Mass Customisation of Medical Devices and Implants: State of the Art and Future Directions

K. W. Dalgarno[1], J. H. Pallari[1], J. Woodburn[2], K. Xiao[1], D.J. Wood[3], R.D. Goodridge[4], C. Ohtsuki[4]

[1]School of Mechanical Engineering,
[2]Academic Unit of Musculoskeletal Disease, School of Medicine,
[3]Leeds Dental Institute
University of Leeds, Leeds, UK.

[4]Graduate School of Materials Science
Nara Institute of Science and Technology, Nara 630-0192, Japan.

Abstract

The medical field is one in which the need for customisation can be clear cut, as providing tailored devices and implants for unique physiologies can provide for a better overall treatment than the use of "off the shelf" devices and implants. Customisation in the production of medical products can be roughly divided into consideration of medical devices, and of implantable parts or systems. This paper will outline the current state of the art in both of these areas, present details of projects which are ongoing at the University of Leeds, and outline future research directions.

Keywords: mass customisation, medical devices, medical implants

1 INTRODUCTION

The medical professions have for a long time used customisation at a craft based level in order to generate treatments and devices which are individual. In recent years more technological approaches to customisation have emerged within the medical arena, driven by advances in scanning technology, manufacturing technologies, and approaches to regenerative medicine. These advances have been in parallel with advances in computing technology which have allowed the data required to be communicated and analysed within a useful time scale. This paper seeks to present an overview of where these advances have lead us and where they might take us next, with the focus of the paper mostly on situations where adaptation to a specific human anatomy is the significant issue, rather than situations where software is used to personalise the behaviour of an electronic device.

These types of application are predominantly based on the use of scanning techniques and rapid or layer manufacturing technologies, creating an entirely digital supply chain.

The scanning techniques may be laser scanning, to create a better fit to the outside of a patient, or MRI or CT scanning where information regarding the internal structure of the body is required. CT scanning is generally considered to be the more accurate approach for hard tissue, whilst MRI offers the better approach for soft tissue.

The attraction of manufacturing processes which have emerged from rapid prototyping (or layer manufacturing) techniques is that they are able to create arbitrary geometries without the need for extensive planning or data processing, thus allowing personalised geometries to be created quickly and easily. Stereolithography (SLA), selective laser sintering (SLS), 3-dimensional printing (3DP), and fused deposition modelling (FDM) are the most commonly used processes and each can create arbitrary geometries to differing levels of accuracy in a range of different systems [1]. A key advantage of layer manufacture systems is that the data format used by most of the machines (.stl) is very close in nature to the output created by scanners, meaning that the conversion of scan data to machine control data through CAD systems is readily available. Conventional machining based CAD/CAM approaches can generally also be used, although an advantage of layer manufacture systems is that they are additive, and so can create geometries which subtractive or moulding processes cannot [2].

Broadly speaking the applications of mass customisation within the medical field can be divided into two major classifications. The first of these is medical devices, normally defined as articles which

achieve some diagnostic or therapeutic effect without interacting chemically with the body. The second classification is that of implantable parts or systems where there is an expectation that the implanted device will interact *in vivo* as a part of the biological system to a lesser or greater extent. Developments in these two areas have been significant and within this paper the current state of the art is outlined for each classification, before giving consideration to future research directions.

2 MEDICAL DEVICES

For medical devices the current state of the art is customisation to the body shape of a patient, in order to provide for an improved fit of some sort, with a cut-to-fit modularity [3] the standard approach to achieving the customisation.

The very general definition for medical devices means that some sort of further classification is always required, and in medical circles this will normally be related to the area of the body, or the particular disease, or both. For the purposes of this paper however, a user centred definition will be adopted, and we will consider devices which are intended for use by a surgeon, and devices which are intended to remain with the patient outside of a clinical environment.

2.1 Surgical Medical Devices

The assistance which is offered to surgeons from customised components is normally related to situations where some removal of tissue must occur in order to locate or secure an implant. One of the first areas researched was drill guides for spinal surgery [4,5]. Spinal surgery can be required for a number of reasons (degenerative diseases, scoliosis, traumatic injury), all of which can lead to a need for instrumentation of the spine with pedicle screws. These screws are used to support a frame around one or more vertebrae, effectively isolating the vertebrae from load and/or displacement. However, drilling into the spine to create holes into which screws may be positioned is complex as there is a relatively small amount of material available, and the neural canal is in close proximity. The technical solution developed in response to this problem was to (i) use a CAD-like system to provide pre-operative information on the position and orientation of the pedicle screws in the vertebrae, and (ii) construct a personalized drilling jig to assist the surgeon in positioning the drill to achieve the required position and orientation.

The starting point is a CT scan of the patient's spine, with the images used in software to allow the surgeon to virtually choose the location and orientation of the required screws, and then designing a drill guide around the vertebrae and the required screw positions. The guide can then be manufactured in a material approved for temporary use inside the body using layer manufacture techniques, with SLA and SLS used in the published case studies. The software to support the planning and design in the spinal drill guides research application was developed by Materialise, who have moved to commercial exploitation of the same principles in the dental arena, with SimPlant and SurgiGuides as commercial pieces of software to support similar that exploitation [6]. The principle focus of the commercialised systems is situations where patients have missing teeth, and need an implant into the jaw to which an artificial tooth can be connected, and works in the same way by allowing the surgeon to virtually choose the location and orientation of the required screws, then designing a drill guide around the jaw and the required screw positions, and then manufacturing using a layer manufacture process.

2.2 Medical Devices for Long Term Patient Use

Two examples of the state of the art for these types of product are in-the-ear hearing aids [7,8] and lower limb prostheses [9,10].

The Phonak in-the-ear hearing aid system (marketed as "e-shell" [11]) is probably the best known of these approaches. An in-the-ear hearing aid is shown in Figure 1 and would commonly be made in two halves (the "shells"), with the amplification system encapsulated within the two shells. A traditional approach to creating such a hearing aid would be to take an impression of the patients ear, and then use manual manufacturing techniques to create a replica of the impression. The digital approach, however, is to use a laser scanner to capture the geometry of the impression, then use automated CAD based design tools to add the internal geometry necessary to hold the amplification system in place, and then to produce the shells using a layer manufacture system. The amplification system has the same geometry from hearing aid to hearing aid but may be programmed or adjusted to give individual settings.

A lower limb prosthesis is illustrated in Figure 2. In this case it is the socket into which the upper part of

the limb is placed which is adapted to the user on the basis of laser scanning of the patient's residual limb. The other components would remain the same from patient to patient, but be adapted for limb length, with the exception of the foot model, which would be chosen from stock. Whilst this system has been trialled effectively, it does not yet have clinical approval.

Figure 1: In-the-ear Hearing Aid

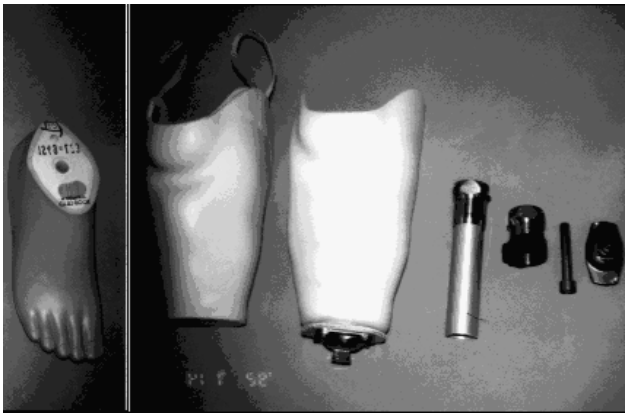

Figure 2: Lower Limb Prosthesis

The use of CAD tools can also be valuable in situations where the part of the body which is to be covered no longer exists [12]. For the manufacture of a facial prosthesis for a patient who had undergone surgery for cancer, the researchers had no geometry information for the side of the face which the prosthesis was being manufactured for, but after laser scanning, could, in CAD, mirror the other side of the patients face to create an appropriate prosthesis, which was then produced using CAD/Cam techniques.

The production of customised dental products in this area is also possible. The process chain of CT scan, clinician planning, manufacture utilising layer manufacture techniques has also been used in the manufacture of denture frameworks [13]. In this case the layer manufactured part was not directly used as the denture framework, but the dental framework was cast from a personalised pattern created by layer manufacture.

An approach which integrates support for the surgeon and the development of a device for long term patient use has been developed in the production of titanium plates for use in bone reconstruction, where the titanium plate has been customised to the implantation location [14]. This is again an approach which has been based on CT imaging to determine the required geometry, software for planning, with the layer manufacture technique in this case used to create a mould against which the titanium plate can be formed. The titanium plate was for use after the removal of a tumour, and was required to provide for immediate stability and to aid bone regeneration by acting as a "lid" on the outside of the cavity created by removing the tumour to retain bone graft material. The bone graft material could then be packed tightly into the defect, better facilitating the development of new bone. As the exact amount of material removed by the surgeon could not be known beforehand, the titanium plate was made oversize, together with a Perspex replica of the titanium plate. In surgery, after the tumour had been removed the surgeon could use the transparent plate to assess how big the titanium plate needed to be for appropriate coverage, then trim the plate to size before attaching it to the outside of the bone.

2.3 Future Directions

We consider that further developments technically in this area will focus on developing the design systems for more complex devices, in order to allow for automated or semi-automated design of the

medical device. It is clear from the situations we have reviewed so far that commercialisation has only come about where relatively straightforward design systems which offered the user the ability to quickly and easily specify what they wanted have been developed. The challenge in moving forward is, therefore, ensuring that the design system remains simple even if the application becomes more complex.

An example is in the mass customisation of orthoses (externally applied devices used to modify the structural or functional characteristics of the neuromuscoskeletal system), which are used as in-shoe inserts for patients who have deformed feet, and who require treatment either to promote corrective walking behaviour or to relieve pain [15].

Within the design of orthoses there is a clear need for the orthotic to adapt to the foot geometry, but also to offer comfort to painful areas and and at the same time dynamically promote a corrective gait. Incorporation of the different features required to offer this level of adaptation to the disease state is a significant challenge, complicated by the fact that orthoses are commonly used in response to diseases like rheumatoid arthritis, which can deteriorate very quickly, giving a need for the design and manufacture of the orthoses to happen in a very short time frame.

The proposed solution to this need is an automated design process working with an automated manufacturing process. The previous examples have shown that layer manufacture systems offer automated manufacture, and the automated design process for this application is currently a research project at the University of Leeds.

Figure 3 shows an outline of the proposed design system. The first step is to use motion capture equipment to "record" the gait of the patient together with pressure plate data (labelled 1 in Figure 3), see Figure 4. The 3D-geometries of the patient's feet are also scanned at this time (2).

Motion capture and pressure plate data are next exported to MS Excel (3), where the information is filtered so that only the relevant information is left in the files.

The motion capture data will be used in ADAMS (4), a general multi-body simulation software tool used in a large number of engineering applications. In this project, it is used together with Life Modeler, produced by BMG (Biomechanics Research Group, San Clemente, USA), which enables the incorporation of the human body into ADAMS. The model human has simulated bones, joints, and muscles. It can be modified within certain limits to represent adults or children of various sizes, see Figure 5.

When the motion capture measurement data (marker coordinates/time) is imported into ADAMS/LifeMod, it can be used to drive the model. When the model is animated by the motion capture data, we can analyse various aspects of its movement, in a "virtual" gait analysis. The pressure plate data recorded at (1) is used to validate the analysis.

In parallel, the previously scanned 3D-geometry data is processed using scanning software and exported to Magics (5). The surfaces are then smoothed and made coherent (if necessary), cut to the correct size and combined into a "base orthosis", which is then divided into sections, according to the foot model used. The resulting orthosis can be then incorporated into the virtual model in ADAMS (6) and the interactions between the orthosis and the model can be analysed.

The local stiffness properties of the base orthosis can then be adjusted, to correct the gait. This step takes advantage of the freedom offered by layer manufacture to create cavities in components or honeycomb type structures in order to provide a locally more compliant device. This can be done in either Magics, or in Ideas (8). The new design is then evaluated in the simulation, and changes are made as needed. This design/simulate cycle is repeated as many times as necessary, until the desired changes to the gait have been achieved. When the design is complete, the orthosis can be evaluated using FE analysis if required (9). The orthosis is now ready for production (10).

The complexity of this proposed system clearly goes beyond that which the cut-to-fit modularity of the current state of the art offers towards a sectional modularity, where unique components are created from standard modules.

The commentary above has focussed on the technical requirements of a mass customisation solution within the medical device arena. Alongside the technical needs in this area and, in common with all other mass customisation applications, a key issue in the development of medical customised products is the identification of customer needs and desires. As a result of products being commonly being ordered by a clinician on behalf of a patient there are two agenda's which must be met: that of the clinician who will focus on the clinical need, and that of the patient who will wish to minimise any

stigmatising impact that the products may have, so there is both an engineering design and an industrial design role in the development of these components, which makes the design automation task harder to achieve.

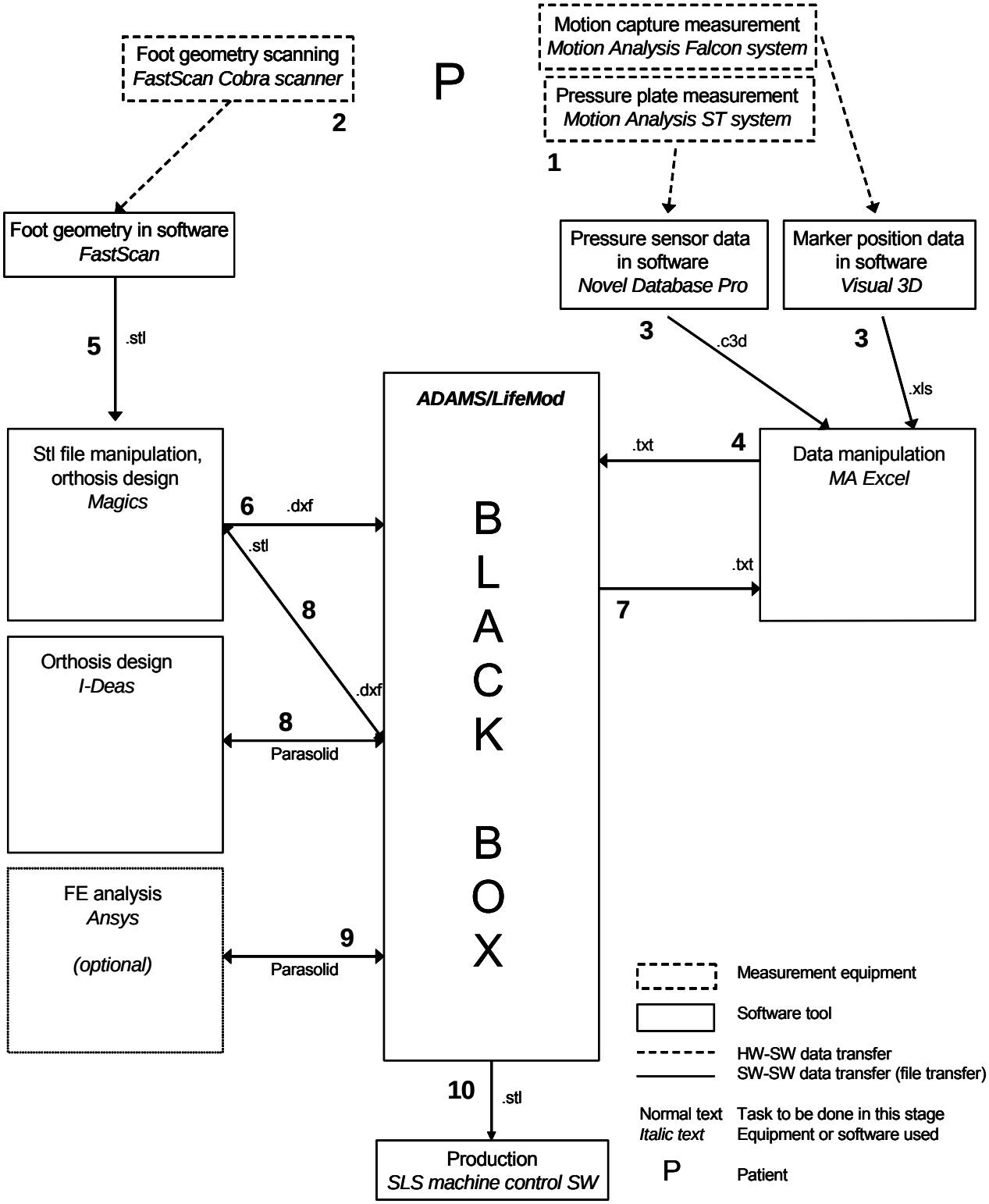

Figure 3: Outline Orthosis Design Process Chain

3. BIOACTIVE AND RESORBABLE IMPLANTS

A wide range of researchers have identified the potential for layer manufacture systems to deliver implants which are personally tailored to the individual patient, and which have been created in materials which will interact positively with the body (rather than be biologically inert). State of the art

commercially in this area is Therics™ [16]. Therics™ manufacture, using 3D printing layer manufacture technology, a range of bone grafts and bone void fillers. The layer manufacture technology is not used to create bone void fillers which conform directly to the void shape, but it is used to create complex internal architectures in a small range of products, with structured internal porosity to support bone ingrowth and subsequent vascularisation [17]. The materials used by Therics™ are resorbable (and so over time they will be broken down by the body and replaced with natural bone) and are based on hydroxyapatite and tricalcium-phosphate materials held in a polymer matrix.

The ability to develop their approach to create personalised shapes is something which Therics™ may develop in the future. In the research arena a number of research groups have examined the scope for the creation of bone replacements or tissue engineering scaffolds, with the tissue engineering scaffolds aimed at both hard and soft tissues. The tissue engineering scaffold approach operates through first creating a structure (the scaffold) and then seeding this structure *in vitro* with stem cells and proteins. The stem cells will then proliferate and differentiate into the required type of cell whilst secreting the extracellular matrix required to create the type of tissue needed. Once the type of tissue desired has been created implantation occurs.

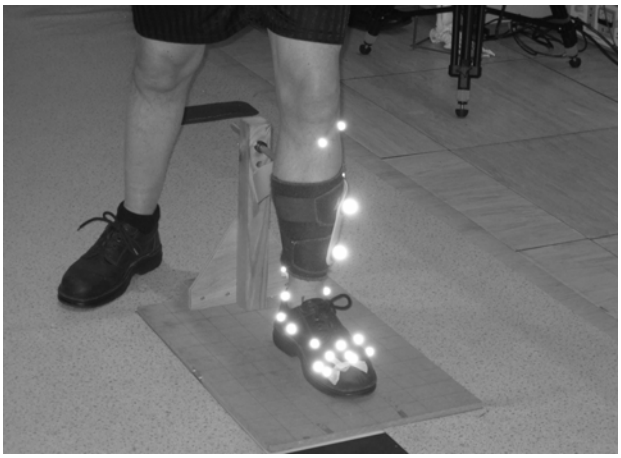

Figure 4: Motion Capture

Figure 5: ADAMS/LifeMod Model of Lower Limb

Whilst tissue engineering is still a young field It is likely that tissue engineered products will be based on a mixture of autologous and allogeneic approaches. The allogeneic approach is based on the use of stem cells which can be implanted into a group of people, and so lends itself to a batch or mass production route, although the geometry of the organic system may be tailored for a patient, normally through using a customised scaffold as the base on which the biological system can be constructed [18]. The autologous route uses cells harvested from a patient to develop a tissue engineered implant for that patient and requires facilities which can produce bespoke tissue engineered medical products with geometric, physical and biological customisation.

Much of the work aimed at producing tissue engineering scaffolds has looked to exploit a range of layer manufacturing techniques to create scaffolds in resorbable polymers, notably poly-(ε-caprolactone) [18,19], poly(L)lactide (PLA) [20], and poly(propylene fumarate) [21]. In addition a number of polymer-ceramic composite materials have been fabricated, using PLA and hydoxyapatite [20], poly (D,L-lactide-co-glycolide) and tricalcium phosphate [22], and poly(L-lactic acid) and tricalcium

phosphate [23] . Hydroxyapatite and tricalcium phosphate are both bioceramics, and so by definition have chemical compositions close to the mineral content of bone, and their use together with resorbable polymers seeks to create a more biomimetic bone-like material, as bone itself can be considered to be a polymer/ceramic (collagen/calcium phosphate) composite [24]. Collagen itself has also been used with layer manufacture methods to create a tissue engineering scaffold [25]. Collagen is a natural hydrogel (a colloidal gel in which water is the dispersion medium) and this has inspired work with other hydrogel materials [26]. In all of the cases where tissue engineering scaffolds have been created using layer manufacture methods the ability of the layer manufacture techniques to (i) create biomimetic architectures, and (ii) create a scaffold which can be adapted to a required external geometry, have been cited as major advantages of the routes.

A number of researchers have also investigated processing bioceramics for bone replacement and tissue engineering applications [27,28], and work at Leeds in this area has focussed on processing bioceramics, in particular apatite-mullite (A-M) and apatite-wollostonite (A-W) [29-31], with bone replacement or hard tissue engineering scaffolds the intended application areas. This work has been carried out in collaboration with the Nara Institute of Science and Technology in Japan. The processing route which has emerged as being best able to create highly porous components is what is known as indirect selective laser sintering. This uses layer manufacture techniques to create a “green part”, which is ceramic powder bound together by a polymer, and then a heat treatment is used to burn off the polymer and consolidate the bioceramic. Figure 6 shows a simple test component in the green stage, prior to heat treatment, and Figures 7 and 8 respectively shows the microstructure of green and heat treated parts, clearly showing the impact of the heat treatment. The structure shown in Figure 8 is a solid structure with open porosity, and is approximately 50% dense. Figure 9 shows a micro CT image of one of the heat treated samples, which gives an indication of the architecture achieved. Note that using the indirect selective laser sintering technique it will also be possible to build in macroporosity, for example channels with 1-2 mm diameter in order to support vascularisation, whilst retaining the microporosity shown in Figures 8 and 9.

Figure 6: A-W “Green Part” (15 x 15 x 4 mm).

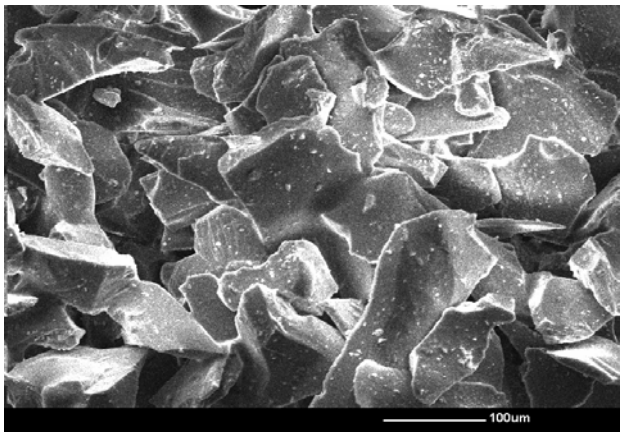

Figure 7: SEM of A-W Green Part. Scale Bar 0.1 mm.

In assessing the quality of the bone replacement or tissue scaffold there are two main elements to consider, the mechanical properties and the biological response. Figure 10 shows a comparison of the

bending strength of A-M and A-W components produced using this manufacturing route. The figure shows that the A-M (when infiltrated with a phosphate glass) has mechanical properties in line with those of cancellous bone. A-W has a higher strength, even without infiltration, and when infiltrated has the strength of cortical bone. That A-W can offer the full range of strengths from cancellous to cortical, depending upon its porosity, is seen as very valuable, as it will allow the properties of an implant to be tuned to the implant site.

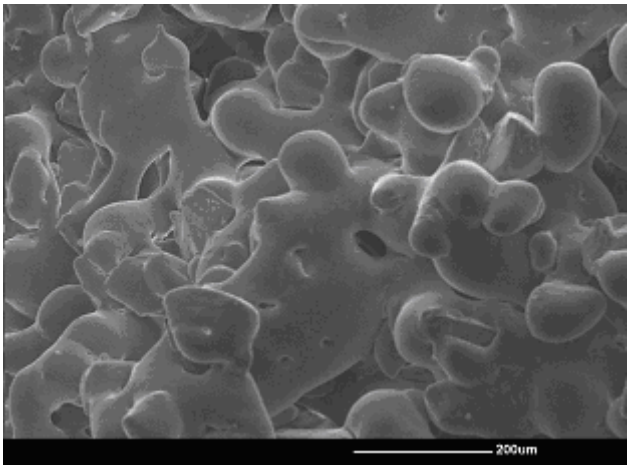

Figure 8: SEM of A-W Heat Treated Part.
Scale Bar 0.2 mm.

The biological properties must be assessed using *in vitro* and *in vivo* testing. The *in vitro* approach used relies upon the observation that a prerequisite for an artificial material to bond to bone is the formation of a bone-like apatite layer on its surface when implanted into a bony defect. This same type of apatite layer can be observed on the surfaces of bioactive glasses and glass-ceramics when they are exposed to a simulated body fluid (SBF) [32]. Figure 11 shows the results of an SBF study on an A-W sample, produced by indirect SLS, showing the apatite layer having formed at the top of the image, with the A-W at the bottom.

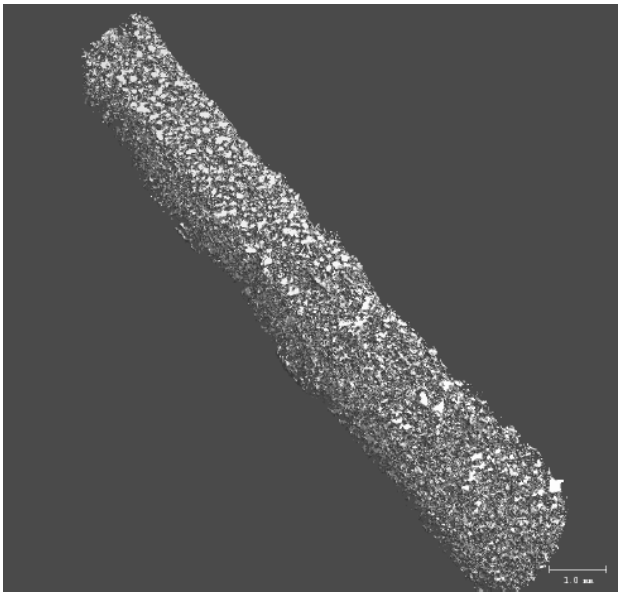

Figure 9: µCT Image of A-M Part. Scale bar 1 mm.

The results of *in vivo* assessment of the A-M material through implantation in a rabbit tibia is shown in Figure 12, with the natural bone on the left hand side having grown into the porous A-M on the right hand, and showing close contact between the bone and the A-M. Overall our work to date in these areas indicate that the materials have excellent bioactivity and mechanical properties, and that the processing route produces internal architectures which natural bone finds it attractive to grow into. Further work in this area will develop the tissue engineering application further, and seek to develop tailored products for specific medical application areas.

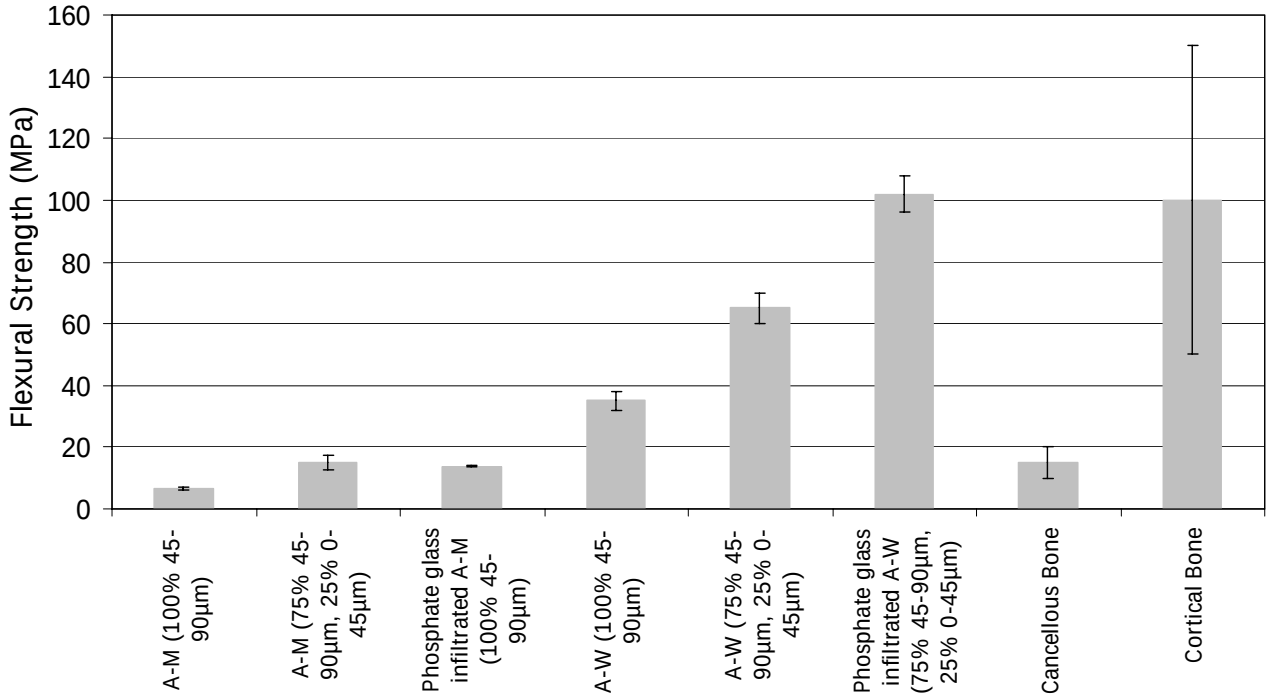

Figure 10: Strength of A-M and A-W Scaffolds

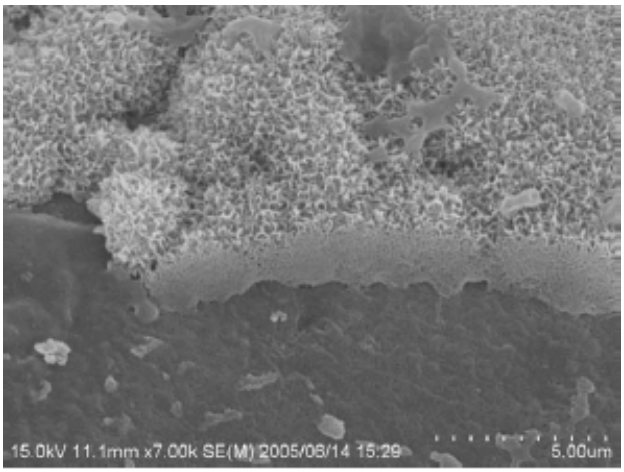

Figure 11: SEM of A-W Soaked in SBF for 14 days.
Scale Bar 5 µm.

In more general terms future directions in this area will move beyond the development of manufacturing routes for tissue engineering scaffolds to consider the manufacture of organs. The projected growth in regenerative medicine [33] over the next 15 years presents a significant challenge to the medical industry in terms of the delivery of tissue engineered products to the marketplace. Seen from a manufacturing point of view this scale up in provision will require the development of new, highly productive, processes and supply chains in order to provide the capacity required to deliver on a local, national and international scale. This manufacturing challenge will be most keenly felt for three dimensional implants and organs, where there is a need to manufacture structures which match human anatomy from biomaterials together with cells, genes, and proteins, with the relative concentration of each component of the system varying throughout the structure [34,35].

There are relatively few approaches to manufacturing 3D structures which allow for multiple materials to be processed alongside cells and proteins. Two approaches have emerged from layer manufacturing techniques: 3D printing techniques [36,37] and 3D plotting (or dispensing) techniques [38,39]. Both of these techniques have as key advantages (i) the ability to process cells and proteins alongside biomaterials, (ii) the ability to vary the concentration of the different constituents throughout the 3D structure, and (iii) the ability to create 3D structures of any arbitrary geometry. The first two of

these advantages overcome limitations with the scaffold/seeding approaches to developing tissue engineered 3D structures. Both the approaches use nozzles (either printing or plotting) to deposit materials within a 2D array (or layer), before depositing a further layer, composed again of a range of materials, on top of the first layer, and continuing with subsequent layers until the required structure has been created. The number of constituent materials (or fixed material combinations) which is possible is defined by the number of nozzles, and there clearly must be a mechanism for the layers to bond together. These approaches allow every part of the volume of the structure to have a tailored combination of cells, genes, and proteins, giving the freedom required to create truly biomimetic microstructures, and further work in these areas represents a significant research challenge over the decade to come.

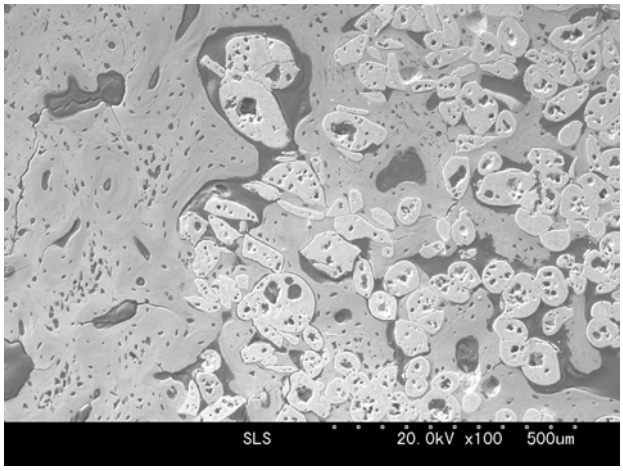

Figure 12: Bone Ingrowth into Porous A-M.
Scale Bar 0.5 mm.

Within the tissue engineering and regenerative medicine fields there is clearly a biological element to customisation where an autologous route is taken. There is some way to go in engineering, chemistry and biology before we are able to consider it a solved problem, but regenerative medicine based on autologous tissue engineering would represent a new benchmark in mass customisation.

However, it is also clear in looking back at the development of the medical device mass customisation industry that it will be the quality of the overall system and how well it addresses the needs of its users which will determine what succeeds commercially and what does not.

4 REFERENCES

[1] Levy, G.N., Schindel, R., Kruth, J.,P., 2003, Rapid manufacturing and rapid tooling with layer manufacturing (LM) technologies, state of the art and future perspectives", CIRP Annals – Manufacturing Technology, Vol. 52, pp 589-609.

[2] Hague, R., Campbell, I., Dickens, P., 2003, Implications on design of rapid prototyping, Proc. IMechE Part C, Journal of Mechanical Engineering Science, Vol. 217C, pp 25-30.

[3] Ulrich, K. and Tung, K., 1991, Fundamentals of product modularity, Proceedings of ASME Winter Annual Meeting Symposium on Design and Manufacturing Integration, held in Atlanta, USA, November 1991, pp 73-79.

[4] Van Brussel, K., Vander Sloten, J., Van Audekercke, R., Swalens, B., Richard, F., Assaker, R., Kulik, J.F., 1997, Medical image based design of and individualized surgical guide for pedicle screw insertion, Proceedings of the 18th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, (Cat. No.96CH36036), Vol. 1, Pt. 1, pp 225-226.

[5] Berry, E., Cuppone, M., Porada, S., Millner, P.A., Rao, A., Chiverton, N., Seedhom, B.B., 2005, Personalised image-based templates for intra-operative guidance, Proc. IMechE Part H: Journal of Engineering in Medicine, Vol. H219, pp 111-118.

[6] http://www.materialise.com/MEDICAL/ main_ENG.html, 29/6/5, 15:21 GMT.

[7] Anon, 2003, Rapid shell moulding – its use in production of hearing aids, Materials World, Vol. 11, pp 8.

[8] Tognola G., Parazzini, M., Svelto, C., Ravazzani, P., Grandori, F., 2003, Three-dimensional laser scanning and reconstruction of ear canal impressions for optimal design of hearing aid shells, Proc. SPIE, Vol. 5009, pp 19-26.

[9] Ashley, S., 1993, Rapid prototyping for artificial body parts, Mechanical Engineering, Vol. 115, pp 50-53.

[10] Rogers, W., Stephens, S., Gitter, A., Bosker, G., Crawford, R., 2000, Double-wall transtibial prosthetic socket fabricated using selective laser sintering: a case study, Journal of Prosthetics and Orthotics, Vol. 12, pp 97-100.

[11] http://www.phonak.com/consumer/products/eshell.htm, 23/6/5, 16:28 GMT.

[12] Tsuji, M., Noguchi, N., Ihara, K., Yamashita, Y., Shikimori, M., Goto, M., 2004, Fabrication of a maxillofacial prosthesis using a computer-aided design and manufacture system, Journal of Prosthodontics, Vol. 13, pp 179-183.

[13] Eggbeer, D., Bibb, R., Williams, R., 2005, The computer-aided design and rapid prototyping fabrication of removable denture frameworks, Proc. IMechE Part H: Journal of Engineering in Medicine, Vol. H219, pp 195-202.

[14] Pattijn, V., Samson I., Vander Loten J., Van Audekercke, R., Swaelens, B., De Buck, V., 2002, Medical image based, preformed titanium membranes for bone reconstructions: design study and first clinical evaluation, Proc. IMechE Part H, Vol. H216, pp 13-21.

[15] Pallari, J.H.P., Dalgarno, K.W., Woodburn, J., Barnes, C.J., 2005, Mass customation of foot orthosis for rheumatoid arthritis, presented at the 6th National Conference on Rapid Design, Prototyping and Manufacture, held at Buckinghamshire Chilterns University College, UK, 10th June.

[16] http://www.therics.com, 10th May 2005, 09:48 GMT.

[17] Gauthier, O., Bouler J.M., Aguado, E., Pilet, P., Daculsi G., 1998, Macroporous biphasic calcium phosphate ceramics: influence of macropore diameter and macroporosity percentage on bone ingrowth, Biomaterials Vol. 19, pp 133-139.

[18] Zein, I., Hutmacher, D.W., Tan, K.C., Teoh. S.H., 2002, Fused deposition modelling of novel scaffold architectures for tissue engineering applications, Biomaterials, Vol. 23, pp 1169-1185.

[19] Ciardelli, C., Chiono, V., Cristallini, C., Barbani, N., Ahluwalia, A., Vozzi, G., Prevetti, A., Tantussi, G., Giutsi, P., 2004, Innovative tissue engineering structures through advanced manufacturing technologies, Journal of Materials Science: Materials in Medicine, Vol. 15, pp 305-310.

[20] Taboas, J.M., Maddox, R.D., Krebsbach, P.H., Holister, S.J., 2003, Indirect solid freeform fabrication of local and global porous, biomimetic and composite 3D polymer-ceramic scaffolds, Biomaterials, Vol. 24, pp 181-194.

[21] Cooke, M.N., Fisher, J.P., Dean, D., Rimnac, C., Mikos, A.G., 2002, Use of stereolithography to manufacture critical sized 3D biodegradable scaffolds for bone ingrowth, Journal of Biomedical Materials Research Part B: Applied Biomaterials, Vol. 64B, pp 65-69.

[22] Sherwood, J.K., Riley, S.L., Palazzolo, R., Brown, S.C., Monkhouse, D.C., Coates, M., Griffith, L.G., Landeen, L.K., Ratcliffe, A., 2002, A three-dimensional osteochondral composite scaffold for articular cartilage repair, Biomaterials, Vol. 23, pp 4739-4751.

[23] Xiong, Z., Yan, Y., Wang, S., Zhang, R., Zhang, C., 2002, Fabrication of porous scaffolds for bone tissue engineering via low-temperature deposition, Scripta Materialia, Vol. 46, pp 771-776.

[24] Suchanek, W., Yoshimura, M., 1997, Processing and properties of hydroxyapatite-based biomaterials for use as hard tissue replacement implants, Journal of Materials Research, Vol. 13, pp 94-117.

[25] Sachlos, E., Czernuszka, J.T., 2003, Making tissue engineering scaffolds work. Review on the application of solid freeform fabrication technology to the production of tissue engineering scaffolds, European Cells and Materials, Vol. 5, pp 29-40.

[26] Landers, R., Hubner, U., Schmelzeisen, R., Mulhaupt, R., 2002, Rapid prototyping of scaffolds derived from thermoreversible hydrogels and tailored for applications in tissue engineering, Biomaterials, Vol. 23, pp 4437-4447.

[27] Chu, T.M., Orton, D.G., Halloran, J.W., Hollister, S.J., Feinberg, S.E., 2002, Mechanical and in vivo performance of hydroxyapatite implants containing controlled internal architecture,

Biomaterials, Vol. 23 pp1283-1293.

[28] Vail, N.K., Swain, L.D., Fox, W.C., Aufdlemorte, T.B., Lee, G., Barlow, J.W., 1999, Materials for biomedical applications, Materials and Design, Vol. 20, pp123-132.

[29] Lorrison, J.C., Dalgarno, K.W., & Wood, D.J., 2005, Processing of an apatite-mullite glass-ceramic and an hydroxyapatite/phosphate glass composite by selective laser sintering", Journal of Materials Science: Materials in Medicine, Vol. 16, pp 775-781.

[30] Goodridge, R.G., Dalgarno, K.W., Wood, D.J., 2004, Layer manufacturing of porous bioactive glass-ceramics using selective laser sintering, in ICMA 2004, Proceedings of the International Conference on Manufacturing Automation, held in Wuhan, China, October 26-29th 2004, pp 739-746.

[31] Xiao, K., Dalgarno, K.W., Wood, D.J., 2005, Selective laser sintering of apatite-wollastonite glass ceramics, presented at the 6th National Conference of Rapid Design, Prototyping and Manufacturing, held at Buckinghamshire Chilterns University College, High Wycombe, UK, 10th June 2005.

[32] Kokubo, T., Kushitani, H., Ohtsuki, C., Sakka, S., 1992, Chemical reaction of bioactive glass and glass-ceramics with a simulated body fluid, Journal of Materials Science: Materials in Medicine, Vol. 3, pp 79-83.

[33] Mason, C., 2003, Automated tissue engineering: a major paradigm shift in healthcare, Medical Device Technology, Jan/Feb 2003, pp 16-17.

[34] Beaman, J.J., Atwood, C., Bergman, T.L., Bourell, D., Hollister, S., Rosen, D., 2004, WTEC Panel Report on Additive/Subtractive Manufacturing Research and Development in Europe, http://www.wtec.org/ additive/additive-report.pdf.

[35] Sun, W., Darling, A., Starly, B., Nam, J., 2004, Computer aided tissue engineering: overview, scope and challenges, Biotechnology and Applied Biochemistry, Vol. 39, pp 29-47.

[36] Wilson, W.C., Boland, T., 2003, Cell and organ printing 1: protein and cell printers, The Anatomical Record Part A, Vol. 272A, 491-496.

[37] Saunders, R., Gough, J., Derby, B., 2005, Ink jet printing of mammalian primary cells for tissue engineering applications, Nanoscale Materials Science in Biology and Medicine Symposium (Materials Research Society Symposium Proceedings Vol. 845), pp 57-62.

[38] Landers, R., Pfister, A, Hubner, U., John, H., Schmelzeisen, R., Mulhaupt, R., 2002, Fabrication of soft tissue engineering scaffolds by means of rapid prototyping techniques, Journal of Materials Science, Vol. 37, pp 3107-3116.

[39] Yan, Y., Wang, X., Xiong, Z., Liu, H., Liu, F., Lin, F., Wu, R., Zhang, R., Lu, Q., 2005, Direct construction of a three-dimensional structure with cells and hydrogel, Journal of Bioactive and Compatible Polymers, Vol. 20, pp 259-269.