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Biomodels of Bone: A Review

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Abstract

In this paper a definition of a biomodel is presented, based on which different specific types of biomodels are identified, viz., virtual biomodels, computational biomodels and physical biomodels. The paper then focuses on both physical and virtual biomodels of bone, and presents a review of model generation methodologies, giving examples of typical biomodel applications. The use of macroscale biomodels for such issues as the design and pre-clinical testing of surgical implants and pre-operative planning is discussed. At the microscale, biomodels of trabecular bone are examined, and the link with scaffolds for tissue engineering is established. Conclusions are drawn on the state of the art and the major developments necessary for the continued expansion of the field are identified. Finally, arguments are given on the benefits of integrating the use of the different types of biomodels reviewed in this paper, for the benefit of future research in biomechanics and biomaterials.

Keywords:

Bone Biomodels, Rapid Prototyping, Implants, Trabecular Bone, Tissue Engineering Scaffolds

1. Introduction

Models, both numerical and physical, are invaluable tools for engineers and scientists to help understand physical phenomena, to analyse physical objects and systems, and to perform design. In particular, computer modelling has revolutionised almost all areas of engineering and science over the last thirty years, allowing the practitioner to work in a virtual environment, where numerical models of great complexity can be handled with relative ease. In addition, new and efficient production processes, based around rapid prototyping technologies, are currently revolutionising the generation of physical models, allowing the engineer to efficiently and accurately produce physical models with high levels of geometric intricacy.

These developments have had a considerable impact in the areas of bioengineering and medical implant design, not least when applied to the musculoskeletal system. Here, models have been used for a wide and quite diverse range of purposes, including pure visualisation of anatomical structures, detailed investigations of fundamental biomechanical processes, the design and prototyping of surgical implants, and surgical training. A very good review of computer modelling in such areas, which shows the truly significant levels of advancement that have been achieved, is presented in Vander Sloten.[70] However, advancements have not been restricted to computer modelling alone; rapid prototyping is currently becoming increasingly important in the musculoskeletal bioengineering area for the generation of physical models that can be used in studies addressing the above-mentioned diverse range of objectives.

Motivated by the developments in both computer modelling and physical modelling in the area of musculoskeletal biomechanics, the first objective of this paper is to establish a definition of a *biomodel*. This definition is adapted from that presented by D'Urso et al. in the

context of a study that employed physical craniofacial models.[19] The definition is extended here to include computer-based models and is motivated by the fact that both types of models can be generated from the same type of source data, using protocols and processes that overlap to considerable extents. More significantly, both types of biomodels can be used for complementary, and individually equally important, purposes. For example, physical biomodels have great potential as validation tools for computer-based predictive biomodels, such as those generated using the finite element (FE) method.

The definitions presented here allow a framework to be established to categorise and link together areas of study and research that heretofore have been considered somewhat distinct, e.g. generation of physical models of bone for preoperative planning, computer visualisation of bone for implant design and generation of FE models of bone for biomechanics studies. The definitions allow for all such activities to be viewed as different forms of biomodel generation and usage.

Once definitions have been established, the second objective of the paper is to review biomodels of bone, in the context of macroscale or whole bone applications and microscale applications. Without a doubt, the former is the most common, while the latter is growing in importance and prominence. The present paper primarily reviews physical biomodels. It also includes a limited discussion on virtual biomodels where appropriate because of the strong commonality between physical and virtual biomodels in terms of generation and application. It is important to point out that the definitions as established potentially classify an immense range of studies and as such it is necessary to limit the scope of the review.

1.1 Definitions

According to D'Urso et al., "Biomodelling is a generic term that has been coined to describe the ability to replicate the morphology of a biological structure in a solid substance".[19] Based on this, and extending the scope to include computer-based models, the following definition is presented here:

A *biomodel* is an entity that replicates the geometry or morphology of a biological structure, that can be realised in either a computer-based form or a solid physical form.

From this basic definition, one can identify a *computer-based biomodel* and a *physical biomodel*. Focusing on the computer-based biomodel, one can define two different types:

A *virtual biomodel* is a computer-based biomodel created for the purpose of visualisation of biological structures, for example a 3D computer-based image of a skeletal structure generated from CT scans, used for surgical planning. This definition also includes computer-based models that can be manipulated by CAD software, for example as used in designing implants and prostheses.

A *computational biomodel* is a computer-based biomodel created for the purpose of performing biomechanical analysis on a biological structure, for example an FE model of a skeletal structure used for determination of stress and strain distributions. In the context of this definition, the material properties of the biological structure are equally as important in the generation of the biomodel as is the geometry of the structure. This feature generates a clear distinction between computational biomodels and virtual biomodels. It should be noted here that computational biomodels are not the topic of the present paper and will be discussed in a future publication.

A *physical biomodel* is a biomodel rendered in a solid physical form that can be produced by engineering technologies such as CNC (computerised numerically control) milling or rapid prototyping (RP) techniques. In general, physical biomodels originate from computer-based biomodels, in particular virtual biomodels as defined above. Physical biomodels can be built to actual size, or can be scaled to yield advantages in different situations.

1.2 Scope of Review

Given the generality of these definitions that could be applied across the full range of anatomical structures, including for example, cardiovascular, gastrointestinal and endoctrinal organs, the focus here is on the musculoskeletal system and bone in particular. *The review is primarily concerned with biomodels of bone with a focus on model generation methodologies and applications.* It is important to recognise that there is an obvious interrelationship between the different biomodel types and although the primary focus of the review is on physical biomodels, discussion will be presented on the appropriate aspects of virtual biomodels that complement the physical biomodel review. Virtual and computational biomodels themselves represent very broad topics and an in-depth review of these topics is considered outside the scope of the present paper.

As mentioned above, the review is organised in terms of macro and micro size scales, which in the context of bone means whole bone models at the macroscale and trabecular bone (TB) models and scaffolds for tissue engineering (TE) at the microscale. A hierarchical organisation of bone into five structural levels has been established by Liebschner, namely into i) a whole-bone level, ii) an architectural level, iii) a tissue level, iv) a lamellar level, and v) an ultrastructural level.[46] In the present paper a distinction in the view of the physical sizes appeared to be reasonable, i.e. macro size scale for whole bone and a micro size scale for the structures discussed here which are at the architectural level. The primary reason for making

this size scale distinction is that the small physical size scale associated with TB introduces complexities in model generation that warrant discussion separately. It can be stated at this stage, that in contrast to whole bone modelling, TB modelling in the literature has been reported almost exclusively in terms of computer-based biomodels, both virtual biomodels and computational biomodels. Following the review of model generation methodologies and examples of applications, the final section of the paper draws conclusions on the benefits of biomodelling, discusses the main impediments to biomodel development, and looks to the future for areas in which biomodels can make a significant impact.

2. Biomodels at the Macroscale

2.1 Physical Biomodel Generation

In clinical practice physical biomodels, in particular, have been found to be very useful for diagnostics and surgical reconstruction. Both physical and virtual biomodels are based on Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans to acquire accurate individual biomodel geometry. These two imaging techniques are widely used in clinical practice and provide sectional views or slices of the human body.[4] A series of 2D slices are used to get an idea of the 3D shape of hard and soft tissue like bones, organs and tumours. Alberti was the first to publish the idea of producing 3D computer based models from CT scan slices for visualisation purposes.[2] The subsequent introduction of suitable software enabled a stack of 2D images to be converted into a single 3D volume.[4] Techniques such as depth shading and surface and volume rendering have enhanced the visual realism of such images[4, 20] and consequently have increased their effectiveness. These images fall under the definition of virtual biomodels as defined in this paper.

When preparing or simulating surgical procedures, the disadvantage of a virtual representation is that it doesn't allow the surgeon to get a "feeling" for the thickness of the

bone, that would be very useful when planning manual procedures like resections and drilling, nor does it allow physical practising of such procedures. However, it is worth mentioning here that haptic interfaces for virtual environments, which provide the surgeon with a “feeling” he or she would have when handling physical tissue, are already available and their development and improvement is currently on going.[12, 63]

When computer aided manufacturing (CAM) techniques were first introduced to the medical field, it became possible to extract geometric information from CT scan images to manufacture physical biomodels.[4, 6] Now the surgeon could prepare, simulate and assess surgical procedures, with normal surgical tools, on a reproduction of the actual anatomy of a living person.

Initially, physical biomodels of bone structures had been fabricated by milling polyurethane.[6, 20, 48] However this technique can be problematic when one is dealing with complex anatomy and shapes like undercuts, cavities, and thin structures. In some cases this method is not suitable due to collision of the cutting tool with the model.[4, 6, 48] Not all of these problems can be solved by dividing a model into two or more parts for separate milling and assembly.

Rapid prototyping (RP) techniques have shown significant potential in the medical field. Biomodels manufactured using RP techniques are typically generated in a layer by layer manner from 3D images derived from medical scans. A wide variety of structures can be fabricated using this method depending on the accuracy required. Current techniques include stereolithography (SLA), selective laser sintering (SLS), fused deposition modelling (FDM), and three dimensional printing (3DP).[5, 42, 54, 57, 59] To produce structures meeting the definition of physical biomodels given in this paper, the techniques SLA, SLS, FDM, and 3DP are employed extensively. Stereolithography was the first method developed and most early RP produced biomodels were fabricated using this technique.[3] An inherent advantage of these

models lies in the fact that they can be sterilised for use in an operating theatre.[6] Colour stereolithography, i.e. applying colours to selected regions of the model by raising the duration of laser irradiation,[40] permits regions of interest in the biomodel to be highlighted, e.g. clearly marking a tumour to differentiate it from the healthy bone. Figure 1 shows an example of a biomodel produced by colour stereolithography, where the blood vessels are highlighted against the skull. This model was used to prepare the separation surgery of conjoined twins.

SLS, in contrast, provides opaque models which have the advantage that they look and feel very much like bone material.[5] Figure 2 shows physical models of human vertebrae produced in-house from polyamide using the SLS process; high quality models with excellent geometrical accuracy are possible. An advantage of both of these types of biomodels lies in the fact that the surgeon can practise an operation involving osteotomies on the model with the usual surgical tools available in the theatre.[57]

FDM machines extrude heated thermoplastic material from a nozzle. This and related techniques have been used, for example, to create scaffolds for tissue engineering from poly(ε-caprolactone) (PCL).[71, 76] 3DP spreads a liquid binder on a powder material like ink in an inkjet printer process. The binder material often contains organic solvents, but efforts are being made to produce models without solvents that harm living tissue.[42]

At the early stage of introducing rapid prototyping to medical applications Barker et al. developed a seven-step route to produce biomodels of the skull from CT scan images.[4] The steps described included (i) data acquisition from a human dry-bone skull which was placed in a water bath to reduce edge artefacts and to simulate the realistic segmentation situation, (ii) the transfer of scan data to a workstation, (iii) object segmentation, (iv) meshing of the object surface, (v) creation of the support structure (which is essential for stereolithographic

models), (vi) postprocessing of SLA data and finally (vii) solid model creation. For object segmentation, version 5.0 of the software Analyze from Biotechnology Computer Research was used, however, other software is available for the same purpose, e.g. MIMICS from Materialise[3, 48] or Anatomics Biobuilt from Anatomics[6]. With object segmentation the unwanted area is removed from the biomodel. A threshold for grey values is taken to divide bones from soft tissue and artefacts. A connectivity check separates loose parts from the main skull. Following this, 3D meshing of the surface is carried out with an appropriate algorithm. Thereafter, support structures are created for the production of the stereolithographic model. Recently, software packages have included these functions and are able to perform all the steps needed to obtain data for building a model. The software transfers the resulting region of interest into the standard file format for rapid prototyping systems, i.e. STL. Depending on the RP technique used, and on the manufacturer of the system, this file may need further transformation to a sliced file format, e.g. SLI, SLC, or CLI. For models fabricated by RP, the literature reveals that this route is commonly used and has been established as a standard. In biomodel manufacture, an alternative to RP technology is direct machining, including milling.

An important aspect where technology plays a crucial role in the generation of biomodels is accuracy. The measurement of the skull model manufactured by stereolithography by Barker et al. was compared to the original data of a scanned skull.[4] Maximum absolute differences ranged between 4.62 mm and 0.1 mm, corresponding to relative differences between 3.6 and 0.6 %. The maximum absolute differences were displayed by measurements of the width of the skull (skull 126.16 mm, model 130.78 mm); bone thickness was used to measure the maximum relative differences (skull 2.3 mm, model 3.6 mm, corresponding to a relative difference of 56.5 %). These results indicate that further enhancement of the segmentation and data processing stages may be required if the models are to be used for designing highly accurate customised implants. Limitations in accuracy resulted from CT scan resolution, and generated steps in the model structure.

The accuracy of rapid prototyping has been discussed in several papers.[50, 57, 60, 61, 74] Compared to milling of polyurethane with a rather poor accuracy of +/- 1.5 mm, RP techniques offer geometric accuracy of +/- 0.2 to +/- 0.1 mm.[57] Santler et al. reported that biomodels produced both by RP and milling had sufficient precision for clinical use.[60] Milled models showed very high precision within the CT scan planes, but in the z-direction low CT scan resolution and systematical errors resulted in deviations up to 3.15 mm. In comparison, the stereolithography model had overall higher but evenly distributed deviations, with a maximum of 2 mm. The milling machine was calibrated to 0.1 mm, however the fine milling tool had a diameter of 2 mm, which was therefore the limit for the smallest hole size. With 80 % (SLA) and 90 % (milling) of the deviations of the models below 1 mm, both techniques were considered to be sufficiently accurate.

Yang et al. reported that the laser beam of a typical SLS machine has a diameter of 400 µm.[74] This, in combination with the Gaussian distribution of the laser energy and the nature of powder bonding, which can occur in areas neighbouring the laser scan vector due to heat conduction and diffusion, would make it impossible to build features smaller than 400 µm. With a small-spot stereolithography system it was demonstrated that structures as small as 70 µm can be fabricated, however the common laser spot size used in SLA is about 250 µm.

While the current resolution of SLA and SLS is sufficient for macroscale biomodels, microscale models will need higher resolutions. In building models derived from CT scans, the resolution of the CT is the limiting factor in accuracy. The distance between two scan planes is greater than the geometric resolution of the manufacturing processes. Reproducing two scan slices without an appropriate volume and shape calculation of the intermediate missing region means that steps on the surface in the final model are likely to occur.

Due to the size of milling tools and the nature of the subtractive process, the milling technique is less suitable or not applicable for microscale models and complex structures with regions that cannot be reached by the milling tool. However, when a model has to be manufactured from a material which cannot be processed by RP, milling still can be an appropriate technique. Both methods have their applications, and as previously mentioned both of them are sufficiently accurate.

2.2 Applications

The reconstruction of bone defects with intraoperatively modelled prostheses restricts the choice of materials, the biocompatibility and the prediction of the aesthetical results.[24] As a result, operation planning and design/prefabrication of implants seem to be the most common applications of physical biomodels. Bill et al. suggested that stereolithographic model based operation planning in malformations, including craniofacial surgery, tumour surgery, traumatology, orthognatic surgery and implantology, was viable.[6] They used this technique to prefabricate drilling templates for dental implant insertion after mandibular and maxillary reconstruction, for facial or calvarial bone reconstruction after larger tumour resections, for craniofacial surgery and for traumatology.

In D'Urso et al. the application of stereolithographic models in craniofacial surgery was examined.[19] In forty cases of patients having complex craniofacial abnormalities, physical biomodels were used to assist the surgeon where standard imaging failed to clearly differentiate the anatomical pathology. Furthermore, the models were used for patient education and operative planning. As judged by the surgeons, the most important application was the ability to physically reconstruct the biomodels and shape bone grafts intraoperatively using a biomodel template. In some cases more models were used; one to visualise the desired endpoint of the operation and one or more to practise osteotomies and realignment of bones,

cf. Figure 3. Ten cases were taken into account to assess the utility of these models, and a significant improvement in operative planning and diagnosis was reported. In essence, D'Urso et al. believe that biomodels have reduced operation times by a mean of 16 %.[19]

In 1995 Lindner et al. reported the indications and applications of stereolithographic models for surgery after reviewing 124 cases of trauma, tumours, deformities and implantations.[48] Three cases were described in detail, where biomodels were used for preoperative planning. The reconstruction of facial bones was practised by determining defect sizes and shapes on the biomodels. In many cases it was found that biomodels were very useful for a range of applications, including performing osteotomies and syntheses on models of skulls or other bones of the same patient which were acting as donor sites, bending plates to be implanted on a model preoperatively or practising the reposition of bone segments after a fracture, as it reduced operation time and enabled the reconstruction of the correct skeletal anatomy. In a separate study, D'Urso and Redmond reported a case where a planned tumour resection was altered after observing that the intended osteotomy was entering the frontal sinus on the biomodel.[21] Therefore, the planning of surgical procedures on biomodels may significantly enhance safety for patients.

In the cases described above mainly replicas of bone structures were used, as these cases involved bone resection. It is clear that biomodels of other anatomical structures are also very useful in surgery and can complement the use of bone biomodels. For example cerebrovascular biomodels were found to be very effective in craniofacial surgery planning,[22] and often gave a better view of the disease whereby the position of the patient's head could be adjusted to the best approach angle before operation.

Physical biomodels have advantages compared to 3D virtual biomodels displayed on a 2D screen. For example in the field of cardiac surgery, Binder et al. confirmed this by stating that

although the clinical potential of 3D echocardiography was obvious, its application in routine clinical practice was limited; however, a stereolithographic model had the potential for much more widespread use.[7] Physical biomodels as true 3D representations provide both visual and tactile information that is not possible to obtain from a screen.

Peckitt described two cases where stereolithography was employed to develop biomodels for the design of facsimile implants of bone structures.[55] The shape of titanium implants, the fixations and the resection margins were planned on the biomodels. By fitting these implants to the models before insertion an exact match to the actual bone was assured.

D'Urso et al. performed a resection on a biomodel.[21] A wax master was fitted into the defect on the biomodel. This was then used to prepare a thermally polymerised acrylic cranioplasty which was fixed to the bones intraoperatively with miniplates and screws. It was estimated that 1 hour of surgery was saved by avoiding the need to fashion the cranioplasty intraoperatively.

Winder formed titanium sheets in dental stone moulds under high pressure for covering cranial defects,[72] see Figure 4. The dental stone mould was originally obtained from the patient's skull by taking an impression of the defect through the shaved overlying skin. The use of a rapid prototype biomodel resulted in improved plate fit and aesthetic quality. Aung et al. used a biomodel to design an acrylic plate for a cranial defect.[3] This was used preoperatively to bend a titanium mesh to cover the cranial defect. The metal sheet was not very malleable and as a result was difficult to shape properly during the operation.

Heissler used rapid prototyping to make moulds for titanium cast implants.[33] Compared to the wax models for casting, titanium has the advantage that shrinkage can be compensated for during design of the implant. Furthermore, casting versus milling of titanium[24] allows very

thin and complex geometrical structures, which cannot be milled, to be produced by rapid prototyping.

As is clear from the above examples, physical biomodels have great potential for use in indirect fabrication of an implant, i.e. where the implant is made in a number of steps, and where the implant shape is determined by that of the biomodel. This has been reiterated in Berry et al.[5], however, in Eufinger et al.[24] it is pointed out that limited accuracy is achieved and significant effort is expended using an indirect process.

Generating an implant directly from a physical biomodel typically involves one of the following procedures, (i) cutting the implant from autolysed, antigen-extracted, allogeneic (AAA) bone material to fit the defect in the physical biomodel, (ii) manufacturing a model of the implant to generate moulds for the casting of a variety of biocompatible materials including titanium and methylmetacrylate, and (iii) the bending of plates on biomodels to produce a desired shape. These indirect procedures, while flexible, do have the disadvantage that they can lead to geometrical inaccuracies.

Processing of biocompatible materials via RP to produce implants has been possible for a number of years. However, it has usually involved binders, coatings or second phase materials that were necessary to generate an initial solid object. These materials had to be removed in a subsequent processing step, e.g. burn-out or dissolving; they would potentially harm the body if not fully removed.

More recently, “selective laser melting”, a free form fabrication technique related to SLS, has been introduced, which allows the manufacture of metallic parts directly from metallic powders such as titanium without the need of binders or coatings.[53] This is an alternative route to cast metallic prostheses. The combination of novel biomaterials and the adaptation of

rapid prototyping techniques to process these materials offers significant future opportunities for physical biomodelling at the macroscale.

Additional applications of physical biomodels are measurement of loads where *in vivo* measurements are impossible or unfeasible and checking the results of calculations performed using computational biomodels. In some cases *in vivo* measurements may be possible but may not be feasible, due to physical impracticalities and ethical approval difficulties. Heckmann et al. used a stereolithographic model of the patient's mandible to obtain loads and moments on oral implants and the denture bearing area using strain gauges.[32] The SLA model was found to be reliable with an error of 10 to 20 %.[31] This application is a very good example for a link of physical and computational biomodels. Measurements of biomechanical values and properties, which cannot be gained *in vivo*, can be derived to a good approximation from copies of the tissue with similar material properties and biomechanical behaviour. Validation of computational models and finite element calculations performed with them is a major and very valuable function of biomodels for biomechanics.

The method to shape implants using a virtual biomodel is even more sophisticated than on a physical model. CAD/CAM technologies enable the design of an implant on a virtual basis. Healthy bone structures can be mirrored to defects, not only to view the desired endpoint of the operation, but also to get the shape of an implant to fill a defect. This can be done by Boolean operations of the mirrored bone and the defect.

Bill et al. reported a method whereby a virtual biomodel was used to design an implant to close a defect in the skull.[6] The implant was designed by mirroring healthy bone to the side of the defect. Subsequently, physical models of the skull and implant were made using SLA and the physical implant model fitted perfectly into the defect in the skull model. Finally, guided by the contour of the implant model, an identical bone chip was cut out from an autolysed,

antigen-extracted, allogeneic (AAA) bone calvaria. This fitted exactly to the borders of the bony defect and was fixed with miniplates.

Eufinger and Machtens transferred contours of bones into a CAD system.[24] Free form surfaces were generated by extrapolating the surface contours of defects surrounding bones. The thickness of an implant, which was a plate for covering a defect, was created by translating the free form surface. The implant border was derived from the defect border, preserving a small gap to facilitate insertion of the implant. Some overlapping areas were included for fixation of the plate. When the design was finished, the data were translated and the implant was milled from titanium.

The applied method was novel from the point of view of implant design, which was based on computer images, i.e. using a virtual biomodel. However, in contrast to other implant manufacturing methods which involved forming the implant “over” a physical craniofacial biomodel, the subtractive milling method used here resulted in a considerable waste of material. Apparently, a block of titanium was milled down to produce a 3 mm thick curved plate. An additive RP based technique for processing titanium, such as are becoming available at the present time, would circumvent this disadvantage.

The manifold applications of biomodels indicate their value for medicine. Surgeons and patients benefit from surgeries with improved preparation possibilities, implants that are prefabricated but customised, and reduced operation times. Communication between the surgeon and the patient and the patient’s comprehension is facilitated by having 3D models for explanations of the proposed operation. Finally, RP techniques allow quick production of complex models.

2.3 Virtual Biomodels

Model generation

As mentioned previously, the generation of virtual biomodels is similar to that of physical biomodels, dispensing with the fabrication process. Basically, a series of CT or MRI scans is integrated and noise is eliminated for the region of interest.[14, 49] The data format chosen for the virtual model depends on the purpose of the model, i.e. will it be used for visualisation only or also for simulation of procedures. For the former, a format like STL, which is used for RP processes, is sufficient in most cases. For the latter, e.g. when realistic response to virtual surgical procedures is required, the model must be capable of showing deformations. Most of the virtual reality (VR) modelling algorithms use polygons to represent complex objects.[49] The simplest form is a wireframe model. Surface rendering fills the polygons and gives a realistic appearance. Using volumetric rendering, the internal structures of organs and bones remain accessible.[49] Deformable models fall under the heading of computational biomodels as defined in this paper.

A detailed description of methods to generate 3D virtual biomodels and physical biomodels can be found in a review paper of Sun and Lal.[65] As reported by Sun and Lal 2D segmentation and 3D region growth are used to integrate CT/MRI images for 3D reconstruction.[65] For 2D segmentation the inner and outer contours of the living tissue are detected in each slice independently. The stack of contours is then used to create a solid model. In 3D segmentation voxels bounding the bone are recognised within the CT data set, and a surface is derived from these voxels. The marching cubes algorithm is the most popular algorithm for this. For anatomic tissue modelling, Sun and Lal presented (i) the contour-based method, (ii) the 3D shaded surface extraction method and (iii) the CAD-based medical modelling method.[65] These routes and methods are described in many papers and therefore have obviously proven to be useful.

Note that bone contours from scan conversion software have also been used to produce virtual biomodels in CAD software.[25, 36] Jans applied filters and algorithms to these curves and reduced the amount of data to a level which could be used to generate the model with Non-Uniform Rational B-Spline (NURBS) surfaces for the region of interest.[36] One disadvantage of NURBS surfaces is that they are not suitable for complex structures.[36, 65]

Facial bones for example are complex, and as such, NURBS surfaces cannot match the bone contours precisely. For a femoral bone, on the other hand, this technique may give appropriate results. Polylines, which represent the bone contour, consist of a high number of short lines to reflect any change in the direction of the bone contour in one scan slice. Transferring these polylines into CAD software and extruding a surface between the polylines in two successive scan slices can result in a very rough surface. Unlike data stored in IGES files, a popular data format used to transfer designs between dissimilar systems, the triangulated surfaces stored in STL-files have the drawback that they cannot be used as reference data for model generation in all CAD systems, and adding or editing sections can be difficult.

Therefore, whichever method is used to generate a virtual biomodel depends on complexity, purpose, and required accuracy. Greater usage of virtual biomodels in the future will drive the development of software to handle these computer-based entities.

Applications

As mentioned above, the field of virtual biomodels is too large to be covered comprehensively in the present paper. Therefore, only few representative applications are reviewed here.

Notwithstanding the disadvantage of virtual biomodels in terms of not providing tactile information (“feel”) without an additional device, virtual biomodels can still be used very

effectively for preoperative diagnosis and planning of surgical procedures. In addition to the fabrication of physical biomodels, these models are used in particular for dealing with complex procedures. Computed surfaces facilitate virtual manipulation of bones, i.e. changing the shape of a surface and performing estimations of the risk of fracture during bending.[36] Osteotomies have been simulated on virtual models and bending tests have been modelled with resected bones to evaluate the feasibility of the intended surgical intervention. The advantages of this system are that simulation on a virtual model is non-destructive and therefore a wider range of alternatives can be evaluated. Furthermore, the time-consuming and expensive production of a physical model (relative to that of a virtual biomodel) is not required.

Girod et al. reported the simulation of a surgical procedure for a patient with scaphocaphalus on a virtual biomodel of the patient's skull.[27] The complete segmentation and reconstruction of the cranial vault was performed on the model prior to operation, see Figure 5. Transferring the surgical planning into the operation theatre with an image guided navigation system offers the possibility of reducing the operating time.

Handels et al. used a virtual operation planning system in orthopaedic surgery.[29] The system was applied to plan operations and for the endoprosthetic reconstruction of the hip and the hip joint in bone tumour surgery. The construction and placement of a custom-made modular endoprothesis was supported by the system. This operation was said to require exact 3D planning of the cutting planes in the bone to be successful. Resection of the tumour and positioning of the artificial hip joint and of the fixation plates were planned on the virtual biomodels displayed by the software.

Meier discussed applications for virtual reality in surgery containing virtual biomodels, as defined in the present paper, in education and training, preoperative diagnostics, preoperative planning, intraoperative and postoperative applications.[49]

Chao reported on a graphics-based musculoskeletal model which can be used for biomechanical analyses and animation.[14] His simulation combined expertise in biomechanical analysis and graphic modelling to investigate joint and connective tissue mechanics and to visualise the results in static and animated forms.

A large amount of scan data was collected by Brief et al. to set up a catalogue of 3D data of skulls.[10] The aim was to gain norm data to determine the most likely appearance the patient would have without any defects. The data base can be used as a basis for virtual patient-specific operation planning and simulation.

In Computer Assisted Surgery navigation systems require virtual biomodels to guide the surgeon through the procedure. After marking the contours of the object on the CT or MRI slices, objects like skin or bone surfaces, vessels or tumour margins can be displayed in 3D. While this segmentation may take 15 to 30 minutes, depending on the number of objects and the experience of the user, the computation of 3D objects can be done within 1 minute.[30]

The Image Overlay system, as presented by Blackwell et al., visualises internal structures, e.g. bones, and projects them onto the actual body.[8] It appears to the surgeon that this structure is visible and this facilitates surgical procedures. Compared to other so-called ‘augmented reality’ systems, the Image Overlay system has the advantage that the view is always onto the patient, as the virtual images are dependant on a tracking system which tracks the position of the surgeon’s head. It is suitable for intraoperative guidance as well as for surgical education, but essentially for orthopaedic applications only. This is due to the rigid nature of bones,

where images gained preoperatively remain valid during surgery, while soft tissue would deform during surgery and Image Overlay would need intraoperative sensing for an accurate display.

Exact virtual representations of hard and soft tissue are vital for further development of engineering systems in medicine, e.g. robots used for surgery. However, these technologies are very expensive at present and their use is a controversial issue. In the future, they may facilitate surgery as they enable the specialists to operate across continents via the web. Digital data can enhance communication between surgeons around the world and very complex surgical procedures can be planned based on the opinions of many individuals. Clearly, virtual biomodels present many advantages in terms of cost saving relative to physical biomodels and ease of use internationally via digital communication. In the authors' opinion the range of applications of virtual biomodels can be expanded much further than is presently the case, for example they will from a vitally important part of remote, digital communication based, robotic surgery, when this technology reaches maturity.

3. Biomodels at the Microscale

3.1 Generation of Models

In contrast to macroscale biomodels of large bones those at the microscale represent very small structures. Trabecular bone (TB) is a typical example of such a microscopic structure. For these fine models, the resolution of conventional CT is not sufficient. Therefore, high resolution Micro CT (μCT) scanning is required to obtain all information necessary to generate accurate models.[51] Having the μCT scans, the model data can be conditioned as described in the previous section for macroscale models. Depending on the process used to fabricate a physical model, when the resolution of the process is not sufficient, enlargement of the model is advantageous. This is especially valid when mechanical tests will be carried out

with the model. Compression testing of TB biomodels would be useful, for example, in determining relationships between changes in TB micro-architecture and changes in overall elastic stiffness and failure strength. In such situations enlarging the model would yield greater geometrical accuracy and hence more reliable results. It would also facilitate optical inspection of both structure and deformation patterns. Enlarged models of trabecular bone produced from polyamide via SLS are shown in Figure 6. Models similar to those shown in Figure 6 could be used for studying liquid flow through TB micro-architecture. Larger models would facilitate greater liquid flow visualisation and dimensional analysis could be used to ensure that combinations of liquid inlet velocity, viscosity and density, at the large scale, are representative of the true small scale conditions. For example, the Reynolds number could be kept the same using a smaller liquid velocity at the large scale, balancing the larger inter-trabecular flow channel dimension.

Engelke et al. produced models of trabecular bone using stereolithography.[23] Limitations of the process prevented the generation of exact 1:1 replicas of the real bone. Enlarging the model by a factor of at least 2.5 prior to generation resulted in excellent replications.

In the field of tissue engineering (TE) of bone and cartilage scaffolds, the microarchitectures which guide a tissue culture to grow in a predetermined three-dimensional manner, represent microscale biomodels since they reflect biological structures. For instance, scaffolds can be used to define the ultimate shape for growing tissue. This may be necessary when one is seeking to replace a defective region of bone with a regenerated bone implant rather than an artificial implant. While the present paper provides a brief overview on generation methods and applications of microscale biomodels for tissue engineering, a detailed insight into the latest development concerning computer-aided tissue engineering (CATE) can be found in a recently publishes review paper of Sun et al.[64]

The generation of bone and cartilage by autogenous cell/tissue transplantation is one of the most promising techniques in orthopaedic surgery and biomedical engineering. Among the scaffold materials that have been investigated are hydroxyapatite, poly(α-hydroxyesters) and natural polymers like collagen and chitin.[35] It is most important that the material used is not detrimental to the body.

Structures mimicking trabecular bone help its regeneration by providing a scaffold which ideally resorbs into the body at the same rate that new bone is formed.[37] Jones and Hench investigated the development of bioactive ceramic structures for this purpose.[37] Porous structures are required to model trabecular bone. Two processes that allow control of the pore size range are a) gel-casting to produce macroporous bioactive hydroxyapatite ceramics and b) direct foaming of sol-gel derived bioactive glasses. However, in both processes it is difficult to control interconnectivity and pore anisotropy. As mentioned in the previous section, rapid prototyping techniques offer the possibility of manufacturing highly complex 3D objects, with a geometry generated on a computer, for example, and could be useful in such applications.

Sun et al. described the application of a CATE approach to tissue modelling, design and characterisation of scaffold unit cells and the fabrication of scaffolds.[66] While capabilities and potential of CATE were shown, it was also stated that it is still in its infancy and will mature with progress in computer technology, specific software and freeform fabrication.

Taboas et al. have reported difficulties processing ceramics directly using RP, and have proposed an indirect rapid prototyping process.[67] In this technique the mould pattern for lost wax moulding is manufactured via 3D printing and is used to cast the structure with a biocompatible material, see Figure 7. The combination of RP techniques, which are also

referred to as solid freeform fabrication (SFF) methods, and conventional sponge scaffold fabrication offers a high degree of freedom in design and choice of material.

In a review paper, Hutmacher summarises the fabrication technologies for 3D polymeric scaffolds with high porosity and surface area.[35] Most techniques have the disadvantage that they do not allow the fabrication of 3D scaffolds with varying multiple layer design. Rapid prototyping, in contrast, permits multiple layer design, as shown in Figure 8, and hence presents very good potential for manufacturing scaffolds for tissue engineering. The ability to control the porosity of scaffolds is a major advantage of RP. Commonly used techniques are 3D printing,[42] which allows fabrication at room temperature, and fused deposition modelling (FDM).[35, 39, 75] However, some SFF methods demand certain conditions which can include organic solvents or high temperatures. These conditions are problematic when handling or processing scaffolds for living tissue. Incomplete removal of the solvent will have detrimental effects on adherent cells, biological active agents and nearby tissue.[44] Newly invented SFF processes and modifications of known RP processes as described elsewhere[43, 67, 73] have been designed to deal with the special requirements of these new applications.

The SLS rapid prototyping technique is capable of fabricating complex objects from a variety of materials, including thermoplastic powders,[57] ceramics, and metals,[69] without the use of organic solvents. Biocompatible materials such as hydroxyapatite (HA) can be coated with a polymeric binder, e.g. polymethylmetacrylate (PMMA), to fabricate a "green part".[69] Das et al. utilised the SLS process to fabricate scaffolds from Nylon-6.[17] To overcome the issue of relatively high minimum feature size of commercial available SLS systems compared e.g. to 3D printing, a "hopper-nozzle" deposition system for implementation in an SLS system to produce small features is under development.[16, 41]

Tan et al. recently sintered bioinert polyetheretherketone (PEEK) blended with hydroxyapatite by SLS.[68] The high temperatures associated with SLS may be prohibitive for biodegradable and biofunctional materials such as living cells or bioactive markers, if these have to be added prior to the sintering. As a result, other rapid prototyping techniques such as 3D plotting may be required to fabricate scaffolds where a wide variety of synthetic and natural materials can also be processed.

The selection of materials for scaffolds for tissue engineering is much more critical than for viewing purposes in surgical applications and strongly influences the fabrication process. Since standard materials for RP processes are not bioresorbable, Zein et al. have developed a bioresorbable polyester which can be processed with FDM to fabricate scaffolds.[75]

Landers et al. reported the use of a 3D plotter to dispense hydrogels in a liquid medium.[43] This methods offers the advantage that cells can be incorporated into a centimetre-scaled scaffold. Hydrogels are used for simple scaffolds and find their application predominantly in soft tissue engineering since the mechanical stability is low, though it can be reinforced.

In MIT's (Massachusetts Institute of Technology) initial studies of their 3D printing process aliphatic polymers were used which required organic solvents.[42] In contrast, Lam et al. fabricated scaffolds of different shapes made from a mixture of cornstarch, dextran and gelatin and destilled water as a binder via 3D printing.[42]

Leong et al. reported on the efforts being made to employ RP production techniques for tissue engineering scaffolds and on their own investigations concerning the suitability of biopolymers for SLS processing.[44] They concluded that the SFF technology may be a generic solution in automatic scaffold production, easily permitting the implementation of variations in shapes and requirements of different tissues and organs and also size variations between

different individuals. It promises cost-effective and rapid solutions to customised TE scaffold production.

Computational modelling in combination with rapid prototyping can be employed to produce custom made scaffolds, with a range of pore sizes, pore shapes and interconnectivities from computerised images for different tissue engineering applications. Hollister et al. used computational models to optimise scaffold design.[34] To ensure adequate cell/gene delivery, a minimum porosity threshold was introduced. An image-based homogenisation optimisation approach was used to design scaffold microstructure to meet complementary design requirements such as sufficient overall scaffold material stiffness and tissue regeneration effectiveness, etc. The scaffolds were subsequently fabricated using SFF techniques as described in Taboas et al.'s paper.[67] Recently, the modelling process was extended to develop scaffold microstructures that nearly match the mechanical properties of trabecular bone while providing desired porosity for biofactor delivery.[47] An example of a scaffold with 55 % porosity designed for the human distal femur is depicted in Figure 9.

It is clear that in this newly evolving field of tissue engineering scaffold generation, a wide variety of processing techniques are required. This is chiefly because of the ever increasing range of potential scaffold materials, each with its own specific processing requirements. Additionally, modifications of the manufacturing processes and newly developed materials may produce biomodels with properties meeting those of living tissue. This is a very challenging task, but will potentially yield great benefits in the future.

3.2 Applications

Trabecular bone biomodels, such as those shown in Figure 6, are very useful for validation of finite element model predictions obtained from computational biomodels.[77] Another

application is using them for fluid flow experiments, for example to examine experimentally details of physiological fluid flow through cancellous bone microarchitecture. In cases where the biomodels do not have the exact mechanical properties of the tissue they represent, e.g. polyamide models of bone, they can, at the very least, be used to assess the relative importance of different geometrical or structural variations in the tissue. In addition, the models allow one to focus on the importance of geometry alone, given that the biological variability in mechanical properties between different real bone samples is eliminated. These advantages over real bone are very important in the research of osteoporosis, where stereolithographic and laser sintered models are already applied.[9, 23]

Traditional methods to repair bone defects include autografting and allografting of cancellous bone, applying vascularised grafts of the fibula and iliac crest, and using other bone transport techniques. However, the shortcomings inherent in these methods are that the new bone volume maintenance can be problematic due to unpredictable bone resorption. Furthermore, allografting bears the risk of infection.[11] In contrast to these traditional methods, tissue engineering, which involves bone regeneration, has the potential to provide an alternative.

Scaffolds are used in tissue engineering to support or even promote growth of bone and cartilage as well as soft tissue. Several matrices and scaffolds have been developed to act as growth factor and cell delivery systems and have been tested for tissue repair.[13] Recent reports have highlighted TE of the liver,[18] heart valves,[45, 56, 62] blood vessels,[52, 58] cardiovascular tissue,[38] the bowel,[15] the epidermis,[28] and for nerve regeneration.[26]

Results from preclinical animal models and clinical pilot studies are very promising for therapeutic repair of skeletal tissues by TE.[13] In bone tissue engineering, scaffolds mimic the extracellular matrix in a regenerating bone environment and as such do more than act as a simple mechanical support, but they also have to be ‘informative’ to the cells.[13]

While minimally invasive techniques have reduced morbidity at the operative site in mandibular reconstructive procedures, these techniques have not addressed the graft donor site. Abukawa et al. used a model of a porcine mandibular condyle to fabricate porous biodegradable polymer scaffolds.[1] Osteoblasts were transferred to the scaffolds and cultured for six weeks. The engineered constructs were white and hard and had a shape similar to that of the model condyle. Bone was observed on the entire surface of the scaffold with an average thickness of 0.03 mm.

Unlike the macroscale models, which were initially used for visualisation, microscale models have had the clear goal from the outset to be functional. Scaffolds used in tissue engineering are vital for the future of medicine, and their usefulness is obvious from the high number of publications about novel methods, materials and designs for their fabrication.

4. Summary and Conclusions

Definitions of biomodels have been presented in this paper and they allow for the classification of a wide range of representations of anatomical structures.

The first major finding of this review is that both physical and virtual macroscale biomodels are very useful in reconstructive surgery. Preoperative planning using these biomodels allows for the reduction of operation time and patient trauma and it can increase the patient's safety. Modern rapid prototyping techniques facilitate visualising the situation a surgeon will be confronted with in the theatre using increasingly detailed models. An additional advantage is to be able to see the likely outcome of the planned procedure in advance. From humble beginnings as simple visualisations of bone only, biomodels are now used not only to design implants, where necessary, but can be directly converted into implants by choosing an

appropriate biocompatible material for manufacturing; since they mimic anatomical structures, implants fall under the definition of a biomodel as presented in this paper. Both milling and rapid prototyping allow the production of macroscale biomodels with sufficient accuracy for clinical applications, although RP has proven to be more flexible regarding feature size and biomodel complexity. Whatever production route is used, being able to manufacture an implant preoperatively and without harvesting autologous bone from a second site reduces theatre time as well as trauma to the patient. In addition, these implants are most likely more geometrically accurate than those created intraoperatively.

Physical biomodels have the advantage that they are tangible. It is easy and intuitive for a surgeon to work with them – it is as if one is actually holding real bone. They also allow the surgeon to physically plan and practise an operation involving osteotomies using surgical tools. On the other hand, virtual biomodels have the advantage that they can be used for quite sophisticated and streamlined implant design, and can result in implants with better geometrical accuracy than those produced "indirectly" using physical biomodels. Additionally, simulation with a virtual biomodel is non-destructive, which allows one to evaluate a much wider range of alternatives or to repeat analysis of the same structure. The introduction of matured haptic devices into operating theatres can certainly boost the use of virtual biomodels in surgery. Image Overlay systems are very suitable for intraoperative guidance. Being able to use images acquired intraoperatively would be a major step forward. Additionally, the omission of physical parts (projectors, mirrors, etc.) in the surgeons's work area would give him or her more liberty of action.

Depending on the complexity of the original structure, the purpose of the biomodel and the required accuracy, one can choose between a variety of methods to generate a virtual biomodel or the preliminary step of a physical biomodel, respectively. These methods include visualisation by (i) NURBS surfaces, (ii) extrusion of polylines, and (iii) STL-files.

The major deficiency in producing biomodel of bone is the need of CT scanning and therefore exposing the patient to radiation. Therefore, CT scanning to obtain biomodels might not be used when routine procedures are to be performed. MRI scanners are better when it comes to radiation levels, but they have the disadvantage of the length of time the patient has to be exposed and stay motionless. The cost of the physical biomodels as well as manufacturing time is another issue hindering their use. Manufacturing time is most critical when emergency treatment is needed.

For macro- and microscale biomodels there is already a variety of solid freeform processes available, each with its own advantages for individual applications. Looking to the future, in addition to the obvious necessity to speed up and cheapen production methods for physical biomodels, using existing materials, the most challenging and exciting growth area comes from the realm of materials science. A literature review showed that there is signifcantly less research on technology than a couple of years ago. Most recent papers in the field of solid freeform fabrication are about the use of materials on the present machines. That gives the impression that the technology has matured and the focus is on materials now. Micromechanics shows that it is feasible to create parts at very small scales, but it seems to be a challenge to handle the present materials at that size scale which may prevent progress on the mechanical side of SFF. If biomaterials, either bioactive or bioinert, can be manufactured by rapid prototyping, then the next generation surgical implants could be readily generated with complex geometries, and with properties close to those of living tissue. To achieve this, modifications to existing RP technologies will probably be necessary to avoid the use of biologically harmful substances and to achieve a high accuracy even at a very small size scale. In addition, such technology opens the door to the production of scaffolds for tissue engineering.

From the literature review it is clear that macroscale biomodels have matured and the focus of research is now on microscale biomodels. The latter, e.g. trabecular bone biomodels, have great potential for validating the predictions of computational biomodels, such as TB finite element models. Large models for whole bone applications can be created by the state of the art techniques and at present there is a strong move to smaller, finer and more complex structures. But geometry is not the only issue. Significant efforts are currently being put into the development of biocompatible or bioresorbable materials, which can be processed by the new rapid techniques or other methods. These allow the generation of tiny but well defined structures that suit the demands of modern medicine and tissue engineering. Ultimately, this new generation of biomodels is epitomised by bioactive scaffolds whose geometry and morphology is motivated by natural tissue microarchitecture.

In the context of the definitions of biomodels and review of the state of the art presented in this paper, the following technologies can be exploited in the future.

- *Patient specific implants*. As mentioned previously, computer scanning methodologies and image analysis software can be employed to create patient specific models. Traditional implants are produced in a range of sizes and shapes for a given design, however these devices do not take individual patient criteria, for example tumour based defects, into account. Patient specific implants give surgeons a better selection of devices with the required structural properties for specific implant applications.

- *Gradient structures*. In the field of biomedical engineering gradient structures can be used in a range of applications where different materials properties are required on the surface of a device compared to the bulk. Using biomodels, biomaterials with a

porosity gradient can be designed, computationally analysed and used to create a wide range of devices from patient specific implants to scaffolds.

- *Scaffold design at micro/macro levels*. One of the essential requirements for a scaffold for tissue engineering is the ability to transfer nutrients to the cells and remove waste matter without introducing adverse side effects for the cells. Therefore pore size, pore shape and interconnectivity are key parameters in scaffold design. The use of biomodels will allow scaffold implants to be developed that will have optimal scaffold structure at the microscale (at the level of the pores), depending on cell type required, and correct macroscale geometry (at the level of the implant) for patient specific applications.

- *Scaffold/graft manufacture*. Tissue engineered bone grafts and scaffold devices offer great potential in the area of biological implant development. At present scaffolds are produced on a small scale in laboratories, employ the use of toxic chemicals and have poor reproducibility on a batch-to-batch basis. Biomodels can help significantly in the manufacture of scaffold and grafts with a high degree of accuracy and in high volumes through the manipulation of computer images and rapid prototyping technology, and without the use of toxic chemicals.

- *Materials combinations*. Another exciting aspect of implant design is the use of material combinations. For example in biodegradable scaffold design both the degradation profile, i.e. degradation rate and the degradation by-products, and the mechanical performance must be optimised. This is further complicated where drug release is also considered; in some instances drug release may need to be tailored over a specific period of time. Using a combination of materials the possibility of tailored

scaffold biodegradation and tailored drug release may be achieved. In this case biomodels (physical and computational) can be of great assistance in predicting both mechanical performance and degradation/drug release profiles, allowing implant optimisation for different applications.

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Figure 1: Colour Stereolithographic biomodel of conjoined twins showing blood vessels (Photo courtesy of Medical Modeling LLC)

Figure 2: Selective Laser Sintering (SLS) reproduced vertebral bodies

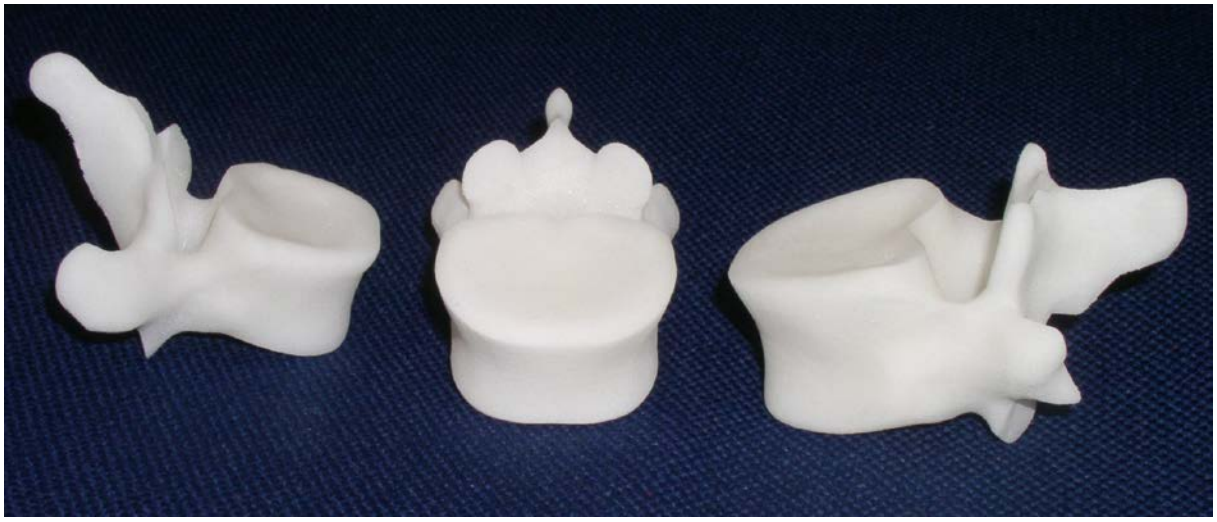

Figure 3: Biomodel of child with mirrored "half" biomodel to aid reconstruction (left) and reconstructed biomodel showing proposed outcome (right).[19] Reprinted with permission from The British Association of Plastic Surgeons.

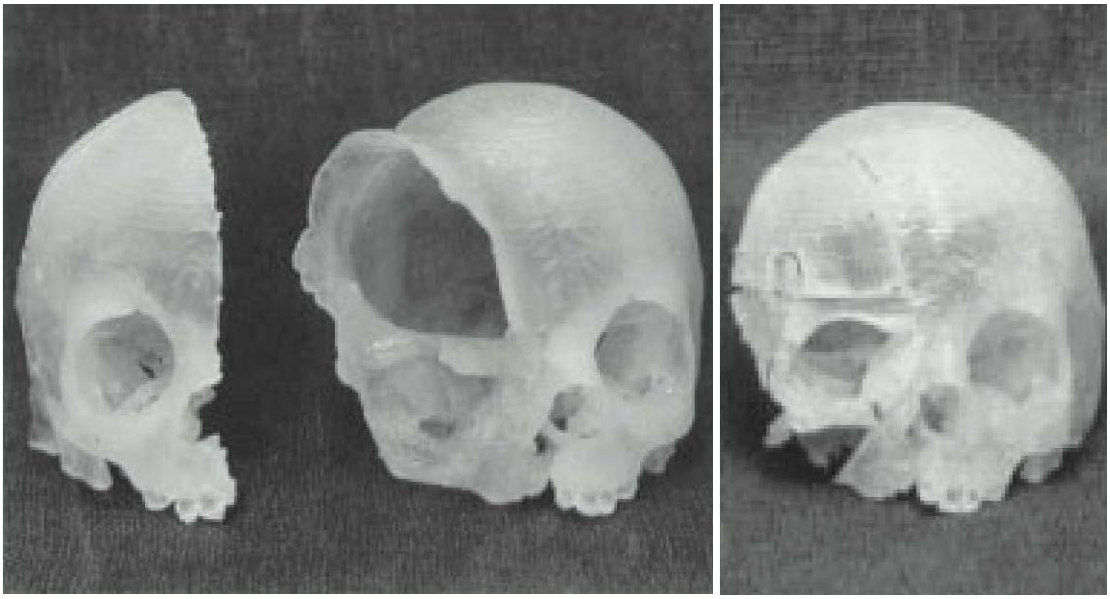

Figure 4: Stereolithographic model of full skull and custom titanium plate in place.[72] Reprinted with permission from Taylor & Francis. (http://www.tandf.co.uk/journals)

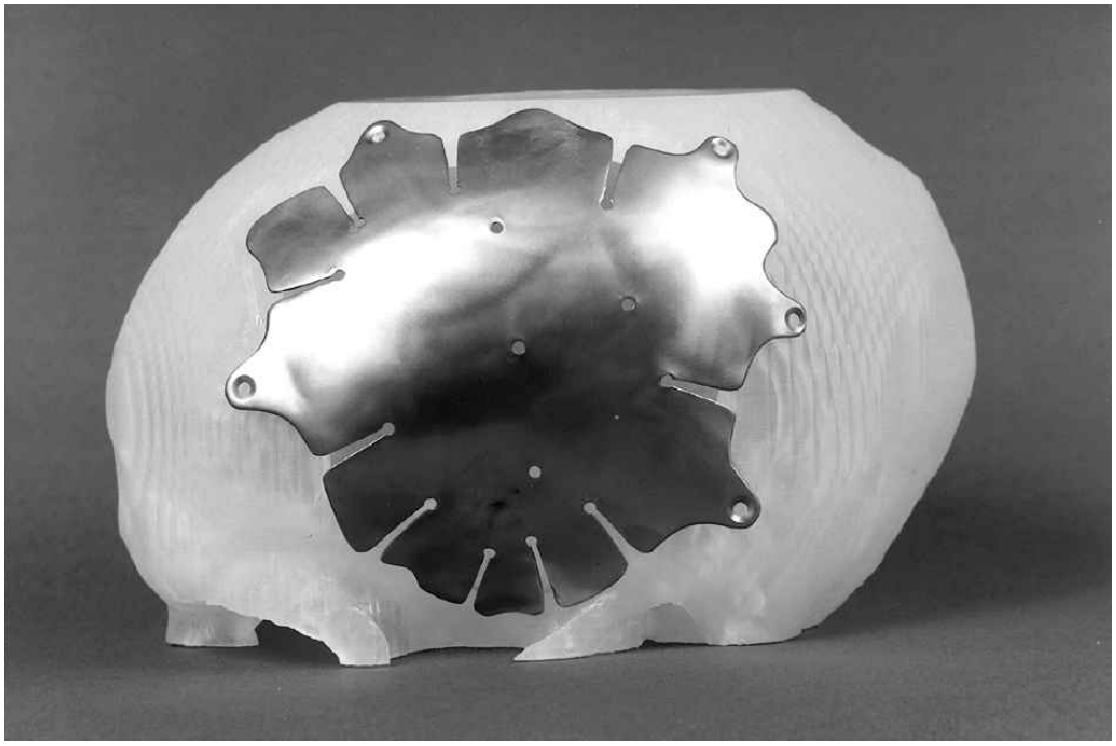

Figure 5: Complete segmentation of the cranial vault.[27] Reprinted with permission from European Association for Cranio-Maxillofacial Surgery.

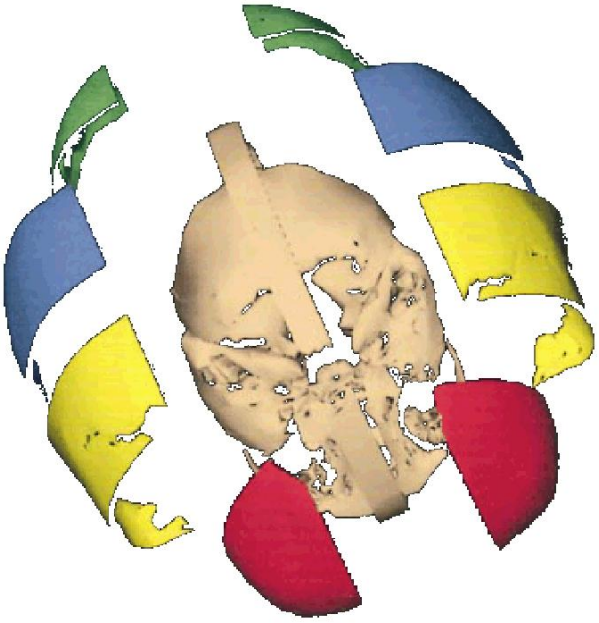

Figure 6: Biomodels of osteoporotic trabecular bone produced using SLS

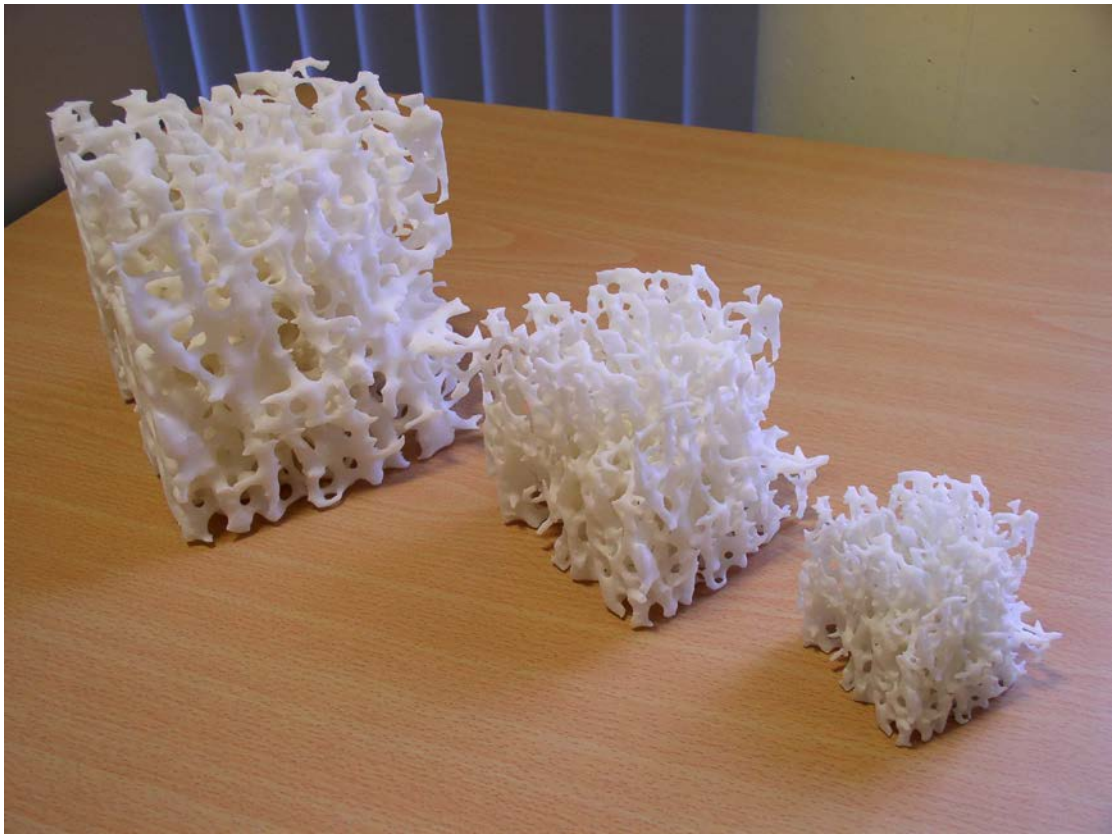

Figure 7: Indirect wax mould (left) and cast ceramic mould (right).[67] Reprinted with permission from Elsevier.

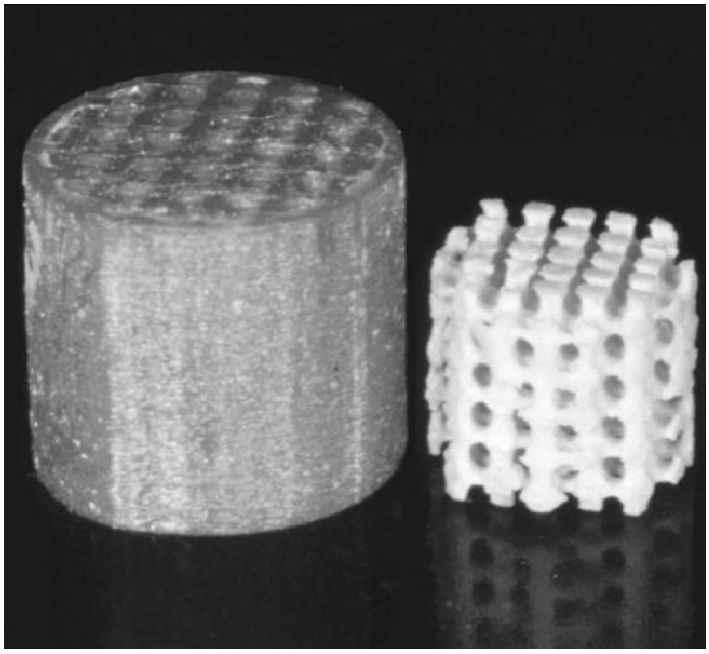

Figure 8: Variations in micro/architecture of FDM produced scaffolds.[44] Reprinted with permission from Elsevier.

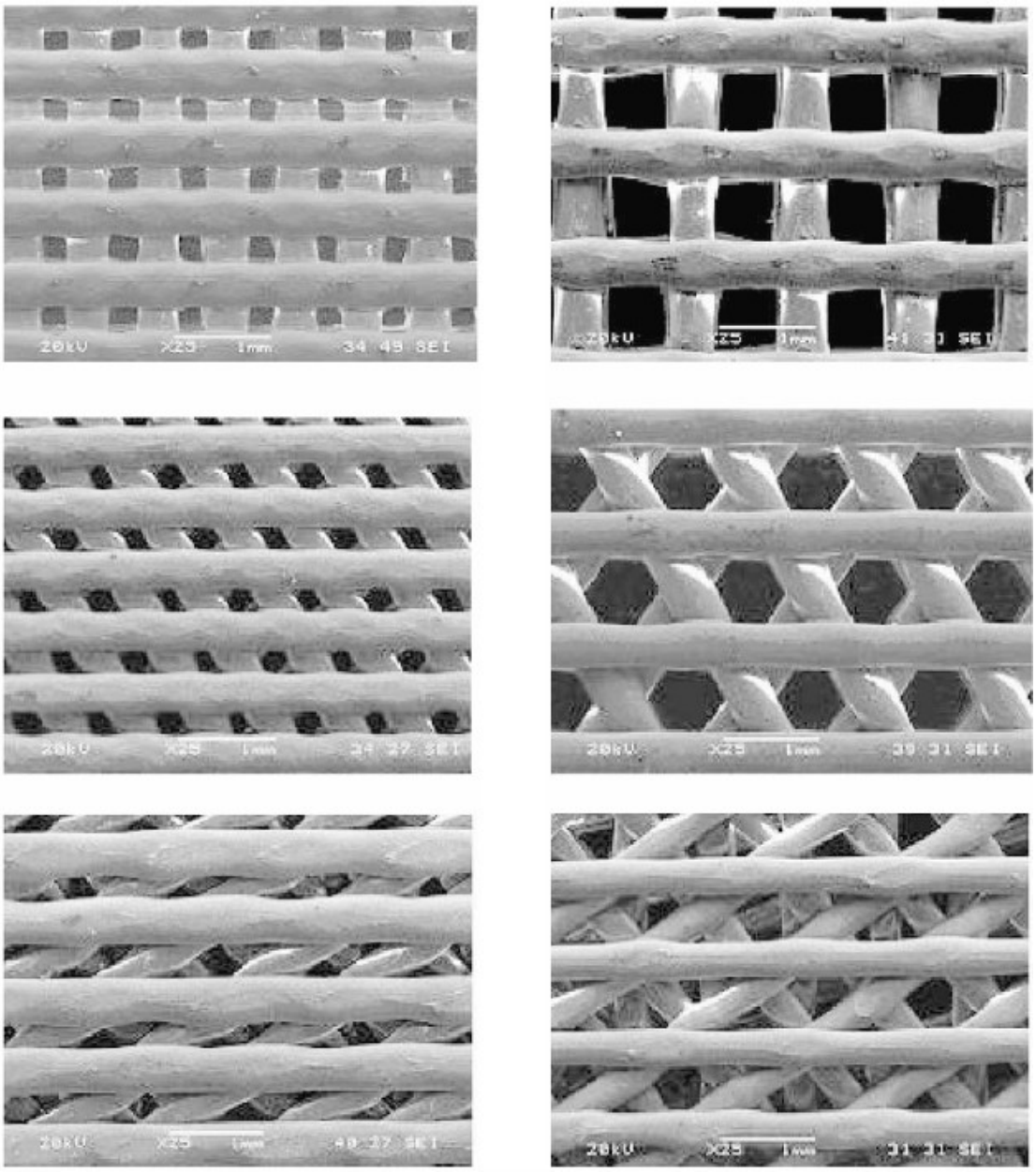

Figure 9: Designed microstructure for human distal femur. Prototype fabricated by 3D Ink Jet Printing, 10 mm x 10 mm x 10 mm.[47] Reprinted with permission from Elsevier.