CAS INSIGHTS™

BIOMATERIALS
EIGHT EMERGING AREAS RESHAPING MEDICINE

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Introduction

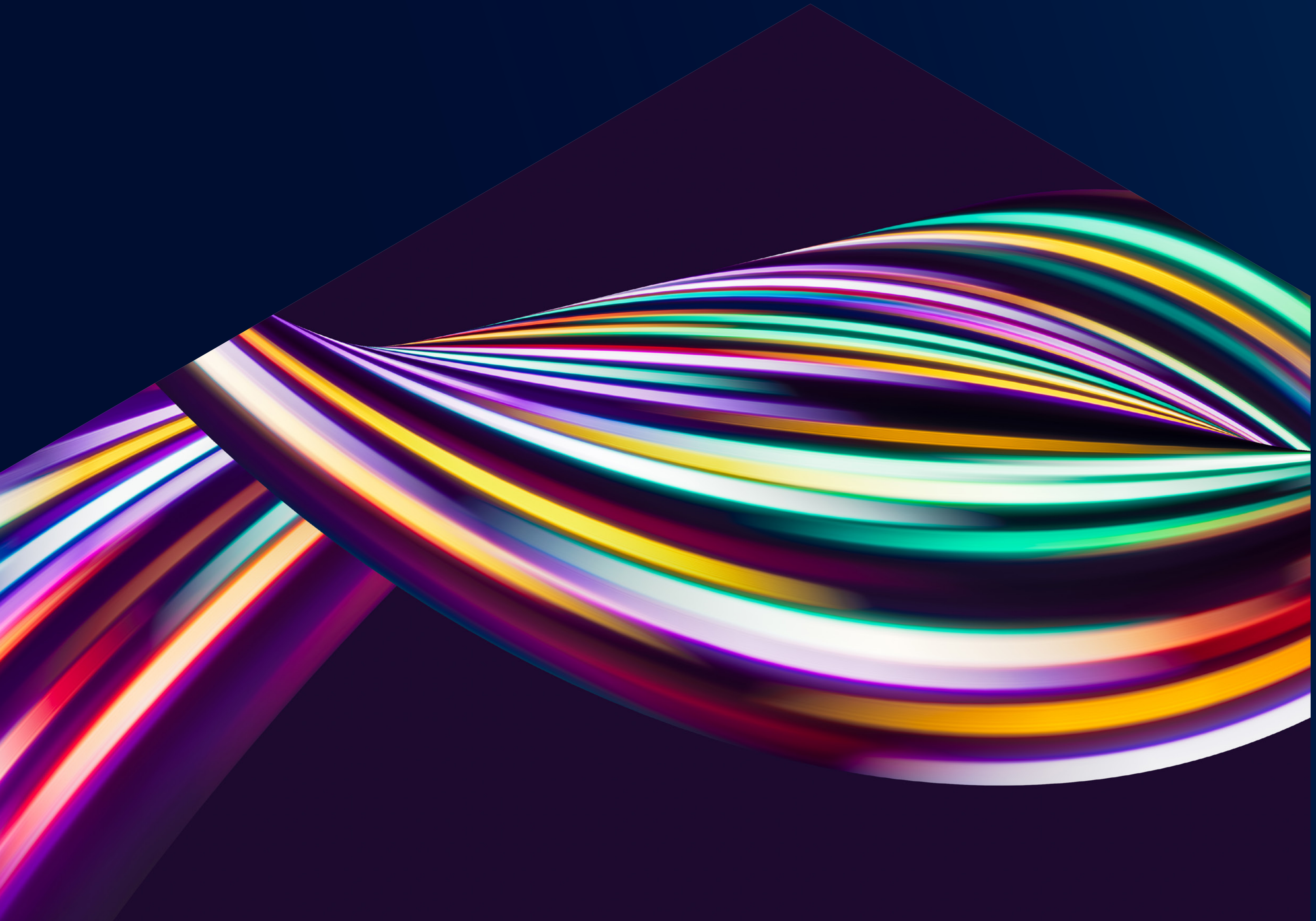
The research and development of materials used in biomedical applications, or biomaterials, has seen rapid expansion and diversification over the last 20 years. From highly engineered synthetic polymers to biodegradable metals to naturally derived substances, their unique properties can be used for diverse functions and applications in medicine. In this report, we have selected eight topic areas that represent the most active and promising biomaterials research fields, ranging from more established fields such as protein-based materials to rapidly expanding ones like bioinks.

To identify these key topics, we used natural language processing to identify candidate concepts with a high growth rate in journal and patent publications between 2020–2022, then classified and narrowed these candidates further based on discussions between subject matter experts (SMEs) at CAS and Westlake University.

After using this method to identify eight key topics, we analyzed the most prominent materials, material classes, applications, and other parameters within each topic. Our data source was the CAS Content Collection′ — the world's largest repository of diverse scientific knowledge.

To identify the relevant set of documents for each topic from the CAS Content Collection, search queries were developed and iteratively optimized by SMEs. The number of documents extracted for each topic ranged from around 4,000 to 120,000.

Through this report, we aim to provide a comprehensive overview of the evolving landscape of biomaterials research and offer insights that may be useful for determining future research directions.



Protein-based materials

Protein-based materials include well-known examples such as silk,[1–3] collagen,[4,5] and keratin.[6–8] Due to their natural origin, many exhibit desirable properties such as biocompatibility, bio-absorbability, and self-assembly that are crucial for their widespread use in biomedical applications.[1] However, the development of new hybrid or composite materials based on naturally occurring protein materials[9,10] is a much more recent endeavor.

Proteins offer ideal mechanical and physical properties for use in the biomedical field, for example, in drug delivery,[11–13] tissue engineering,[14–17] hydrogels,[10,18,19] wound healing,[20,21] surface functionalization of implants,[22–24] and electronic skin.[25,26]

Publication trends

We observed a sustained increase in interest in protein-based materials, evidenced by the growing number of journal publications over the last two decades. Compared to journal publications, the growth in patent publications appears to be relatively flat. This suggests that researchers in the field are more focused on solving fundamental scientific challenges over-commercialization.

Key materials and applications

Based on their function, protein-based materials can be split into four categories: structural, elastomeric, adhesive, and others.

We found the most active class in terms of research activity to be structural proteins (**Figure 1**). In this category, publications related to collagen have shown a moderate increase since 2003, particularly post-2019. Silk-based materials have also shown a steady rise in publications since 2003, reflecting their wide usage. Mussel foot protein and elastomeric proteins such as elastin and resilin also showed a steady increase (**Figure 2A and B**).

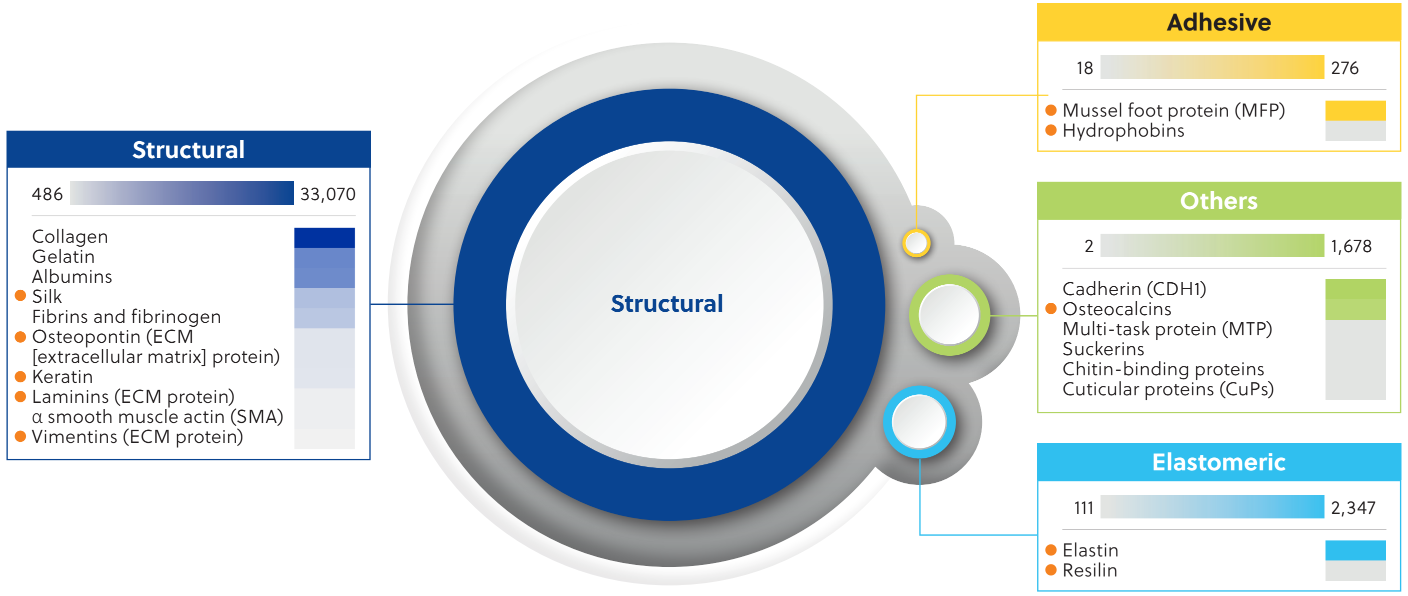
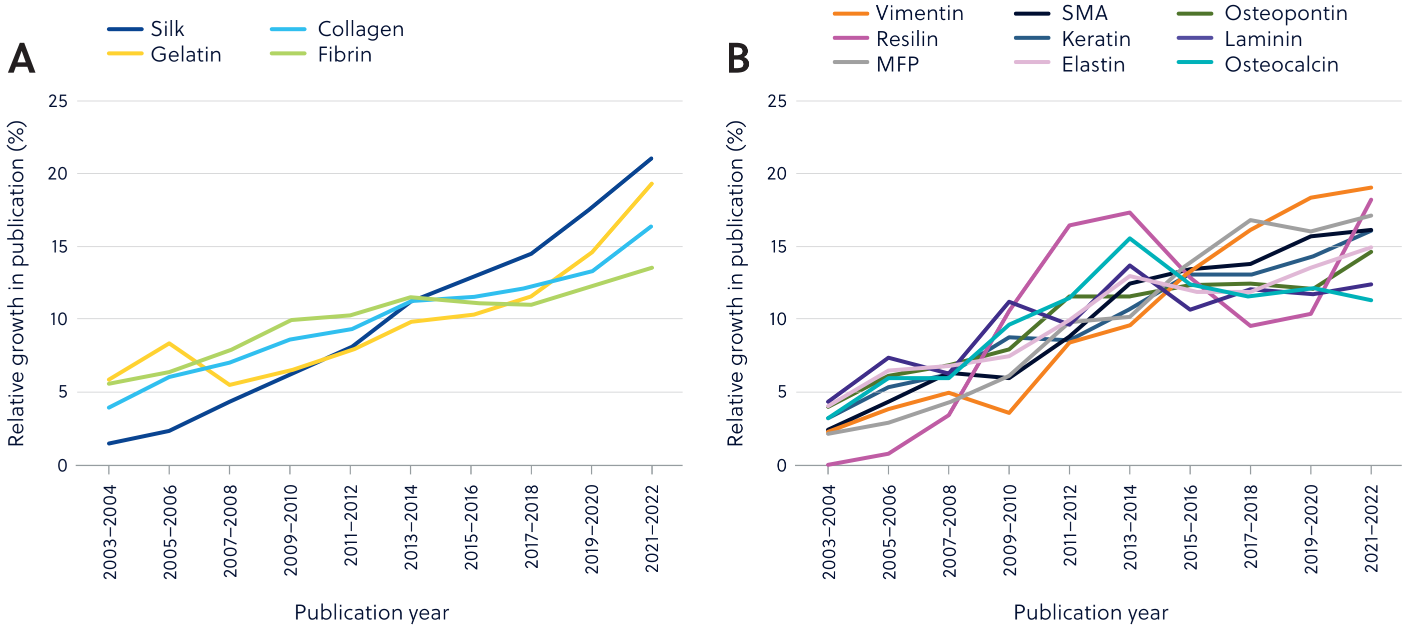


Figure 1. Distribution of proteins in publications (journals and patents) from 2003–2023. The size of the colored circles corresponds to the number of publications. Materials marked with an orange dot (•) demonstrated considerable growth in recent years.

Publication growth over the last two decades indicates an upward trend across all applications of protein-based materials. Drug delivery remains the top category, though we noted a sharp increase in bioprinting[27–29] and electronic skin[30,31] after 2014 and 2020, respectively. Wound healing[32,33] and hydrogels[34,35] also showed considerable growth (**Figure 2C**).



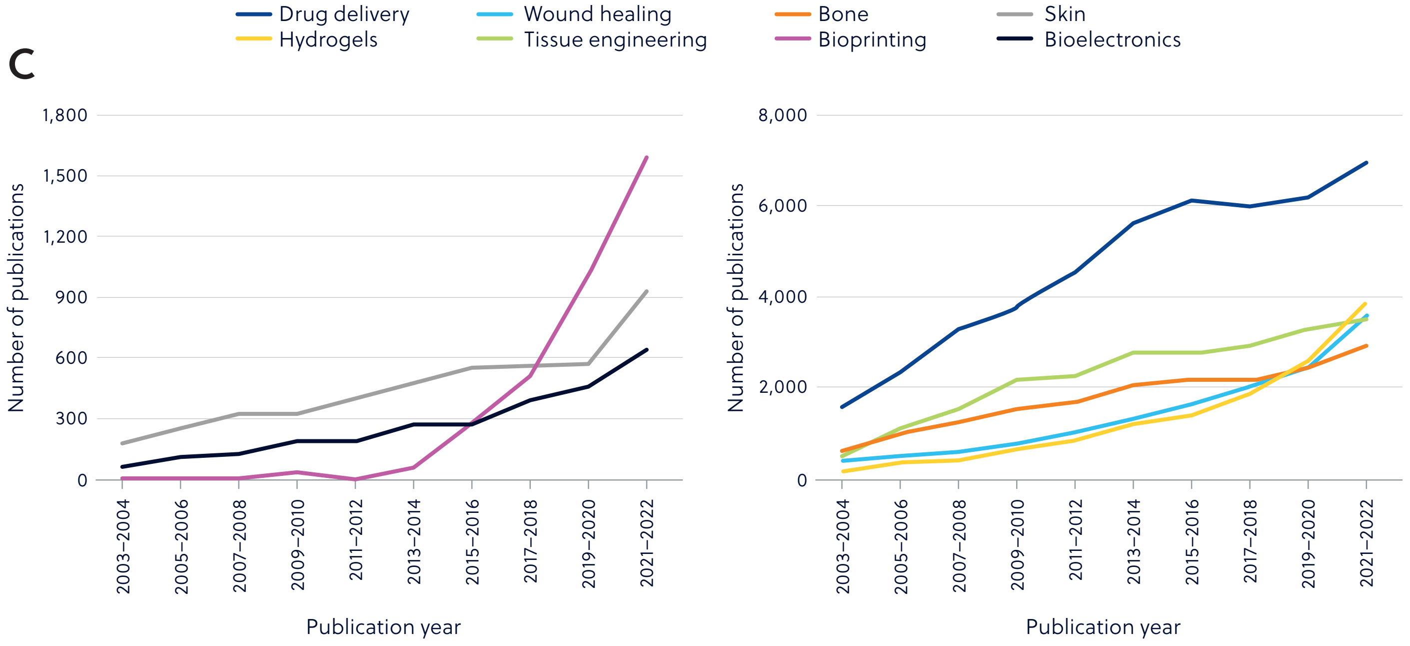
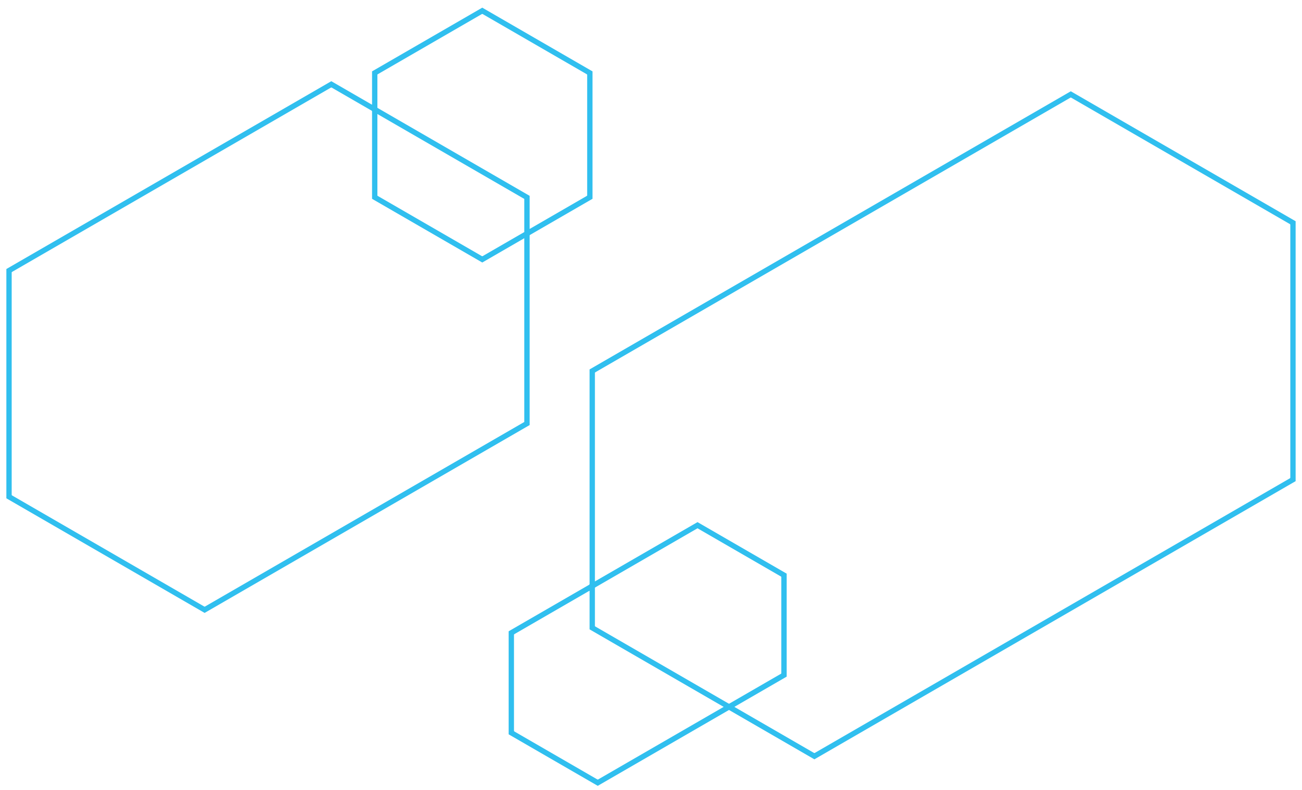


Figure 2. (A and B) Emerging trends of protein-based materials; (C) Growth in applications of protein-based materials based on data from the CAS Content Collection from 2003–2023.

Future challenges

Proteins will continue to play a large role in biomedical materials, and through recent advances, researchers have been able to identify and characterize new methodologies to accelerate the development of new protein-based materials. However, challenges remain, including yield and consistency in recombinant proteins[36–38] and finding new approaches to increase the practical usability of protein-based materials in new biomedical applications.[39–41]



Lipid-based materials

Traditionally, drug delivery has been a complex puzzle, often challenged by the limited solubility, stability, and bioavailability of many therapeutic agents. Among the transformative advancements in drug delivery technologies, lipid-based drug delivery systems have emerged as a formidable force, offering a dynamic range of solutions that transcend traditional pharmaceutical boundaries. This is due to their inherent biocompatibility and versatility, which allows lipid-based drug delivery systems to encapsulate, transport, and release a wide array of therapeutic agents, including drugs, genes, and biologics.

There are various types of lipid nanocarriers, including solid lipid nanoparticles, nanostructured lipid carriers, liposomes, lipid-based micelles, and lipid prodrugs.[42] They have revolutionized drug delivery by overcoming limitations related to drug solubility, stability, bioavailability, and targeted delivery, and they continue to play a pivotal role in expanding treatment options and enhancing patient outcomes across a wide spectrum of diseases and conditions.

Publication trends

The overall growth in patent publications across the last decade shows a positive upward trend. However, the actual number of patents for lipid-based materials remains relatively low. Journal publications have seen more steady growth but, in combination with the more modest increase in patents, could represent unmet commercial potential.

Key materials and applications

Key materials used in the development and application of lipid-based materials can be broadly broken down into lipids, payloads, and emulsifiers. Lipids can be further dissected, as shown in **Figure 3**.

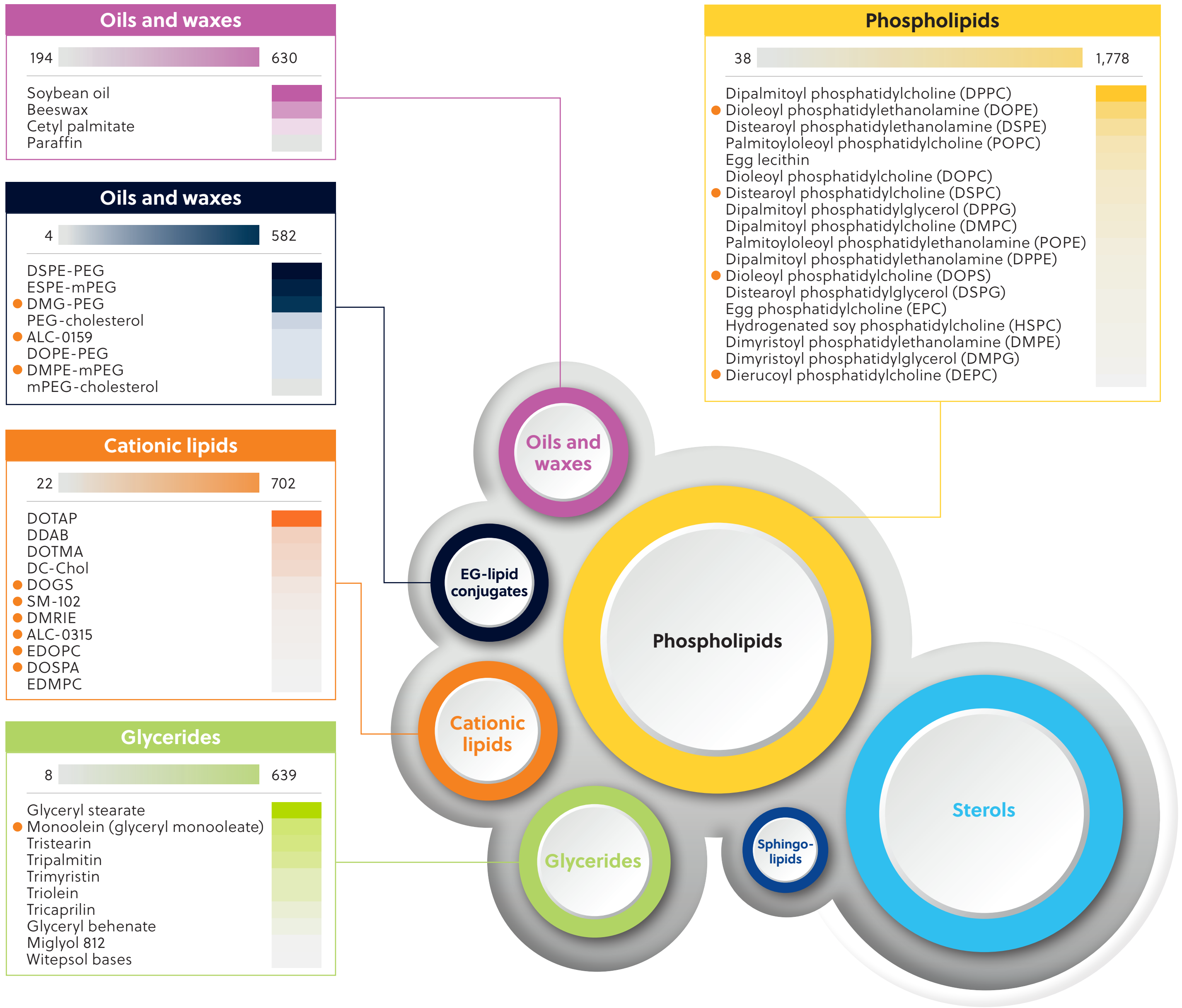
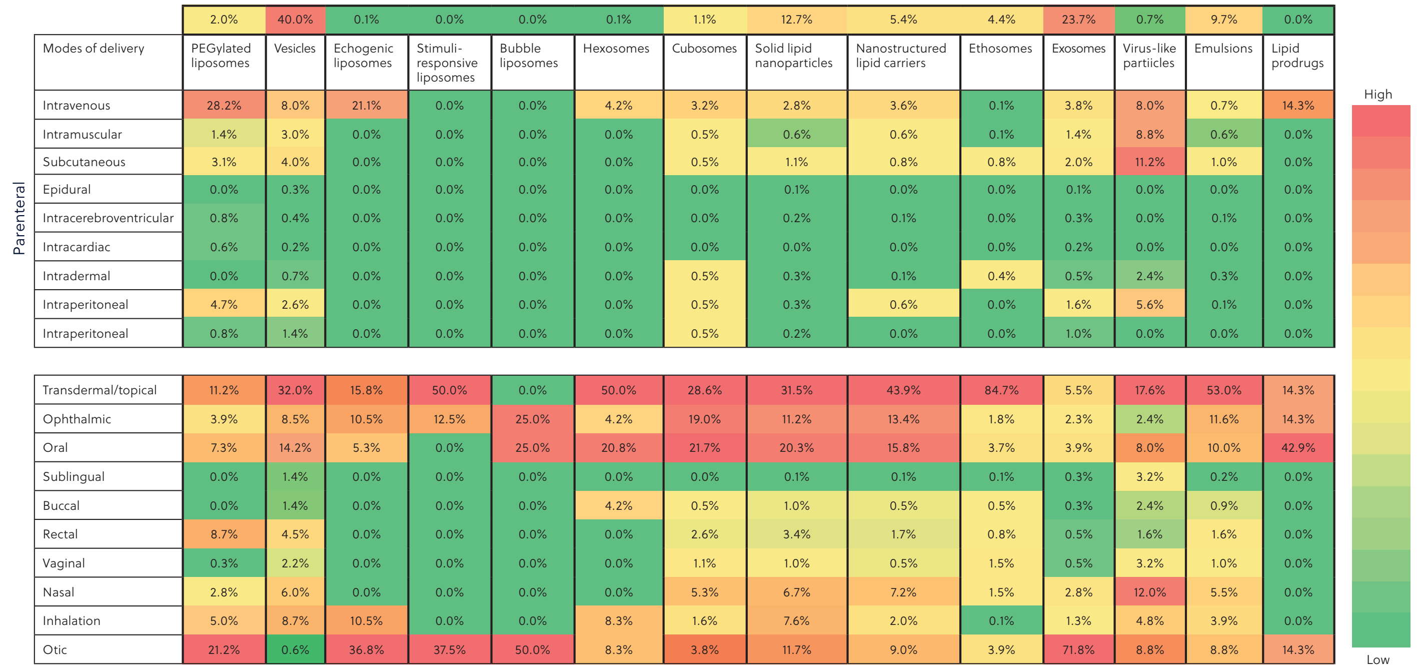


Figure 3. Distribution of lipids in publications (journals and patents) from 2012–2023. The size of the colored circles corresponds to the number of publications. Materials marked with an orange dot (●) demonstrated considerable growth in recent years.

Of the identified lipids, cationic lipids and the Polyethylene glycol (PEG)-lipid conjugate 1,2-dimyrisotyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)] (DMPE-mPEG) exhibited a sharp increase in publications after 2018. Part of the sharp growth of interest in a diverse range of lipids can be attributed to the use of lipids in COVID-19 vaccines.

Drug delivery is the major application for lipid-based materials, representing 86% of related entries in the CAS Content Collection from 2003–2023. Within this application, diverse types and subtypes of lipid nanocarriers are used for formulations administered via various routes, including oral, topical, transdermal, inhalation, and parenteral. We can see from **Figure 4** that most lipid nanocarriers show a distinct preference for one administration route over the others, a pattern pronounced for exosomes and ethosomes.



		2.0%	40.0%	0.1%	0.0%	0.0%	0.1%	1.1%	12.7%	5.4%	4.4%	23.7%	0.7%	9.7%	0.0%
	Modes of delivery	PEGylated liposomes	Vesicles	Echogenic liposomes	Stimuli-responsive liposomes	Bubble liposomes	Hexosomes	Cubosomes	Solid lipid nanoparticles	Nanostructured lipid carriers	Ethosomes	Exosomes	Virus-like partiicles	Emulsions	Lipid prodrugs
Parenteral	Intravenous	28.2%	8.0%	21.1%	0.0%	0.0%	4.2%	3.2%	2.8%	3.6%	0.1%	3.8%	8.0%	0.7%	14.3%
	Intramuscular	1.4%	3.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.6%	0.6%	0.1%	1.4%	8.8%	0.6%	0.0%
	Subcutaneous	3.1%	4.0%	0.0%	0.0%	0.0%	0.0%	0.5%	1.1%	0.8%	0.8%	2.0%	11.2%	1.0%	0.0%
	Epidural	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%
	Intracerebroventricular	0.8%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	0.1%	0.0%	0.3%	0.0%	0.1%	0.0%
	Intracardiac	0.6%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	0.0%	0.0%	0.0%
	Intradermal	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.5%	0.3%	0.1%	0.4%	0.5%	2.4%	0.3%	0.0%
	Intraperitoneal	4.7%	2.6%	0.0%	0.0%	0.0%	0.0%	0.5%	0.3%	0.6%	0.0%	1.6%	5.6%	0.1%	0.0%
	Intraperitoneal	0.8%	1.4%	0.0%	0.0%	0.0%	0.0%	0.5%	0.2%	0.0%	0.0%	1.0%	0.0%	0.0%	0.0%
	Transdermal/topical	11.2%	32.0%	15.8%	50.0%	0.0%	50.0%	28.6%	31.5%	43.9%	84.7%	5.5%	17.6%	53.0%	14.3%
	Ophthalmic	3.9%	8.5%	10.5%	12.5%	25.0%	4.2%	19.0%	11.2%	13.4%	1.8%	2.3%	2.4%	11.6%	14.3%
	Oral	7.3%	14.2%	5.3%	0.0%	25.0%	20.8%	21.7%	20.3%	15.8%	3.7%	3.9%	8.0%	10.0%	42.9%
	Sublingual	0.0%	1.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.3%	3.2%	0.2%	0.0%
	Buccal	0.0%	1.4%	0.0%	0.0%	0.0%	4.2%	0.5%	1.0%	0.5%	0.5%	0.3%	2.4%	0.9%	0.0%
	Rectal	8.7%	4.5%	0.0%	0.0%	0.0%	0.0%	2.6%	3.4%	1.7%	0.8%	0.5%	1.6%	1.6%	0.0%
	Vaginal	0.3%	2.2%	0.0%	0.0%	0.0%	0.0%	1.1%	1.0%	0.5%	1.5%	0.5%	3.2%	1.0%	0.0%
	Nasal	2.8%	6.0%	0.0%	0.0%	0.0%	0.0%	5.3%	6.7%	7.2%	1.5%	2.8%	12.0%	5.5%	0.0%
	Inhalation	5.0%	8.7%	10.5%	0.0%	0.0%	8.3%	1.6%	7.6%	2.0%	0.1%	1.3%	4.8%	3.9%	0.0%
	Otic	21.2%	0.6%	36.8%	37.5%	50.0%	8.3%	3.8%	11.7%	9.0%	3.9%	71.8%	8.8%	8.8%	14.3%

Figure 4. Heat map depicting co-occurrences of various types of lipid nanocarriers with modes of delivery in the field of lipid-based materials based on CAS Content Collection data from 2003–2023.

Future challenges

Challenges in the development of lipid nanocarriers include drug-limited loading capacity and encapsulation[43,44] as well as stability issues,[45,46] scale-up complexities,[47] biocompatibility concerns,[48] drug release control, regulatory hurdles,[49] cost considerations,[50] and long-term storage requirements.[45] Ongoing research and innovation in lipid-based drug delivery systems aim to overcome these challenges to harness the full potential of these systems.

Bioelectronic materials

Bioelectronics is an interdisciplinary field in which electronic devices interface with biological systems, including the human body,[51–55] through implantation or attachment to the skin. It involves the development of new devices, often using novel materials and methodologies, that allow electronic systems to communicate with biological components at the molecular, cellular, and organ levels. This approach capitalizes on the intrinsic ability of living organisms to sense, process, and respond to external stimuli in combination with the precision and speed of modern electronics. It has unlocked a diverse range of applications that hold significant promise across various sectors, such as real-time monitoring of brain activity or heart rate, delivering therapeutic electrical signals, chemical sensing, and new prosthetic devices.

As bioelectronics requires effective integration with biological tissue, the materials used in devices are engineered to have specific, application-dependent properties that are critical to their performance. These can include multiple properties that are not commonly found in a single material like softness, stretchability, and electrical conductivity. Achieving this usually involves combining multiple substances into one hybrid or composite material.

Publication trends

We observed a substantial increase in journal publications from 2017 to 2022, though the number of patent publications did not show an equivalent trend. This suggests an increase in academic research in the last five years, which has yet to result in commercialization.

Key materials and applications

Classifying biomaterials by chemical substance, we note several key groups:
- Metals and inorganic compounds, which include the most commonly mentioned substances from 2003–2023.
- Polymers, including conductive polymers, notably poly(3,4-ethylenedioxythiophene) (PEDOT), hydrogel-forming polymers, biodegradable polymers, and polymers derived from natural sources. This group has shown significant research interest in recent years, as highlighted in **Figure 5**.
- Carbon nanomaterials, which have unique properties that make them particularly useful for bioelectronic applications.

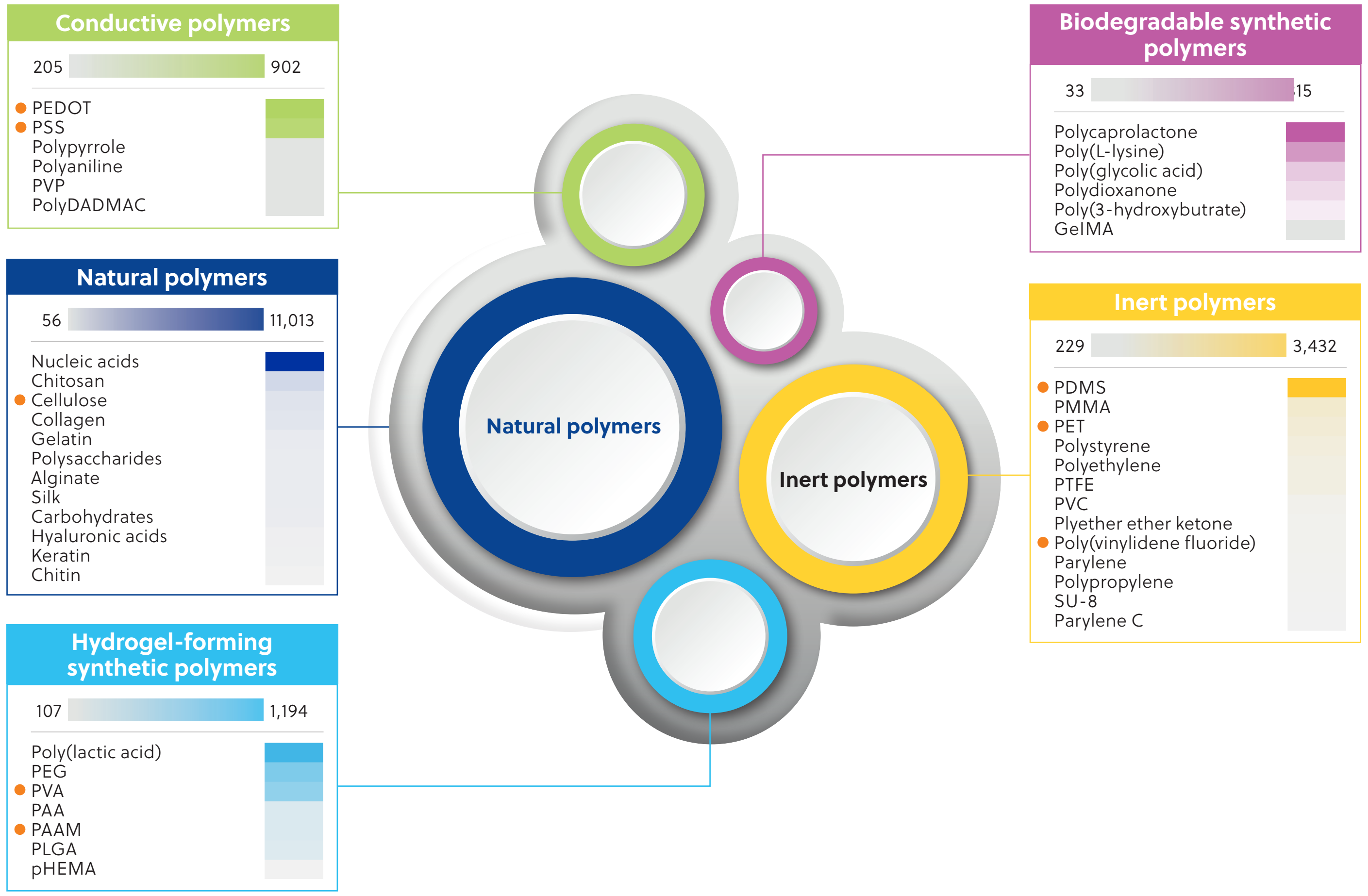
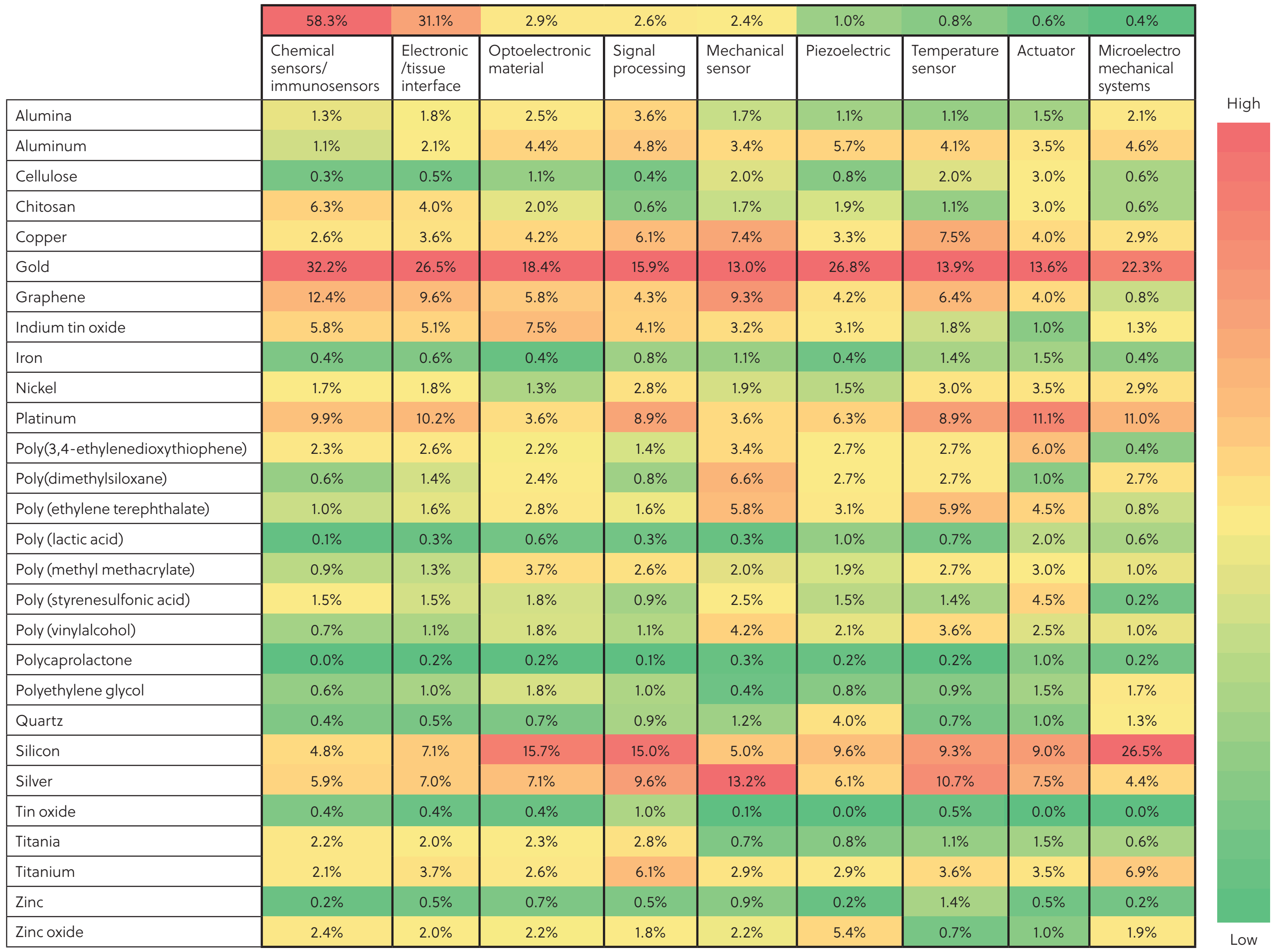


Figure 5. Distribution of polymers used in the field of bioelectronic materials in publications (journals and patents) from 2003–2023. The size of the colored circles corresponds to the number of publications. Materials marked with an orange dot (●) demonstrated considerable growth in recent years.

In terms of device function, we found the majority of bioelectronic materials are used in active sensor components and at the interface between electronic components and biological tissues (**Figure 6**).



	58.3%	31.1%	2.9%	2.6%	2.4%	1.0%	0.8%	0.6%	0.4%
	Chemical sensors/ immunosensors	Electronic /tissue interface	Optoelectronic material	Signal processing	Mechanical sensor	Piezoelectric	Temperature sensor	Actuator	Microelectro mechanical systems
Alumina	1.3%	1.8%	2.5%	3.6%	1.7%	1.1%	1.1%	1.5%	2.1%
Aluminum	1.1%	2.1%	4.4%	4.8%	3.4%	5.7%	4.1%	3.5%	4.6%
Cellulose	0.3%	0.5%	1.1%	0.4%	2.0%	0.8%	2.0%	3.0%	0.6%
Chitosan	6.3%	4.0%	2.0%	0.6%	1.7%	1.9%	1.1%	3.0%	0.6%
Copper	2.6%	3.6%	4.2%	6.1%	7.4%	3.3%	7.5%	4.0%	2.9%
Gold	32.2%	26.5%	18.4%	15.9%	13.0%	26.8%	13.9%	13.6%	22.3%
Graphene	12.4%	9.6%	5.8%	4.3%	9.3%	4.2%	6.4%	4.0%	0.8%
Indium tin oxide	5.8%	5.1%	7.5%	4.1%	3.2%	3.1%	1.8%	1.0%	1.3%
Iron	0.4%	0.6%	0.4%	0.8%	1.1%	0.4%	1.4%	1.5%	0.4%
Nickel	1.7%	1.8%	1.3%	2.8%	1.9%	1.5%	3.0%	3.5%	2.9%
Platinum	9.9%	10.2%	3.6%	8.9%	3.6%	6.3%	8.9%	11.1%	11.0%
Poly(3,4-ethylenedioxythiophene)	2.3%	2.6%	2.2%	1.4%	3.4%	2.7%	2.7%	6.0%	0.4%
Poly(dimethylsiloxane)	0.6%	1.4%	2.4%	0.8%	6.6%	2.7%	2.7%	1.0%	2.7%
Poly (ethylene terephthalate)	1.0%	1.6%	2.8%	1.6%	5.8%	3.1%	5.9%	4.5%	0.8%
Poly (lactic acid)	0.1%	0.3%	0.6%	0.3%	0.3%	1.0%	0.7%	2.0%	0.6%
Poly (methyl methacrylate)	0.9%	1.3%	3.7%	2.6%	2.0%	1.9%	2.7%	3.0%	1.0%
Poly (styrenesulfonic acid)	1.5%	1.5%	1.8%	0.9%	2.5%	1.5%	1.4%	4.5%	0.2%
Poly (vinylalcohol)	0.7%	1.1%	1.8%	1.1%	4.2%	2.1%	3.6%	2.5%	1.0%
Polycaprolactone	0.0%	0.2%	0.2%	0.1%	0.3%	0.2%	0.2%	1.0%	0.2%
Polyethylene glycol	0.6%	1.0%	1.8%	1.0%	0.4%	0.8%	0.9%	1.5%	1.7%
Quartz	0.4%	0.5%	0.7%	0.9%	1.2%	4.0%	0.7%	1.0%	1.3%
Silicon	4.8%	7.1%	15.7%	15.0%	5.0%	9.6%	9.3%	9.0%	26.5%
Silver	5.9%	7.0%	7.1%	9.6%	13.2%	6.1%	10.7%	7.5%	4.4%
Tin oxide	0.4%	0.4%	0.4%	1.0%	0.1%	0.0%	0.5%	0.0%	0.0%
Titania	2.2%	2.0%	2.3%	2.8%	0.7%	0.8%	1.1%	1.5%	0.6%
Titanium	2.1%	3.7%	2.6%	6.1%	2.9%	2.9%	3.6%	3.5%	6.9%
Zinc	0.2%	0.5%	0.7%	0.5%	0.9%	0.2%	1.4%	0.5%	0.2%
Zinc oxide	2.4%	2.0%	2.2%	1.8%	2.2%	5.4%	0.7%	1.0%	1.9%

Figure 6. Heat map of co-occurrence between of the most used substances in bioelectronic materials with their most common applications, based on CAS Content Collection data from 2003–2023. Note that the electronic/tissue interface category also includes electrical sensing and stimulation.

Finally, looking at the parts of the body where bioelectronic materials are used, we found that they are most applied in the facial region (e.g., retinal implants),[56,57] followed by the brain and nervous system (e.g., deep brain stimulation),[58–60] but also have applications in the spinal cord, heart, skin, and other organs or regions of the body such as arms and legs.

Future challenges

The bioelectronics field has seen a surge in research, though, as mentioned, patent activity has not grown as quickly. So far, work in this area has focused on combining highly engineered materials into hybrid or composite devices to impart them with necessary and often unique properties.

The most significant challenges ahead include developing a better understanding of the biocompatibility, toxicity, and immune response of materials, device degradation,[61,62] and avoiding mismatches in mechanical properties between human tissues and devices.[63]

Bioinks

Bioinks are composed of a complex mixture of substances, often containing desired cell types with natural or synthetic polymers and other supporting materials.

Bioprinting can use bioinks to fabricate biological structures, including three-dimensional scaffolds, tissues, and organs. This approach can be used in tissue engineering, as well as wound healing,[64–66] disease modeling,[67–69] personalized medicine,[70,71] drug testing and development,[72,73] and even drug delivery.[74–77]

Bioprinting encompasses various established methods, including laser-assisted, droplet-based, and extrusion-based techniques.[78–80] Selecting the appropriate bioink and bioprinting technique depends on several factors, such as the intended structure, the mechanical design of the bioprinter, and the bioink's inherent properties.[78,80,81]

Publication trends

Interest in bioinks has steadily increased over the last two decades, with an acceleration around 2015. In general, journal publications outnumber patent publications in this field by a ratio of 5:1 in 2022, indicating that the field is still in its nascent stages (**Figure 7**). This accelerated interest has led to an expansion in different aspects of bioprinting, including the types of materials used in bioinks, the bioprinting technique itself, and various application fields.

It’s worth noting that, despite an upward trend, the overall number of publications in this field is still relatively small.

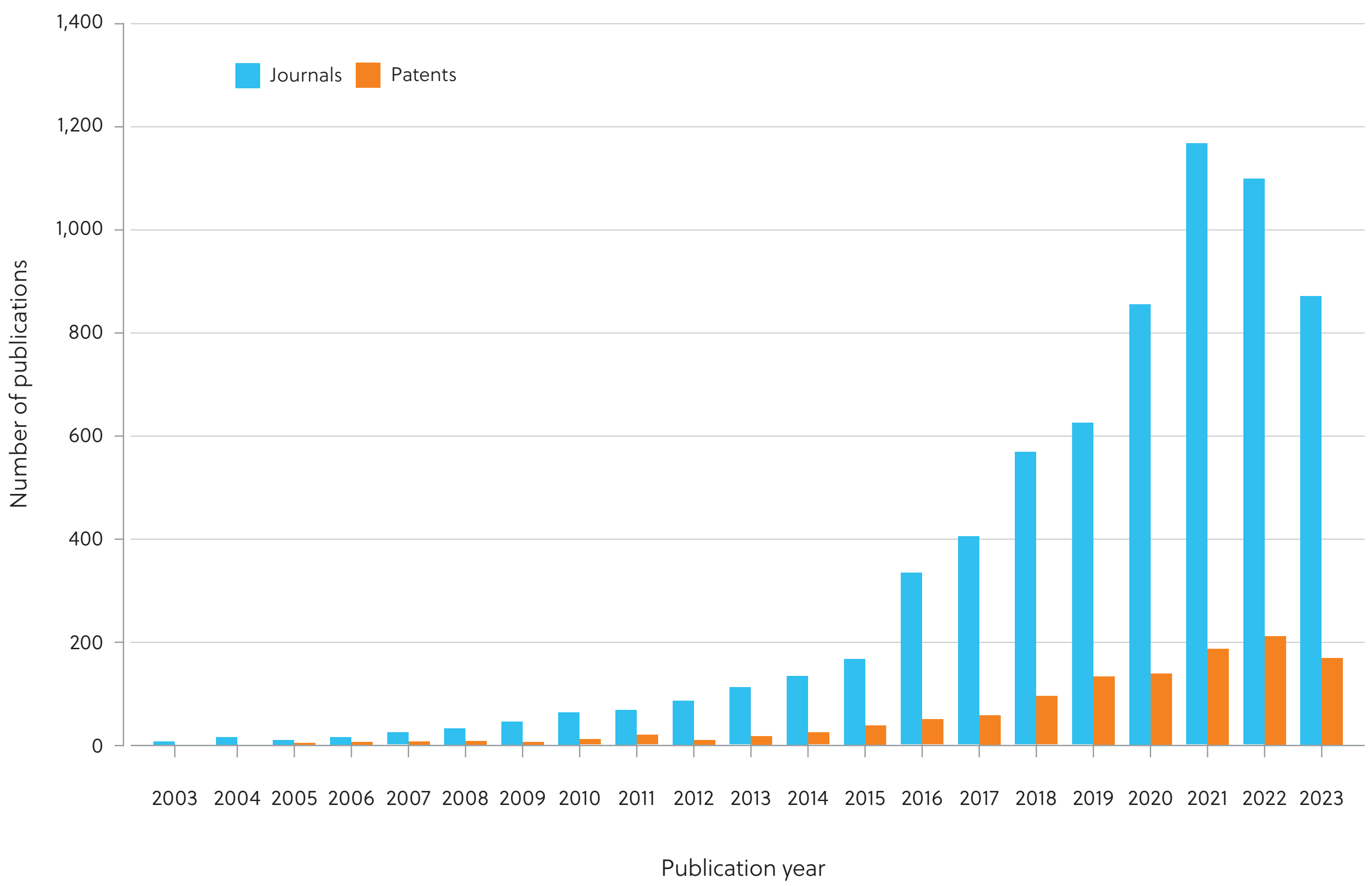


Figure 7. Number of journal and patent publications per year in the field of bioinks over the period of 2003–2023. *The data for 2023 only includes months from January to August.

Key materials and applications

Live cells are one of the primary building blocks of bioinks, including stem cells,[82–85] endothelial cells,[86] and tissue-specific cells.[87–89] Growth factors are used to stimulate specific behaviors and enhance development,[90–96] synthetic polymers can be incorporated to provide mechanical strength and structure,[97–102] and natural polymers like collagen,[93,96] fibrin,[103] and gelatin[104–106] offer bioactivity and biocompatibility. Our research found that each of these categories of bioink materials has shown notable growth, often with a few key materials leading the way. **Figure 8** provides details of the various material groups and highlights emerging materials within them.

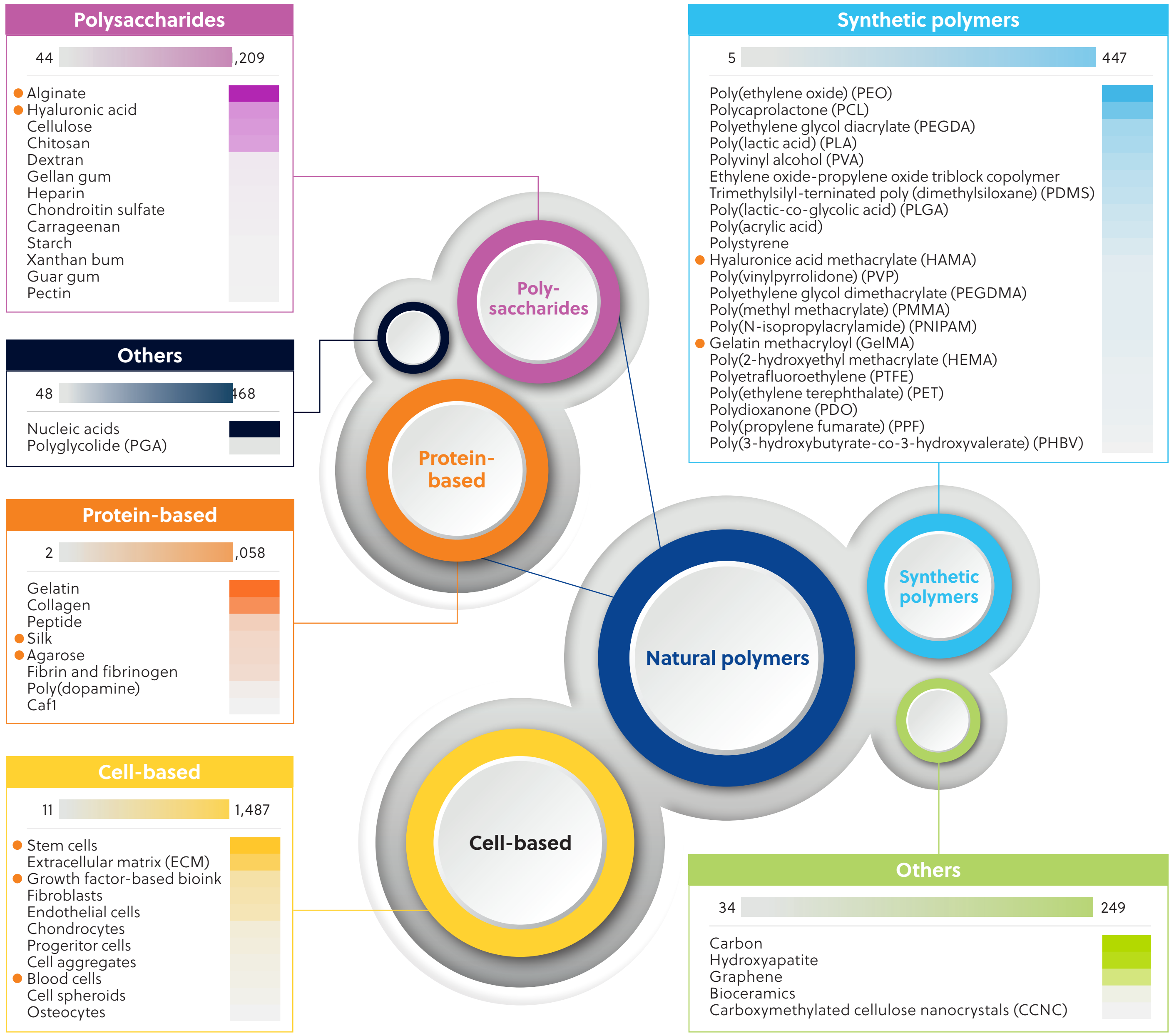


Figure 8. Distribution of materials in the field of bioinks in publications (journals and patents) from 2003–2023. The size of the colored circles corresponds to the number of publications. Materials marked with orange dot (●) demonstrated considerable growth in recent years.

While bioinks are typically associated with tissue engineering, various other applications have been gaining momentum in recent years. We found that personalized medicine, drug testing, wound healing, drug delivery, disease modeling, and antibacterial applications all showed strong relative publication growth in the past decade.

Future challenges

Despite being a relatively new field, commercially available bioinks are already starting to appear on the market. Similarly, commercially available bioprinters are also on the rise.[107] However, further advancements are required to increase cell viability, minimize cell loss, maximize cellular interactions, improve the physical, chemical, mechanical, and rheological properties of bioinks, and make them compatible and scalable for clinical applications.

Self-healing materials

Self-healing materials are defined by their ability to recover from mechanical, thermal, and chemical-induced damage to restore their original properties without external assistance.

For example, a self-healing polymer-based gel can be designed with reversible crosslinks that are broken when it experiences shear forces during injection, allowing it to flow like a liquid through a narrow needle. After the material is at rest inside the body, the crosslinks are reformed, restoring its gel-like rheological properties.[108] The same approach can be used to repair cracks, cuts, or breaks in bulk material under static conditions. When two disconnected faces of a self-healing material are placed into contact, reversible bonds can be reformed, which, combined with interdiffusion, results in the joining of the two faces. In biomedical applications, this can make wound dressings, implanted devices, and scaffolds[109] more resilient, robust, and reliable.[110,111]

Self-healing has been extensively studied in polymers, polymer composites, ceramics, concrete materials, and metals. Of these, self-healing polymers are the most widely used in biomedical applications, primarily because of the ease of chemical functionalization and modification of polymeric systems, the relatively low temperature required to induce mobility over the short-length scales required for self-healing, and the biocompatibility of many polymers.[112]

Publication trends

We found a steady growth in journal publications in the past 20 years, and the number of patent publications also showed similar growth, with some deceleration from 2020–2022. The increase in the journal-to-patent ratio in 2021 and 2022 suggests that research into self-healing materials is focused on early-stage research rather than commercial development (**Figure 9**).

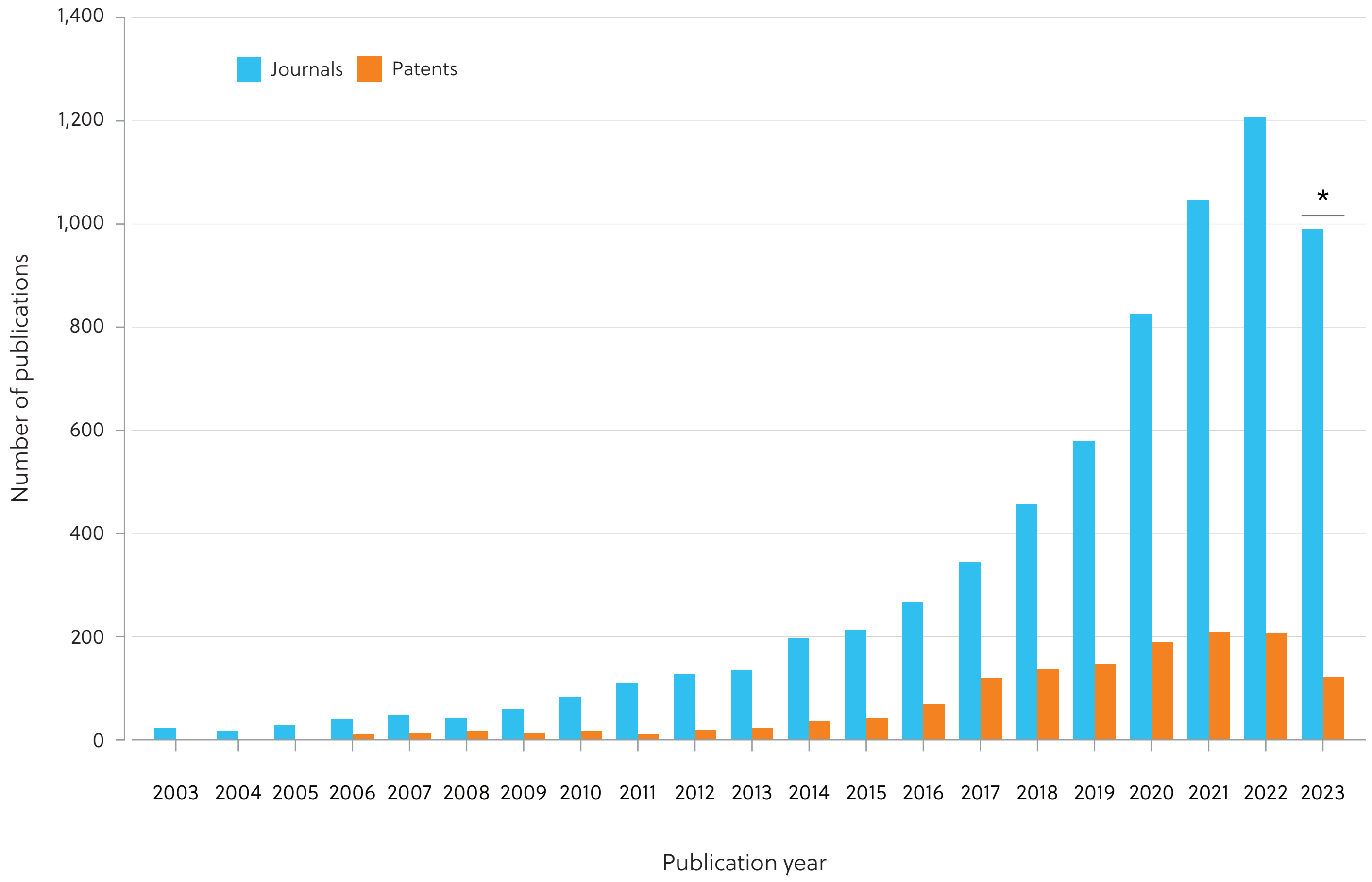


Figure 9. Number of journal and patent publications per year in the field of self-healing biomaterials over the period of 2003–2023. *Partial year data for 2023.

Key materials and applications

A variety of reversible chemical interactions can be used to impart self-healing properties to polymers. These include hydrogen bonding,[113,114] as well as other non-covalent[115-118] and dynamic covalent interactions.[122-124] It is also common to use multiple self-healing chemical functionalities in the same material to cover many mechanical properties and self-healing time scales.[125–127]

We found that the most frequently used self-healing approaches involve hydrogen bonding (with a marked increase in publications, most notably from 2019), Schiff base formation, and metal coordination bonding. Publications relating to these mechanisms are shown in **Figure 10**.

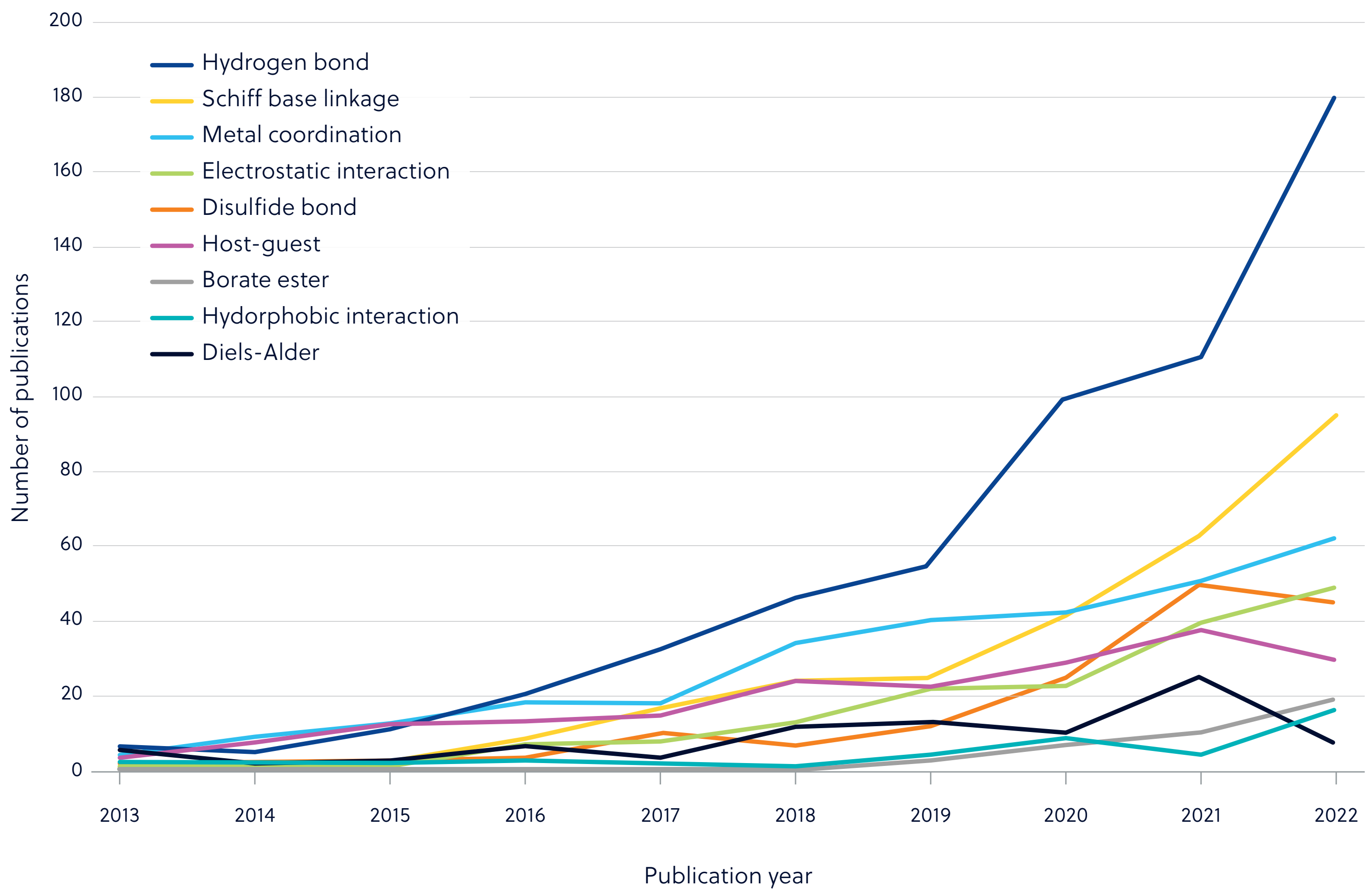


Figure 10. Number of journal and patent publications referencing self-healing mechanisms from 2013–2022.

Polymers make up the largest group of substances used in self-healing biomaterials research and development (**Figure 11**).

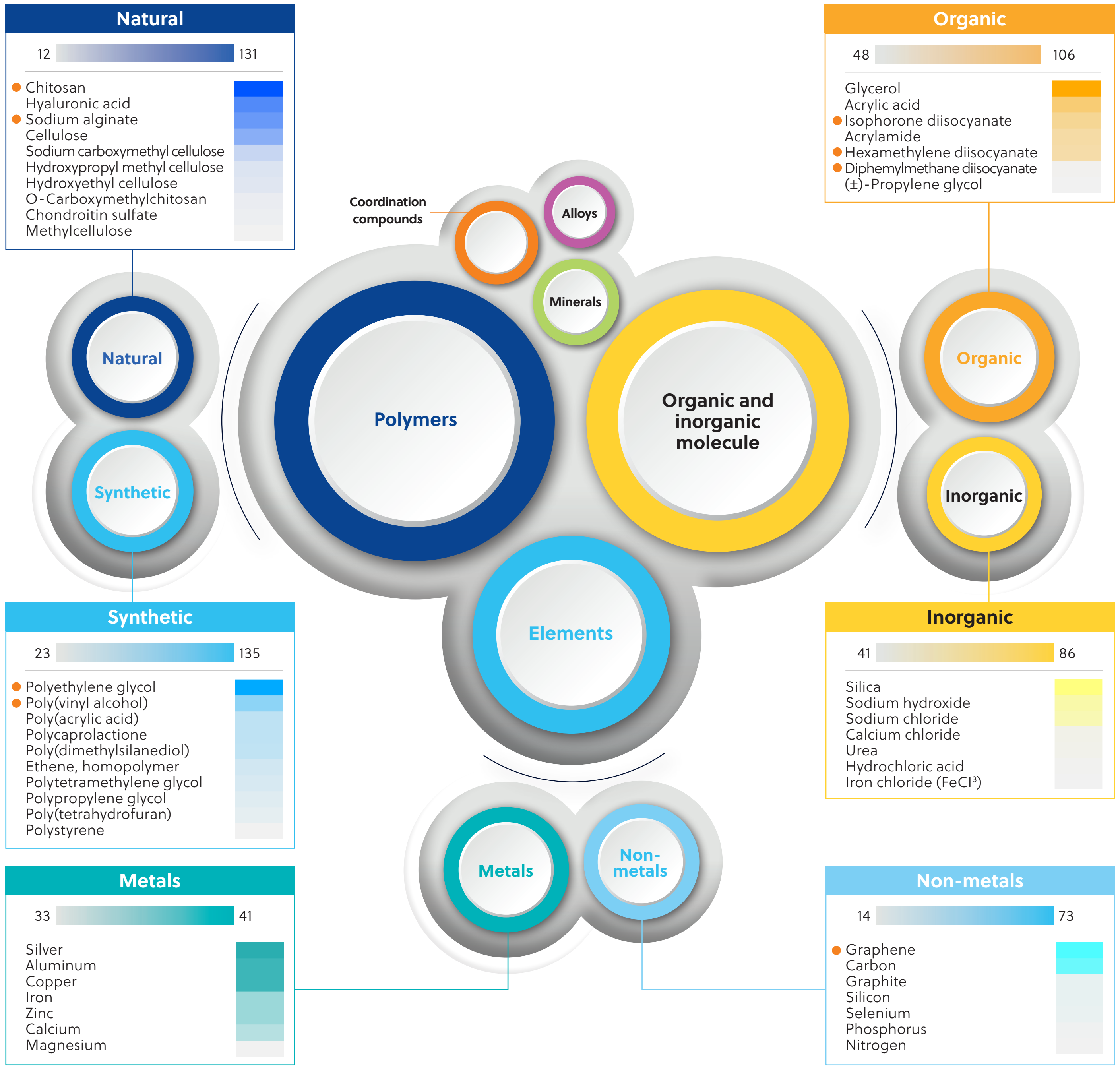


Figure 11. Distribution of substances used in self-healing biomaterials in publications (journals and patents) from 2003–2023. The size of the colored circles corresponds to the number of publications. Materials marked with an orange dot (•) demonstrated considerable growth in recent years.

The materials that have shown the most relative growth in journal and patent publications in the last five years are diisocyanates (which are used to produce polyurethanes), followed by alcohols, the natural polymers chitosan and sodium alginate, and graphene.

The most common uses for self-healing materials are wound healing/dressings (representing 27.6% of documents), drug delivery (25.7%), sensors (17.7%), pharmaceutical hydrogels (9.8%), prosthetics/implants (8.3%), tissue engineering (6.7%), and 3D printing (4.1%).

Future challenges

Self-healing materials have shown significant potential in many biomedical applications. However, further development is needed for these materials to reach their full potential. This includes efforts to develop multifunctional devices that combine self-healing with other functions such as sensing.[128] In this area, more extensive use of computational tools to predict the properties of multifunctional composites should reduce the experimental costs of developing self-healing materials.

Programmable materials

Programmable materials can change their morphology, physical properties, and/or chemical functionalities in a pre-determined sequence in response to an external stimulus or a change in the surrounding environment.[129] This is useful in applications such as drug delivery, where they can enable additional, time-dependent methods of control.[130] Programmable materials are also used in implants, sensors, and other areas of biomedicine.

The substances used in programmable biomedical materials include natural and synthetic polymers,[131] lipids, metal alloys (such as the nickel-titanium alloy nitinol), metallic nanoparticles, DNA-based materials, and others. The programmability of these materials originates from their ability to respond to small changes in their environment, for example, pH,[132,133] temperature,[134] light,[135,136] electrical[137] and magnetic fields,[138,139] and a specific chemical or biological signal.[140] DNA-based materials represent a special class of programmable biomaterials.[148] One reason for this is that DNA offers precise structural tunability through base pairings. Directed self-assembly of single-stranded DNA can lead to diverse 2D and 3D structures, the formation and dynamics of which can be controlled at the molecular level. DNA can also be engineered to respond to specific cues or chemical environments or through using CRISPR technology.

Publication trends

Journal publications referencing programmable materials increased significantly from 2003 to 2023, though patent activity has grown more slowly, particularly since 2015.

Key materials and applications

Figure 12 shows the most frequently referenced substances in publications on programmable biomaterials. Not all these materials are intrinsically programmable. Generally, the non-programmable materials found in these publications serve other complementary purposes in combination with a programmable material.

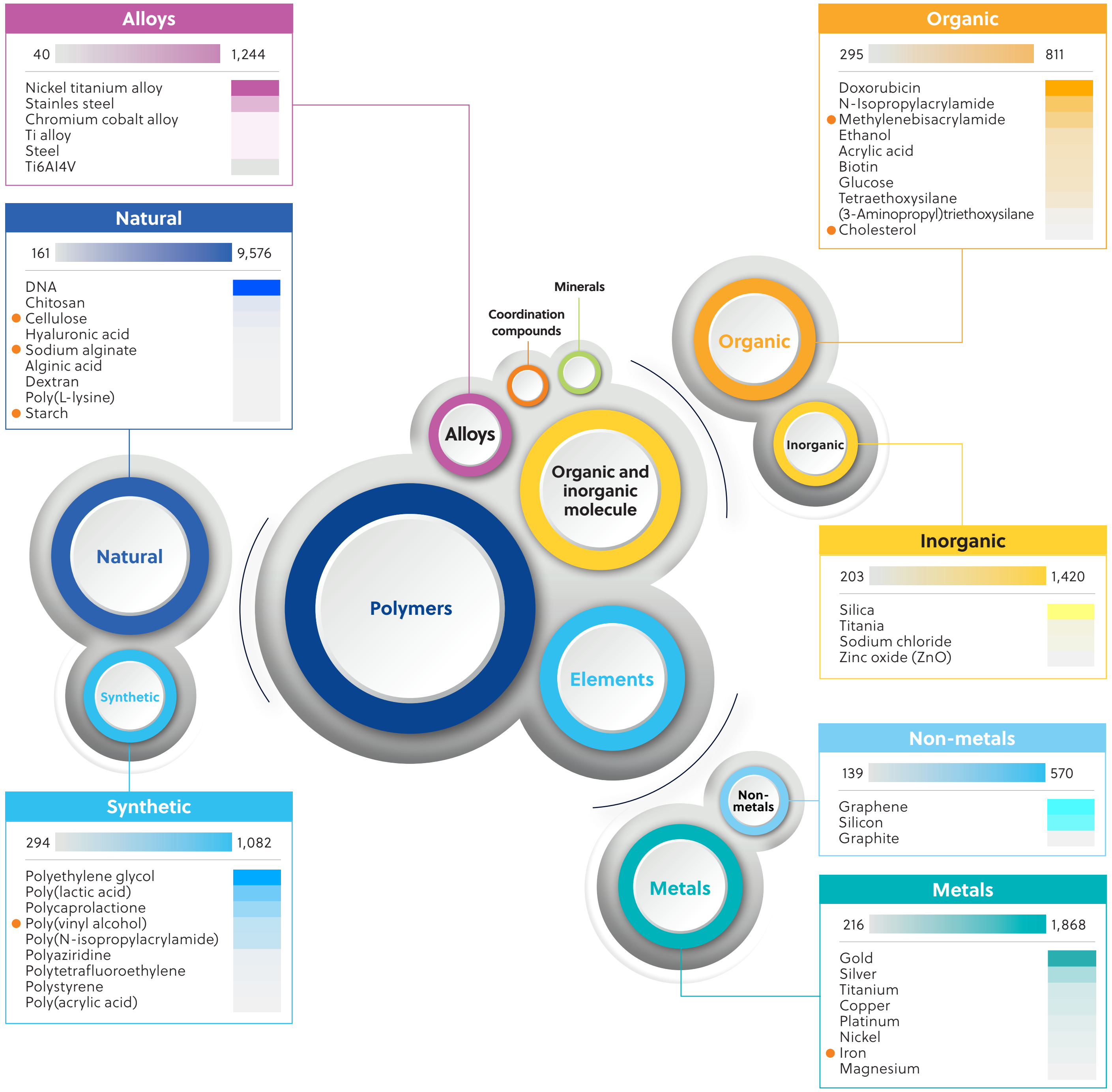


Figure 12. Distribution of substances used in self-healing biomaterials in publications (journals and patents) from 2003–2023. The size of the colored circles corresponds to the number of publications. Materials marked with an orange dot (•) demonstrated considerable growth in recent years.

Emerging materials that have increased in use in the last five years include lignin, likely due to its natural abundance, biodegradability, and ability to confer a wide range of stimulus responses through chemical modification,[141–144] as well as the versatile metal-organic frameworks (MOFs).[145] This can be seen from the increase in publications from 2013 to 2022 (**Figure 13**).

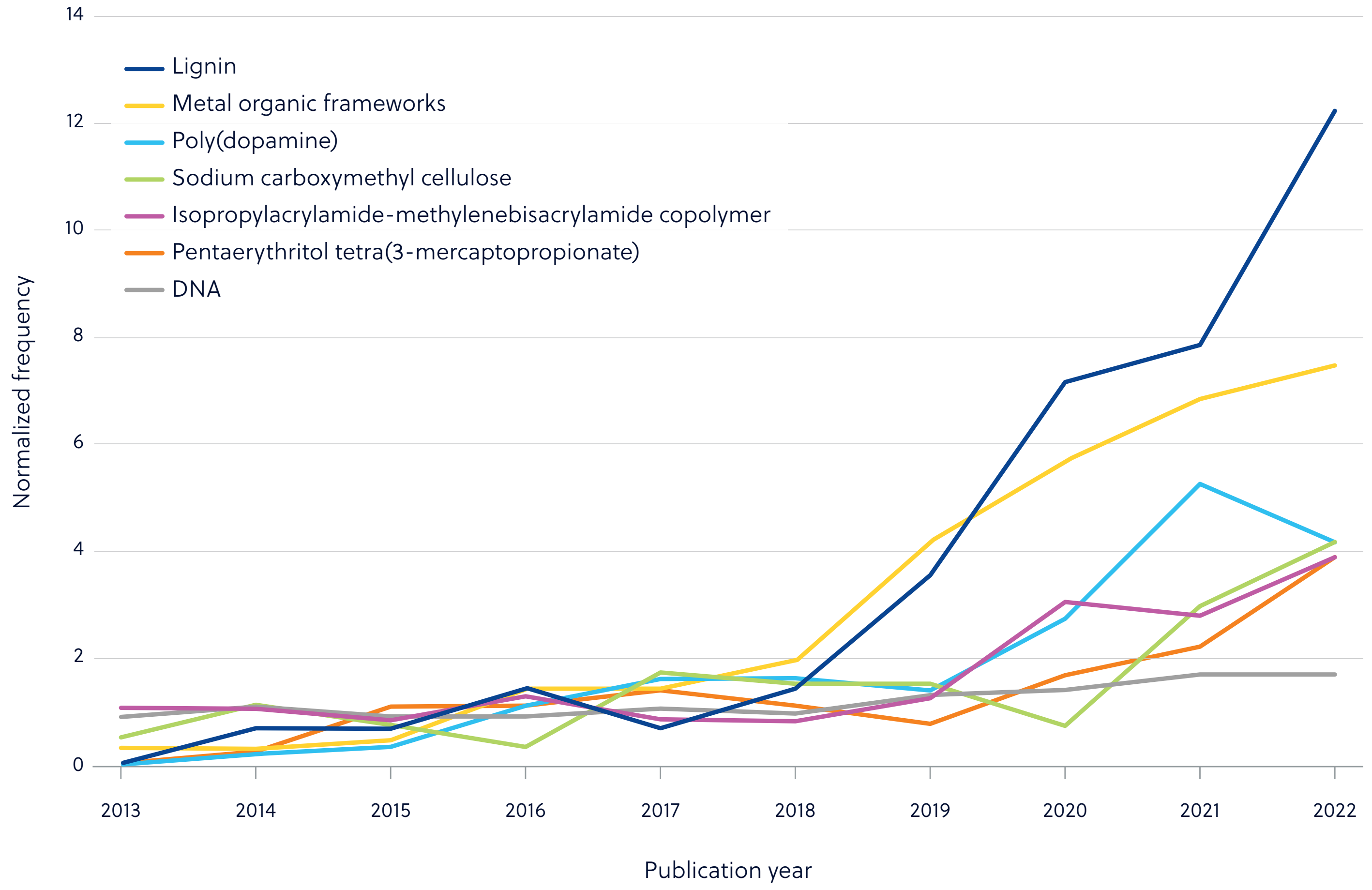
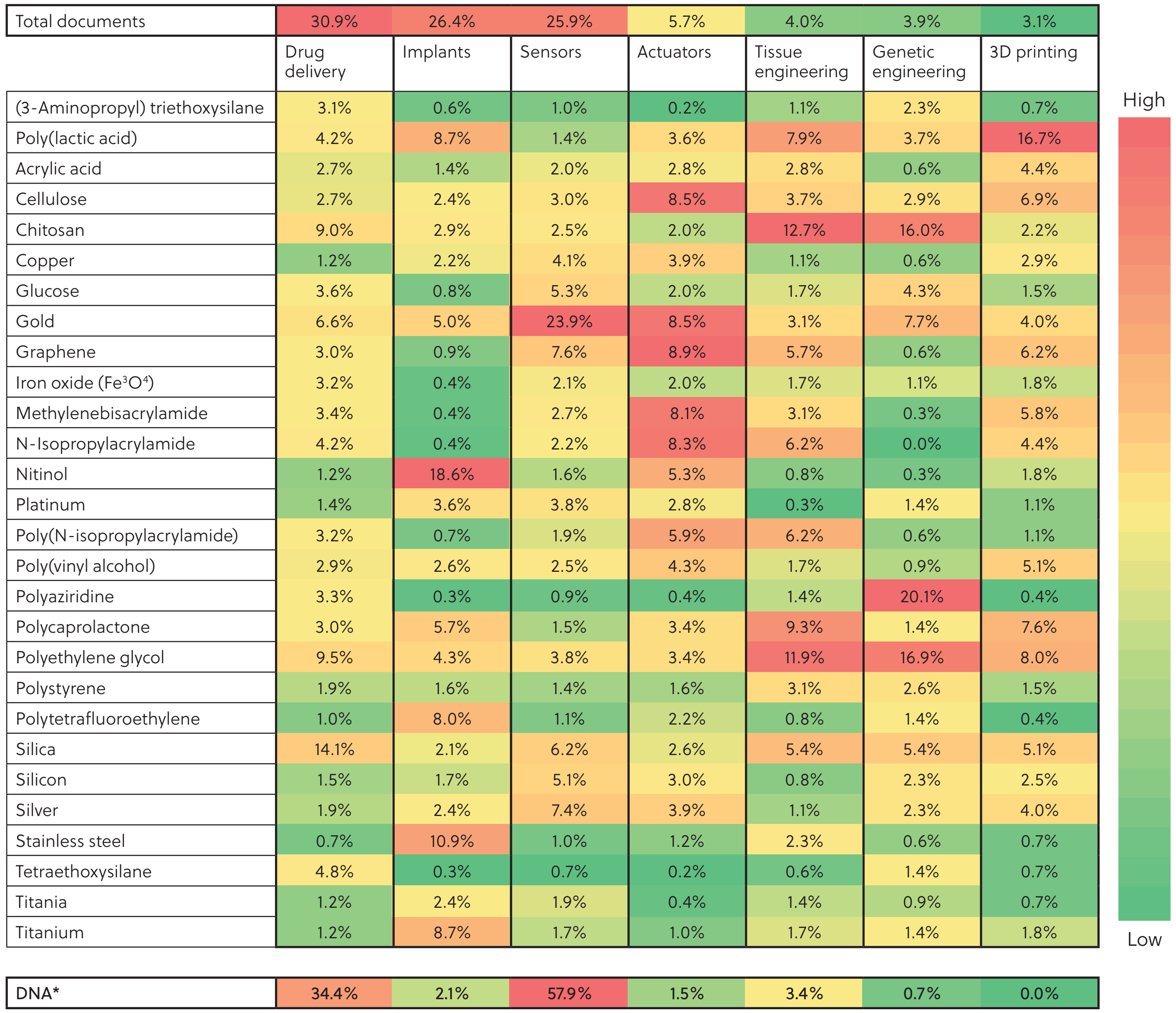


Figure 13. Normalized frequency of representative materials in journal and patent publications from 2013–2022.

We found drug delivery to be the most common biomedical application of programmable materials, followed by implants and sensors (**Figure 14**). DNA has been separated from other materials as it is not classified as a single chemical substance. Although the journal and patent publication frequency for DNA has not increased as much as other materials, publications in the specific areas of sensors/diagnosis, drug delivery, and antitumor agents have rapidly increased since around 2010.



Total documents	30.9%	26.4%	25.9%	5.7%	4.0%	3.9%	3.1%
	Drug delivery	Implants	Sensors	Actuators	Tissue engineering	Genetic engineering	3D printing
(3-Aminopropyl) triethoxysilane	3.1%	0.6%	1.0%	0.2%	1.1%	2.3%	0.7%
Poly(lactic acid)	4.2%	8.7%	1.4%	3.6%	7.9%	3.7%	16.7%
Acrylic acid	2.7%	1.4%	2.0%	2.8%	2.8%	0.6%	4.4%
Cellulose	2.7%	2.4%	3.0%	8.5%	3.7%	2.9%	6.9%
Chitosan	9.0%	2.9%	2.5%	2.0%	12.7%	16.0%	2.2%
Copper	1.2%	2.2%	4.1%	3.9%	1.1%	0.6%	2.9%
Glucose	3.6%	0.8%	5.3%	2.0%	1.7%	4.3%	1.5%
Gold	6.6%	5.0%	23.9%	8.5%	3.1%	7.7%	4.0%
Graphene	3.0%	0.9%	7.6%	8.9%	5.7%	0.6%	6.2%
Iron oxide (Fe^3O^4)	3.2%	0.4%	2.1%	2.0%	1.7%	1.1%	1.8%
Methylenebisacrylamide	3.4%	0.4%	2.7%	8.1%	3.1%	0.3%	5.8%
N-Isopropylacrylamide	4.2%	0.4%	2.2%	8.3%	6.2%	0.0%	4.4%
Nitinol	1.2%	18.6%	1.6%	5.3%	0.8%	0.3%	1.8%
Platinum	1.4%	3.6%	3.8%	2.8%	0.3%	1.4%	1.1%
Poly(N-isopropylacrylamide)	3.2%	0.7%	1.9%	5.9%	6.2%	0.6%	1.1%
Poly(vinyl alcohol)	2.9%	2.6%	2.5%	4.3%	1.7%	0.9%	5.1%
Polyaziridine	3.3%	0.3%	0.9%	0.4%	1.4%	20.1%	0.4%
Polycaprolactone	3.0%	5.7%	1.5%	3.4%	9.3%	1.4%	7.6%
Polyethylene glycol	9.5%	4.3%	3.8%	3.4%	11.9%	16.9%	8.0%
Polystyrene	1.9%	1.6%	1.4%	1.6%	3.1%	2.6%	1.5%
Polytetrafluoroethylene	1.0%	8.0%	1.1%	2.2%	0.8%	1.4%	0.4%
Silica	14.1%	2.1%	6.2%	2.6%	5.4%	5.4%	5.1%
Silicon	1.5%	1.7%	5.1%	3.0%	0.8%	2.3%	2.5%
Silver	1.9%	2.4%	7.4%	3.9%	1.1%	2.3%	4.0%
Stainless steel	0.7%	10.9%	1.0%	1.2%	2.3%	0.6%	0.7%
Tetraethoxysilane	4.8%	0.3%	0.7%	0.2%	0.6%	1.4%	0.7%
Titania	1.2%	2.4%	1.9%	0.4%	1.4%	0.9%	0.7%
Titanium	1.2%	8.7%	1.7%	1.0%	1.7%	1.4%	1.8%
DNA*	34.4%	2.1%	57.9%	1.5%	3.4%	0.7%	0.0%

Figure 14. Heat map showing co-occurrence between the most commonly used substances in programmable materials with their most common applications, based on CAS Content Collection data from 2003–2023.

Future challenges

To enable more widespread use of programmable materials in biomedical applications, a few challenges must be overcome, including scale-up and cost optimization,[130] the ability to combine multiple independent functions in a single material while reducing interference between them,[146,147] and coupling the direction of the stimulus to the direction of the response.[147] In addition, there are concerns regarding the use of programmable materials in the human body, and therefore, extensive in vivo testing is required before use in clinical settings.[130] In particular, long-term safety is a concern that must be addressed.[120,148]

Antibacterial materials

Various classes of antibacterial drugs have been developed since the discovery of Penicillin G in the 1940s. Antibacterial resistance has become an urgent problem, designated by the World Health Organization (WHO) as one of the top 10 global health threats.[149]

Traditional small molecule-based antibiotics continue to be developed to counter increasing drug resistance. However, development has been slow, and novel classes remain elusive. The continued necessity for newer antibiotics and the lack of novel small-molecule antibiotic classes have led researchers to explore other avenues. In addition to traditional antibacterials, biomaterials containing polymers, metals, nano-based materials, antimicrobial peptides (AMPs), bacteriophages, and antimicrobial enzymes are being explored as alternatives to traditional antibacterials.[150–154]

Publication trends

The interest in this field is exemplified by the increase in journal publications on antibacterial biomaterials over the last two decades. Growth in patent publications appears to be more modest, indicating a gap between the research and commercialization of antibacterial biomaterials.

Staphylococcus and *Escherichia* species accounted for half of all publications focused on bacterial species. Strong interest was also expressed for species with drug-resistant strains identified and classified as threats by the WHO and Centers for Disease Control and Prevention (CDC).

Key materials and applications

Polymers, organic molecules, and metals form the most prominent groups of materials occurring in antibacterial research, as well as carbon and protein-based and other materials.

Relative publication growth of a selection of emerging materials in the last 20 years is shown below in **Figure 15A**, as well as that for the most prolific classes of antibiotics in **Figure 15B**. Established classes such as tetracyclines, macrolides, and others have reportedly been used in conjunction with biomaterials, often to aid in their delivery and to boost their antibacterial effectiveness in applications such as tissue engineering and wound healing.[155–158]

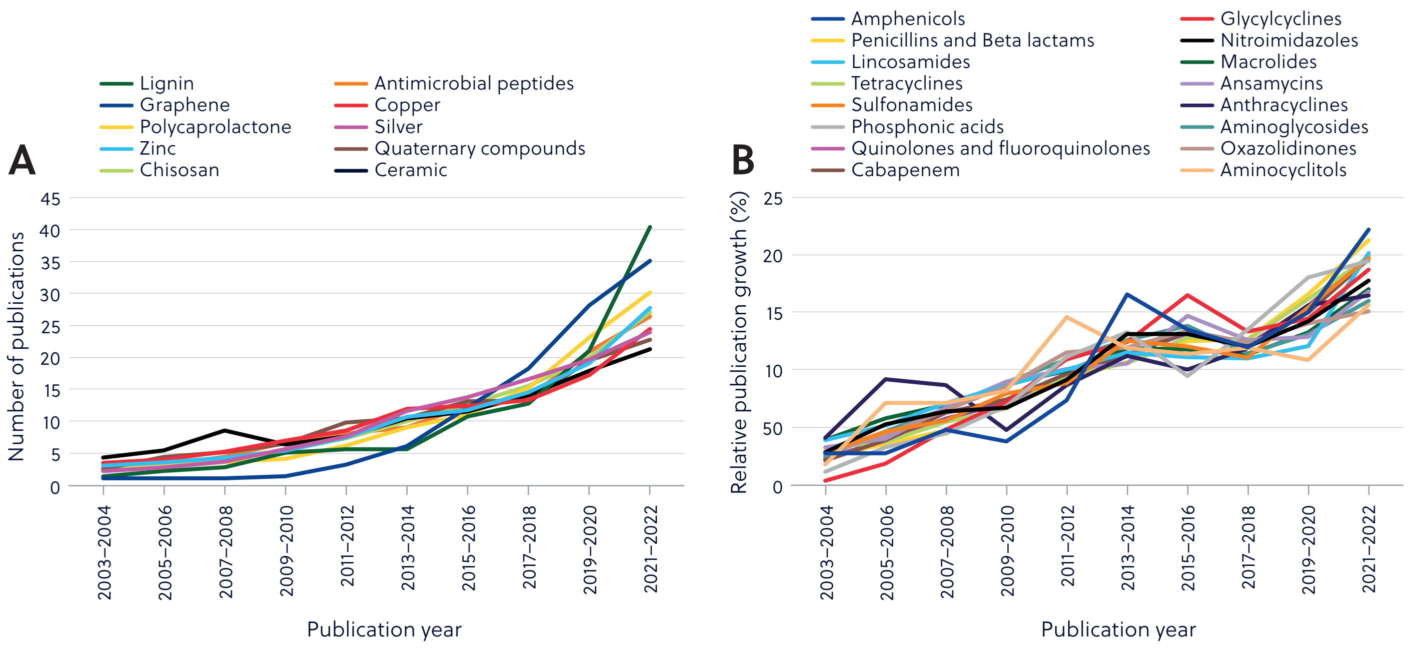


Figure 15. Growth in publications for (A) emerging materials and (B) major classes of antibiotic drugs in the antibacterial biomaterials field from the CAS Content Collection for 2003–2022. Data includes both journal and patent publications.

The use of biomaterials to target and deliver antibiotics has accounted for nearly 12,000 publications in the last two decades. Biomaterials such as antimicrobial peptides, enzymes, and biopolymers are being used effectively in this field.[150] Other major applications involve the use of antibacterial biomaterials in the design and fabrication of medical apparatuses, devices, and implants to reduce the risk of infections (**Figure 16**).

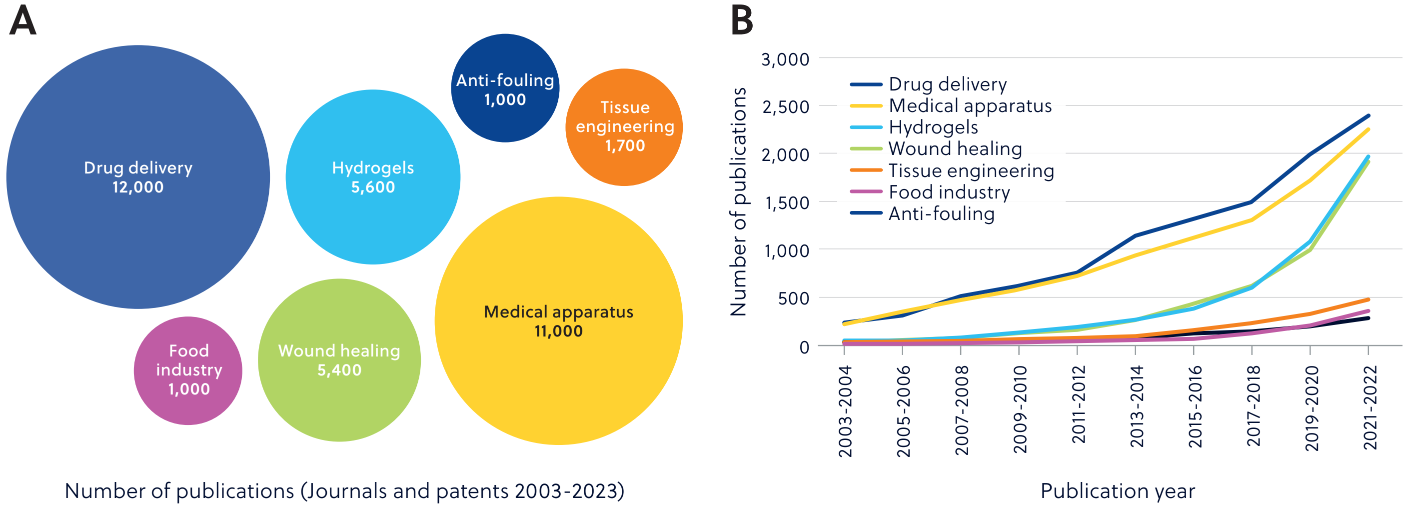


Figure 16. (A) Distribution of applications in the antibacterial biomaterials field (B) and growth in publications related to these applications over 2003–2023 based on data from the CAS Content Collection.

Future challenges

The biggest challenge remains antimicrobial resistance,[159] which is developing faster in bacterial species than novel antibiotics are being created.[160,161] Other challenges include individual host differences leading to differential results,[162] more challenging Gram-negative bacteria,[163,164] and reduced incentive to invest due to limited market size, short treatment duration, and reduced price of antibiotic agents.[165]

Various emerging approaches, such as the use of antimicrobial peptides, enzymes, bacteriophages, and CRISPR-Cas technology, are being explored to enhance the efficacy of antibiotics and counter the rapid development of antimicrobial resistance. However, continued advancements are needed to translate more antibacterial materials into various clinical applications.

Sustainable materials for biomedical applications

This final section will focus on the increasing use of sustainable materials in the context of how they are being developed for biomedical applications. Here, sustainability involves the use of materials that are biodegradable or compostable, are made using bio-based, naturally abundant, and/or renewable raw material sources, or are otherwise more environmentally benign compared to the incumbent materials. Examples of biomedical applications where sustainable materials can be used include personal protective equipment (PPE), medical packaging, textiles, and other single-use, disposable lab or clinic supplies in health and life science settings.

In general, the desired properties of these materials include biocompatibility, non-toxicity, mechanical and thermal stability, processability, as well as other application-specific functionality.[166,167] A major theme in sustainable biomaterials is adapting, modifying, or combining intrinsically sustainable materials (such as biodegradable polymers and naturally derived materials) with other substances to give them these properties.

Publication trends

Compared with other areas in this report, the number of journal and patent publications is low but has been growing quickly since 2015. Journal publication frequency has shown a steady increase since 2003, with China showing greater academic research activity than other countries. Patent publication activity has also generally increased since 2003, but less quickly, though a rise was observed from 2019 to 2021.

Key materials and applications

The substances that appear most frequently in sustainable materials-related publications can be grouped into polymers (natural and synthetic), inorganic and organic small molecules, salts, elements (metals and nonmetals), alloys, minerals, and coordination compounds (**Figure 17**). Natural polymers, primarily cellulose, starch, and chitosan, appear prominently in the data set, likely due to desirable properties like abundance, high biodegradability, and low cost.[168–173]

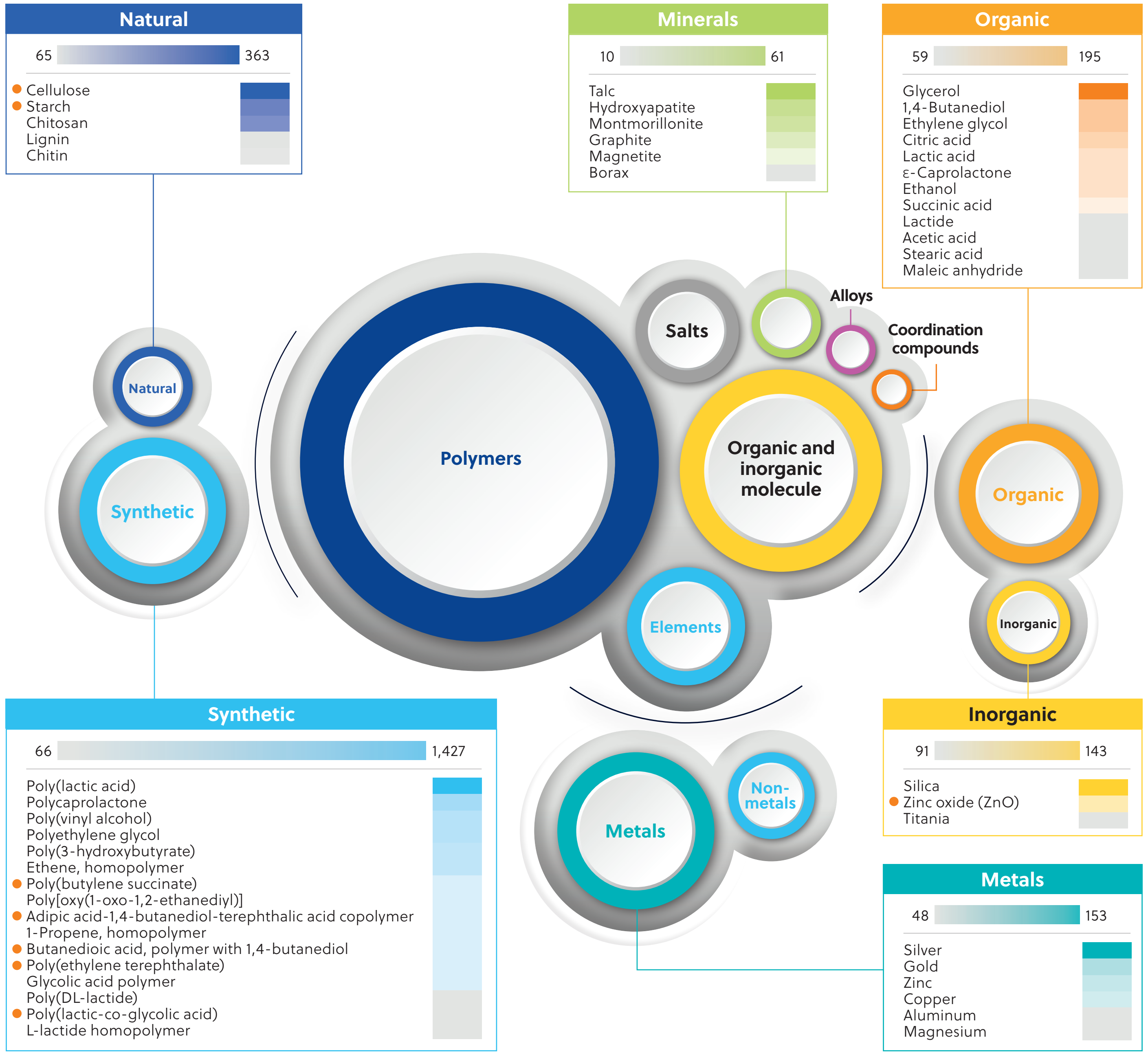


Figure 17. Distribution of substances used in sustainable biomaterials publications (journals and patents) from 2003–2023. The size of the colored circles corresponds to the number of publications. Materials marked with an orange dot (•) demonstrated considerable growth in recent years.

From this data set, the prevalent applications of sustainable biomaterials can be broken down into three major areas:

- Disposable medical clinic and laboratory supplies, such as face masks, gloves, surgical gowns, bandages, and labware
  - Materials used in face masks include poly(lactic acid) (PLA),[174,175] poly(butylene succinate),[176] cellulose,[177] and chitosan.[178] For mask filter applications, electrospinning is a prominent technique for forming nanoscale fibers from these materials.[179–181]
  - The performance of these materials can be further enhanced by embedding antimicrobials,[182] or through the incorporation of polar functionality in the filter, for example, by adding chitosan.[175]
- Packaging used in medical settings
  - Sustainable materials such as algae-derived starch, PLA, and lignin have been used in this area.[171,183,184]
- Materials used for various medical purposes, manufactured using alternative or novel methods that are environmentally benign compared to traditional methods
  - Examples include gold,[185] silver, platinum,[186] and ZnO[187–189] nanoparticles, mxenes,[190] and polyesters (through lipase catalysts).[191]

Outlook and challenges

Overall, packaging accounts for nearly 40% of all plastics produced.[192] For these reasons, research attention has been directed towards developing sustainable packaging for biomedical applications.[193]

Challenges to the wider adoption of sustainable biomaterials in biomedical applications include their sensitivity towards common sterilization methods,[194] high costs of synthesis and fabrication compared to incumbent non-sustainable materials,[179,195] faster degradation in performance, hydrophilicity, and difficulty with processing.[179,196] Addressing these issues is an active area of research.

Conclusions

The exploration of biomaterials across the sections of this report demonstrates the significant advancements that are being made in this continually evolving field. These materials hold the potential to refine and revolutionize areas of healthcare. Notably, a representative list of substances that appear in this report includes naturally derived polymers, such as silk, chitosan, and DNA, chemically modified and synthetic polymers, including PEDOT: PSS, metals, alloys, and nanoscale materials such as carbon nanotubes.

Notable applications include drug delivery, wound healing, tissue engineering, implantable devices, and sensors, among others.

Though all topics were chosen based on their high publication growth, the fields of bioinks and self-healing materials have both seen around a tenfold increase in publication frequency in the last decade. In areas where patent activity is relatively flat, including programmable, protein-based, and, to a lesser extent, lipid-based materials, there may be fundamental material challenges preventing widespread commercialization that still need to be solved through scientific research. Indeed, in all areas, challenges persist. Due to their complex applications, there is a need for materials that combine highly controlled and specific functions with durability, resilience, and predictable functioning in the body. Overcoming these challenges will involve extensive in vivo and clinical testing, which is made more complex by using materials not traditionally found in biomedical applications and materials whose structure and properties are affected by conditions used in their synthesis. For some of the materials discussed here, economically viable, high-quality, high-yield manufacturing processes do not yet exist.

As shown by the data presented in this report, researchers are tackling these challenges through extensive research into both novel materials and materials repurposed for biomedical applications. A less explored area, but one with immense potential, is the use of artificial intelligence (AI), computational modeling, and other computing tools to aid in the development of biomaterials.[197]

The combination of diverse material types, coupled with engineered stimuli-response behavior and AI tools, represents multifaceted approaches to address current challenges, paving the way for reshaping healthcare practices through the use of new materials.

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