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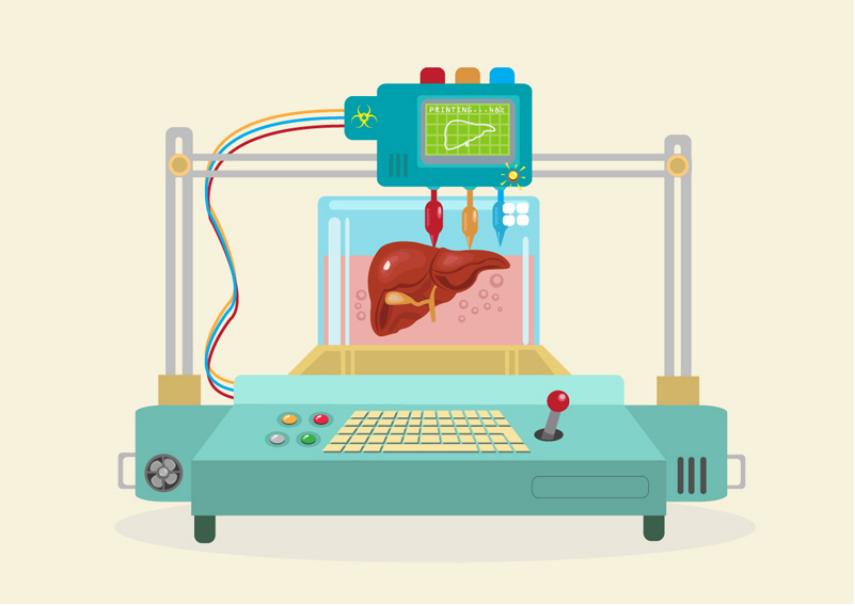
3D bio-printing for medical and enhancement purposes



IN-DEPTH ANALYSIS

Science and Technology Options Assessment

EPRS | European Parliamentary Research Service
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PE 614.571

3D bio-printing for medical and enhancement purposes

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Abstract

3D bio-printing is defined here as the use of 3D printing technology for applications related to the body, whether the products themselves include biological material or not, and whether their purpose is medical or not. It includes any application for rehabilitating, supporting or augmenting any kind of biological functionality. The impacts of 3D bio-printing are uncertain, and it is not clear which actions may be required to foster responsible development of the technology.

A STOA study 'Additive bio-manufacturing: 3D printing for medical recovery and human enhancement' responded to these uncertainties by describing the state of the art and future development prospects of 3D bio-printing technology, analysing their wide-ranging impacts – including social, ethical and economic aspects – and identifying key policy challenges along with options to respond to them. Key challenges and responsive options were identified in the approach to regulation, in managing the distribution of costs and benefits, and in the role of citizens in technology development.

This In-depth Analysis draws upon the findings of the STOA study, summarising and reflecting upon its key findings. The conclusions highlight key trends and offer further reflections on the study in the context of responsible research and innovation.

PE 614.571

This document presents the key insights of the STOA project 'Additive bio-manufacturing: 3D printing for medical recovery and human enhancement'. The project was requested by the European Parliament's Science and Technology Options Assessment (STOA) Panel. It was carried out by the European Technology Assessment Group (ETAG), led by the Institute for Technology Assessment and Systems Analysis at Karlsruhe Institute of Technology (KIT/ITAS) and including the Institute of Technology Assessment of the Austrian Academy of Sciences (ITA/OEAW), the Rathenau Institute, the Danish Board of Technology (DBT) Foundation and France-based Responsible Technology (RT). It was managed by the Scientific Foresight Unit (STOA) within the Directorate-General for Parliamentary Research Services (DG EPRS) of the European Parliament.

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Scenario illustrations by LUC – le Laboratoire d'Usages Collaboratifs – luc-lab.com

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1. Introduction

3D printing refers to the production of physical artefacts by the gradual **addition** of layers of material. Also referred to as additive manufacturing, this contrasts with traditional manufacturing techniques whereby material is **subtracted** (removed by cutting, drilling etc.), to create products. The technology has developed significantly through the 1990s and 2000s. At first, the expense and skill requirements restricted their use to industry applications such as rapid prototyping. In recent years, however, the technology has become cheaper, smaller and easier to operate, and is now accessible to a wider range of people through the purchase of a domestic 3D printer, or using local shops and 'maker spaces'.

The 3D printing sector has proven its commercial viability and is now associated with several applications, from the production of small parts for vacuum cleaners to high-spec components for space shuttles. It is often credited for its material efficiency and support for creativity. Since it is well suited to decentralisation of production and individual customisation, and enables 'do-it-yourself' (DIY) production of items that would traditionally require significant skills and investment, 3D printing is also associated with the democratisation of design and production. While most 3D printing applications use plastic, metal or ceramics as 'ink', they can also use textiles, foods, and other biological materials.

The technology is already used in some medical domains, such as dentistry, and many scientists are now exploring methods of printing biological materials. While the term 'organ printing' was only introduced in 1999, by 2003 Mironov et al. felt 'safe to predict' that they would be as widely used for biomedical research in the 21st century as the electron microscope was in the 20th century. Even if reports about lifesaving 3D-printed hearts are certainly premature, some of the most eagerly anticipated developments in the sector fall into the wider category of health and medical care.

3D-printed materials allow medical doctors to take advantage of detailed scans by using them to fabricate models of patients' bodies for practising procedures or teaching purposes. They can build accurate frames on which to construct titanium parts for reconstructive surgery, as well as surgical guides, knives and other tools to support specific medical interventions. Orthoses & prostheses (O&P, devices to support and replace limbs, respectively) could also benefit from 3D-printing technology, which is coupled with advanced imaging techniques to deliver products that are highly tailored to the individual patient and may offer better results than 'off-the-shelf' solutions. The same advantages apply to a wide range of moulds, supports and other items that are worn by the patient. Hearing-aid manufacturers were early adopters of 3D-printing technology. In the space of 500 days, the entire American hearing aid industry converted to 3D-printing.

3D printing technology could also be deployed for individually tailored drug delivery, with tablets designed and printed using porous materials that disintegrate according to a well-defined schedule, releasing the active ingredients embedded within them according to an optimal pattern. In the future, pharmacists may be able to combine all the drugs in a patient's prescription into a single tablet, adapted to their specific situation.

Appliances for 3D-printing food are already commercially available and have been used in nursing homes to offer more appetising fare to residents that have difficulties chewing and swallowing. While such printers face stiff barriers in market acceptance, customers may one day be able to print their own food that is tailored to their taste and texture preferences, as well as their nutritional (and perhaps even pharmaceutical) requirements.

There has been some clinical success with 3D-printed scaffolds being transplanted directly in the patient to encourage controlled bone, cartilage and skin growth, as well as more limited success in producing blood vessels, nerves, skin and bones outside the body. In 2008, Mironov et al. envisaged a future whereby the problem of organ shortages is resolved by 'industrial-scale robotic bio-fabrication of complex human tissues and organs'. While significant technical barriers to the production of tissues and organs remain, even minor advances can yield substantial benefits in producing materials for training, testing, education and experimentation purposes. Further success in producing viable organs from a

patient's own cells is not expected any time soon but, such success could one day resolve the challenge of timely identification of compatible organs for transplant.

As with many innovations in the biotech sector, 3D bio-printing may raise questions about standards and accessibility. Standards and approval procedures for medical devices are often more demanding than those for other products. Higher innovation costs can make life difficult for smaller biotech businesses and inflate the costs of new medical products and services.

3D printing is often considered a driving force in the decentralisation of manufacturing. Low costs coupled with speed, proximity and customisation make it an attractive option for many SMEs and individual households. In the context of 3D-printed surgical guides, prostheses and supports, for example, local production could take place at hospitals and doctors' surgeries rather than at distant laboratories. Such decentralisation could allow patients to benefit from more personalised treatment with fewer visits to the hospital and reduced waiting times. It may also see the emergence of a new generation of on-site 3D-printing medical professionals. On the other hand, the high levels of expertise required and tight controls over medical products may mean 3D-printing capacity develops within the existing laboratory infrastructure, ensuring survival of the centralised production model.

3D-printing has also been associated with the 'democratisation' of production, whereby substantial gains in accessibility are achieved through massive reductions in the financial and technical barriers to production. While some expertise and capital investment are required, they remain within reach of most enthusiastic amateurs. The same trend is now emerging for 3D bio-printing, and there is a growing trend of '3D-biohackers', that is, DIY biologists using 3D-printers to experiment outside the usual scientific, medical and commercial institutions.

Some innovations in medical 3D-printing may also be used for non-therapeutic purposes. For example, cosmetic surgeons can produce implants for 'body enhancement' procedures, and show potential clients detailed 3D-printed models of their post-operative bodies. There might also be opportunities for novel body art procedures. Since food and drugs both present large global markets, 3D-printing could be deployed in non-medical contexts such as recreational drugs and gastronomy. 3D-printing techniques may also be deployed for artistic purposes, such as Diemut Strebe's living piece, a 'recreation' of Vincent van Gogh's ear.

In July 2016, STOA launched the **Additive bio-manufacturing: 3D printing for medical recovery and human enhancement** project. The project followed STOA's foresight methodology, which begins with the identification of broad trends and their potential impacts, before moving on to the development of scenarios to support the exploration of possible futures and, finally, back to the present day and reflections on how to prepare for and shape the future.

The project team consisted of a consortium led by the Institute for Technology Assessment and Systems Analysis at Karlsruhe Institute of Technology (ITAS/KIT) and including the Institute of Technology Assessment of the Austrian Academy of Sciences (ITA/OEAW), the Rathenau Institute, the Danish Board of Technology (DBT) Foundation, and France-based Responsible Technology. Interim findings were presented to the STOA Panel in Strasbourg in May 2017. The project concluded in March 2018, and its findings were compiled into a single study report . This paper draws upon the study, summarising and reflecting upon its key findings.

The following section explains more about 3D bio-printing, its key techniques and applications. Section 3 describes some of the most important social, ethical, cultural, economic and environmental aspects of 3D bio-printing development that were identified in the course of the study, before Section 4 briefly explains the scenario approach adopted in the project. Section 5 outlines the key challenges identified by the project team, as well as the options they presented for responding to them, before the final section offers some concluding reflections. Boxes are provided throughout the document, guiding the reader to sections of the full report where the issues are discussed in more detail.

2. 3D bio-printing definition, techniques and applications

3D bio-printing usually refers to techniques that use 3D printing in the production of biological material. This might conjure images of printing ready-made biological materials, as per the organ printer illustrated in figure 1. Setting aside the fact that such techniques are far beyond current capabilities, such a printer would more likely work by producing a structure which could then serve as a scaffold on which cells can be cultivated.

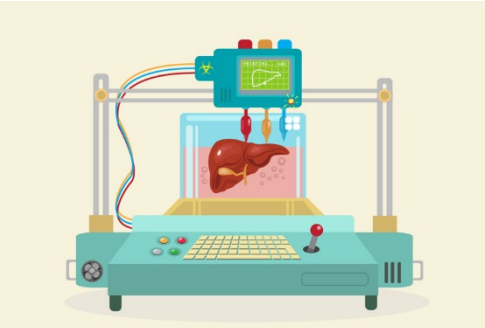

Figure 1: Imagined 3D bio-printer
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In the present project, a more inclusive definition of 3D bio-printing is adopted, including any application that uses 3D printing to produce any kind of artefact for some biological use, whether or not the artefact itself is biological. These applications usually have a therapeutic, medical purpose, but other applications which have some leisure, artistic or human enhancement purposes are not excluded. As such, the definition includes supports and frames that are used internally or externally to rehabilitate, support or augment biological functionality, as well as the use of 3D printers for the production of food or drugs.

Techniques

Several techniques come under the broad umbrella of 3D printing that can be used for medical and other biologically relevant purposes. The key unifying characteristic of all 3D printing techniques is that the artefact is produced by adding layers of material. This is what differentiates 'additive' from traditional 'subtractive' manufacturing. Developments in 3D printing are very closely linked to developments in digital imaging and modelling.

> An overview of 3D bio-printing techniques, including illustrations, is presented in section 2.1 of the study.

While some 3D printers are differentiated more by their branding than their technique, a wide range of approaches exists for accomplishing 3D printing, including the use of different materials and the application of different methods for following digital models to produce physical artefacts. The material is usually plastic, but other products are also used, ranging from metal compounds to edible food products. These materials can be introduced to the printer in solid, semi-solid, liquid or powder form, and can be manipulated by controlling movement, temperature, pressure, light and/or chemical processes to continually add new layers to the artefact until the digital model is reproduced in a physical form.

Applications

The study included a wide review of biologically relevant applications of 3D printing, before focusing upon three particular niches; O&P, dentistry, and tissue and organ printing. These three were selected to maximise the study's understanding and coverage of the most important issues that were identified in the early stages of the research. Here, an overview of some of the more interesting and promising application areas is presented. The illustrations are taken from the scenarios, which are described in section 4.

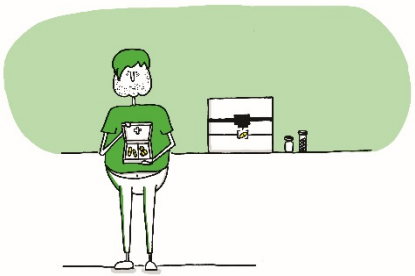
> Read more about application areas for 3D bio-printing in section 2.2 of the study. Further discussion of O&P, dentistry and tissue and organ printing is presented in section 5.

One area where 3D printing could have a major impact is in the production of surgical tools and other medical instruments. These applications build upon advances in medical imaging, allowing highly customised items to be designed and produced for individual medical procedures. They could include, for example, knives that have a particular profile for performing a specific task in an operation with a high degree of accuracy, or drilling and cutting guides to help surgeons work more precisely. 3D printing

could also be deployed to produce highly customised implants, such as plates and grafts. Here, the advantage is not only accuracy but also time savings, as the materials can be produced before surgery begins, and require less adaptation during the procedure. This can have several positive effects, including a less intrusive procedure for the patient and reduced fatigue and chance of human error amongst the medical team.

Besides instruments, doctors may also produce anatomically accurate models of a patient, which would allow them to practice for a specific operation, or could be used on a larger scale by medical students as part of their training, which may be more effective than using mass produced models or cadavers since they can, thanks to detailed medical imaging techniques, provide a closer resemblance to the patient. Such anatomical models could also be used to facilitate discussions about procedures with patients, and might even be used to produce 'before and after' mock-ups of a patient's body which could be useful for reconstructive, therapeutic or cosmetic surgery. Of course, the preparation of such models – as well as surgical tools and other medical instruments – could impose a significant financial and time cost.

Scenario illustrations by LUC – le Laboratoire d'Usages Collaboratifs



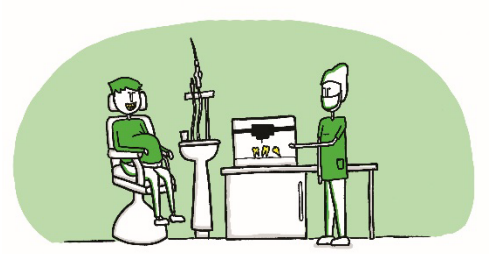
Scenario illustrations by LUC – le Laboratoire d'Usages Collaboratifs

Another interesting application for 3D printing is in drug delivery, with the production of tablets that are highly customised for individual patients. Indeed, multiple drugs could be 'printed' into a single tablet, with its shape and porousness altered to control the way that the tablet dissolves so that active ingredients are released into the patient's body at an appropriate rate or interval. This 'mass customisation' could significantly reduce the cost of producing personalised tablets for patients. These could respond better to individual patients' needs and, in combining all drugs into a single tablet, reduce the scope for human error. While few applications of these techniques are identified outside medical treatment, 3D printed delivery mechanisms might also be deployed in the production of recreational drugs.

Taking a strict definition of additive rather than subtractive manufacturing, robotic food production could be considered as a form of 3D food printing. Recently, however, food has been made by machines that more closely resemble the 3D printers described above. Three useful categories of material emerge; first, items that are readily printed such as cake frosting and purees. Second, traditional produce such as such as rice, fruit and meat including processed foods such as pasta. And finally, alternative products such as extracts from insects, fungi and algae. In the far future, these could pave the way for home food printers that allow consumers to print their meals, choosing the colour, shape, flavour and texture they prefer. Food printers might straddle the boundary between medical and non-medical applications by responding to medical needs from nutritional profiles to drug prescriptions. Practical examples include their use in German nursing homes for elderly people with chewing difficulties, who appreciate printed food as an alternative to pureed food. However, consumers with greater choice might be less willing to accept printed food products.

Scenario illustrations by LUC – le Laboratoire d'Usages Collaboratifs

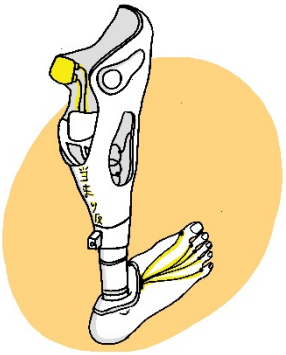
Hearing aid manufacturers were early adopters of 3D printing techniques. 3D printing is now the dominant method of mass producing individually customised shells which, to function well, must fit the ear very closely while providing an appropriate casing for several components.



Scenario illustrations by LUC – le Laboratoire d'Usages Collaboratifs

Dentistry has a significant potential for 3D printing applications because the site is more accessible than other parts of the body and the biomaterials in question – principally teeth – are easier to fabricate than other body parts. While the use of casts prepared by conventional physical impressions remains commonplace, the dental sector has long made use of advanced digital imaging techniques, which provide a fertile starting point for 3D printing development. While conventional production techniques, including machining and milling, continue to dominate dental implant manufacturing, there is a healthy niche market for 3D printed implants that could develop into the mainstream. One particular benefit of 3D printed implants is that they can be tailored to both the hard and soft tissue in the mouth, leading to potential improvements in their integration in the patient's body. This could also allow for a higher level of automation in the supply chain. The production of surgical tools, drilling guides and plates, as discussed previously, can also be applied in the dental sector to improve accuracy.

3D printing has substantial development potential in the production of O&P. Orthoses are external devices that control, restrict and assist movements, perhaps to correct the shape or function of the body, or to provide support for specific activities. Prostheses replace parts of the body that are entirely missing due to, for example, amputation or congenital conditions. Either artefact can be internal or external. While 3D printing is not yet widely used, the level of personalisation it allows could bring improvements in their functionality, aesthetics and fit, the latter being a crucial factor in their success. While usually considered medical, to recuperate or restore functionality, O&P can also be cosmetic or augmentative. However, while augmentative external O&P may be desirable for specific functions, such as heavy lifting, many medical O&P users request devices that resemble the look and functionality of 'normal' body parts.



Scenario illustrations by LUC – le Laboratoire d'Usages Collaboratifs

Scenario illustrations by LUC – le Laboratoire d'Usages Collaboratifs

Tissue and organ printing is one of the most evocative application areas of 3D printing, and simultaneously one of the least advanced. While 3D printing can be deployed in efforts to regenerate bodily tissues with the ultimate aim of restoring, maintaining or improving its functionality. This is usually achieved by printing a scaffold on which biological material can be placed and propagated. Success depends upon the scaffold's ability to support cell placement and interaction, the transportation of materials such as gases and nutrients to maintain the cells, and the rate at which the scaffold degrades. There has been some success with 'simpler' organs such as skin, and smaller components such as heart valves. In one example, ears were produced for children with congenital deformities. Similar methods have been deployed outside medical contexts for artistic purposes. However, the technique is not sufficiently advanced to deliver more complex organs. In the coming decades, 3D printed models are more likely to be used for training and testing purposes than for transplant.

3. Social, ethical, cultural, economic and environmental aspects

During a '360° Envisioning' project workshop conducted as part of the STOA study, experts and stakeholders met with the project team to discuss wide ranging potential future impacts of developments in 3D bio-printing. The discussions focused in particular on tissue and organ printing, O&P and dentistry, and the insights were further augmented by literature reviews and interviews. Highlights of the social, ethical, environmental, economic and demographic aspects identified are highlighted below.

> Read about the 360° Envisioning Workshop in section 6 of the study.

Cultural aspects

When considering emerging and future technologies, public responses cannot be predicted. Large studies are often dedicated to this task, often using focus groups and other forms of public engagement to assess the acceptability of the technology. This falls out of the scope of the present study. However, the study did include a review of how 3D bio-printing is embedded in cultural narratives, for example, the 'socio-technical imaginaries' of film and books. The review considered 46 titles from 1930 to 2016, with the aim of gathering clues about the hopes, fears, expectations and fantasies associated with visions of the technology in the future. Three main archetypal stories about 3D printing were identified. The first – **the Pandora's box** – sees 3D bio-printing inadvertently unleashing powerful threats to society. The second – **the cornucopia** – presents it as the provider of near limitless valuable resources, which can have mixed effects on society. The third – **the magic bag** – depicts the technology as a mysterious element that is presented as a gift or reward, but has the power to conceal or trick. To be clear, these are not read as predictions or proposals for the technology itself, but as glimpses of social and cultural responses to its development.

> Read the review of socio-technical imaginaries of 3D bio-printing in section 3 of the study.

These three archetypal stories of 3D bio-printing, as seen through the lens of science fiction, prompt us to reflect upon some further cultural aspects of the technology. First of all, it leads us to consider the 'trojan horse effect', whereby the opportunities presented by the technology could usher us towards a dangerous path. This could inspire a precautionary approach to development, associated with extensive risk assessment. They also lead us to consider our relationship with our bodies, particularly as the boundaries between 'natural' and manufactured body parts may be blurred.

Social aspects

As with many new technology developments, a key aspect to consider is the distribution of benefits. For medical products, this principally concerns ensuring that new treatments are accessible to citizens. On a global level, this could mean technology transfer initiatives to ensure that developing countries can take advantage of the latest developments in 3D bio-printed O&P for amputees.

> Read more about social, ethical, economic, environmental and other aspects of 3D bio-printing in section 4 of the study.

Another key aspect that applies to many new technologies is their impact on employment. In the case of 3D bio-printing, the infrastructure used by and activities of laboratory technicians could be affected by the adoption of 3D bio-printing in the medical sector. However, given the demand for human attention to meet the high standards that apply in this field, this appears unlikely to lead to an overall reduction in the number of jobs.

Applications of 3D bio-printing vary substantially, with some already in use and others far from clinical trial. It is important to observe and manage 'hype cycles', taking advantage of opportunities without raising expectations that cannot be fulfilled in the short or medium term.

Ethical aspects

Under the banner of ethical aspects, the STOA study considered safety, security, animal experimentation, organ donation, data protection and intellectual property (IP) rights.

The increased level of customisation of products, and the potential for more decentralised infrastructures, may make it more difficult for consumers and authorities to verify the safety of products. Higher safety standards apply to medical products than for other consumer goods, and there are also rules governing the use of living tissues in laboratories. Such standards present barriers to personalised 3D printed medical devices reaching the market. While these standards could be changed to support the development of 'mass customisation' for all kinds of medical devices, the changes are likely to be precautionary, continuing to prioritise patient safety. This would affect how a 3D printing infrastructure could emerge within the medical sector, for example, the high overhead cost of facilities could discourage decentralisation.

Security and dual-use aspects should also be considered, since almost any civil technology development can be, to a greater or lesser extent, transferred to military technology development. For example, a minor controversy ensued when blueprints for 3D printing guns at home were freely distributed on the internet. While no credible security threat has yet been associated with 3D bio-printing, the increased accessibility of 3D bio-printing facilities – in terms of cheaper and more readily available equipment combined with reduced expertise required to use it – opens the possibility of the technology being used to create bioweapons and other biohazards. Environmental health and other security-related ethical concerns could be raised with non-military applications, for example in the case of DIY genetic engineering or the production of hazardous materials outside controlled environments.

Ownership is an interesting topic in the case of 3D bio-printing, and the study considered the rights of developers to protect their IP, as well as the rights of citizens to protect and control data about themselves. When a developer uses their tools to produce highly personalised items, IP and personal data can be embodied in an artefact that might be placed inside the body.

One interesting future possibility emerging from the development of 3D bio-printing is the reduced need for experiments on animals, as appropriate biomaterials could be produced in a laboratory. However, despite the ban on cosmetic testing, animal experimentation maintains a pivotal role in medical trials that will not be easily displaced. Similarly, producing reliable biological materials on demand might reduce our reliance on human (and animal) organ donors, resolving ethical dilemmas in the prioritisation of the recipients of donated organs. However, even assuming the substantial advances in organ printing that would be needed to make this happen, the cost and production capacity may mean that the familiar waiting lists remain in use for some time. Furthermore, even if this development is one day considered a realistic prospect, other questions such as the accessibility of procedures and the patentability of organs will have to be resolved. Until then, the management of 'hype cycles' seems to be a more pressing concern.

Economic and environmental aspects

Estimates of the potential economic impacts of 3D printing vary significantly, although they are usually very positive. For the 3D bio-printing sector, it is perhaps even more difficult to cite figures with confidence, as some applications can develop extremely rapidly. For example, all US manufacturers of hearing aids shifted to 3D printing in less than two years, with late adopters pushed out of the market. Such anecdotes provide no guarantees, but illustrate the potential game-changing economic power of 3D printing for 'mass customised' products.

While additive techniques may offer greater material efficiency than their subtractive counterparts, the total environmental impact of 3D bio-printing development is not necessarily positive. Savings in the production of individual items could, for example, be negated by increases in the total demand for new, cheaper products with a higher rate of obsolescence.

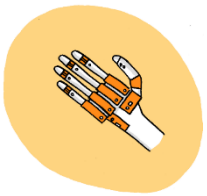
4. Scenarios

As part of the study, four scenarios were created. These describe alternative, plausible 3D bio-printing futures and highlight their associated impacts. The aim of these scenarios was neither to predict nor suggest specific development paths but, rather, to provide an accessible format for discussing a range of opportunities and challenges associated with the technology.

More information about the scenario approach can be found along with the full texts in section 7 of the study.

Each of the four scenarios are set in a context with different levels of technical development and different regulatory frameworks. Each tells the story of fictional characters that encounter 3D bio-printing in their lives. Similar to short science fiction stories, they are accompanied by illustrations, and reveal different aspects of technology development that were identified in the course of the study, including the analysis of the technology, as well as its possible wider social, cultural, ethical and economic impacts. Care is taken to ensure that each scenario is firmly grounded in the research and, taken together, they can be used as an alternative format for presenting the findings, and as an accessible entry point for a wide range of stakeholders to reflect and discuss the key issues highlighted in the study. Figure 2, below, presents a brief introduction to the context and story of each of the scenarios.

Arms and legs for solidarity



This scenario takes place in a future Europe with relatively slow technical development, with strong EU regulation on 3D bio-printing, privacy and IP protection.

In this scenario, an EU funded NGO that operates outside Europe, provides prostheses for child victims of landmines. They must balance their compliance with EU regulation and respect for IP against the more immediate needs of the children they are trying to help.

New teeth, new life

This scenario takes place in a future Europe that enjoys a very high level of technical development, and a strong focus on preventative healthcare. Unhealthy lifestyle choices can affect citizens' access to the health system and attract social prejudice.

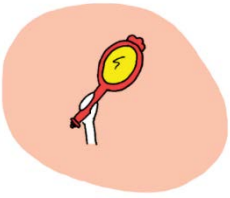
A wide range of 3D bio-printing techniques are encountered in this scenario in which a single father struggles to maintain a healthy lifestyle for him and his son.

Skin valley

This scenario takes place in a future Europe with relatively high level of technical development, and particularly advanced DIY communities that operate outside of the formal laboratory environment.

This scenario tells the story of two teenagers that travel to a DIY studio to have colourful biomaterials grafted onto their bodies, as a kind of next-generation 3D tattoo.

Mr Perfect



This scenario takes place in a future Europe with slow technical development. Following strong public opposition, there is very limited adoption of 3D bio-printing for medical purposes, but greater uptake in other sectors.

The vain protagonist of this scenario undergoes a cosmetic procedure to make him resemble a celebrity, but does not achieve the results that he anticipated.

Figure 2: Summary of scenarios. All images by LUC – le Laboratoire d'Usages Collaboratifs

5. Challenges and options

Three key sets of challenges were identified in the course of the study; one set associated with regulatory approaches, a second regarding social justice and the distribution of benefits, and a third about the role of citizens in shaping development. Sets of policy options, responding to these challenges, were also developed. These options should not be taken as mutually exclusive choices. Packages of actions may well combine elements of different paradigms, or be designed to fall in a middle ground that responds to specific opportunities and challenges raised by 3D bio-printing development. In the following sections, each set of challenges is introduced, along with a brief description of the responsive policy options.

Read more about the key challenges and policy options in sections 8 and 9 of the study, respectively.

Challenges and options associated with regulatory approaches

3D bio-printing technology could have impacts that are relevant to various different regulatory areas including medical devices, pharmaceuticals, food, chemicals, privacy and IP protection. Participants in the workshops that were organised as part of the STOA study highlighted the regulatory framework as a crucial overarching issue. Four key regulatory challenges are identified. First, the regulatory consequences of the classification of products (e.g. as medical or therapeutic, as biological or non-biological), second, the protection of data IP and privacy, third, questions of safety and informed consent, and fourth, standards. These challenges can also intersect, for example, when the patentability of some 3D bio-printed materials depends upon whether it is defined and classified as having therapeutic medical purposes or not. Here, each of these regulatory challenges are discussed in turn, and consequences of responding with several niche policies, or with fewer comprehensive policies, are explored.

The first regulatory challenge is in defining and categorising the processes and products associated with 3D bio-printing. Some 3D bio-printed items will blend biological and non-biological components, and might defy definition as, for example, medical devices or advanced therapies. Different regulations apply to biological and non-biological materials, leading to complications for combined products, such as a 3D printed scaffold on which living cells are cultivated. Further complications emerge for products that blend biological and non-biological components that each require separate licenses. Similarly, while medical devices have stronger standards and higher barriers to market approval than non-medical devices, the standards and barriers for advanced therapies are even stronger and higher. Developers and innovators in the field may benefit from clearer guidance on how their products are defined and classified, to help them to understand which regulations, standards and procedures apply to them.

The second regulatory challenge is in the protection of data, IP and privacy. For example, a decentralised network of 3D imaging and bio-printing services that deliver customised medical devices might have access to sensitive medical data and other personal information. Illegal file sharing amongst some communities – with blueprints for objects unlawfully traded in the same way as MP3 or video files – might present an additional threat to IP protection. Advances in 3D bio-printing may lead to questions about the ownership of devices and biomaterials implanted in patient's bodies, and also about the patentability of novel biological materials which differ substantially from 'natural' biomaterials. Some of these issues were encountered in the **arms and legs for solidarity** scenario.

The third regulatory challenge is in safety, in particular the risks associated with undertaking procedures and manufacturing products outside of professional environments. This does not have to mean black markets for 3D printed organs for transplant. Risks may be present with simpler devices for external and non-medical uses. The key consideration is how standards can be maintained if 3D bio-printing techniques are accessible outside traditional professional environments. A related dimension of the safety problem of bio-printing in non-professional contexts is how to maintain ethical standards, such as informed consent. These safety concerns should, however, be balanced against potential benefits of democratising technology. For example, DIY 3D bio-printing may facilitate innovation with good social

outcomes, and could engage a new generation of citizens to learn about science, technology, engineering and medicine.

The fourth regulatory challenge is in testing and product standards. In particular, to what extent 3D bio-printed products can be submitted to the same testing approaches that are applied to traditional products. The key issue is not the fact that the item is 3D printed, but that each item is highly personalised. As the trend for mass production develops towards mass customisation, the cost and time required to test each unique product grows increasingly burdensome. This suggests that – where permitted by the optimisation of patient outcomes and safety – testing and standards may focus on the process of 3D bio-printing and the broad parameters of its products, rather than on specific products.

Responding to these challenges requires a balance in the regulatory approach, for example, to ensure high standards for medical products without blocking beneficial innovations from the market. The STOA study identified and evaluated two broad policy options for how such regulations could be structured, one favouring fewer comprehensive regulations that cover the full spectrum of 3D bio-printing technologies, and the other favouring several more case-specific regulations that target smaller niches.

The broad option of a comprehensive regulatory framework would attempt to maximise coverage of developments and applications of the technology with wide geographic reach. This could help support safer and more standardised development across Europe, which respects ethical standards and embeds appropriate liability rules to encourage responsible development and deployment. On the other hand, comprehensive frameworks are more difficult to put into place, as they are more complex and affect more policy areas. This could slow innovation, taking longer to respond to immediate challenges and opportunities presented by the technology as it develops. The approach could also lead to higher costs, exacerbating the challenges associated with the distribution of benefits, discussed below.

The broad option of adopting several different case-specific regulations which respond to specific opportunities and challenges could allow quicker and more adept policy responses, since each would be less complicated, involve fewer policy areas, and could respond more precisely to subtle features of development. This strategy could also allow greater control, so that development can reflect the boundaries of public acceptability more closely. Niche policies could also be adapted to specific contexts, with 3D bio-printing for medical and human enhancement purposes a case in point. There are also drawbacks to this approach, such as the emergence of grey areas where an application is covered by several regulations or 'falls between the gaps' and is not covered by any.

Challenges and options associated with the distribution of benefits

Social justice and the distribution of benefits can be framed as a regulatory challenge. However, those described in the previous section focused upon the structure of regulations that control 3D bio-printing development while, here, the focus is upon more general questions about the uneven impact that 3D bio-printing technology may have on different social groups. One key factor is the cost, and the need for medical treatments to be accessible and affordable for citizens. Claims that 3D bio-printing will reduce public health costs might prove accurate, although, at this point, there is not enough evidence to support good estimations. Another factor is employment, with 3D bio-printing likely to have both positive and negative effects, depending upon the sector and location considered. However, evidence for both job gains and job losses is not equivalent to evidence for a neutral or insignificant overall impact. It is crucial to continually analyse the overall impact on both the quantity and quality of jobs across the whole supply chain. Such analyses can inform strategies to counteract adverse effects on employment and to address skills gaps. Further, 3D bio-printing appears to present a substantial opportunity to provide limb prosthesis for people living outside Europe that do not have access to appropriate healthcare, perhaps via grassroots organisations collaborating with traditional healthcare providers or large companies.

So how can the EU ensure that that the benefits of 3D bio-printing development – from medical treatment to employment prospects – are distributed fairly? The study identified two broad options, mission-oriented and open innovation polices.

Mission-oriented policies focus on targeting specific outcomes, and could facilitate the development of 3D bio-printing solutions for specific medical problems. While these can be shaped to target developments that deliver the greatest and widest social value, there may still be risks that the outcomes will not be affordable and accessible to all.

Open innovation policies aim at creating conditions that are broadly favourable to new developments in a wide range of fields. Such policies could focus on encouraging a wider range of actors – including universities, companies and DIY communities – to work together and to share data, findings and solutions. While this approach is expected to foster an environment that is conducive to innovation in a wide range of fields, it may make it more difficult for regulators to target specific outcomes and could make future efforts to harmonise standards more difficult.

Challenges and options associated with citizens' roles in the innovation process

Here, a third set of challenges related to two particular roles that citizens can play in the development of 3D bio-printing are considered. The first role sees the citizen as a participant in public dialogues about how the technology should develop. Citizens could enact this role as participants in formal public engagement activities, or simply by thinking about and discussing the acceptability of specific applications in the most informal of contexts. Citizens in this role could be pivotal in the success or failure of 3D bio-printing, as this is how they come to define whether and why certain applications are considered acceptable or not. Stakeholders could make efforts to support a healthy debate by, for example, managing the expectations of citizens and avoiding damaging 'hype cycles'.

A broad approach for responding to this challenge is to conduct public engagement activities. Engagement activities are distinguished from information or education campaigns in that they foster two-way dialogue, focusing on giving citizens the opportunity to give their informed perspectives about wide ranging aspects of the technology and its development, and to do so in their own terms. These can be designed to identify the boundaries of acceptability of different 3D bio-printing process applications, or to understand and manage 'hype cycles' in the sector. Whatever their specific aims, they should be transparent about their objectives, and the mechanisms by which the engagement activities can make a meaningful difference in the outcome.

The second role for citizens sees them as active innovators or scientists, playing a more hands-on role in the development of the technology, experimenting with 3D printers at home or in a 'fab lab', perhaps for the pleasure of learning the craft, to save money, or as part of a social innovation or profitable initiative. Citizens in this role could also have a substantial impact with grassroots innovations perhaps responding more directly to social needs. However, citizen scientists and members of other DIY communities may have new responsibilities. This is particularly important to recognise in a medical context, where strict standards and professional norms must be followed, but also in wider contexts, for example to comply with various consumer IP protection laws. Activities conducted by and for citizen scientists should not be designed to provide cheap sources of data or analytical effort but, rather, to create innovative spaces and enable synergetic relationships between different organisations and communities.

A broad approach to responding to this challenge is to support citizen-driven activities. This may mean ensuring that some of the budget devoted to supporting research and development is allocated to grassroots organisations that are engaged with the technology. Innovation policies could also encourage cooperation between a wider range of stakeholders, including citizens and CSOs as well as traditional players such as universities and firms.

Further legal and ethical aspects

A further report, produced alongside the study, elaborates upon legal and ethical issues in the context of European policy, highlighting the most relevant committees and legislative acts for the legal classification of 3D bio-printing, IP rights, data protection, liability, safety and security.

Read more about ethical and legal issues in the context of European policy in the analysis on legal and ethical aspects.

6. Concluding remarks

Three key trends: decentralisation, DIY movements and mass customisation

Three trends encountered in the study – decentralisation, DIY movements, and mass customisation – are closely linked with 3D printing and bio-printing, and could have a significant disruptive influence on society.

3D printing has a strong association with decentralised infrastructures. Major hubs supplying a wide network of users could gradually be replaced by a greater number of in-house production and services. This is enabled by reduced overhead costs and reduced expertise requirements, and is driven by call for more customised goods and services that can be delivered on-demand. However, in the context of medical applications, this trend may be less pronounced because the higher standards that are required for medical products and devices call for tightly controlled production and testing infrastructures which imply higher overhead costs and greater reliance on specialist expertise. As such, while there may be some degree of decentralisation, the hub structure is unlikely to disappear completely.

This brings us to a second key trend associated with 3D printing; the emergence of DIY and 'maker' communities. As 3D bio-printing becomes more affordable and accessible, increased activity is likely outside the professional laboratory environment. These activities might be for non-medical purposes, perhaps for commercial, artistic or aesthetic reasons, or simply for the pleasure of meeting a technical challenge. Whatever their goals, DIY cultures could be a valuable source of innovation, with direct benefits including new products and services, as well as indirect benefits such as enabling creative and engaged techno-scientific activities amongst citizens. However, they may also raise both real and perceived risks about the safety and security of 3D bio-printing outside the norms and standards demanded by professional laboratories. Attempting to limit this trend could also carry risks, not only in curtailing the potential benefits of DIY innovation, but also in pushing potentially dangerous activities further underground.

Finally, 3D printing is also associated with the trend of 'mass customisation', the (semi-)automated production of highly personalised items at a massive scale. This is, perhaps, one of the key benefits of 3D bio-printing because it may allow cheaper, more automated manufacturing of bespoke products that are really tailored for individual patients' bodies. This trend, however, clashes with current testing regimes that were designed with more traditional 'mass production' in mind. These regimes focus on the quality of the final product which, in the case of medical devices, must meet the highest standards. However, if the batch size is just one, the cost of testing each individual product would present a serious barrier to market. It may be possible to find alternative ways of maintaining the same high quality standards under a mass customisation paradigm, for example, by shifting the focus of the tests away from the products themselves, and towards the processes and materials that are used to make them.

Ambiguous boundary between medical recovery and human enhancement

The STOA study showed that 3D bio-printing can be deployed for medical and non-medical purposes. Defining an application as medical can have implications for the regulations that apply, as well as coverage by medical insurance. Where applications that involve some bodily intervention to enhance human capacity, but are defined as non-medical, they may be evaluated negatively by many citizens. However, the difference between medical recovery and human enhancement is not always clear. Devising an unambiguous boundary between medical and non-medical procedures would require a fixed definition of normality. Reaching this point to compensate for some disability or illness would be considered medical recovery, and going beyond it to further improve capability would be enhancement. However, concepts such as normality and disability are relative, flexible and context sensitive. As such, some interventions may be considered medical in one context, and as frivolous or cosmetic in another context. Since this boundary is likely to remain ambiguous for some time, but can have important legal and social consequences, it is important to monitor this boundary continually.

Responsible research and innovation

Responsible research and innovation (RRI) is a pluralistic approach to managing innovation that is increasingly integrated in EU research and innovation initiatives. It is frequently used as a framework for developing meaningful public and stakeholder engagement activities. RRI can also be deployed as a lens to consider social, ethical, environmental, governance, economic issues, or as a carrier of other well-known strategies for the sound management of technology development, such as the precautionary principle. It is often associated with calls for the inclusion of a wider range of stakeholders in shaping technology development from the earliest stages of the innovation process, as well as demands for greater transparency about the goals and expected outcomes of innovation.

Certainly, the degree of uncertainty and wide ranging impacts of 3D bio-printing justify serious collective reflection about the direction its development, and RRI can help structure the debate. RRI approaches in this context have faced some difficulties in communicating the underlying concepts, generating interest and incentivising wide participation. Nonetheless, there has been some progress in the field. Vermeulen et al. have presented a review of 3D bio-printing in the context of RRI. One case study of the ongoing Horizon 2020 funded **SMART-Map** project will develop concrete roadmaps for the responsible development 3D printing technologies and services in biomedicine.

Managing expectations

The STOA study showed that some current applications in 3D bio-printing are relatively uncontroversial and have substantial benefits, for example in the field of O&P. The study also showed that some of the more ambitious potential future applications of 3D bio-printing, such as organ printing, are less straightforward, since they might raise questions about safety, security, responsibility, liability, data and IP protection and, in any case, face such steep technical and regulatory barriers that they might never emerge.

Snappy headlines about lifesaving 3D printed hearts and portable skin printers might attract attention, but exaggerated reports might also raise expectations and contribute to the emergence of 'hype cycles' that could distract from taking full advantage of the opportunities that are presented by 3D bio-printing today. On the one hand, it is important to manage expectations and keep public debate grounded in current and realistic near future capabilities. On the other hand, RRI calls for transparency about the goals and full range of expected future outcomes of research and innovation in the field. Finding a balance between the conflicting impulses to keep debates grounded and to pay attention to the far future is a difficult task, one that is further complicated by the science-media ecosystem which includes academic laboratories and commercial enterprises competing for attention, as well as media outlets competing for 'clicks'.

How to develop socially acceptable technologies?

Technologies are social, and social values change over time. Ethical, social and cultural forces could all influence the future direction of 3D bio-printing development just as much as technical developments. They can also lead to changes in our understanding and expectations of technology. As such, it is important to continuously reflect upon the boundaries of acceptability of different applications.

While it is possible to proactively change social attitudes, it is much more difficult to convince people to accept unpopular technologies than it is to find ways of ensuring that technologies develop in a way that is acceptable to the people. Insights from social studies of science and technology – including responsible research and innovation – can help in this regard.

3D bio-printing is defined here as the use of 3D printing technology for applications related to the body, whether the products themselves include biological material or not, and whether or not their purpose is medical. It includes any application for rehabilitating, supporting or augmenting any kind of biological functionality. The impacts of 3D bio-printing are uncertain, and it is not clear which actions may be required to foster responsible development of the technology. A STOA study, 'Additive bio-manufacturing: 3D printing for medical recovery and human enhancement, responded to these uncertainties by describing the state of the art and future development prospects of 3D bio-printing technology, analysing their wide-ranging impacts – including social, ethical and economic aspects – and identifying key policy challenges along with options to respond to them. Key challenges and responsive options were identified in the approach to regulation, in managing the distribution of costs and benefits, and in the role of citizens in technology development. This In-depth Analysis draws upon the findings of the STOA Study, summarising and reflecting upon its key findings. The conclusions highlight key trends and offer further reflections on the study in the context of responsible research and innovation.

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