3D Printing of Magnetic Multi-Material Hydrogels

IIB Project Technical Milestone Report
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EXECUTIVE SUMMARY

In this project, I aim to investigate, optimise and synthesise a novel class of soft, printable, magnetically-responsive, biocompatible materials, suitable for use in a mould for an *in vitro* lung model. Actuation of the lung by an external electromagnet will be used to mimic the mechanics of breathing, and seeding of the material with epithelial cells will allow for investigation of cell proliferation on the organ. As of the beginning of Lent term, the materials for the magnetic fibres have been selected after a series of experimental investigations, and work on the hydrogel component will begin shortly. The materials developed in this project have a variety of applications in both academia and industry, with organ modelling being a rapidly developing field for organoid studies, personalised and regenerative medicine, organ-on-a-chip technology and soft robotics.

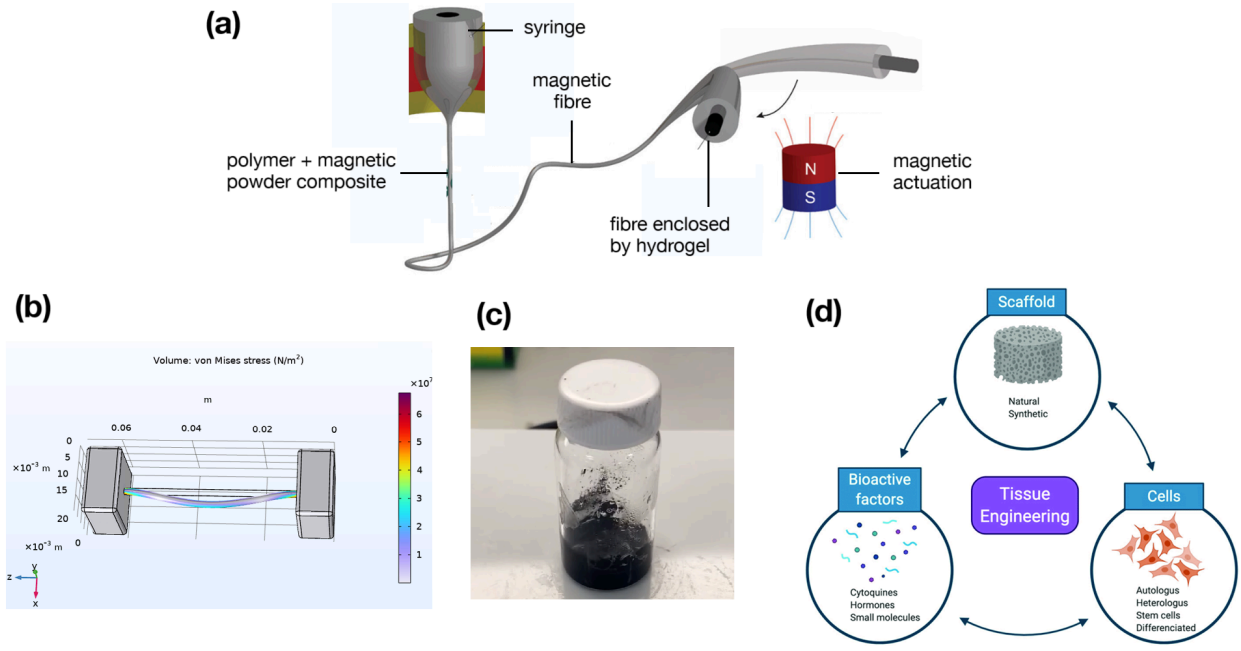


Figure 1. Overview of project, showing some specific components.

(a) Sequence of processing steps for the main materials: extrusion of magnetic fibre and unification with hydrogel. **(b)** Computational modelling of the fibre mechanics. **(c)**

Experimental synthesis of the fibre solution. **(d)** Typical application: the interplay between the components in tissue engineering.

BACKGROUND

Organoid technology is a rapidly developing field that aims to recreate the complex structure and function of human organs in a miniaturised, *in vitro* system. Organoids have the potential to revolutionise drug discovery and development, disease modelling, as well as personalised and regenerative medicine. These novel approaches to medicine tailor treatment to the individual patient's unique genetic characteristics, repair or replace damaged or diseased tissues and organs. Organoids can be used to study the effects of drugs and treatments on individual patients, and to develop new therapies for diseases such as cancer and heart disease.

There are a number of challenges that need to be overcome in order to make organoids a viable clinical tool, primarily at the materials selection level. Materials must be:

1) biocompatible and mimic the structure and function of human tissues.
2) manufactured at a size small enough to be mass-produced and affordable.
3) integrated with methods for accurately measuring the response of cells.

This project aims to produce a model lung organoid capable of fulfilling these challenging constraints, suitable for scale-up or repurposing into further biomedical applications.

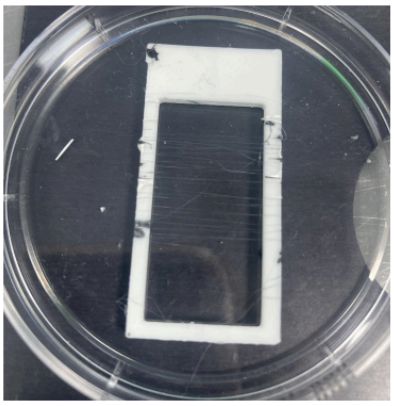
The chief design focus of the projects is around responsive materials, which are materials whose shape can be influenced in a controllable manner by means other than externally-applied mechanical forces, such as changes in temperature, pH, electric and magnetic fields. Many materials with these properties are unsuitable for biomedical applications, such as semiconductors and thin-film materials, but a class of materials known as hydrogels provides an alternative route to this functionality. A hydrogel is a soft solid material formed when a biopolymer forms a single-phase gel in water above (for UCST hydrogels) or below (for LCST hydrogels) a critical temperature, and these materials are known to be highly biocompatible, making them an excellent choice for use in an organ model. In order to accurately reflect the dynamic operating range of *in vivo* bodily tissues, the model organ must be capable of changing its shape remotely. A practical option for achieving this is to use magnets to deform the material, however hydrogels do not possess any magnetic activity in their native state, and a composite of magnetic fibres with the hydrogel as a matrix must be developed. The use of fibres adds additional constraints on the material properties as the mechanical interactions between the hydrogel and fibres must be accounted for.

In order to be suitable for extrusion bioprinting, the rheological properties of the hydrogel ink, including gelation kinetics, surface tension, viscoelasticity, shear-dependent and time-dependent viscosity, are important design parameters. With

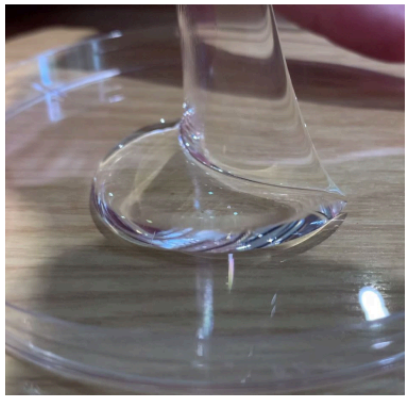
suitable choices of biopolymer, incubation temperature and addition of electrolytes, the optimal composition for printing can be determined experimentally. The hydrogel must also be sufficiently flexible and strong to not be cut by the magnetic fibres on deformation. The magnetic fibres must be produced by a spinning method, in which magnetic particles are mixed into a polymer-laden solvent and extruded steadily to form a bed of parallel, homogeneous fibres. Tight control over the geometry of the fibres is required to produce consistently-predictable deformation in a magnetic field. Due to the cyclic nature of breathing in a lung model, fatigue loading must be accounted for, significantly lowering the tolerant range of stresses allowed in the fibres.

The use of composite and synthesised materials calls for a detailed investigation when seeking to characterise and optimise the nonlinear properties of the material, combining both computational modelling and experimental approaches for collecting data. Experimental work for this project will be undertaken in the Nanoscience Centre, primarily in the biolab clean room, while computational studies may be done in CAD packages such as SOLIDWORKS and COMSOL remotely.

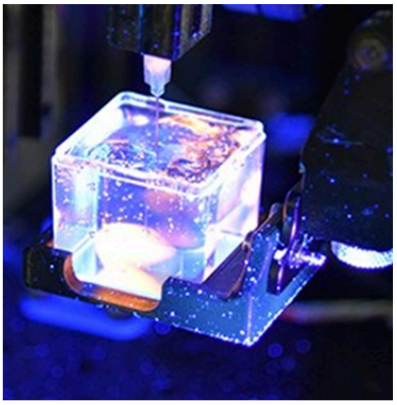
PROJECT GOALS



(a) Michaelmas



(b) Lent



(c) Easter

Figure 2. The main goal of each term's work for the project.

The timeline of the project is divided clearly into three parts:

1) Michaelmas: designing the magnetic fibres.
2) Lent: designing the hydrogel.
3) Easter: printing with cell culture

In Michaelmas, the goal was to find a magnetic fibre composition suitable for spinning, testing a variety of polymers to make the fibres. A reliable technique for spinning in a consistent manner should be developed, and the fibres should be tested in their responsiveness to a magnet.

In Lent, the goal is to find a hydrogel with compatible mechanical properties for the magnetic fibres selected. The hydrogel should be synthesised in the sol state (liquid), and cross-linked in the suspended fibres to enclose them with the gel state (solid) hydrogel. The magnetic responsiveness should then be tested to check for structural integrity and reliable deflection.

In Easter, the best hydrogel will be used as part of a cell proliferation mixture and printed into a specified shape.

CURRENT WORK

Currently, a good candidate for the magnetic fibre material has been selected after a series of laboratory tests. This involves a binary solvent of *N*,*N*-dimethylformamide (DMF) and acetone in a 0.85 : 0.15 volumetric ratio. Polystyrene was chosen as the polymer, added at 20% by weight, and iron oxide powder was used as the magnetic component at 30% by weight. After warming and stirring for approximately one hour, this composition produced readily spinnable fibres. A programmable robot arm was used to steadily extrude the fibre through a syringe onto a spinner to create the fibre matrix, which could then be examined under a light microscope. The diameter of the fibres was regularly in the vicinity of 10 micrometres, and the consistency of the fibres was sufficient to ensure a reliable performance.

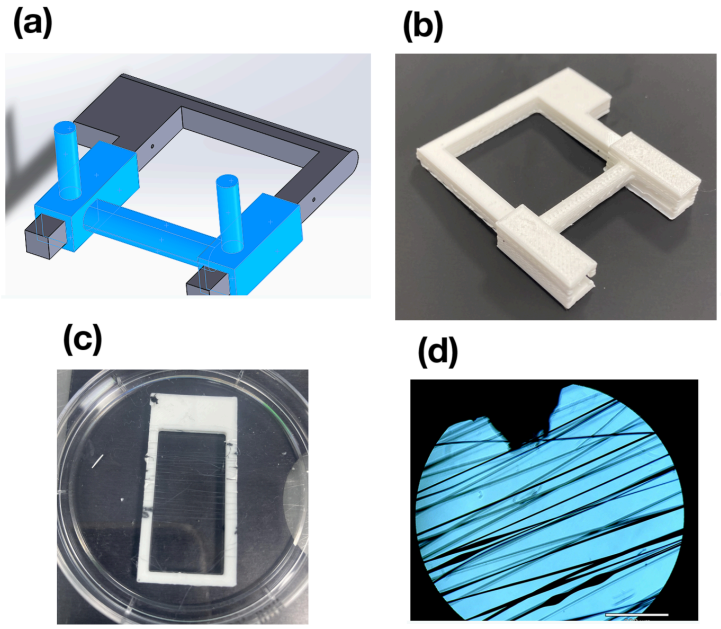


Figure 3. Components produced so far as part of the project.

(a) CAD model of newest frame. The moving section (highlighted blue) is used to vary the effective length of the fibres. **(b)** 3D printed frame. **(c)** Original frame with fibres spun across, forming a bed of fibres. **(d)** MIcroscopic view of fibres.

PLANNED FUTURE WORK

Some of the initial goals set for the end of Michaelmas term were not met as of today, and therefore the work to be done at the start of Lent will involve finishing off these targets. This primarily includes testing some other fibre materials (polyurethane), but also finding the optimal spinning rate for the robot arm when forming the fibres onto the frame. In the meantime, a new frame has been designed with flexibility in mind, which allows for variation of the fibre length, to be printed at the earliest instance.

I will undertake significantly more experimental work in the term to come, as I made overall insufficient progress in Michaelmas, primarily due to not visiting the laboratory enough. During Lent term, I will attend the Nanoscience Centre every weekday for approximately 3 hours per day in the afternoon, after performing any software-only analysis from home in the morning to use the time in the lab most efficiently. I will also be attending an open workshop on 3D bioprinted gelatin implants in Cambridge on Tuesday 23rd January, which will provide valuable insights into the some of the applications of this project, and I will have the opportunity to discuss with professionals in the field and enquire about potential ideas for improving the material selection process.

The main focus on Lent term will be the hydrogel synthesis. A first formulation will involve a composition of 6% gelatin and 1% alginate in water, which will be prepared in bulk once the alginate is purchased from the chemical supplier. This will be used as the basis composition for testing the properties of the magnetic fibre composite. An electromagnet purchased recently will be used to induce consistent forces on the fibres. The bending angle and maximum deflection of the fibres in the gel will be measured and this data will be used to inform any necessary adjustments to the composition of the matrix.

Towards the end of the Lent term, once a hydrogel is selected, it will be tested in the bioprinter Printer.HM, available in the biolab. Initially a simple shape will be made, aiming to work towards the more complex geometry of a lung model in the Easter term.

CONCLUSIONS

In conclusion, this project aims to develop a model lung organoid capable of fulfilling the challenging constraints of biocompatible, miniaturised, and remotely deformable materials. The current work has focused on designing the magnetic fibres, and a good candidate material has been selected. The next step is to design the hydrogel and test its compatibility with the magnetic fibres. This will be done in Lent term, and the results will be reported in the next progress report.

REFERENCES AND ATTRIBUTION

Figure 1(a) adapted from
H. Banerjee, A. Leber, S. Laperrousaz, R. La Polla, C. Dong, S. Mansour, X. Wan, and F. Sorin, “Soft multimaterial magnetic fibers and textiles,” Adv. Mater., vol. 35, p. e2212202, Aug. 2023

Figure 1(d) sourced from
L. R. Doblado, C. Martinez-Ramos, and M. M. Pradas, “Biomaterials for neural tissue engineering,” Front. Nanotechnol., vol. 3, Apr. 2021.

Figure 2(c), as well as documentation on Printer.HM, adapted from,
I. M. Lei, Y. Sheng, C. L. Lei, C. Leow, and Y. Y. S. Huang, “A hackable, multi-functional, and modular extrusion 3D printer for soft materials,” Sci. Rep., vol. 12, p. 12294, July 2022.