Layer manufacturing for *in vivo* devices

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Abstract: Traditional *in vivo* devices fabricated to be used as implantation devices included sutures, plates, pins, screws, and joint replacement implants. Also, akin to developments in regenerative medicine and drug delivery, there has been the pursuit of less conventional *in vivo* devices that demand complex architecture and composition, such as tissue scaffolds. Commercial means of fabricating traditional devices include machining and moulding processes. Such manufacturing techniques impose considerable lead times and geometrical limitations, and restrict the economic production of customized products. Attempts at the production of non-conventional devices have included particulate leaching, solvent casting, and phase transition. These techniques cannot provide the desired total control over internal architecture and compositional variation, which subsequently restricts the application of these products. Consequently, several parties are investigating the use of freeform layer manufacturing techniques to overcome these difficulties and provide viable *in vivo* devices of greater functionality. This paper identifies the concepts of rapid manufacturing (RM) and the development of biomanufacturing based on layer manufacturing techniques. Particular emphasis is placed on the development and experimentation of new materials for bio-RM, production techniques based on the layer manufacturing concept, and computer modelling of *in vivo* devices for RM techniques.

Keywords: rapid manufacturing, drug delivery devices, implants, scaffolds, *in vivo* devices

1 INTRODUCTION

In vivo devices are artificial devices put into the human body or living organisms to replace or restore functions of living tissues [**1**]. The manufacture of *in vivo* devices for bone replacement was conceived in the 1950s by Sir John Charnley [**2**]. The concept of implantation devices was partly invoked by the restrictions of restoration by transplantation. Autografting (transplantation of surplus tissue, typically bone, from one location to another in the same patient) and allografting (transplantation of a tissue or organ from a donor to the patient, typically the kidney or heart) both require additional procedures and incur higher cost and risk of infection/transfer of disease, and they are fundamentally limited by the amount of surplus tissue in the desired morphology or the shortage of donors. An increase in the shortage of donors, limited amount of surplus tissue, high rejection potential, and complications as a result of donor site morbidity, patient distress, potential of transmission of infectious diseases, reduced speed of treatment and quality of life, and increased life expectancy have led to thousands of patients spending the rest of their lives before they receive an organ from a suitable donor [**3**–**7**]. Approximately one-quarter of patients in need of organ transplants in the United States die while waiting for a suitable donor [**8**]. Such figures and patient distress and poor quality of life have further driven the continued investigation of synthetic or artificial replacements.

The construction and composition of implant devices for tissue replacement or regeneration are dictated by the requirements of their application, i.e. relatively solid products for bone replacement or deliberately porous structures for tissue growth scaffolds, but also by the restrictions of their production method.

The production of extremely complex porous structures is a particularly hot topic owing to developments in tissue engineering. Tissue engineering is

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a largely laboratory-based activity that begins with living tissue cells which are multiplied through cell culture. These are then seeded into a carrier/scaffold which facilitates the directed three-dimensional growth and proliferation. This form of regenerative medicine may provide replacement tissue and organs and is widely foreseen as one of the next great breakthroughs in medical treatment. Subsequently, there is significant competition to formulate and exploit a suitable three-dimensional containment structure to facilitate the growth of tissue-engineered *in vivo* devices.

2 BACKGROUND

2.1 Biomaterials

In vivo devices are fabricated using materials of natural or man-made origin and are used to direct, supplement, or replace the functions of living tissues of the human body [**9**]. Over the years the importance of avoiding risk, rejection, or complications in the body [**9**–**13**] has been highlighted because these may hinder normal development and physiological behaviour of cells, result in secondary infections, and inhibit the function of devices. Fundamental requirements of an implant device include biocompatibility and surface and structural compatibility.

Biocompatibility is a descriptive term of the ability of a material to perform with an appropriate tissue response, in a specific condition. This is a most critical characteristic and precludes all other selection criteria. To achieve the required biocompatibility, two routes are often employed:

(a) the fabrication of *in vivo* devices using off-the-shelf materials with application of a suitable biocompatible coating layer;
(b) the fabrication of *in vivo* devices using biocompatible materials.

This section only discusses the latter. The materials used to fabricate *in vivo* devices may be grouped into metals, ceramics, polymers, and composites thereof. Biomaterials have been further classified on the basis of their function, such as bioinert, bioactive, biostable, and biodegradable [**14**, **15**]. No one material is suitable for all biomaterial applications. Advantages and limitations of each individual material and the suitability of materials for specific applications have been studied through laboratory experimentation and clinical investigations [**16**]. Table 1 lists a variety of commonly used biomaterials.

The surface and structural compatibility of a material refers to the suitability of its chemical, biological, physical, and mechanical properties. These properties are not only determined by the inherent material properties but also by the implant design and its internal architecture [**19**–**21**].

Table 1 Biomaterial examples [**9**, **16**–**18**]

Material type	Biomaterials
Ceramic	Hydroxyapatite (HA) Oxyfluorapatite and wollastonite glassy matrix (A–W glass) Tricalcium phosphate (TCP) Alumina (Al_2O_3) Zirconia (ZrO_2) Carbon
Metal	Pure titanium and alloys (Ti) Grade 300 stainless steel (mainly 316 and 316L) (AISI classification) Cobalt–chromium Dental amalgam Shape memory alloys (SMA)
Polymers	Ultrahigh molecular weight polyethylene (UHMWPE) High-density polyethylene (HDPE) Polyethylene (PE) Polyurethane (PU) Polytetrafluoroethylene (PTFE) Polyamides (PA) Polyester Polydimethyl silicones (PDS) Polymethyl methacrylate (PMMA) Polyethylene terepthalate (PET) Silicone rubber (SR) Polysulphone (PSU) Poly(vinyl chloride) (PVC) Polyther ether ketone (PEEK) Poly(lactic acid) (PLA) Poly(glycolic acid) (PGA) Poly(ε-caprolactone) (PCL) Polyhydroxybutyrate (PHB) Hydrogels Poly(lactide-co-glycolide) (PLGA) Poly(L-lactic acid) (PLLA) Poly(D-lactic acid) (PGLA)

2.2 Types of *in vivo* device

Increased life expectancy and greater healthcare capabilities has led to the development of a large number and diverse range of *in vivo* devices. Currently, *in vivo* devices such as pins, plates, rods, screws, drug delivery devices, valves, sutures, grafts, and fixations are produced to assist in the treatment and recuperation of patients for a variety of conditions. Subsequently, *in vivo* devices serve a variety of functions. These may include the replacement of a damaged tissue or organ, provision of temporary or permanent mechanical support, and the controlled release of drugs in relation to the individual patient and treatment. An ideal would be for one device to serve a combination of functions, e.g. a bone replacement implant would provide complementary geometry according to the bone defect site,

a Young's modulus nearly equal to the local bone, selective designed porosity to facilitate growth of tissue into the device, and osteogenic stem cell delivery for faster integration of surrounding tissue. Such ideals would place great demands on manufacturing process technology.

To date, conventional *in vivo* device fabrication techniques have included compression/injection/melt moulding [**22**–**24**], fibre bonding [**25**, **26**], phase separation [**3**, **5**, **11**], solvent casting/particulate leaching [**3**, **27**, **28**], membrane lamination [**26**], gas foaming/high-pressure processing [**29**], the lost mould method [**30**], emulsion freeze drying [**31**], and combinations of these techniques [**32**] and machining techniques.

With particular regard to scaffold structures, several production methods are capable of fabricating foam structures. However, to date these processes have been unable to achieve all the desired characteristics of an optimum scaffold design – precisely controlled variation of external geometry, pore size, pore geometry, spatial pore distribution, pore interconnectivity, and construction of internal channels which govern interactions between cells. An example of the effort of these restrictions is provided by Sachlos and Czernuszka [**33**]: the growth of bone tissue is limited to the external surface (less than 500 μm in depth) owing to the diffusion constraints (i.e. interconnectivity, pore size, etc.) of the foam constructed using conventional techniques including fibre bonding, solvent casting/particulate leaching, etc.

2.3 Rapid manufacturing

Rapid manufacturing (RM) is the direct production of finished goods from a layer manufacturing device, known commonly as rapid prototyping (RP). Various RP techniques exist which utilize several different processing fundamentals, but they all share the characteristic of producing an object by a sequential layer manufacturing technique. RP processes directly produce a physical geometry from data derived from a three-dimensional representation (i.e. three-dimensional CAD), and they are characterized by generation of the geometry by an additive, layer-by-layer manufacturing sequence, which, when initiated, runs unattended [**34**]. Further reference to RP and particular processes can be found elsewhere [**35**].

RP has largely been used to date in the medical field for producing models for visualization and evaluation. RP applications have included preoperative planning and simulation [**36**–**40**], preforming of fixation components, the indirect manufacture of surgical guides and templates [**41**], fit evaluation of implants [**42**, **43**], and as an enabling process in facial prosthetics [**44**]. Some of the benefits (i.e. increased speed, customization, and efficiency) that have been realized through this work have prompted continued research and further applications of layer manufacturing technologies, leading to the investigation of their use for the direct production of medical devices.

RM is the use of layer manufacturing processes to deliver finished parts directly from digital data. The concept of RM offers a compelling list of benefits. With RM, tooling is eliminated, thus substantially reducing time and cost. There are other powerful advantages that result from the tool-less process, including increased design freedom, heterogeneous materials, custom products, just-in-time production, and decentralization of production [**45**].

In particular reference to *in vivo* devices, the potential advantages include the following.

1. *Fewer design constraints.* RM greatly reduces the number of design constraints that are typically imposed by many manufacturing processes. This is a result of the freeform nature of RM as compared with conventional techniques which rely on tooling for their fabrication process and commonly limit the ability to achieve complex geometries and inhibit the production of internal features [**46**, **47**].
2. *Customization.* The tool-less and direct nature of RM allows the economic production of one-off articles. This enables product customization while sustaining economic viability as compared with traditional techniques which must manufacture on mass in order to obtain economic viability. This would offer the potential to provide *in vivo* devices designed in response to specific customer requirements.
3. *Greater speed from image capture to finished device.* Direct device production by RM has relatively few process steps and subsequently a short lead time. RM is able to manufacture the parts in hours and days, as opposed to weeks and months for tooling processes, as a result of the streamlined process, automation, and little manual interaction [**48**].
4. *Functionally graded materials (FGMs).* An FGM can be defined as a material exhibiting spatially inhomogeneous properties and microstructure. This is a possibility in RM methods by varying the composition of two or more materials across the surface, interface, or bulk of the product during the build sequence. An FGM allows for the

positional variation of physical properties and characteristics. Potential applications of FGMs in implant devices are illustrated in Fig. 1.

5. *Processing without toxic solvents.* Several RM techniques operate without the use of solvents as employed by some conventional techniques (e.g. particulate leaching, hydrocarbon templating, etc.). Incomplete removal of solvents may result in harmful residues that have adverse effects on adherent cells, incorporated biological active agents, or nearby tissues.
6. *Controllable structure and porosity.* The freeform fabrication technique utilized by RM allows for the production of virtually unrestricted geometries. Owing to the additive nature of the process, control over internal structure is possible. This would allow the internal structure and porosity to be controlled and dictated. Implant applications may include selective areas of greater/lesser structural integrity and selective areas of encouraged blood flow. Absolute dictation of geometrical structure would allow highly complex customized tissue scaffolds to be produced.

Conventional RP processes and materials were developed in response to the desire of several industries to be able quickly and automatically to produce representative or functional prototypes of objects that would later be manufactured in large quantities by tooling processes [**50**]. The interest from the medical field has grown recently, which, after very positive results, has subsequently resulted in various investigations and research into the RM of *in vivo* products. The following sections present details on the research efforts to date in the fabrication of *in vivo* devices using RM techniques.

3 SPECIFIC ADVANCES IN MODELLING AND DESIGN

Computer aided design (CAD) anatomical models are most commonly derived by reverse engineering, typically by computed tomography (CT) and/or magnetic resonance imaging (MRI) techniques [**51**, **52**]. CAD data are a primary process in RM and subsequently the full exploitation of RM as a production method for *in vivo* devices is also dependent upon synchronous developments in associated design software. Various research groups have used CAD systems to conduct simulated predictive analysis prior to production [**53**]. Although some of the CAD developments being investigated by various research groups are not necessarily solely aimed at the direct manufacture of *in vivo* devices, with some adaptation it may be feasible to adopt some of these techniques for the design of *in vivo* devices. However, it should be noted that there are ongoing discussions regarding the amount of current potential applications for custom prosthesis. Several cases are summarized below.

Bibb [**54**] reported the production of physical stereolithography (SLA, an RP technique based on the selective curing of a photosensitive resin) models of cancellous bone structures (see Fig. 2). The structure could be controlled using commercial voxel-based CAD software. Emphasis was placed on the ability of RP to generate controlled structures and the impossibility of using any other approach.

Werner *et al.* [**55**] reported the use of CAD systems to help design anatomical hip joint endoprosthesis by applying the non-uniform rational B-spline (NURBS) technique in describing curves and surfaces. The redesigned endoprosthesis aimed to

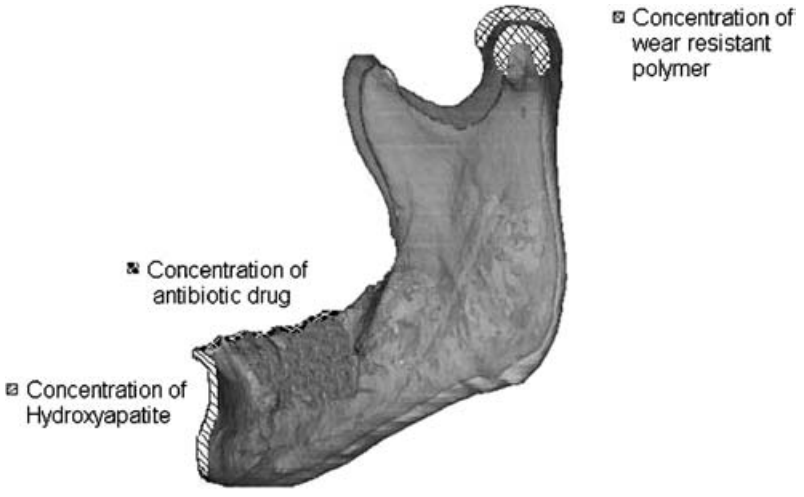

Fig. 1 Example of FGM application [**49**]

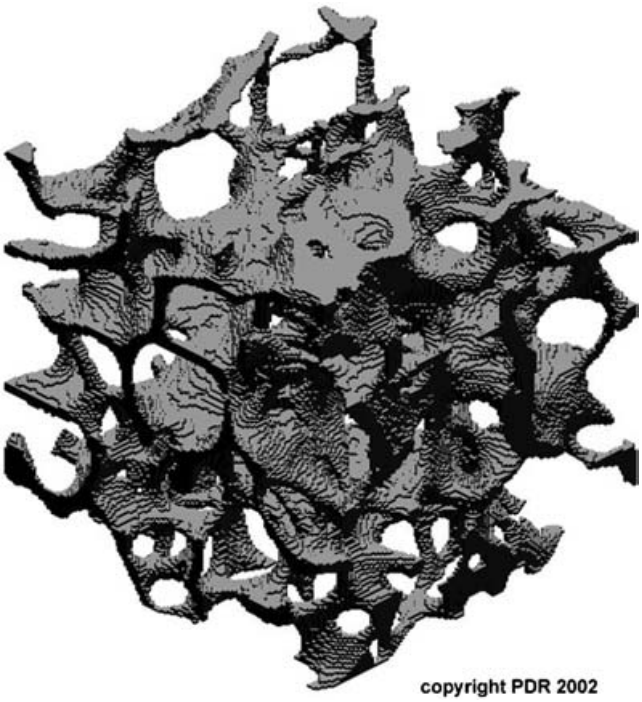

Fig. 2 Cancellous bond (STL file image) [**22**]

provide greater stability and minimize loosening of the implant.

Zysset *et al.* [**56**] demonstrated the use of CAD for predictive mechanical analysis of modelled bone structures. The trabecular bone structure from the human proximal femur was modelled to investigate its mechanical integrity for managing issues such as osteoporosis or implant fixation. Mechanical tests of scaled physical models [fused deposition modelling (FDM, an RP technique based on the extrusion of a semi-molten plastic filament) and stereolithography (SLA)] correlated with the results of a digital finite element analysis conducted through CAD.

Current CAD systems are geared towards the design of parts manufactured by traditional manufacturing technologies and hence represent a solid object by its surface [**57**]. Researchers at the Nanyang Technological University have taken a step forward in exploring a new approach to modelling complex objects. This is based on NURBS-based volume modelling which not only represents the surface boundary but also the interior of a three-dimensional object. The key idea of the NURBS-based volume modelling is to exploit the flexibility of NURBS modelling and use the voxelized NURBS volumes as components for constructing complex objects, in particular with respect to medical applications [**57**, **58**]. Valid STL file (the input format required by most RP processes) generation through volume modelling and isosurface extraction makes the constructed/reconstructed models manufacturable. Subsequently, two areas of future work were recommended:

(a) the ability to establish a relationship between a NURBS volume and its corresponding volume model to gain structural information that would make it easier to manipulate and control a volume;
(b) solving the problem of long computational time and large files generated by the marching cubes algorithm (an algorithm used to generate an STL file from volume models).

4 RM PROCESS TECHNOLOGIES FOR *IN VIVO* DEVICES

A number of research groups have investigated the utilization of layer manufacturing in the development and production of *in vivo* devices, including scaffolds, pins, screws, drug delivery devices, and valves. Many of these are indirect techniques where layer manufacturing is an enabling process and constitutes only part of a multiprocess chain, and do not fully exploit the potential of RM. Such indirect examples include: tissue scaffolds for heart valves by Sodian *et al.* [**59**], biodegradable scaffolds using SLA by Levy *et al.* [**60**], hydroxyapatite implants by Chu *et al.* [**19**], hydroxyapatite scaffolds using the ModelMaker II RP system [**61**], and biomimetic and composite three-dimensional polymer–ceramic scaffolds using three-dimensional printing (3DP) (see section 4.3 for a short definition) [**62**].

In recent years there has been increasing emphasis placed on the research of RM for the direct production of *in vivo* devices. Several parties have investigated the adaptation of existing commercialized RP processes for producing *in vivo* devices, as described in the following subsections according to process types.

4.1 Stereolithography for *in vivo* devices

Stereolithography is an RP technique based on the selective curing of a photosensitive polymer resin. SLA is the most developed commercial RP process, its development began in the early 1980s, and it is capable of high degrees of accuracy (± 0.005 *XY*, ± 0.002 *Z*). However, traditional SLA materials contain toxic components that prohibit their application for *in vivo* use. Commercial SLA materials that may be used in limited bodily fluid exposure have emerged, but there is none for *in vivo* use. Subsequently, applications for implant production have

been restricted to indirect techniques. Some noteworthy investigations on the development of biomaterials for SLA have been conducted by Matsuda and Mizutani [**63**, **64**], and the feasibility of SLA to build and control three-dimensional multilayer parts made from biodegradable, biocompatible resin polypropylene fumarate has been demonstrated by Cooke *et al.* [**65**].

4.2 Fused deposition modelling for *in vivo* devices

Fused deposition modelling is an RP technique based on the extrusion of a semi-molten plastic filament. It is an uncomplicated and reliable process and has been the subject of several investigations regarding use with different biocompatible materials. The porosity of FDM parts is easily altered according to the raster pattern utilized, but functionally graded material (FGM) applications are inherently limited by the material format (filament).

Kalita *et al.* [**66**] investigated the development and fabrication of controlled-porosity structures using polypropylene (PP) polymer and tricalcium phosphate (TCP) ceramic, employing FDM for the healthy ingrowth of bone cells. Samples with 36 per cent volume porosity and an average pore size of 160 μm showed the best compressive strength of 12.7 MPa, which lies in the lower range of properties reported for trabecular bone. The results showed that samples were non-toxic and also supported excellent cell attachment and growth during the first 2 weeks of *in vitro* (simulation of conditions inside a living organism) studies.

Hutmacher [**67**] reported the fabrication of bone scaffolds for complex craniofacial skeletal reconstruction utilizing medical imaging, computational modelling, and FDM. The study indicated that the use of polycaprolactone (PCL) scaffolds produced by FDM for the reconstruction of craniofacial defects resulted in higher amounts of new bone ingrowth than clinically used poly(L-lactic acid)/poly(D-lactic acid) (PLLA/PDLA) 70/30 foil. Results indicated that scaffolds coated with bone marrow resulted in higher bone formation.

Zein *et al.* [**68**] investigated the effect of process variation in the fabrication of PCL porous scaffolds using FDM for an intended application in bone tissue engineering. Various processing parameters were used to fabricate scaffolds with a channel size of 160–700 μm and a porosity of 48–77 per cent. A great variation in mechanical properties was demonstrated in accordance with varied porosity (compressive stiffness 4–77 MPa, yield strength 0.4–3.6 MPa, yield strain 4–28 per cent). The highest compressive stiffness and yield strength were found in specimens built with a combination of 0/90° laydown orientation and a porosity of 53 per cent, which lie in the lower range of properties reported for trabecular bone.

Too *et al.* [**69**] investigated the development and feasibility of three-dimensional non-random porous structures (i.e. scaffolds) using FDM for various applications in tissue engineering. Acrylonitrile–butadiene–styrene (ABS) test specimens were generated using a road width (distance between consecutive filaments) of 0.315 mm, a slice thickness of 0.254 mm, and a varied raster gap of 0–0.5 mm in increments of 0.05 mm. Micrographs indicated that three-dimensional interconnecting pore structures existed within specimens. It was noted that the raster gap settings had a major influence on the microstructure of the specimens. Porosity values ranged between 22 and 68 per cent, while compressive strength values ranged between 5 and 20 MPa.

4.3 Three-dimensional printing for *in vivo* devices

Three-dimensional printing (3DP) is an RP process operating by the selective deposition of a binding liquid onto a powdered material to form a solid mass [**70**]. The 3DP process was developed at the Massachusetts Institute of Technology and has subsequently been licensed to machine producers [**52**, **71**, **72**]. This process has been subject to considerable investigations for RM, in particular for scaffolds and drug delivery applications [**73**, **74**]. The process has the potential to incorporate different material options owing to the flexibility of the material format (liquid and powder). The material format may also facilitate the possibility of functionally graded materials (FGMs), but may also be the source of difficulties for complex internal structures owing to powder entrapment.

Lam *et al.* [**75**] investigated the development of scaffolds using 3DP. A blend of starch-based polymer powders (50 per cent cornstarch, 30 per cent dextran, and 20 per cent gelatin) was developed for use in various tissue engineering applications. The scaffolds were built and characterized for several properties, including porosity, compression, and water absorption, using scanning electron microscopy (SEM) and differential scanning calorimetry (DSC). Five different designs were fabricated and post-processed by infiltrating scaffolds with different amounts of copolymer solution, with half of them being soaked in deionized water for 10 min and dried to enhance

the mechanical and chemical properties. As a result of the post-processing employed, the shrinkage ranged between 2 and 12 per cent depending on the design. Microporosity values decreased after infiltration because the copolymer infiltrated the micropores and voids. A linear and inversely proportional relationship between compressive stiffness and porosity was found.

Other research work has investigated the use of three-dimensional printing for the fabrication of customized polymeric drug delivery systems to overcome the drawback of decreased drug release rate as a function of time. A drug concentration profile is generated in a computer model, which is produced by 3DP. By this means, complex drug delivery regimes can create multiple drugs or the multiphase release of a single drug.

4.4 Selective laser sintering for *in vivo* devices

Selective laser sintering (SLS) is a commercialized RP technique that operates by the selective melting and fusion of a powdered material by laser exposure. SLS was developed in the late 1980s at the Mechanical Engineering Department of the University of Texas at Austin [**35**, **76**, **77**]. The process has a relatively large range of materials that may be processed, but equipment and ancillary costs are high.

Pioneering work by Lee and Barlow [**78**, **79**] on polymer-coated calcium phosphate for the fabrication of artificial bone implants first revealed the potential capabilities of employing SLS for *in vivo* devices.

Improvements in the SLS process are expected and are being researched to enable RM to be used for the production of desired scaffolds for tissue engineering. These include developing the ability to create smaller features by using a smaller laser spot size, powder size, and thinner layer thickness [**80**].

Cruz and Simoes [**46**] reported the production of poly(L-lactide)/hydroxyapatite composite (PLLA/HA) implants for lower load bearing applications using SLS. Authors have emphasized that the production of implants using RM technologies is still at an embryonic stage and far from the industrial production stage.

Rimell and Marquis [**81**] reported the investigation of SLS using ultrahigh molecular weight polyethylene (UHMWPE) for clinical applications including patient-tailored prostheses. This study raised a number of concerns, including material shrinkage, the porosity formed, degradation in terms of chain scission, crosslinking, and oxidation. It was concluded that the development of new powders with increased density was required.

Tan *et al.* [**82**] investigated the use of a polyether ether ketone (PEEK) and hydroxyapatite (HA) composite with different percentage composition ratios using a commercial SLS machine for the intended application of scaffold-guided tissue engineering. The laser power, part bed temperature, and scan speed were the three SLS parameters investigated. Results indicated that 40%HA was an ideal composition to produce structures with good integrity. Optimum SLS processing occurred at a low part bed temperature complemented by a higher laser power. Further studies [**83**] have been conducted with various biodegradable polymers including polycaprolactone (PCL) and Poly(L-lactic acid) (PLLA) for applications where anchorage-dependent cells rely on the use of temporary three-dimensional scaffolds to guide cell proliferation. This study has ascertained the possibility of using biocompatible polymers in SLS. The technique enables the production of the well-defined pore interconnectivity required by tissue engineering, which gives SLS the edge over conventional manual-based fabrication techniques.

Das *et al.* [**84**, **85**] investigated the use of SLS with nylon-6 to fabricate scaffolds with periodic and biomimetic internal architecture which had been produced by computational design methods with intended application for hard tissue engineering scaffolds. *In vitro* results indicated that 51–65 per cent of the pore space was occupied by the regenerated bone, which is consistent with monolithic hydroxyapatite scaffolds. The level of cell viability was less than 70 per cent on average. Studies have also indicated the possibility of constructing functionally tailored tissue scaffolds in a single step via SLS of multiple materials, which would enable the simultaneous growth of multiple tissues, tissue interfaces, and blood vessels.

Chua *et al.* [**86**, **87**] reported the fabrication of poly(vinyl alcohol) (PVA) and hydroxyapatite (HA) composites by SLS to fabricate three-dimensional tissue engineering scaffold structures. The PVA/HA powder showed promising sintering results. Simulated body fluid (SBF), which has an ionic concentration and pH almost equal to those of human blood plasma, was used to analyse chemical and morphological changes of HA in the test specimens by imitating actual physiological interaction between the HA surface and the implant site. Bioactivity analysis indicated the presence of hydroxycarbonate apatite (HCA) on specimens soaked in SBF.

Goodridge *et al.* [**88**] reported a study of the direct SLS of both apatite–mullite glass ceramic and hydroxyapatite (HA) with lower-melting calcium sodium phosphate (CNP – resorbable glass) for bone

replacement implants. Success with the glass ceramic was observed with a powder size range between 0–45 μm and 45–90 μm. HA-CNP was sintered into 10 mm × 10 mm × 5 mm blocks by direct SLS. However, no success was achieved in producing samples of similar strength to typical bone.

Savalani and Harris [**49**] studied the effect of varying particle size of a commercial hydroxyapatite-reinforced polyethylene (HA–HDPE) bioactive polymer/ceramic composite material for the direct production of bioactive implants and tissue scaffold structures using selective laser sintering. It was found that particles within 100 μm fused irrespective of the particle morphology. Further studies [**89**] illustrated the effects on the degree of sintering of HAPEX® of a varying laser power and scan speed. Preforms fabricated at various power and speed settings resulted in a porous or relatively dense morphology.

Chua *et al.* [**90**] reported the production of scaffold structures with consistent and reproducible microarchitectures by using a scaffold library algorithm together with SLS for various tissue engineering scaffolds. The scaffolds were not built with a biomaterial but with commercial SLS nylon (Duraform™), since this particular research focused largely on assessing the design possibilities. Pore sizes of between 0.616 and 0.905 μm were fabricated. However, removing the loose powder within the pores proved to be difficult.

Williams *et al.* [**91**] experimented with the SLS of polycaprolactone (PCL), which is bioresorbable, with potential applications for bone and cartilage repair. Scaffold designs were produced by computational methods, and porous PCL structures were fabricated using SLS. The compressive modulus and yield strength values ranged from 52 to 67 MPa and from 2.0 to 3.2 MPa respectively, lying within the lower range of properties reported for human trabecular bone. It was concluded that the integration of computational scaffold design and layer manufacturing techniques could prove highly useful for the construction of scaffolds that have anatomy-specific exterior architecture derived from patient CT or MRI data and an interior porous architecture derived from computational design optimization.

Other research work conducted by Nanyang Technological University Singapore for healthcare applications leans towards the production of drug delivery devices [**92**–**96**].

4.5 Limitations of traditional RP/RM processes

Some of the established commercial RP processes have been investigated for the RM of *in vivo* applications with varying degrees of success. Most of these processes possess different limitations that derive from their development for use as models/prototype production processes and not as dedicated manufacturing technologies for the RM of specific *in vivo* devices. Along with those discussed in the previous sections, other limitations include the following.

1. Among the greatest restrictions are the current material limitations – very few biocompatible or bioactive materials are currently available that have undergone the necessary development for regulatory use. The majority of RP/RM materials developed and introduced to date have been largely based upon improvements in mechanical integrity.
2. Several current processes rely on high temperatures during and after manufacture. Heating to elevated temperatures influences the integrity of several biomaterials, some even beyond body temperature levels.
3. Little attention has been paid to the RM of sterile products, either in terms of their manufacture (clean room compatible processes) or in terms of the ability of materials to withstand post-manufacture sterilization processes.
4. Paramount to the full exploitation of RM for *in vivo* devices is the integration of complex internal structures and variable composition. There have been several developments regarding the integration of such capabilities in the production process, but there have been relatively few related developments in the design capabilities for this. Three-dimensional CAD is a primary enabling technology in RM, and there has been little advance in capabilities for internal design, both geometrical and compositional, through CAD software.
5. Removal of powders – powder-based techniques (e.g. SLS and 3DP) require post-processing techniques to enable the removal of trapped powder. This process may be a limiting factor of the internal architecture that can be produced. Moreover, it may also result in reduced biocompatibility of *in vivo* devices owing to the media containing leach-out products which result in detrimental cellular response and, in turn, reduced cell viability.

5 NOVEL RM TECHNOLOGIES

The investigation of novel RM technologies for *in vivo* devices has been prompted by the limitations

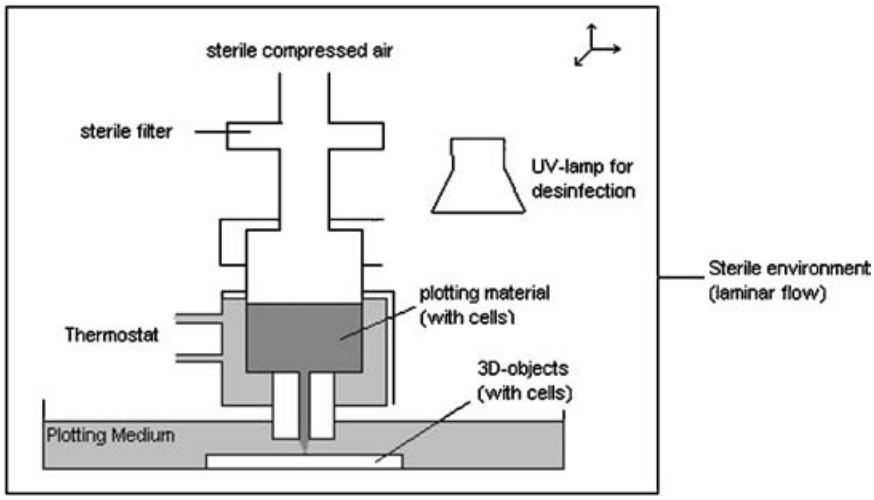

Fig. 3 Bioplotter process schematic (adapted from reference [**99**])

of conventional RP and RM techniques that have been used in other applications for modelling, reverse engineering, etc. Novel techniques developed by various research groups include the following.

The Bioplotter, invented at the Freiburg Materials Research Centre and developed by Envisiontech GmbH, is a commercially available system that incorporates cultures of the patient's own cells to build scaffold structures (see Fig. 3). The principle of the process involves a plotting material (with cells) being dispensed through a nozzle by air-pressure control into a bath of liquid with matching density and polarities, thus preventing gravity-induced structural collapse [**97**–**99**]. This technique has been used by Landers *et al.* [**100**] who reported the building of scaffolds derived from thermoreversible hydrogels (a polymer network with high water content) for soft tissue engineering. This work produced hydrogel scaffolds with a specific external shape and a defined internal pore structure. The geometry of a nose was fabricated to demonstrate the potential for soft tissue implant generation. Further studies have indicated the need for more basic research to improve the performance of hydrogel scaffolds in tissue engineering [**101**].

Mironov *et al.* [**102**] reported the concept, practical aspects, and development of an RM cell printer for direct soft tissue engineering. The cell printer aims to overcome the limitation of RP techniques, which are not capable of precisely placing cells aggregated into a printed scaffold. The process involves three sequential steps: preprocessing or development of *blueprints* for organs; processing or actual organ printing; and post-processing or organ conditioning and accelerated organ maturation. Cell or cell aggregates are placed in a three-dimensional gel with sequential maturation of the three-dimensional organs using a thermoreversible gel or matrix that solidifies upon fusion. Thus far, a cell printer has been developed that could fuse closely placed cell aggregates and heart mesenchymal (cushion tissue) fragments into ring and tube-like structures in three-dimensional gel (see Fig. 4).

Xiong *et al.* [**103**, **104**] reported the fabrication of porous poly(L-lactic acid) (PLLA) scaffolds using an RM technique termed precise extrusion manufacturing (PEM). This extrusion-based system feeds a heated thermoplastic material onto a working platform using a special sprayer extruder for precise extrusion. The extruder is designed with compressed

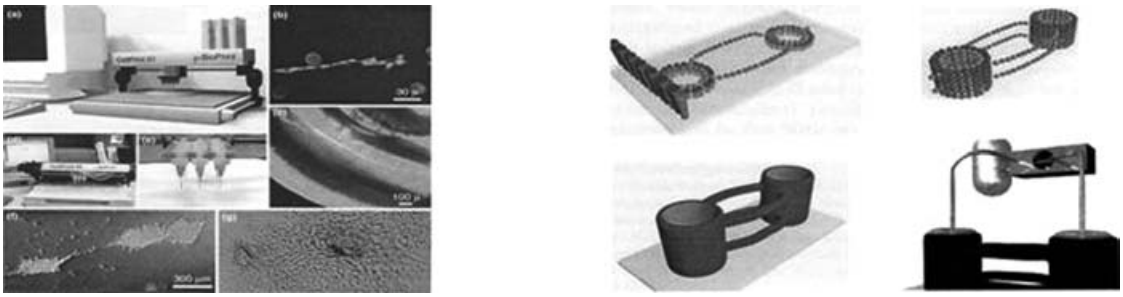

Fig. 4 Cell printer process [**89**]

air and a tie-in as opposed to the driving wheels used in a commercial FDM machine. The extruder is controlled using software that will not scan the contour but only scan the filling-in network of the object, which ensures an open porous architecture of the scaffolds. The process builds physical objects in a layer-by-layer fashion directly driven by three-dimensional CAD data. The scaffolds exhibited controlled porous architectures of 200–500 μm. It is made clear that the design of scaffold material and the modelling techniques of porous scaffolds are pivotal questions. Further studies on degradation evaluation *in vitro* showed that a 90 per cent mass loss was experienced after samples were immersed in pancrelipase phosphate buffer saline (PBS) for 2 weeks. Based on the enzyme activity, it was estimated that those PLLA scaffolds would degrade almost wholly within 100 days *in vivo*, which was considered appropriate for the bone repair process.

Xiong *et al.* [**104**, **105**]reported the fabrication of poly(L-lactic acid)/tricalcium phosphate (PLA–TCP) scaffolds for tissue engineering using a technique termed low-temperature deposition manufacturing (LDM) (see Fig. 5). LDM is based on a droplet assembly process that may maintain the bioactivity of scaffold materials because of its non-heating liquefying process compared with RP technologies such as SLA, SLS, and FDM which work at high temperatures. A composite of PLA and TCP was used to form a bone scaffold. These scaffolds possessed a high porosity level of 90 per cent with controlled interconnectivity and macrocellular and microcellular morphology while retaining mechanical property values close to human spongy bones. *In vivo* results showed good bone conductivity and appropriate biodegradation property for bone repair. Concurrent studies with regard to the PLA degradation rate are being carried out by several researchers including Kim *et al.* [**106**].

An extension of the LDM process, namely the multinozzle (four-nozzle) deposition manufacturing (MDM) system [**104**, **107**, **108**], has been investigated for the fabrication of bone tissue engineering scaffolds with gradient materials and morphologies. Further investigations have led to the possibility of extruding poly(ε-caprolactone) (PCL) for the free-form construction of three-dimensional tissue scaffolds at room temperature and low pressures [**12**].

Wang *et al.* [**109**] reported the fabrication of cellular PCL scaffolds using a novel precision extruding deposition (PED) technique which involves a mini-extruder system delivering the PCL in a fused form through the deposition nozzle. The major difference between the PED process and the conventional FDM process is that the scaffolding material can be directly deposited through the PED process without involving filament preparation. Scaffolds with a controlled pore size of 250 μm and designed structural orientations were fabricated. Further work has been conducted by Darling and Sun [**110**] to characterize the microstructure of scaffolds made using PED. The micro-CT imaged pores were between 200 and 300 μm, the optimal size suggested for tissue scaffolds. The greatest asset of samples manufactured by this technique is the possibility of obtaining porous interconnectivity greater than 98 per cent.

Ciardelli *et al.* [**111**] investigated the testing and fabrication of poly(ε-caprolactone) (PCL) and poly(ε-caprolactone)–poly(oxyethylene)–poly(ε-caprolactone) (PCL–POE–PCL) scaffolds using a pressure-assisted microsyringe (PAM) technique and SLS. Scaffolds were successfully produced using these two means of fabrication. Emphasis was placed on the substantially different structure resolution achievable in the two processes, as PAM allows the fabrication of fine-featured microstructures down to 5-10 μm wide and 5 μm high, whereas SLS structures demonstrated a resolution of about 300 μm height × 700 μm width.

Vozzi *et al.* [**112**] reported the fabrication of poly(D,L-lactide-co-glycolide) (PLGA) scaffolds with a feature size of approximately 10–30 μm using a

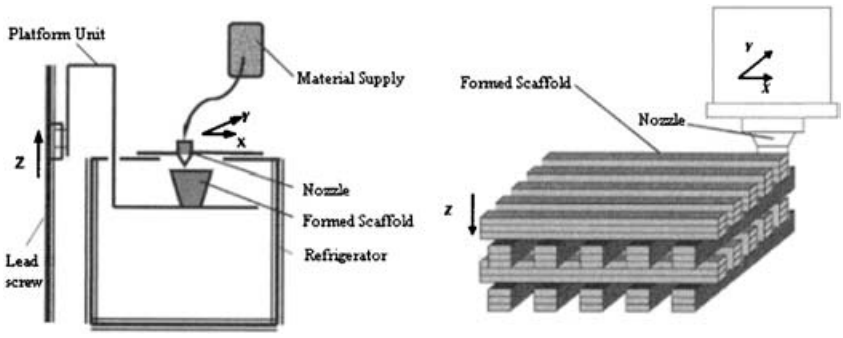

Fig. 5 Low-temperature deposition manufacturing process [**105**]

pressure-assisted microsyringe (PAM). PAM is based on the use of a microsyringe that utilizes a computer-controlled, three-axis micropositioner, which allows the control of motor speeds and position. A PLGA solution is deposited from the glass capillary needle of a syringe by the application of a constant pressure, resulting in a controlled polymer deposition. Prior attempts to manufacture scaffolds using microsyringe techniques have achieved resolutions of 50 μm [**113**]. The adapted PAM technique enables a resolution of 10 μm in the horizontal direction and 5–10 μm in the vertical direction. Although this system is highly automated and provides the possibility of dynamically altering polymer composition, a limited number of materials can be used owing to the narrow range of viscosities that can be employed to obtain high-resolution structures.

Ang *et al.* [**114**] reported the fabrication of three-dimensional chitosan (a naturally occurring amino-polysaccharide) and HA (0, 20, and 40%HA) scaffolds with regular and reproducible macropore architecture using a robotic dispensing system. The system was an extrusion-based system consisting of a computer-guided desktop robot and a single-component pneumatic dispenser. *In vitro* cell culture studies indicated that the scaffolds were capable of cell seeding and strong proliferation throughout the culture period.

Woodfield *et al.* [**115**] reported the production of three-dimensional biodegradable poly(ethylene glycol)terephthalate–poly(butylene terephthalate) (PEGT/PBT) block copolymer scaffolds with a 100 per cent interconnecting pore network using a three-dimensional fibre-deposition RM technique for engineering of articular cartilage. The technique enabled the production of desired scaffold characteristics by accurately controlling the deposition of molten copolymer fibres from a pressure-driven syringe onto a computer-controlled x–y–z table. The pressure-driven syringe unit contained thermostatically controlled heating rods capable of evenly conducting heat for uniform heating of the copolymer fibres. By varying PEGT/PBT composition, porosity, and pore geometry, three-dimensional deposited scaffolds were produced with a range of mechanical properties. The equilibrium modulus and dynamic stiffness ranged between 0.05–2.5 and 0.16–4.33 MPa. These results were similar to native articular cartilage (0.27 and 4.10 MPa). Further studies were needed in respect of the effects of scaffold composition and pore architecture on articular cartilage tissue formation.

Cesarano [**116**] reported the fabrication of hydroxyapatite structures with controlled porosity for porous bone grafts using robocasting. Robocasting is an additive freeform fabrication technique that robotically deposits ceramic suspensions for the fabrication of HA structures with controlled internal architectures. Structures with controlled pores in the size range from 100 μm to 1 mm have been produced.

6 BIOMATERIALS FOR RM TECHNIQUES

For the development of novel RM techniques for *in vivo* devices, it is essential that it be accompanied with appropriate material development. A relatively small amount of research has been conducted in the field of biomaterials for RM.

Tian *et al.* [**117**] demonstrated the preparation and characterization of HA suspensions by wet chemical synthesis for layer manufacturing in 2002.

Pfister *et al.* [**118**] reported the development and use of zinc polycarboxylate ionomers as a powder material for 3DP. These ionomers demonstrated stiffness and water-resistant properties without requiring post-printing treatments.

The Bioplotter technology allows the incorporation of natural materials including aqueous solution and pastes. However, the key feature of this technology is the three-dimensional dispensing of liquids and pastes onto a plotting medium with similar density to compensate for gravity forces through buoyancy [**99**, **100**]. As a consequence, complex structures may be produced without requiring the construction of sacrificial support structures which are typical for most of the other RP/RM technologies. This effect can be further increased by using a thixotrope medium [**99**]. Moreover, in the presence of a temperature-controlled plotting medium, the solidification of the material during plotting into the medium can be caused by precipitation, phase transition, or chemical reaction.

The low-temperature deposition manufacturing (LDM) process requires the material to be fed in a slurry form. This material has to be able to perform in a low-temperature environment below 0 °C. Once this material is deposited onto the surface, it freezes. Hence, control over the glass transition temperature, melting temperature, and freezing temperature plays an important role in the realization of this technology.

7 CONCLUSIONS

In vivo devices have been, and contine to be, fabricated to replace or restore functions of living tissues.

Currently, a number of conventional techniques are used for the commercial manufacture of *in vivo* devices. Their limitations for economic customization, their geometrical restrictions, both internal and external, and their constraints of compositional uniformity restrict the possibilities and application of *in vivo* devices. Computer-controlled fabrication via layer manufacturing has demonstrated the potential production of *in vivo* devices of controlled structure, shape, and composition that are not possible by conventional techniques. The need for controlled structures in the restoration and regeneration of tissue has resulted in multiple efforts and techniques to fabricate *in vivo* devices via layer manufacturing. Among these techniques, three-dimensional printing, selective laser sintering, and fused deposition modelling have been significantly investigated for intended use in scaffold-based tissue regeneration and drug delivery. However, there are significant hurdles to be overcome for the practical and industrial realization of these production technologies. The most pertinent of these include material restrictions, ancillary processes such as design, and regulatory approval. There have been, and continue to be, extensive research efforts conducted worldwide to enhance and latterly exploit the capabilities of layer manufacturing and rapid manufacturing for the production of future *in vivo* devices. Among these efforts, the Bioplotter developed by Envisiontech shows the true validity of these techniques for producing *in vivo* products. Looking towards the future, layer and rapid manufacturing hold great potential in the fabrication of *in vivo* devices for a variety of applications including solid implants, porous scaffolds, and drug delivery devices. However, any future developments should be based on biomaterial requirements driven by tissue engineering. Moreover, success and continual investigation is reliant on the success and adoption of tissue engineering.

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