promotional activity in relation to the cartilage-bone research

(S10) Online source for Thermo Fisher Scientific DVC module in relation to the research