



CAS INSIGHTS

FROM POLYMERS TO PROSTHETICS

The growth of 3D printing in biomedicine

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Introduction

3D printing is the process of making three-dimensional solid objects from a digital file. The process is also known as additive manufacturing, as the 3D-printed object is achieved by laying down successive layers of material until the object is created.¹ Once only accessible to those who held patents in the technology, 3D printing has now become available to the masses, with several companies gaining traction by turning 3D printing into an everyday tool.²

3D printing-based applications are being used across a variety of fields, from manufacturing of consumer products to reconstructing evidence in forensic pathology.¹ However, one of the most promising and fastest growing areas of

advancement of 3D printing technology is in biomedicine. With the ability to manufacture pharmaceutical products, prosthetic ears and even artificial organs, the potential of 3D printing in biomedicine is seemingly limitless.

In this insight report, we analyze the CAS Content Collection™ to provide a unique landscape of 3D printing in biomedicine. In addition to summarizing the trends in 3D printing technologies and materials, we will also highlight the exciting innovations in tissue and organ fabrication, implants and prosthetics, pharmaceuticals and, beyond.



40 years in the making: A history of 3D printing

Though the idea for 3D printing was envisaged as early as the 1940s,³ it was not until the early 1980s that this idea became a reality, when Hideo Kodama filed a patent for a photopolymer rapid prototyping system with a laser beam curing process.^{2,3} The idea was never commercialized; however, innovations from other inventors soon followed. In 1983, Charles Hull invented the first stereolithography apparatus (SLA) machine and was granted the first patent in this technology. This was swiftly followed by the invention of two other pivotal 3D-printing technologies: Selective laser sintering (SLS) in 1987 and fused deposition modeling (FDM) in 1989. These three technologies paved the way for advanced technology development and multidisciplinary applications.²

The first decade of the 3D printing industry was dominated by only a few companies such as 3D Systems and Stratasys Inc. With the expiry of early patents and the invention of the RepRap, an open-source 3D printing concept, 3D printing became increasingly democratic. As of 2019, there were over 170 3D printer system manufacturers worldwide.²

With 3D printing becoming increasingly mainstream, technological advancements came rapidly. A major biomedical breakthrough came in 1999 when Wake Forest Institute of Regenerative Medicine grew a urinary bladder; this was the first 3D-printed organ used

for transplant surgery.² In 2008, the first 3D-printed prosthetic limbs that required no further assembly were developed. This development has improved many lives with its accuracy, customization ability, and lower costs compared with standard manufacturing techniques. This innovation was followed in 2012 by the printing of the first prosthetic jaw, which was successfully implanted into a human patient within the same year.³

Today, 3D printing is booming, particularly in the field of biomedicine. To identify the research trends emerging in 3D printing, we analyzed the CAS Content Collection™ to build a picture of the research landscape related to biomedical application over the past two decades. The CAS Content Collection is the largest human-curated collection of published scientific knowledge, empowering quantitative analysis of global scientific publications against variables such as time, research area, application, and chemical composition. Currently, there are over 22,000 scientific publications (journal articles and patents) in the CAS Content Collection related to biomedical applications of 3D printing.⁴

According to the CAS Content Collection, annual trends of journal and patent publications for biomedical applications of 3D printing indicate that innovation in this area is growing, and the commercialization of novel ideas also increases steadily despite a decline in patent publications in 2021 (**Figure 1**).

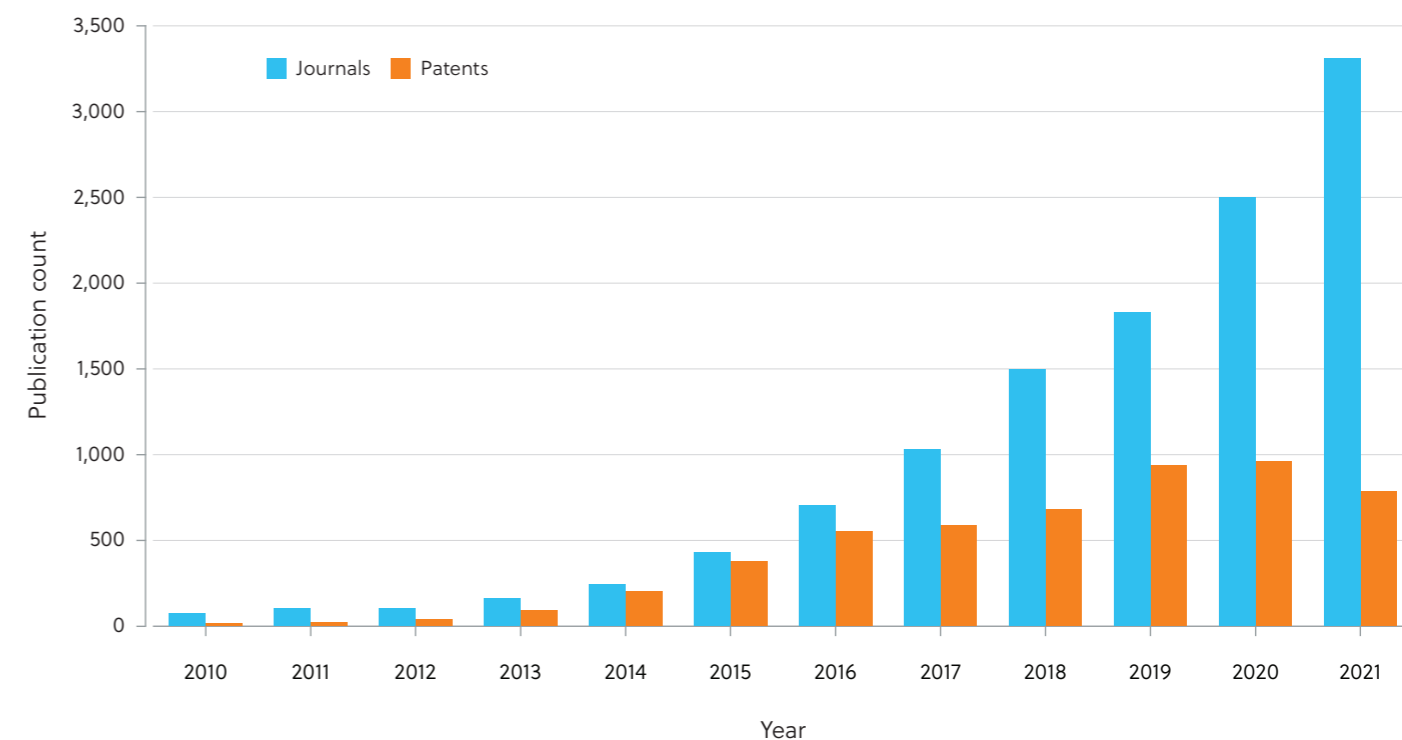


Figure 1. Annual trends of journal and patent publications for biomedical applications of 3D printing

The top contributing countries in terms of journal publications and patent publications are China and the United States. However, over 90 countries and regions were found to have contributed to this body of research, demonstrating the importance of 3D printing techniques for biomedical applications around the world (Figure 2).

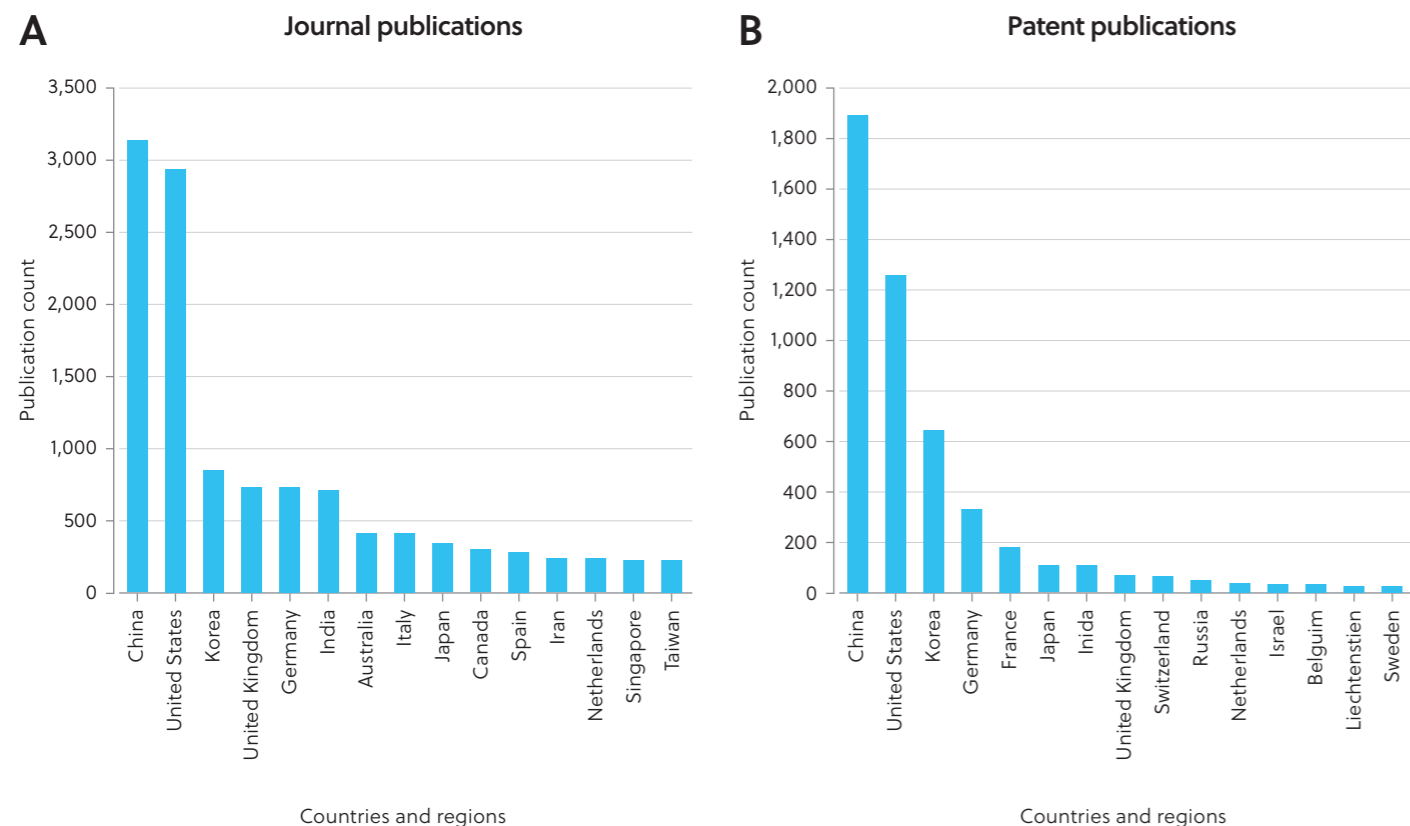
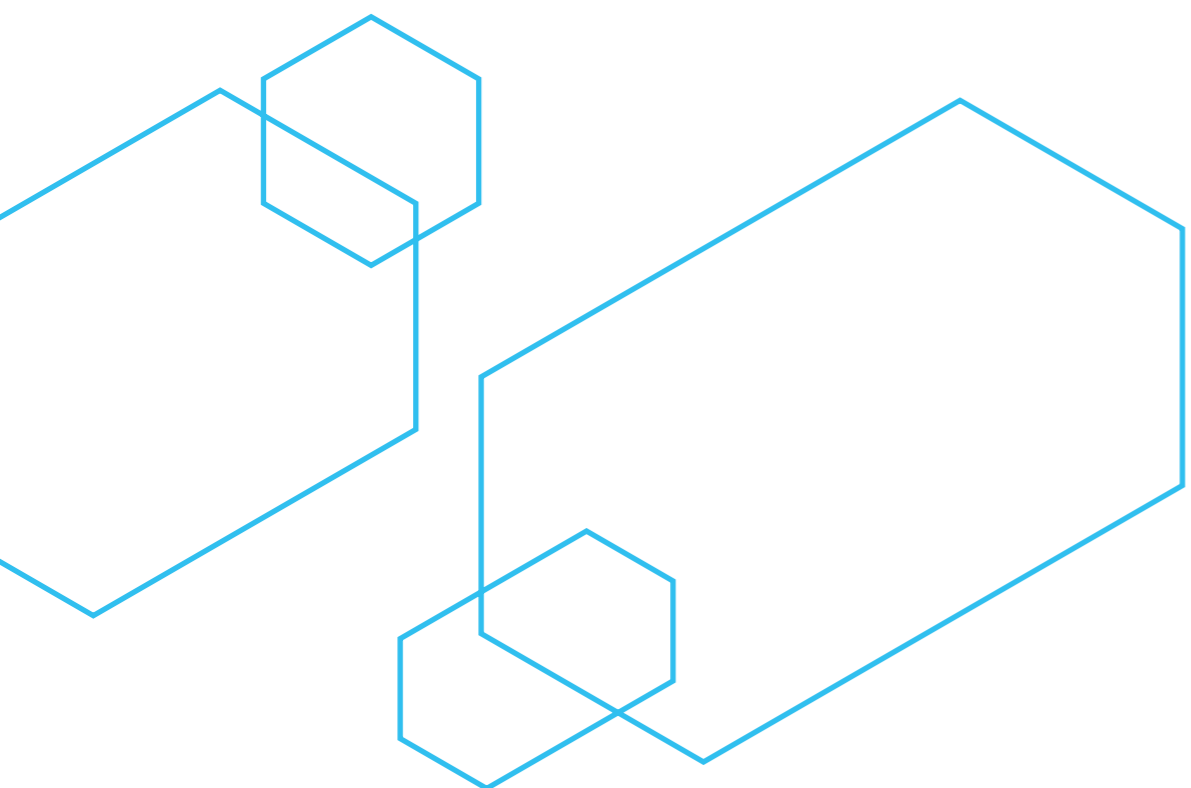


Figure 2. Top 15 countries and regions in a) journal publication and b) patent publication volume related to biomedical applications of 3D printing



How 3D printing works

As discussed previously, the past two decades have seen an influx of 3D printing innovations, particularly in biomedicine. Before we delve further into these 3D printing trends, we will review the key printing technologies utilized, and the materials used to fabricate tissues, implants, and more.

3D printing technologies

3D-printing technology falls into four broad categories: Powder bed fusion, jetting, extrusion, and photopolymerization. Each technique has its own strengths and limitations, and specific applications in biomedicine.⁵

Powder bed fusion

Powder bed fusion (PBF) is a 3D-printing technique that involves spreading layers of powder-based material over the build platform, followed by the rapid solidification for each layer of the 3D-printed product. Examples of this technique include SLS and electron beam melting, which use a laser or electron beam respectively to melt and fuse the powder together across successive layers.⁵⁻⁷ The PBF process uses any powder-based materials, though the most common materials used include ceramics, thermoplastic particles, metal powders, alloys, plasters, and composites.⁵

Jetting

The concept of jetting is based on the regular inkjet printer. The liquid materials are injected as droplets through nozzles and quickly solidify to form a layer of material based on the path of computer-aided design (CAD). The material jetting process can be applied to any materials in the fluid phase or in suspension, such as polymers, nanoparticles, metals, ceramics, and bio-related materials.^{8,9}

Extrusion

Extrusion uses a nozzle to deposit the heated material layer-by-layer on a path determined by CAD software to build up the 3D product. FDM, one of the most common 3D printing methods, is an example of extrusion. Another extrusion-

based technique that has gained popularity in pharmaceutical applications is pressure-assisted microsyringes (PAM). In PAM, semi-solids (gels or pastes) are extruded continuously layer-by-layer through a syringe-based tool-head. Though FDM printing methods offer the advantage of low cost, PAM requires lower temperatures to print products, and does not require a drying time, during which a printed product can deform or shrink.¹⁰ Extrusion is most used with solid materials like thermoplastics (e.g., polyamides, poly(lactic) acid, and acrylonitrile butadiene styrene copolymer).^{10,11}

Photopolymerization

In photopolymerization, the building platform is gradually lowered inside a vat of liquid polymer resin. As the platform lowers, an ultraviolet light selectively cures the photopolymer layer-by-layer from top to bottom. SLA is a common example of the photopolymerization approach, and was the first system of additive manufacturing that offered high resolution and high printing speed. The photopolymerization process uses biocompatible or biodegradable photopolymers such as polyvinyl alcohol (PVA), polyethylene glycol (PEG), and polyethylene glycol diacrylate (PEGDA).¹²

Trends in 3D printing technologies

All four major 3D printing technologies have been used in biomedical applications, and analysis of the CAS Content Collection shows that the number of publications for each technique has increased markedly from 2014 onwards. Extrusion has seen the most dramatic growth in biomedical applications, followed by PBF. In contrast, jetting technologies have seen a more gradual rise (Figure 3). The journal and patent publication trends for each technology indicate that the volume of journal publications exceeds patent publications (Figure 4). Interestingly, patents account for a markedly lower proportion of jetting publications compared with the other technologies (Figure 2B), indicating that less innovation has occurred overall with this type of 3D printing technique.

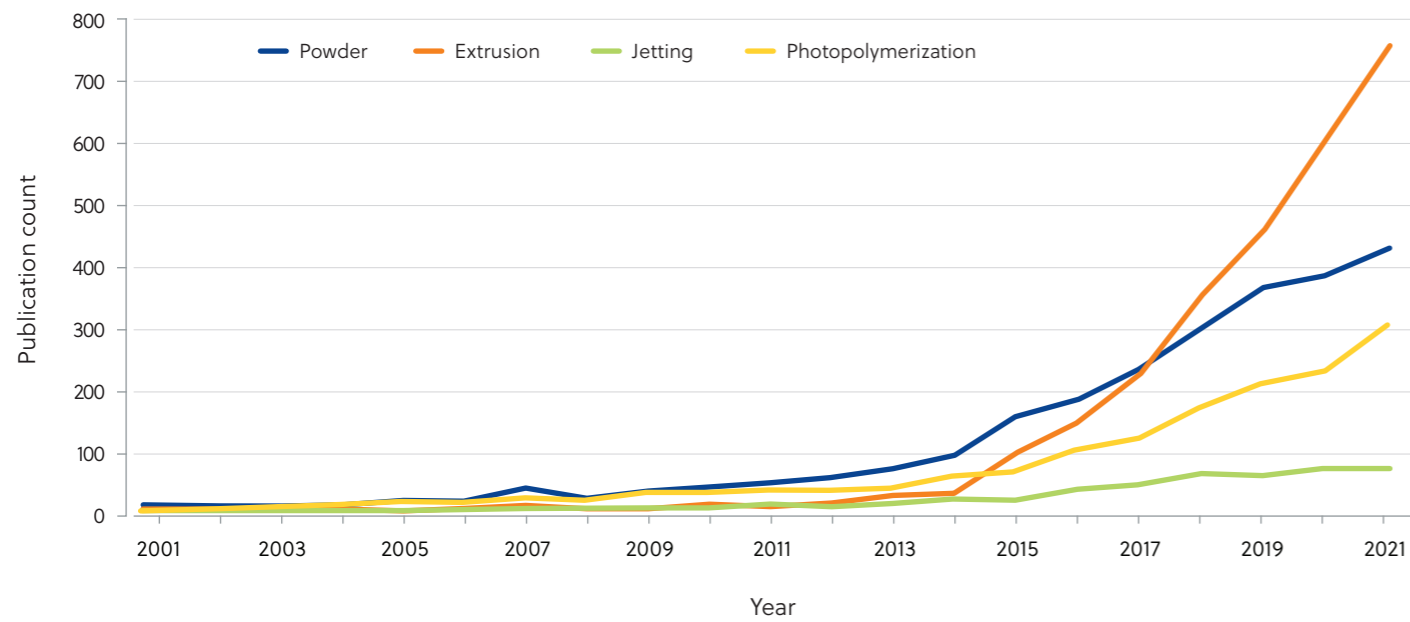


Figure 3. Publication trends for different techniques of 3D printing used in biomedical applications

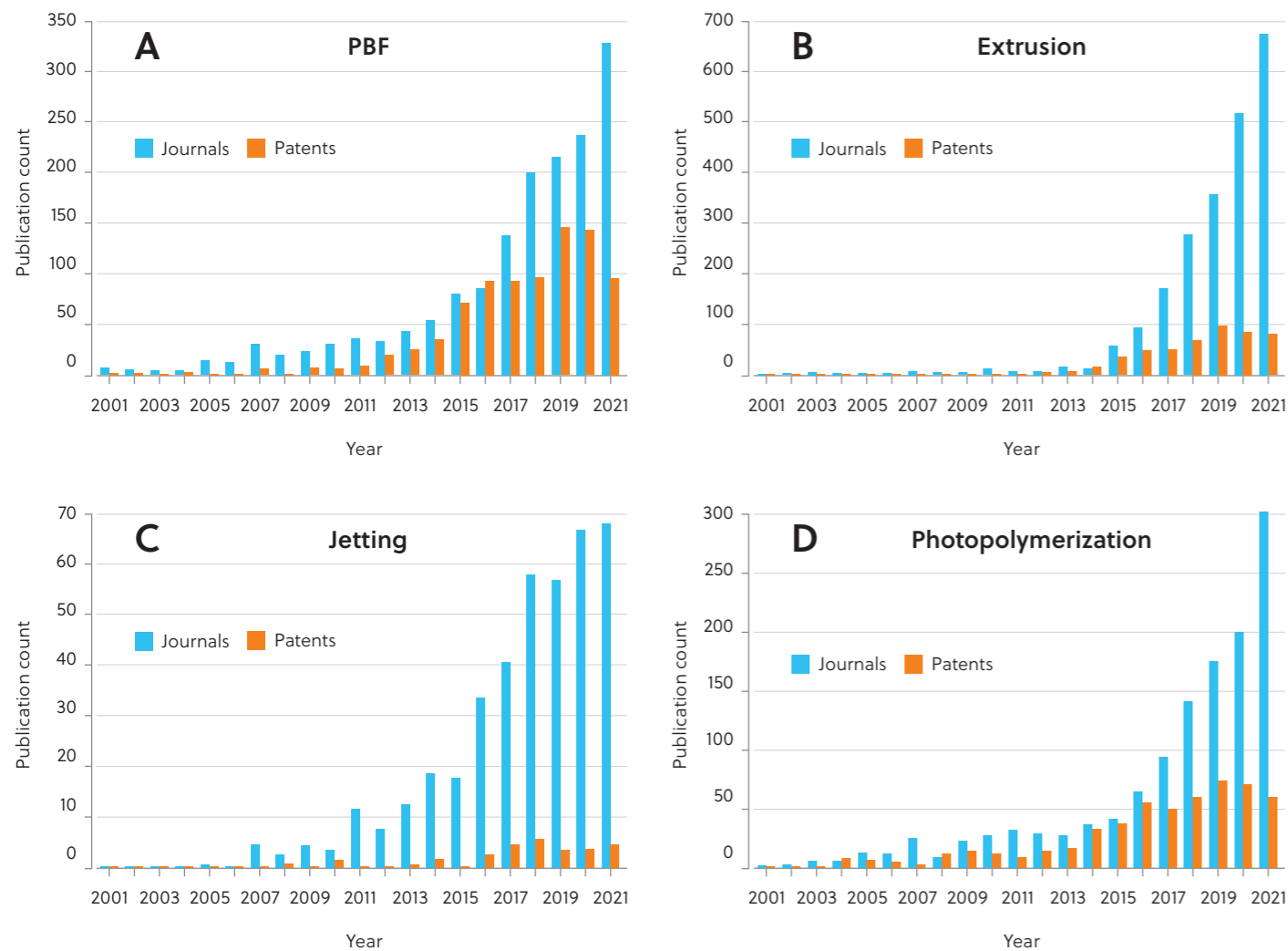


Figure 4. Comparison of journal and patent publication trends for 3D printing techniques used in biomedical applications. (a) PBF; (b) extrusion; (c) jetting; (d) photopolymerization

3D printing materials

Over the past 20 years, several synthetic polymers have been utilized in 3D printing for biomedical applications (summarized in Table 1). The unique properties of each polymer can be harnessed for different purposes. For example, polycaprolactone (PCL) and poly(lactic acid) (PLA) are both linear polyesters used extensively for 'organ-on-a-chip' platforms. These polymers

are non-toxic and have relatively low melting points (60°C) in comparison with other biocompatible thermoplastics, meaning that they produce high cell viability during the printing process.^{13,14} Polyethylene is another commonly used polymer, with its porous, high-density form making it the ideal material for medical implants and prosthetics.¹⁵

Table 1. Synthetic polymers and their biomedical applications

Material	Applications
Polycaprolactone	Liver-on-a-chip; bone generation; cartilage reconstruction ^{13,14}
Polyethylene	Medical implants, facial and cranial reconstruction ¹⁵
Poly(lactic acid)	Tissue engineering; medical implants, screws and stitches ¹⁶
Poly(vinylpyrrolidone)	Tissue engineering ¹⁷
Polystyrene	Bioreplication/biotemplating ¹⁸
Poly(methyl methacrylate)	Dental materials (e.g., orthodontics), drug loading/drug delivery ^{19–21}

Made up of crosslinked polymer chains with 3D network structures, hydrogels have unique properties that make them closely resemble living tissues: they have a high water content, they are soft in structure and highly porous. When combined with 3D printing technology, synthetic hydrogels can be used to create 3D scaffolds for use in tissue engineering. Hydrogels made of PEG and PVA are widely used for 3D scaffolds. Their biocompatibility, absence of immunogenicity, and adjustable stiffness make them ideal for use as biomaterial inks to produce vascular structures, as well as for cartilage tissue engineering.^{12,22} PEGDA, a derivative of PEG, has been utilized in vascular construction and in ear construction as a sacrificial material.¹² Polymers can also be combined to create synthetic hydrogels with specific properties. Poly(lactic-co-glycolic acid) is a co-polymer of PLA and poly(glycolic acid) that has been used for bone and cartilage implants due to its low melting point (120°C) and its biocompatibility properties.²³ Other PEG-based hydrogels including poly(ethylene glycol)methacrylate and poly(ethylene glycol)-tetra-acrylate have too been assessed for application in the reconstruction of bone and cartilage and the construction of vascular networks.¹²

Natural hydrogels

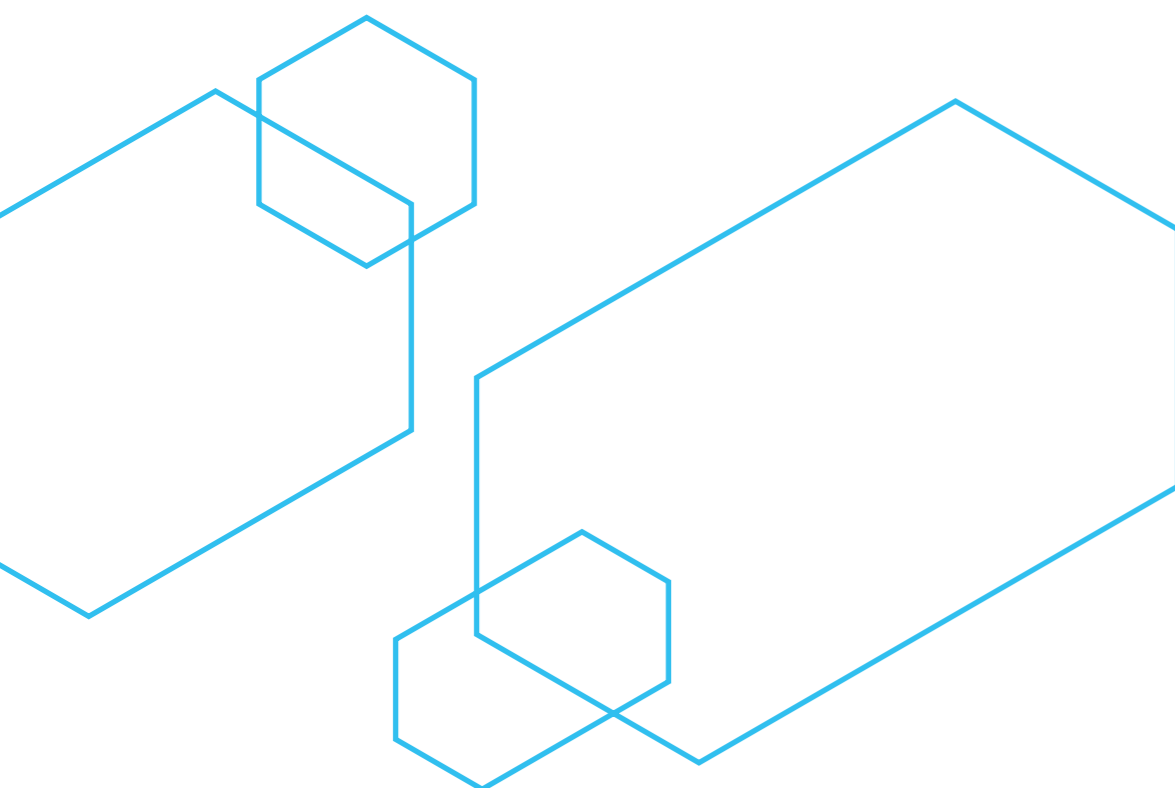
The most commonly utilized natural hydrogels in 3D printing are gelatin, collagen, alginate, and hyaluronic acid. Natural hydrogels are biodegradable and can effectively replicate native extracellular matrix-like environments required for cellular activities. Due to these properties, natural hydrogels can be used in various applications such as organs-on-a-chip or as scaffolds for cartilage, vascular networks, skin tissue, and muscle constructs. Though the applications of natural hydrogels are numerous, they are limited by low mechanical strength, immunogenicity, and stability compared with synthetic hydrogels.¹²

Inorganic substances

Inorganic substances are widely utilized in biomedical applications of 3D printing due to their unique structural properties. Common substances and their biomedical applications are summarized in Table 2.

Table 2. Inorganic substances and their biomedical applications

Material	Applications
Hydroxylapatite, HAp (Ca ₅ (PO ₄) ₃ (OH))	Filler in dental material and bone repair ²³
Tricalcium phosphate	Filler for bone regeneration and repairs in combination with other biopolymers ²³
Graphene/graphene oxide	Bone regeneration and repair (as an additive to reinforce polymers such as PLC) ²⁴⁻²⁶
Zirconium dioxide (Zr(OH) ₂)	Filler in dental prosthetics or bone implant materials in combination with other polymers ²⁷⁻²⁹
Alumina	Dental crown model, artificial teeth, and denture base materials ³⁰
Silica	Dental crown model, artificial teeth, and denture base materials ³¹
Silicon	Dental crown model, artificial teeth, and denture base materials ³²
Carbon	As implants for bone tissue remodeling and microlattice 3D hybrid scaffolds for tissue engineering ³³
Titanium (Ti ₆ Al ₄ V)	Bone tissue remodeling, bone defect repair, and knee implants ³⁴⁻³⁶
Gold	Nanotubes or nanowires combined with decellularized extracellular matrices to form hydrogel for tissue engineering, or directly for medical implant ^{37,38}



Using data from the CAS Content Collection, we extracted publication counts based on substances related to the 3D printing in biomedical applications (Figure 5). Polycaprolactone, hydroxylapatite, and poly(lactic) acid are the three most commonly mentioned 3D printing materials in published articles, which may reflect their widespread use in medical implants, bone/cartilage repair, and dental materials.

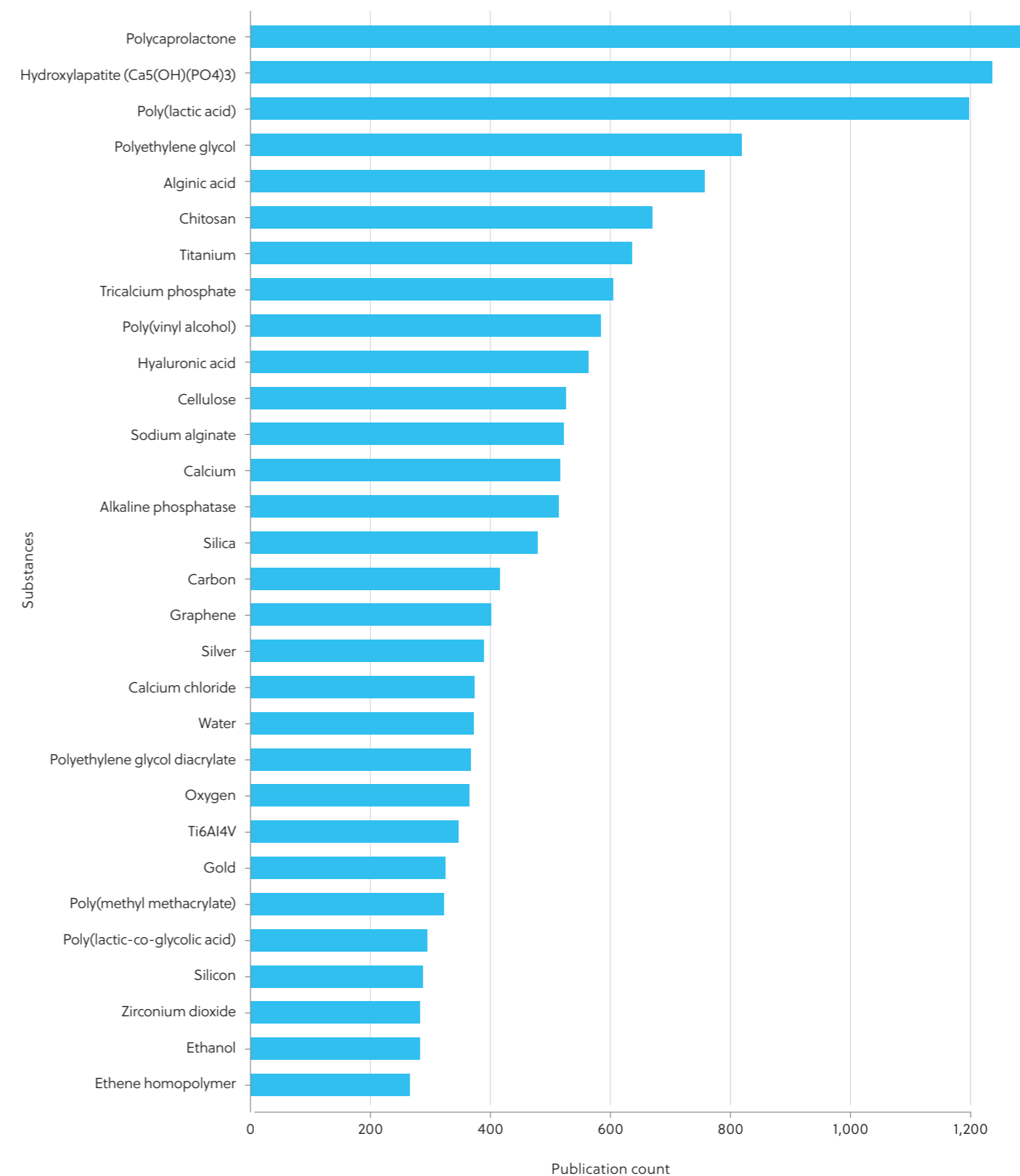


Figure 5. Top 30 substances having appeared most frequently in publications on biomedical applications of 3D printing

The biomedical applications of 3D printing

3D printing techniques have been extensively applied to various fields. We have briefly discussed the key technologies and materials used in biomedical applications of 3D printing. Now we will delve into the most recent developments in this area, with further insights from the CAS Content Collection.

Tissue and organ fabrication

Tissue and organ fabrication, or biofabrication, is an evolving research field that has recently received significant attention, particularly in the field of tissue engineering and regenerative medicine. Biofabrication can be defined as “the automated generation of biologically functional products with structural organization from living cells, bioactive molecules, biomaterials, cell aggregates such as micro-tissues, or hybrid cell-material constructs, through Bioprinting or Bioassembly and subsequent tissue maturation processes”.³⁹ By utilizing cells, biomaterials, and 3D printing technology, it is possible to produce constructs that mimic the function and design of their counterparts within the human body.⁴⁰

Cartilage fabrication

Cartilage damage through conditions such as osteoarthritis leads to progressive impairment of joint structure and function, lowering patient quality of life and resulting in substantial costs for health and social care systems. Therefore, tissue engineering applications with cartilage have become a popular focus in the biomedical field. Articular cartilage and menisci can be fabricated with bioprinted scaffolds loaded with stem cells (used to prevent complications such as immune response rejection). This technique allows for the development of complex structures and can be used to construct different types of cartilage based on the patient’s specific needs.⁴¹

Muscle tissue engineering

Skeletal muscle tissue engineering strives to develop tissue constructs to replace or restore diseased or injured skeletal muscle tissue. 3D bioprinting is an excellent tool for this purpose, capable of mimicking the hierarchical structure of native muscle tissues.⁴²

A key breakthrough in this area was the development of a bioprinter to fabricate 3D patches of smooth muscle cells encapsulated within collagen. The resulting patches were able to replicate the cell distribution of the tissue, while maintaining viability over long-term culture.⁴³

Muscles from vital organs, such as the heart, can also be created. Researchers at Tel Aviv University in Israel have successfully bioprinted vascularized cardiac patches using a patient’s own cells. The patch allows stem cell adhesion, differentiation, and proliferation to a damaged heart, improving wound healing and functional preservation.⁴⁴

Several materials have been explored to create muscle tissue constructs with tunable properties. For instance, the hydrogel methacryloyl (GelMA) has been combined with alginate to achieve the desired properties for bioprinting, enabling the material to effectively mimic the native skeletal muscle tissue environment.⁴²

Skin tissue fabrication

Tissue-engineered skin substitutes have widespread applications, from replacing animals in in vivo research to aiding patients in tissue regeneration. Skin is a complex organ composed of three layers, each with its own individual role and cellular components. As such, skin tissue fabrication has posed unique challenges in tissue engineering. A laser-assisted bioprinting technique can overcome these challenges, allowing for the positioning of different cell types in the exact required 3D spatial pattern.⁴⁵

Trends in tissue and organ fabrication

Analysis of the CAS Content Collection shows that concepts such as “tissue engineering”, “tissue scaffolding”, and “bioprinting” appear frequently in 3D printing publications related to tissues and organs (**Figure 6**). These research trends demonstrate that tissue and organ fabrication is a key focus in regenerative medicine.

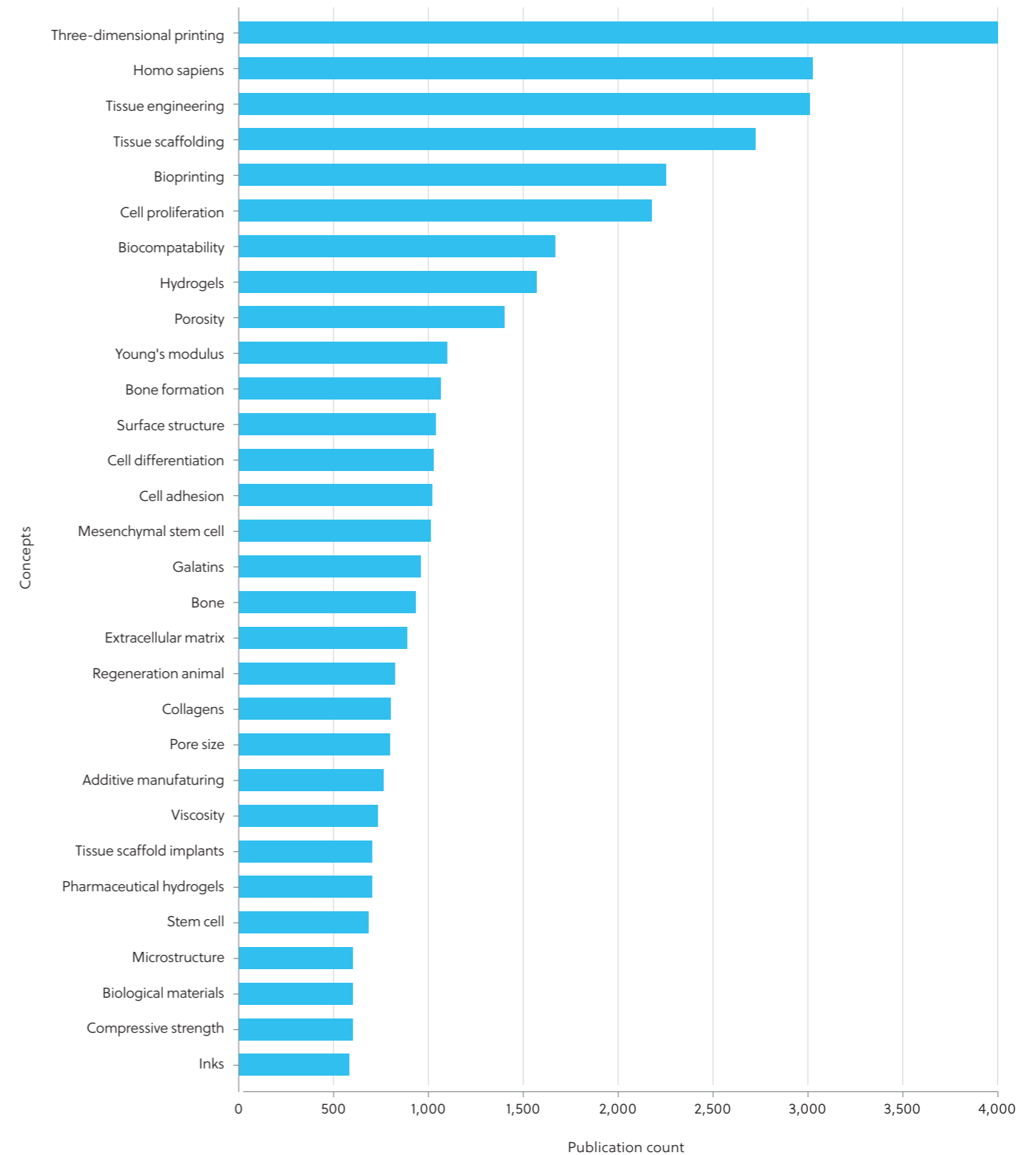


Figure 6. Top 30 concepts having appeared most frequently in publications on application of 3D printing in tissue/organs

Pharmaceuticals

3D printing has several potential applications in pharmaceuticals, including developing drug products, implants, and drug delivery systems. Several of the main 3D printing technologies have been successfully applied to pharmaceutical research, with extrusion-based techniques such as FDM most intensively investigated.⁴⁶

Personalized medicine has often been seen as an unattainable goal in the field of pharmaceuticals; yet 3D printing may help to make this a reality, allowing medicines to be tailored to the individual needs of each patient. The technology enables us to modify the dosage, shape, size and release characteristics of pharmaceutical products.⁴⁷

3D printing is not just for manufacturing tablets; powder bed fusion techniques have been used to develop implants that offer sustained release of the active pharmaceutical ingredient. Stereolithography has also been applied to creating microneedles for transdermal delivery of drugs and vaccines, though these manufacturing technologies are still difficult to apply to the pharmaceutical industry.⁴⁶

Implants and prosthetics

Due to high manufacturing costs, traditional prosthetics remain inaccessible for those who need them. However, 3D printing has opened new capabilities in creating prosthetics and implants.⁴⁸ Images from x-ray, magnetic resonance imaging (MRI) or computerized tomography (CT) can be translated into .STL 3D print files. Using this information, the healthcare sector can rapidly fabricate customized prosthetic limbs and surgical implants occasionally within 24 hours.^{49,50}

Body parts can be replicated not only in appearance, but also in function. Prosthetic ears have now been developed with the ability to detect electromagnetic frequencies. These prosthetics, which are fabricated with silicon, chondrocytes, and silver nanoparticles, may allow the recipient to detect sounds.⁵¹

3D printed implants have been effectively utilized in orthopedic oncology. Malignant bone tumors can occur across the skeleton, and limb salvage surgery is a common approach to remove the affected bone. 3D printing-customizable implants can replace the traditional tumor prosthesis and auto/allobone grafts. Titanium alloy powder is used for bone reconstruction and common printer types include electron beam melting or selective laser melting. Implants can not only focus on filling bone defects but attempt functional reconstruction. Though implants are currently made of metal, there is potential for biologic reconstruction using biodegradable or bioprinted materials in the future.⁵²

Use of 3D printing in prosthetics and implants is projected to expand. Analysis of the CAS Content Collection shows that concepts such as "prosthetic implants", "prosthetic materials" and "dental implants" appear frequently in 3D printing publications related to orthopedics and prosthetics (Figure 7).

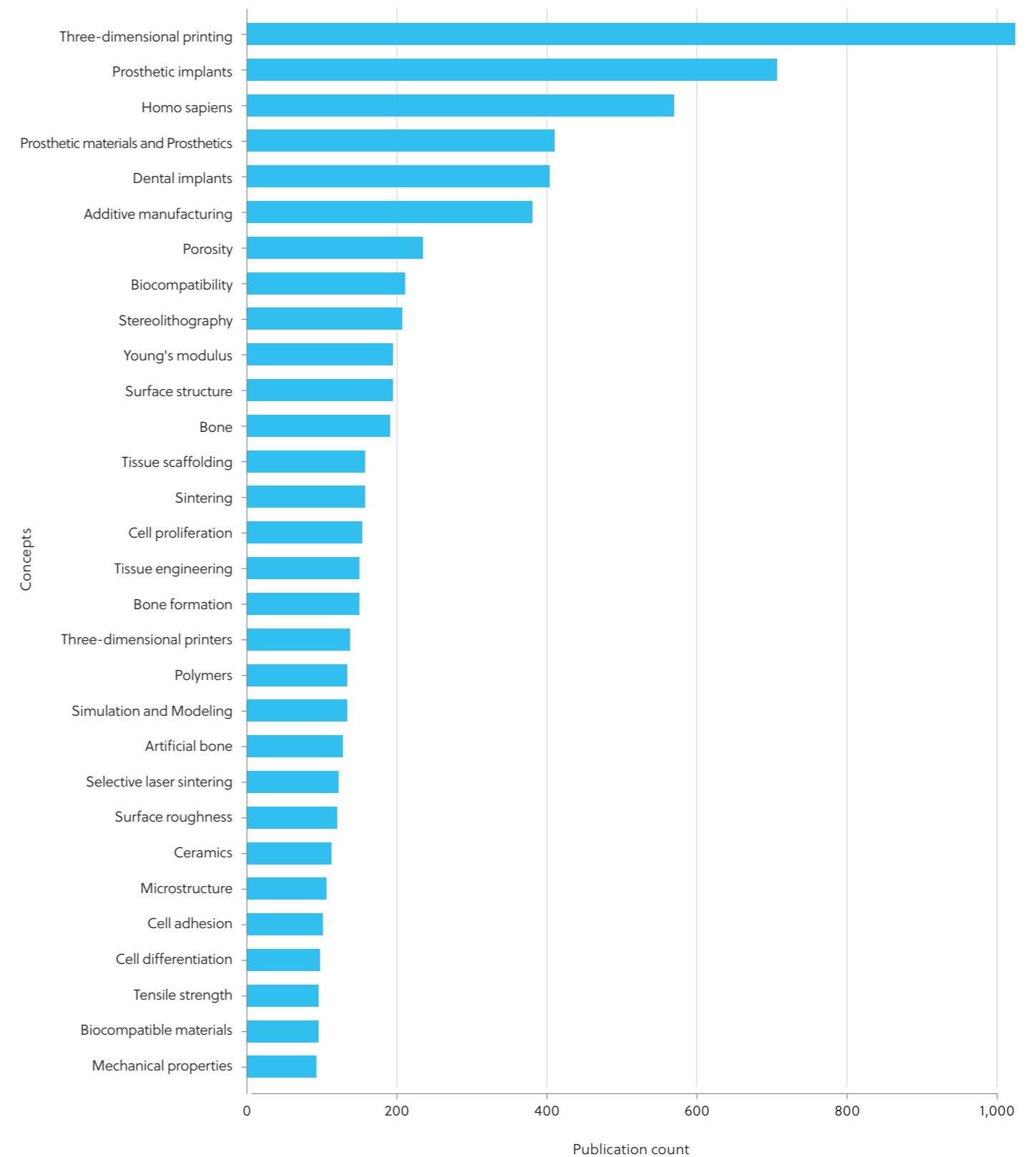


Figure 7. Top 30 concepts having appeared most frequently in publications on application of 3D printing in orthopedics/prosthetics

Other biomedical applications

The potential of 3D printing technology in the biomedical field is vast, with exciting applications in microfluidics, surgical instrumentation, and anatomic modelling described.

Microfluidics

Microfluidics, defined as “the handling and analyzing of fluids at the micrometer scale level”, offers significant advantages over traditional assays used in cell biology by enabling several laboratory functions to be combined onto a single chip. Advancements in 3D printing have helped to speed up and simplify the fabrication of microfluidic devices. Furthermore, 3D printing can enhance the development of more intricate and sophisticated structures such as ‘organ-on-a-chip’ devices, which are designed to simulate the function of organs or systems within the body.⁵³

Several 3D-printing technologies have been applied to this growing field, including SLA, inkjet, and FDM. SLA in particular has a wide number of applications in microfluidics, from fabrication of the master mold to the creation of biological assays. Materials commonly utilized include polydimethylsiloxane, glass and thermoplastics.⁵³

Anatomic modeling

Previously, surgeons primarily relied on two-dimensional (2D) analyses of X-ray, CT, or MRI images when planning surgery. However, 2D representation has its limitations when it comes to the interpretation of complex patho-anatomies. 3D printing can help overcome these limitations by creating an accurate and intricate patient-specific anatomical model of the area being operated upon. Used prior to surgery, these models can aid in accurate sizing and placement for future implants, account for unexpected anatomy, and create models for surgical resection and reconstruction. This planning can serve to decrease overall surgery time, helping to reduce the risk to the patient. Biomodels can also be used as educational aids to augment the

patient’s understanding and capacity for consent prior to surgery. The most common technologies applied to anatomic modeling are FDM, PBF, and SLC, with each approach providing its own strengths and limitations.⁵⁴

Surgical instrumentation

The applications of 3D-printing in surgery are expanding. In addition to the fabrication of models for preoperative planning mentioned previously, 3D printing also allows for the preadaptation of surgical instructions such as fixation plates, shortening operation duration and improving precision.⁵⁵ The CAD package SolidWorks has been used to design a surgical set consisting of hemostats, needle drivers, scalpel handles, retractors, and forceps. The designs were printed using an SLS system and evaluated by practicing surgeons for their ergonomic functionality and performance. The surgeons’ feedback was used to rapidly redesign and refabricate the surgical sets until a fully functional and reproducible set of instruments was created.⁵⁶

Trends in biomedical applications of 3D printing

Analysis of the CAS Content Collection showed that all four of the 3D printing biomedical applications described have risen in popularity in the past decade, particularly tissue and organ fabrication (**Figure 8**). A closer look into the breakdown of publications revealed that the number of journal publications far exceeds the number of patent publications for all biomedical applications (**Figure 9**). This may reflect the time taken for patents to be issued and for inventions to be commercialized. Publications related to bioprinting, a sub-category of tissue/organ printing, were also analyzed (**Figure 9d**), and indicated the growing popularity of this research field.

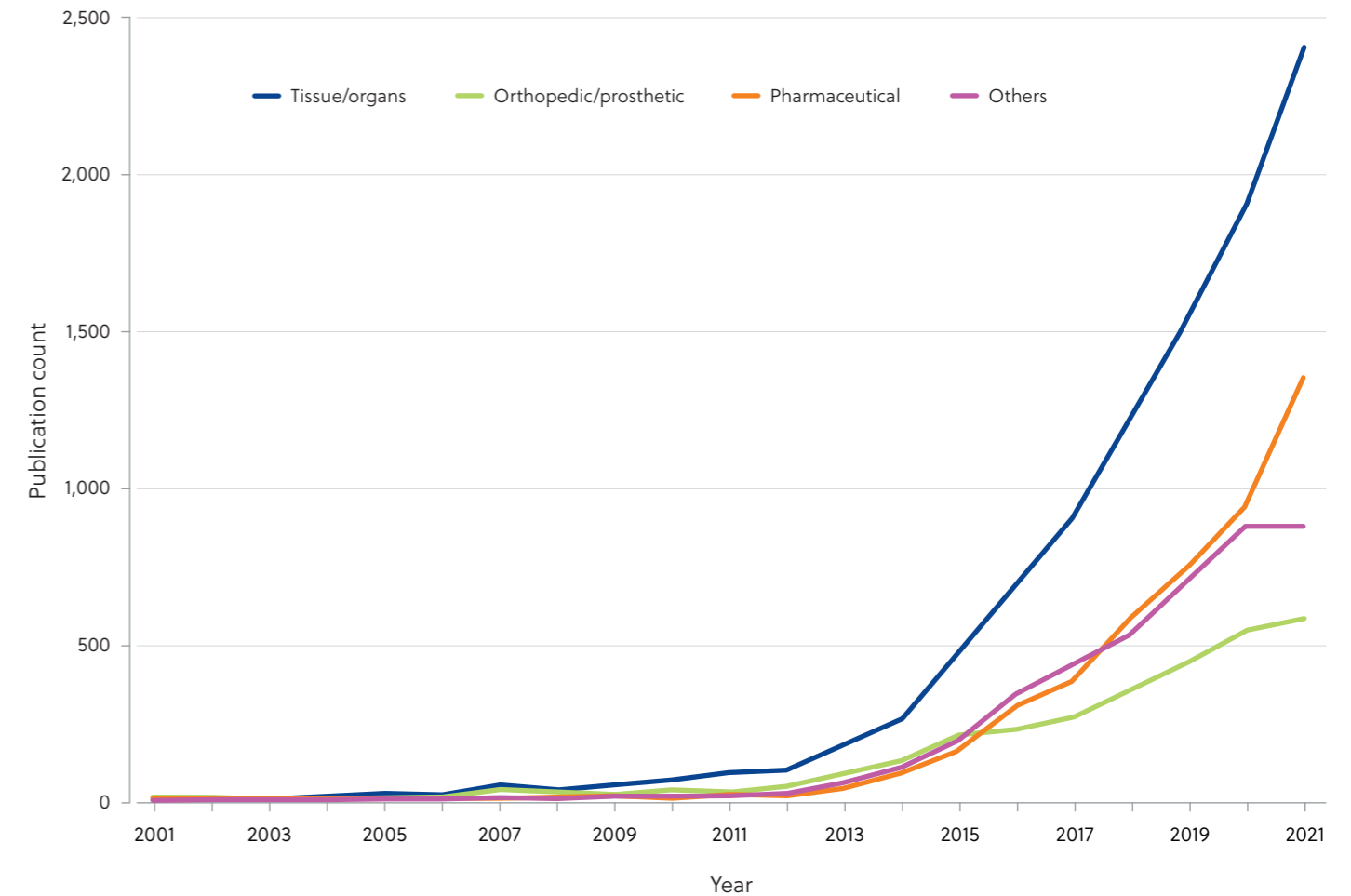


Figure 8. Annual publication trends for different biomedical applications of 3D printing

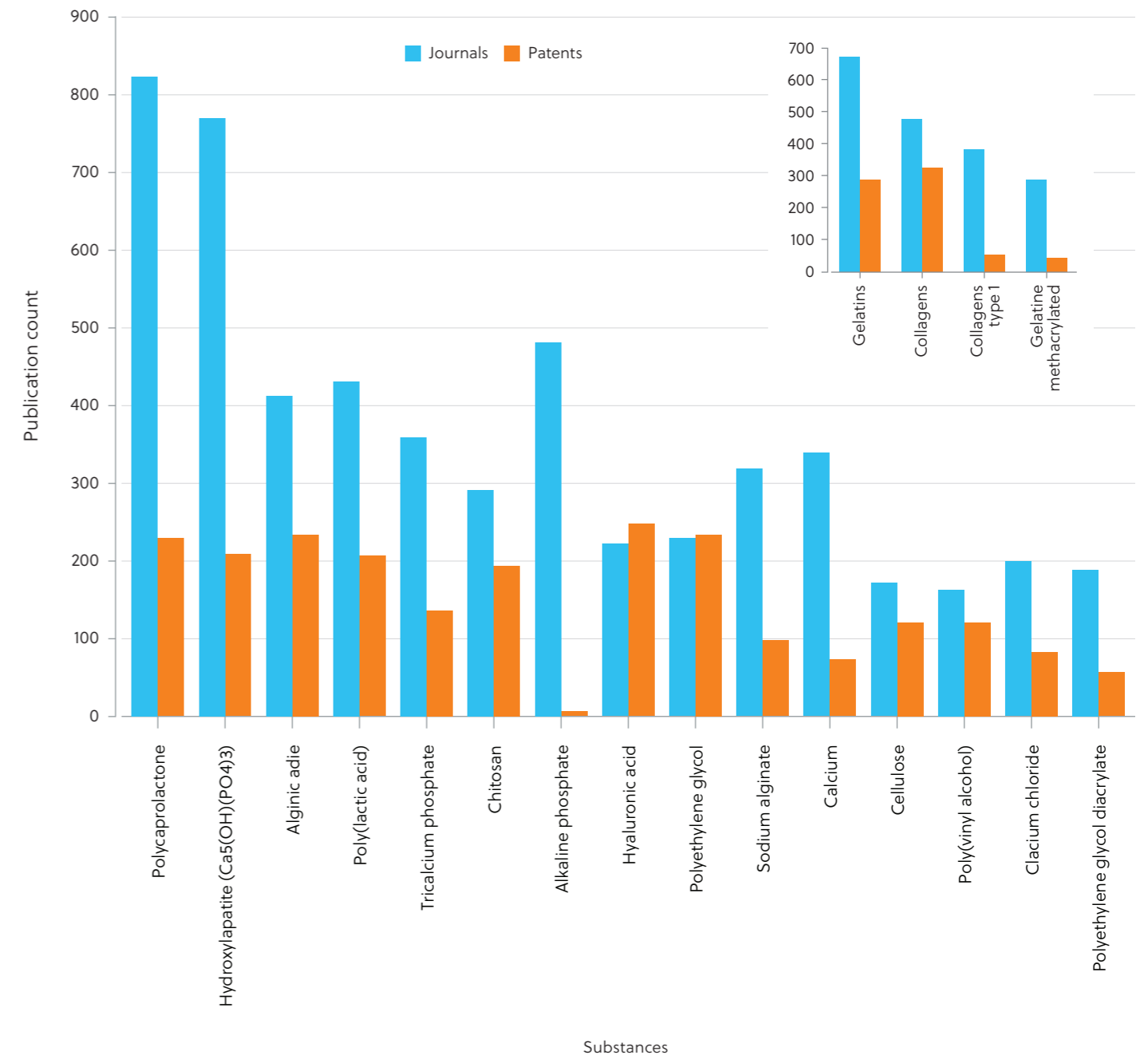
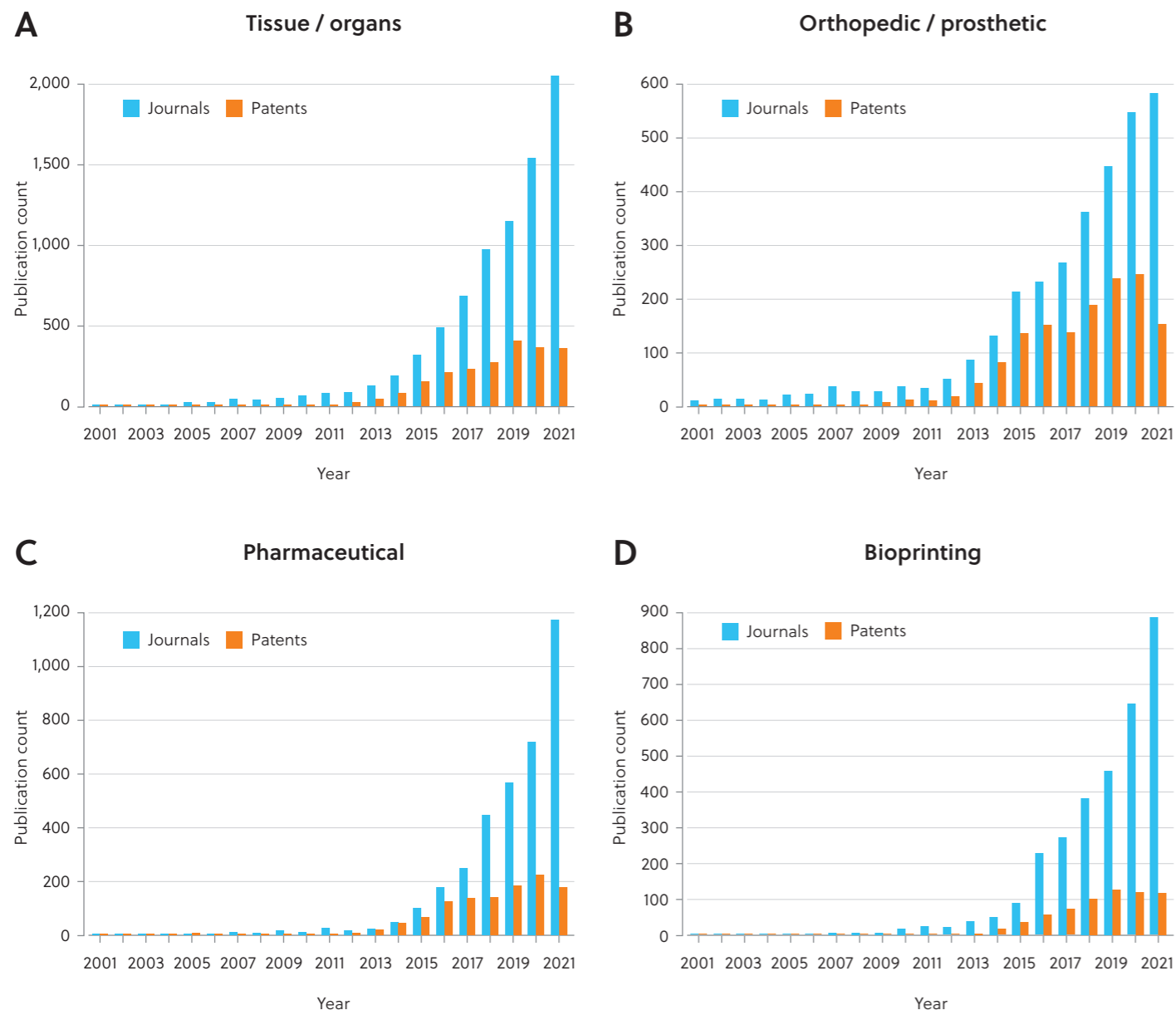


Figure 9. Comparison of journal and patent publication trends for different biomedical applications of 3D printing. (a) tissue/organs; (b) orthopedic/prosthetic; (c) pharmaceutical; (d) bioprinting

Figure 10. Journal and patent publication volumes involving the top 15 frequently occurring substances (as well as top substance concepts) for 3D printing applications in tissue/organs

To further understand 3D printing applications in tissues and organs, we investigated the top 15 frequently occurring substances used in this field (Figure 10). Natural polymers such as gelatin, collagen, alginate, and chitosan were most widely cited, though synthetic

polymers like polycaprolactone and poly(lactic) acid were also featured. For many of these substances, the proportion of patent publications were relatively low; this may represent the potential development of commercialized application using these substances.

In contrast to applications in tissue and organs, analysis of journal and patent publications in orthopedics and prosthetics showed that inorganic substances are generally favored in this field, with hydroxylapatite and titanium featuring most prominently (Figure 11). Interestingly, there is less of a gap between journal publications and patent publications for many of the substances, indicating that many of these may not yet be commercialized.

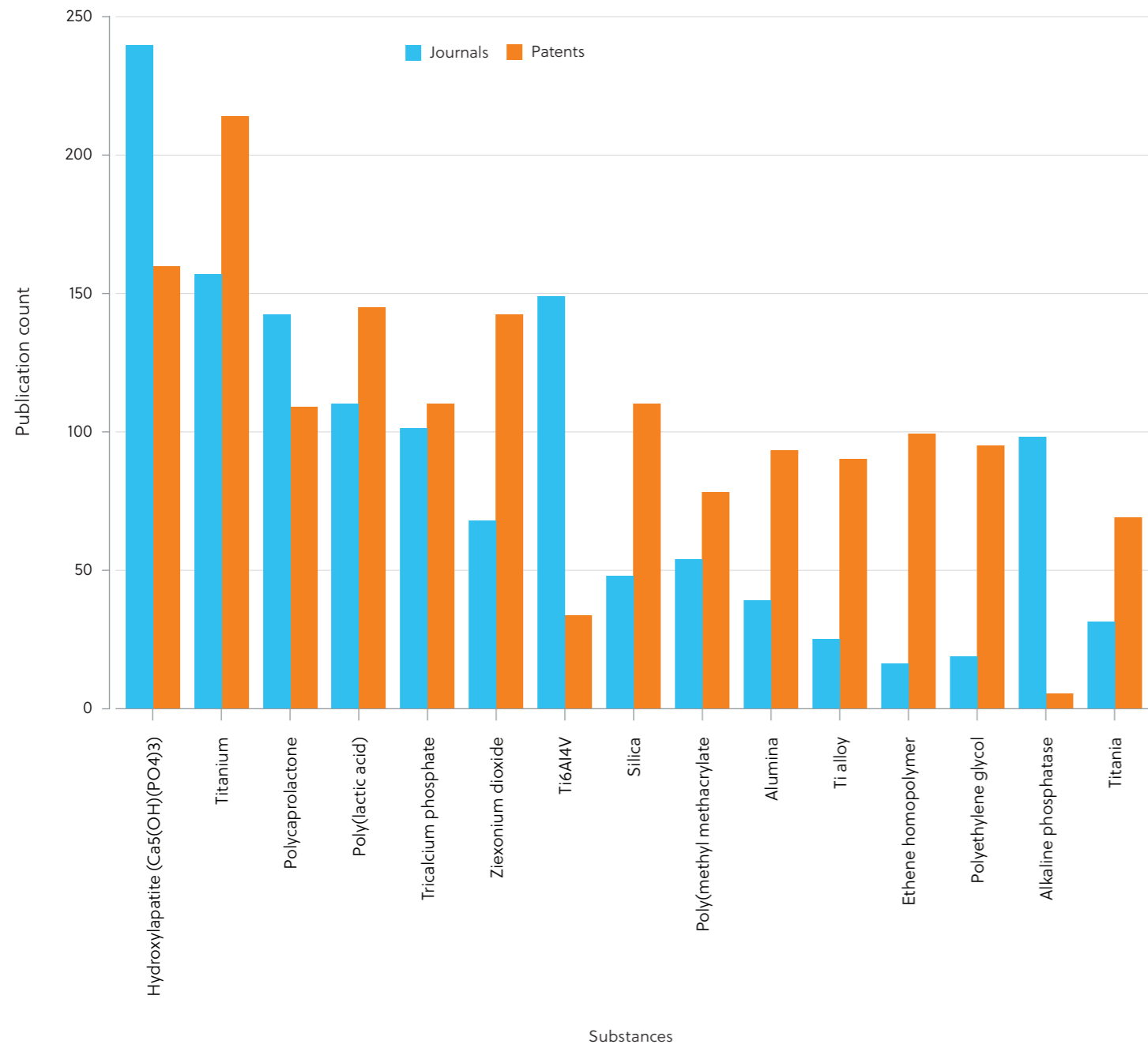


Figure 11. Journal and patent publication volumes involving the top 15 most frequent substances for 3D printing applications in orthopedics/prosthetics

Conclusions

From tissue and organ fabrication to the creation of customized prosthetics and anatomical models, the biomedical applications of 3D printing are expanding. This is reflected in publication trends from the CAS Content Collection, which show an exponential growth in journal articles over the past decade. In contrast, the number of patent publications have plateaued, which may reflect the rapid commercialization of the technology. 3D printing is used most extensively in the fields of tissue/organ engineering. Fabrication of cartilage, muscle, and skin features most prominently in publications, highlighting that this is a key research focus. The main 3D printing technologies utilized across all applications include powder and

extrusion methods, with materials such as PLA, PCA, and hydroxylapatite featuring prominently in publications. In the emerging field of bioprinting, natural polymers are generally favored. Despite these promising advances, several challenges with 3D printing tissue and organs remain, including donor site morbidity and graft failure. Biomechanical limitations and functionality of the fabricated tissue can also be an issue. However, advances in bioinks, media use, and the application of stem cells have made great strides in overcoming these limitations. While challenges remain, the 3D printing industry is projected to grow in the innovative and dynamic field of biomedicine.

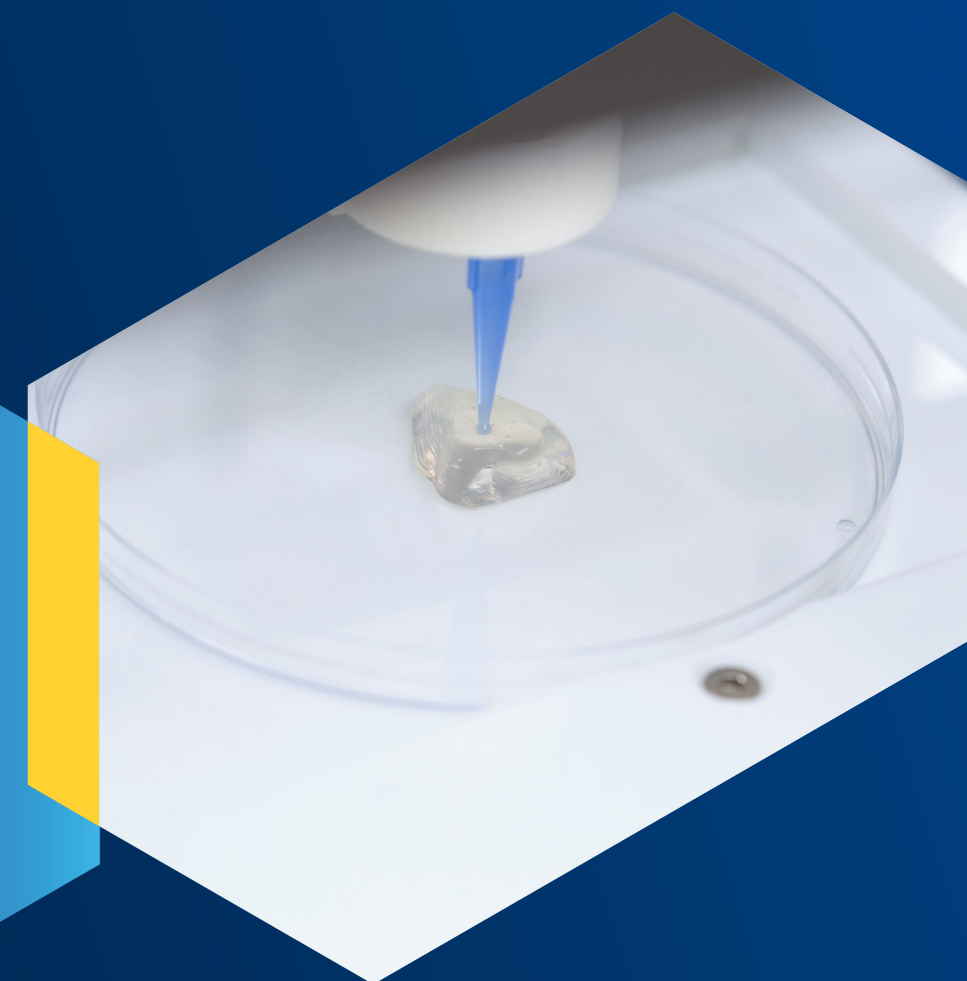
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