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Medical 3D Printing: Techniques, Advances, Applications, Challenges, and Regulatory Implications

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ABSTRACT

3D printing is transforming the medical field. This publication covers its essence, applications, regulations, and challenges. We discuss its origins, advantages, patient-specific products, and regulatory insights. We also explore biological material printing, organ transplantation, and drug research. This technology has the potential to revolutionize healthcare, but further research and collaboration are needed.

Introduction

Revolutionizing innovations come in all different shapes and sizes. Some are big, some are small; some are in STEM, some are in the Arts; some make worlds collide, like printers. Wait, printers? While printers are known to save hours, days, months, and even years when mass-producing media, they do more than just print literature. Printers are becoming known to not just save lives on test day, but also in cars, buildings, space, and the operating theatre.

Medical 3D printing, where medicine and technology meet, is taking healthcare, in every field, by storm, from orthopedics to neurosurgery to cardiac healthcare. 3D-printed models can enhance understanding and teaching compared to conventional 2D imaging such as X-rays, CT, or MRI scans, requiring strong visualization skills. 3D printing can provide anatomical models, patient-specific guides, and prosthetics which widen the applications and outcomes compared to standard care. In addition, 3D printing has applications in regenerative medicine, expanding utility in organ transplantation by creating complex tissues and organs using organized cell arrangements.

This article discusses the process, challenges, and potential of bioprinting, highlighting its benefits in tissue repair and the current use of 3D printing and bioprinting in human medicine, particularly surgery and tissue engineering. A systematic literature review was conducted to identify common applications, advantages, disadvantages, and cost implications of these technologies. This review covers various areas, such as bone, cartilage, heart, lung, liver, and nerve tissue printing while addressing challenges like cost and compatibility issues.

What is Medical 3D-Printing?

To understand what Medical 3D Printing is, we first must understand the foundations of both 3D Printing and 3D Printing Devices. 3D Printing, introduced by Charles Hull in 1984, builds solid objects by layering raw materials like plastics, ceramics, and metals, and began with the practice of creating digital data models to

produce 3D objects. These objects are rendered from a computer-aided design (CAD) or magnetic-resonance image (MRI) drawing, allowing the manufacturer to change the product easily. (Daley & Powers, n.d.)

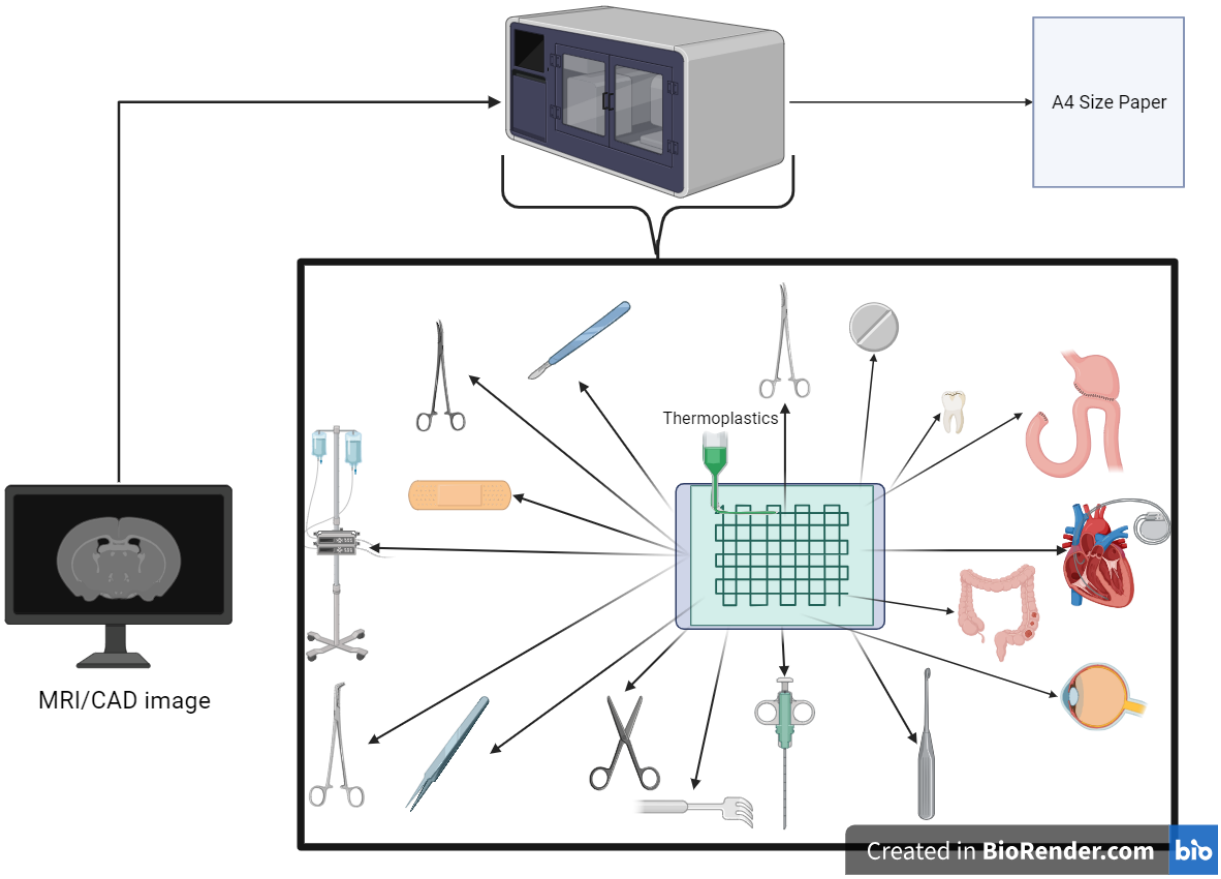

Figure 1. Bioprinting Process. Created with BioRender.com

Advantages of Medical 3D Printing

Uses of 3D Printing Techniques

With this revolutionary production technique come revolutionary new medical products. 3D Printing creates the whole medical product/device simultaneously, while traditional manufacturing techniques require several small components to be created individually and adhered together. (Little & Wallace, n.d.) These 3D Printing Techniques are, for example, used to create medical devices with complex geometric structures (like porous knee replacements that facilitate tissue regeneration) and customizable, patient-specific medical products. 3D Printing could, in the future, combine many drugs into a "polypill," and has already manufactured drugs in patient-specific dosages and forms. (*FDA Approves The First 3d Printed Drug Product*, 2015)

Examples of 3D Printed Medical Technologies/Products

One such patient-specific drug's name is SPRITAM. With three million people in the US alone diagnosed with epilepsy, (500,000 of whom are children) this drug couldn't have come at a better time. Although young, New Jersey's Aprecia Pharmaceutical Company (who claim themselves as the only company using 3D Printing

Technology to create drugs) says that SPRITAM is only the first of many upcoming 3D-printed, central nervous system drugs. SPRITAM aims at treating primary generalized tonic-clonic, myoclonic, and partial onset seizures. While there are many epilepsy drugs on the market, patients have found it difficult to swallow such large pills. So Aprecia employs its own ZipDose Technology, a 3D printing technology inspired by MIT's 3DP Technology. Using Powder-liquid 3D Printing Techniques, ZipDose creates porous pills that dissolve at contact with any type of liquid, as shown in an experiment between an over-the-counter fast-melt drug and Aprecia ZipDose: In less than one second, Aprecia's product has already disintegrated, while the fast-melt drug takes nearly 45 seconds to completely dissolve. The possibilities of 3D Printing technology are seemingly endless, and SPRITAM and other future 3D-printed drugs could quickly be included as official treatment options: With the support of the US government, doctors already can share medical treatment designs to aid in medical treatment, and this repository could very soon house 3D-printed drugs as well. (*FDA Approves The First 3d Printed Drug Product*, 2015)

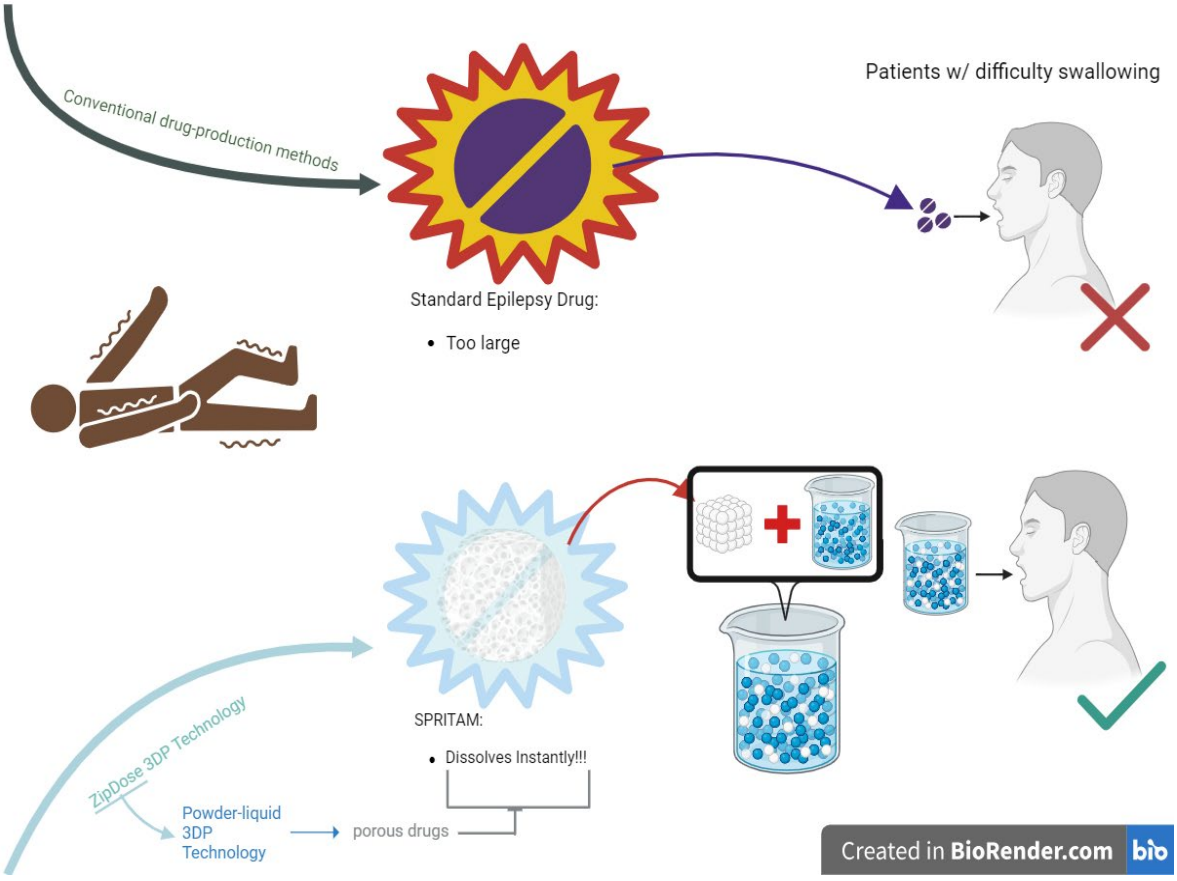

Figure 2. Standard epilepsy drugs vs. 3D-printed SPRITAM. Created with BioRender.com

FDA Regulation and Oversight in Medical 3D Printing

FDA Classification and Regulation of Medical 3D Printing Products

As with any new technology, regulation is necessary. The FDA's very own Center for Devices and Radiological Health (CDRH) focuses primarily on regulating Medical 3D Printing products, by classifying them based on their risk levels. Class One is the least risky and may include small surgical instruments (ex. scalpels), bandages,

and crutches. Although all products must meet quality control and manufacturing standards, most products from Class One (and some from Class Two) do not require premarket review. Class Two includes moderately risky devices and products like infusion pumps and certain prosthetic devices and wheelchairs. So in addition to standard manufacturing/quality control regulations and premarket review, most Class Two products must also undergo 510(k) review, where the product's manufacturer shows that their product/device is just as effective as existing medical devices/products. Class Three devices include various life-support devices, like pacemakers and breast implants, or other products that significantly assist in preventing some form of mental/physical/psychological impairment. Because the patient who needs to use a Class Three device would be extremely reliant on it, (or may not be able to survive without it) and because of its level of complexity, it is extremely risky to use a Class Three Device on a patient. So Class Three products must fill out a full premarket approval application, (with clinical trial data) and only if there is sufficient evidence to prove that the new product is both effective and safe will the FDA approve the product. However, under certain conditions, certain custom devices can be exempted from certain scrutinization procedures. For example, if the manufacturer creates only a small supply of the product each year, a product may be exempted from some levels of inspection. There are also scenarios where no other existing product can treat the patient. We also saw that, in the state of a medical emergency, the FDA can relax scrutiny somewhat, as seen when, in the COVID-19 pandemic, 3D-printed ventilators had to be used. (*Learn if a Medical Device Has Been Cleared by FDA for Marketing*, 2017; *CFR - Code of Federal Regulations Title 21*, n.d.; "What Is Medical 3D Printing—And How Is It Regulated?" 2020)

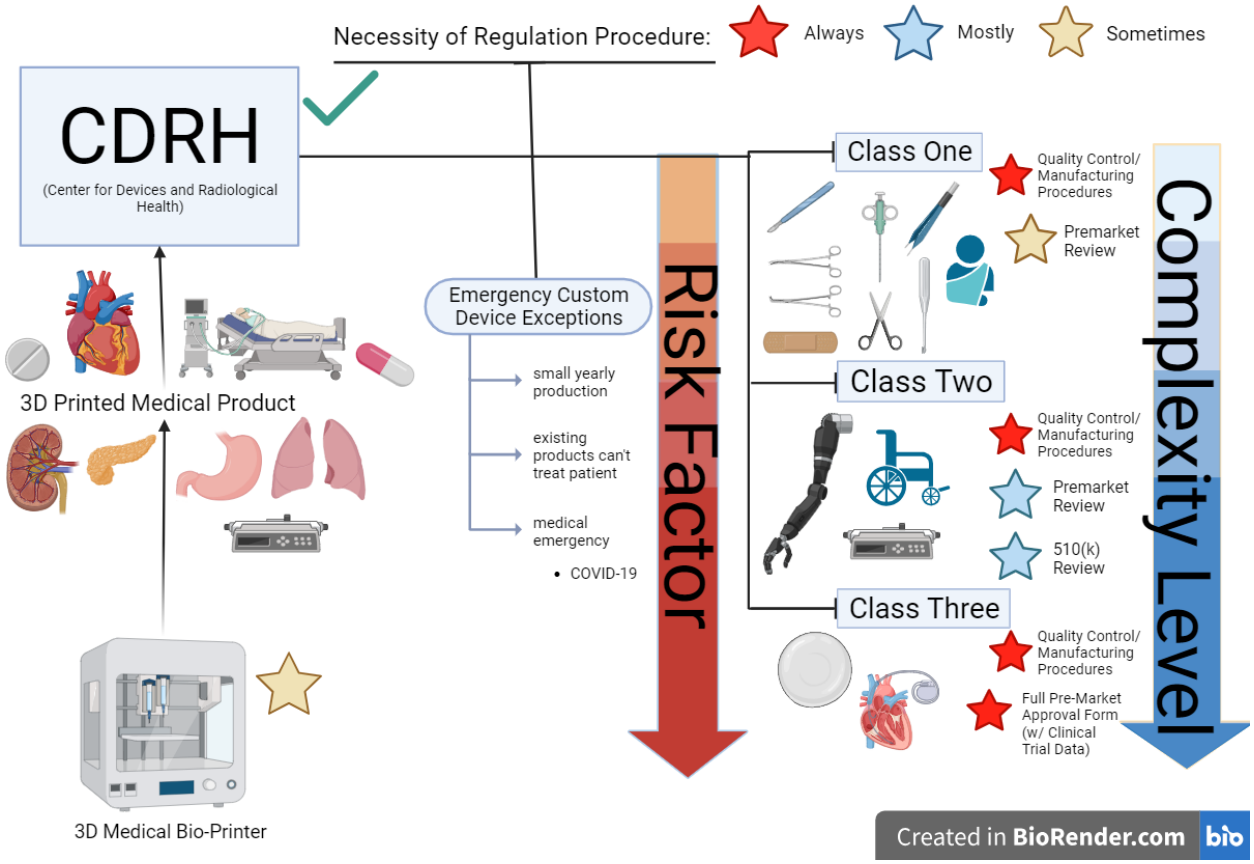

Figure 3. Medical Device/Product Classification and Regulation Procedures. Created with BioRender.com

Issues with the FDA's 3D-Printed Device Application Review Rubric (2017)

To make the application process easier, the FDA published a "rubric" for what would need to be included in the applications of various 3D-printed devices that were subject to review, including custom devices. However, gaps were immediately recognized by the community, mainly the fact that the rubric does not specifically address point-of-care manufacturing: With the rapid rate at which hospitals have been uptaking 3D printers in the last few years, and with the FDA giving the green light for software programs that generate patient-specific 3D anatomy models, "with great power comes great responsibility." (a responsibility not everyone is confident that each medical facility can uphold if there are no definitive guidelines). ("What Is Medical 3D Printing—And How Is It Regulated?" 2020)

Guidance Under FDA Pathways

Even if the FDA has not yet provided specific guidance on biologic and drug 3D printing, it does provide "guidance" through the CDER (Center for Drug Evaluation and Research) and CBER (Center for Biologics Evaluation and Research). The Office of Pharmaceutical Quality (CDER) has had its hands full trying to understand and implement 3D printing's potential role in drug development with pharmaceutical manufacturers. While the CBER investigates the potential for 3D Printing biomaterials. In 2017, the FDA stated that they had plans to investigate whether or not additional regulations outside of the regenerative medicine regulatory framework were needed, but there has been no update since then. ("What Is Medical 3D Printing—And How Is It Regulated?" 2020)

How Medical Authorities React to Unsafe 3D Medical Technologies

There is little that the FDA can do about 3D printing that occurs outside of its regulatory boundaries. Regional medical boards mostly just react to safety complaints, rather than proactively conducting investigations beforehand. A lack of oversight and oversight variability within regional boards means that even though other regional medical associations (ex. Radiological Society of North America) may come out with point-of-care guidelines, they cannot feasibly enforce them, partially due to point-of-care itself: In centralized facilities, all 3D-printed products are subject to FDA inspection, and Medical 3D printing is treated no differently than any other manufacturing technolog. However in point-of-care medicine, due to such oversight variability, the FDA finds it difficult to change its 3D-printing regulation requirements. However, improvements are being made: the CDRH is currently making a risk-based assessment. ("What Is Medical 3D Printing—And How Is It Regulated?" 2020)

Biological Material Printing

Organ Shortage - Public Health Crisis

17 patients in the US die every day waiting for an organ transplant. Even when the transplant comes, there is always the question of the body rejecting it. Since 2013, the number of recipients has doubled, but the number of donor organs remains static. In 2014, Organovo, a California-based company, successfully engineered human livers and kidneys. This breakthrough opened up a world of possibilities for the future of healthcare. (Becher, 2023)

Organ Printing

Everything starts with the cells, including 3D-printed products. To create organ cells, a sample of a patient's cell is taken, placed in a controlled environment (ex. sterile bioreactor/incubator), fed nutrient-rich "media," mixed with adhesive gel, and loaded into a printing chamber. There are several methods used in organ printing. (Becher, 2023)

"Ingredients" Needed to Print

When it comes to printers, an ink cartridge is a must-have. There are numerous types of inks available, such as bioink, which is a low-viscosity mixture comprising viable cells and biomaterials. It is used for non-contact printing on substrates like hydrogels, culture dishes, or polymer constructs. Bioinks are made by combining a variety of biocompatible materials, mimicking the extracellular matrix environment, and cultured cells. However, bioink is entirely different from other types of 3D printing ink. Bioink's body temperature is still higher than or equal to its print temperature, the ink can adapt and grow with the body, and its bioactive components must be non-toxic and modifiable by cells post-printing. (*3D Bioprinting: Bioink Selection Guide*, n.d.)

Acellular materials are permanent porous structures that adhere to the original ECM's biochemical and mechanical properties. They can be combined with bio-inks to provide structural support for tissue constructs. The porosity of the acellular materials allows for cell viability, tissue growth, cell migration, and vascular formation in these constructs. To meet such standards, ink is commonly made out of materials such as Agarose and Alginate, which promote high biocompatibility/stability and non-toxic/mild crosslinking conditions; chitosan and collagen, containing high biological relevance and antibacterial properties; decellularized ECM, which create an ink with a high survival rate and that is specific to the type of tissue being created; fibrinogen/Fibrin, proteins that are known for helping with rapid gelation; gelatin, which gives certain bio-inks high water solubility and thermally-reversible gelation; graphene, a flexible conductor; hyaluronic Acid and Hydroxyapatite, known to promote fast gelation, cell proliferation, and strength/rigidity; PCL/PLA/PLGA and Pluronic®, which makes bio-ink shear-thinning and printable, even at room temperature. (*3D Bioprinting: Bioink Selection Guide*, n.d.)

In organ printing, we combine ink and one of two methods: scaffold-based, which produces a customizable, curved structure, or scaffold-free, which creates a linear "structure," to make the final product. (Agarwal et al., 2020, 2-8)

Types of Printing Methods

Extrusion-based bioprinting is a way of printing 3D structures using materials that can be extruded from a nozzle. This process is achieved through methods like Direct Ink Writing (DIW) and pressure-assisted bioprinting. Suitable materials must have specific properties that allow for extrusion and shape retention. The process involves solidification through UV-curing, thermal curing, or extrusion into a support bath. (Agarwal et al., 2020, 2-8; *FDA Approves The First 3d Printed Drug Product*, 2015; Ferris et al., 2013, 2-26)

Pressure-assisted deposition has also been used for scaffold design, incorporating polymers and ceramics for controlled pore architecture. Organ bioprinting focuses on cell-encapsulated hydrogels using pressure-assisted multi-syringe systems, enabling simultaneous deposition of cells and biomaterials. Gelatin-based hydrogels have been utilized for functional liver constructs, while Matrigel® has facilitated the incorporation of various cells into biomimetic constructs. (Ferris et al., 2013, 2-26; Daley & Powers, n.d.)

Inkjet printing is another way of printing using small droplets to create high-resolution patterns. There are two types of inkjet printing: continuous inkjet (CIJ) and drop-on-demand (DOD) inkjet. DOD, primarily used for cell printing and microarray fabrication, generates droplets through pressure pulses and deposits them onto a substrate, allowing for precise cell patterns while maintaining the living cells' viability. Bioink properties, nozzle size, substrate distance, and temperature all affect the droplet size and quality. (Ferris et al., 2013, 2-26; Daley & Powers, n.d.; Little & Wallace, n.d.)

Stereolithography is an additive manufacturing technique that projects light onto a heat-curable bioink to build designs, directed with clinical imaging, and possibly direct laser writing or mask projection. The process relies on photocurable moieties to induce light-initiated polymerization for tissue construct formation. It encompasses various single-photon and multiphoton techniques and creates a variety of biocompatible scaffolds, from bone regeneration to cardiac tissue constructs. (Ferris et al., 2013, 2-26; Daley & Powers, n.d.)

A derivative of the conventional bioprinter is the BioPen, created by Australian researchers led by Professor Gordon Wallace at the University of Wollongong, which promises increased surgical precision, reduced procedure time, and accelerated bone and cartilage regeneration. Professor Peter Choong, co-developer of the BioPen and orthopedics director at St Vincent's Hospital Melbourne, has noted the pen's ability to customize solutions for real-time bone/joint reconstruction and has been using the pen in clinical trials since 2013. (Little & Wallace, n.d.)

One application of the BioPen is creating constructs to help heal damaged tissue: As a surgeon draws on the damaged bone/cartilage, the BioPen dispenses a mixture of cellular material and protective gels. With the addition of each successive layer, the pen's attached UV light source solidifies the gel, eventually forming a 3D structure. After the surgeon places this biomaterial at the targeted site, the protective gels slowly degrade, making room for new tissue. (Little & Wallace, n.d.)

Other methods include Selective Laser Sintering (SLS) and Fused-Deposition Modeling (FDM). (Ferris et al., 2013, 2-26)

Strengths and Weaknesses of Organ Printing/Organ Printing Methods

Organ printing is a technique that uses self-assembly and developmental biology principles to construct tissue structures. This approach involves depositing tissue fragments, typically cell-packed spheroids, in close arrangement, allowing them to merge and form organ-like constructs. This method is unique because it has the potential to create intricate tissue constructs with enhanced physiological relevance and functionality compared to traditional layer-by-layer bioprinting techniques. (Ferris et al., 2013, 2-26)

However, for organ printing to be used in more widespread clinical applications, it will require improved efficiency and reliability. The complex processes involved in depositing and fusing tissue fragments can be time-consuming and challenging. The fusion of tissue aggregates may result in distortions and imperfect structures, which can impact precision and reproducibility. The scaling up of tissue spheroid fabrication and deposition into capillaries remains a challenge, limiting scalability for larger constructs. The need for specialized bioprinting tools, modifications to printing methods, and appropriate support gels further complicates implementation. (Ferris et al., 2013, 2-26)

Each printing method has its strengths and weaknesses: Extrusion printing is best for creating simple 3D hydrogels; tissue fragment printing can make physiologically relevant shapes; laser-based printing has high resolution; microvalve printing allows for adjustable droplet volume; and inkjet printing offers high-throughput deposition with single-cell resolution. (Ferris et al., 2013, 2-26)

The main challenges include multi-material fabrication and spatiotemporal control of material deposition. (Ferris et al., 2013, 2-26)

Other Applications of Bioprinting

The above methods may primarily be used for organ printing, but that doesn't mean that they don't have other uses:

Annually, more than 2.2 million people worldwide require bone graft procedures to address defects. Current methods using synthetic cement-based materials and patient bone have limitations in mechanical integrity and tissue creation. Keeping this in mind, Swansea University researchers have developed a bioprinting process using durable, regenerative materials to create custom-shaped artificial bone matrices, which, when

transplanted, gradually integrate with natural bones over months. The University of Nottingham is also engaged in similar research, bioprinting bone cells to promote bone formation. (Little & Wallace, n.d.)

Research at Harvard University has also yielded developments in creating complex multilayered tissues for specific organogenesis. The use of multiple cell types and hydrogels creates multi-material structures, which is a novel platform for in vitro and in vivo modeling of various organs. Developing branching networks for vascular structures and liver tissue, these bioprinting developments have the potential to create functional organs and in vitro models for drug testing and disease modeling. (Little & Wallace, n.d.)

Conclusion

3D printing in the medical field presents countless opportunities and challenges. It can provide custom medical devices, and patient-specific drugs, and even revolutionize the organ transplantation process. However, it also raises complex questions about regulation, patient safety, and the need for standardized guidelines. As technology continues to advance, regulators, healthcare providers, and researchers must collaborate and adapt to this new era in healthcare. With ongoing research and innovation, 3D printing has the potential to significantly improve patient care and outcomes, making it an exciting and promising area of study.

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In the process of creating this text, I employed Grammarly to assist me with various aspects of the writing, including generating responses to the following AI prompts:

Prompts created by Grammarly:

- "Make it sound academic"
- "Simplify it"
- "Improve it"
- "Paraphrase it"
- "Shorten it"

I also utilized Grammarly AI to write the following prompts:

- "Simplify this"
- "simplify"
- "paraphrase 'proper device & manufacturing process/testing considerations'"
- "sound academic"

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