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The Possibilities of Design in Bio-printing
Commission on the Future of Surgery
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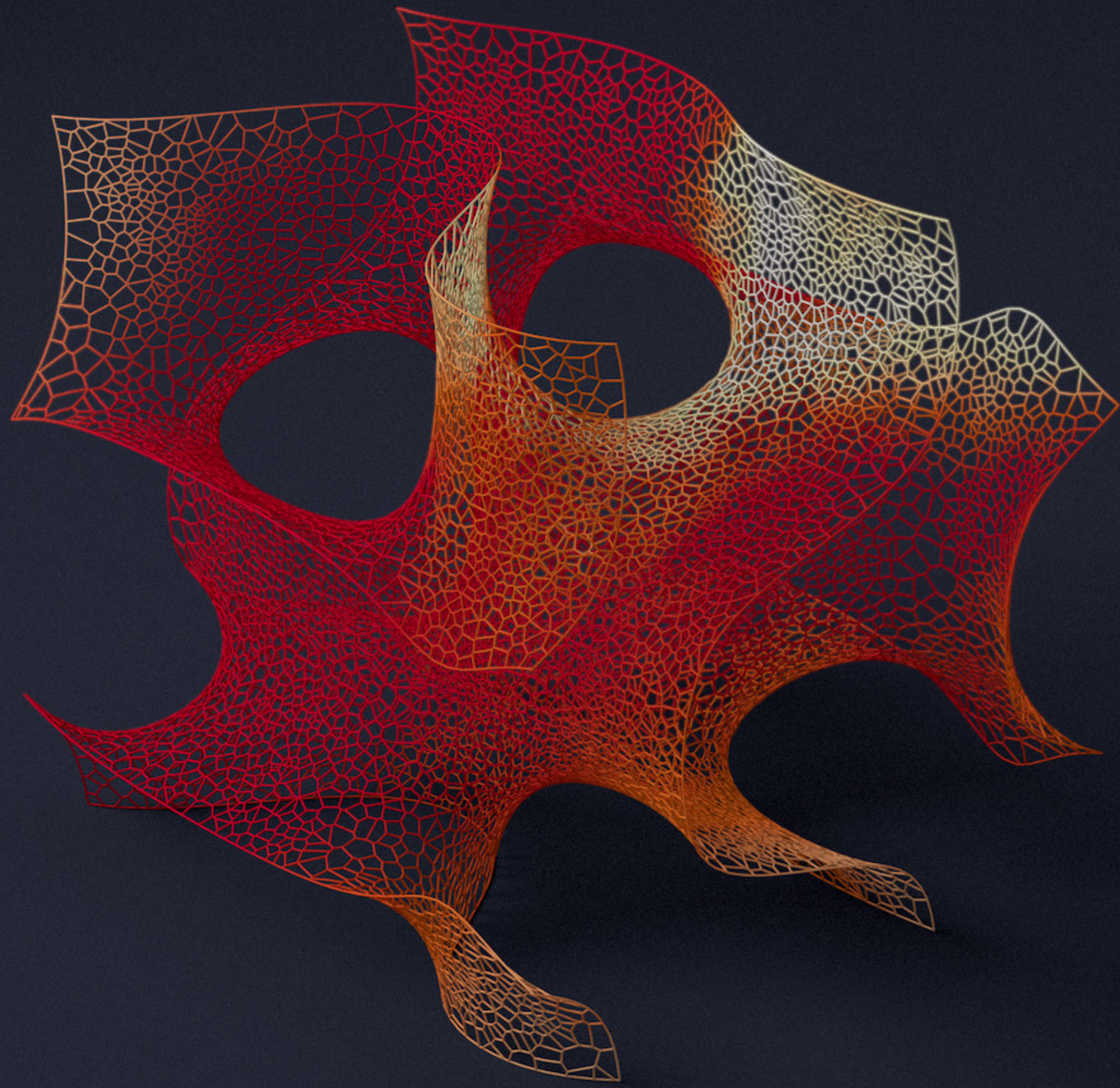
Introduction

Tissue engineering is a multidisciplinary field that aims to restore, improve or replace the function of biological tissue. Often, this involves fabricating 3-dimensional scaffolds to guide growth of native or implanted cells. Development of technologies such as 3D printing and bio-printing have enabled exciting advances in scaffold manufacture. This work considers the possibilities of applying principles of design to the production of these scaffolds.

I am a doctor and designer working in East London. In working as a Research Assistant at the Tissue Engineering department at the Royal Free Hospital, I noticed very careful consideration was given to the scaffold material, whereas the design was sometimes an afterthought. By considering both the design and the material in concert, emergent properties may evolve - such as scaffolds that have controllable deformation within the body or that have different mechanical properties in different dimensions. Also, one can mimic natures own design processes to produce biomimetic scaffolds very rapidly. For instance, simple computer models of processes such as angiogenesis can be used to produce convincing vascularised tissue. Furthermore, this vascularised tissue could be fully personalised to the patient by using perfusion maps of the implantation site.

Developments in tissue engineering and 3D printing will hopefully mean tissue damaged by significant trauma or disease can be fully restored. This is likely to involve creating bespoke scaffolds, depending on the tissue involved and the nature of the injury. My intention is that the techniques demonstrated here could be used by the surgeon, or a member of the team, without any specialised design or tissue engineering experience. One can simply vary simple parameters in order to have precise control over the final scaffold.

Design at the cellular scale is largely overlooked by both designers and scientists but offers unique challenges and exciting possibilities for the future. Moreover, a distinctive aesthetic naturally arises from approaching these problems, which may influence design at larger scales in fields such as architecture. Hopefully this submission demonstrates how considering the design of 3D printed scaffolds could have relevance in the future of surgery.



I. MINIMAL SURFACES

Minimal periodic surfaces are versatile mathematical structures that can be found in nature (1). Their variants have been explored for applications in tissue engineering (2). In the hands of the designer, they offer a tunable surface, which can be made anisotropic through varying the coefficients of the underlying equation (fig.1). A surface made of a versatile, controllable, repeating unit is generated that avoids non-biomimetic hard edges found in other computer generated lattices.

They provide a surface which is continuous and on which further customisation can take place, such as the voronoi fragmentation shown here, already shown to closely mimic bone (3). Combination of these techniques enables rapid prototyping of different structures with varying strengths and properties (Fig 5). Additionally, non-repeating minimal surfaces can be created which use the minimum possible amount of material for a given boundary condition or structure (Fig 3).

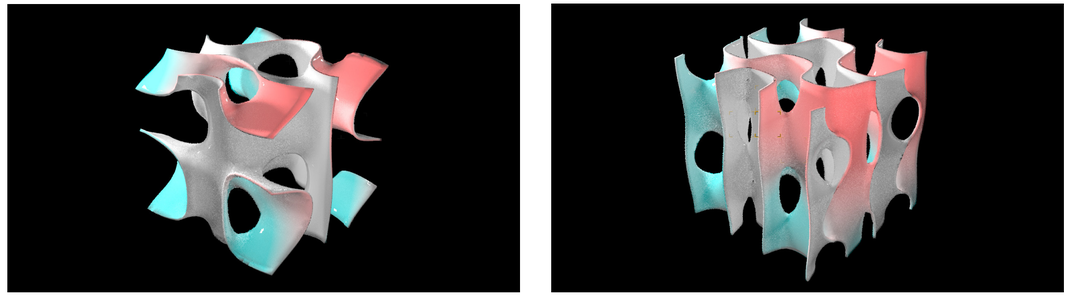
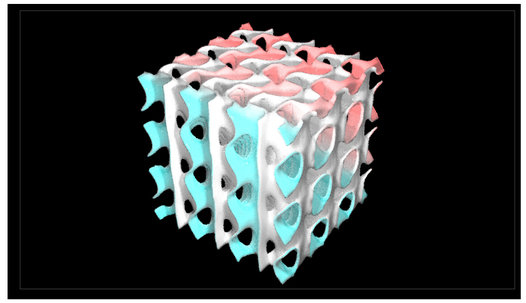


Fig 1. Variation in co-efficients A, B, C in the equation:
*A*sinxcosy + B*sinycosz + C*sinzcosx = 0*
This creates lattices with different anisotropy and density.



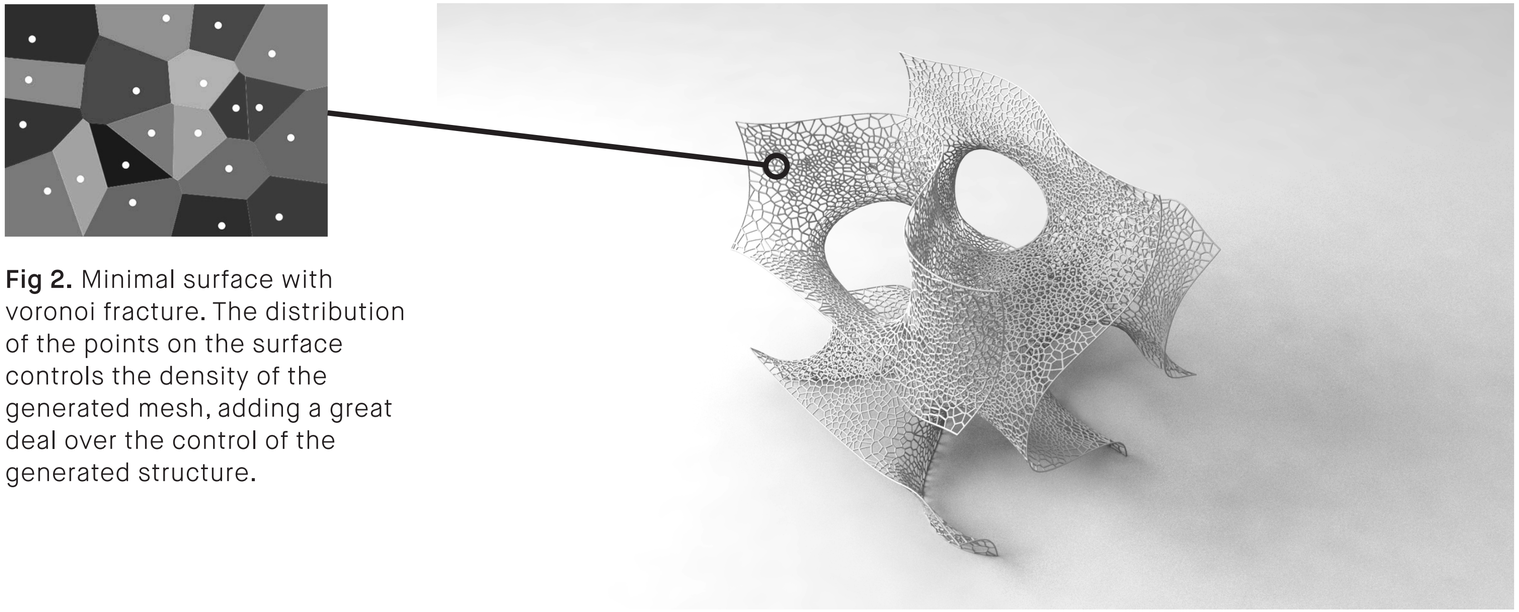


Fig 2. Minimal surface with voronoi fracture. The distribution of the points on the surface controls the density of the generated mesh, adding a great deal over the control of the generated structure.

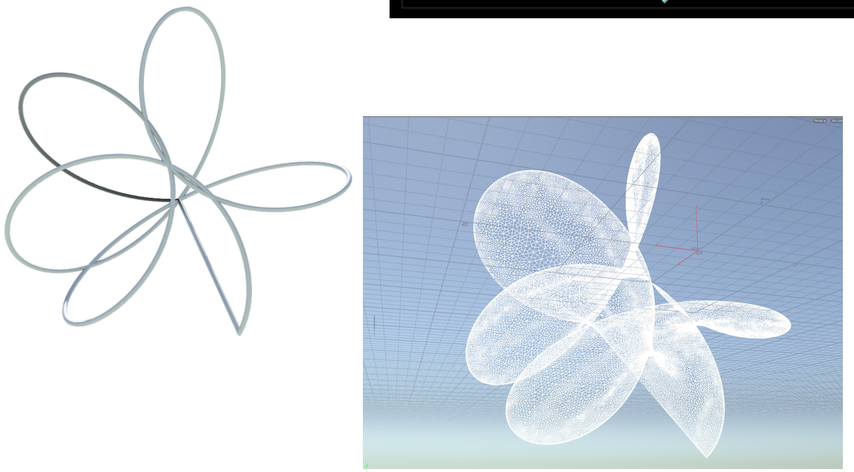


Fig 3. Minimal surface (above right) for a torus knot (above left).

1. Michielsen K, Stavenga D. Gyroid cuticular structures in butterfly wing scales: biological photonic crystals. Journal of the Royal Society Interface. 2008;5(18):85-94. doi:10.1098/rsif.2007.1065.

2 Sebastian C. Kapfer, Stephen T. Hyde, Klaus Mecke, Christoph H. Arns, Gerd E. Schröder-Turk, Minimal surface scaffold designs for tissue engineering, Biomaterials, Volume 32, Issue 29, October 2011, Pages 6875-6882, ISSN 0142-9612, https://doi.org/10.1016/j.biomaterials.2011.06.012.

3. S. Gómez, M.D. Vlad, J. López, E. Fernández, Design and properties of 3D scaffolds for bone tissue engineering, Acta Biomaterialia, Volume 42, 15 September 2016, Pages 341-350, ISSN 1742-7061, https://doi.org/10.1016/j.actbio.2016.06.032.

I. MINIMAL SURFACES

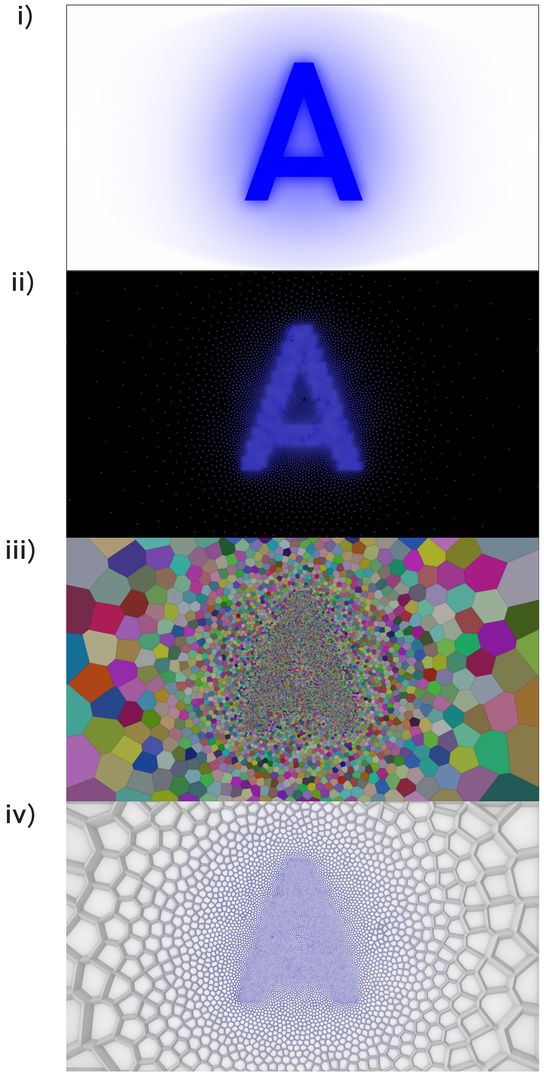


Fig 4. Steps in voronoi fragmentation. An image (i) is used to generate points (ii). These points determine the partitioning of the surfaces (iii), which can then be used to generate a mesh (iv), with variable density and porosity. This process can be used to intuitively control the density of a mesh across a surface, by simply 'painting on' density.

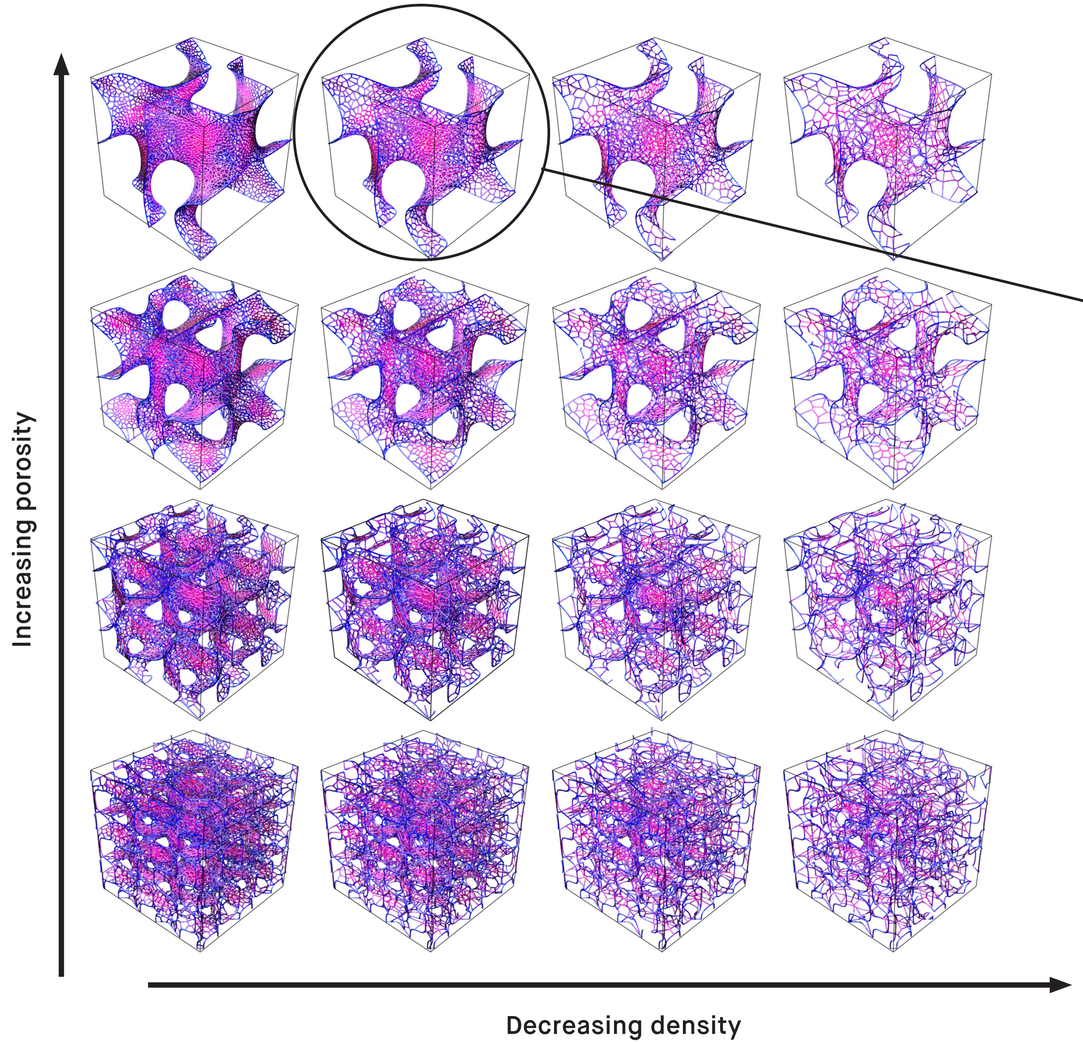


Fig 5. Prototyping and iteration. Many different scaffolds with slightly different parameters can be rapidly generated allowing an optimum structure to be selected.

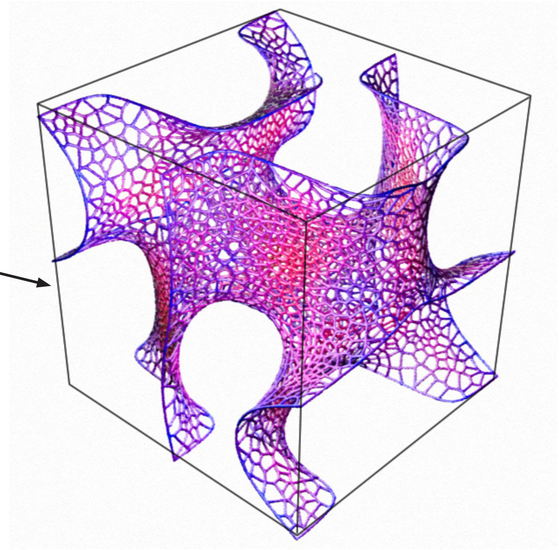
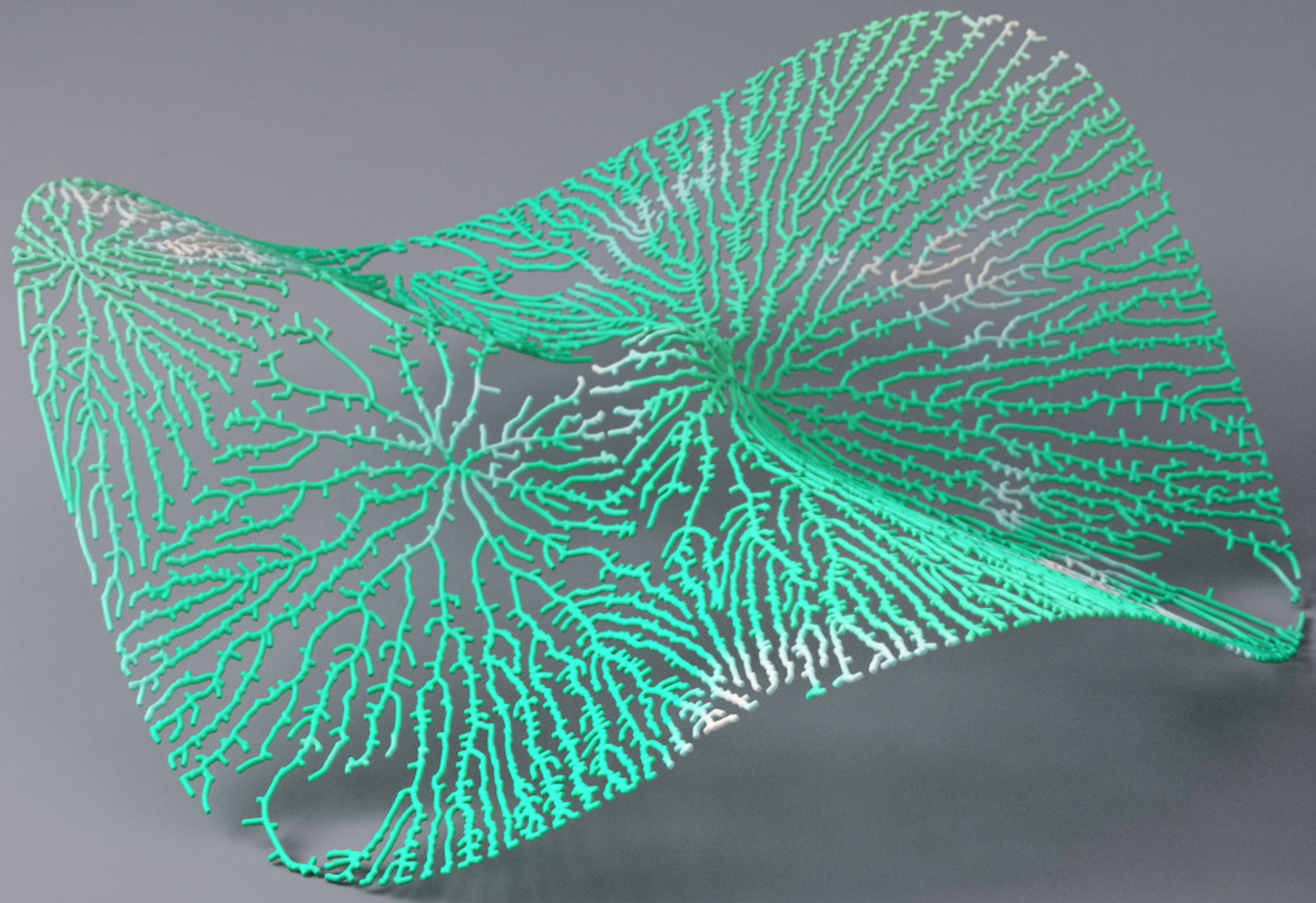
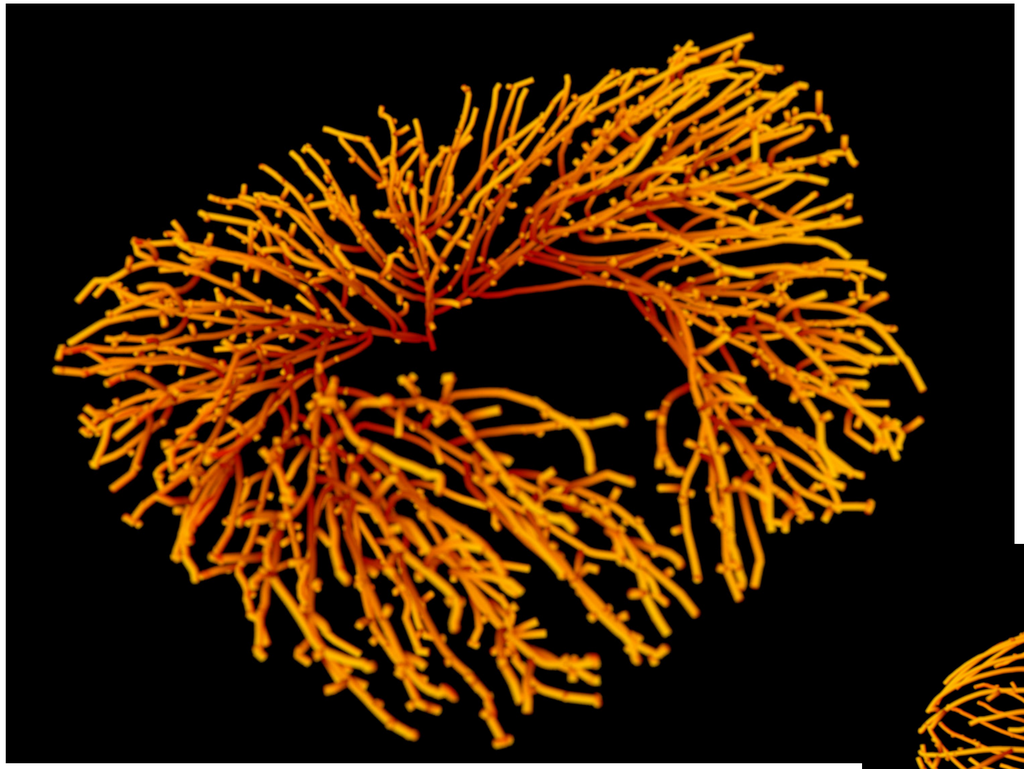
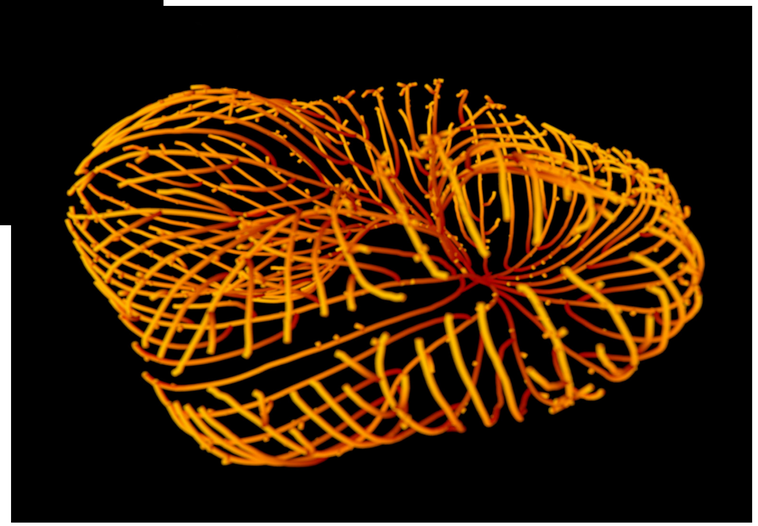


Fig 6. The selected scaffold can then be tested either by 3D printing and mechanical testing, or finite element analysis using software.



IIa. GROWN STRUCTURES





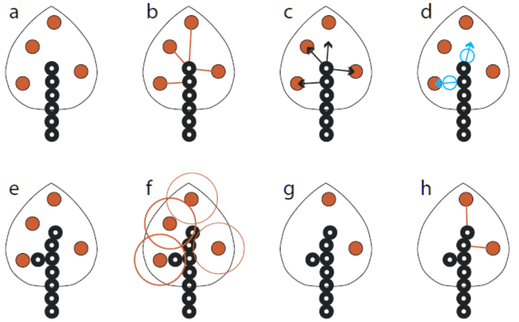
^ Fig 1a and > 1b. Space colonisation in a deformed torus.

The algorithm can be applied to growth vessels either within the volume (1a), or on the surface (1b). By controlling the density of the seed points, one can control the architecture of the vessel growth.

SPACE COLONISATION

The ability to create 3D, vascularised tissue remains a difficult challenge. Success would have far reaching consequences.

Current methods in bio-printing often use very crude models of blood vessels that are in no way biomimetic (1). Algorithms, such as space colonisation demonstrated here, can be used to rapidly create vascular networks that mimic those in nature (Fig 1). The density of the vascular bed can be controlled with the density of the food points (Fig 2) or could be controlled with perfusion maps of the desired tissue.



^ Fig 2. Steps of space colonisation.

Point growth of the seed points (black) is dependant on the vector towards the food points (orange). A new point is placed on this vector. If sufficiently close, the seed point is removed; the algorithm proceeds until all food points are killed or there are no more points within the search radius.

1. Kolesky, D. B., Truby, R. L., Gladman, A. S., Busbee, T. A., Homan, K. A. and Lewis, J. A. (2014), 3D Bioprinting of Vascularized, Heterogeneous Cell-Laden Tissue Constructs. Adv. Mater., 26: 3124–3130. doi:10.1002/adma.201305506

IIb. GROWN STRUCTURES

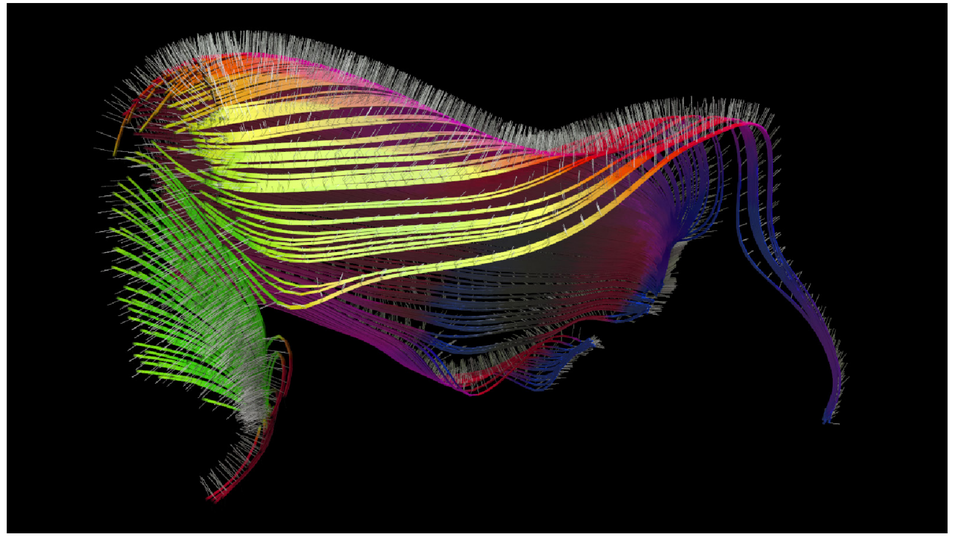


Fig 3. Fibres grown along a surface. The normal of each point is indicated.

REACTION DIFFUSION

Reaction diffusion systems are mathematical models that can be used to represent physical phenomena. They can be used to create the flowing organic patterns found in nature. Using reaction diffusion, convoluted continuous tubes can be made to fill a space (Fig. 6), offering an alternative to space colonisation systems for creating vascularised tissue.

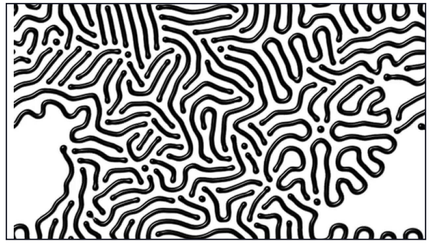


Fig 5. A typical reaction diffusion pattern.

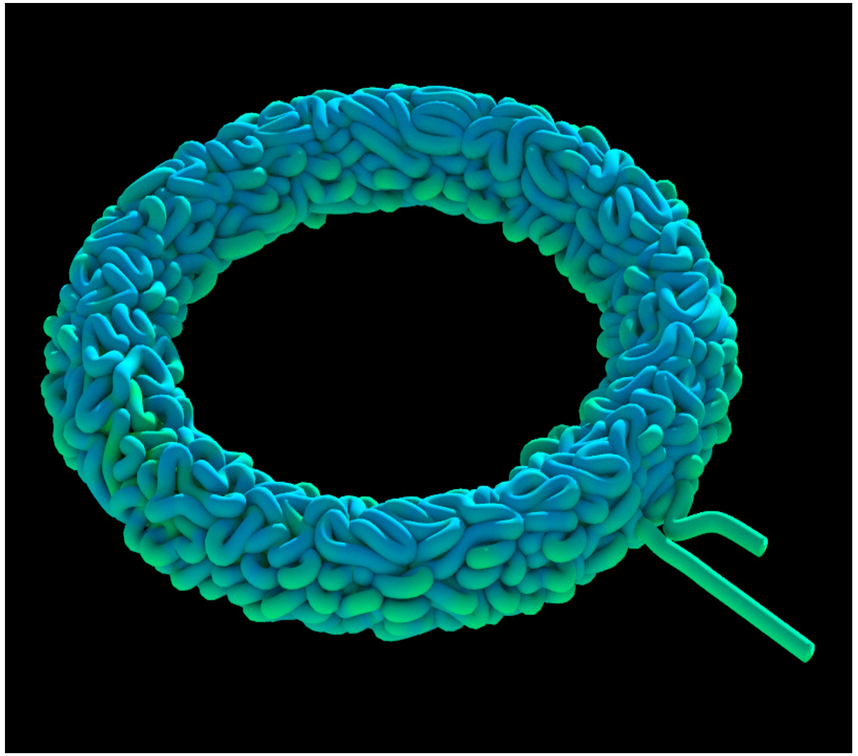


Fig 6. Reaction diffusion within the volume of a torus, the two unjoined ends of the tube are visible.

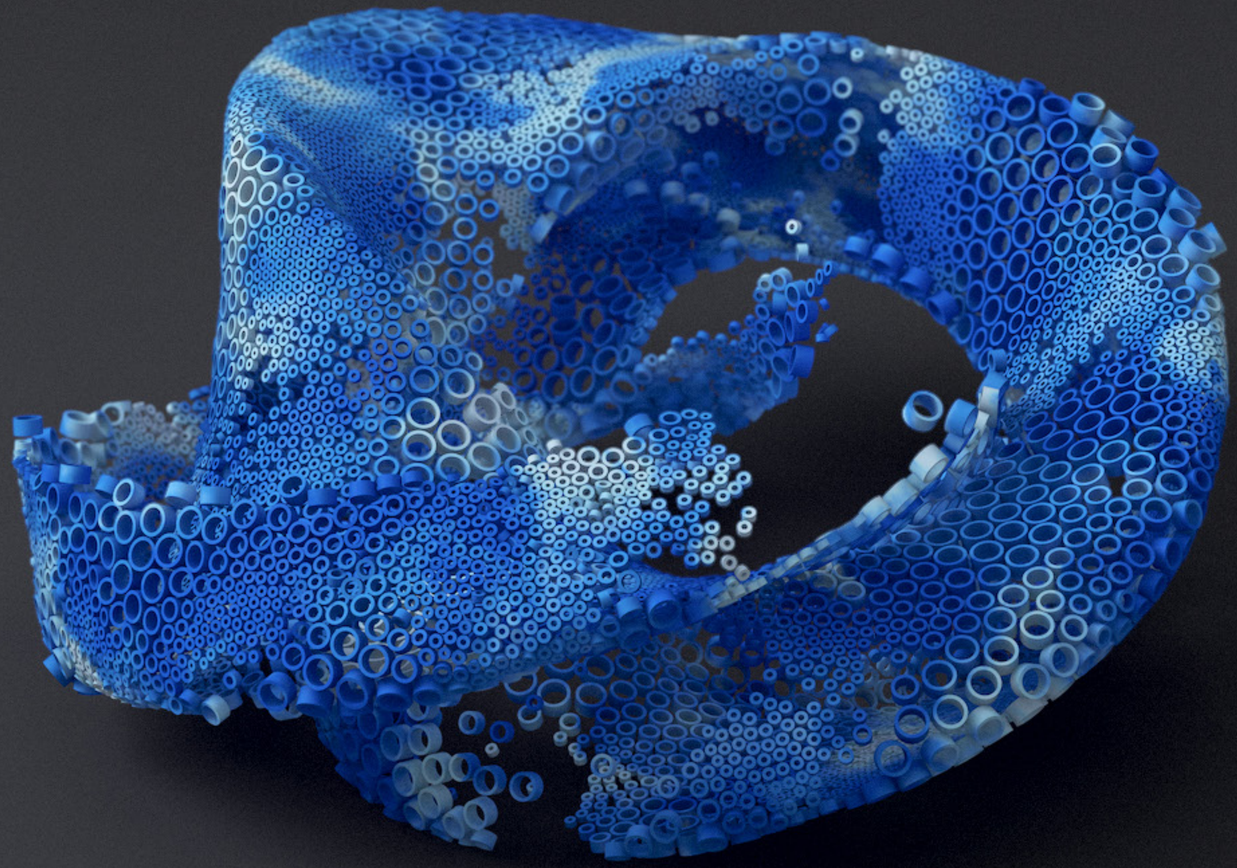
FIBRE GROWTH AND ORIENTATION

Non-intersecting fibres can be grown along any surface (Fig. 3) with control over the orientation of the fibres, enabling mimicry of collagen fibres in muscle (2).

Alternatively, fibres can be created throughout a volume. A single slice (Fig. 4) somewhat mimics the microscopic structure of bone.

Fig 4. A slice from a volume showing the aligned orientation of fibres.

2. Rules of tissue packing involving different cell types: human muscle organization. Sánchez-Gutiérrez D, Sáez A, Gómez-Gálvez P, Paradas C, Escudero LM. Sci Rep. 2017 Jan 10;7:40444. doi: 10.1038/srep40444



III. CONTROLLED VARIATION IN DENSITY & POROSITY

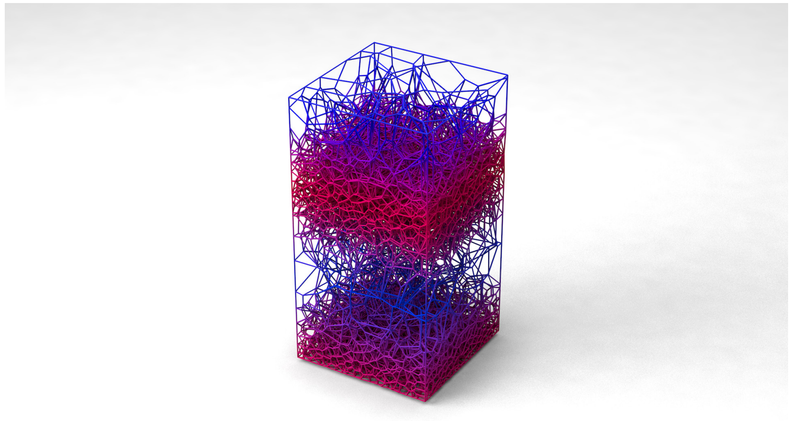


Fig 1. Variation in density in the y axis. Density varies from high (pink), to low (blue).

Manufactured materials are typically homogeneous and do not replicate the spatial variation present in nature. Tissues have heterogeneous distributions of their component cells. In order to replicate tissues, the distribution of the material must be controlled in each dimension with gradual variation if necessary.

Controlling the density of the structure can lead to new bulk properties and anisotropy. For instance, the structure in Fig 2 could be compressible along its long (y) axis and less compressible in the x and z directions. This is a direct result of controlled variation in density, rather than a property of the material.

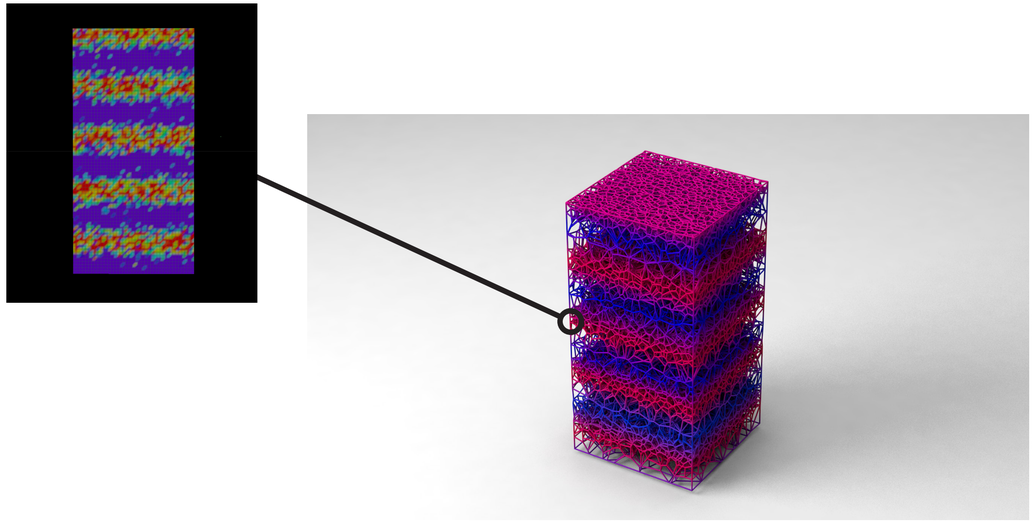


Fig 2. Density map and the resulting 3D structure.

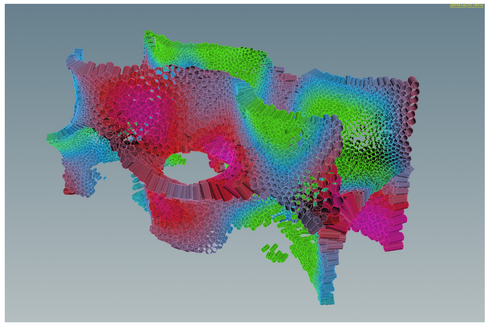


Fig 3. The spatial variation of the porosity, ranging from green (smallest pore size) to red (largest pore size).

Porosity can be controlled by generating tessellating tubes on a structure. The size of the tubes, and therefore the porosity, can be controlled with a coloured map on the surface (Fig 3). The tubes are orientated to be perpendicular to the surface. Any repeating unit can be used to tessellate on the surface, and the orientation relative to the surface can easily be changed (Fig 4).

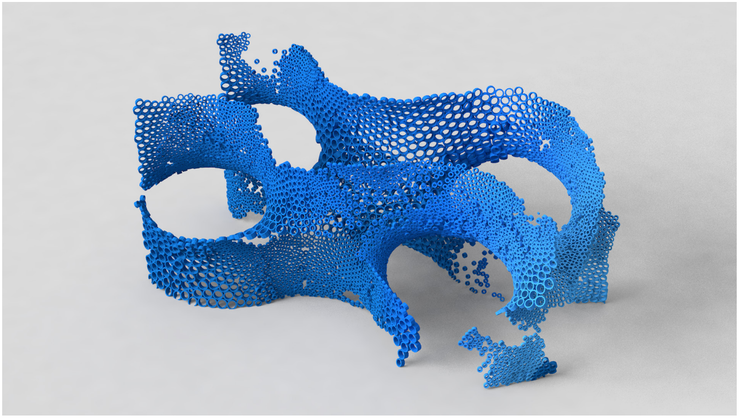


Fig 4. The resulting 3D structure, comprising tubes perpendicular to a minimal surface.

CASE STUDY: TRACHEAL STENT

To demonstrate the principles above, I produced a tracheal stent that had a controlled spatial variation in density and porosity using CT scans (Fig.1). The model needed to have flexibility and the rigidity of the trachea, with the density variation mimicking the tracheal rings. The resulting model was printed with a photo-coaguable polymer (Fig. 3).

Presented at the Royal College of Surgeons, London in 2016. Awarded the Grant Bates prize at the ENT UK 5th Foundation Conference.

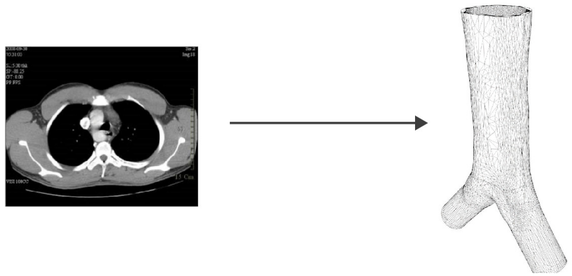


Fig. 1. CT scans were used to determine the dimensions of the model.

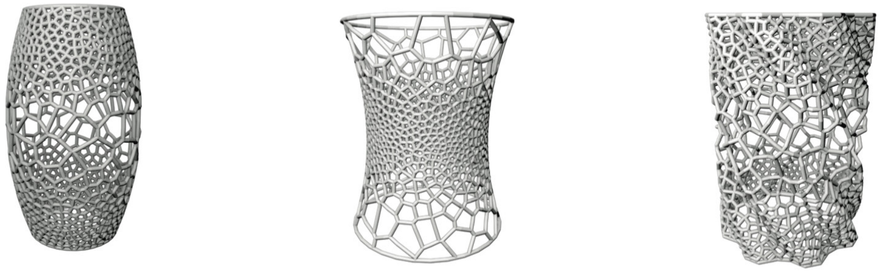


Fig 2. Different stent designs

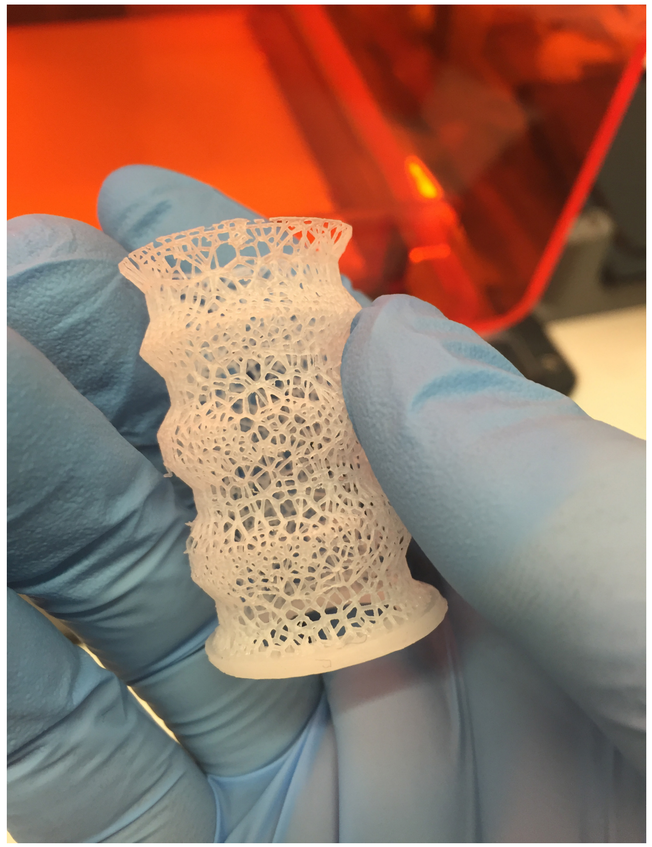


Fig 3. The 3D structure printed using SLA.

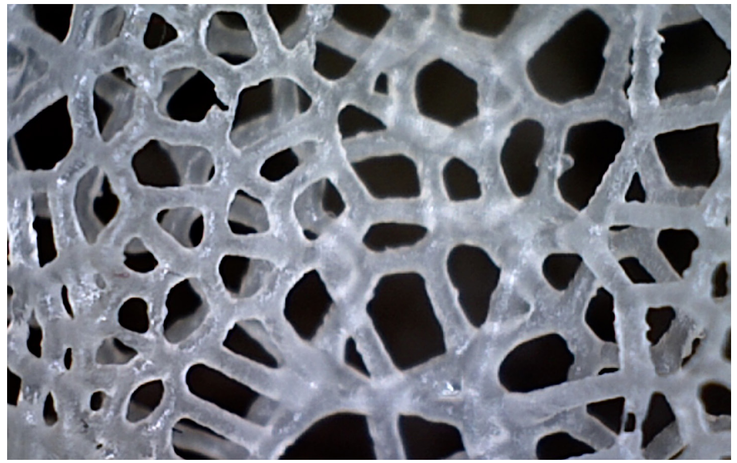
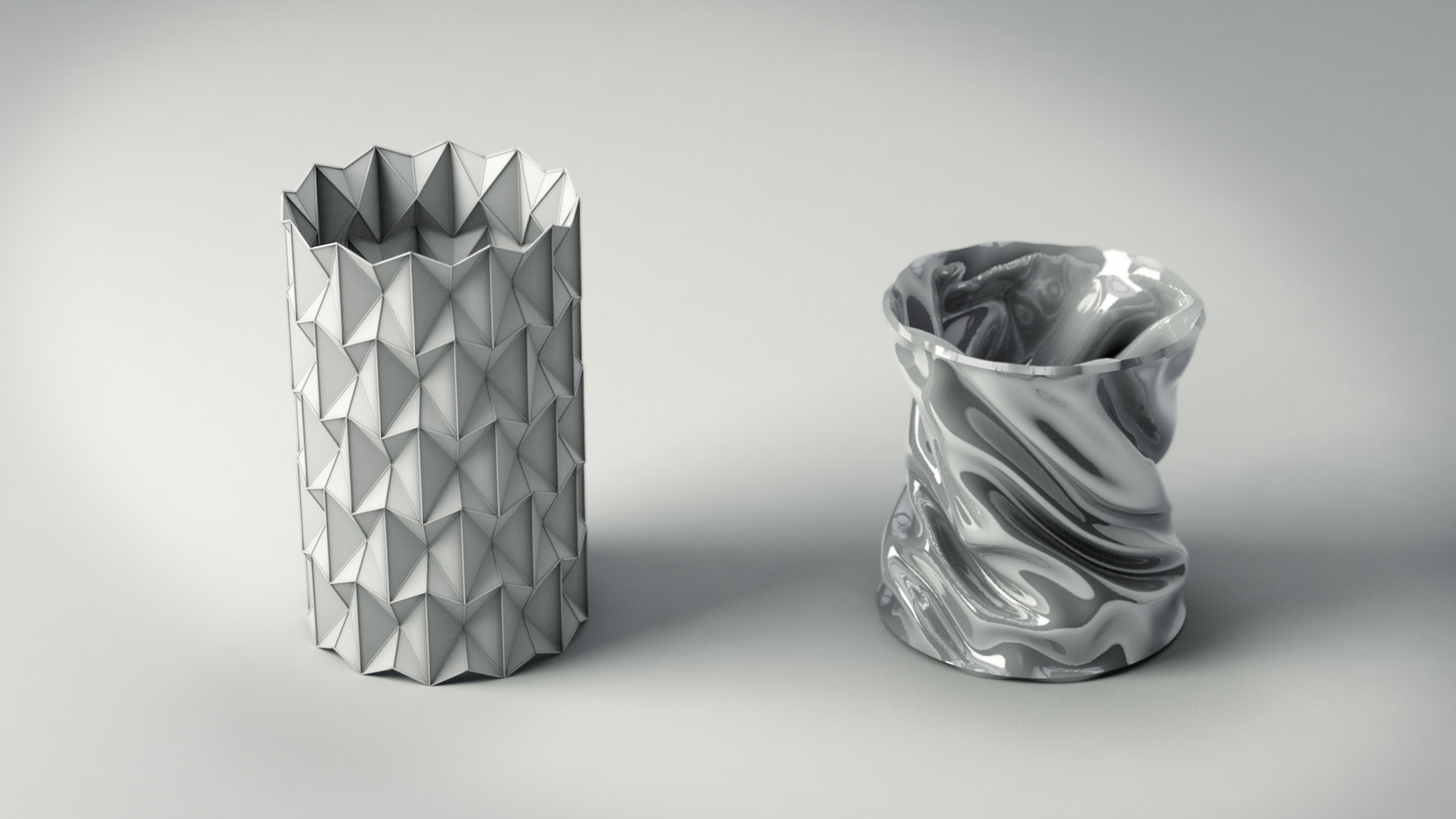
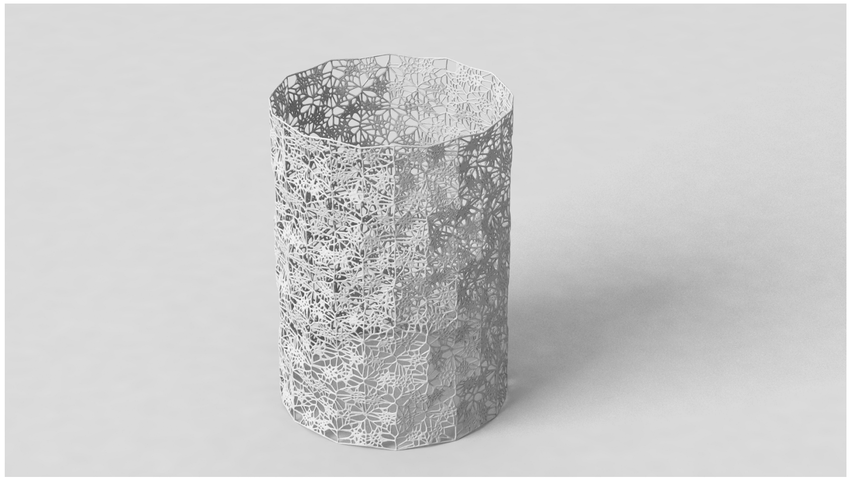


Fig 4. Magnified (x10) view showing the variation in density.



IV. FOLDING & 4-DIMENSIONAL TRANSFORMATION



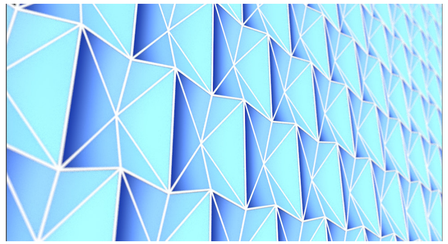
^ **Fig 1.** A folding stent with lower density at creases

^ **Fig 2.** An example of modular origami.

ORIGAMI-LIKE FOLDING

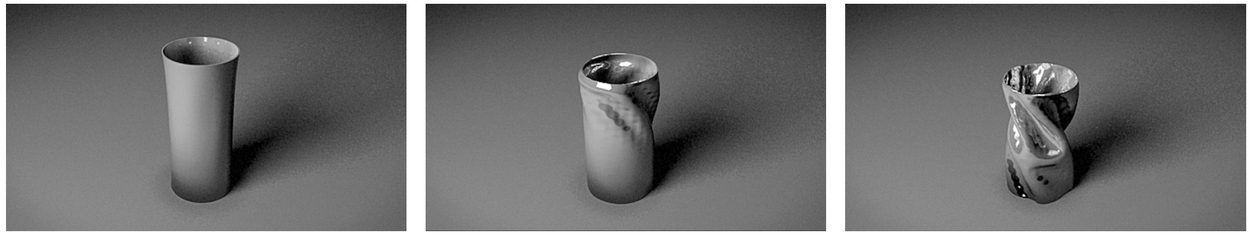
4D transformation (1) refers to structures which change shape with time, an exciting prospect in tissue engineering (2). This concept may enable responsive scaffolds which conform or change within the body when exposed to certain stimuli (3).

In modular origami, simple repeating units of folding paper (Fig 2) are combined to create complex collapsible structures. These principles could be applied to make scaffolds that can be compressed and then expand over time, like the stent modelled here (Fig 4).



^ **Fig 3.** A repeating unit cell in a planar arrangement. This could be used to create structures that can be folded and then exert an outward force in two dimensions.

^ **Fig 4.** Different structures can be rapidly produced by varying the number of folding unit cells in each dimension

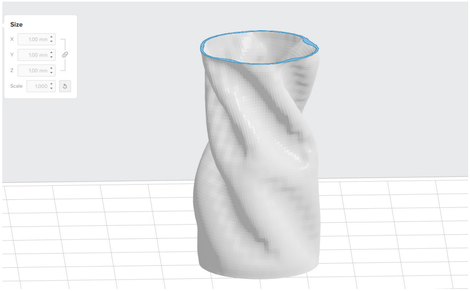


^ **Fig 5.** Cloth deformation of a tube in sequence.

CLOTH SIMULATION

Cloth simulations deform meshes in a manner that simulates physical cloth (Fig 5). This is a non-destructive process and the original structure can be recovered as the mesh relaxes. This could enable structures to be printed in a contracted, deformed state that could then resolve to the desired structure after manufacture or within the body (Fig 6).

A compressed structure could be used in minimally invasive surgery, or to optimise the use of a limited manufacturing area.



^ **Fig 6.** Print model in the contracted state

1. Tibbits S. 4D printing: multi-material shape change. Archite Design. 2014;84:116–21. doi: 10.1002/ad.1710.

2. 4D Bioprinting for Biomedical Applications. Gao, Bin et al. Trends in Biotechnology , Volume 34 , Issue 9 , 746 - 756

3. 4D bioprinting: the next-generation technology for biofabrication enabled by stimuli-responsive materials. Li YC, Zhang YS, Akpek A, Shin SR, Khademhosseini A. Biofabrication. 2016 Dec 2;9(1):012001.